SIMONE APPENZELLER

O SISTEMA NERVOSO CENTRAL NO LÚPUS ERITEMATOSO SISTÊMICO:

ANÁLISES CLÍNICA E DE RESSONÂNCIA MAGNÉTICA

Universidade Estadual de Campinas/SP

2006

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Tese de Doutorado apresentada ao Curso de Pós-Graduação em Clínica Médica da Faculdade de Ciências Médicas da Universidade Estadual de Campinas para obtenção do título de doutor em Clínica Médica, na área de concentração em Clínica Médica

ORIENTADORA: *PROF. DRA. LÍLIAN TEREZA LAVRAS COSTALLAT*

CO- ORIENTADOR: *PROF. DR. FERNANDO CENDES*

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Banca examinadora**:**

Profª Drª. Lílian Tereza Lavras Costallat

Profª Drª Eloísa Silva Dutra de Oliveira Bonfá

Profª Drª Emilia Inoue Sato

Profª Drª Sandra Regina Muchinechi Fernandes

Profº Drº Manoel Barros Bertolo

BANCA EXAMINADORA DA TESE DE DOUTORADO

Orientadora: Prof. Dra. Lílian Tereza Lavras Costallat

Membros:

1. Prof. Dra. Eloísa Silva Dutra de Oliveira Bonfá

2. Prof. Dr. Emilio Inoue Sato

3. Prof. Dra. Sandra Regina Machinechi Fernandes

4. Prof. Dr. Manoel Barros Bertolo

5. Prof. Dra. Lílian Tereza Lavras Costallat

Curso de Pós-Graduação em Clínica Médica, área de concentração em Clínica Médica da Faculdade de Ciências Médicas da Universidade Estadual de Campinas.

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AVC	acidente vascular cerebral
Anti-P	anticorpos anti-ribossomal P
CA1, CA2, CA3	subdivisões arquitetônicas do cornu ammonis (1, 2, 3)
CAR	Colégio Americano de Reumatologia
Cho	cholina
Cr	creatina
DM	diabetes melitos
DTI	diffusion tensor imaging
ERM	espectroscopia por prótons
FAN.	Fator anti-núcleo
FLAIR	Fluid atenuation inverson recovery
HAS	hipertensão arterial sistêmica
^{1}H	núcleos de hidrogênio
LES	lúpus eritematoso sistêmico
MNP	manifestações neuropsiquiátricas
MTI	magnetic tensor imaging
Ms	milisegundos
NAA	N-acetyl aspartato
NMDA	N-metil-D-aspartato

NP	neuropsiquiátrico
PET	tomografia por emissão de pósitrons
Ppm	partículas por milhão
RM	ressonância magnética
SAAF	síndrome do anticorpo antifosfolípide
SB	substância branca
SNA	sistema nervoso autonômico
SNC	sistema nervoso central
SNP	sistema nervoso periférico
SPECT	Single Photon Emission Computer Tomography
TC	tomografia computadorizada cerebral
TVC	trombose venosa central
UNICAMP	Universidade Estadual de Campinas
VBM	Morfometria baseada em voxels

RESUMO

As manifestações do sistema nervoso central (SNC) no Lúpus Eritematoso Sistêmico (LES) são complexas, podendo ser causadas diretamente pela atividade do LES ou serem secundárias a comorbidades. O nosso objetivo foi avaliar as manifestações do SNC no LES e correlacioná-las às alterações cerebrais estruturais e funcionais à ressonância magnética. Todos os pacientes preenchiam quatro ou mais critérios classificatórios de LES e foram selecionados no ambulatório de Reumatologia da UNICAMP. Observamos que crises epilépticas ocorreram em 11,6% dos pacientes, estando associadas a acidente vascular cerebral e a presença de anticorpos antifosfolípides. A recorrência de crises foi rara, associada somente a presença de anticorpos antifosfolípides. A migrânea ocorreu mais frequentemente no LES que no grupo controle e estava associada a atividade de doença, ao Fenômeno de Raynaud e a presença de anticorpos antifosfolípides. Pacientes com história pregressa de migrânea apresentavam mais dano permanente. Analisando as ressonâncias magnéticas em pacientes com LES, observamos tanto atrofia de substância branca como de substância cinzenta. Embora ambos estivessem associados à presença de manifestações pregressas do SNC e ao maior tempo de doença, somente a atrofia de substância cinzenta esteve associada à dose cumulativa de corticosteróides. Pacientes com distúrbios cognitivos apresentaram mais frequentemente atrofia de corpo caloso e de hipocampo. Observamos também uma disfunção axonal no LES, associada a atividade de doença. De acordo com os nossos resultados, os métodos de neuroimagem estruturais e funcionais são úteis na confirmação do envolvimento do SNC e também na identificação do envolvimento subclínico no LES.

ABSTRACT

Central nervous system (CNS) manifestations in systemic lupus erythematosus (SLE) are complex. They may be directly caused by SLE disease activity or may be secondary to comorbities. Our objective was to determine CNS manifestations in SLE patients and to determine structural and functional neuroimaging abnormalities associated with its occurrence. Patients with four or more classification criteria for SLE, followed at the Rheumatology Unit of the State University of Campnas were included. We observed 11.6% of epileptic seizures in SLE patients. The occurrence of epileptic seizures was associated with the presence of stroke and antiphospholipid antibodies. Recurrence of seizures was rare and associated only with the presence of antiphospholipid antibodies. Migraine was more frequently observed in SLE patients than controls and was associated with disease activity, Raynaud's phenomenon and antiphospholipid antibodies. Pacients with past history of migraine had more frequently organ damage. We observed white and gray matter atrophy in SLE patients. Although both were associated with disease duration and past history of CNS involvement, only gray matter atrophy was associated with the total corticosteroid dose. Patients with cognitive impairment had more frequently corpus callosum and hippocampal atrophy. A transient axonal dysfunction, secondary to disease activity and not to CNS involvement, was observed in SLE. Our results suggest that structural and functional neuroimaging methods are useful in confirming CNS involvement, but also identify subclinical involvement in SLE patients.

1. INTRODUÇÃO E REVISÃO DA LITERATURA

O Lúpus Eritematoso Sistêmico (LES) é uma doença do tecido conjuntivo com manifestações clínicas diversas, caracterizada por períodos de remissão e exacerbação, com participação intensa do sistema imunológico (Dubois e Tuffanelli, 1964).

1.1. EPIDEMIOLOGIA

A prevalência de LES é de aproximadamente 0,1% na população geral (Siegel e Lee, 1973; Petri, 2002). Quanto às diferentes raças, observa-se a freqüência de 1 para cada 250 mulheres negras nos Estados Unidos da América; 22,4 para cada 100.000 asiáticos e 10,3 para cada 100.000 caucasianos (Fessel, 1974; Hopkinson et al., 1994; Alarcon, 2001; Petri, 2002). Apresenta-se, entretanto, como uma rara patologia entre os negros africanos (Molina et al., 1997; Molokhia et al., 2001). No Brasil observa-se uma freqüência maior entre os caucasóides, principalmente na região sudeste do país (Chahade et al., 1995).

Apesar de surgir geralmente na segunda e terceira década de vida, o LES pode se manifestar em qualquer idade, inclusive na primeira infância (Dubois e Tuffanelli, 1964; Siegel e Lee, 1973; Petri, 2002). Nas crianças, a relação entre sexo feminino e masculino é de 1,4 a 5,8:1; nos adultos varia de 8:1 a 13:1; nos indivíduos de idade mais avançada, esta relação é de 2:1 (Marini et al., 1999; Costallat et al., 2002).

1.2. CRITÉRIOS CLASSIFICATÓRIOS DE LES

Não existem critérios definitivos para o diagnóstico do LES. O Colégio Americano de Reumatologia definiu critérios classificatórios de LES, segundo o qual são

necessários no mínimo quatro critérios clínicos e/ou laboratoriais entre onze (Tan et al., 1982), após cuidadosa investigação e exclusão de doenças infecciosas, neoplásicas, entre outras.

Os critérios considram as seguintes manifestações:

- "Rash" malar
- Lesão discóide
- Fotossensibilidade
- Úlceras da mucosa oral
- Artrite não-deformante
- Serosite (pleurite, pericardite).
- Doença renal (proteinúria persistente, cilindrúria).
- Envolvimento do sistema nervoso central (convulsão e psicose)
- Alterações hematológicas (anemia, leucopenia ou plaquetopenia).
- Alterações imunológicas: células LE, anti-DNA, anti-Sm ou VDRL falso-positivo.
- Fator anti-núcleo (FAN)

Uma proposta de modificação destes critérios foi feita por Hochberg (1997), excluindo as células LE e substituindo o VDRL falso-positivo pela presença do anticorpo anticardiolipina.

1.3. MANIFESTAÇÕES NEUROPSIQUIÁTRICAS (NP) NO LES

As manifestações NP no LES são complexas e podem ser definidas como manifestações neurológicas do sistema nervoso central (SNC), periférico (SNP) e autonômico (SNA) e de síndromes psiquiátricas observadas em pacientes com LES. Podem ser causadas diretamente pela atividade do LES, serem secundárias a comorbidades como hipertensão arterial sistêmica (HAS), diabetes mellitos (DM), uremia e infecção. Poderiam ocorrer também ou ainda serem patologias primariamente distintas e concomitantes em pacientes com LES, sendo consideradas associações fortutas. Por definição, para ser considerada primariamente decorrente do LES, outras possíveis causas necessitam ser cuidadosamente excluídas (Hanly, 2005; Hanly e Harrison, 2005).

1.3.1. Histórico

A primeira menção à doença "lupus" ocorreu no século X por Hebernus of Tours na biografia de St Martin (Estes e Christian, 1971; Smith e Cyr, 1988). Porém, a primeira descrição do quadro clínico do Lúpus Eritematoso foi feita vez por Biett em 1828 (Skinner, 1949; Smith e Cyr, 1988), sendo que Kaposi observou a sua natureza sistêmica, descrevendo alguns pacientes com lesões viscerais (Kaposi, 1875). Osler (1904), enfatiza o acometimento sistêmico, alertando sobre a possibilidade de alterações viscerais sem concomitância com as lesões cutâneas; descreveu também a instabilidade do quadro clínico e suas fases alternadas de agudização e remissão dos sintomas. A partir de 1945 surgem os primeros estudos de grandes casuísticas descrevendo as principais manifestações clínicas e do SNC (Daly, 1945; Clark e Bailey, 1956; Dubois e Tuffanelli, 1964; Klippel e Zvaifler, 1975; Sergent et al., 1975; Feinglass et al., 1976; Ellis and Verity, 1979; Adelmann et al., 1986; Kaell et al., 1986).

1.3.2. Classificação

Desde as primeiras descrições das manifestações NP (Daly, 1945; Clark e Bailey, 1956; Dubois e Tuffanelli, 1964; Johnson e Richardson, 1968; Klippel e Zvaifler, 1975; Sergent et al., 1975; Feinglass et al., 1976; Ellis and Verity, 1979; Adelmann et al., 1986; Kaell et al., 1986; Pistiner et al., 1991) observou-se que muitas destas não eram contempladas pelos critérios classificatórios originais descritos (Tan et al., 1982). A falta de padronização fez surgir diferentes critérios e definições destas manifestações (Kassan & Lockshin., 1979; How et al., 1985; Singer e Denburg, 1990; West, 1994; Hanly, 1998) e assim, obteve-se resultados diversos e de difícil comparação. Em 1999, o Colégio Americano de Reumatologia elaborou um consenso para a terminologia e definição das síndromes NP que ocorrem no LES (ACR, 1999), com a participação de reumatologistas, neurologistas, psiquiatras, entre outros, que definiu as 19 síndromes da doença (Tabela 1).

Tabela 1. Manifestações NP no LES.

Manifestações do SNC	Manifestações do SNP
Cefaléia	Desordem autonômica
Convulsão	Miastenia Grave
Desordens de ansiedade	Mononeuropatia
Desordens do humor	Neuropatia craniana
Desordens do movimento	Plexopatia
Distúrbios cognitivos	Polineuropatia
Doença cerebrovascular	Polirradiculopatia inflamatória desmielinizante aguda
Estado confusional agudo	
Meningite asséptica	
Mielopatia	
Psicose	
Síndromes desmielinizantes	

SNC: sistema nervoso central; SNP: sistema nervoso periférico

Posteriormente, estes critérios foram validados, apresentando uma especificidade de 46% (Ainiala et al., 2001). Porém, este mesmo estudo demonstrou que, excluíndo-se cefaléia, ansiedade, depressão leve, distúrbio cognitivo leve e polineuropatia sem confirmação por eletroneuromigrafia, a especificidade aumenta para 93%. Portanto, apesar desta classificação ser atualmente a mais aceita, há ainda limitações que podem ser futuramente modificadas (Hanly, 2004).

A avaliação de cada uma destas manifestações envolve uma série de testes neurofisiológicos (Omdal et al, 1989; Omdal et al., 1991; Omdal et al., 1993; Omdal et al., 1996; Costallat et al., 1997), técnicas laboratoriais (Blustein et al., 1981; Bluestein e Woods, 1982; Bluestein e Zvaifler, 1983; Gharavi et al., 1987; Bonfa et al., 1987; Robbins et al., 1988; Temesvari et al., 1983; Costallat et al., 1990; Denburg et al., 1994) e de neuroimagem, incluindo a tomografia computadorizada cerebral (TC) (Gonzales-Scarano et al., 1979; Carette et al., 1982; Kaell et al., 1986; Yang et al., 1993; Zanardi et al., 2001; Omdal et al.,1989) e a ressonância magnética (RM) (Miller et al, 1992; Stimmler et al., 1993; Jarek et al., 1994; McCune et al., 1998; Kozora et al., 1998), quando necessários.

Vários estudos utilizaram estes critérios para descrever a freqüência ou prevalência das manifestações NP no LES, sejam do SNC (Tabela 2) ou SNP (Tabela 3). Apesar de ainda ser observada uma grande variabilidade entre as freqüências, o uso desta mesma classificação permite supor que estas diferenças possam ser devidas ao número de pacientes incluídos e à diferenças loco-regionais (Hanly, 2005).

Tabela 2. LES: Critérios classificatórios das manifestações neuropsiquiátricas: análise do sistema nervoso central

Autores/ Ano	No de pac.	Prev. NP (%)	Cef. (%)	Crises conv. (%)	Ans. (%)	Humor (%)	Des. mov. (%)	DC (%)	DCV (%)	ECA (%)	MA (%)	Miel. (%)	Psic. (%)	S. Desm. (%)
Ainiala et al., 2001	46	91	54	9	13	44	2	80	15	7	2	0	0	2
Costallat et al., 2001	527	34	3*	7,4	0,8*	3,0*	0,8	1,3*	2,5	3	0,4	1	5,3	0,2
Mok et al., 2001	518	19	4	28	1,5	6	2	NA	19	14	1	8	11	1,5
Brey et al, 2002	128	80	57	16	24	23,0	1	79	2	0	0	5,0	6,5	0
Alfreta et al., 2003	61	72	21	11	6	27	0	52	24	0	0	0	0	3
Sanna et al., 2003	323	57,3	24	8,3	7,4	16,7	1,2	10,8	17,6	3,7	0	1,2	7,7	0,9
Hanly et al., 2004	111	37	24,4	2,4	2,4	9,8	0	7,3	9,8	7,0	2,4	0	7,3	2,4
Mikdashi et al., 2004	130	56,9	NA	7,6	0	NA	0	27,3	25,7	0	0	6,1	15,1	0
Hanly et al., 2005	53	31	9,4	0		0	0	1,9	0	3,8	0	0	0	1,9
Shimojima et al., 2005	25	100	12	36	0	0	0	12	24	0	0	4	32	0
Robert et al., 2006	50	78	55,6	20,5	0	0	23,1	18	16,2	16,2	0	0	16,2	0

Ans.: ansiedade; Cef.: Cefaléia; conv.: Convulsivas; Des. Mov.: Desordens do movimento; DC: distúrbios cognitivos; DCV: doença cérebro vascular; ECA: estado confusional agudo ; MA: Meningite asséptica; NA: não avaliado; No: número; pac.: Pacientes; Psic.: Psicose; Prev.: Prevalência; Miel.: Mielopatia; S. Desm.: síndrome Desmielinizante.
*referido pelo paciente

Tabela 3. LES: Critérios classificatórios das manifestações neuropsiquiátricas: análise do sistema nervoso periférico

Autores/ Ano	No de pacientes	Desordens autonômicas (%)	Miastenia Grave (%)	Mononeuropatia (%)	Neuropatia craniana (%)	Plexopatia (%)	Polineuropatia (%)	Poliradiculopatia inflamatória desmielinizante aguda (%)
Ainiala et al., 2001	46	0	2	0	7	0	28	2
Costallat et al., 2001	527	0	0,2	1,3	1,5	0	4	0,2
Mok et al., 2001	518	0	0	1,5	3	0	1	0
Brey et al., 2002	128	0	0	8	2	0	22	0
Alfreta et al., 2003	61	3	0	0	4	0	13	0
Sanna et al., 2003	323	0	1,5	1,8	1,5	0	2,8	0,6
Hanly et al., 2004	111	0	0	0	4,9	0	4,9	0
Mikdashi et al, 2004	130	0	0	0	0	0	18,2	0
Hanly et al., 2005	53	0	0	0	0	0	0	0
Shimojima et al., 2005	25	0	0	0	0	0	12	0
Robert et al., 2006	50	NA	0	7,9	0	0	0	0

NA: não avaliado; No: número

Os sintomas NP podem se apresentar isoladamente ou em conjunto, ocorrendo em episódios únicos durante a fase de exacerbação da doença, associados ou não a outros sinais de atividade do LES. Ocorrem em qualquer tempo da doença, podendo ser o seu primeiro sinal clínico (McCune e Golbus, 1988; Costallat et al., 1990; Pistiner et al., 1991). Os principais problemas diagnósticos consistem na distinção entre as alterações neurológicas causadas pelo LES, com anormalidades imunológicas tendo papel preponderante, e eventos secundários, como complicações da HAS, distúrbios metabólicos, distúrbios de coagulação, infecção grave e corticoterapia (How et al., 1985; Hanly, 2004), que podem ocorrer em até 41% dos pacientes (Hanly et al., 2004).

Portanto, como não existe diagnóstico definitivo para o acometimento NP, em especial do SNC, outras causas como as infecciosas, metabólicas ou por drogas devem sempre ser exaustivamente excluídas.

1.3.3. Importância clínica das manifestações do SNC no LES

A importância das manifestações do SNC no LES pode ser determinada analisando a influência na mortalidade, qualidade de vida e índice de dano permanente (Feng et al., 1973; Cheatum et al., 1973; Sergent et al., 1975; Lee et al., 1977; Ginzler et al., 1982; Sibley et al., 1992; Kovacs et al., 1993; Carlomagno et al., 2000; Jonson et al., 2002; Mikdashi e Handwerger, 2004).

Apesar de não haver consenso em diferentes estudos quanto a uma maior mortalidade nos pacientes com manifestações do SNC (Swaak et al., 1989; Jonsonn et al., 1989; Jonson et al., 2002), já foi observado que estes pacientes apresentam um aumento dos escores de incapacidade (Jonson et al., 2002), maior fadiga (Mikdashi e Handwerger, 2004) e uma pior qualidade de vida (Hanly et al., 2004). Em um estudo para determinar o índice de dano em pacientes com manifestações do SNC observou-se que a presença de doença ativa na instalação e a presença de anticorpos antifosfolípides eram fatores preditivos para maior dano permanente em pacientes com LES (Mikdashi e Handwerger, 2004).

Poucos estudos analisaram o comprometimento do SNC de forma longitudinal (Hanly et al., 1994; Hay et al., 1994; Carlomagno et al., 2000; Karassa et al., 2000; Waterloo et al., 2002). Em pacientes que foram internados devido ao comprometimento do SNC e seguidos por dois anos, observou-se uma boa evolução em 69% e uma estabilização do quadro em 19% dos casos, sendo que o número de manifestações NP prévias e a presença da síndrome do anticorpo antifosfolípide indicaram pior prognóstico (Karassa et al., 2000). Em relação ao distúrbio cognitivo, também foi observado que a maioria dos pacientes apresenta flutuações da cognição, não evoluíndo, portanto para demência (Hanly et al., 1994; Hay et al., 1994; Carlomagno et al., 2000; Waterloo et al., 2002).

1.3.4. Etiopatogenia do comprometimento do SNC no LES

Estudos anatomopatológicos de cérebros de pacientes com LES, com e sem comprometimento do SNC, evidenciaram predominantemente comprometimento microvascular, com poucos sinais de vasculite (Johnson e Richardson, 1968; Ellis and Verity, 1979; Zvaifler and Bluestein, 1982; Hanly, 1992; Abbott et al.; 2003). Embora alguns destes estudos tenham demonstrado um comprometimento microvascular, aparentemente estes achados não justificam a maioria das manifestações do SNC no LES. Portanto, a etiopatogenia do SNC no LES parece ser multifatorial, envolvendo, além do comprometimento da pequena circulação, a produção de autoanticorpos e o processo inflamatório (Hanly 2005; Hanly e Harrison, 2005).

A presença de anticorpos contra neurônios, ribossomos e fosfolípides já foram associados às manifestações do SNC no LES. Em modelo animal foi demonstrado que anticorpos antineuronais induzem déficits de memória, convulsões e alterações neuropatológicas (Kobiler e Allweis, 1976; Morris et al., 1986). Um aumento de anticorpos antineuronais foi observado por Hanson et al (1992), embora nenhuma manifestação clínica específica estivesse associada a este achado. Em pacientes com manifestações do SNC observou-se um aumento dos receptores N-metil-D-aspartato (NMDA), NR2a e NR2b, o

que parece ter uma consequência funcional que leva a lesão neuronal (Lipton e Rosenberg, 1994). Foi demonstrado que anticorpos anti NR2 estão associados a déficit de memória (Akbarian et al., 1996) e psicose (Teh e Isenberg, 1998). Os anticorpos anti-ribosomal P (anti P) apresentam uma prevalência de 13-20% no LES, dependendo do grupo étnico estudado (Arnett et al., 1996), e estão associados a psicose e depressão (Bonfa et al., 1987; Tzioufas et al., 2000; Gerli et al., 2002). Os anticorpos antifosfolípides estão relacionados primariamente a manifestações focais, porém já foram descritas associações com convulsão, coréia, mielite transversa e disfunção cognitiva (Love e Santoro, 1990; Menon et al., 1999; Chapman et al.,1999; Hanly, 2003; Hanly, 2005).

Vários estudos têm analisado o papel dos processos inflamatórios no LES (Hirohata e Miyamoto, 1990; Shiozawa et al., 1992; Jara et al., 1998; Trysberg et al., 2000; Faber-Elmann et al., 2002; Schenatto et al., 2006). Interleucinas (Hirohata e Miyamoto, 1990; Jara et al., 1998; Trysberg et al., 2000), fator de necrose tumoral (Shiozawa et al., 1992), metaloproteinases (Faber-Elmann et al., 2002; Ainiala et al., 2004) e S 100 beta (Schenatto et al., 2006) parecem estar associados às manifestações do SNC no LES e aos achados à RM.

1.4. MÉTODOS DE NEUROIMAGEM PARA AVALIAÇÃO DO COMPROMETIMENTO DO SNC

Os métodos de neuroimagem são utilizados para estabelecer a presença de anormalidades cerebrais difusas e/ou focais. Podem ser classificados em métodos de avaliação estrutural e funcional.

1.4.1 Métodos de avaliação estrutural

Os métodos de análise estrutural visam determinar alterações morfológicas e a sensibilidade depende do método utilizado.

Tomografia computadorizada

A tomografia computadorizada tem a vantagem de ser disponível na maioria dos serviços de médio porte e tem um custo operacional relativamente baixo. A tomografia computadorizada tem como princípio o uso de raio-X para gerar o contraste na imagem, o qual resulta da diferença dos coeficientes de atenuação entre duas estruturas adjacentes, na ordem de alguns pontos percentuais. Os coeficientes de atenuação estão relacionados com as densidades dos elétrons, que são proporcionais aos números anatômicos dos elementos constituintes dos compostos químicos. Portanto, a gordura, que é rica em carbono, é mais transparente do que a água, uma vez que o oxigênio tem um número anatômico maior que o carbono.

A tomografia computadorizada pode detectar grande parte dos tumores, malformações arteriovenosas e malformações cerebrais extensas, acidentes vasculares, lesões infecciosas e é sensível para detecções de lesões calcificadas. Entretanto, é pouco sensível para detectar lesões na base do crânio e pequenas lesões corticais, de um modo geral.

No LES a tomografia computadorizada tem sua validade para detectar ainda lesões cerebrais focais agudas e na hidrocefalia, sendo, porém, pouco sensível na doença cerebral difusa ou na identificação de alterações na substância branca (Gonzalez-Scarano et al., 1979; Vermess et al., 1983; Kaell et al.,1986; Waterloo et al., 1999; Zanardi et al., 2001). Vários estudos têm utilizado a tomografia computadorizada de crânio como método de investigação no comprometimento do SNC no LES (Tabela 4).

Tabela 4. LES: Estudos utilizando a tomografia cerebral

Autores/ Ano	No de pac.	Tipo de análise	AVCi (%)	AVCh (%)	Atrofia (%)	Lesões de SB (%)	Outros achados	Associações	Observações
Bilaniuk et al., 1977	14	Visual	14.3	0	50	0	Meningioma (7%)	Correlação com clínica	----------
Gonzalez-Scarano et al., 1979	29	Visual	13.8	13.8	72.4	0	Pseudotumor cerebral (3.4%)	Alterações associadas à psicose e demência	20 com MNP Regressão dos achados em 1 paciente
Carrett et al., 1982	23	Visual	13	0	82.6	0	-	Atrofia sem associação com MNP, secundário a CE	12 pacientes com sintomas e 11 sem sintomas do SNC
Gaylis et al., 1982	36	Visual	0	0	55.6	0	-	Atrofia associada à “cerebrite”	-
Ostrov et al., 1982	32	Visual	0	0	62.5	0	-	Atrofia mais freqüênte e intensa com MNP	Sem associação com CE
Vermess et al., 1983	9	Visual	0	0	0	66.7	-	RM mais sensível para detecção de lesões	-
Weisberg, 1986	17	Visual	41.1	11.8	35.3	0	-	Atrofia associada com DC	Todos com sintomas neurológicos
Sibbitt et al., 1989	21	Visual	4.8	4.8	9.5	0	-	-	Todos com MNP agudas RM mais sensível que TC
Omdal et al., 1989	30	Visual	21	0	71	0	-	Atividade de doença associada com AVCi	AVCi em pacientes anti SSA/Ro-
Yang et al., 1993	22	Visual	23	18	68	0	Edema cerebral (18%) Hidrocefalia (14%)	Achados a TC modificaram a conduta em 41% dos casos	Ajuda no diagnóstico, mas não muda o prognóstico
Waterloo et al., 1999	36	Visual	7	0	74.4	2.3	-	Achados sem correlação com disfunção cerebral	-
Zanardi et al., 2001	107	Medição linear	0	0	66.1	0	-	Atrofia secundária a CE; mais intensa em pacientes com convulsões	-

AVCi: acidente vascular cerebral isquêmico; AVCh: acidente vascular cerebral hemorrágico; CE: corticosteróides; DC: distúrbio cognitivo; MNP: manifestações neuropsiquiátricas; No.: número; pac.: pacientes; RM: ressonância magnética; SB: substância branca; TC: tomografia cerebral.

Ressonância Magnética

A RM utiliza como princípio, a propriedade dos núcleos de hidrogênio (^{1}H) em emitir um sinal eletromagnético em resposta a um pulso de radiofreqüência. Alterações sutis no conteúdo de água do tecido resultam em variações neste sinal do próton ^{1}H. Após ser captada, a diferença de intensidade neste sinal em vários pontos do espaço (que reflete a estrutura molecular dos tecidos) é transformada em uma imagem em preto e branco através de processos de computação gráfica. As características únicas desse método possibilitam a modificação da intensidade de sinal relativa dos tecidos através da alteração de parâmetros operacionais específicos. Além disso, as imagens podem ser obtidas em qualquer plano, minimizando dificuldades técnicas relacionadas à posição do paciente.

O exame de RM é complexo, constituindo-se de diferentes técnicas e seqüências de pulso. As seqüências de pulso podem de uma maneira simplificada, ser divididas em seqüências ponderadas em T1 e T2. O sinal obtido nas seqüências ponderadas em T1 é resultante da liberação de energia que ocorre quando a interação entre os núcleos de ^{1}H excitados com o meio molecular regional (relaxamento *spin-lattice*). As seqüências ponderadas em T1 permitem o estudo do sinal proveniente do parênquima cerebral, enfatizando, assim, a morfologia. As seqüências ponderadas em T2 (T2, densidade de prótons, e *Fluid atenuation inverson recovery* (FLAIR)) baseiam-se na aquisição do sinal proveniente da interação entre os núcleos ^{1}H excitados e outros núcleos em diferentes estados de energia (relaxamento *spin-spin*). Estas seqüências possuem alta sensibilidade na detecção de alterações patológicas, que determinam aumento do conteúdo local de água e/ou alterações intersticiais, tais como gliose, desmielinização, edema e infiltração tumoral, por exemplo. As imagens ponderadas em T1 e T2 podem ser obtidas utilizando-se diferentes técnicas de parâmetros que influenciam as características das imagens obtidas e o tempo de duração do exame.

Nas técnicas de processamento as imagens obtidas podem ser manipuladas em uma estação de trabalho (*Workstation*) para atender a diversos propósitos. O processamento das imagens obtidas pela RM permite quantificar e qualificar as alterações encontradas, de modo que, ao determinarmos a sua relação biológica com variáveis clínicas, obtem-se resultados objetivos e reproduzíveis. Estes resultados podem ser utilizadas no seguimento destes pacientes, quando a comparação com imagens obtidas posteriormente, se tornar necessária.

Na RM de pacientes com LES podem ser observadas atrofia cerebral localizada ou difusa e lesões em substância branca. A atrofia cerebral é vista na RM em 33 a 67% dos pacientes com LES, sendo fatores causais, entre outros, a longa duração da doença, o infarto cerebral prévio, a idade mais avançada dos pacientes e o uso de corticosteróides (Walecki et al., 2002; Kozora et al., 1998). Os padrões de lesão de substância branca descritas no LES são áreas puntiformes de hipersinal em imagens T2 e FLAIR, localizadas na região periventricular ou subcortical. As áreas focais hiperintensas também podem envolver córtex, núcleos da base e tronco cerebral. Outras alterações observadas em RM de pacientes com LES incluem infarto, hemorragia e atrofia cerebral (Walecki et al., 2002). No entanto, o freqüente aparecimento de áreas de hipersinal na substância branca e sua possível associação com atividade da doença, bem como sua associação com distúrbios cognitivos são assunto ainda controversos, dificultando a correlação entre as manifestações clínicas e os achados de neuroimagem (Walecki et al., 2002).

A RM é, portanto, o exame mais sensível para se detectar as alterações cerebrais, tanto no LES como em outras doenças difusas do tecido conjuntivo. Alguns estudos têm utilizado a RM para avaliação do comprometimento do SNC no LES (Tabela 5).

Tabel 5. LES: Estudos utilizando a resonância magnética

Autores/ Ano	No de pac.	AVCi (%)	AVCh (%)	Atrofia (%)	Lesões de SB (%)	Associações e observações
Vermess et al., 1983	9	0	0	0	88.9	Todos com comprometimento do SNC; RM mais sensível que TC
Mc Cune et al., 1988	28	0	0	67%	53	Associadas a défcits neurológicos focais e convulsões; RM importante para detectar dano cerebral
Sibbitt et al, 1989	21	47.6	4.8	33.3 Ed.focal(38%)	0	Todos os pac. tinham comprometimento do SNC; RM mais sensível que TC
Baum et al; 1993	21	-	-	52,4	57,1	Alterações mais frequentes em pac. com sintomas focais
Stimmler et al., 1993	51	0	0	21,9%	15,6	Todos pac. hospitalizados; associados a HAS e nefrite; pac. com lesões focais têm mais alterações a RM; sugere vasculopatia (presente também em idosos)
Cauli et al., 1994	40	-	-	-	37,5	Alterações mais frequentes em pac. com sintomas orgânicos e maior índice de atividade
Jarek et al., 1994	32	0	0	0	16	Freqüência similar a da população normal
Chinn et al., 1997	47	8,5		32,5	23	Segmentação semi-automática; RM mostra alterações crônicas de origem isquêmica
Kozora et al., 1998	20	0	0	35	35	Paci. sem MNP; Sem relevância clínica
Sanna et al.; 2000	68	4,4			44	SLICC com anormalidades à RM; LB mais freqüentes em pac. com MNP
Walecki et al.; 2002	50	20	2	54	54	Associação entre a gravidade dos sintomas e achados a RM; associação entre SAAF e lesões de substância branca
Oku et al., 2003	44	0	0	42	84	Correlação dos achados da RM com sintomas clínicos
Cotton et al., 2004	58	6,9	0	37,9	59	70 % dos pac. com alterações a RM; independente da presença de MNP
Abreu et al., 2005	23	13	0	0	65,2	Alterações mais frequentes em pac. com MNP
Ainialia et al; 2005	43	pres.	pres.	pres.	pres.	Associação com dano permanente (SLICC-ACR/DI) Atrofia associada com CE
Sundgren et al., 2005	15	18	9	54,5	81,8	RM é importante para definir a etiologia de eventos isquêmicos agudos

CE: corticosteróides; Ed.: edema; HAS: hipertensão arterial sistêmica; MNP: manifestação neuropsiquiátrica; No: número; pac.: pacientes; Pres.: presente; RM: ressonância magnética; SAAF: Síndrome do anticorpo antifosfolípide; SB: substância branca; SNC: sistema nervoso central; TC: tomografia computadorizada.

1.4.2. Métodos de avaliação funcional

Espectroscopia por prótons

A espectroscopia por prótons (ERM) permite a quantificação não invasiva *in vivo* de alguns compostos químicos de importância biológica que estão presentes em concentrações muito menores que a água nos tecidos. O sinal de ERM proveniente de ^{1}H é inerentemente mais forte do que qualquer outro núcleo. Quase todos os metabólitos de alta concentração contém núcleos de ^{1}H, que em princípio, podem ser utilizados para identificá-los na ERM.

Espectros de prótons com supressão de água do cérebro humano utilizando um tempo de echo entre 136 e 272 milisegundos (ms) revelam três ressonâncias principais:

(1) uma em 3,2 partículas por milhão (ppm), que se origina das tetrametil-aminas, sobretudo as colinas, ricas em fosfolípides (Cho), marcadores, em certas circunstâncias, da quebra de mielina;

(2) uma em 3,0 ppm, que se origina primariamente da creatina e fosfocreatina (Cr);

(3) uma em 2,0 ppm que se origina em grupos N-acetil, principalmente N-acetilaspartato (NAA), marcador de integridade neuronal;

Várias evidências indicam que o NAA pode ser usado como um marcador neuronal, já que é encontrado exclusivamente em neurônios e processos neuronais (Birken

et al., 1991; Moffett et al., 1991; Simmons et al., 1999). Em espectros do cérebro humano *in vivo*, como nas doenças neurodegenerativas (Van der Knaap et al., 1992), acidentes vasculares (Graham et al., 1992; Duijin et al., 1992) e tumores (Arnold et al., 1992; Preul et al., 1996) observa-se uma diminuição da NAA em relação a Cr. Quando reduções relativas do sinal do NAA ocorrem, devido à degeneração axonal e/ou neuronal, alterações irreversíveis são esperadas. Entretanto, existem observações de redução reversível do NAA em várias doenças, demonstrando que uma disfunção neuronal ou uma mudança relativa do volume neuronal, pode provocar redução do NAA (Destefano et al., 1995; Destefano et al., 1995; Davie et al., 1994). A habilidade de quantificar perda ou dano neuronal é uma das aplicações da ERM na investigação de doenças que acometem o SNC. Mudanças na intensidade de ressonância da Cho provavelmente resultam da elevação das concentrações de equilíbrio da fosfocolina e da glicerofosfocolina. Estes fosfolípides de membrana são liberados no meio extracelular durante a destruição da mielina. Portanto a intensidade da ressonância da Cho aumenta na presença de lesões dismelinizantes agudas (Arnold et al., 1992). A concentração total de creatina é relativamente constante no tecido cerebral. Portanto é plausível a idéia de se utilizar a creatina como um padrão interno para normalizar a intensidade da ressonância de sinal (devido à falta de homogenieade do campo magnético e do campo utilizado).

Os principais estudos com ERM no LES (Tabela 6) demonstram uma redução do NAA/Cr associada a atividade de doença (Sibbitt et al., 1997), a presença de atrofia (Sibbitt et al., 1994) e manifestações NP (Sibbitt et al., 1997, Axford et al., 2001, Handa et al., 2003). Já o aumento da Cho/Cr está associada principalmente à infartos cerebrais (Friedman et al., 1998), na presença da síndrome do anticorpo antifosfolípide (Sabet et al., 1998) e na presença de distúrbios cognitivos (Kozora et al., 2005).

Tabela 6. LES: estudos utilizando a espectroscopia por prótons

Autor/ Ano	Localização da ERM	No de pacientes	Alterações da ERM	Associações clínicas
Sibbitt et al., 1994	SB, superior aos ventrículos nos dois hemisférios	21	↓NAA/Cr	Mais intenso na presença de atrofia
Davie et al., 1995	Lesões de SB (5 pacientes) e SB normal (7 pacientes)	13	↓NAA/Cr	Sem correlação com MNP; ↓NAA/Cr nas lesões
Brooks et al., 1997	Lesões e SB normal nas regiões periventricular e occipital e substância cinzenta occipital	14	↓NAA/Cr	Em todas as areas estudadas; mais intenso nas lesões
Chinn et al., 1997	SB frontal e parieto-occipital	47	↓NAA/Cr ↓Cho/Cr	Associação com corticosteróides
Sibbitt et al., 1997	SB normal parietal	36	↓NAA/Cr	Atividade da doença e MNP
Sabet et al., 1998	SB profunda occipito-parietal	43	↓NAA/Cr	↑Cho/Cr com SAAF
Friedman et al., 1998	SB normal occipito-parietal	42	↓NAA/Cr ↑Cho/Cr	↓NAA/Cr em lesões focais ↑Cho/Cr com infartos cerebrais
Brooks et al., 1999	Lesões e SB normal nas regiões periventriculares e occipitais e substância cinzenta occipital	12	↑Cho/Cr	Distúrbio cognitivo SLICC
Lim et al., 2000	Ganglios basais e SB periventricular	26	↓NAA/Cr em ganglios da base ↑Cho/Cr periventricular	MNP maiores; sem associação com achados à RM
Axford et al., 2001	Substância branca parietal normal	9	↓NAA,↑mI ↑Cho	↓NAA: MNP maiores ↑mI na substância branca normal ↑Cho: MNP menores
Handa et al., 2003	SB parieto-occipital e frontal normal	20	↓NAA/Cr	MNP
Castellino et al., 2005	Áreas hipoperfundidas e normoperfundidas no SPECT	8	↓NAA/ Cho em areas hipoperfundidas ↑Cho/Cr em áreas normoperfundidas	Lesões de substância branca; Aparecimento de lesões de substância branca em áreas hipoperfundidas com ↓NAA/ Cho
Kozora et al., 2005	SB normal frontal e periventricular	7	↑Cho/Cr	↑ na presença de distúrbios cognitivos

Cho: cholina; Cr: creatina; ERM: espectroscopia por ressonância magnética; mI: mioinusitol; MNP: manifestações neuropsiquiátricas; ms: milisegundos; NAA: N-acetyl aspartato; RM: ressonância magnética; SAAF: síndrome do anticorpo antifosfolípide; SB: substância branca; SLICC: SLICC/ACR-DI; SPECT: single photon emission computer tomography.

Single photon emission computed tomography (SPECT)

No SPECT observa-se alterações na função cerebral e na barreira hemato-encefálica e não de estruturas cerebrais como na RM. A distribuição do contraste é proporcional ao fluxo sanguíneo na hora da injeção e ao metabolismo cerebral. O SPECT pode ser um método sensível, mostrando alterações no fluxo cerebral dos pacientes com sintomas NP. Pacientes com manifestações difusas NP tem áreas simétricas e disseminadas de hipoperfusão e aqueles com manifestações focais não tem áreas tão disseminadas (Rogers et al., 1992; Rubbert et al., 1993; Szer et al., 1993; Emmi et al., 1993; Colamussi et al., 1995; Kodama et al., 1995; Kovacs et al.,1995; Russo et al., 1998; Nossent et al., 1991; Lin et al., 1997; Huang et al., 2002; Liu et al., 2003; Oku et al., 2003; Handa et al., 2003; Sundgreen et al., 2005; Zhang et al., 2005).

Estas alterações de perfusão são mais comuns em regiões parietal, frontal, temporal e gânglios da base, ou seja, aquelas supridas pela artéria cerebral média (Rubbert et al., 1993; Szer et al., 1993; Emmi et al., 1993; Kovacs et al.,1995; Colamussi et al., 1995; Kodama et al., 1995; Lin et al., 1997; Russo et al., 1998; Nossent et al., 1991). As alterações, tanto difusas quanto focais, muitas vezes ocorrem sem alterações da tomografia computadorizada ou RM, principalmente nas manifestações do SNC leve (Tabela 7).

Tabela 7: LES: Estudos que utilizaram SPECT cerebral

Autores/Ano	No. de pac.	Tipo de contraste	Técnica de análise	Achados
Lin et al., 1998	72	99mTc-HMPAO	Visual	Boa correlação com clínica
Lass et al, 1989	50	99mTc-HMPAO	Visual	Maior alteração na em pacientes com SAAF
Kao et al., 1999	37	99mTc-HMPAO	Visual	Mais sensível que PET ou RM
Kao et al., 1999	25	99mTc-HMPAO	Visual	Alteração no SPECT e PET estão associadas a MNP
Shen et al., 1999	109	99mTc-HMPAO	Visual e apresentação 3D	Esta técnica permite avaliar melhor o fluxo cerebral no LES
Kikukawa et al., 2000	32	99mTc-ECD	Visual e semi-quantitativa	Melhora clínica; Não houve melhora nas áreas de hipoperfusão
Waterloo et al., 2001	52	99mTc-HMPAO	Visual	Sem associação com clínica
Chen et al., 2002	20	99mTc-ECD	Visual	Pacientes com MNP leves e RM normais: sem indicação de SPECT
Huang et al., 2002	78	99mTc-ECD	Visual	Útil no diagnóstico precoce do envolvimento do SNC
Borelli et al., 2003	20	99mTc-HMPAO	Visual e co-registro com SPM	Útil para co-registro, sugere que alterações anatômicas ocorrem mais tardiamente
Handa et al., 2003	20	99mTc HMPAO	Visual	Mais sensível que RM
Liu et al., 2003	12	99mTc-ECD	Visual	Hipoperfusão cerebral melhorou com pulso de metilpredinisolona
Lopes-Longo et al., 2003	67	99mTc-ECD	Visual	Hipoperfusão com atividade de doença, maior índice de dano e história de MNP
Sun et al., 2004	15	99mTc-HMPAO	Visual	Hipoperfusão melhorou após tratamento com metilpredinisolona em 13/15 pacientes
Abreu et al., 2005	23	99mTc-ECD	Visual	Não correlacionado a achados de RM e a clínica
Omdal et al., 2005	56	99mTc-HMPAO	Comparativo-visual	Fadiga não estava associada a alteração no fluxo cerebral
Oda et al., 2005	20	99mTc ECD	VBM	Redução do fluxo no giro do cíngulo posterior e tálamo em MNP graves
Zangh et al., 2005	43	99mTc-ECD	Visual	Mais sensível que RM em pacientes com MNP

ECD: Etilcisteinato dímero; HPMAO: Hexametilpropilenoamina oxima; MNP: manifestação neuropsiquiátrica; No: número; pac.: pacientes; PET: tomografia por emissão de pósitrons; RM: ressonância magnética; SAAF: síndrome do anticorpo antifosfolípide; Tc: tecnésio

1.4.3. Outros métodos de imagem

Outros métodos de imagem estruturais (*magnetic transfer imaging, diffusion tensor imaging*) e funcionais (ressonância magnética funcional, tomografia de emissão de pósitrons) têm sido utilizados para avaliação do comprometiento do SNC no LES, porém não foram aqui descritos por não terem sido utilizados no presente trabalhos.

2. OBJETIVOS

2.1. OBJETIVO GERAL DA TESE

O objetivo geral foi avaliar as manifestações do SNC no LES e correlacioná-las a alterações cerebrais estruturais e funcionais através de técnicas de neuroimagem.

2.2. OBJETIVOS ESPECÍFICOS DE CADA ARTIGO

Artigo 1: Neurolupus.

Revisão sobre o histórico do comprometimento do SNC no LES.

Artigo 2: Central nervous system manifestations in systemic lupus erythematosus

Revisão sobre as manifestações do SNC no LES, incluíndo classificação, etiologia, investigação e tratamento.

Artigo 3: Magnetic resonance spectroscopy in the evaluation of central nervous system manifestations of systemic lupus erythematosus.

Revisão da literatura sobre a utilização da espectroscopia por RM na avaliação das manifestações do SNC no LES.

Artigo 4: Epileptic seizures in systemic lupus erythematosus.

Determinar a freqüência de epilepsia no LES e fatores de risco associados a sua ocorrência.

Artigo 5: Clinical implications of migraine in systemic lupus erythematosus: relation to cumulative organ damage.

Avaliar a importância clínica da migrânea no LES e sua relação com o dano permanente.

Artigo 6: Acute psychosis in systemic lupus erythematosus.

Determinar a freqüência de psicose aguda no LES e fatores de risco associados. Determinar variáveis clínicas que diferenciem psicose aguda daquela induzida por corticosteróides.

Artigo 7: Cerebral venous thrombosis: influence of risk factors and imaging findings on prognosis.

Determinar achados clínicos, de neuroimagem e de prognóstico associados a ocorrencia de trombose venosa central de diferentes etiologias.

Artigo 8: **Cerebral and corpus callosum atrophy in systemic lupus erythematosus**.

Determinar o volume cerebral e do corpo caloso em pacientes com LES e fatores clínicos, laboratoriais e de tratamento associados.

Artigo 9: **Longitudinal analysis of gray and white matter loss in patients with systemic lupus erythematosus.**

Determinar a presença e a progressão de atrofia de substância branca e cinzenta através da análise de morfometria baseada em voxels de pacientes com LES.

Artigo 10: **Hippocampal atrophy in systemic lupus erythematosus**.

Determinar a freqüência e progressão da atrofia hipocampal em pacientes com LES e fatores associados.

Artigo 11: Voxel-based morphometry of brain SPECT can detect the presence of active central nervous system involvement in systemic lupus erythematosus.

Avaliar se a análise do SPECT cerebral pela técnica de VBM é sensível para detectar alterações funcionais em pacientes com comprometimento do SNC no LES.

Artigo 12: Evidence of reversible axonal dysfunction in systemic lupus erythematosus: a proton MRS study.

Avaliar a presença de disfunção axonal no LES.

Artigo 13: **Increased choline/creatine ratio on MRS may predict appearance of white matter lesions in systemic lupus erythematosus.**

Determinar se o aumento da relação cholina/creatina na ERM pode predizer o aparecimento de lesões de substância branca no LES.

3. PACIENTES E MÉTODOS

Todos os artigos que compõe esta tese apresentam metodologia semelhante no que concerne à seleção de pacientes, critérios de inclusão e exclusão, aspectos éticos, análise clínica e laboratorial e metodologia aplicada a artigos específicos (atividade de doença, índice de dano, métodos de neuroimagem). Excetua-se o artigo #7 que trata de trombose venosa central não somente no LES, mas de diferentes etiologias.

3.1. METODOLOGIA COMUM À TODOS OS TRABALHOS

3.1.1. Seleção da casuística

Os pacientes que participaram do estudo clínico e de RM foram selecionados no ambulatório de LES da Reumatologia da UNICAMP.

3.1.2. Critérios de inclusão

Foram incluídos pacientes com diagnóstico de LES segundo os critérios estabelecidos pelo Colégio Americano de Reumatologia (Tan et al., 1982).

3.1.3. Critérios de exclusão

Foram excluídos os pacientes que:

1. Pacientes com investigação incompleta.
2. Pacientes que perderam seguimento.
3. Pacientes com prontuários incompletos.

Alguns outros critérios de inclusão e exclusão são pertinentes à diferentes artigos e estes estão adequadamente detalhados nos respectivos trabalhos (artigos #5, #7, #8-#13).

3.1.4. Aspectos Éticos

Todos os diferentes estudos foram aprovados pelo Comitê de Ética em Pesquisa da Faculdade de Ciências Médicas da Universidade Estadual de Campinas (UNICAMP). No caso dos estudos prospectivos com grupo controle, todos os pacientes e voluntários participantes foram devidamente esclarecidos quanto às finalidades da pesquisa, e assinaram, previamente, os formulários de consentimento informado.

3.1.5. Análise clínico-laboratorial

Em todos os estudos, as variáveis clínicas, laboratoriais e o uso de imunossupressores foram analisadas em dois períodos: ao diagnóstico do LES e durante o seguimento destes pacientes, através da revisão dos prontuários dos pacientes: presença de adinamia; emagrecimento (> 4 kg); febre ($\geq$37,8^{o} C); artrite (não erosiva em duas ou mais articulações periféricas, vista pelo médico); necrose asséptica (documentada por radiografia simples, cintilografia ou ressonância nuclear magnética); deformidades articulares (geralmente redutíveis, vistas pelo médico); eritema malar (eritema fixo sobre as eminências malares e/ou pregas naso-labiais); lesões discóides (placas eritematosas com descamação,podendo ocorrer atrofia nas lesões antigas); alopécia; úlcera oral e/ou nasal (ulceração oral e/ou em nasofaringe, geralmente dolorosa, observadas por médico); fotossensibilidade ("rash" cutâneo resultado da exposição à luz solar, relatado na história clínica ou observada por médico); nefrite (definida pela presença de proteinúria maior que 0,5 g/l em 24 horas, aumento progressivo de creatinina sérica ou ainda alterações histopatológicas quando compatíveis com nefrite lúpica, segundo critérios da Organização Mundial de Saúde); HAS: pressão sistólica maior que 130 mmHg e/ou pressão diastólica maior que 90 mmHg; síndrome nefrótica (proteinúria maior que 3 g/l em 24 horas); serosite (presença de pleurite, pericardite ou ambas documentada no exame clínico e por imagem);

outras manifestações pulmonares como hipertensão pulmonar, pneumonite e hemorragia pulmonar; outras manifestações cardíacas como miocardite, endocardite própria do LES e infarto do miocárdio; miopatia (revelada por fraqueza muscular, alterações enzimáticas, alterações da biópsia muscular e /ou da eletromiografia).

Foram considerados também o envolvimento intestinal, hepático, e do sistema retículo-endotelial, presença de tromboembolismo pulmonar e alterações oculares e a presença do fenômeno de Raynaud.

Todos os exames laboratoriais e autoanticorpos foram realizados seguindo técnicas de rotina utilizadas no Laboratório de Patologia Clinica e no Laboratório de Investigação em Alergia e Imunologia. As alterações hematológicas quando induzidas por drogas ou infeções foram excluídas. Foram considerados: leucopenia (4000 células/mm^3); linfopenia (1500 cels/mm^3); anemia hemolítica (Coombs direto positivo, aumento de bilirubina indireta, anemia aguda); trombocitopenia (100000 cels/mm^3); FAN (por imunofluorescência indireta, positivo em títulos maiores que 1:40); anticorpo anti-DNA (por imunofluorescência indireta com *Crithidia luciliae* como substrato); anticorpo anti Sm (por imunodifusão dupla); Anticorpo anti cardiolipina (por método imunoenzimático) (Harris et al., 1987); anticoagulante lúpico (por TTPA e Russel) (Brandt et al., 1995). Pacientes com seguimento no ambulatório antes de 1999 tiveram a dosagem do anticorpo antifosfolípide e anticardiolipina realizados após esta data.

A terapêutica atual e pregressa foi analisada através da revisão dos prontuários. Doses de diferentes corticosteróides foram convertidas para doses equivalentes de prednisona. Dose total de prednisona foi calculada através da somatória das doses diárias, através de um programa especificamente desenvolvida para esta finalidade.

3.2. METODOLOGIA APLICADA A ARTIGOS ESPECÍFICOS

Além da metodologia comum a todos os artigos, metodologias específicas, tanto clínicas como de neuroimagens, foram aplicados a diferentes artigos, a saber:

3.2.1; Investigação clínica:

3.2.1.1. Avaliação das manifestações NP

- retrospectiva (artigos #4-#7, #8-#13)

- prospectiva (artigos #8-#13)

As manifestações neuropsiquiátricas foram analisadas retrospectivamente, através da revisão dos prontuários, conforme as orientaçõs do Colégio Americano de Reumatologia de 1999 (ACR, 1999).

Nos estudos prospectivos os seguintes testes foram aplicados aos pacientes com objetivo de determinar a presença de manifestação NP:

- Distúrbios cognitivos:
    - Minimental (Folstein et al., 1975): Neste teste foram verificados a orientação, a atenção e o registro, a atenção e o cálculo, a memória imediata, a linguagem, a praxia e a fluência verbal. Para cada item foi dado um determinado número de pontos, somados ao final. Considerou-se como normal um escore de 28±2, como depressão um total de 19±3, e como demência um total de 10±3.
    - Memória lógica (Spranoel, 1992): Para a avaliação da memória lógica foram lidos para o paciente dois textos, cada um com 23 idéias, que deveriam ser recontados e para cada idéia corretamente memorizada era aplicado um ponto. Os pontos foram somados e anotados.
    - Teste de atenção (Spranoel, 1992): Também foi testada a atenção do paciente tendo este que repetir certos números em ordem direta e inversa. Os números variaram de 3 a 9 algarismos e os pontos foram dados de acordo com o número de algarismos. Os pontos foram somados e anotados.

- Depressão: Escala de depressão de Beck (Beck e Beamesderfer, 1974; Beck et al., 1974)
- Ansiedade: *Hospital anxiety and depression scale* (HAD/CAGE) (Hermann, 1997)
- Manifestações psiquiátricas: *Brief Psychiatric Rating Scale* (BPRS) (Overall e Beller, 1984)

3.2.1.2. Atividade de doença

- SLEDAI (artigos #6, #8-#13)

- MEX-SLEDAI (artigo #5)

A atividade de doença do LES foi avaliada através do SLEDAI (Bombardier et al., 1992). O MEX-SLEDAI (Guzman et al., 1992) por não incluir cefaléia como atividade de doença foi utilizado no trabalho sobre migrânea (artigo #5). Atividade de doença foi considerada quando ocorreram *scores* maiores ou iguais a 8.

3.2.1.3. Índice de dano

- SLICC/ACR-DI (artigos #5, #8-#13)

O índice de dano permanente foi avaliado através do SLICC-ACR/DI (Gladman et al., 1997). Todos os dados foram obtidos através da revisão dos prontuários.

3.2.2. Investigação com técnicas de neuroimagem:

3.2.2.1. RM

- Segmentação manual (artigo #10)

- Segmentação semi-automática (artigo #8)

- Segmentação automática (artigo #9)

- Espectroscopia por ressonância magnética (ERM) (artigos #12e #13)

Aquisição das imagens de RM

Todos os indivíduos (pacientes ou controles) foram convidados para realização de exame de RM de alta resolução. Os exames foram realizados após assinatura do termo de consentimento para pesquisa.

As imagens foram obtidas em sistema de 2 Tesla (Elscint Prestige□, Halifa, Israel), com aquisições nos planos coronal, sagital e axial, além de aquisições em 3 D (volumétricas), para reconstrução multiplanar em qualquer plano ou inclinação. Os parâmetros de imagens para as diferentes aquisições foram:

- Imagens sagitais T1 ponderadas "spin echo" (espessura de 6 mm, ângulo de excitação – " tip angle" –de 180º; TR=430ms, TE=12ms, matriz de 200x350, FOV=25x25cm). Estas imagens serão utilizadas para orientar o plano de aquisição das demais imagens.

- Imagens no plano coronal (T2 ponderadas, FLAIR)

    - T2 ponderadas (espessura de 6 mm, ângulo de exitação de 180º, TR=1800ms, TE=90ms, matriz de 165x256, FOV=20x24cm) ou "fast spin echo" T2 ponderadas (espessura de 4mm, ângulo de exitação de 120º, TR=6800ms, TE=129ms, matriz de 252x328, FOV=21x23cm);

    - FLAIR (TR= 8500ms e 2000ms ou 100ms e 2200ms, TE=72ms ou 90ms, matrix= 256 X 296 ou 250 X 256, FOV= 200 X 220 ou 220 x 220 mm);

- Imagens no plano axial: duplo "spin echo" (T2 ponderadas e densidade de prótons); T2 ponderadas (espessura de 6 mm, ângulo de exitação de 180º, TR=1800ms, TE=90ms, matriz de 165x256, FOV=20x24cm) ou "fast spin echo" T2 ponderadas (espessura de 4mm, ângulo de exitação de 120º, TR6800ms, TE=129ms, matriz de 252x328, FOV=21x23cm.

- Aquisições em 3D obtidas no plano sagital "gradient echo" T1 ponderadas com espessura de 1mm, ângulo de exitação de 35º TR=22ms, TE=9ms, matriz de 256x220, FOV=230x250 cm, pixel 1x1.

- Espectroscopia obtida em região supraventricular posterior (PRESS (*Point-Resolved Spectroscopy*), TE=135ms, TR=1500ms, ângulo de exitação 90º, nex=1, matriz de 20x1024, FOV=5x2cm; precedida por calibração com supressão de sinal de água e homogeneização do campo magnético (*Shimming*).

Análise de imagens de RM

Análise visual

A análise qualitativa das imagens foi realizada em estação de trabalho (OMNIPRO□) por dois investigadores, sendo um deles radiologista que desconhecia a presença ou não de doença do paciente (AVF). As imagens foram avaliadas quanto à presença de alterações de substância branca e cinzenta, presença de atrofia (dilatação de sulcos e ventrículos), sendo classificadas de acordo com a localização, provável etiologia e número total de lesões (Cotton et al., 2004).

Segmentação manual

A volumetria dos hipocampos foi realizada utilizando as sequências de cortes coronais T1-IR, através do programa Scion□. O programa Scion é de distribuição gratuita (http://www.rsb.info.nih.gov/scion) de plataforma Windows e utiliza a segmentação manual como base. Os parâmetros anatômicos utilizados para o estudo da volumetria de hipocampos são os descritos em protocolos publicados previamente (Cendes et al., 1993; Watson et al., 1992; Watson et al., 1997).

Segmentação semi-automática

A volumetria do corpo caloso, ventrículos laterais, cerebelo e contorno cerebral foi realizada utilizando-se as sequências de cortes sagitais ponderadas em T1, através do

programa Neuroline , desenvolvido no próprio Laboratório de Neuroimagem (LNI). Este programa utiliza para o processamento de imagens o método de *watershed*, caracterizando uma segmentação semi-automática, na plataforma Windows. Os parâmetros anatômicos utilizados para o estudo da volumetria destas estruturas foram definidos visualmente. O programa foi elaborado como uma alternativa à segmentação manual, em que as estruturas são delineadas através de contorno manual das regiões de interesse. A forma de interação do operador com o sistema é através da definição de marcadores, pontos ou linhas desenhadas pelo operador, através dos quais o método obtém os contornos. Os marcadores são coloridos, sendo que cada cor está associada a uma determinada estrutura que se deseja segmentar. A cada marcador é associado um rótulo para identificação da estrutura segmentada. A saída do processo de segmentação é provida de três formas. Uma das formas é a gravação das imagens segmentadas. Outra forma é a gravação de marcadores que, ao serem carregados, refazem a segmentação. A terceira forma é a gravação dos volumes de cada estrutura, por corte, em um arquivo de texto.

O método de segmentação utilizado no sistema é a transformação *Watershed* com marcadores no campo da Morfologia Matemática. Este método baseia-se nas variações de níveis de cinza e na localização dos "pixels" marcados para a obtenção de contornos (Beucher et al., 1993).

A imagem em escala de cinza é modelada como uma superfície topográfica, em que os tons de cinza são proporcionais à altitude da superfície. Os marcadores rotulados localizados na imagem são equivalentes à perfuração de buracos na superfície (Beucher et al., 1993).

Pós processamento das imagens segmentadas

Os volumes totais das estruturas obtidos pela segmentação manual ou semi-automática foram calculados através da soma dos volumes segmentados multiplicados pela espessura do corte. Estes valores foram posteriormente corrigidos pelo volume cerebral total do pacientes, a fim de evitar que estruturas de cérebros pequenos sejam consideradas atróficas (Watson et al., 1997).

Para evitar que o cerebelo, o ventrículo e o corpo caloso em cérebros pequenos sejam identificados como atróficos, os volumes absolutos, em milímetros cúbicos, foram corrigidos pelo volume cerebral total (VCT) segundo a fórmula:

Volume normalizado (cerebelo ou corpo caloso) = volume (cerebelo ou corpo caloso) absoluto do indivíduo *X* média VCT dos controles/ VCT do indivíduo

O índice de assimetria (IA) foi determinado pela razão dos volumes entre a menor e a maior estrutura.

Identificação de atrofia ou dilatação ventricular

Para avaliar a presença de atrofia das estruturas segmentadas nos pacientes e controles foi calculado o valor de *Z score* (número de desvios-padrão acima ou abaixo da média do grupo controle) para cada estrutura (VC = cerebelo/corpo caloso volume normalizado) e para o IA, segundo a fórmula abaixo:

Z score VCD=(VC do paciente – média dos VC dos controles)/desvio-padrão da média dos VC dos controles.

Foi considerada atrofia de uma determinada estrutura quando o volume das estruturas normalizado e/ou índices de assimetria foram inferiores a 2 desvios-padrão da média dos controles (valor de *Z score* menor ou igual a -2).

Dilatação ventricular foi considerada quando o *Z score* dos ventrículos foi maior que 2 desvios-padrão da média dos controles (valor de *Z score* maior ou igual a +2).

Segmentação automática

A morfometria baseada em voxels (VBM) foi realizada utilizando as sequências de cortes volumétricos T1-IR. Através do programa MRIcro (www.MRIcro.com), obtido da INTERNET, as imagens foram processadas para extração do crânio e realinhadas a partir de um ponto comum que foi considerado a comissura anterior. As análises subseqüentes foram realizadas no programa *Statistical Paramtric Mapping* [SPM 2 (http://www.fil.ion.ucl.ac.uk/spm/)] obtidos pela INTERNET e rodados pelo MATLAB 6.1

na plataforma Windows segundo protocolos previamente publicados (Ashburner e Friston 1997; Ashburner e Friston 2000). Os resultados são expressos em coordenadas esteriotáxicas que foram visualmente confirmadas pelo programa Talairach Daemon client, disponível gratuitamente pela INTERNET (http://ric.uthscsa.edu/projects/talairachdaemon.html).

Espectropscopia por prótons (ERM)

A ERM foi analisada no console do aparelho de RM, Elscint Prestige 2T, por meio de quantificação manual através de um programa da própria Elscint. Após a correção da linha de base as áreas sob os picos dos compostos de N-Acetylaspartato (NAA) em 2.01 da escala partes por milhão (ppm), colina (Cho) em 3.2 ppm e compostos contendo creatina e fosfocreatina em 3.0 ppm. Para análise foram utilizadas razões, sendo a Cr o denominador comum. A análise dos espectros foi realizada por um investigador (SA) e checadas independentemente por dois outros investigadores (FC e LML) que não tinham conhecimento sobre o sujeito (paciente ou controle). Espectros com linha de base de difícil avaliação ou pouca diferenciação entre os picos individuais foram excluídos.

3.2.2.2. SPECT cerebral (artigo #11)

Aquisição das imagens com SPECT

As imagens foram obtidas 15 minutos após a injeção venosa de 20mlides ECD-99Tc e em ambiente isento de estímulos visuais e sonoros. Foi utilizada uma câmera de cintilação tomográfica, sendo adquiridos 60 imagens a cada seis graus, em um total de 360 graus. Foram utilizadas aquisição em modo “byte” e matrix 64x64.

Análise das imagens

As imagens obtidas foram analisadas e, se presentes artefatos, repetidas. As imagens foram reconstruídas nos cortes trans-axial, coronal, sagital e trans-supra-órbito-

meatal e analisadas por um médico especialista de Medicina Nuclear sem o conhecimento da história clínica. As imagens também foram processadas utilizando-se o programa MATLAB 6.5 for windows (MathWorks, Natrick, MA) e SPM 02 (Wellcome Dept Cogn. Neurol, London) conforme protocolos do laboratório de neuroimagem da UNICAMP. A morfometria baseada em voxels (VBM) foi utilizada para comparar as imagens. A VBM envolve vários processos, incluindo a normatização espacial das imagens para o mesmo espaço esterotáxico e a segmentação de imagens. Como o SPECT depende de áreas ricamente vascularizadas, utilizou-se somente a análise da substância cinzenta neste estudo.

3.2.3. Análise estatística

- Teste de qui-quadrado (artigos #4-#13)

- Teste T (artigos #8, #11)

- ANOVA (artigos #8-#13)

- Teste t-pareado (artigos #9, #10, #12, #13)

- Regressão simples (artigos #4, #5, #6, #8-#13)

- Regressão logística (artigos #4 e #6)

As diferentes freqüências foram analisadas pelo teste de qui quadrado. A correção de Yates e o teste exato de Fischer foram utilizados no caso em que a freqüência em uma ou mais caselas, respectivamente, tenha sido inferior a cinco. ANOVA com correção de Tukey foi utilizada para comparação entre gupos. As variáveis não numéricas foram avaliadas por testes não paramétricos apropriados.

Para a análise das RM pela técnica de VBM foi utilizado o teste t. Para a comparação entre o mesmo indivíduo nos estudos longitudinais foi utilizado o teste t-pareado.

A regressão simples foi utilizada para determinar a associação entre variáveis clínicas e volumes cerebrais, de corpo caloso e de hipocampos.

A regressão logística multivariada com correção para múltiplas comparações foi utilizada para determinar a associações entre as variáveis clínicas.

3.3. APRESENTAÇÃO E ANÁLISE DOS DADOS

Os resultados referentes à investigação clínica e por neuroimagem estão apresentados sob a forma de artigos, com enfoque específico a cada aspecto da avaliação no capítulo 3.

Os artigos de um a três referem-se sobre a revisão histórica do Neurolupus (artigo #1), das manifestações do SNC (artigo #2) e da ERM na investigação do comprometimento do SNC (artigo #3).

Os aspectos clínicos são investigados nos artigos de quatro a seis. Assim, a freqüência de crises epilépticas e fatores de risco associados a sua ocorrência estão descritas no artigo # 4. A importância clínica da migrânea no artigo #5 e a freqüência da psicose e fatores de risco associados no artigo #6. Fatores de risco e achados de neuroimagem na trombose venosa central (TVC) de diferentes etiologias, incluíndo o LES, estão no artigo #7.

Os artigos referentes a análise das imagens estão descritos nos artigos oito a treze. Assim, a descrição da atrofia cerebral e do corpo caloso está no artigo#8. A análise longitudinal da atrofia de substância branca e cinzenta está descrita no artigo #9. A freqüência e a progressão da atrofia hipocampal e suas implicações clínicas estão descritas no artigo#10. A análise funcional com SPECT está descrita no artigo #11. A utilização da ERM em pacientes com LES está contida nos artigos #12 e #13.

4. RESULTADOS

(ARTIGOS)

ARTIGO 1

Neurolupus

Appenzeller S, Costallat LT, Cendes F

Neuroiupus

Arch Neurol 2006; 63:458-460

Neurolupus

Simone Appenzeller, MD; Lilian T. L. Costallat, MD, PhD; Fernando Cendes, MD, PhD

Systemic lupus erythematosus (SLE) is an autoimmune disease frequently manifested by neuropsychiatric involvement, which occurs in up to 75% of patients, depending on the type of manifestations included. Primary involvement may vary from subtle signs, such as headache and mood disorders, to severe, life-threatening conditions, such as stroke, myelopathy, and acute confusional state. Any part of the peripheral or central nervous system (CNS) may be affected by the disease. The diagnosis of primary CNS involvement in SLE is often difficult because both focal and diffuse manifestations may occur. A wide range of differential diagnoses has to be considered, including metabolic abnormalities, infections, uremia, hypertension, and drug therapy.

LUPUS: TERM DEFINITION

Lupus is the Latin word for wolf and was frequently used in Roman art and poetry. The reason the term *lupus* gained a medical connotation is unknown. In *The Origin of Medical Terms*, Skinner suggested that lupus was introduced to describe skin lesions that were akin to a wolf's gnawing marks.[1] In the medieval period, the term *lupus* was used to describe several cutaneous diseases.[2] In 1865, Virchow[3] tried to elucidate the use of the term *lupus* in the medieval period, noting that for 3 centuries, from Rogerius (1230) to Manardus (1530), the term had been used for boils of the lower extremities.[2,3] For diseases of the face, including lupus vulgaris, cancer, and lepra, a collective term, derived from the biblical passage *noli me tangere*, was used.

FIRST CLINICAL DESCRIPTIONS OF LUPUS AS A DISEASE

The first description of the medical illness "lupus" was in the 10th century biography of St Martin by Hebernus of Tours. "He [Eraclius, the Bishop of Liege] was seriously affected and almost brought to the point of death by the disease called lupus. . . . "[2(p3)] But it was only in the 19th century that lupus erythematosus was clearly described by Biett, as reported by Cazenave:

> . . . very rare occurrence, and appears most frequently in young people, especially in females, whose health is otherwise excellent. . . . It generally appears in the form of round patches, slightly elevated . . . and gradually increases in circumference. . . . [4(p299)]

In 1872, Kaposi first described the systemic nature of lupus erythematosus, noting that "various grave and even dangerous constitutional symptoms may be intimately associated with the process in question. . . . "[5(p53)] Shortly thereafter, CNS involvement was recognized and described as a clinical manifestation of SLE. In 1875, Hebra and Kaposi described coma for the first time in patients with SLE: " . . . death ensues being preceded by increased mental disturbance, coma, ..."[5(p60)] Psychosis and mood disorders were mentioned in 1896 by Bowen: "I have often met with cases of extreme melancholia . . . and in a number of instances the mind has become really affected."[6(p700)] Between 1895 and 1904 Prof Dr William Osler published 29 reports of skin diseases with a variety of systemic manifestations. The majority of the cases were patients with Henoch-Schonlein pur-

Author Affiliations: Rheumatology Unit, Departments of Internal Medicine and Neurology, State University of Campinas (UNICAMP), Campinas, Brazil.

pura, but 2 patients clearly had SLE and both had CNS involvement.[2,7] One patient had delirium and the other developed recurrent episodes of hemiplegia and aphasia. Osler considered that hemiplegia and aphasia were associated "with changes in the brain of essentially the same nature which subsequently occurred . . . in the skin."[7(p22)] Seizures were well described as a manifestation of SLE in 1951, including the observation that they could precede the diagnosis of SLE by years.[8]

CLINICAL STUDIES

In 1945, Daly[9] conducted the first clinical study of CNS SLE and correlated clinical symptoms with abnormal spinal fluid findings as well as vasculitis. Several clinical reports followed and focused on varying aspects of CNS function.[10] Dubois wrote that he was " . . . continually impressed by the differing presenting neurologic aspects of SLE."[11(p2)] Longitudinal observation documented that CNS involvement may occur at any time in the disease course.[10] No clinical or serological markers distinguished the patient at risk for developing neuropsychiatric manifestations.[12] Although features of active systemic disease were usually found at the time that neuropsychiatric signs developed, well-documented causes occurred in which neurological or behavioral manifestations preceded the diagnosis of SLE by years.[13]

CLASSIFICATION CRITERIA

Until 1999, studies involving CNS involvement in SLE lacked a uniform method. Most terms used to describe these manifestations reflected pathological findings. The most common denominations were based on pathological findings. *Lupus cerebritis* reflected the inflammatory nature of the disease and was supported by the findings of inflammatory cells in cerebral spinal fluid. *Lupus vasculitis*, on the other hand, was used when pathological findings in other organs occurred. In the absence of strict nosographic criteria for CNS SLE, the prevalence of CNS manifestations varied in different reports, from 24% to 74% of patients with SLE.[10] In 1999, the American College of Rheumatology (Atlanta, Ga) developed case definitions that included appropriate terminology, classification criteria, and complementary examinations for 19 neuropsychiatric syndromes (**Figure**).[14]

PATHOGENESIS

The pathogenesis of SLE has been a mystery for decades, as described by Kaposi: "We are unable to adduce any very satisfactory data bearing on the cause of Lupus Erythematosus. . . . "[5(p53)] Until the mid 1940s, CNS manifestations were considered to be secondary to fever and uremia. Cerebral vasculitis was first described by Jarcho in 1936[15] and Daly in 1945.[9] Further pathological studies led to the consensus that SLE involves predominantly small vessels, producing microinfarcts and hemorrhage.[16-18] Although the importance of small-vessel arteritis in the pathogenesis of SLE has been demonstrated in animal models, true vasculitis is considered a rare pathological finding in patients who die in the midst of neuropsychiatric manifestations of SLE.[16-18] Contrary to other organ involvement, there is no pathognomonic lesion of SLE in the CNS.

The pathogenesis of neuropsychiatric involvement of SLE is still unknown, although most authors agree that several pathogenic mechanisms are responsible for the great variety of symptoms. Possible mechanisms for the primary involvement of the CNS by SLE include vascular occlusion or hemorrhage, cytokine effects, autoantibody-mediated lesions, choroid plexus dysfunction, and abnormal hypothalamic-pituitary axis response.[10]

TREATMENT

References from early treatment of CNS SLE are rare. In 1894, Payne suggested that SLE was caused by a "vascular disturbance . . . very much influenced by quinine."[19(p223)] Radcliffe-Crocker commented at the meeting of the British Medical Association in 1898 that "In violent inflammatory cases . . . good results from salicin, as well as from quinine, and less frequently, from ichfluyol internally"[20(p375)] were observed. Although lupus erythematosus is not described in *The Principles and Practice of Medicine* by Osler and Mc Crae in 1922,[21] a variety of symptomatic treatments are described. For arthritis, "hydrotherapy is useful, locally in the form of compresses . . . ,"[21(p342)] and "salicylates may aid in relieving pain, but should not be given for long periods. Iron, arsenic, and iodine are often useful."[21(p342)] Later, corticosteroids became the most widely used treatment for suppression of the primary CNS involvement of SLE, although there have been no controlled studies. In patients with severe involvement or who do not respond to corticosteroids, several other immunosuppressants have been used including pulse therapy with intravenous cyclophosphamide, azathioprine, methotrexate, and plasmapheresis.

Acute Inflammatory Demyelinating Polyradiculoneuropathy
Acute Confusional State
Anxiety Disorder
Autonomic Disorders
Cerebrovascular Disease
Cognitive Dysfunction
Cranial Neuropathy
Demyelinating Syndrome
Headache
Movement Disorder
Mood Disorders
Myelopathy
Myasthenia Gravis
Plexopathy
Psychosis
Polyneuropathy
Seizures

Figure. Central nervous system manifestation following American College of Rheumatology case definitions (adapted from American College of Rheumatology Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature[14]).

PROGNOSIS

Since 1875, when Kaposi emphasized the findings of SLE being a systemic disease, a potential fatal outcome was frequently described: "In the course of 2-3 weeks death ensues being preceded by increased mental disturbance, coma, ..."[5(p51)] Osler observed death in 13 of 61 cases and wrote in 1895: " . . . the mortality of the cases with severe visceral complications is remarkable."[7(p633)]

The better understanding of SLE pathological features, the earlier diagnosis, and the use of immunosup-

pressants for SLE activity and antibiotics for secondary infections has improved the survival of patients with SLE in the last decades. Despite the aggressive treatment, CNS SLE still has a guarded prognosis and mortality is elevated, occurring in 7% to 19% of patients. In particular, seizures, stroke, and acute confusional state are poor-prognosis markers.

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Correspondence: Simone Appenzeller, MD, Department of Internal Medicine, State University of Campinas (UNICAMP), CEP 13081-970, Campinas, Brazil (appenzel@unicamp.br).

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ARTIGO 2

Central Nervous System Manifestations in Systemic Lupus Erythematosus

Appenzeller S, Costallat LT, Cendes F

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Central Nervous System Manifestations in Systemic Lupus Erythematosus

Simone Appenzeller MD[1, 2], Lilian Tereza Lavras Costallat MD, PhD [1], Fernando Cendes MD, PhD [2, 3]

[1]Rheumatology Unit - State University of Campinas [2] Neuroimaging Lab-State University of Campinas; [3] Department of Neurology, State University of Campinas

The authors have nothing to disclose.

Running Title: CNS in SLE

Address all correspondence to:

Dr Fernando Cendes, Department of Neurology,

State University of Campinas (UNICAMP),

Cidade Universitaria Zeferino Vaz, CEP 13083970 Campinas-SP-Brazil

Tel: +55 1937887734

Fax: +55 19 32891818

E-mail: fcendes@unicamp.br

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Abstract

Neurologists are often called to evaluate central nervous system (CNS) manifestations in patients with suspected or definite systemic lupus erythematosus (SLE). The manifestations are highly diverse and often have major prognostic consequences. The major difficulties are to determine if the given manifestation is primarily due to SLE activity in the brain, or a consequence of metabolic disturbances, infection, or corticosteroid use.

The true incidence of CNS manifestations attributable to SLE is not entirely clear, but several studies show prevalence rate between 15-75%, depending on different methods and classification criteria applied.

This paper has the objective to review the main clinical manifestations according to the American College of Rheumatology (ACR) Criteria, possible etiological mechanism and neuroimaging features associated with these manifestations. We further discuss the most important tools that can help bedside diagnosis.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease with central nervous system (CNS) involvement occurring in up to 75% of patients. However the frequency of these manifestations in SLE studies varies widely, depending on the type of manifestations included and the method use for evaluation (1-3). CNS involvement may be considered primary if directly related to SLE activity in the CNS or secondary when related to treatment, infections, metabolic abnormalities or other systemic manifestations as uremia and hypertension (4).

The involvement may vary from subtle signs such as headache and mood disorders to severe, life threatening conditions, as stroke, myelopathy and acute confusional state. Any part of the peripheral or CNS may be affected by the disease (5). The diagnosis of primary CNS involvement by SLE is often difficult, as both focal and diffuse manifestations may occur and there is no gold standard for diagnosis (4).

The aim of this study was to review the main clinical manifestations according to the American College of Rheumatology Criteria (ACR) (6), possible etiological mechanism and neuroimaging features associated with these manifestations. We further analyze the most important tools that can help bedside diagnosis.

Search strategy and selection criteria

References for this review were identified by searches of PubMed from 1966 until February 2006 with the terms "central nervous system", "neuropsychiatric", "systemic lupus erythematosus". Only papers published in English were reviewed. Reviews and original publications (articles and letters), including those about single cases, were accepted. In order to uniform description of clinical manifestations we included only studies that included the 1999 ACR case definitions for NP SLE (6).

We asked first for articles covering the combinations 'SLE and CNS' and 'SLE and CNS diseases'. Subsequently, we asked for combinations of SLE and specific CNS syndromes. In addition to the selected articles, the references in these articles were screened for other studies of interest.

Classification criteria

The large number of papers published about CNS manifestations in SLE evidence more manifestations attributable to SLE than seizures and psychosis described in the original classification criteria by Tan (7). In addition, the several distinct pathologic mechanisms of CNS disease predispose to different presentations, including focal and diffuse disease, in addition to central and peripheral involvement. The lack of definitions of individual manifestations and the absence of standardization for investigation were reflected in the prevalence and frequency of CNS in different reports, varying from 24-74% of SLE patients (1, 8).

In 1999, the American College of Rheumatology developed case definitions that included appropriate terminology, classification criteria and complementary

examinations for 19 neuropsychiatric syndromes (Table 1) (6). These criteria were a result of a consensus meeting of experts of several subspecialties (rheumatologist, neurologist, immunology, and psychiatrist). Furthermore, in 2001, these criteria have been validated in a cross-sectional study with a specificity of 46% (9). Several studies have used these classification criteria in order to determine frequency and prevalence of CNS involvement in SLE population (Table 2) (10-19). Although this studies show a substantial variability between the frequency of CNS manifestations, suggesting differences between cohorts or bias in data acquisition, this classification allows us to compare the results (4).

Clinical relevance

The clinical relevance of NP manifestations in SLE has been determined by analyzing the impact of these manifestations in mortality, quality of life and overall damage scores (16, 17, 20-29).

Using mortality as indicative for poor outcome in NP manifestations, there are studies suggesting that patients with NP have increased mortality when compared to patients without these manifestations (20-24). Although some studies did not find an increased mortality among patients with CNS manifestations when compared to SLE patients without CNS manifestations and controls (24-28), the presence of CNS manifestations, independently of its etiology, seems to have a negative impact in quality of life (4), increased disability scores (29), and higher fatigue scores (16).

The ACR damage score (ACR/SLICC-DI) has been developed to determine irreversible damage in SLE patients, irrespectively if attributed to disease itself or secondary to comorbidities or medications. In the ACR/SLICC-DI scores seizures, psychosis, mood disorders, cerebrovascular disease, neuropathy, mononeuritis multiplx, acute confusional state and myelopathy are scored in addition to several other clinical manifestations in order to determine the global damage score. Using the items of NP in order to create a NP damage score, the strongest risk factors for the development of significant NP damage was the presence of greater disease activity at the time of CNS involvement onset and the presence of antiphospholipid antibodies (17).

Furthermore it is necessary to determine the course of NP manifestations. There are only a limited amount of follow-up studies evaluating NP manifestations in SLE patients (30-35). CNS involvement seems to have a general good prognosis, with improvement or stabilization of symptoms in most of the cases (31). The presence of antiphospholipid antibodies, higher number of NP events and hippocampal atrophy were negative prognostic factors (31, 32). Furthermore the progression of hippocampal atrophy was a predictor for progressive cognitive impairment (32). Perhaps the absence of abnormalities on MRI may suggest reversibility or stabilization of NP manifestations, whereas the presence of progressive atrophy may be related to worse prognosis over time. In another study cognitive impairment was a stable symptom over time and more frequently observed in patients with other NP manifestations in SLE, although intellectual deterioration may occur in patients without other symptoms of NP-SLE (30). In this study, four SLE patients without other NP involvement showed stable cognitive impairment over time that did not differ from that in NP-SLE subjects. These findings were consistent with the hypothesis of subclinical CNS functional involvement, as suggested by magnetic resonance spectroscopy study (36, 37).

Pathology

The rationale for identifying the etiology and pathogenic mechanisms underlying NP disease in SLE is to facilitate the logical development of appropriate and effective therapies (4, 38).

Histopathological studies of brains of SLE patients with and without CNS manifestations revealed a predominant small vessel infarction, with little signs of true vasculitis (4, 39-43). Multiple microinfarcts, noninflammatory thickening of small vessels with intimae proliferation, small-vessel occlusion, and intracranial embolism or hemorrhage have all been shown in SLE patients (39-43). Although small vessel vasculopathy is frequently found in autopsy findings, a parallel between these and CNS symptoms was not always evident. Therefore, in addition to vasculopathy, autoantibodies and inflammatory mediators may be involved in different disease expression in CNS SLE.

Autoantibodies directed against neurons, ribosomes and phospholipids-associated proteins have been associated with CNS manifestations and may be locally produced or cross the blood-brain barrier (38, 44). Antineuronal antibodies have been shown to induce memory deficits, seizures and neuropathological changes in animal models (45, 46). In SLE patients, the presence of antineuronal antibodies has been increased in patients with NP manifestations, although no clinical manifestations and no diagnostic specificity could be identified (38). The NMDA (N-methyl-D-aspartate) receptors NR2a and NR2b have been shown to occur in patients with NP manifestations and appear to have a functional consequence leading to neuronal injury. Anti NR2 antibodies have been shown to be involved in learning, memory (47) and psychosis (48). Anti-ribosomal P (anti-P) antibodies are quite specific for SLE with a prevalence of 13–20%, depending on the ethnic group (49, 50). Clinically they are associated with psychosis and depression (51-53). Antiphospholipid antibodies are associated with predominately focal manifestations of NP-SLE. The most common neurological disorders are those of vascular origin, such as transient cerebral ischemia or stroke, but other associations include seizures, chorea, transverse myelitis and cognitive dysfunction (12, 54-57). More recently, serum S100B protein level have been shown to be increased in NPSLE, reflecting continuing neurological damage. (58).

Several studies have analyzed the role of inflammatory process in the manifestations of CNS manifestations. Interleukins (58-60), tumor necrosis factors (61) and metaloproteinases (62, 63) have been shown to be increased in CSF in patients with CNS manifestations and even associated with some specific clinical manifestations and MRI findings (60, 62).

Therefore the three primary immunopathogenic mechanisms involved in CNS manifestations of SLE patients seem to have a final common pathway: the involvement of the cerebral microvasculature (4, 38).

The strict exclusion of patients with other etiologies of CNS than SLE disease, in addition to the analysis of individual manifestations may provide a more homogenous clinical population and may favor elucidation of pathological mechanism involved.

Diagnosis

The correct diagnosis of CNS manifestations, attributing individual manifestations to SLE disease activity or to a secondary cause remains a challenge in clinical practice (4). Because of the absence of diagnostic gold standard for most of the individual manifestations, clinical, laboratory and neuroimaging features are necessary for exclusion of alternative etiologies (4). The ACR nomenclature provides tools for accessing these manifestations in a systematic manner (4). Using these guidelines, Hanly et al (13) were able to determine that 41% of the CNS manifestation in their cohort was secondary to non-SLE causes. Furthermore, several studies have shown the occurrence of subclinical NP involvement, which clinical significance has still to be determined (31, 37).

Clinical and laboratory investigation

CNS infection should always be excluded by cerebrospinal fluid (CSF) examinations. Non-specific abnormalities may be found in the CSF of 33% of patients with NP disease and include pleocytosis and elevated protein levels (64). The clinical usefulness of measuring CSF autoantibodies, cytokines and biomarkers of neurological damage (65) is still a subject of research (4, 38). In considering circulating autoantibodies, those that are most likely to provide the greatest diagnostic yield are antiphospholipid antibodies. The value of measuring anti-P antibodies remains uncertain, given the conflicting results to date, and the role of anti-NR2 antibodies in NP-SLE is currently unknown (4).

Neuroimaging

In SLE, both structural and functional neuroimaging methods may be useful for determine CNS abnormalities. Cranial tomography (CT) may be the preferred technique in several centers for the diagnosis of gross structural abnormalities, especially because it may be used in severe ill patients and its availability in most centers around the word. But magnetic resonance imaging (MRI) has largely replaced CT, because of the excellent soft-tissue contrast observed with MRI and the ability to acquire multiplanar images (66).

Although MRI abnormalities may be found in 19-70% of SLE patients, its clinical significance has still to be determined, because these abnormalities may occur in both, patients with and without CNS manifestations (4, 67-69). Atrophy was described in 6-12% of SLE patients, depending upon linear or segmentation methods have been applied. Age, disease activity, the presence of past history of CNS manifestations and the use of corticosteroid have all been associated with the occurrence of atrophy (64, 70-75). Although most studies have analyzed cerebral atrophy as a hole, some studies (66, 76, 77) have determined that that there are different patterns in cortical and subcortical involvement in SLE patients. The impact of cerebral atrophy has been studied, indicating that cognitive impairment may be present more frequently in both corpus callosum and hippocampal atrophy (33, 66).

White matter lesions have been detected SLE patients, but may occur in both symptomatic in asymptomatic patients. In a large prospective population-based study involving healthy individuals, the presence of these lesions were associated with cognitive impairment (NEJM, 2000-78). Fluid-attenuating inversion recovery (FLAIR) images are more sensible for detecting theses lesions than T2 images (69). Although these white matter lesions are often considered nonspecific, they may be attributed to age, hypertension, disease duration, small vessel disease and the presence of NP manifestations (69, 72). In the presence of large lesions, the different diagnosis with multiple sclerosis is mandatory (72).

Magnetization transfer imaging (MTI) is particularly suited to the detection and quantification of diffuse brain damage (79, 80). Diffusion weighted imaging (DWI) is highly effective in the detection of hyperacute brain injury, in particular acute ischemia following stroke (81).

Magnetic resonance angiography (MRA) permits visualization of cerebral blood flow, although it is probably not optimum for visualization of flow in small caliber vessels that are the ones primarily involved in NP-SLE (82).

Functional studies may be performed using SPECT, PET, MRS. Positron emission tomography (PET) scanning, but practical considerations limit its applicability (4). Single photon emission computed tomography (SPECT) scanning provides semi-quantitative analysis of regional cerebral blood flow and metabolism. It is exquisitely

sensitive and in studies of SLE patients has identified both diffuse and focal deficits which may be fixed or reversible (84-87). Magnetic resonance spectroscopy (MRS) allows the identification and quantification of brain metabolites, which reflect the quantity and integrity of neuronal cells, is reduced in SLE patients (36, 37, 88).

Treatment of primary CNS manifestations

Due to the large number of CNS manifestations and the great spectra of different diagnosis, individual approach is necessary for each patient. But some recommendations may be applied to all patients. First to identify and treat potential aggravating factors such as hypertension, infection and metabolic abnormalities and second, symptomatic therapy should be considered, such as anticonvulsants, antidepressants and antipsychotic medications, if necessary (4).

Immunosuppressive therapies with high-dose corticosteroids, azathioprine and cyclophosphamide, mycophenolate mofetil and rituximab have all been used in association with corticosteroids in patients with CNS disease.(89-100) But there are only a few controlled studies for treatment of CNS manifestations in SLE (89-100.). Anticoagulation is indicated for focal disease when antiphospholipid antibodies are implicated (101, 102)

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Table 1. Central nervous system manifestation following ACR case definitions

Central nervous system manifestations	Peripheral nervous system manifestations
Aseptic meningitis	Acute Inflammatory Demyelinating Polyradiculoneuropathy
Acute Confusional State	Autonomic Disorders
Anxiety Disorder	Cranial Neuropathy
Cerebrovascular Disease	Mononeuropathy
Cognitive Dysfunction	Plexopathy
Demyelinating Syndrome	Polyneuropathy
Headache	Myasthenia Gravis
Movement Disorder	
Mood Disorders	
Myelopathy	
Psychosis	
Seizures	

Addapted from ACR Ad hoc Committee on Neuropsychiatric Lupus Nomenclature (6).

Table 2. NP manifestations in studies using ACR classification criteria

Authors	Number of patients	Overall prevalence (%)	Cognitive dysfunction	Mood disorders	Cerebrovascular disease	Seizures	Headache	Psychosis	Polineuropathy
Ainiala et al, 2001 (10)	46	91	81	43	15	9	54	0	28
Brey et al, 2002 (11)	128	80	79	23.3	2	16	57	6.5	22
Alfreta et al, 2003 (12)	61	72	52	27	24	11	21	0	13
Hanly et al, 2005 (13)	53	31	1.9	0	0	0	9.4	0	0
Sanna et al, 2003 (14)	323	57.3	10.8	16.7	14.5	8.3	24	7.7	2.8
Mocc et al, 2001 (15)	518	19	NA	6	19	28	4	11	1
Hanly et al, 2004 (16)	111	37	7.3	9.8	9.8	2.4	24.4	7.3	4.9
Mikdashi et al, 2004 (17)	130	56.9	27.3	NA	25.7	7.6	NA	15.1	18.2
Robert et al, 2006 (18)	50	78%	18	0		20.5	55.6	16.2	0
Shimojima Y et al, 2005 (19)	25	NA	12	0	24	36	12	32	12

NA: not available

ARTIGO 3

Magnetic resonance spectroscopy in the evaluation of central nervous system manifestations of systemic lupus erythematosus

Appenzeller S, Costallat LT, Li ML, Cendes F

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REVIEW ARTICLE

Magnetic Resonance Spectroscopy in the Evaluation of Central Nervous System Manifestations of Systemic Lupus Erythematosus

SIMONE APPENZELLER, LILIAN T. L. COSTALLAT, LI MIN LI, AND FERNANDO CENDES

Introduction

Neuropsychiatric (NP) systemic lupus erythematosus (SLE) is characterized by a large spectrum of physical and behavioral manifestations. One major difficulty is the absence of diagnostic tools for assessing disease activity and severity of NP manifestation. The neurologic symptoms can be of new onset, chronic, or of a former or resolved nature (1). Although several studies have used different neuroimaging tools, including computed tomography, magnetic resonance imaging (MRI), and single-photon–emission computed tomography, no single technique has proven to be definitive for diagnosis of NP manifestations in persons with SLE (1).

Magnetic resonance spectroscopy (MRS) permits chemically specific, noninvasive measurements of some compounds of biologic importance in living tissues. MRS was discovered in 1946, but was only first used in living animal brain in 1980 (2), followed by use in human brains in several pathologies. In the human brain, phosphate energy stores, intracellular pH, lactate concentrations, and the neuronal marker *N*-acetylaspartate are examples of MRS-measurable variables (3).

The purpose of this article is to review studies using MRS in SLE and to discuss the clinical utility of this technique in determining central nervous system (CNS) involvement in individuals with SLE. We will also discuss future applications of MRS in the evaluation and treatment of NP manifestations in patients with SLE.

History

The nuclear magnetic resonance (NMR) phenomenon was discovered independently in 2 laboratories in 1946 by Bloch and Purcell, which led them to receive the Nobel Prize for physics in 1952. When imaging methods using the NMR signal were first developed, the term NMR imaging had been applied. But because of increasing danger of nuclear energy in the 1980s and because MR techniques do not use ionizing radiation, the term nuclear was dropped in clinical use, being maintained only to describe the physical phenomenon itself (3).

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Simone Appenzeller, MD, Lilian T. L. Costallat, MD, PhD, Li Min Li, MD, PhD, Fernando Cendes, MD, PhD: State University of Campinas, Campinas, Brazil.

Address correspondence to Fernando Cendes, MD, PhD, Department of Neurology, University of Campinas-UNICAMP, Cidade Universitária, Campinas SP, Brazil, CEP 13083-970. E-mail: fcendes@unicamp.br.

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MRS physics

Spectroscopy deals with the interaction of electromagnetic radiation with matter; therefore, because the structure of atomic nuclei have magnetic properties, they respond to strong magnetic fields. During relaxation from the excitation of a magnetic field, atomic nuclei emit oscillating signals at a frequency that perturbs the nuclei. These signals may be detected by coils and then converted into spectra or images. The position of peaks in the spectrum is determined by its molecular characteristics. Information about their metabolites can be extracted based upon the amplitude or area under a given peak (3).

Advantages of MRS

There are several advantages to performing MRS in vivo. Metabolic studies of organs in their normal environment can increase understanding of the function of complex organisms and enable researchers to evaluate changes during diseases. The noninvasive nature of MRS allows repeated measurements in order to evaluate kinetic and longitudinal studies and to study human tissues that are inaccessible by invasive techniques. At the strength of the magnetic field needed for human studies in vivo, no deleterious effect on living tissue has been noted (3). Precautions such as excluding magnetic objects from the magnet are the main recommendation.

Disadvantages of MRS

The major disadvantage of MRS is its lack of sensitivity, which depends on a wide range of factors, including the nucleus investigated, the volume of the region of interest, and the magnetic field strength, among others. In general,

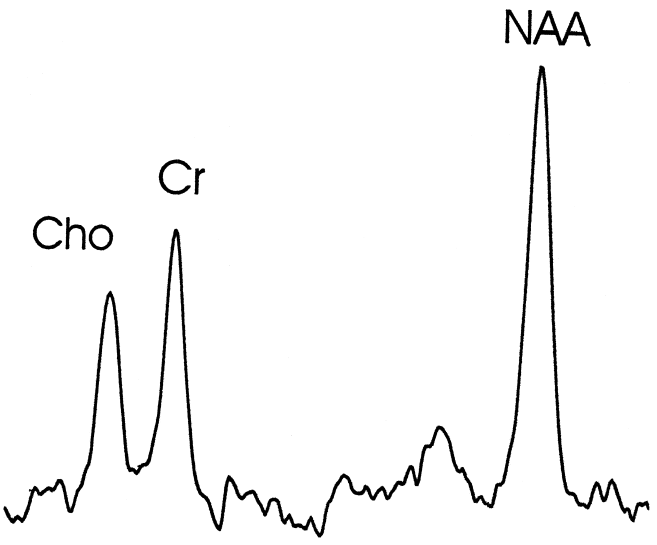

Figure 1. Water-suppressed, localized magnetic resonance spectroscopy of normal human brain. Cho = choline; Cr = creatinine; NAA = *N*-acetylaspartate.

only small molecules that tumble rapidly in solution create an MRS signal strong enough to be detected in vivo (3). MRS findings are specific to the area analyzed in the study. Therefore, MRS studies can only been compared if the same anatomic area is analyzed.

Proton spectra of the human brain

The brain tissue consists of the cortex, a layer of gray matter 1.5–4 mm thick that covers the white matter of the cerebral hemispheres. The gray matter consists of neuronal cell bodies and neuroglial cells, such as astrocytes and oligodendroglia cells. The white matter consists of neuronal axons involved by myelin sheets and neuroglial cells. The water concentration in theses tissues varies due to different concentrations and properties of lipids and proteins (4). Water-suppressed, localized MRS of normal human brain at echo times (TEs) between 136 msec and 272 msec reveals 4 major resonances (Figure 1) (3).

***N*-acetyl groups.** Several studies suggest that the peak of *N*-acetyl groups, at 2.0 parts per million, which originates largely from *N*-acetylaspartate (NAA), can be used as a neuronal marker because NAA is found exclusively in neurons and their processes in the mature brain (3). In human brain spectra, NAA is reduced in conditions known to be associated with neuronal loss, such as in neuronal degenerative disorders, stroke, and glial tumors (4). When a decrease in the relative NAA signal arises from neuronal or axonal degeneration, irreversible changes are expected. However, several studies have shown reversible decreases in NAA in a number of conditions, emphasizing that neuronal dysfunction or transient relative volume change can also lead to a decrease in NAA (4). The ability to quantify specifically neuronal loss or damage is one of the interesting applications of MRS in vivo.

Several studies observed that CNS manifestations in patients with SLE are associated with reduction in NAA:creatinine ratios and NAA:choline ratios not only in lesions, but also in normal-appearing white matter when compared with controls. Reduced NAA:creatinine ratios were observed in SLE patients with severe atrophy when compared with SLE patients with mild atrophy and controls (5), suggesting that atrophy in patients with SLE is caused by neuronal and axonal dropout or damage. Brooks et al (1) demonstrated that patients with white matter lesions also had a more pronounced reduction in these metabolites, when compared with patients without lesions, suggesting that NP manifestations are associated with a complex multifocal and diffuse neurotoxic process. We further demonstrated that the reduction in NAA:creatinine ratios correlated with disease activity, independently of CNS manifestations, and that NAA:creatinine ratios in normal-appearing white matter returned to normal range after remission (6).

Some studies suggest that the amount of reduction in relative and absolute concentrations of NAA is associated with the severity of clinical manifestations (6,7) and CNS manifestations (7–10), although no distinction between acute and chronic disease has been demonstrated (7,11, 12). The NAA reduction reflects both neuronal loss and dysfunction and has been correlated with cognitive dysfunction and extent of brain damage (7,13), suggesting that it could be used as a disease outcome measurement.

Tetramethyl-amines (mainly from choline-containing phospholipids). Changes in the resonance intensity of choline probably result from an increase in the steady state levels of phosphocholine and glycerol phosphocholine. These choline-containing membrane phospholipids are released during active myelin breakdown. Therefore, the resonance of choline increases in acute demyelinating lesions in humans. Chronic, slowly progressive leukodystrophies are associated with normal choline over creatine ratios, presumably because the loss of myelin is so slow that significant increases in released membrane phospholipids do not accumulate.

Increased choline over creatine ratios were also observed in patients with SLE, especially in those with major NP events, although this increase did not enable the distinction between acute and chronic CNS manifestations. Choline metabolites have been shown to increase in CNS involvement in SLE, which can be due to the inflammatory process (14) or the increased amount of lipids secondary to myelin breakdown. Increased choline was associated with the presence of cognitive dysfunction in patients with SLE (9,12,13). Furthermore, one study (10) demonstrated that increased choline over creatine ratios in normal-appearing white matter may predict the appearance of white matter lesions. Smaller fixed focal lesions evident on T2-weighted MR images may represent small infarcts in subcortical or deep white matter. Similar findings are observed in healthy adults, often associated with older age. However, if neurometabolic changes are observed within these lesions, it could be inferred that these white matter lesions represent a serious pathologic process resulting in focal neuronal death or injury (14). Furthermore, if the presence of increased choline over creatine ratios in normal-appearing white matter may predict the appearance of

fixed white matter lesions, new treatment strategies could be introduced.

Creatine and phosphocreatine. Total creatine concentration is relatively constant throughout the brain and tends to be relatively resistant to changes; however, variations in creatine levels do occur, as in the gradual loss of creatine together with other major metabolites in tissue death or necrosis (4). Creatine may increase as a hyperosmolar response to craniocerebral trauma, or may be absent as in the case of creatine deficiency, a rare congenital disease (3,6). It is reasonable to use creatine as an internal standard to normalize NAA and choline resonances to correct for artifactual variations in signal intensities due to magnetic fields and radiofrequency inhomogeneity (7). However, some studies suggest the loss of information by using this approach. An alternative is the use of external concentration reference, but factors such as radiofrequency field inhomogeneity and coil tuning and coupling have to be controlled (3).

In a large study, we observed constant creatine values in 50 patients with SLE followed for 19 months (6). Similar findings were observed by Axford et al (8).

Lactate. Lactic acid is the end product of glycolysis and accumulates when oxidative metabolism cannot meet energy requirements. Elevation of lactic acid in cerebral neoplasms correlates approximately with relative rates of glucose uptake. However, because lactic acid is present in the intracellular and extracellular compartments, a large amount can be accumulated outside actively anaerobic tissue (4). In inflammation, lactate accumulation may also reflect metabolism of inflammatory cells rather than brain parenchyma itself. The lactate peak is above the baseline when the TE is low (20–35 msec) or high (270–288 msec). At an intermediate TE (135–144 msec), the lactate peak inverts to project below the baseline, a feature that enables its distinction from lipids and some macromolecules seen at a similar location on the spectrum (15).

Only a few studies have analyzed the presence of lactate in patients with SLE. Brooks et al (14) did not find an increased lactate over creatine in patients with normal-appearing white matter or white matter lesions when compared with controls. AQ: 14

Other metabolites. Myo-inositol (mI) is an osmolyte and astrocyte marker. Its resonance at 3.56 ppm is visualized when performing MRS using a short TE (15,16). Only in one study was mI measured, where all patients with major CNS involvement had higher values of mI than patients with minor manifestations (8).

Normal variations

There are age-related and regional variations in the concentrations of various metabolites in the brain, especially a constant reduction of NAA:creatinine ratios in the elderly. Regional variations of metabolite concentrations in the brain are seen between gray and white matter (NAA is higher in white matter and creatine and choline are higher in gray matter) and within different parts of the brain (1,15,16).

MRS techniques

Commonly used spectroscopic techniques include the single-voxel spectroscopy, with a spatial resolution in the order of 1–8 cm^3 (16), and the multivoxel technique, allowing the derivation of metabolite maps (16). Although single-voxel spectroscopy allows evaluation of only small volumes of tissue, it is time efficient and allows the acquisition of quantitative data. Multivoxel MRS allows examination of different areas of the brain at the same time (15,16). Most SLE studies have used single-voxel MRS, especially because patients with SLE included in the studies were severely ill and needed shorter time necessary for examinations (Table 1). T1

The selection of appropriate MRS techniques, including measurement parameters such as repetition time (TR) and TE, depends on the clinical question. Short TE (20–35 msec) evaluations are required when there is a need for detection of metabolites with short relaxation times, such as glutamine, glutamate, mI, and certain amino acids (15,16), whereas long TE studies (135–270 msec) are sufficient for the detection of the major metabolites such as NAA, choline, creatine, and lactate/lipids (16). Different TR and TE used in patient with SLE are shown in Table 1.

Proton MRS studies in specific NP manifestations

Most studies using MRS in patients with SLE have included patients with or without CNS involvement. No study has used MRS for investigating specific manifestations. Brooks et al (1) and Kozora et al (17) observed increased choline:creatinine ratios in patients with cognitive impairment. AQ: 15

Laboratory and treatment features

The use of corticosteroids and the presence of antiphospholipid antibodies may also influence neurometabolic markers. One study (18) demonstrated that patients receiving corticosteroids had lower NAA:creatinine ratios than patients not receiving corticosteroids.

The presence of antiphospholipid antibodies is associated with epilepsy and stroke in patients with SLE. We did not observe a difference in NAA:creatinine ratios between patients with and those without antiphospholipid antibodies (6), although one previous study showed a correlation between the presence of IgG antiphospholipid antibodies and NAA:creatinine ratios (19).

Conclusion

MRS allows the quantification of changes in neuronal markers and the monitoring of disease progression. MRS seems to be more sensitive than MRI in detecting neuronal damage or dysfunction in patients with SLE. Although different MRS techniques and different localization of the MRS volume of interest were used in SLE studies, we observed that most authors report a significant decrease in NAA:creatinine ratios in patients with SLE when compared with controls. Although some studies correlate the

Table 1. MRS findings in systemic lupus erythematosus: literature review*

Author (reference)	Localization MRS	No. of patients	Voxel size	MRS parameters	MRS findings	Clinical associations	Others
Sibbitt et al (5)	White matter, superior to the ventricles, extending through both hemispheres	21	2 × 2 × 2 cm^3	TR = 1,500; TE = 19	↓NAA/Cr		More pronounced in severe atrophy
Davie et al (11)	White matter lesions (5 patients) or NAWM in frontal region (7 patients)	13	3.5–6 ml	TR = 2,000 msec; TE = 10 and 135 msec	↓NAA/Cr	No correlation with neurologic and psychiatric involvement	↓NAA/Cr in lesions
Brooks et al (14)	Lesions and NAWM in periventricular white, occipital white, and occipital gray matter	14	1 ml	TE = 270 msec; TR = 2,300 msec	↓NAA/Cr	In all regions of the brain	More pronounced in lesions
Chinn et al (19)	Frontal white matter and the parieto-occipital white matter	47	8 ml	TR = 1,600 ms; TE = 135 msec	↓NAA/Cr; ↓Cho/Cr		Corticosteroids
Sibbitt et al (7)	NAWM parietal lobe	36	8 cm^3	TE = 26 and 136 msec; TR = 2,000 msec	↓NAA/Cr	Major NP; disease activity	
Sabet et al (18)	Deep occipitoparietal white matter; multislice	43	10 cm^3	TE = 19 msec; TR = 2000 msec TE = 270 msec; TR = 2,300 msec	↓NAA/Cr		↑Cho/Cr in SAAF
Friedman et al (12)	NAWM in occipitoparietal region	42	4 cm^3	TE = 19 msec; TR = 2,000 msec	↓NAA/Cr; ↑Cho/Cr		↓NAA/Cr associated with small focal lesions ↑Cho/Cr associated with cerebral infarct
Brooks et al (1)	Lesions and NAWM in periventricular white, occipital white, and occipital gray matter	12	1 ml	TE = 270 msec; TR = 2,300 msec	↑Cho/Cr	Cognitive impairment; SLICC	
Lim et al (13)	Basal ganglia and left peritrigonal periventricular white matter	26	8 cm^3	TE = 30 msec; TR = 3,000 msec	↓NAA/Cr in basal ganglia ↑Cho/Cr in periventricular white matter	Major NP manifestations	No correlation with MRI findings
Axford et al (8)	Parietal NAWM	9	8 cm^3	TE = 30 msec; TR = 2,020 msec	↓NAA, ↑mI; ↑Cho	Major NP manifestations; Minor NP manifestations	↑mI in NAWM
Handa et al (9)	Frontal and parieto-occipital NAWM	20	1–8 ml	TE = 135 msec, 270 msec; TR = 3,000 msec	↓NAA/Cr	NP manifestations	
Castellino et al (10)	Hypoperfused or normoperfused frontal areas by SPECT	8	8 cm^3	TE = 135 msec; TR = 2,000 msec	↓NAA/ Cho in hypoperfused ↑Cho/Cr in normoperfused area	White matter lesions	New white matter lesions on previous areas of hypoperfusion and ↓NAA/Cho
Appenzeller et al (6)	NAWM superior to posterior region of corpus callosum	90	10 cm^3	TE = 135 msec; TR = 1,500 msec	↓NAA/Cr	Active disease, reversible with inactivity	
Kozora et al (17)	NAWM frontal periventricular	7	2 × 2 × 2 cm	TE = 135 msec; TR = 1,500 msec	↑Cho/Cr	↑ in cognitive impairment	

* MRS = magnetic resonance spectroscopy; TR = repetition time; TE = echo time; ↓ = decreased; ↑ = increased; NAA = *N*-acetylaspartate; Cr = creatinine; NAWM = normal-appearing white matter; Cho = choline; NP = neuropsychiatric manifestations; SAAF = XXXXX; SLICC = Systemic Lupus International Collaborating Clinics; MRI = magnetic resonance imaging; SPECT = single-photon–emission computed tomography.

ARTIGO 4

Epileptic seizures in systemic lupus erythematosus

Appenzeller S, Cendes F, Costallat LT

Epileptic seizures in systemic lupus erythematosus

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Epileptic seizures in systemic lupus erythematosus

Simone Appenzeller, MD; Fernando Cendes, MD, PhD; and Lilian T.L. Costallat, MD, PhD

Abstract—*Objective:* To evaluate the frequency and risk factors of epileptic seizures in a large cohort of patients with systemic lupus erythematosus (SLE). *Methods:* Five hundred nineteen consecutive patients with SLE were studied, with follow-up ranging from 4 to 7.8 years. The type and frequency of risk factors associated with acute and recurrent epileptic seizures in SLE were determined. *Results:* Sixty (11.6%) patients with epileptic seizures were identified. Epileptic seizures occurred at the onset of SLE symptoms in 19 (31.6%) and after the onset of SLE in 41 of 60 (68.3%) patients. Fifty-three of 60 (88.3%) patients had acute symptomatic epileptic seizures, and 7 of 60 (11.7%) had recurrent epileptic seizures. Variables associated with acute epileptic seizures at SLE onset were stroke ($p = 0.0004$) and antiphospholipid antibodies ($p = 0.0013$). Epileptic seizures during follow-up were related to nephritis ($p = 0.001$), antiphospholipid antibodies ($p = 0.005$), and epileptic seizures at disease onset ($p = 0.00001$). All seven patients who presented recurrent epileptic seizures had antiphospholipid syndrome and interictal epileptic abnormalities on EEG. *Conclusions:* Epileptic seizures were observed in 11.2% of systemic lupus erythematosus (SLE) patients. Antiphospholipid antibodies and stroke were related to epileptic seizures at SLE disease onset. Patients with renal flares, epileptic seizures at SLE disease onset, and antiphospholipid antibodies were at greater risk for acute symptomatic seizures during follow-up. Recurrence of epileptic seizures occurred in 1.3% of patients and was associated with antiphospholipid syndrome.

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Neuropsychiatric involvement in systemic lupus erythematosus (SLE) is considered as one of the major manifestations of the disease.[1-3] Single epileptic seizure episodes have been documented in about 10 to 20% of patients with SLE.[1-6] Most studies analyzed risk factors associated with the occurrence of epileptic seizures,[1-12] whereas specific risk factors associated with recurrence of epileptic seizures have been rarely reported.

Epileptic seizures can be a primary event resulting from the direct effect of active SLE manifestation in the CNS or occur independently of lupus activity itself, being associated with CNS infections, uremia, hypertension, or electrolytic disturbance.

Generalized tonic-clonic seizures are by far the most common, but simple partial and complex partial seizures have also been described.[3,6] The pathogenesis of epileptic seizures in SLE remains unknown, but ischemic vascular disease or antibodies that bind to cerebral tissues have been considered as probable causes.[2,13-15]

We sought to determine the frequency and risk factors for epileptic seizures in a large cohort of patients with SLE. We also analyzed clinical and laboratory features associated with the occurrence of single episodes and recurrence of epileptic seizures.

Patients and methods. The records of 519 consecutive patients with four or more criteria for SLE diagnosis[16] from January 1974 to December 2002 had their medical histories and clinical and serologic characteristics documented in computer database programs. All patients were followed and examined by one of the authors at the Rheumatology and Neurology Unit of the State University of Campinas. Therefore, medical records and protocols for investigations were homogeneous among patients. All patients had their clinical and laboratory evaluation performed at diagnosis and quarterly during the follow-up period. Patients with incomplete clinical and laboratory evaluations or who were lost to follow-up were not included in this series. The mean duration of follow-up of these patients was 5.7 years (SD 1.2 years), ranging from 4.0 to 7.8 years.

Only patients with epileptic seizures indicating CNS involvement by SLE[17] were included in this study. Patients who had epilepsy and associated structural MRI abnormalities diagnosed prior to SLE and patients with seizures secondary to acute metabolic causes such as uremia, hypertension, diabetes mellitus, and electrolytic abnormalities were not included in the frequency determination and in analysis of epileptic seizures, although they were followed to observe if they would have recurrent seizures attributable to SLE.

Neurologic evaluation. Epileptic seizures were classified according to the criteria suggested by the International League Against Epilepy.[18] EEGs were recorded in the interictal period in a 16-channel analog or 32-channel digital EEG recorder with the International 10–20 System of electrode placement for 20 to 30 minutes in 38 (63.3%) patients. We tabulated the presence and localization of interictal epileptiform abnormality and slow wave abnormality.

Clinical features. The age at onset of epileptic seizures was determined in relation to the age at which the first well-described sign or symptom indicating SLE occurred. Patients with a diagnosis of seizures before the onset of SLE had their clinical history carefully evaluated to determine if SLE was drug induced or occurred concomitantly to seizures. In seizures occurring at disease onset or during follow-up, SLE disease flares and other triggering events were searched for. To determine the risk factors for occurrence of epileptic seizures, we analyzed clinical manifestations

From the Rheumatology Unit (Drs. Appenzeller and Costallat), Department of Internal Medicine, and Department of Neurology (Dr. Cendes), State University of Campinas, Brazil.

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Address correspondence and reprint requests to Dr. F. Cendes, Department of Neurology, State University of Campinas (UNICAMP), Cidade Universitaria Zeferino Vaz CEP, 13083970 Campinas-SP, Brazil; e-mail: fcendes@unicamp.br

Table 1 *SLE patients with seizures before diagnosis of SLE*

Patient no.	Age at seizure onset, y	Age at SLE diagnosis, y	Type of seizures	Abnormality on MRI	Treatment	Recurrence of seizures
1	20	28	Complex partial	Giant aneurysm	Surgery	No
2	13	32	Complex partial	Mesial temporal sclerosis	Phenobarbital	Yes
3	29	33	Simple and complex partial and secondary generalized	Mesial temporal sclerosis	Surgery + carbamazepine	No
4	10	26	Complex partial	Mesial temporal sclerosis	Carbamazepine	No
5	5	24	Generalized tonic-clonic	Cryptogenic	Carbamazepine	Lost to follow-up

SLE = systemic lupus erythematosus.

and serologic features at disease onset and during follow-up according to the American College of Rheumatology criteria.[16,17]

Laboratory features. Anticardiolipin antibodies of the IgG and IgM isotypes were measured by the ELISA method as described.[19] They were recorded as negative titers (<5 IgG antiphospholipid antibodies [GPL] units or <3 IgM antiphospholipid antibodies [MPL] units), low positive titers (5 to 15 GPL units or 3 to 6 MPL units), moderate positive titers (15 to 80 GPL units or 6 to 50 MPL units), or high positive titers (>80 GPL units or >50 MPL units). The lupus anticoagulant activity was detected by coagulation assays in platelet-free plasma obtained by double centrifugation, following the recommendation of the Subcommittee on Lupus Anticoagulant of the Scientific and Standardization Committee of the International Society of Thrombosis and Homeostasis.[20] Patients with SLE diagnosis prior to 1991 had their anticardiolipin antibodies and lupus anticoagulant assays done during the follow-up period.

Statistical analysis. We used multivariate logistic regression with stepwise selection, including all variables, to determine the association between clinical and laboratory features and the presence of epileptic seizures. This model included corrections for multiple comparisons. A p value of <0.05 was considered as indicative of significance.

Results. Epileptic seizures were observed in 88 (17%) SLE patients. In 23 of these patients, acute metabolic causes such as uremia (6), hypertension (10), diabetes mellitus (2), and electrolytic abnormalities (5) were identified as underlying the epileptic seizures. These patients were followed for a minimum of 25 months (mean 28 months, SD 3.2 months). As none of these patients had recurrence of seizures after correction of the underlying acute metabolic disorder, these events were not attributed to primary CNS manifestations of SLE. Therefore, these patients were excluded from further analysis.

Five patients had epilepsy diagnosis before the onset of SLE (table 1). Structural MRI abnormalities that were considered epileptogenic were observed in four of them (60%). Three had MRI signs of mesial temporal sclerosis (figure 1), and one patient had a giant cerebral aneurysm of the posterior communicating artery. All these patients were excluded from the analysis after careful follow-up because of the lack of evidence of primary CNS involvement by SLE. One patient (Patient 5; see table 1) was followed at the Neurology Unit with clinical and EEG diagnosis of juvenile myoclonic epilepsy for 10 years when she developed clinical evidence of SLE. As she was lost to follow-up before completing SLE investigation, she was also excluded for further analyses.

Sixty patients (11.6%) had epileptic seizures that were considered as a primary manifestation of CNS involvement of SLE. Nineteen (31.6%) of these 60 patients had epileptic seizures at disease onset. Epileptic seizures occurred after the onset of the SLE in 41 of 60 (68.3%) patients. Fifty-three (88.3%) patients had a single seizure episode, and 7 (11.7%) had recurrent epileptic seizures. There was no statistical difference in the follow-up period of patients with single and recurrent epileptic seizures.

Twenty-five of 60 patients with epileptic seizures were referred from primary care centers or emergency units where general physicians prescribed 100 mg of phenobarbital once a day. Because all patients tolerated phenobarbital well and a high rate of seizure relapse was observed during early tapering down, phenobarbital was maintained in most patients. If seizures relapsed while phenobarbital was being used, we introduced carbamazepine or phenytoin and discontinued phenobarbital. For patients with single epileptic seizures who were already taking antiepileptic drugs (AEDs), the medications were maintained for the period of 1 year. We did not introduce AEDs for patients with single epileptic seizures who were not on AED treatment. We introduced carbamazepine for patients with recurrent epileptic seizures.

Seizures at onset of SLE. Epileptic seizures at onset of SLE occurred in 19 (31.6%) of 60 patients with epileptic seizures: all women with mean age of 22.9 years. Twelve patients presented with generalized tonic-clonic seizures and seven with complex partial seizures. None of these patients had a family history of epilepsy. Variables associated with acute epileptic seizures at SLE onset were the occurrence of stroke ($p = 0.0004$; odds ratio [OR] = 10.36; 95% CI = 2.8, 38.2) and the presence of IgG antiphospho-

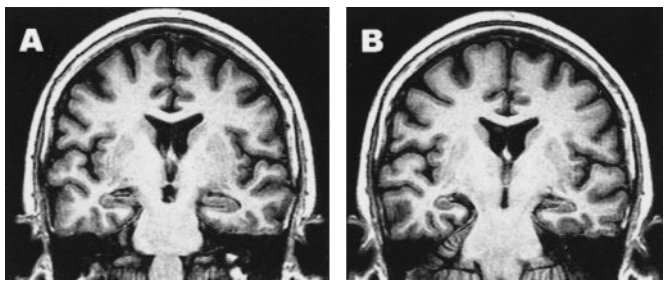

Figure 1. Coronal T1 inversion recovery images showing right hippocampal atrophy in a patient with temporal lobe epilepsy prior to onset of systemic lupus erythematosus.

Table 2 *SLE: interictal EEG findings in patients with single and recurrent seizures*

EEG finding	Single seizures, n = 31	Recurrent seizures, n = 7
Epileptiform activity	2 (6.5)*	7 (100)†
Intermittent slow waves	1 (3.2)	7 (100)
Normal EEG	28 (90.3)	0

Values in parentheses are percentages.

* Left temporal region.
† Left temporal region in 5 and left frontotemporal region in 2.

SLE = systemic lupus erythematosus.

lipid antibodies in moderate to high titers ($p = 0.0013$; OR = 6.69; 95% CI = 2.1, 21.4).

Seizures during SLE disease course. Forty-one of the 60 (68.3%) patients with epileptic seizures had their first seizure during the course of SLE. All these patients had generalized tonic-clonic seizures, without partial onset identified or recorded. None of them had a family history of seizures. There were 39 (95%) women and 2 (5%) men. Mean age at SLE diagnosis was 23.8 years, similar to the age of patients with acute epileptic seizures at disease onset. The occurrence of nephritis, in the absence of uremia and arterial hypertension ($p = 0.001$; OR = 3.2; 95% CI = 1.6, 6.5), the presence of IgG antiphospholipid antibodies in moderate to high titers ($p = 0.005$; OR = 3.9; 95% CI = 1.5, 9.9), and epileptic seizures at disease onset ($p = 0.00001$; OR = 8.27; 95% CI = 2.9, 23.3) were variables associated with epileptic seizures during disease course in this study.

Recurrent seizures. Recurrent, unprovoked epileptic seizures were observed in 7 of 60 (11.7%) SLE patients. All seven patients had clinical and laboratory evidences of antiphospholipid syndrome.

Mortality. Death was observed in 58 patients in this cohort of 519 patients during the follow-up period of 2 to 27 years. Status epilepticus was the primary cause of death in two patients with recurrent, unprovoked epileptic seizures since SLE onset. No clinical evidence of other major organ system involvement could be identified at the time of death in these two patients who died secondary to status epilepticus.

EEG findings. Interictal EEG was performed in 38 of 60 (63.3%) patients with epileptic seizures (table 2). Twenty-eight of 31 patients with single epileptic seizure had normal interictal EEG findings. All patients with recurrent epileptic seizures had abnormal EEG findings, with predominant interictal epileptiform abnormalities in temporal lobe regions.

MRI findings. MRI was performed in all patients with recurrent epileptic seizures and in 25 of 53 patients with single seizure episodes. Global cerebral atrophy was identified in all patients with recurrent seizures and in 11 of 25 patients with single epileptic seizures (figure 2). Multiple small periventricular and cortical–subcortical lesions (figure 3) suggestive of small-vessel occlusive disease were more frequently observed in patients with recurrent epileptic seizures than in patients with single seizures ($p = 0.06$). The small number of patients with recurrent epileptic seizures may account for these results. Ischemic lesions were identified in 2 of 7 patients with recurrent seizures and in 6 of 25 patients with single epileptic seizures (table 3).

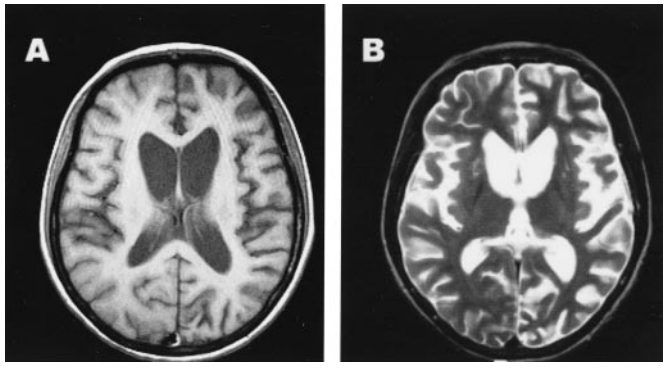

Figure 2. Axial T1-weighted and T2-weighted images showing diffuse cerebral atrophy and multiple small periventricular lesions in a patient with systemic lupus erythematosus and recurrent epileptic seizures.

Discussion. In this cohort of 519 patients, 60 (11.6%) had epileptic seizures associated with SLE disease activity. The frequency of epileptic seizures in previous studies ranged between 8.3 and 28%.[1,5-10,21] Epileptic seizures at disease onset were identified in 19 (31.7%) of these 60 patients. Epileptic seizures occurred after the onset of the disease in 41 (68.3%) patients. Fifty-three (88.3%) patients had a single epileptic seizure episode, and 7 (11.7%) had recurrent epileptic seizures. Generalized tonic-clonic and complex partial seizures were the most common epileptic seizures observed in this study. At disease onset, epileptic seizures were associated with stroke and the presence of moderate to higher titers of IgG antiphospholipid antibodies. The association between higher titers of antiphospholipid antibodies and seizures has been demonstrated previously.[2,4,9,22-26]

Epileptic seizures may occur in isolation or accompany other neurologic manifestations,[4,5,10,27-29] especially stroke, as demonstrated in this study. Previous studies suggested that antiphospholipid antibodies

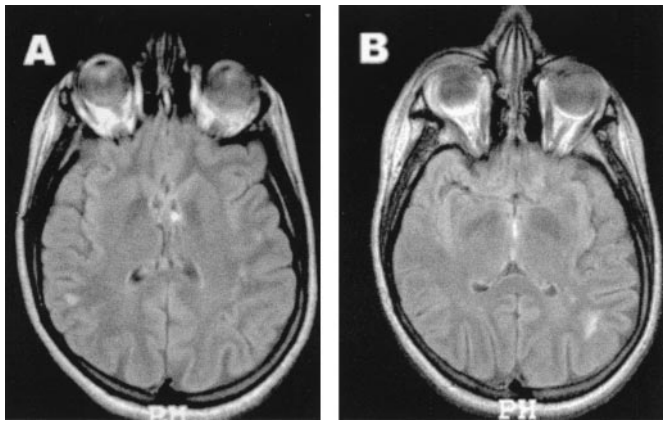

Figure 3. Axial fluid-attenuated inversion recovery (FLAIR) images showing small cortical–subcortical hyperintense lesions in two patients (A and B) with systemic lupus erythematosus who had single epileptic seizures.

Table 3 *SLE: Clinical and MR findings of SLE patients with recurrent seizures*

Patient no.	Age at seizure onset, y	Type of seizures	Abnormality on MRI
1	20	Simple and complex partial and secondary generalized	Global cerebral atrophy, multiple small hyperintense periventricular and subcortical lesions
2	17	Complex partial	Global cerebral atrophy, multiple small hyperintense subcortical lesions
3	14	Complex partial and secondary generalized	Global cerebral atrophy, cortical–subcortical ischemic lesions
4	22	Complex partial and secondary generalized	Global cerebral atrophy
5	25	Complex partial and secondary generalized	Global cerebral atrophy, cortical–subcortical ischemic lesions
6	32	Generalized tonic-clonic	Global cerebral atrophy, multiple small hyperintense periventricular and subcortical lesions
7	28	Simple and complex partial and secondary generalized	Global cerebral atrophy, multiple small hyperintense subcortical lesions

SLE = systemic lupus erythematosus.

may have a direct effect in seizure genesis by increasing neuronal excitability through inhibition of γ-aminobutyric acid receptor–ion channel complex[30] or as consequence of antibody binding to neurons.[31] Other studies concluded that epileptic seizures in patients with antiphospholipid antibodies may be the expression of ischemic events secondary to hypercoagulability.[11,32-34] We believe that stroke and antiphospholipid antibodies are confounding factors: Antiphospholipid antibodies cause ischemic strokes that may be directly responsible for the occurrence of seizures. However, the design of our study does not allow definite conclusions about the underlying mechanisms of seizures in SLE.

During follow-up of SLE, epileptic seizures were related to nephritis, the presence of antiphospholipid antibodies, and seizures at disease onset. Our study also supports the idea that disease flares are not solely responsible for epileptic seizures in SLE. Except for the relation between the presence of nephritis and seizures during disease course, other clinical manifestations were not related to the development of epileptic seizures in SLE patients.

Although most seizure episodes were usually self-limited in this study and the study design did not allow us to determine mortality, we observed two deaths secondary to status epilepticus. These two patients had epileptic seizures since SLE onset, and no other cause of death could be determined.

MRI was not performed in all our SLE patients, because several patients were investigated before the MRI era. MRI was available in 32 of 60 patients with SLE who had epileptic seizures. Although the MRI of patients with recurrent epileptic seizures showed more frequently multiple hyperintense lesions, suggestive of small-vessel disease, these findings did not reach significance, probably because of the small sample size. These findings underscore the need of MRI investigations in SLE patients with CNS manifestations.

EEG findings, although not performed in all patients, showed interictal epileptic activity in all patients with recurrent epileptic seizures. On the other hand, the majority of patients with single epileptic seizures had normal interictal EEG. These findings are important, as interictal EEG abnormalities may help to predict recurrence of seizures. We suggest that SLE patients with single seizure episode should be investigated with interictal EEG and MRI. Patients with antiphospholipid antibodies and single epileptic seizures should be followed carefully, because the risk of recurrent seizures is greater than in patients without antiphospholipid syndrome. However, most SLE patients who present with first epileptic seizure will not need to be treated with AEDs as only 1.3% had recurrent, unprovoked epileptic seizures.

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ARTIGO 5

Clinical implications of migraine in systemic lupus erythematosus: relation to cumulative organ damage

Appenzeller S, Costallat LT

Clinical implications of migraine in systemic lupus erythematosus: relation to cumulative organ damage

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Clinical implications of migraine in systemic lupus erythematosus: relation to cumulative organ damage

S Appenzeller & LTL Costallat

Unit of Rheumatology, Department of Internal Medicine State University of Campinas Faculty of Medical Sciences, Campinas, Brazil

Cephalalgia

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The aim of this study was to determine the clinical implications of migraine in systemic lupus erythematosus (SLE) using the cumulative organ damage scores (SLICC-DI). Eighty SLE, 40 rheumatoid arthritis (RA) patients and 40 controls (non SLE, nor RA out-patients), all women, were included. Migraine was defined according to the International Headache Society (IHS) criteria for neuropsychiatric SLE. Disease activity was measured by MEX-SLEDAI and cumulative organ damage by SLICC-DI. Statistics were obtained by Chi-square and Fischer's exact tests. ANOVA was used for comparing means. Migraine was identified in 42.5% of SLE patients, compared to 12.5% of RA patients ($P < 0.05$) and 10.0% ($P < 0.05$) in the control group. In the SLE group, a significant association between migraine and Raynaud's phenomenon ($P = 0.003$, OR = 10.1; 95%CI 2.9–35) and antiphospholipid antibodies ($P = 0.0012$; OR = 7.5; 95%CI 2.5–22.9) was noted. SLE patients with active migraine had higher MEX-SLEDAI scores than SLE patients without migraine. SLE patients with past history of migraine had significantly higher SLICC scores than SLE patients without migraine. History of migraine was associated with greater organ damage. Active migraine was associated with higher disease activity, antiphospholipid antibodies and worsening of Raynaud's phenomenon. The increased cumulative organ damage in SLE patients with past history of migraine justifies the routine evaluation of migraine in clinical practice.

□*Migraine, systemic lupus erythematosus, cumulative organ damage, antiphospholipid antibodies*

Dr Simone Appenzeller, Departamento de Clínica Médica, Faculdade de Ciências Médicas/UNICAMP, CEP 13081–970 Campinas, SP-Brazil. Tel. +55 193788369, fax +55 0193788369, e-mail appenzel@unicamp.br *Received 20 September 2003, accepted 27 February 2004*

Introduction

Systemic lupus erythematosus (SLE) is a chronic, inflammatory, immune-mediated disease with diverse clinical manifestations. Central nervous system (CNS) involvement in SLE has been more frequently recognized and reported in recent years, occurring in up to 50% of the patients during the disease course (1). The incidence varies because of the heterogeneity of methods applied and the small number of patients in different studies (2). Several neurological manifestations have been considered to be important features of SLE and indicative of CNS involvement (2–4), but only a few studies (3, 5, 6) included headache as a CNS manifestation.

The exact prevalence of migraine in SLE patients is unknown (7), but several studies published prevalence that varied between 31 and 45% (1, 6–9). The limitations of research in this area are the small sample size, the large variability between study designs and the different classification criteria applied (6).

The clinical importance of migraine has been addressed by several studies (1–7, 10), but the association between migraine and disease activity,

antiphospholipid antibodies and Raynaud's phenomenon remains unclear.

Headaches are considered to be associated with a significant source of patient disability (7); therefore the aim of this study was to determine the relation between migraine and cumulative organ damage in a SLE cohort followed prospectively during a one-year period.

Patients and methods

Patients and controls

The frequency of migraine in 80 patients with SLE (11), classified according to the revised criteria of the ACR (12) was compared to that found in 40 controls.

In order to study the relationship between migraine and the chronic conditions of rheumatic diseases, the frequency of migraine in SLE patients was also compared to that found in 40 RA patients (13). All patients and controls were women and were followed up in the outpatient Rheumatology Unit of the State University of Campinas, Brazil, a tertiary reference centre for rheumatic diseases. The control subjects were selected among out-patients women attending other clinics in our hospital and were not related to the RA patients or to other patients with autoimmune diseases.

The patients and controls were examined by the same investigator (SA) on a quarterly basis, during a one-year period. All of the patients and controls signed an informed consent document prior to beginning study procedures.

Exclusion criteria

Migraine has a high rate of familial occurrence, suggesting an underlying genetic factor. In order to determine if SLE influences the occurrence of migraine, patients and controls with a family history of migraine were excluded from this study. Patients with history of migraine prior to diagnosis of rheumatic disease, suggesting that migraine and SLE or RA were coexisting conditions, were also excluded. Patients with headache secondary to infection, hypertension, uraemia, metabolic disorders, lesions or traction of intra- and extra-cranial structures were excluded through history, clinical and laboratorial examinations, performed at every visit. Acute episodes of nonrecurrent headache of very low intensity or frequency were not included in the analysis. As hormonal changes influence the occurrence of migraine, we also excluded post-menopausal women.

Demographic, clinical, serological and treatment features

In SLE patients, constitutional, cutaneous, musculoskeletal, respiratory, cardiac, haematological and renal manifestations of the disease were scrutinized. The diagnosis of Raynaud's phenomenon was based on at least two-phase colour reactions of bilateral distribution described by the patient or observed by a physician. Worsening of Raynaud's phenomenon was defined as worsening of the pain referred by the patient or appearance or worsening of pre-existing digital ulcers. Data on sex, race, age at disease onset and disease duration were collected for each patient. All clinical manifestations and laboratory test findings were recorded. Nephritis was diagnosed on the basis of proteinuria exceeding 1.0 g/l with abnormal urinary sediment and/or histological findings. Nephrotic syndrome was defined as proteinuria in excess of 3.5 g/day. Haematological alterations were ascribed to lupus only in the absence of bone marrow suppression (leucopenia $< 4 \times 10^6$ cells/l; thrombocytopenia $< 100 \times 10^6$ cells/l; haemolytic anaemia with positive Coombs test). Antinuclear antibodies (ANA) were determined by indirect immunofluorescence using mouse liver as the substrate and regarded as positive if higher than 1 : 40. Anti-double-stranded DNA (AdsDNA) antibodies were determined by indirect immunofluorescence using Chrithidia as substrate and considered positive if higher than 1 : 10. Precipitating antibodies to extractable nuclear antigens (ENA), including Ro (SSA), La (SSB) and Sm were detected by immunodiffusion and/or microhemagglutination. Anticardiolipin antibodies (aCL) of the IgG and IgM isotypes were measured by the ELISA method as described (14). Lupus anticoagulant (LA) activity was detected by coagulation assays in platelet free plasma obtained by double centrifugation, following the recommendation of the subcommittee on LA of the Scientific and Standardization Committee of the International Society of Thrombosis and Homeostasis (15).

Current treatment options were analysed and changes were made when considered necessary.

RA patients and controls had also a complete clinical examination performed during the visits. Antinuclear antibodies, antiphospholipid antibodies and lupus coagulant were searched in these groups.

Disease activity and cumulative organ damage

At every visit, SLE patients had their systemic disease activity measured by MEX-SLEDAI, a simplified modification of the SLEDAI with a good

convergent validity in relation to other disease indexes (16). Patients were considered to have SLE flairs when the MEX-SLEDAI scores were three or more points higher than the previous scores (17). The patients were treated accordingly to their clinical manifestations.

Cumulative SLE-related damage was determined by SLICC-DI (18) in all SLE patients at the beginning and at the end of the study.

Neurological evaluation

A complete neurological examination was performed in all patients and controls during all visits by the same investigator (SA).

Headache

Primary headache syndromes were assessed at every visit according to the criteria of the International Headache Society (19), previously validated in Brazil (20, 21) and also adopted by the ACR (12). As a data-collecting instrument, a form based on one described by Bensenor et al. (22) was used. It followed the IHS diagnostic criteria (19) and was validated for the headache diagnosis.

Patients and controls were encouraged to report current changes in migraine characteristics, such as alterations in frequency, type, intensity and responsiveness to medication.

In order to analyse if migraine was associated with disease flares and SLE related organ damage, we divided patients with migraine in two groups: patients with active migraine and patients with past history of migraine. Patients and controls with migraine according to the IHS (19), but symptom free for a minimum of 12 weeks before the beginning of the study were considered to have past history of migraine. Patients and controls that did not meet these criteria were considered to have active migraine.

Statistics

χ^2 analyses and Fischer's exact test were used to compare clinical manifestations and migraine. ANOVA was used to compare means. The Bonferroni inequality was used to adjust the *P*-values for multiple comparisons.

Results

Demographic characteristics

Eighty SLE patients, 40 RA patients and 40 controls fulfilled the inclusion and exclusion criteria. The strict inclusion and exclusion criteria led to the exclusion of five SLE patients, two RA patients and six controls, prior the study entry.

The SLE and RA patients as well as the controls had similar demographic data (Table 1). The mean age was 32.3 years (range 15–45, standard deviation (SD) 10.9) for SLE, 35.2 years (range 18–47, SD 11.04) for RA and 32.8 years (range 20–48, SD 8.27) for controls. A predominance of Caucasians was observed in all groups. The mean duration of disease was 7.2 years in SLE (range 1–20, SD 5.0) and 8.1 years (range 2–25, SD 6.8) in RA.

Migraine

Diagnostic criteria for migraine were met in 42.5% of SLE patients compared to 12.5% ($P < 0.001$) of RA patients and to 10.0% ($P < 0.001$) of the controls, during the study. Aura was referred by 13 of 34 (38.2%) SLE patients, by 1 of 5 (20.0%) RA patients and by 2 of 4 (50.0%) controls with migraine.

Headache prevention drugs were used by 13 of 34 (38.2%) SLE patients, by 2 of 5 (40.0%) RA patients, and by 2 of 4 (50.0%) controls. At study onset and at visit 1, 23 SLE patients, 3 RA patients and 3 controls were classified as having past history of migraine. At visit two, active migraine was identified in 12 SLE patients, 4 RA patients and 2 controls. At the end of the study, active migraine was identified in 9 SLE patients, 2 RA patients and 1 control.

Clinical, serological and treatment features

In order to search for the association between disease activity and migraine, SLE patients were asked to

Table 1 Demographic data of the study subjects

Demographic data	SLE	RA	Controls
Mean age (years ± SD)	32.3 ± 10.9	35.2 ± 11.0	32.8 ± 8.3
Caucasians (%)	81.3	75.0	77.5
Mean disease duration (years ± SD)	7.2 (±5.0)	8.1	

SD, standard deviation.

record recent changes in their symptoms. The most frequent changes observed were greater intensity of pain (37.5%), new episodes of migraine after being on effective therapy for 12 weeks (39.1%) and change in aura characteristics (46.1%).

No difference was noted when we compared the mean MEX-SLEDAI scores of SLE patients during all 3 visits. However, when we compared the mean MEX-SLEDAI scores of patients with active migraine (13.7 ± 2.19) to patients without them (4.6 ± 1.5), at the end of the study, a statistically significant difference was observed ($P < 0.001$) (Fig. 1).

Raynaud's phenomenon was more frequent in SLE patients with active migraine ($P < 0.0001$, OR = 14.0; 95% CI = 4.2–41.0) (Table 2). Worsening of Raynaud's phenomenon shortly before severe migraine episodes was referred by 44.1% of SLE patients. Eleven of 13 (84.6%) patients with migraine referred worsening of Raynaud's phenomenon during aura.

Antiphospholipid antibodies were more frequent in SLE with migraine when compared to SLE without migraine ($P < 0.0001$; OR = 11.7; 95% CI = 3.7–37.1). No difference between the frequencies of other auto antibodies in these two groups was observed (Table 3).

No difference was noted when mean SLICC scores from SLE patients at the beginning and at the end of the study were compared. However, the mean value of SLICC scores was 4.0 (±2.19) for SLE patients with past history of migraine compared to 0.8 (±0.83) ($P < 0.001$) for SLE patients without past history of migraine (Fig. 2) at the end of the study. Renal, musculoskeletal and peripheral vascular systems were significantly more frequently affected ($P < 0.05$) in SLE patients with past history of migraine (Fig. 3).

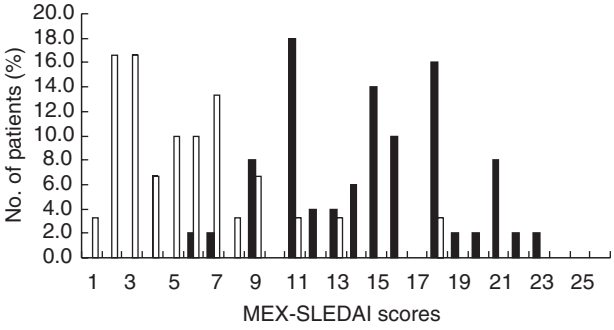

Figure 1 SLE: MEX-SLEDAI scores in patients with (■) and without (□) active migraine at the end of the study.

Table 2 SLE: Clinical manifestations in patients with and without migraine

Manifestations	Migraine *n* (%)	No migraine *n* (%)	Total *n* (%)
Total no. patients	34	46	80
Arthritis	27 (79.4)	42 (91.3)	69 (86.3)
Avascular necrosis	6 (17.6)	1 (2.3)	10 (12.5)
Discoid rash	13 (38.2)	10 (21.7)	23 (28.7)
Fever	31 (91.2)	40 (87.0)	71 (88.8)
Haemolytic anaemia	10 (29.4)	8 (17.4)	18 (22.5)
Leucopenia	15 (44.1)	27 (58.7)	42 (52.5)
Malar rash	17 (50.0)	20 (43.5)	37 (46.2)
Nephropathy	15 (44.1)	14 (30.4)	29 (36.3)
Oral ulcers	6 (17.6)	8 (17.4)	14 (17.5)
Photosensitivity	24 (72.0)	29 (63.0)	53 (66.3)
Raynaud's phenomenon	30 (88.2)	16 (34.8)*	36 (45.0)
Serositis	19 (56.0)	22 (47.8)	41 (51.3)
Thrombocytopenia	5 (16.0)	6 (13.3)	11 (13.8)
Thrombosis	7 (20.6)	2 (4.3)	9 (11.3)

*$P < 0.003$.

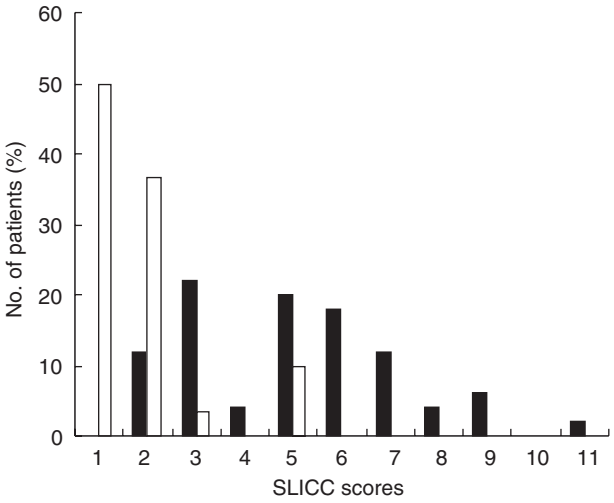

Figure 2 SLE: SLICC scores in patients with (■) and without (□) past history of migraine at the end of the study.

Table 3 SLE: Immunological features in patients with and without migraine

Immunological feature	Migraine *n* (%)	No migraine *n* (%)	Total *n* (%)
ANA	32 (94.1)	43 (93.5)	75 (93.8)
Antiphospholipid antibodies	20 (58.8)	5 (10.9)*	25 (31.3)
ds-DNA	23 (67.6)	24 (52.2)	47 (58.8)
SSA/Ro	8 (23.5)	14 (30.4)	22 (27.5)
SSB/La	3 (8.8)	7 (15.2)	10 (12.5)
Sm	7 (20.6)	12 (26.0)	19 (23.7)

*$P < 0.008$.

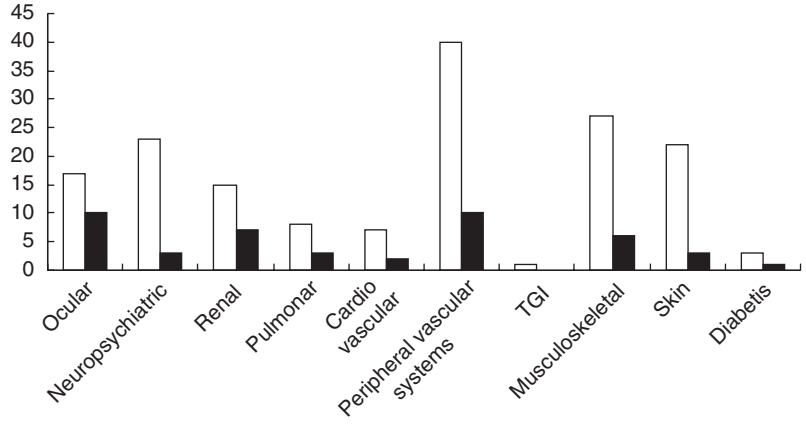

Figure 3 SLE: SLICC-DI scores in different organ involvement at the end of the study. Without (■) and with (□) migraine.

No relation between past or current drug use (corticosteroids, nonsteroid anti-inflammatory drugs or other immunosuppressive drugs) and the incidence of new episodes of migraine was found. Patients, who were treated with corticosteroids or other immunosuppressive drugs for other systemic manifestations of SLE than headache, had a 41.2% improvement in migraine symptoms. No RA patients or control had positive antiphospholipid antibodies or Raynaud's phenomenon.

Neurological evaluation

Neurological examination was normal in all SLE patients and controls during all visits. Twenty (50%) of RA patients presented some degree of muscle atrophy and 5 (12.5%) had gait disturbance, secondary to hip involvement at the beginning and at the end of the study. These abnormalities could be explained by articular sequelae secondary to RA.

Discussion

Although a number of studies analysed the importance of disease activity in migraine (2, 8, 10), no study, to our knowledge, analysed the impact of migraine in SLE using the cumulative organ damage scores. Our study shows that SLE patients with past history of migraine have higher SLICC-DI scores than patients without this manifestation. Although most previous controlled studies (1–7) did not find an association between SLE and migraine, we demonstrate that, patients with active migraine had higher disease activity scores than patients without migraine and were therefore more often treated with corticosteroids to control SLE activity than patients without migraine. Both the chronic use of corticosteroids and the presence of SLE flairs are features associated with greater organ damage in SLE patients.

Headache is a common complaint of the general population, especially among young women and influenced by hormonal and psychosocial factors (23). The epidemiological similarities between SLE and migraine require a control group paired by age and sex, but not related to the patients themselves. In order to analyse all these factors, we included only premenopause women. In addition, the frequency of migraine in SLE was also compared to the frequency of migraine in RA, another chronic rheumatic disease, in order to exclude the assumption that nonspecific factors related to systemic diseases, may act to precipitate migraine in susceptible individuals (24, 25). The increased prevalence of migraine in SLE when compared to RA suggests that the presence of migraine could not be explained solely by the presence of an underlying chronic disease.

There is clinical experimental evidence that extracranial arterial vasodilation, extracranial neurogenic inflammation, and decreased inhibition of central pain transmission are involved in the pathogenesis of the migraine headache (24). Raynaud's phenomenon is frequently observed in patients with migraine in general population surveys (26–28), suggesting that these conditions may share a common pathogenic mechanism, such as similar vascular reactions (26, 27) and vascular endothelial cell dysfunction (29, 30). Proposed mechanisms include antibody-mediated interference with coagulation homeostasis, activation of platelets and endothelial cells and a T-cell immune response to serum phospholipid-binding proteins. Several studies have examined the specific interaction between antiphospholipid

antibodies, in especially, antibodies to β_2-glycoprotein I and in-vitro endothelial cell function (31–36). The direct binding of β_2-glycoprotein I to the endothelial cell surface is facilitated by the constitutive negative charge on the surface of endothelial cells, enhanced surface expression of negatively charged phosphatidylserine during apoptosis (31) and the fact that annexin II acts as a receptor for the binding of β_2-glycoprotein I to cultured endothelial cells (32). Thus, antiphospholipid antibody binding to the endothelial cell surface in a β_2-glycoprotein-I–dependent manner leads to endothelial cell activation, which is manifested by up regulation of cell surface adhesion molecules and increased secretion of interleukin-6 and prostaglandins (33–36). So they may induce endothelial damage by complement and or antibody dependent cytotoxicity. Endothelial cells are involved in the regulation of many substances that are involved in the pathogenesis of migraine: inactivation of vasoactive substances such as serotonin and bradicynin and production, for example, of endothelin 1 and prosatcycline. Endothelial cell dysfunction is a relevant pathogenic mechanism explaining the interaction between migraine, antiphospholipid antibodies and Raynaud's phenomenon.

Some studies have analysed the associations between migraine and Raynaud's phenomenon in SLE (24, 25, 37, 38). We found not only a higher prevalence of Raynaud's phenomenon in SLE patients with migraine, but also a worsening of Raynaud's phenomenon prior to migraine episodes in 44.1% of our SLE patients. The majority of our patients with aura referred worsening of Raynaud's phenomenon during the aura occurrence, supporting the idea that both conditions may have a common pathogenic mechanism. Several neurological disorders have been associated with the presence of antiphospholipid antibodies (39–42), but there are still controversies in relation to migraine (7, 24, 25, 37, 38). However, the majority of study groups are small, making statistic analysis more difficult. In our study, the presence of antiphospholipid antibodies was more frequent in SLE patients with migraine.

The Rheumatology Unit of the Sate University of Campinas is a reference centre for rheumatic diseases and this fact explains the high frequency of some clinical SLE manifestations, such as nephropathy.

Our study has some limitations. First, this is not an unselected sample of SLE patients. Only women were included in this study because both migraine and SLE have hormonal influence. Second, the number of patients with active migraine is small and no headache diary was used, making difficult to extract conclusion in a prospective manner. Also, the strict inclusion and exclusion criteria used could introduce bias, especially in relation to the number of persons affected by migraine in all three groups. But as the primary objective of our study was to determine the relation of disease activity and cumulative organ damage and migraine in SLE, and not to determine the overall prevalence of migraine in this population, we consider that these limitations were not relevant to determine this issue. Third, no neurological consultation was performed in this study.

In summary, history of migraine was associated with greater organ damage using SLICC-DI. Active migraine was associated with higher disease activity, measured by MEX-SLEDAI, antiphospholipid antibodies and worsening of Raynaud's phenomenon. The increased cumulative organ damage in SLE patients with past history of migraine justifies the routine evaluation of migraine in clinical practice.

Acknowledgements

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ARTIGO 6

Acute psychosis in SLE

Appenzeller S, Cendes F, Costallat LT

Acute psychosis in SLE

submetido

Acute psychosis in systemic lupus erythematosus

Simone Appenzeller MD[1, 2], Fernando Cendes MD, PhD [2, 3], Lilan Tereza Lavras Costallat MD, PhD [1]

[1]Rheumatology Unit - State University of Campinas [2] Neuroimaging Lab-State University of Campinas; [3] Department of Neurology, State University of Campinas

Running Title: acute psychosis in SLE

Address all correspondence to: Prof Dr Lilian TL Costallat, Department of Internal medicine, State University of Campinas (UNICAMP), Cidade Universitaria Zeferino Vaz, CEP 13083970 Campinas-SP-Brazil

Tel: +55 1937887734

Fax: +55 19 32135106

E-mail: appenzel@unicamp.br

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Abstract

Objective: To evaluate the frequency and risk factors of acute psychosis in a large cohort of patients with systemic lupus erythematosous (SLE). To identify clinical and laboratory variables useful in differentiating acute psychosis as a primary manifestation of CNS from corticosteroid induced psychosis.

Methods: Five hundred thirty seven consecutive patients with SLE were studied, with follow-up ranging from 4 to 8.8 years. A standardized medical history, neurological, rheumatologic, and psychiatric examinations and serologic testing were performed in all patients. The type and frequency of risk factors associated with acute psychosis as a primary manifestation of CNS system and corticosteroid induced psychosis was determined using multivariate regression with automatic backward stepwise selection.

Results: We identified acute psychosis in 89 of 520 (17.1%) SLE patients. Psychosis primary to CNS involvement was diagnosed in 59 of these patients, corticosteroid induced psychosis in 28 and primary psychotic disorder not related to SLE or medication in 2 patients. Psychosis secondary to SLE at disease onset occurred in 19 patients and was associated with disease activity (p=0.001; OR=2.4; CI=1.5-6.2). Psychosis during follow-up of SLE was observed in 40 patients and associated with positive antiphospholipid antibodies (p=0.004; OR=3.2; CI=1.9-4.5) and less frequently with renal (p=0.002; OR=1.9; CI=0.0-0.6) and cutaneous (p=0.04; OR=1.1; CI=0.0-0.8) involvement. We identified 28 patients with 38 episodes of psychosis associated with corticosteroid therapy. All patients had severe active disease and 10 of these patients had hypoalbuminemia when psychosis developed. At time of psychotic event, all patients were taking prednisone in doses varying from 0.75 to 1 mg/kg/day. Psychosis resolved after tapering prednisone down in all patients.

Conclusion: Acute psychosis related to SLE was observed in 11.3% of our cohort. Recurrence of primary psychosis was associated with other CNS manifestations related to SLE.

Introduction

Central nervous system (CNS) manifestations in systemic lupus erythematosus (SLE) are very heterogeneous in clinical presentations, involving multiple pathophysiological mechanisms (1-3). Neuropsychiatric involvement in SLE could be defined as neurological syndromes of the central, peripheral and autonomic nervous system and psychiatric syndromes observed in SLE patients, after excluding other possible causes not related with SLE (3).

A challenging problem in the diagnosis and management of SLE is psychiatric disorder. Abnormal behavior was first described in SLE by Hebra and Kaposi (4), followed by Osler (5). Many psychiatric symptoms can be observed in SLE patients, such as depression, anxiety, mood disorders, but psychosis was considered one of the most important and included in the classification criteria for SLE in 1982, despite the widely diverse clinical manifestations (6) and varying degree of severity (7, 8). Psychosis may be a primary event of CNS manifestation of SLE or associated with a variety of drugs and infections, such as corticosteroids and antimalarics (9). Adverse psychiatric effects, including mild euphoria, emotional lability, alteration of behavior, panic attacks, psychosis and delirium, are seen in 3 to 10% of all patients receiving corticosteroids and are unpredictable from the regimens of corticosteroids used (10-14).

In this study we reviewed the frequency of acute psychosis in our cohort and determined the frequency of corticosteroid induced psychosis. We further tried to identify risk factors for occurrence of acute and corticosteroid induced psychosis, as well as for the recurrence of psychosis.

Patients and Methods

537 consecutive patients with four or more criteria for SLE diagnosis (6), had their medical histories, clinical and serological characteristics documented regularly in computer database programs. All patients had their clinical and laboratory evaluation performed at diagnosis and quarterly during follow-up period and were followed and examined by one of the authors (LTLC, SA) throughout the years. Therefore, medical records and protocols for investigations were very homogenous among patients followed at

the Rheumatology Unit of the State University of Campinas. In this study, we included all patients that were regularly evaluated in our unit from January 1999 to December 2003. The mean duration of follow-up of these patients was 5.3 years (SD 1.1 years), ranging from 4.0 to 8.8 years.

Seven patients with incomplete clinical and laboratory evaluations or who lost follow up were not included in this series. This study has been approved by our local Ethics Committee.

Psychiatric evaluation

Acute psychosis as a primary manifestation of CNS involvement by SLE was defined by the presence of disturbance of reality characterized by delusions and/or hallucinations, severe enough to cause significant distress or social impairment. All symptomatic patients were evaluated by a psychiatrist and events were classified using the *Diagnostic and Statistical Manual of Mental Disorders* (4th edition) (15). Patients with psychosis were carefully evaluated, in order to differentiate primary psychotic disorders unrelated to SLE, substance or drug-induced psychotic disorders and psychologically mediated reactions to SLE as major stressor. In all patients with psychosis, other causes such as infection, metabolic disturbance and structural lesions were carefully excluded by clinical, laboratory and MRI when indicated.

Corticosteroid-induced psychiatric disturbances were defined as new symptoms that appeared temporally within 8 weeks of institution or augmentation of steroids and resolved completely after reduction of steroid dosage without additional immunosuppressive agents. Ten patients who had psychosis previously to SLE diagnosis or previously to the evaluations in our service were not included in the analysis, although they were followed in order to observe if they would have recurrent psychotic episodes. Patients with diagnosis of psychosis before 1999, had their medical charts carefully reviewed in order to determine if they complete ACR criteria (16). Therefore 17 patients were excluded and the remaining 520 patients were included in the final analysis.

Clinical features

The age at onset of psychosis was determined in relation to the age at which the first well-described sign or symptom indicating SLE occurred. To determine the risk factors for occurrence of psychosis we analyzed clinical manifestations, serologic features at disease onset and during follow-up, according to the American College of Rheumatology (ACR) criteria (6, 16). For the purpose of statistical analyses, some of the clinical features were grouped under renal, neuropsychiatric, and hematologic disease. Renal disease was defined as any 1 of the following: 1) persistent proteinuria of >=0.5 g/day; 2) the presence of cellular casts; and/or 3) biopsy evidence of lupus glomerulonephritis. Neuropsychiatric disease referred to any of the manifestations defined by ACR criteria (16), after careful review of medical records. Hematologic disease was defined as any 1 of the following: 1) hemolytic anemia; 2) leukopenia (<4.0 × 10^9/L); and 3) thrombocytopenia (<100 × 10^9/L), on at least 2 occasions that were not due to the effect of medications.

Global disease activity was quantified by the SLE disease activity Index (SLEDAI) (17), cumulative organ damage by the ACR/Systemic Lupus (SLICC) (18).

Patients with neuropsychiatric manifestations or complains were evaluated. A complete neurological examination, as well as cognitive and psychiatric charts, were applied. Cognitive impairment was analyzed using a standardized neuropsychological tests in order to screen for possible impairment in one or more of the subsequent cognitive domains: simple attention, complex attention, memory, visuo-spatial processing, language, reasoning/problem solving, psychomotor speed, and executive functions (19-22). The individual test results were converted into standard scores, which were compared with the available normative data (19-22). Regarding any of the eight cognitive domains, subjects with a total score of two or more standard deviations (SD) below the normative value were considered to be impaired. Cognitive dysfunction was classified as mild if there were deficits in less than three dimensions, as moderate if there were deficits in three or four dimensions, and as severe if there were deficits in at least five dimensions (23, 24).

Assessment of depression was based on clinical interview and the Beck Depression Inventory (BDI) (25, 26). On BDI, scores from 10 to 17 were considered to indicate mild depression, from 18 to 24 moderate depression, and greater than 24 severe

depression. Anxiety was evaluated by anxiety through the Hospital Anxiety and Depression scale (27). The presence of psychosis was determined through the Brief Psychiatry Rating Scale (aBPRS) (28).

Laboratory features

Anticardiolipin antibodies (aCL) of the IgG and IgM isotypes were measured by the ELISA method as described previously (29). They were recorded as negative (<5GPL units or <3MPL units), low positive titers (5-15 GPL units or 3-6 MPL units), moderate positive titers (15-80 GPL units or 6-50 MPL units), or high positive titers (>80 GPL units or >50 MPL units). The lupus anticoagulant (LA) activity was detected by coagulation assays in platelet free plasma obtained by double centrifugation (30). Patients with SLE diagnosis prior to 1991 had their aCL and LA essays done during the follow-up period.

Statistical analysis

Values in this study were expressed as mean ± standard deviation (SD). Comparison of categorical data among groups was made by the chi-square test. Comparison of continuous data was performed by 1-way ANOVA. Post-hoc multiple comparisons were performed using the Tukey test for unequal samples.

First, the baseline features of those patients with psychosis were compared to patients without psychosis. Comparisons were done by χ^2 for categorical variables and by analyses of variance for continuous variables. Furthermore, patients were divided into groups as follows: psychosis at disease onset, psychosis during follow-up period and corticosteroid induced psychosis. Because of the small sample size, we excluded patients with psychosis not related to SLE from the analysis and used the data only in a descriptive manner. Their baseline features were also compared. The independent variables chosen to enter the multivariate analysis model were those that presented a level of statistical significance $\leq 5\%$ at the univariate analyses.

We initially performed one multiple regression including significant variables to differentiate acute psychosis due to SLE, independently to the time of disease onset, to patients with acute psychosis related to corticosteroids therapy. Then we performed an automatic backward stepwise multiple regression, including the variables SLEDAI and SLICC scores, malar rash, photosensitivity, arthritis, renal, neuropsychiatric, and hematologic disease, moderate to high antiphospholipid antibodies, ANA antibodies, anti DNA antibodies, hypoalbuminemia in the model, to determine clinical and laboratory features associated with psychosis at disease onset and at follow-up. These models included corrections for multiple comparisons. A p value <0.05 was considered as indicative of statistical significance. MRI findings and CSF were not included in the analysis.

Results

Acute psychosis was identified in 89 of 520 (17.1%) patients (78 women) of our cohort with mean age of 26.3 years. We did not observe any statistical difference in mean age of disease onset, time to disease diagnosis and any other demographic variable between patients with acute psychosis and without psychosis (Table 1). Nineteen (21.3%) patients had acute psychosis at disease onset and 40 (45%) during course of SLE. Twenty eight (31.5%) patients had corticosteroid induced psychosis and 2 (2.2%) patients were identified with psychosis not related to SLE or drugs.

Acute psychosis at disease onset

Acute psychosis at disease onset was identified in 19 of 89 patients (17 women) with mean age of 25.6 years (SD=5.6; range 16-38 years). All patients had acute psychosis as one of the first manifestations of SLE and were off steroid when psychotic episode occurred. They were subsequently referred to our service because of clinical manifestations suggestive of SLE during further investigations. Further investigations excluded infections and revealed positive ANA titers in all patients. Cerebral spinal fluid (CSF) analysis was normal in 14 and revealed mild pleocitosis in 5 patients. MRI was normal in 8 of 9 patients (Table 2). All patients completed classification criteria for SLE during follow-up period. The psychotic episodes resolved after introduction of psychiatric medication and

corticosteroid doses that varied from 0.5 to 1 mg/kg/day of prednisone, depending on the severity of clinical manifestations. After a mean time of follow-up of 6.2 years (SD=2.3, range 2.3-10.2 years), 11 patients were off psychiatric medications.

In automatic backward stepwise regression analyses we observed that the disease activity was independently associated with psychosis (p=0.001; OR=2.4; CI=1.5-6.2). Furthermore, the absence of malar rash (p=0.002; OR=1.6; CI=0.1-0.9) and photosensitivity (p=0.01; OR=0.5; CI=0.01-0.085) were also variables independently associated with psychosis when compared to patients without psychosis at disease onset.

Recurrence of acute psychosis not related to corticotheraphy was observed in 8 patients. They all had other CNS manifestations related to SLE in addition to psychosis, including severe cognitive impairment in 5, headache in 5, mood disorder in 4, seizures in 3, anxiety in 2 and stroke in 2 patients. Recurrence of psychosis in this group of patients was associated with disease activity (p=0.001; OR=3.4; CI=1.9-6.0) and the presence of other CNS manifestations (p=0.02; OR=1.9; CI=1.3-3.5) in automatic backward stepwise regression analyses.

Acute psychosis during follow-up

During the course of SLE, acute psychosis was observed in 40 patients (35 women). Mean time of SLE diagnosis before psychosis occurred was 14 months (range 7-40 months) (Table 1). CSF analyses during acute psychosis were performed in 32 of 40 patients and were negative for infections in all. Fifteen patients had mild pleocitosis and 10 mild protein elevations in CSF. MRI performed in 15 patients was abnormal in 10 and revealed hyperintense lesions in 10, cerebral atrophy in 8 and diffuse white matter involvement in 2 patients (Table 2).

In automatic backward stepwise regression analyses, the presence of positive antiphospholipid antibodies in moderate to high titers (p=0.004; OR=3.2; CI=1.9-4.5) and SLEDAI scores ≥8 (p=0.001; OR=2.0; CI=1.5-2.3) were independent risk factors for occurrence of psychosis. The absence of renal (p=0.002; OR=1.9; CI=0.0-0.6) and cutaneous manifestations (p=0.04; OR=1.1; CI=0.0-0.8) were also variables associated with psychosis during follow-up period.

During mean follow-up period of 4.6 years after the occurrence of psychosis, these patients developed more frequently other primary CNS manifestations related to SLE, including cognitive impairment in 20, mood disorder in 7, stroke in 5, seizures in 4 and anxiety in 2 patients.

Recurrence of acute psychosis was identified in 10 of 40 patients. After carefully investigations, recurrences were associated with SLE disease activity in all patients (p=0.001; OR=3.2; CI=1.6-4.6).

Acute psychosis related to corticosteroids therapy

We identified 28 patients (25 women) with 38 episodes of acute psychosis associated with corticosteroid treatment. All patients had severe active disease and 10 of these patients had hypoalbuminemia (albumin < 2mg/dl) when psychosis developed. Nephritis was diagnosed in 11, serositis in 6, systemic vasculitis in 5, autoimmune hepatitis in 3, and pericarditis in 3 patients. At time of psychosis, all patients were using prednisone in dose varying 0.75 to 1 mg/kg/day. Psychosis resolved after tapering prednisone down in all cases after a median time of 13.3 (SD±5.2) days. In 15 episodes of psychosis, antipsychotic medications were required. Haloperidol was used in 13 of 15 patients. CSF analyses during psychosis were performed in 14 of 28 patients and were normal in 14 and negative for infections in all.

In the automatic backward stepwise regression analyses, the only variable associated with psychosis associated with corticosteroid treatment was hypoalbuminemia (p=0.03; OR=2.2; CI=1.9-2.5). Recurrences of psychosis were observed in 10 of these patients: in eight after increment of prednisone dose for systemic manifestations and in 2 with lower doses.

Acute psychosis not related to SLE

Two patients (2 women) were identified with acute psychosis not related to SLE. One patient had mental retardation secondary to perinatal anoxia and developed severe psychiatric disturbance during development. The other patient had initially several

hallucinations and psychotic manifestations after epileptic seizures, and was diagnosed during the follow-up period as having temporal lobe epilepsy due to her clinical and electroencephalogram findings. In addition, her MRI showed signs of hippocampal sclerosis ipsilateral to the epileptic focus. Psychotic episodes resolved after introduction of antiepileptic medication.

Acute psychosis due to SLE x acute psychosis related to corticosteroids therapy

When we compared SLE patients with acute psychosis due to SLE, independently to the time of disease onset, to patients with acute psychosis related to corticosteroids therapy using automatic backward stepwise regression analyses, we observed that patients with psychosis due to SLE had more frequently other CNS manifestations related to SLE (p=0.03; OR=2.1; CI=1.2-3.9) and positive antiphospholipid antibodies (p=0.01; OR=2.2; CI=1.4-3.5) than patients with acute psychosis related to corticosteroids therapy. The presence of hypoalbuminemia was a risk factor (p=0.03; OR=2.2; CI=1.9-2.5) for development of corticosteroid induced psychosis in automatic backward stepwise regression analyses.

Discussion

We identified acute psychosis in 89 of 520 (17.1%) symptomatic SLE patients. Acute psychosis primary to CNS involvement was diagnosed in 59, corticosteroid induced psychosis in 28 and primary psychotic disorder not related to SLE neither to medication in 2 patients. We observed that the presence of other CNS manifestations associated to SLE and positive antiphospholipid antibodies were more frequently observed in patients with psychosis due to SLE when compared to corticosteroid induced psychosis. We further observed that corticosteroid induced psychosis was more frequently observed in patients with hypoalbuminemia. Because of the small sample size, we excluded patients with psychosis not related to SLE from the analysis and used the data only in a descriptive manner.

We observed that acute psychosis secondary to SLE at disease onset was more frequently associated with disease activity, whereas cutaneous manifestations were less frequently seen. This may be one of the reasons why these patients are usually first seen by psychiatrist. However a carefully investigation is necessary, especially because all patients are usually young women, and develop severe systemic manifestations if not treated promptly. In patients who had acute psychosis during the course of disease, it was associated with the presence of antiphospholipid antibodies and they had more frequently other CNS manifestations related to SLE activity. Depression, stroke, seizures, cognitive dysfunction, and psychosis have all been associated with antiphospholipid antibodies (2, 3). The presumed pathophysiological mechanism underlying these manifestations is thought to be a result of cerebral ischemia in some, but not all patients. An interaction between antiphospholipid antibodies and central nervous system cellular elements rather than antiphospholipid antibodies associated thrombosis seems to be a more plausible mechanism for most of these clinical manifestations (2, 3, 31). Renal and cutaneous manifestations of SLE were less frequently seen. Recurrence of acute psychosis was observed in 18 of 59 patients. These patients had also more frequently other CNS events due to SLE activity. Therefore patients with acute psychosis should be followed carefully in order to determine if they develop other primary CNS manifestations secondary to SLE.

In our study we observed 38 episodes of corticosteroid induced psychosis in 28 patients during the follow-up period. All patients had active SLE disease and were receiving prednisone in moderate to high doses. As previously described (11-13, 19-33), hypoalbuminemia may be a risk factor for corticosteroid induced psychosis. In our study we observed hypoalbuminemia in 10 patients who developed corticosteroid induced psychosis. The explanation for these findings may be that corticosteroid binding globulin does not bind to synthetic steroids, whose transport depends on serum albumin which, by contrast, presents low affinity but a great capacity to transport the steroids because of its high plasma concentration. Steroids are biologically inactive when bound to albumin. Therefore, the free (and active) fraction of steroids is higher in patients with low plasma albumin levels, and this will expose the patient to more adverse effects (35). Due to the retrospective nature of our study, we were not able to determine the albumin level of all our patients; therefore we could not determine the cut off values for an increased risk of

psychosis. The incidence of psychiatric reactions to corticosteroid treatment in SLE is not significantly higher than the expected one in ulcerative colitis, rheumatoid arthritis or lymphoma. However, patients with SLE do have a higher incidence of corticosteroid-induced psychiatric symptoms (35).

In patients with SLE, corticosteroid-induced psychiatric events may be difficult to distinguish from primary neuropsychiatric manifestations of SLE. The antiribosomal P antibody is specific for SLE and has been shown to be associated with psychosis related to disease activity and other CNS manifestations, including depression (33), but the low sensitivity limits its clinical usefulness for the diagnosis of lupus psychosis (13). Therefore, a temporal relationship between the beginning of corticosteroid therapy and psychiatric events, and the resolution of symptoms after reduction of corticosteroids is an important feature in diagnosis of corticosteroid induced psychosis. We did not search for antiribosomal P antibodies in our studies and steroid induced psychosis was based on clinical judgment (34).

MRIs were done in 30 patients during acute psychosis. Patients with psychosis at disease onset had more frequently normal MRI when compared to patients with psychosis at follow-up and corticosteroid induced psychosis, although none of the findings observed in MRI could be directly related to psychotic event.

A limitation of this study is its retrospective nature. However, all patients' clinical and laboratory findings were constantly updated on our computer database by one of the authors, reducing the bias. Recurrence of psychosis and factors associated with its occurrence has not been frequently reported before.

In conclusion we observed acute psychosis related to SLE in 11.3% of our cohort. Recurrence occurred in 30% of these patients and was related to the presence of other CNS manifestations. Hypoalbuminemia was a risk factor for development of corticosteroid induced psychosis, whereas disease activity, CNS manifestations and the presence of antiphospholipid antibodies were risk factors for psychosis due to SLE.

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Table 1. Characteristics of SLE patients with psychosis when compared to SLE patients without psychosis

Number of patients	Psychosis at SLE onset N=19	Psychosis during SLE N=40	Corticosteroid induced psychosis N=28	Other causes of psychosis N=2	SLE patients without psychosis N=520
Age (years±SD)	25.6 (SD=5.6)	28.1	27.3	19.2	28.6
SLE duration (months±SD)	1.8 (1.2)	14 (5.2)	16 (4.2)	-------	67.3 (14.8)
Follow-up time (years±SD)	6.2 (2.3)	4.6 (3.1)	5.2 (1.2)	4.2 (3.2)	5.7 (1.2)
Features of psychosis N(%)					
Paranoia	7 (36.8)	15 (37.5)	6 (21.4)	0	----
Visual hallucinations	10 (52.6)	22 (55)	15 (53.6)	2 (100)	
Auditory hallucinations	6 (31.6)	7 (17.5)	13 (46.4)	1 (50)	
Delusion of grandiosity	9 (47.4)	14 (35)	10 (35.7)	0	
Other CNS events	8/19	29/40	2/28	0	190/527
Recurrence	8	10	10	2	---------

Table 2. CSF and MRI findings in patients with psychosis

	Psychosis at SLE onset	Psychosis during SLE	Corticosteroid induced psychosis	Other causes of psychosis
CSF	19/19	32/40	14/28	2/2
Normal	14	13	11	2
Mild protein elevation/pleocitosis	5	19	3	0
MRI	9/19	15/40	6/28	2/2
Normal	8	5	0	0
Hyperintense lesions	1	10	4	0
Structural abnormality	0	0	0	2
Atrophy	1	8	4	0
Diffuse white matter involvement	0	2	1	0

ARTIGO 7

Cerebral venous thrombosis: influence of risk factors and imaging findings on prognosis

Appenzeller S, Zeller CB, Annichino-Bizzachi JM, Costallat LT, Deus-Silva L, Voetsch B, Faria AV, Zanardi VA, Damasceno BP, Cendes F

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Cerebral venous thrombosis: influence of risk factors and imaging findings on prognosis

Simone Appenzeller[a], Carlos Borelli Zeller[a], Joyce M. Annichino-Bizzachi[a], Lilian T.L. Costallat[a], Leonardo Deus-Silva[b], Barbara Voetsch[b,1], Andreia V. Faria[c], Verônica A. Zanardi[c], Benito P. Damasceno[b], Fernando Cendes[b,*]

[a] *Department of Internal Medicine, Rheumatology Unit, State University of Campinas, UNICAMP, Brazil*
[b] *Department of Neurology, FCM, UNICAMP, Cidade Universitária, Campinas, SP 13083-970, Brazil*
[c] *Department of Radiology, State University of Campinas, UNICAMP, Brazil*

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Summary

Purpose: To investigate imaging findings, risk factors and outcome in patients with cerebral venous thrombosis (CVT).
Methods: Records of all patients with diagnosis of CVT between 1992 and 2002 were reviewed. Patients with CNS infection and with CVT secondary to invasive procedures were excluded. Inherited and acquired thrombophilia were searched in all patients.
Results: Twenty-four patients (18 women, 6 men) with mean age of 29.5 years (range 3–48 years) were identified. Mean follow-up was 44 months (range 11–145 months). The most common symptoms were headache (75%), vomiting (33%) and impairment of consciousness (21%). Probable causes of CVT could be determined in 21 (88%) patients: pregnancy or puerperium in six (25%), oral contraceptive use in four (17%), head trauma in two (8%), mastoiditis in one (4%), nephrotic syndrome in one (4%), systemic disease in three (13%), and inherited thrombotic risk factors in four (17%) patients. CVT associated with pregnancy, puerperium and use of oral contraceptives had a significant better outcome than CVT caused by inherited thrombophilia or systemic disease (OR = 14.4; $p = 0.02$). CT scans were abnormal in 15 (62.5%) patients and MRI with gadolinium was abnormal in all. Those with parenchymal involvement had neurological sequelae during follow-up. All were treated with heparin followed by oral anticoagulants, and none had new or worsening of pre-existing intracerebral hemorrhage.
Conclusion: MRI is superior to conventional CT for diagnosing CVT. Patients with parenchymal lesions, thrombophilia and antiphospholipid syndrome had greater risk to be left with neurological sequelae. Anticoagulant therapy did not predispose to further intracerebral hemorrhage.

Keywords: Cerebral venous thrombosis; Magnetic resonance imaging; Inherited thrombophilia; Outcome

1. Introduction

The diagnosis of cerebral venous thrombosis (CVT) may be very difficult due to the large spectrum of clinical manifestations and the multiple associated conditions and etiologies [1].

CVT was considered to be a rare disease with high morbidity, but more recent studies indicate that this condition is more frequent and more benign than previously thought [1–4], although patients with thrombophilic risk factors seem to have a less favorable outcome [3,5]. Risk factors for CVT include inherited thrombophilia (e.g. factor V Leiden mutation, protein C and S deficiency), acquired prothrombotic state (pregnancy, purperium and postoperative period), systemic disease (e.g. Behçet syndrome, systemic lupus erythematosus), neoplasia (e.g. leukemia, systemic carcinoma), systemic infectious disease (e.g. septicemia), local causes (e.g. otitis, mastoiditis) and use of oral contraceptives [3,5].

We report here 24 patients with CVT. We determined the frequency of inherited and acquired thrombophilia in patients

* Corresponding author. Tel.: +55 19 37887734; fax: +55 19 32891818.
E-mail address: fcendes@unicamp.br (F. Cendes).
[1] Present address: Whitaker Cardiovascular Institute, Evans Department of Medicine, Boston University School of Medicine, Boston, MA, USA.

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with CVT and their influence on clinical outcome. In addition, we searched whether other clinical, laboratory and neuroimaging features influenced outcome in these patients.

2. Methods

2.1. Subjects

The records of 24 patients with a diagnosis of CVT followed in the Neurology and in the Hematology unit between 1992 and 2002 were revised. We included patients with a clinical hypothesis of CVT (headache, focal neurological deficits, and cranial hypertension) supported by appropriate neuroimaging studies including "delta sign" on cranial computed tomography (CT) or magnetic resonance imaging (MRI), a partial or complete absence of filling of one dural sinus on two projections using gadolinium enhanced T1-wheighted MRI. Magnetic resonance venography (MRV) was used as additional evidence whenever possible.

Patients with CNS infections, patients who did not complete laboratory investigations and patients with CVT secondary to invasive procedures (central venous catheter, neurosurgery proceedings) were excluded from this study.

All patients had a complete neurological examination at admission and during the follow-up period.

2.2. Laboratory investigation

The laboratory investigation performed in all patients included: complete blood count, basic blood biochemistry and urinalysis. Cerebrospinal fluid (CSF) study was performed in all patients in order to exclude central nervous system (CNS) infections. Antinuclear antibodies and antibodies to extractable nuclear antigens were performed when systemic disease was suspected.

The diagnosis of lupus anticoagulant (LA) was based on Kaolim clotting time (KCT) and diluted Russel viper venom (dVV) as screening methodologies. The confirmatory test for LA was carried out by dVV confirmatory test [6]. Anticardiolipin antibodies were determined in serum by an enzyme-linked immunoasorbent assay (ELISA), and the normal range was considered <5 GPL U/ml or MPL U/ml. For all patients more than one sample was obtained in order to avoid a transient LA diagnosis.

The general screening for thrombophilia includes the search for deficiency of protein C and protein S by a clotting assay (Stago®Protein C, Stago®Protein S Stago, France), or antithrombin by an amydolitic assay, using the chromogenic substrate S-2338, according to the manufacturer's instruction (Kabivitrum, Stockholm, Sweden). Detection of inherited thrombophilia risk factors such as factor V Leiden, the prothrombin gene variant (allele 20210 A) and the 677C → T transition in the methylenetetrahydrofolate reductase gene (MTHFR) were carried out as previously described [7–9].

2.3. Imaging investigation

The site and extent of the thrombus and the appearance of associated brain lesions were determined for all patients.

Enhanced CTs were obtained with a conventional scanner (Elscint HeliCat, Elscint, Haifa, Israel; or Somatom AR, Siemmens, Erlangen, Germany). The section thickness was 2.5 mm for the posterior fossa and 5 mm for the supratentorial region. Radiological techniques ranged from 200 to 275 mAs and 100–120 kVp, using a 512 × 512 matrix.

MRIs were performed in a 2T scanner (Elscint Prestige®, Haifa, Israel), with T1 and T2 acquisitions in three orthogonal planes, including T1-weighted spin echo (SE) gadolinium enhanced images. MRI acquisition parameters were: Sagital T1 SE, 6 mm thick, flip angle = 180°; repetition time (TR) = 430, echo time (TE) = 12, matrix 200 × 350, field of view (FOV) = 25 cm × 25 cm; T2-weighted and proton density "fast spin echo" (FSE), 3 mm thick, flip angle = 160°; TR = 4800, TE = 108/18, matrix 256 × 256, FOV = 22 cm × 22 cm; coronal T1-weighted inversion recovery (IR), 3 mm thick, flip angle = 200°; TR = 2800, TE = 14, inversion time (TI) = 840, matrix 130 × 256, FOV = 16 cm × 18 cm or T1-weighted SE; axial T1-weighted SE and T2-weighted fluid-attenuated inversion recovery (FLAIR) images TR = 8500 and 2000 or 100 and 2200, TE = 72 or 90, matrix of 256 × 296 and FOV of 22 versus 22 cm. T1-weighted SE gadolinium enhanced images were obtained in the three orthogonal planes.

MRVs were performed with 2D phase contrast, 1.2 mm thick, flip angle = 28°, TR = 38, TE = 6, matrix 170 × 256, FOV = 17 mm × 23 mm.

2.4. Statistical analysis

Differences in proportions were tested with chi-square test, or Fisher's exact test when required. Confidence intervals and odd ratios were also obtained when indicated.

3. Results

3.1. Demographics

During the study period, 33 patients had an initial diagnosis of CVT based on clinical features. In 24 patients the diagnosis was confirmed with CT or MRI. Of the remaining patients, seven had a final diagnosis of atypical migraine, one had a central nervous system tumor and one had nonconvulsive status epilepticus due to cortical dysgenesis.

There were 18 women and 6 men, with age ranging from 3 to 48 years (mean 29.5 years). Twenty (83%) patients were Caucasians and four (17%) were Afro-Brazilians. The follow-up period ranged between 11 and 145 months (mean 46 months). The patients were followed-up in the Neurology

Table 1
Patients characteristics, risk factors for thrombophilia and outcome

Patient no.	Sex, age at CVT	Clinical symptoms	Thrombosed sinus	Parenchyma involvement	Risk factor for CVT	Neurological outcome
1	F, 47	H, V, meningeal signs, focal deficits, P	SSS, ICV	No	Purperium	Normal
2	F, 35	H, IIIrd np	SSS, TS, SRS	Yes	Factor V Leiden + antithrombin III + MTHFR	H, cognitive dysfunction
3	M, 43	H	TS	No	None	Normal
4	F, 48	DOC, IIIrd np, focal deficits, P	SSS	Yes	Purperium	Cognitive dysfunction
5	M, 3	H	SSS	No	Head trauma	Normal
6	M, 48	H, focal deficits, P	TS, SSS, SIGS	Yes	Prothrombin gene mutation	H, focal deficits
7	M, 3	V, meningeal signs, focal deficits, P	SRS, GS	Yes	Protein C deficiency	Focal deficits
8	M, 7	H, V, DOC, seizures	SSS	No	Nephrotic syndrome	Seizures
9	F, 25	H, V, focal deficits, P	SIGS	No	Oral contraceptive use	Normal
10	F, 23	V, psychosis, DOC, seizures	TS	No	AAFL	Normal
11	F, 24	IIIrd np, DOC, focal deficits, P	ICV	Yes	Oral contraceptive use	Cognitive dysfunction
12	F, 34	H, IIIrd np	TS, SIGS	No	Purperium	Normal
13	F, 43	H, IIIrd np, focal deficits, P	TS, SIGS	No	Oral contraceptive use	Normal
14	F, 35	H	SSS	No	Purperium	Normal
15	F, 40	H	ICV	No	Purperium	Normal
16	M, 36	H, focal deficits, P	SSS	No	None	Normal
17	F, 38	H	ICV	No	Purperium	Normal
18	F, 24	H, seizures, V, focal deficits, P	SSS, SRS	Yes	Prothrombin gene mutation	Seizures, H
19	F, 19	H, psychosis, focal deficits, P	TS, SRS	Yes	SLE, AAFL	Cognitive dysfunction, H
20	F, 35	H, seizures, focal deficits, P	SSS	Yes	AAFL	Seizures, H
21	F, 29	DOC, focal deficits, P	TS	Yes	Head trauma	Focal deficits
22	F, 33	H, V, meningeal signs	SSS	No	Infection	Normal
23	F, 17	H	SSS	No	Oral contraceptive use	H
24	F, 18	H, seizures, V, focal deficits, P	SSS, TS, SIGS	No	None	Normal

IIIrd np: third nerve paralysis; AAFL: antiphospholipid antibodies; CVT: cerebral venous thrombosis; DOC: disturbances of consciousness; F: female; H: new onset of severe headache; ICV: internal cerebral veins; M: male; P: papilledema; SLE: systemic lupus erythematosus; SIGS: sigmoid sinus; SSS: superior sagital sinus; SRS: straight sinus; TS: transverse sinus; V: vomiting.

and Hematology Units of the State University of Campinas (UNICAMP).

3.2. Clinical and laboratory features

The clinical presentation was variable (Table 1), but the most common complaints were headache (75%), vomiting (33%) and disturbances of consciousness (21%). Signs and symptoms of intracranial hypertension were present in 13 (54%), focal signs on neurological examination in 13 (54%) and cognitive abnormalities (aphasia, apraxia, visual agnosia, memory dysfunction) were present in five (21%) patients. Psychosis, associated with focal neurological signs, was the initial manifestation in two (8%) patients.

The mode of onset of symptoms was acute (<48 h) in 10 (42%) patients, subacute (<1 month) in 13 (54%) patients and progressive over several months in one (4%) patient.

Two (8%) patients reported a history of a spontaneous miscarriage before the episode of CVT. Three (13%) patients had had previous arterial or venous thrombotic events in lower limbs. None of the patients reported a family history of thrombophilia.

The probable etiology of CVT could be determined in 21 (88%) patients (Table 1). CVT occurred during pregnancy or after delivery in six (25%) patients. Use of oral contraceptives was the triggering event in four (17%) patients, head trauma in two (8%), nephrotic syndrome in one (4%) and mastoiditis in one (4%) patient. Antiphospholipid syndrome was diagnosed in three (12.5%) patients (primary antiphospholipid syndrome in two and secondary to systemic lupus erythematosus in one). An inherited thrombophilia was identified in four patients (17%). The G20210A in the prothrombin gene was identified in two and protein C deficiency in one patient. Factor V Leiden associated with heterozygous

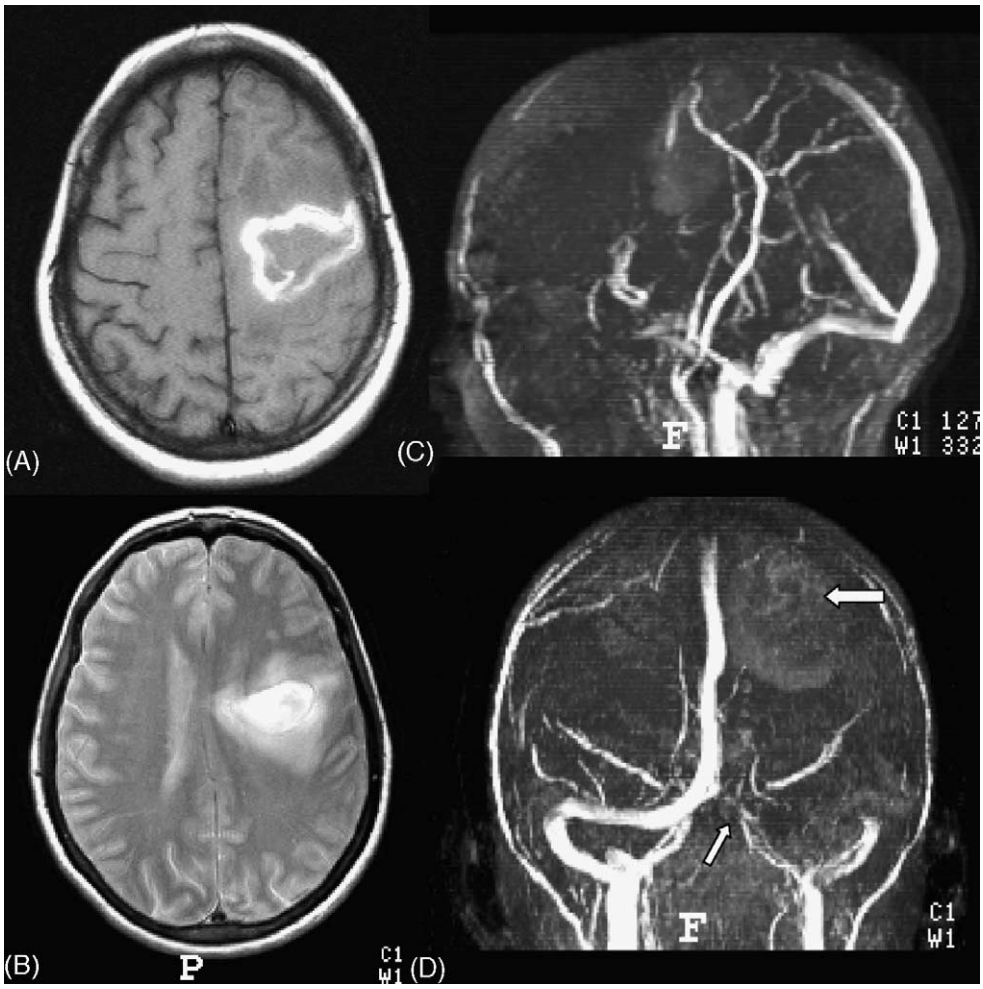

Fig. 1. MRI of patient (#6) with CVT secondary to the G20210A mutation in the prothrombin gene showing axial T1-weighted image (A) and proton density image (B) showing intraparenchymal hemorrhage and perilesional edema in the convexity of the left frontal region secondary to CVT. MRV (C, D) showing a signal dropout of blood flow in the left transverse sinus (small arrow) (D) with hyperintensity (large arrow) corresponding to the area of hemorrhagic infarct. There is also signal dropout in the superior sagital sinus.

antithrombin III deficiency and C677T homozygosity in the MTHFR gene was identified in one patient.

3.3. Neuroimaging features

Neuroimaging studies were available for review in all patients. Cranial CT was performed in all patients, MRI in 17 patients and MRV in seven patients.

CT images were abnormal in 15 (62.5%) patients. Parenchymal involvement was seen in 9 of 24 (37.5%) patients: Eight had hemorrhagic and one had ischemic parenchymal lesions. Signs of diffuse cerebral edema were observed in four (17%) patients. The sites of CVT are shown in Table 1.

MRI scans were performed in 17 patients, including all nine patients who had normal CT scans. All patients with normal CT had abnormal MRI. MRI showed signs of sinus thrombosis in all 17 patients. MRI showed parenchymal lesions in nine patients (Table 1): in all four patients with thrombophilia (Fig. 1), in two of six patients with CVT during purperium (Fig. 2), in one of two patients with a history of head trauma, in one of four patients with CVT associated with the use of oral contraceptives and in one of three patients with antiphospholipid syndrome (Fig. 3). Four patients with diffuse cerebral edema on CT had this diagnosis confirmed by T2-weigheted MRI.

MRV showed a stop in the involved sinus in all seven patients. Hyperintensity, corresponding to parenchymal hemorrhagic infarct, was seen in one patient.

3.4. Treatment

All patients received heparin for 3–5 days followed by oral anticoagulants for 6 months, unless there was an underlying disease carrying a thrombotic risk, in which case anticoagulation was not interrupted. Hemorrhagic infarcts were identified prior to anticoagulation in nine (37.5%) patients. There was no clinical worsening after introduction of heparin and no signs of further intracranial hemorrhage on follow-up scan. Anticoagulation did not cause intracerebral bleeding in those

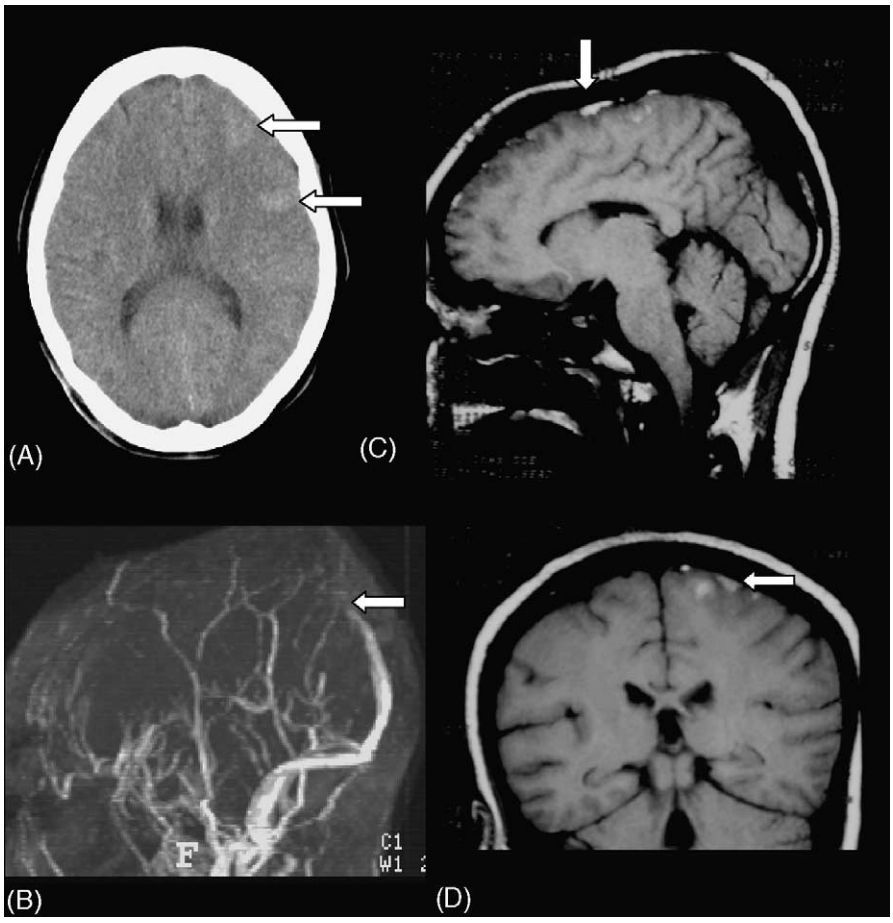

Fig. 2. Imaging of patient (#4) with CVT during puerperium showing (A) cranial CT with an hemorrhagic infarct in the left frontal region (arrows); (B) MRV with signal dropout at the superior sagital sinus (arrow); (C) sagital T1 image (without gadolinium) showing a thrombus in the superior sagital sinus and (D) coronal T1 image showing the thrombus and an hemorrhagic infarct (arrow).

who did not have signs of central nervous system hemorrhage before treatment. Antiepileptic drugs were used in six (25%) patients who had seizures acutely. Antibiotics were given to one (4.2%) patient with mastoiditis.

3.5. Outcome

No fatalities were observed in this cohort. Thirteen (54%) patients were symptom-free at the time of hospital discharge and had no neurological sequelae during follow-up. Eleven (46%) patients, while improving to a considerable extent, continued to suffer from various degrees of neurological impairment, as summarized in Table 1. Migraine-like headache was the most frequent complaint on follow-up and was reported by six (25%) patients. Patients who had focal neurological signs during the acute stage were left with various cognitive (17%) or focal motor deficits (13%). Recurrent symptomatic epileptic seizures (12.5%) were only observed in patients who had focal signs and seizures in the acute stage and occurred in the first year after CVT. None of these patients had optical atrophy secondary to raised intracranial pressure.

Patients with CVT associated with pregnancy, purperium or oral contraceptive use had better outcome than patients with inherited thrombophilia or systemic disease. Five of 17 patients without thrombophilia had neurological sequelae during follow-up compared to six of seven patients with inherited thrombophilia or antiphospholipid syndrome ($p = 0.02$; OR = 14.4; 95% CI = 1.35–152.62).

All patients with signs of parenchymal involvement (hemorrhagic or ischemic) on CT or MRI had neurological sequelae during follow-up ($p = 0.003$; OR = 67.8; 95% CI = 2.12–132.86). The two patients with thalamic involvement had the most severe cognitive deficits. Isolated superficial sagital sinus thrombosis was observed only during pregnancy and purperium in three patients and associated with excellent long-term prognosis.

We found no differences in outcome between patients with acute and subacute CVT onset. None of these patients suffered recurrence of CVT or other type of proven thrombotic events during the follow-up period. Two patients completed uneventful pregnancies after the episode of CVT that occurred during the previous puerperium. Both patients were treated with low-weight heparin during the gestational period

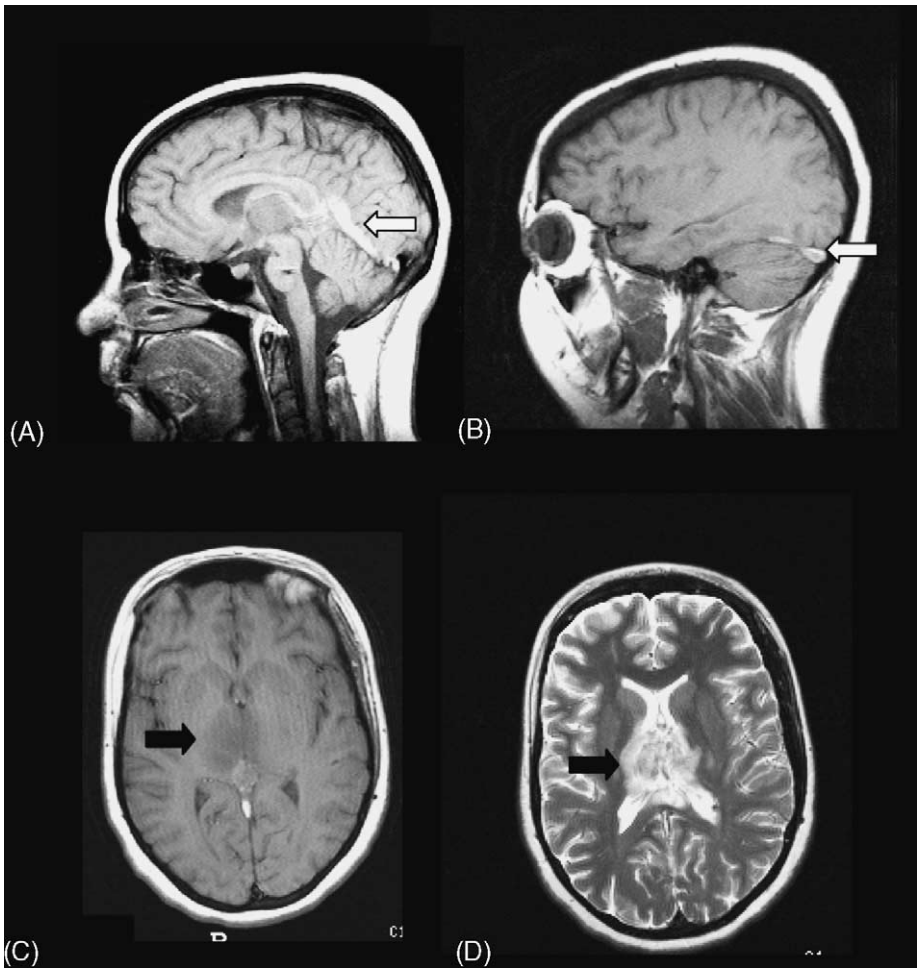

Fig. 3. MRI of patient (#19) with systemic lupus erythematosus and antiphospholipid antibodies showing (A, B) sagital T1 images without gadolinium showing a thrombus (arrow) in the straight (A) and transverse (arrow) (B) sinuses (hyperintense signal); (C) axial T1 image with hypointense signal in thalami (arrow) and (D) axial T2 image with heterogeneous signal intensity, corresponding to bilateral venous infarct and edema in thalami (arrow).

and no thrombotic event was observed during pregnancy or after delivery.

No other clinical variables were associated with worse prognosis in this study.

4. Discussion

Disturbance of cerebral venous drainage due to CVT may lead to reversible or permanent brain lesions [10–18]. The clinical onset is variable and nonspecific, including headache, lethargy, motor or sensory deficits, seizures and, less frequently, neck stiffness and fever. The neurological symptoms and signs encountered in our series were those classically associated with CVT [10–18]. Headache was the most frequent symptom, referred by 72% of patients, as previously reported [10,14–18]. Although disturbance of consciousness is considered a classic sign [1,3–5,10,14–19], in our series only 21% presented with variable degrees of impairment of consciousness.

The recent improvement in MRI techniques and multislice contrast-enhanced CT has improved CVT diagnosis. Cranial CT is still the first examination done in most cases, mostly because it is readily available in most emergency services, and its short scanning time and ability to detect acute hemorrhage [20]. The cord sign and the delta sign in enhanced CT refer to imaging signs suggestive of CVT [20–23]. Conventional CT techniques miss the diagnosis of CVT in up to 40% of the cases, and underestimate both the extent of sinus involvement and the extent of parenchymal involvement [20]. It may also have false positive, especially in young children [20]. CT venography using a multi-slice technique has been reported to be superior to CT [20] and an alternative to MRI and MRV, although not yet used routinely in most services [24]. Contrast-enhanced MR venography [25] is also a new MR technique that provides a set of complete MRV images in a significantly shorter time than conventional MRV sequencing. It also provides greater coverage of the vessels of the head and neck, more extensive small vein details and a better demonstration of intraluminal defects, despite a slightly lower resolution. However, these MR techniques can-

not difference from reversible and irreversible tissue changes. Diffusion-weighted MRI (DWI), on the other hand, may discriminate between areas at risk of undergoing infarction and those, which are going to recover [3]. In our study, DWI was used in only two patients, because most of the patients were diagnosed before DWI technique was available in our service. In addition to new imaging techniques, newer laboratory measurements also increased CVT diagnosis. Although not performed in this study, d-dimer measurement is useful for acute CVT diagnosis. As previously reported [26], values below 500 mg/ml make acute CVT unlikely.

CVT is associated with coagulation defects or risk factors such as hormonal therapy, pregnancy or increased blood viscosity in about 75% of cases [10]. In our series, etiologies were identified in 88% of the patients. Four (17%) of these patients were found to have inherited thrombophilia. Factor V Leiden is the most frequent encountered mutation in patients with CVT. The frequency of this mutation varies according to ethnicity and has been described as being 2% in the overall Brazilian population [7]. In our study, only one (4%) patient was homozygous for the factor V Leiden mutation. The prothrombin G20210A mutation is found at a rate of 0.7% in our population [8]. The finding of two patients with this mutation in this study suggests that it may be associated with an increased risk for CVT. Contrary to previous study [8] we found no elevation of factor VIII plasma level associated with CVT in this study. Other risk factors for CVT could be identified in 20 patients. The frequency of infection was lower than expected, occurring in only 4% of the cases. This most likely reflects a selection bias, since patients with infections in our center are referred to other clinics and symptoms associated with infections may overwhelm the symptomatology of CVT. This prevalence is similar to that observed in one study [10], but less than observed by other authors [17,18]. In contrast, CVT during gestation and purperium was identified in 20% of our series. It is believed that infection and purperium are the main causes of CVT [19,27–29] especially in developing countries [28]. The use of oral contraceptives was referred by four of 18 (22%) female patients, a frequency higher than in the overall Brazilian population. Primary antiphospholipid syndrome was diagnosed in two (8.3%) and antiphospholipid syndrome associated with SLE was identified in one (4.2%) of our patients. No other thrombophilic risk factor could be identified in these four patients.

Although this was a retrospective study, the long-term prognosis of CVT was favorable, as previously described [29–36]. No fatalities were observed in our series. Thirteen of 24 (54%) patients with CVT recovered without evidence of permanent neurological damage. Eleven patients (46%) were left with sequelae: seizures in three, focal neurological signs in three, cognitive deficits in four, and chronic headache in six. Patients with CVT associated with pregnancy, purperium and use of oral contraceptives had a better outcome than patients with inherited thrombophilia or systemic disease. Patients with thrombophilia and systemic disease had a 14.4-fold increase in risk of having neurological sequelae compared with patients with CVT during pregnancy or purperium. On the other hand, patients with parenchymal involvement documented by CT or MRI had a 67.8-fold increase in risk of suffering neurological sequelae, which is in accordance with previously reported findings [29–36]. Patients with thalamic involvement had the worse prognosis, with important cognitive deficits. Isolated superficial sagital sinus thrombosis was observed only during pregnancy and purperium in three patients and associated with excellent long-term prognosis. We found no difference in outcome between patients with acute and subacute CVT onset.

All patients received heparin for 3–5 days followed by oral anticoagulants [37–42]. No clinical worsening after introduction of heparin or signs of further intracranial hemorrhage on follow-up scans was observed in this series. In addition to heparin treatment, local thrombolisis has been reported in small series [4]. The ability to lise the thrombus more rapidly than heparin has made thrombolisis and alternative option in CVT treatment. However, local thrombolisis is not considered first line treatment because of higher risk of cerebral hemorrhage and the absence of correlation between the resolution of thrombosis and clinical improvement. Until further evidence, local thrombolisis should be used when heparin treatment fails [4].

CVT is probably underdiagnosed and should be considered in patients with new onset of severe headache, progressive unexplained cognitive deficit, unexplained seizures and somnolence. The etiology should be investigated thoroughly and MRI with gadolinium or multi-slice contrast-enhanced CT are the exams of choice. MRV may be helpful as a complementary exam when multi-slice contrast-enhanced CT is not available. Due to the high yield of diagnosis and non-invasiveness of MRI and MRV (“MR venography”) or multi-slice contrast-enhanced CT, we believe that conventional cerebral angiography should be reserved for selected cases, particularly in cases of CVT involving only the cortical veins [43,44]. The course of the disease is variable, but patients with parenchymal involvement and with thrombophilia and antiphospholipid syndrome have greater risk of suffering (or sustaining) neurological sequelae. The use of heparin and oral anticoagulants in this series did not predispose to further intracerebral hemorrhage.

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ARTIGO 8

Cerebral and corpus callosum atrophy in systemic lupus erythematosus

Appenzeller S, Rondina JM, Li LM, Costallat LT, Cendes F

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Cerebral and Corpus Callosum Atrophy in Systemic Lupus Erythematosus

Simone Appenzeller, Jane Maryam Rondina, Li Min Li, Lilian T. L. Costallat, and Fernando Cendes

Objective. **To determine cerebral and corpus callosum volumes in patients with systemic lupus erythematosus (SLE), using semiautomatic magnetic resonance imaging (MRI) volumetric measurements, and to determine possible relationships between a reduction in cerebral volume and disease duration, total corticosteroid dose, neuropsychiatric manifestations, and the presence of antiphospholipid antibodies.**

Methods. **We studied 115 consecutive patients with SLE and 44 healthy volunteers. A complete clinical, laboratory, and neurologic evaluation was performed. MRI scans were obtained through a standardized protocol. Sagittal T1-weighted images were used for semiautomatic volumetric measurements. We compared SLE patients with controls using the 2-sample *t*-test. Analysis of variance was used to test for differences between groups, followed by Tukey's post hoc test for pairwise comparisons, when necessary. Linear regression was used to analyze the association between cerebral atrophy and disease duration and total corticosteroid dose.**

Results. **Cerebral and corpus callosum volumes were significantly smaller in patients with SLE compared with healthy volunteers ($P < 0.001$). Reduced cerebral and corpus callosum volumes were related to disease duration ($P < 0.001$). Patients with a history of central nervous system (CNS) involvement more frequently had a reduction in cerebral and corpus callosum volumes ($P < 0.001$). Patients with cognitive impairment had significantly reduced corpus callosum and cerebral volumes when compared with SLE patients without cognitive impairment ($P = 0.001$). Cerebral and corpus callosum volumes were not associated with the total corticosteroid dose or the presence of antiphospholipid antibodies.**

Conclusion. **In patients with SLE, a reduction in cerebral and corpus callosum volumes is associated with disease duration, a history of CNS involvement, and cognitive impairment. The total corticosteroid dose and the presence of antiphospholipid antibodies were not associated with more pronounced atrophy.**

The central nervous system (CNS) is frequently affected in patients with systemic lupus erythematosus (SLE) (1–3). Neuropsychiatric symptoms vary from overt neurologic and psychiatric disorders to more subtle signs and symptoms such as headache, mood disorders, and impairment of cognitive function (1–5). Although clinical assessment is still the cornerstone of the diagnosis of neuropsychiatric SLE, the diagnosis is often difficult and remains presumptive in some patients (1–5). Magnetic resonance imaging (MRI) is known to be more sensitive than computed tomography (CT) for the detection of structural brain abnormalities in patients with neuropsychiatric SLE, because of the excellent soft-tissue contrast observed with MRI and the ability to acquire multiplanar images (6). In patients with SLE, the frequency of cerebral atrophy has been reported to be variable (7–12). Aging, systemic diseases, corticosteroid treatment, and CNS involvement may lead to cerebral atrophy. Various methods for evaluating cerebral atrophy in the setting of SLE have been described. CT and MRI are the most frequently used methods, but most studies (6,8,13–20) have used linear measurements. Although these procedures have been shown to be useful, new methods, such as semiautomatic quantification, have demonstrated superiority in detecting brain abnormalities in several diseases (21–23).

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Simone Appenzeller, MD, Jane Maryam Rondina, Li Min Li, MD, PhD, Lilian T. L. Costallat, MD, PhD, Fernando Cendes, MD, PhD: University of Campinas, Sao Paulo, Brazil.

Address correspondence and reprint requests to Fernando Cendes, MD, PhD, Department of Neurology, University of Campinas-UNICAMP, Cidade Universitária, Campinas SP, Sao Paulo CEP 13083-970, Brazil. E-mail: fcendes@unicamp.br.

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The aim of this study was to analyze cerebral volume in patients with SLE, using validated semiautomated MRI segmentation. We also analyzed corpus callosum volume in order to determine neuronal loss. In addition, we investigated the relationships between cerebral and corpus callosum volumes and disease duration, corticosteroid treatment, CNS involvement, and the presence of antiphospholipid antibodies.

PATIENTS AND METHODS

Patients. A total of 150 consecutive patients fulfilling ≥4 of the American College of Rheumatology (ACR) criteria for a diagnosis of SLE (24), who were seen regularly at our rheumatology unit, were screened prospectively for participation in this study. All SLE patients were followed up by the same investigators (LTLC and SA), using a standardized protocol. We excluded patients who were unable to undergo MRI, such as those with claustrophobia (8 patients) or a pacemaker (2 patients), as well as patients with previous clinical conditions that could influence cerebral atrophy, such as a history of stroke (10 patients), arterial hypertension (5 patients), diabetes mellitus (5 patients), alcohol and drug abuse (1 patient), and malignancy (1 patient). Patients who fulfilled the ACR criteria for rheumatoid arthritis, systemic sclerosis, Sjögren's syndrome (primary or secondary) (3 patients), or other connective tissue disease and those with drug-induced SLE were also excluded. No patient had renal insufficiency or other pathologic conditions that could influence cerebral atrophy. The remaining 115 patients (109 of whom were women) were included in this study.

To analyze neuropsychiatric involvement, we used the classification system for neuropsychiatric lupus proposed by the ACR (25). The patients' medical records were reviewed in order to determine past CNS events. Patients with CNS manifestations secondary to clinical conditions such as infection, arterial hypertension, uremia, diabetes, and drugs were excluded. The control group consisted of 44 healthy volunteers. This study was approved by the ethics committee at our institution, and informed written consent was obtained from each participant.

Clinical, serologic, and treatment features of patients with SLE. Data on sex, age at disease onset, and disease duration were collected for each patient. Disease duration was defined as the time from the appearance of the initial manifestation clearly attributable to SLE until the day of MRI acquisition. All clinical manifestations and laboratory test results were recorded. The following clinical manifestations were analyzed: malar rash, discoid lesions, subacute cutaneous lesions, photosensitivity, oral ulcers, arthritis, serositis, nephritis, neurologic and psychiatric involvement, thrombocytopenia, hemolytic anemia, Raynaud's phenomenon, thrombosis, myositis, lung involvement, and lymphadenopathy.

Nephritis was diagnosed on the basis of proteinuria (>0.5 gm/liter) with abnormal urinary sediment and/or histologic findings. Nephrotic syndrome was defined as proteinuria in excess of 3.5 gm/day. Hematologic alterations were ascribed to lupus only in the absence of bone marrow suppression (leukopenia <4,000 cells/mm^3; thrombocytopenia <100,000/mm^3; hemolytic anemia with positive Coombs' test). Antinuclear antibodies (ANAs) were determined by indirect immunofluorescence using HEp-2 as the substrate, and a titer >1:40 was considered positive. Anti–double-stranded DNA antibodies were determined by indirect immunofluorescence using *Crithidia* as substrate, and a titer >1:10 was considered positive. Precipitating antibodies to extractable nuclear antigen, including Ro/SSA, La/SSB, and Sm, were detected by immunodiffusion and/or microhemagglutination. Anticardiolipin antibodies of the IgG and IgM isotypes were measured by enzyme-linked immunosorbent assay, as previously described (26). Lupus anticoagulant activity was detected by coagulation assays in platelet-free plasma obtained by double centrifugation, following the recommendation of the Subcommittee on Lupus Anticoagulant of the Scientific and Standardization Committee of the International Society of Thrombosis and Homeostasis (27).

CNS manifestations were classified according to ACR case definitions for neuropsychiatric lupus (25) and were recorded as being present (the patient had active CNS involvement or a history of CNS involvement) or absent (the patient never presented with CNS involvement). A complete neurologic examination (including cognitive and psychiatric charts) was prospectively applied to all patients in order to identify CNS involvement. The mini-mental state examination (28) was applied to all participants.

All patients and controls underwent a battery of standardized neuropsychological tests in order to screen for possible impairments in 1 or more of the following cognitive domains: simple attention, complex attention, memory, visual–spatial processing, language, reasoning/problem-solving, psychomotor speed, and executive functions (29–32). The individual test results were converted into standard scores, which were compared with the available normative data (29–32). Regarding any of the 8 cognitive domains, subjects with a total score ≥2 SD lower than the normative value were considered to be impaired. Cognitive dysfunction was classified as mild if the patient had deficits in fewer than 3 dimensions, as moderate if there were deficits in 3 or 4 dimensions, and as severe if the patient had deficits in at least 5 dimensions (32,33).

The assessment of depression was based on a clinical interview and the Beck Depression Inventory (BDI) (34,35). On the BDI, scores of 10–17 are indicative of mild depression, scores of 18–24 indicate moderate depression, and scores >24 indicate the presence of severe depression. Anxiety was evaluated using the Hospital Anxiety and Depression scale (36). The presence of psychosis was determined using the Brief Psychiatric Rating Scale (37).

A history of CNS involvement was determined by reviewing the medical charts of patients. Disease activity was measured by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), and a score of >8 represented active disease (38). Cumulative SLE-related damage in all patients was determined using the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index (SDI) (39) at the time of MRI.

The total doses of corticosteroids and other immunosuppressant medications used since the onset of disease were calculated by careful review of the medical charts. Doses of oral and parenteral corticosteroids were analyzed and converted to the equivalent doses of prednisone. The cumulative

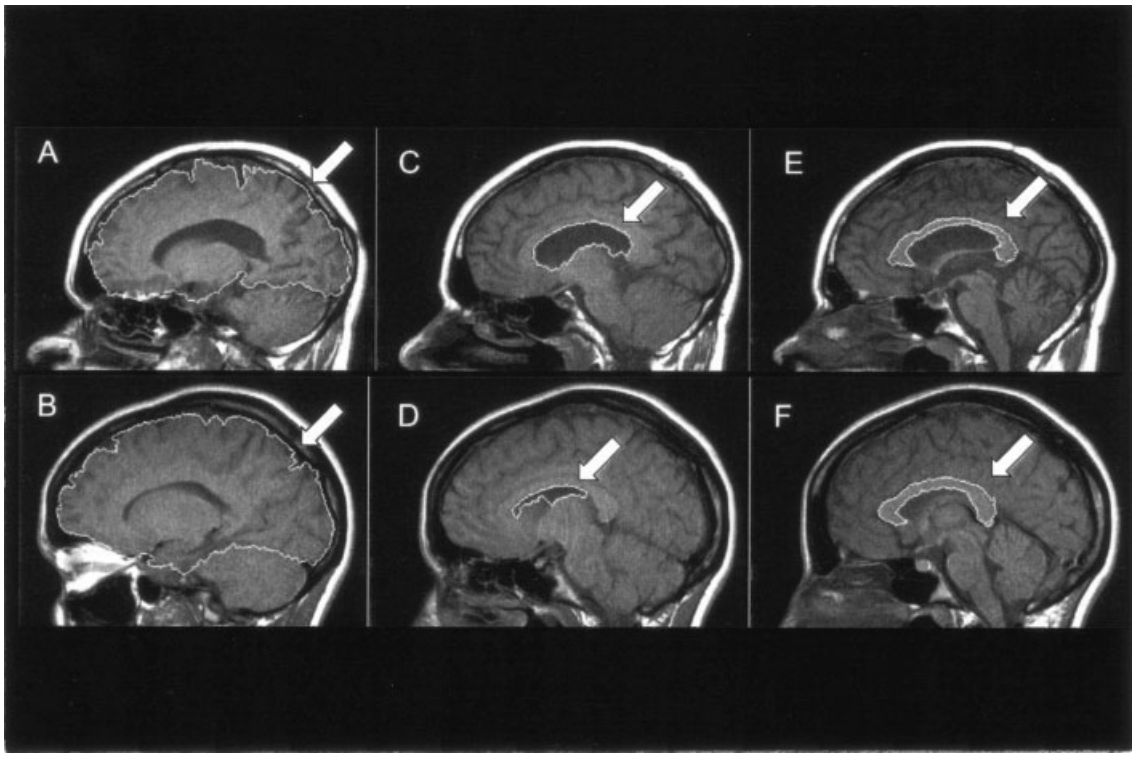

Figure 1. Example of segmentation of cerebral structures using the Neuroline program. **A** and **B,** Cerebral volume in a patient and a healthy control subject, respectively. **C** and **D,** Lateral ventricle volume in a patient and a healthy control subject, respectively. **E** and **F,** Corpus callosum volume in a patient and a healthy control subject, respectively.

dose of corticosteroids was calculated as the sum of daily doses versus the number of days of treatment.

MRI acquisition. All subjects underwent MRI examination with an Elscint Prestige 2T scanner (Haifa, Israel). Sagittal T1-weighted images (6-mm thick, flip angle 180°, repetition time 430 msec, echo time 12 msec, matrix 200 × 350 pixels, field of view 25 × 25 cm) were analyzed using a semiautomated computer program for quantifying cerebral, corpus callosum, and lateral ventricle volumes; this program (Neuroline) was developed in our laboratory and was validated against standard MRI segmentation programs (40) (Figure 1). Quantification and analysis were performed by 1 investigator (SA). The evaluation was cross-checked by another neurologist with experience in MRI analysis (FC). The measurements were done twice in 40 patients, and the intraobserver variation was determined ($r = 0.94$).

The corpus callosum and ventricle volumes were corrected for intracranial volume using the mean cerebral volume of the control group, as follows: normalized structure volume = (patients' structure volume × mean cerebral volume of volunteers)/patients' cerebral volume. Standardized scores that represent the number of SDs away from the mean of the control group (Z scores) were determined for all analyzed structures. Atrophy of a given cerebral structure was determined to be present if the Z score of the normalized volume was less than or equal to −2.

Statistical analysis. We compared patients with SLE and controls, using the 2-sample *t*-test. We further subdivided SLE patients in 2 groups: patients with and those without CNS involvement. We performed analysis of variance to test for differences among controls and these groups, with Tukey's pairwise post hoc comparisons. This procedure includes corrections for multiple comparisons. Linear regression was used to analyze the association between cerebral volume and corpus callosum volume with disease duration and total corticosteroid dose. Volumetric measurements were expressed in cubic centimeters and are shown as the mean ± SD. *P* values less than 0.05 were considered significant.

RESULTS

Characteristics of the participants. One hundred fifteen SLE patients met the inclusion criteria; the mean ± SD age of the patients was 33.5 ± 12.5 years (range 12–60 years). One hundred nine patients were women and 6 were men. The mean ± SD duration of disease was 66.5 ± 58.5 months (range 1–372 months). The control group consisted of 44 normal volunteers (42 of whom were women) with a mean ± SD age of 33.8 ±

13.7 years (range 20–63 years). Patients and controls were statistically comparable in terms of age and sex.

Clinical, laboratory, and treatment features of patients. Antiphospholipid antibodies were positive in 32 patients. Active SLE was observed in 56 patients, and in this group the mean ± SD SLEDAI score was 14.5 ± 6.3 (range 9–20). One hundred thirty-three CNS events were observed in 72 patients (Table 1). Active CNS disease at the time of MRI was observed in 36 of the 72 patients with a history of CNS involvement. At the time of MRI, 105 patients were receiving corticosteroid therapy. The remaining 10 patients had not received corticosteroid therapy for at least 3 months. The mean ± SD SDI score was 2.2 ± 1.9 (range 0–5).

MRI findings in the individual analysis. Cerebral atrophy was observed in 10 patients (8.7%), and corpus callosum atrophy was observed in 25 patients (21.7%). Abnormal ventricular enlargement was observed in 12 patients (10.4%).

MRI findings in the group analysis. The mean ± SD cerebral volume in patients with SLE was 8,694.7 ± 696.4 cm^3, compared with 9,514.1 ± 165.8 cm^3 in healthy volunteers ($P = 0.002$). The mean ± SD normalized volume of corpus callosum was 94.1 ± 18.6 cm^3 in SLE patients compared with 112.0 ± 16.1 cm^3 in healthy volunteers ($P < 0.001$). There was no statistically significant difference ($P = 0.08$) between the mean ± SD lateral ventricle volume in SLE patients (233.7 ± 265.4 cm^3) and that in healthy volunteers (160.5 ± 62.9 cm^3).

When we analyzed SLE patients with CNS involvement and those without CNS involvement, we observed that the cerebral volume was reduced in SLE patients, independently of the presence of CNS involvement, when compared with healthy controls ($P = 0.003$) (Figure 2). No difference in relation to the cerebral volume in patients with and those without CNS involvement was observed. When we analyzed corpus callosum volume, we observed that SLE patients with CNS involvement had a more important corpus callosum volume reduction when compared with SLE patients without CNS involvement ($P < 0.001$) and healthy controls ($P < 0.001$). No statistically significant difference between SLE patients without CNS involvement and healthy controls was observed (Figure 3). When we further subdivided patients with CNS involvement into those with active involvement and those with a history of CNS involvement, we observed that a reduction in corpus callosum volume was associated with a history of CNS involvement ($P < 0.001$) but not with active CNS involvement.

No statistically significant difference between cerebral and corpus callosum volumes and age ($P = 0.4$) and the presence of antiphospholipid antibodies ($P = 0.1$) was observed. Hyperintense areas and areas of cerebral microinfarcts were observed in 53 patients. There was no statistically significant difference between the presence of these findings and cerebral and corpus callosum atrophy ($P = 0.1$).

We also observed that the normalized cerebral

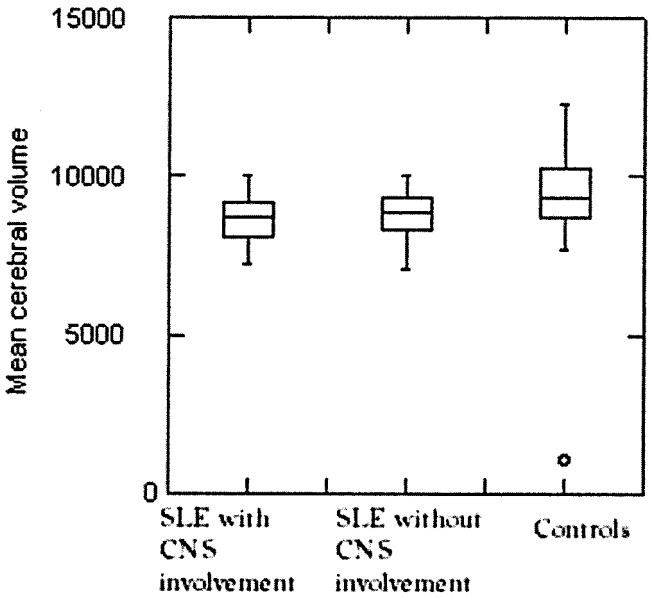

Figure 2. Cerebral volume (in cm^3) in 72 patients with systemic lupus erythematosus (SLE) and central nervous system (CNS) involvement, 43 SLE patients without CNS involvement, and 44 healthy volunteers. Data are presented as box plots, where the boxes represent the 25th to 75th percentiles, the lines within the boxes represent the 50th percentile, and the lines outside the boxes represent the minimum and maximum values.

Table 1. Neuropsychiatric manifestations in 72 patients

Neuropsychiatric manifestation	Central nervous system events*
Headache	40 (30)
Cognitive impairment	36 (27.1)
Seizures	15 (11.3)
Mood disorder	14 (10.5)
Acute confusional state	10 (7.5)
Psychosis	6 (4.5)
Mononeuropathy	4 (3.0)
Cranial neuropathy	3 (2.3)
Myelopathy	3 (2.3)
Aseptic meningitis	1 (0.8)
Movement disorder	1 (0.8)
Total number of events	133 (100)

* Values are the number (%).

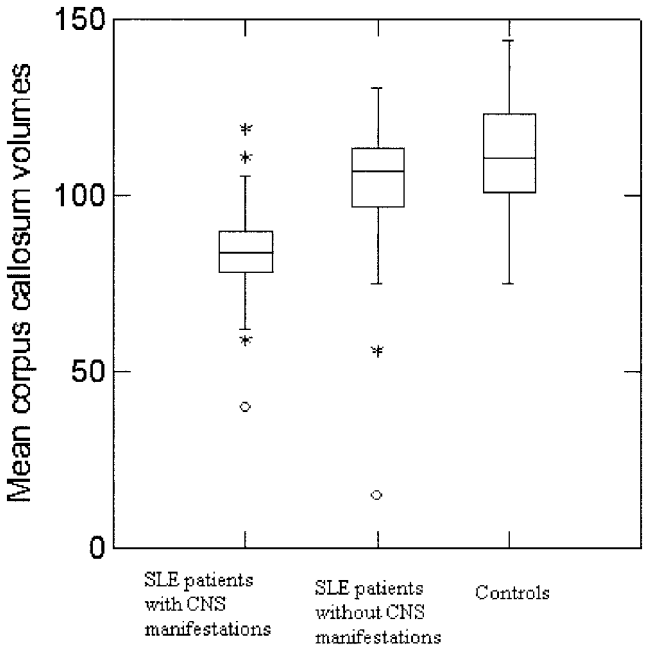

Figure 3. Corpus callosum volume (in cm^3) in 72 SLE patients with CNS involvement, 43 SLE patients without CNS involvement, and 44 healthy volunteers. Data are presented as box plots, where the boxes represent the 25th to 75th percentiles, the lines inside the boxes represent the 50th percentile, and the lines outside the boxes represent the minimum and maximum values. Asterisks and circles represent outliers. See Figure 2 for definitions.

and corpus callosum volumes correlated with the total number of past CNS events ($r = 0.45$, $P < 0.001$) and with disease duration ($r = 0.81$, $P < 0.001$). We did not observe any correlation between cerebral and corpus callosum volumes and total corticosteroid dose or SDI scores.

Functional analysis. We observed cognitive impairment in 35 patients (severe in 20 patients, moderate in 10 patients, and mild in 5 patients). Corpus callosum and cerebral volumes were significantly reduced in patients with cognitive impairment compared with patients without cognitive impairment ($P = 0.001$). Patients with severe cognitive impairment had a more pronounced reduction of corpus callosum volume than did patients with moderate or mild cognitive impairment ($P = 0.002$). In relation to different domains of cognitive dysfunction, no statistically significant difference between the groups was noted. In relation to other individual CNS manifestations, no statistically significant difference between groups was noted ($P = 0.3$).

DISCUSSION

We determined cerebral volume using an objective and validated method. We also performed corpus callosum segmentation as a measure of white matter loss. Our results showed that patients with SLE had significantly reduced cerebral and corpus callosum volumes when compared with normal volunteers. This reduction was related directly to the presence and the total number of CNS manifestations and was more pronounced in patients with a history of CNS manifestations. This reduction was independently related to disease duration. Corpus callosum atrophy was more severe in patients with cognitive impairment compared with patients without cognitive impairment. There was no relationship between cerebral and corpus callosum volumes and the estimated lifetime corticosteroid dose or the presence of antiphospholipid antibodies. Although it is possible that aging had some effect on brain atrophy (41), this effect was minimized by the comparison with healthy volunteers within the same age range.

Some studies have suggested that corticosteroid therapy is the major feature associated with cerebral atrophy in patients with SLE (6,10), whereas other investigators concluded that cerebral atrophy is not related to treatment (2–5), or that both disease and corticosteroids may contribute to cerebral atrophy (5,10). In our individual MRI analyses, we observed cerebral atrophy in 8.7% of patients with SLE. This frequency is less than that previously reported (6–11,42,43) but is probably attributable to the different method used in our study. By using semiautomated segmentation and defining atrophy as a volume score 2 SD lower than the volume score for the control group, only more pronounced atrophy was considered.

Patients with a history of CNS involvement had smaller cerebral and corpus callosum volumes compared with patients without a history of CNS manifestations. An inflammatory process, cytokines, or locally produced autoantibodies may account for these findings. In contrast, the presence of active CNS involvement did not influence brain volume. Antiphospholipid antibodies are involved in small-vessel disease and are associated with strokes secondary to microembolism and therefore could be associated with more severe cerebral atrophy (44–47). In this cross-sectional study, neither the presence of antiphospholipid antibodies nor the presence of microinfarcts on MRI influenced the total cerebral or corpus callosum volume. We also did not observe an association between SDI scores and a reduction in cerebral and corpus callosum volumes. However, the influence of antiphospholipid antibodies and SDI scores in the progression of atrophy has to be determined in followup studies. We used only screening tests in order to determine cognitive dysfunction; therefore, the num-

ber of patients with mild cognitive dysfunction is rather low.

In conclusion, a reduction in cerebral and corpus callosum volumes was associated mainly with the duration of SLE and a history of CNS involvement. The presence of active CNS involvement did not influence cerebral and corpus callosum volumes. The rate of progression of cerebral atrophy and the predictor variables for clinical CNS manifestations of SLE remain to be determined.

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ARTIGO 9

Longitudinal analysis of gray and white matter loss in patients with systemic lupus erythematosus

Simone Appenzeller, Leonardo Bonilha, Pablo A Rio, Li Min Li, Lilan Tereza Lavras Costallat, Fernando Cendes

Longitudinal analysis of gray and white matter loss in patients with systemic lupus erythematosus

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Longitudinal analysis of gray and white matter loss in patients with systemic lupus erythematosus

Simone Appenzeller MD[1, 2], Leonardo Bonilha, MD, PhD[3], Pablo A Rio [2], Li Min Li, MD, PhD[2, 4], Lilan Tereza Lavras Costallat MD, PhD [1], Fernando Cendes MD, PhD [2, 4]

[1] Rheumatology Unit

[2] Neuroimaging Laboratory

[4] Department of Neurology

State University of Campinas, Brazil

[3] Departments of Neuropsychiatry and Communication Sciences and Disorders

University of South Carolina, USA

Running Title: VBM of SLE

Address all correspondence to: Dr Fernando Cendes, Department of Neurology, State University of Campinas (UNICAMP), Cidade Universitária Zeferino Vaz, CEP 13083970 Campinas-SP-Brazil

Tel: +55 1937887734

Fax: +55 1937887483

E-mail: fcendes@unicamp.br

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Abstract

Cerebral atrophy has been described to occur in systemic lupus erythematosus (SLE) with variable frequency. The aim of this study was to determine white and gray matter abnormalities in brain magnetic resonance imaging (MRI) of patients with SLE and to determine if these abnormalities progress over a one year period. Seventy-five patients with SLE and 44 healthy age and sex-matched controls were enrolled in this study. T1-weighted volumetric images were used for voxel based morphometry (VBM) analyses. SLE patients exhibited a significant reduction in white matter and gray matter volume compared to controls (p=0.001). Follow-up images, after an average interval of 19 months, revealed a progressive white matter and gray matter atrophy (p=0.001). Reduced white and gray matter volume was associated with disease duration and the presence of antiphospholipid antibodies. Patients with severe cognitive impairment had a more pronounced white and gray matter reduction than patients with moderate cognitive impairment. Total corticosteroid dose was associated with gray matter reduction and not with white matter loss in SLE patients. We concluded that brain tissue loss associated with SLE is significant and progresses over a relatively short period of time. Disease duration, the presence of antiphospholipid antibodies and cognitive impairment were associated with white and gray matter loss. Corticosteroid was associated only with gray matter atrophy.

Introduction

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease (Feinglass et al., 1976; Denburg & Denburg, 2003; Adelmann et al., 1986) with frequent central nervous system involvement (Waterloo et al., 1999; Omdal et al., 1989; Weisberg et al., 1986; Carette et al 1982; Sibbitt et al 1989; Cotton et al 2004; Csepany et al., 2003; Zanardi et al., 2001). Several methods, including computer tomography (CT) (Waterloo et al., 1999; Omdal et al., 1989; Weisberg et al., 1986; Carette et al., 1982) and magnetic resonance imaging (MRI) (Sibbitt et al., 1989; Cotton et al., 2004; Csepany et al., 2003;

Zanardi et al., 2001), have been applied to analyze structural abnormalities and cerebral atrophy in SLE. MRI is known to be more sensitive and accurate than CT for the detection of anatomic brain abnormalities in patients with neuropsychiatric SLE (Sibbitt et al., 1989; Huizinga et al., 2001).

Cerebral atrophy has been described to occur in SLE with variable frequency (Waterloo et al., 1999; Omdal et al., 1989; Weisberg 1986; Carette et al., 1982; Sibbitt et al., 1989; Cotton et al., 2004; Csepany et al., 2003; Zanardi et al., 2001, Hachulla et al., 1998; Chinn et al., 1997; Baum et al., 1993), but its exact cause remains unclear. For instance, brain pathology in SLE may be due to axonal damage secondary to axonal injury. Axonal injury is associated with neuronal dystrophy through both anterograde and retrograde changes. Altogether, direct cortical pathology or cortical neuronal changes related to white matter pathology can contribute to the brain atrophy in SLE, as previously described in MS (Losseff et al., 1996; Evangelou et al., 2000; Bjartmar et al., 2001).

Several studies have analyzed the frequency of cerebral atrophy in SLE (Waterloo et al., 1999; Omdal et al., 1989; Weisberg 1986; Carette et al., 1982; Sibbitt et al., 1989; Cotton et al., 2004; Csepany et al., 2003; Zanardi et al., 2001; Hachulla et al., 1998; Chinn et al., 1997; Baum et al., 1993). In a previous study (Appenzeller et al., 2005) we have shown that there is a different pattern of white matter atrophy when compared to whole brain atrophy, including different clinical implications. Measurements of brain volume are sensitive to both neuronal and axonal loss. Total and regional brain atrophy can be accurately assessed from conventional T1-wheighted images by means of computational methods allowing automatic or semiautomatic measurements of cerebral volumes (Losseff et al., 1996; Rudick et al., 1999; Fox et al., 2000; Smith et al., 2002). Voxel-based morphometry (VBM) is an automated method used for characterizing regional cerebral volume and tissue volumes differences in structural MRI (Ashburner & Friston, 1997; Ashburner & Friston, 2000; Ashburner et al., 2001; Friston et al., 1995; Genovese et al., 2002).

The purpose of this study is to investigate abnormalities in volume of white and gray matter in SLE patients using VBM. We also aim to determine clinical factors associated with SLE that may contribute to regional and white matter atrophy. Furthermore,

we aim to investigate, using a longitudinal design, if there is a significant progression of regional brain abnormalities in SLE.

Methods

Patients

Eighty nine consecutive patients with SLE, with four or more criteria for SLE (Tan et al., 1982), seen regularly at our Rheumatology Unit, were screened prospectively to participate in the study. All SLE patients were followed using a standardized protocol and followed by the same investigators in the Rheumatology Unit (LTLC, SA). We excluded patients that were not able to undergo MRI, such as patients with claustrophobia (2 patients) and pacemaker (1 patients), as well as patients with previous clinical conditions that could influence cerebral atrophy, such as history of stroke (2 patients), arterial hypertension (2 patients), diabetes mellitus (1 patients), alcohol and drug abuse (0 patient), and malignancy (0 patient). Patients who fulfilled the American College of Rheumatology (ACR) criteria for rheumatoid arthritis, systemic sclerosis, Sjögren syndrome (primary or secondary) (8 patients, 6 associated with other exclusion criteria) or other connective tissue disease and with drug-induced SLE were also excluded. There were no patients with renal insufficiency, or other pathologies that could influence cerebral atrophy. The remaining 79 patients (71 women) were included in this study.

We used the classification proposed by the ACR to analyze neuropsychiatric involvement (ACR 1999). We considered solemnly primary central nervous system (CNS) involvement.

Controls

The control group consisted of 44 healthy controls with age and gender distribution similar to the patients' group.

All patients and controls agreed in participate in the study and signed a written informed consent form, approved by our local ethics committee.

Clinical, serologic and treatment features of SLE patients

Data on gender, age at disease onset and disease duration were collected for each patient. Disease duration was defined as the initial manifestation clearly attributable to SLE until the day of MRI acquisition. All clinical manifestations and laboratory test findings were recorded. Nephritis was diagnosed on the basis of proteinuria exceeding 0.5 g/L with abnormal urinary sediment and/or histological findings. Nephrotic syndrome was defined as proteinuria in excess of 3.5 g/day. Hematologic alterations were ascribed to lupus only in the absence of bone marrow suppression (leukopenia <4000 cells/mm3; thrombocytopenia <100.000/mm3; hemolytic anemia with positive Coombs test). Antinuclear antibodies (ANA) were determined by indirect immunofluorescence using Hep 2 as the substrate and regarded as positive if higher than 1:40. Anti-double-stranded DNA (AdsDNA) antibodies were determined by indirect immunofluorescence using Chrithidia as substrate and considered positive if higher than 1:10. Precipitating antibodies to extractable nuclear antigens (ENA), including Ro (SSA), La (SSB) and Sm were detected by immunodiffusion and/or microhemagglutination. Anticardiolipin antibodies (aCL) of the IgG and IgM isotypes were measured by the ELISA method as described (Brandt et al., 1995). Lupus anticoagulant (LA) activity was detected by coagulation assays in platelet free plasma obtained by double centrifugation, following the recommendation of the subcommittee on LA of the Scientific and Standardization Committee of the International Society of Thrombosis and Homeostasis (Harris et al., 1987). CNS manifestations were recorded following ACR case definitions (ACR 1999) and divided into present (active or past history of CNS involvement) or absent (never presented CNS involvement). A complete neurological examination, as well as cognitive and psychiatric charts, was prospectively applied to all patients in order to identify CNS involvement. Mini Mental State Examination (Folstein et al., 1975) was applied to all participants.

All patients and controls were submitted to a battery of standardized neuropsychological tests in order to screen for possible impairment in one or more of the

subsequent cognitive domains: simple attention, complex attention, memory, visuo-spatial processing, language, reasoning/problem solving, psychomotor speed, and executive functions (Spranoel 1992; Wechsler 1986; Dellis et al., 1987; Lezak 1995). The individual test results were converted into standard scores, which were compared with the available normative data (Spranoel 1992; Wechsler 1986; Dellis et al., 1987; Lezak 1995). Regarding any of the eight cognitive domains, subjects with a total score of two or more standard deviations (SD) below the normative value were considered to be impaired. Cognitive dysfunction was classified as mild if there were deficits in less than three dimensions, as moderate if there were deficits in three or four dimensions, and as severe if there were deficits in at least five dimensions (Heaton et al., 1993).

Assessment of depression was based on clinical interview and the Beck Depression Inventory (BDI) (Beck &Beamesderfer 1993; Beck et al., 1974). On BDI, scores from 10 to 17 were considered to indicate mild depression, from 18 to 24 moderate depression, and greater than 24 severe depression. Anxiety was evaluated by anxiety through the Hospital Anxiety and Depression scale (Herrmann 1997). The presence of psychosis was determined through the Brief Psychiatry Rating Scale (aBPRS) (Overall et al., 1984).

We reviewed the medical charts of patients to determine past history of CNS involvement.

Disease activity was measured by systemic lupus disease activity index (SLEDAI) and considered active with scores higher than eight (Bombardier et al.,1992). Cumulative SLE-related damage was determined by Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI) (Gladman et al., 1997) in all SLE patients at time of MRI.

Total dose of corticosteroids and other immunosuppressant medications used since the onset of disease were calculated by data obtained by careful review of the medical charts. Four patients with incomplete charts were excluded from the analysis. Doses of oral and parenteral corticosteroids were analyzed and the doses converted to the equivalent doses of prednisone to homogenize the data. The cumulative dose of corticosteroids used was calculated by the sum of daily dosages versus time (days) of treatment.

Therefore, 75 patients (70 women) were eligible for this study. MRIs were repeated in these 75 patients after a mean follow-up time of a minimum of 12 months.

Structural MRI scanning protocol

MRI was performed on a 2 Tesla scanner (Elscint Prestige). A volumetric structural MRI was acquired on each subject using a T1-weighted gradient-echo sequence, with slice thickness of 1 mm (TR=22ms, TE=9ms, flip angle=35o, matrix=256x22).

Data pre-processing and analysis

Data were analyzed using SPM 2 (http://www.fil.ion.ucl.ac.uk/spm/). Before processing, all the structural images were checked for artifacts, and when present, these images were excluded. Images were then transformed from Dicom to analyze format using MRIcro (www.mricro.com). VBM of MRI data involves several fully automated pre-processing steps, including spatial normalization of all images to the same stereotactic space, segmentation into white and gray matter and cerebrospinal fluid compartments, correction for volume changes induced by spatial normalization (modulation) and smoothing. Spatial normalization was performed by matching the individual's image to a standard template by estimating the optimum 12-parameter affine transformation (Smith et al., 2002; Ashburner & Friston 2000) to correct for global brain shape differences (Ashburner & Friston 1997). The spatially normalized images were then partitioned into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) by using segmentation in-built SPM2 routines. Images were modulated to correct for spatial deformation induced by spaced normalization (Good et al., 2001). Segmented white and gray matter modulated images were smoothed with a 10-mm full width at half maximum (FWHM) Isotropic Gaussian Kernel, rendering the data more normally distributed.

VBM statistical analysis

Normalized, segmented, modulated and smoothed data were analyzed using statistical parametric mapping (SPM 2) (Ashburner et al., 2001). Regional specific differences in white matter between groups were assessed using a two-tailed contrast, namely testing for an increased or decreased probability of voxel being white or gray matter. This analysis included grand mean scaling and proportional threshold masking and implicit masking. A p-value of 0.001, corrected for multiple comparisons using FDR (False Discovery Rate) (Friston et al., 1995) was used, with an extended threshold of clusters of at least 32 contiguous voxels. Stereotaxic coordinates were visually confirmed and further re-assessed using the Talairach Daemon client (http://ric.uthscsa.edu/projects/talairachdaemon.html).

Results

Demographic data

Seventy five patients with SLE with mean age of 32.3 years (range 18-60 years, SD=12.5) met inclusion and exclusion criteria and were included in the analysis. Seventy patients were women and 5 were men. The control group consisted of 44 healthy volunteers (40 women) with mean age 33.8 (range 18-63, SD=13.7 years).

Clinical, laboratory and treatment features

The disease duration ranged between 1 and 340 months [mean 64.5 (SD=53.5)]. Active SLE disease at the time of MRI scan was observed in 36 of 75 (48%) patients with mean SLEDAI score of 15.3 (range 9-24; SD=8.3). At the dates of MRI, all patients were on steroid use. Antiphospholipid antibodies were positive in 28 patients. 78 episodes of CNS manifestations were observed in 36 patients. Active CNS disease at the time of MRI scan was observed in 15 of 36 patients with CNS involvement. Mean SLICC/ACR DI scores were 2.0 (range 0-7; SD=2.1).

White and gray matter abnormalities

We observed a significant reduction in white and gray matter volume, especially in the corpus callosum, frontal, occipital, temporal lobes, limbic areas and cerebellum of SLE patients when compared to controls (p=0.001) (Figure 1; Table 1). Reduced white and gray matter volume was associated with disease duration (Table 2) and the presence of antiphospholipid antibodies (Table 3). When we compared SLE patients with CNS involvement to SLE patients without CNS involvement and healthy volunteers we observed that the first had a more important white and gray matter reduction than the other two groups (p=0.001) and healthy controls (p=0.001). No difference between SLE patients without CNS involvement and healthy controls was observed. When we further subdivided patients with CNS involvement in active and past history of CNS involvement we observed a more pronounced voxel reduction in the corpus callosum region in patients with past history (Table 4) (p=0.001) and not with active CNS involvement. SLICC/ACR DI scores correlated strongly with the degree of white matter reduction, but when cognitive dysfunction was excluded from the SLICC scores, no difference in white and gray matter reduction of SLE patients was observed. Patients with severe cognitive impairment had a more pronounced white and gray matter reduction than patients with moderate cognitive impairment (Table 5). Total corticosteroid dose was associated with gray matter reduction and not with white matter loss in SLE patients (Table 6).

No relation to disease activity, clinical or laboratory manifestations was observed. We also did not observe an association between age and white matter volume in patients and controls.

Follow-up study

MRI were repeated after a mean follow-up time of 19 months (SD=1.2; range 12-24 months) in all patients included in this study. Analyzing these images we observed a significant reduction in white matter, especially in the frontal and posterior part of the corpus callosum (p=0.001). When we analyzed gray matter, we observed a more

widespread reduction in gray matter in the frontal, dorsolateral and medial temporal lobe (p=0.001) (Table 7).

Discussion

In agreement with several studies (Waterloo et al., 1999; Omdal et al., 1989; Weisberg et al., 1986; Carette et al., 1982; Sibbitt et al., 1989; Cotton et al., 2004; Csepany et al., 2003; Zanardi et al., 2001, Hachulla et al., 1998; Chinn et al., 1997; Baum et al., 1993, Appenzeller et al., 2005) we found cerebral atrophy in patients with SLE when compared to healthy volunteers with similar and gender distribution. We observed that this atrophy was related to both white and gray matter atrophy.

MRI of healthy elderly adults frequently reveals corpus callosum atrophy (Black et al., 2000; Hampel et al., 1998; Janowsky et al., 1996). The largest numbers of neurons projected into corpus callosum are those found in the large pyramidal cells of cortical layer III-IV of the contralateral hemisphere (Leys et al., 1991). Cerebral ischemia may result in damage to neurons in layer III (Leys et al., 1991), thus leading to Wallerian degeneration of the corpus callosum. Therefore corpus callosum atrophy may be considered a marker of neuronal loss (Yamanoushi et al., 1993). In our study, a more pronounced white matter reduction was observed in the corpus callosum and frontal cortex in patients with CNS involvement of SLE. This finding can be explained by locally produced inflammatory mediators may cause axonal injury. Furthermore, we demonstrated that atrophy is progressive in follow up MRIs.

We also observed a substantial reduction of gray matter in SLE patients when compared to controls. Gray matter atrophy was widespread and more diffuse that white matter loss. Gray matter atrophy was significant in the frontal, dorsolateral and medial temporal lobe regions. In addition, gray matter loss was associated with disease duration, number of CNS manifestations and total corticosteroid dose. Longitudinally, gray matter atrophy in these areas was also progressive and associated with cumulative corticosteroid dose.

We previously demonstrated corpus callosum and cerebral atrophy in SLE patients using a semi-automated method (Appenzeller et al., 2005). In this present study using VBM, we confirm our previous findings, but we also demonstrated that the pattern of white and gray matter in patients with SLE is associated with different clinical profiles, and varies in intensity across patients.

The observation that cerebral atrophy is not uniform in all SLE patients and that some cerebral structure may be more affected than others may help determining the etiology of CNS involvement in SLE. We determined that brain tissue loss associated with SLE is not only significant, but progresses over a relatively short period of time. The fact that some clinical variables associated with SLE further increase brain atrophy can help elucidate the mechanisms underlying brain damage in SLE. In particular, the understanding of which mechanisms are primarily involved with brain atrophy may dictate emphasis on their clinical control.

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Table 1. Brain sites where gray and white matter volumes were observed in patients with SLE compared to controls

Brain sites where patients with SLE have less volume of white matter (WM) and gray matter (GM) compared to controls. Height threshold: T = 1.81, cluster ≥ 20 voxels, FDR corrected (p<0.05)							
Cluster size	Voxel wise		spatial coordinates			anatomical location	
	T	Z	X	Y	Z	Side	Location
1449	5.36	5.04	-33	-32	13	Left	Temporal lobe, transverse temporal gyrus, WM
143	5.11	4.83	-10	-35	32	Left	Limbic lobe, cingulated gyrus, WM
23	2.38	2.35	19	-73	-41	Right	Cerebellum, posterior lobe
90	2.38	2.34	36	27	24	Right	Frontal lobe, sub-gyral, WM
60	2.72	2.69	33	16	41	Right	Frontal lobe, middle frontal gyrus, WM
203	3.14	3.00	14	-38	23	Right	Sub-lobar, extra-nuclear, corpus callosum, WM
199	5.12	5.09	18	-38	-25	Right	Sub-lobar, extra-nuclear, corpus callosum, WM
245	4.67	4.13	-14	-37	23	Left	Sub-lobar, extra-nuclear, corpus callosum, WM
100	3.18	3.15	-52	47	-7	Left	Frontal lobe, middle frontal gyrus, GM
143	3.15	3.15	-4	22	38	Left	Limbic lobe, cingulated gyrus, GM
123	3.00	2.99	-33	-92	-11	Left	Occipital lbe, inferior occipital gyrus, GM
456	2.15	2.13	-51	23	22	Left	Frontal lobe, middle frontal gyrus, GM
342	2.15	2.13	46	-26	16	Right	Temporal lobe, insula, GM
233	2.14	2.13	-58	-69	-1	Left	Temporal lobe, inferior temporal gyrus, GM
312	2.12	2.09	-51	19	22	Left	Frontal lobe, inferior temporal gyrus, GM

Table 2. Brain sites where patients with SLE with longer disease duration exhibit volume decline of gray and white matter.

Brain sites where patients with longer disease duration have less volume of white matter (WM) and gray matter (GM) Height threshold: T = 3.53, cluster ≥ 20 voxels, FDR corrected (p<0.05)							
Cluster size	voxel wise		Spatial coordinates			anatomical location	
	T	Z	X	Y	Z	Side	Location
309	19.63	7.8	47	-38	-9	Right	Temporal lobe, sub-gyral, WM
309	16.77	7.41	-29	-9	27	Left	Frontal lobe, sub-gyral, WM
1029	12.73	6.68	-18	-61	-34	Left	Cerebellum, posterior lobe, WM
888	19.24	7.8	-21	10	59	Left	Frontal lobe, middle frontal gyrus, WM
100	16.10	7.72	-36	-49	54	Left	Parietal lobe, inferior parietal lobule, WM
400	4.00	3.99	14	-38	23	Right	Sub-lobar, extra-nuclear, corpus callosum, WM
180	15.42	7.6	-38	10	54	Left	Frontal lobe, middle frontal gyrus, GM
210	15.81	7.67	36	-51	53		Right parietal lobe, parietal lobule, GM
229	17.55	16.65	-14	-25	4	Left	Sub-lobar, thalamus, GM
229	17.55	16.65	31	-47	59	Right	Parietal lobe, subparietal lobule, GM
368	15.16	7.6	-8	-41	56	Left	Frontal lobe, paracentral lobule, GM

Table 3. Brain sites where patients with antiphospholipid syndrome exhibit further gray and white matter volume decline compared to patients with SLE without antiphospholipid antibodies

Brain sites where patients with antiphospholipid syndrome have further volume loss than patients with SLE without antiphospholipid antibodies. White matter (WM); gray matter (GM) Height threshold: T = 2.44, cluster ≥ 20 voxels, FDR corrected (p<0.05)							
Cluster size	voxel wise		Spatial coordinates			anatomical location	
	T	Z	X	Y	Z	Side	Location
1859	4.06	3.65	-11	-49	-42	Left	Cerebelum, posterior lobe, tonsil, WM
216	3.61	3.30	-21	-90	8	Left	Occipital lobe, middle occipital gyrus, WM
70	3.47	3.19	42	-64	32	Right	Parietal lobe, angular gyrus, WM
69	3.41	3.14	43	37	13	Right	Frontal lobe, inferior frontal gyrus, WM
123	3.01	2.82	34	-16	-14	Right	Limbic lobe, parahypocampal gyrus, WM
110	3.00	2.81	27	28	-8	Right	Frontal lobe, inferior frontal gyrus, WM
101	2.91	2.74	-45	-58	31	Left	Parietal lobe, angular gyrus, WM
104	2.84	2.68	23	-93	8	Right	Occipital lobe, middle occipital gyrus, WM
134	4.24	3.75	-2	-18	-4	Left	Red nucleus
74	3.41	3.13	-5	13	-3	Left	Sub-lobar, caudate head
73	3.39	3.11	55	37	17	Right	Frontal lobe, middle frontal gyrus, GM
115	3.21	2.97	15	-58	5	Right	Occipital, lingual gyrus
99	3.10	2.87	16	-52	-28	Right	Cerebelum, anterior lobe
421	3.08	2.86	11	-33	-28	Right	pons
421	2.95	2.75	-1	-38	-24	Left	pons
111	2.98	2.78	-45	-13	45	Left	Frontal lobe, precentral gyrus
53	2.92	2.73	11	-101	7	right	Occipital lobe, cuneus
72	2.92	2.73	7	67	4	right	Frontal lobe, medila frontal gyrus

Table 4. Brain sites where patients with SLE with past CNS involvement have more intense gray and white matter loss than patients with active CNS involvement or no CNS involvement.

Brain sites of more intense white and gray matter loss in patients with SLE with past CNS involvement compared with patients with active CNS involvement or no CNS involvement. White matter (WM); gray matter (GM) Height threshold: T = 2.3, cluster ≥ 20 voxels, FDR corrected (p<0.05)							
Cluster size	voxel wise		Spatial coordinates			anatomical location	
	T	Z	X	Y	Z	Side	Location
4724	4.85	4.26	-30	-60	13	Left	Sub-lobar; extra nuclear, WM
456	4.59	4.08	14	-38	23	Right	Sub-lobar, extra-nuclear, corpus callosum, WM
472	4.12	3.73	13	-30	27	Right	Limbic lobe, cingulated gyrus, WM
1011	4.62	4.10	-19	40	-18	Left	Frontal lobe, superior frontal gyrus, WM
568	4.07	3.69	-33	15	32	Left	Frontal lobe, middle frontal gyrus, WM
621	3.91	3.57	43	26	12	Right	Frontal lobe, inferior frontal gyrus, WM
170	3.24	3.03	52	-38	-7	Right	Temporal lobe, middle temporal gyrus, WM
321	4.32	4.12	-14	37	23	Left	Frontal lobe, medial frontal gyrus, WM
206	3.20	3.00	-19	-39	52	Left	Frontal lobe, paracentral lobule, WM
176	3.00	2.83	-12	28	19	Left	Limbic lobe, parahippocampal gyrus, WM
235	2.84	2.69	36	6	41	Right	Frontal lobe, middle frontal gyrus, WM
432	3.53	3.23	-21	-34	-1	Left	Limbic lobe, parahippocampal gyrus, GM
281	3.46	3.17	51	-32	42	Right	Parietal lobe, inferior parietal lobule, GM
301	3.17	2.94	35	33	-9	Right	Frontal lobe, inferior frontal gyrus, GM
408	3.09	2.87	-49	17	28	Left	Frontal lobe, middle frontal gyrus, GM
910	2.99	2.76	-41	10	2	Left	Sub-lobar, insula, GM
754	2.87	2.69	31	-55	-11	Right	Cerebelum, posterior lobe, GM
1502	2.80	2.63	10	-48	-33	Right	Cerebelum, posterior lobe, GM
197	2.73	2.58	56	-75	4	Right	Occipital lobe, middle occipital gyrus, GM
438	2.64	2.50	11	-95	4	Right	Occipital lobe, cuneus, GM
327	2.62	2.48	49	-25	17	Right	Temporal lobe, uperior temporal gyrus, GM
113	2.46	2.34	-39	-49	48	Left	Parietal lobe, inferior parietal lobule, GM
166	2.39	228	59	-68	-8	Right	Occipital lobe, middle occipital gyrus, GM
345	2.32	2.22	56	-58	-11	Right	Temporal lobe, inferior temporal gyrus, GM
327	2.32	2.22	-66	-33	-2	Left	Temporal lobe, middle temporal gyrus, GM
252	2.18	2.10	56	-9	-21	Right	Temporal lobe, inferior temporal gyrus, GM
199	2.17	2.09	-3	22	22	Left	Limbic lobe
177	2.04	1.97	-12	13	8	Left	Sub-lobar, caudate body
231	2.00	1.94	12	-12	46	Riht	Limbic lobe, cingulated gyrus, GM
100	1.86	1.81	59	1	4	Right	Temporal lobe, superior tempral gyrus, GM

Table 5. Brain sites of more intense gray and white volume loss in patients with severe cognitive impairment compared to patients with moderate and no cognitive impairment.

Brain sites of more intense atrophy in patients with severe cognitive impairment compared to patients with moderate and no cognitive impairment. White matter (WM); gray matter (GM) Height threshold: T = 3.30, cluster ≥ 20 voxels, FDR corrected (p<0.05)							
Cluster size	voxel wise		spatial coordinates			anatomical location	
	T	Z	X	Y	Z	Side	Location
222	3.72	3.29	-37	-74	8	left	Occipital lobe, middle occipital gyrus, WM
200	3.61	3.21	13	40	39	right	Frontal lobe, superior frontal gyrus, WM
14	3.11	2.83	-44	-56	29	left	Temporal lobe, superior temporal gyrus, WM
83	3.10	2.82	41	-67	1	Right	Occipital lobe, inferior temporal gyrus, WM
45	2.98	2.73	-38	44	12	Left	Frontal lobe, middle frontal gyrus, WM
36	2.98	2.73	35	17	40	Right	Frontal lobe, middle frontal gyrus, WM
425	2.88	2.65	30	44	4	Right	Frontal lobe, sub-gyral, WM
150	2.92	2.69	15	26	46	Right	Frontal lobe, superior frontal gyrus, WM
432	3.53	3.23	-21	-34	-1	Left	Limbic lobe, parahippocampal gyrus, GM
327	2.62	2.48	49	-25	17	Right	Temporal lobe, superior temporal gyrus, GM
539	3.06	2.81	51	-5	44	Right	Frontal lobe, precntral gyrus, GM
269	3.73	3.3	-44	13	-9	Left	Temporal lobe, superior temporal gyrus, GM
460	3.11	2.85	53	38	24	Right	Frontal lobe, middle frontal gyrus, GM
345	2.32	2.22	56	-58	-11	Right	Temporal lobe, inferior temporal gyrus, GM

Table 6. Brain sites were corticosteroids influenced atrophy

Brain sites where the use of corticosteroids implecated in further atrophy of white matter (WM) and gray matter (GM) Height threshold: T = 1.71, cluster ≥ 20 voxels, FDR corrected (p<0.05)							
Cluster size	voxel wise		spatial coordinates			anatomical location	
	T	Z	X	Y	Z	Side	Location
180	15.42	7.6	-38	10	54	Left	Frontal lobe, middle frontal gyrus, GM
210	15.81	7.67	36	-51	53		Right parietal lobe, parietal lobule, GM
229	17.55	16.65	-14	-25	4	Left	Sub-lobar, thalamus, GM
229	17.55	16.65	31	-47	59	Right	Parietal lobe, subparietal lobule, GM
368	15.16	7.6	-8	-41	56	Left	Frontal lobe, paracentral lobule, GM
327	2.62	2.48	49	-25	17	Right	Temporal lobe, superior temporal gyrus, GM
539	3.06	2.81	51	-5	44	Right	Frontal lobe, precentral gyrus, GM
269	3.73	3.3	-44	13	-9	Left	Temporal lobe, superior temporal gyrus, GM
460	3.11	2.85	53	38	24	Right	Frontal lobe, middle frontal gyrus, GM
345	2.32	2.22	56	-58	-11	Right	Temporal lobe, inferior temporal gyrus, GM

Table 7. Brain sites where follow-up MRI exhibit progressive atrophy, compared to first MRI in patients with SLE

Brain sites where follow-up MRI shows progressive atrophy compared to first MRI in patients with SLE. White matter (WM); gray matter (GM) Height threshold: T = 3.15, cluster ≥ 20 voxels, FDR corrected (p<0.05)							
Cluster size	voxel wise		spatial coordinates			anatomical location	
	T	Z	X	Y	Z	Side	Location
259	5.49	5.21	29	34	-1	Right	Frontal lobe, sub-gyral, WM
801	531	5.06	-21	-41	54	Left	Parietal lobe, sub-gyral, WM
127	5.21	4.74	-16	29	42	Left	Limbic lobe, anterior cingulated gyrus WM
216	4.30	4.14	50	-3	-29	Right	Temporal lobe, inferior temporal gyrus, GM
212	4.07	3.94	9	-14	37	Right	Limbic lobe, cingulated gyrus, WM
453	4.07	3.94	-41	27	11	Left	Frontal lobe, inferior frontal gyrus, WM
227	3.93	3.82	38	-72	-1	Right	Temporal lobe, sub-gyral, WM
43	3.84	3.74	-54	-50	-8	Left	Temporal lobe, middle temporal gyrus, WM
30	3.56	3.47	55	-45	-11	Right	Temporal lobe, inferior temporal gyrus, WM
60	3.53	3.45	35	-70	13	Right	Temporal lobe, sub-gyral, WM
90	3.47	3.39	-10	23	24	Left	Limbic lobe, anterior cingulated gyrus, GM
187	5.34	5.08	-21	31	52	Left	Frontal lobe, superior frontal gyrus, WM
330	4.98	4.94	-28	64	-8	Left	Frontal lobe, superior frontal gyrus, GM
100	4.4	4.25	-3	35	17	Left	Limbic lobe, cingulated gyrus, GM
176	4.4	423	46	42	29	Right	Frontal lobe, middle frontal gyrus, GM
467	4.35	4.2	37	22	-17	Right	Frontal lobe, inferior frontal gyrus, GM
581	4.3	4.2	36	8	-26	Right	Temporal lobe, superior temporal gyrus, WM
122	4.2	4.07	-3	33	20	Left	Limbic lobe, anterior cingulated gyrus, GM

Figure 1: The first row show regions where gray ('hot' Z score scale bar) and white ('cold') matter volumes were reduce in patients with LES, compared to controls. Numbers above slices represent the vertical distance in mm to the anterior commissure. The areas of gray matter reduction compared with controls are also shown in a tridimensional cortical rendering on the second row. The third row represent areas of reduced gray and white matter volumes in the follow-up image from patients with LES, compared with their first images. Gray matter reduction areas in the follow-up images are shown on a cortical rendering in the fourth row. The fifth row shows areas of reduced white matter in patients with LES correlated with the time of disease.

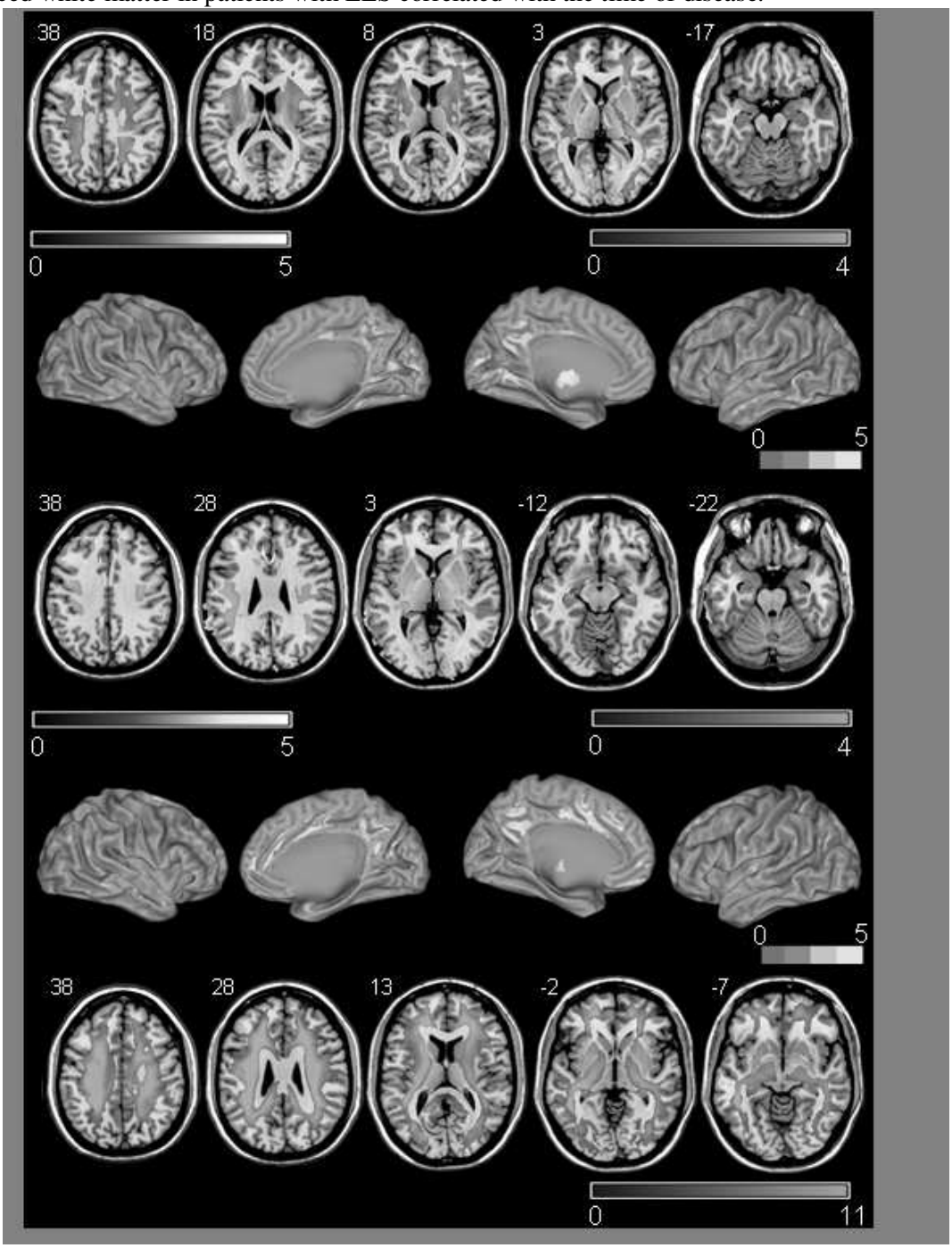


Figure 2: The first and second rows depict areas where gray matter volume was reduced in patients with LES compared to controls (blue Z scale bar), and more intensely atrophied in the follow-up image compared to the first image (red); in purple, areas were both statistical maps overlap. The third row shows areas where white matter volume was reduced in compared to controls (blue), and in the follow-up image compared to the first image (red); in purple, areas were both statistical maps overlap.

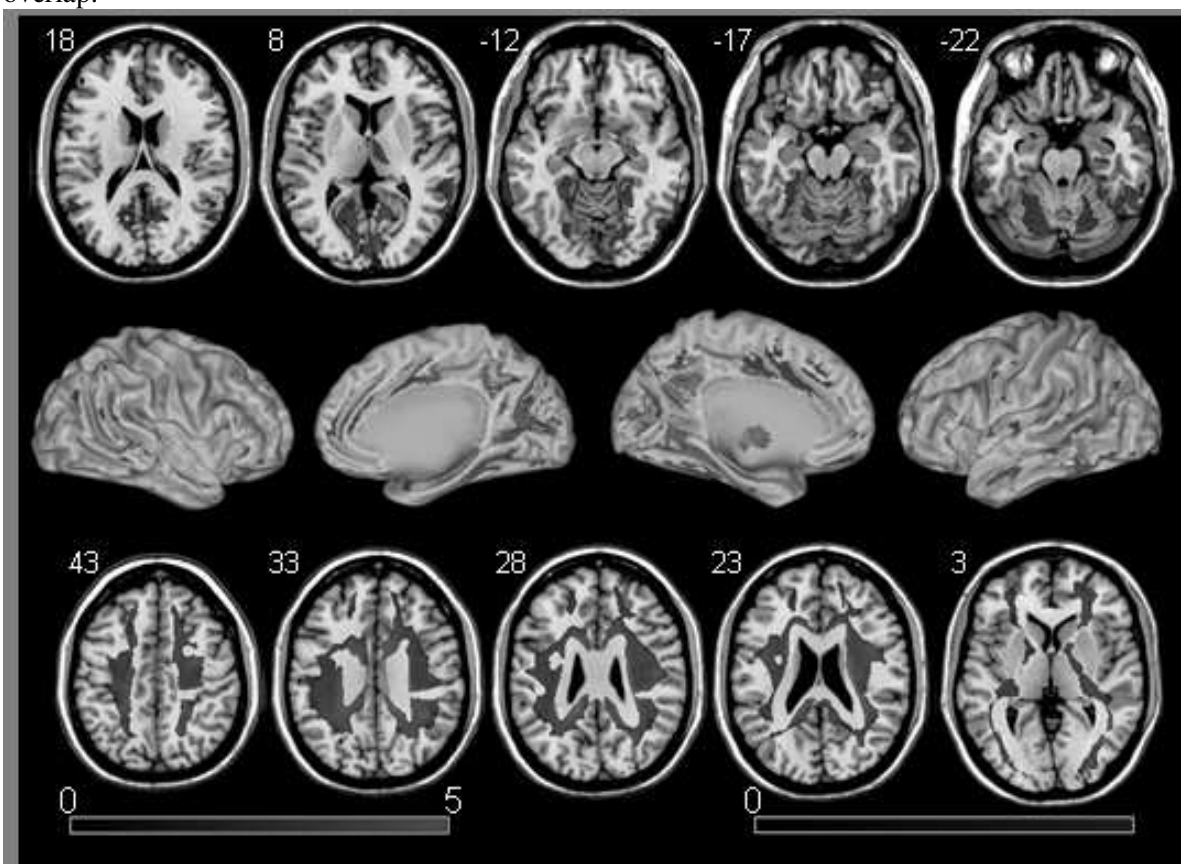
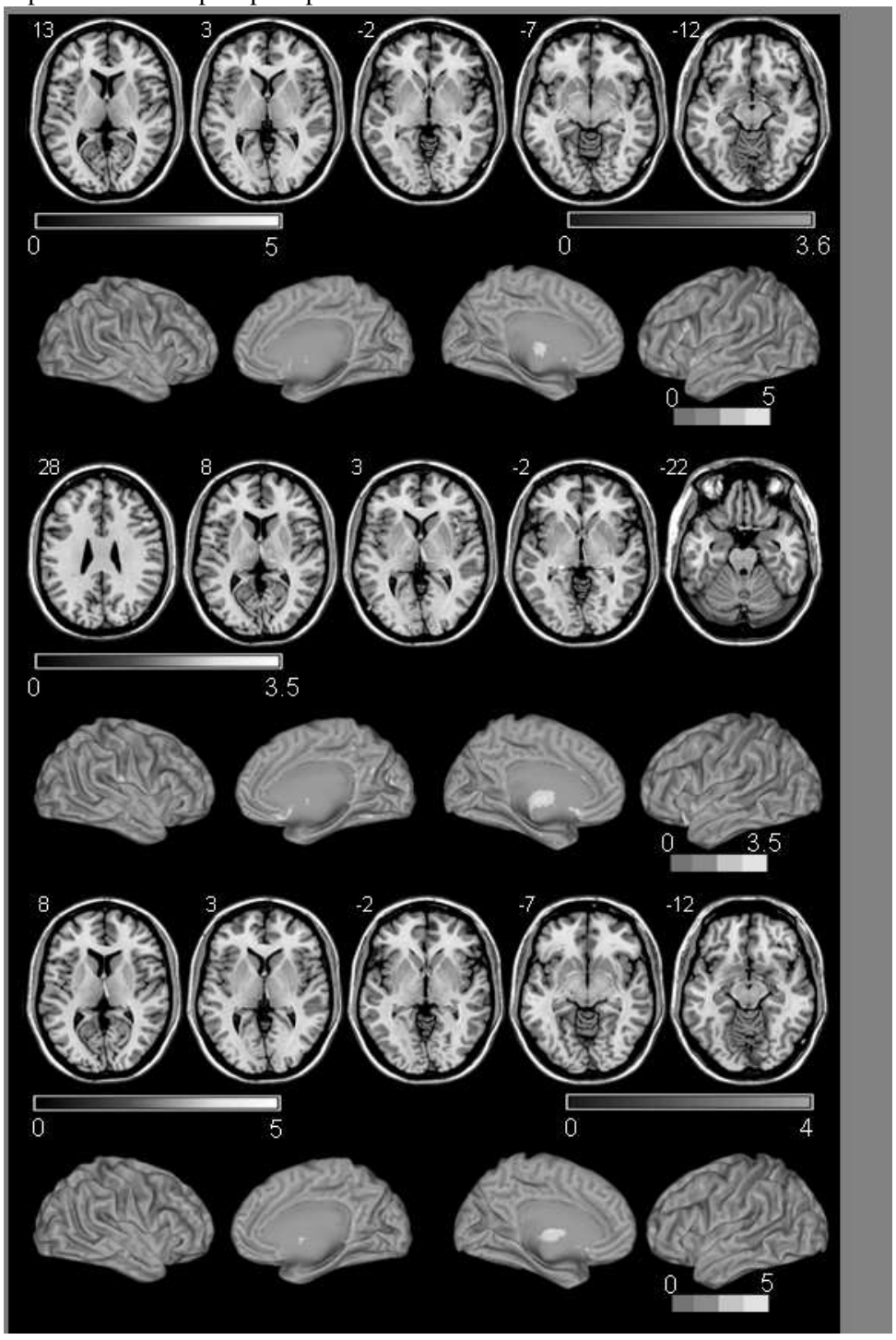


Figure3: The first row show regions where gray ('hot' Z score scale bar) and white ('cold') matter volumes were more reduced in patients with LES and severe cognitive disturbance. Numbers above slices represent the vertical distance in mm to the anterior commissure. These areas of gray matter reduction are also shown in a tridimensional cortical rendering on the second row. The third and fourth rows demonstrate regions where gray matter volume was more reduced in patients with LES with history of central nervous system disease and severe cognitive disturbance. The fifth and sixth rows show regions where gray and white matter volumes were more reduced in patients with LES who tested positive for antiphospholipid antibodies.



ARTIGO 10

Hippocampal atrophy in Systemic lupus erythematosus

Appenzeller S, Carnevalle AD, Li LM, Costallat LT, Cendes F.

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Hippocampal atrophy in systemic lupus erythematosus

Simone Appenzeller[1,3], MD, Aline Daiane Carnevalle[3], Li Min Li[2,3], MD, PhD, Lilian TL Costallat[1], MD, PhD, Fernando Cendes[2,3], MD, PhD

Departments of Rheumatology[1] and Neurology[2], Neuroimaging Laboratory[3]

University of Campinas, São Paulo – Brazil

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Correspondence to: *Fernando Cendes, MD, PhD*

Department of Neurology, University of Campinas-UNICAMP

Cidade Universitária, Campinas SP, Brazil, CEP 13083-970

FAX: +55 19 3289-1818

Email: fcendes@unicamp.br

Abstract

Objective: To determine the frequency and progression of hippocampal atrophy in systemic lupus erythematosus (SLE) and to determine clinical, laboratory and treatment features associated with its occurrence.

Methods: A total of 150 SLE patients and 40 healthy volunteers were enrolled in this study. A complete clinical, laboratory and neurological evaluation was performed. MRI scans were performed in a 2T scanner (Elscint Prestige®) and coronal T1 weighted images were used for manual volumetric measurements. Atrophy was defined as values below 2 standard deviations (SD) from the means of controls.

Results: At study entry, the mean right and left hippocampal volumes of patients were significantly smaller than the hippocampal volumes of healthy controls ($p<0.001$). After the follow-up MRI we observed a significant progression of reduction of right and left hippocampal volume in patients ($p<0.0001$). At study entry we identified atrophy in 43.9% and at follow up in 66.7% of SLE patients. Hippocampal atrophy was related to disease duration, total corticosteroid dose and past history of CNS manifestations. Progression of atrophy was associated with cumulative corticosteroid dose and number of CNS events. Patients with cognitive impairment had more severe hippocampal atrophy than patients without this manifestation.

Conclusion: Disease duration, total corticosteroid dose and greater number of CNS manifestations were associated with hippocampal atrophy in SLE patients. We observed a significant progression of hippocampal atrophy related to total corticosteroid dose and number of CNS events. Further studies are necessary to confirm these findings.

Introduction

Systemic lupus erythematosus (SLE) is a multiorgan autoimmune disease with abnormalities in immune regulation (1-3). Disease activity is characterized through intense inflammatory activity and treatment includes corticosteroids and other immunosuppressive agents (4).

The hippocampus, located in the temporal lobe, is a structure intimately involved with certain aspects of learning and memory consolidation (5). Patients exposed to high level exogenous (6-8) or endogenous (9-11) corticosteroids are more prone to short-term memory deficits. Previous studies have analyzed reversible and irreversible changes in hippocampus after corticosteroid exposure (12, 13). The hippocampus provides negative feedback to the hypothalamic-pituitary-adrenal axis and plays a critical role in declarative memory (14-16). In two studies the reduction of hippocampal volume correlated with mean cortisol level and atrophy was reversible after normalization of cortisol levels (10, 11).

The aim of this study was to determine the prevalence of hippocampal atrophy in SLE through validated manual MRI segmentation and to determine clinical, laboratory and treatment features associated with its occurrence. We also wanted to determine if this atrophy is progressive after follow-up period and which factors were associated with the continuous reduction of hippocampal volume.

Subjects and Methods

Subjects

A total of 150 consecutive SLE patients with four or more criteria for SLE (17) seen regularly at our Rheumatology Unit were screened prospectively to participate in the study. All SLE patients were followed using a standardized protocol and followed by the same investigators in the Rheumatology Unit (LTLC, SA). We excluded patients that were not able to undergo MRI, such as patients with claustrophobia (8 patients) and pacemaker (2 patients), as well as patients with previous clinical conditions that could influence cerebral and hipocamal atrophy, such as history of stroke (10 patients), arterial hypertension (5 patients), diabetes mellitus (5 patients), alcohol and drug abuse (1 patient), epilepsy (8) and malignancy (1 patient). There were no patients with renal insufficiency, or other pathologies that could influence cerebral atrophy. Patients who fulfilled the ACR criteria for rheumatoid arthritis, systemic sclerosis, Sjogren syndrome (primary or secondary) (3 patients) or other connective tissue disease and with drug-induced SLE were also excluded. The remaining 107 patients (100 women) were included. We used the

classification proposed by the ACR to analyze neuropsychiatric involvement (18). Records were reviewed in order to determine past CNS events. Patients with CNS manifestations secondary to clinical conditions such as infections, arterial hypertension, uremia, diabetes and drugs were excluded from this study.

This study was approved by Ethical Committee of our institution and informed written consent was obtained from each subject.

Clinical, serologic and treatment features of SLE patients

Data on gender, age at disease onset and disease duration were collected for each patient. Disease duration was defined as the initial manifestation clearly attributable to SLE until the day of MRI acquisition. All clinical manifestations and laboratory test findings were recorded. The following clinical manifestations were analyzed: malar rash, discoid lesions, subacute cutaneous lesions, photosensitivity, oral ulcers, arthritis, serositis, nephritis, neurological and psychiatric involvement, thrombocytopenia, hemolytic anemia, Raynaud's phenomenon, thrombosis, myositis, lung involvement and lymphadenopathy.

Nephritis was diagnosed on the basis of proteinuria exceeding 0.5 g/L with abnormal urinary sediment and/or histological findings. Nephrotic syndrome was defined as proteinuria in excess of 3.5 g/day. Hematologic alterations were ascribed to lupus only in the absence of bone marrow suppression (leukopenia <4000 cells/mm^3; thrombocytopenia <100.000/mm^3; hemolytic anemia with positive Coombs test). Antinuclear antibodies (ANA) were determined by indirect immunofluorescence using HEp 2 cells as the substrate and regarded as positive if higher than 1:40. Anti-double-stranded DNA (AdsDNA) antibodies were determined by indirect immunofluorescence using Chrithidia as substrate and considered positive if higher than 1:10. Precipitating antibodies to extractable nuclear antigens (ENA), including Ro (SSA), La (SSB) and Sm were detected by immunodiffusion and/or microhemagglutination. Anticardiolipin antibodies (aCL) of the IgG and IgM isotypes were measured by the ELISA method as described (19). Lupus anticoagulant (LA) activity was detected by coagulation assays in platelet free plasma obtained by double centrifugation, following the recommendation of the subcommittee on LA of the Scientific

and Standardization Committee of the International Society of Thrombosis and Homeostasis (20).

CNS manifestations were recorded following ACR case definitions (18) and divided into present (active or past history of CNS involvement) or absent (never presented CNS involvement). A complete neurological examination, as well as cognitive and psychiatric charts, was prospectively applied to all patients in order to identify CNS involvement. Mini Mental State Examination (21) was applied to all participants.

All patients and controls were submitted to a battery of standardized neuropsychologic tests in order to screen for possible impairment in one or more of the subsequent cognitive domains: simple attention, complex attention, memory, visuo-spatial processing, language, reasoning/problem solving, psychomotor speed, and executive functions (21-24). The individual test results were converted into standard scores, which were compared with the available normative data (21-24). Regarding any of the eight cognitive domains, subjects with a total score of two or more standard deviations (SD) below the normative value were considered to be impaired. Cognitive dysfunction was classified as mild if there were deficits in less than three dimensions, as moderate if there were deficits in three or four dimensions, and as severe if there were deficits in at least five dimensions (25, 26).

Assessment of depression was based on clinical interview and the Beck Depression Inventory (BDI) (27, 28). On BDI, scores from 10 to 17 were considered to indicate mild depression, from 18 to 24 moderate depression, and greater than 24 severe depression. Anxiety was evaluated by anxiety through the Hospital Anxiety and Depression scale (29). The presence of psychosis was determined through the Brief Psychiatry Rating Scale (aBPRS) (30).

For past history of CNS involvement we reviewed the medical charts of patients. Disease activity was measured by SLEDAI and considered active if scores were higher than eight points (31). Cumulative SLE-related damage was determined by Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI) (32) in all SLE patients at time of MRI.

Total doses of corticosteroids and other immunosuppressant medications used since the onset of disease were calculated by careful review of the medical charts. Doses of oral and parenteral corticosteroids were analyzed and converted to the equivalent doses of prednisone. The cumulative dose of corticosteroids used was calculated by the sum of daily dosages versus time (days) of treatment.

MRI acquisition

All subjects had MRI examination using Escint Prestige 2T scanner (Haifa, Israel). Coronal T1-IR (4mm thick, flip angle=120º, repetition time=6800 ms, echo time=129 ms, matrix 252x328, field of view=21x23cm) images were analyzed using anatomic guidelines obtained from a standardized protocol (33) for manual segmentations for hippocampal and total brain volume (Figure 1). Quantification and analysis were performed by one investigator (ADC), blind to patients´ clinical data. The evaluation was cross-checked by another investigators with experience in MRI analysis (SA, FC). This method has been previously compared to other segmentation programs (34) and intra-observer (r=0.90)and inter-observer (r=0.85) variation was determined.

The control group for MRI protocol consisted of 40 healthy volunteers (36 women) with mean age of 31.8 (range 20-55, SD=10.2 years). Patients and controls were statistically comparable in age and gender.

Image processing

Manual delineation of hippocampi boundaries was performed using Scion® Image program (NIH). Anatomic guidelines for outlining the hippocampus followed a specific protocol previously described (35). Once the outline had been defined, the slice area was calculated automatically by the computer program. We then calculated the total volumes expressed in cubic millimeters by the sum of each area multiplied by the slice thickness (mm^3). In order to determine hippocampal atrophy even in the presence of diffuse atrophy, and also to correct for individual variation of the size of the head, we performed a correction of all hippocampal absolute volumes for each respective individual cerebral

volume. This correction consisted of dividing the mean total brain volume of the control group by the patient's brain volume. In each patient, the calculated hippocampal volume was then multiplied by this ratio (36). This correction for 'brain volume' assumes a linear relationship between hippocampi and brain volumes (36).

In addition, asymmetry index (AI) was determined by the ratio of the smaller by the larger structure for each subject.

Atrophy was determined when corrected volumes and/or AI were bellow two standard deviations (SD) from the mean of control group.

Statistical analysis

We compared hippocampal volumes of SLE patients to controls using two sample t-test. We further subdivided SLE patients in two groups: patients with and without CNS involvement. We performed analysis of variance (ANOVA) to test for differences among hippocampal volumes in these groups, with Tukey's pairwised post hoc comparisons when necessary. This procedure includes corrections for multiple comparisons. Demographic data between groups were compared with chi-square test. Follow-up volumes were compared by paired t-test with Bonferronis´ correction for multiple comparisons. Linear regression was used to analyze the association between cerebral and hippocampi volume with disease duration and total corticosteroid use.

Volumetric measurements were expressed in cm^3 and are shown in mean ± standard deviation (SD). Statistical significance was considered at α of 5%.

Results

Demographic data

One hundred and seven SLE patients (100 women) met the inclusion and exclusion criteria with mean age of 32.2 years (SD=11.2; range=18 to 54 years). The mean disease duration at study entry was 64.5 months (range 1-372 months; SD=48.50)**.** All

patients were on corticosteroid use with doses varying from 5 to 100 mg of prednisone. Antiphospholipid antibodies were positive in 32 patients. Active SLE disease was observed in 54 patients with mean SLEDAI score of 14.0 (range 9-20; SD=5.9). One hundred twenty two episodes of CNS manifestations were observed in 64 patients (Table 1). Active CNS disease at the time of MRI scan was observed in 30 of 64 patients with history of CNS involvement. Mean SLICC/ACR DI scores at study entry were 2.3 (range 0-5; SD=1.8). The cumulative clinical and CNS events at study entry are shown in Table 1.

MRI scans were repeated in 60 patients after a mean follow-up period of 19 months (SD=2.2, range=12-25 months). Forty of these patients presented CNS events during follow-up period with mean SLEDAI scores of 12.4 (range 3-20; SD=3.8). Mean SLICC/ACR DI scores at follow-up were 3.1 (SD=1.7; range 0-6).

Hippocampal volumes

At study entry, the mean right hippocampal volumes of patients was 3260 mm^3 (SD=330) and the mean left hippocampus was 3080 mm m^3 (SD=330). In controls we observed a mean right hippocampal volume of 3570 mm m^3 (DP=310) and a mean left hippocampal volume of 3480 mm m^3 (SD=330). There was a statistically difference between the right (p=0.002) and the left (p=0.001) hippocampal volume of patients and controls (Figure 2).

Individual analysis

Hippocampal atrophy was identified in 47 of 107 (43.9%) patients and distributed as follows: 20 of 47 (42.6%) with left hippocampal atrophy, 10 (8.3%) with right hippocampal atrophy and 17 (10%) with bilateral hippocampal atrophy.

Group analysis

The degree of hippocampal volume loss correlated independently with disease duration (r=0.89; p<0.001), the presence of CNS manifestations (r=0.65; p=0.01) and

cumulative corticosteroid dose (r=0.74; p=0.01). When we further subdivided patients with CNS involvement in active and past history of CNS involvement we observed that hippocampal reduction was associated with past history (r=0.9; p<0.001) and not with active CNS involvement.

SLICC/ACR DI scores correlated strongly with the degree of hippocampal atrophy (r=0.87; p=0.001), but when cognitive dysfunction was excluded from the SLICC scores, the correlation was not statistically significant (r=0.3; p=0.4). There was a trend between the association of hippocampal atrophy and the presence of antiphospholipid antibodies (r=0.5; p=0.06). No association between hippocampal atrophy and SLEDAI (r=0.43; p=0.08) was observed. On visual analysis, hyperintense areas and areas of cerebral micro-infarcts were observed in 50 patients. There was a statistically significance between the presence of these findings and hippocampal atrophy (p=0.01).

Cognitive evaluation

We observed cognitive impairment in 35 patients, 20 with severe, 10 with moderate and 5 with mild cognitive impairment. We observed that that patients with cognitive impairment had a more significant reduced hippocampal volume when compared to SLE patients without cognitive impairment (r=0.9; p=0.001). Patients with severe cognitive impairment had a more pronounced reduction of hippocampal volumes than patients with moderate and mild cognitive impairment (p=0.002). In relation to different domains of cognitive dysfunction, hippocampal atrophy was associated to lower scores on general memory (p=0.015), verbal memory (p=0.01), and delayed recall (p=0.01).

Follow-up analysis

After the follow-up MRI, group analysis showed a significant progression of reduction of right (mean=28.2 cm^3, SD=3.1) and left (mean=27.9 cm^3, SD=1.2) hippocampal volumes in patients (p<0.0001) (Figure 3).

Individual analysis showed that the follow-up MRI demonstrated a significant increase in number of patients with hippocampal atrophy. We observed atrophy in 40 of 60

(66.7%) patients: 32 (53.3%) bilaterally, 4 (6.7%) with right hippocampal atrophy and 4 (6.7%) with left hippocampal atrophy. Progression of hippocampal atrophy correlated with cumulative corticosteroid dose (r=0.69; p=0.01) and number of CNS events during the follow-up period (r= 0.72, p=0.01).

We observed cognitive impairment in 40 of 60 patients after the follow-up period, 22 with severe, 12 with moderate and 6 with mild cognitive impairment. We observed that patients with hippocampal atrophy and normal cognitive function at study entry, presented with cognitive impairment during the follow-up period (Figure 3). The severity of cognitive impairment was directly associated with the degree of hippocampal volume loss (r=0.89; p=0.001). In relation to different domains of cognitive dysfunction, no difference in relation to study entry was observed, being hippocampal atrophy associated to lower scores on general memory (p=0.01), verbal memory (p=0.02), and delayed recall (p=0.01).

Discussion

We observed a frequency of 44% of hippocampal atrophy in our study and a significant progression of hippocampal volume loss and atrophy during follow-up period. Both the presence and the progression of hippocampal atrophy correlated with disease duration, total corticosteroid dose and the presence of past history of CNS manifestations. The number of CNS events was associated with progression of hippocampal atrophy during the follow-up period. The short follow-up period did not allow us to determine if hippocampal volumes may return to normal ranges or if the progression of hippocampal atrophy stops after corticosteroid withdrawal.

At study entry we observed a small proportion of bilateral atrophy. We did not identify any cause for the predominance of unilateral atrophy in these patients, although after a follow-up period the majority of the patients presented bilateral hippocampal atrophy.

Hipocampal atrophy has been shown in several diseases before, such as epilepsy (36), and it is related to memory impairment (5-11). In addition to the exclusion of clinical conditions that are associated with cerebral atrophy, such as stroke, arterial

hypertension (37) and diabetes mellitus, we excluded patients with epilepsy. The relationship between epilepsy and hippocampal atrophy is well determined in the literature (38).

Although it is possible that aging had some effect in brain and hippocampal atrophy (39), this effect was minimized by the comparison with volunteers with same age range.

Hippocampus is the prominent target structure for the activity of corticosteroids in the brain (40). In animals, corticosteroid hormones have been shown to reduce the number of branch points and length of dendrites in hippocampus of rats, to cause dendritic atrophy of pyramidal neurons (41) and to lead to reduction of CA3 and CA4 hippocampal neurons (42). In patients with Cushing syndrome, previous studies have shown that the reduction of hippocampal volume correlated with mean cortisol level and that atrophy was reversible after normalization of cortisol levels (10, 11).

If corticosteroids cause cell death and neuronal loss or if they cause atrophy or degeneration is not clearly understood. The majority of animal models report only atrophy of dendritic branches (40-42). Although this can be the first step and progress to neuronal loss, neuronal cell death was found only in a few studies (40). Our study suggest that hippocampal atrophy in SLE is one of the consequences of CNS damage induced by the inflammatory process, which is most likely potentiated by prolonged use of corticosteroids.

We observed that hippocampal atrophy was associated with the presence of cognitive dysfunction in SLE, especially memory function. Patients with severe cognitive impairment had more pronounced hippocampal volume loss when compared to patients with mild cognitive impairment and patients without this manifestation. The elevated presence of hippocampal atrophy observed in this study may explain the high frequency of cognitive impairment observed in SLE patients (1-4). We also observed that patients with white matter lesions had more frequently hippocampal atrophy than patients without these MRI findings. Similar findings were described in patients with Alzheimer disease (43). We also observed that the presence of antiphospholipid antibodies had a tendency to be associated with hippocampal atrophy, supporting the theory that small vessel disease may contribute to hippocampal atrophy and cognitive impairment (43). We also observed that

hippocampal atrophy was a predictor for cognitive impairment. The patients that had normal cognitive function test and hippocampal atrophy at study entry presented cognitive impairment during the follow-up study.

In this study we demonstrated new evidence that structural MRI abnormalities may be associated with cognitive dysfunction in SLE patients. We also demonstrated that hippocampal atrophy is progressive over time. Furthermore we showed that the presence of hippocampal atrophy may be predictive of cognitive impairment in SLE patients. Longer follow-up studies are necessary to confirm these findings and to determine if the hippocampal loss is reversible and which factors may contribute to it.

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Table 1: Neuropsychiatric manifestations in 64 patients at study entry and 40 patients at follow-up

Neuropsychiatric manifestations	Number of CNS events (%) at study entry	Number of CNS events (%) during follow-up
Headache	39 (32)	7 (10.3)
Cognitive impairment	35 (27)	40 (58.8)
Mood disorder	13 (11)	5 (7.3)
Acute confusional state	10 (8.1)	3 (4.4)
Anxiety	7 (5.7)	3 (4.4)
Psychosis	6 (4.9)	3 (4.4)
Mononeuropathy	4 (3.3)	0
Cranial neuropathy	3 (2.5)	1 (1.4)
Myelopathy	3 (2.5)	4 (5.9)
Aseptic meningitis	1 (0.8)	2 (2.9)
Movement disorder	1 (0.8)	0
Total number of events	122	68

Figure 1. Example of segmentation of hippocampal volume (A and B hippocampal segmentation of a control; C and D hippocampal segmentation of a patient).

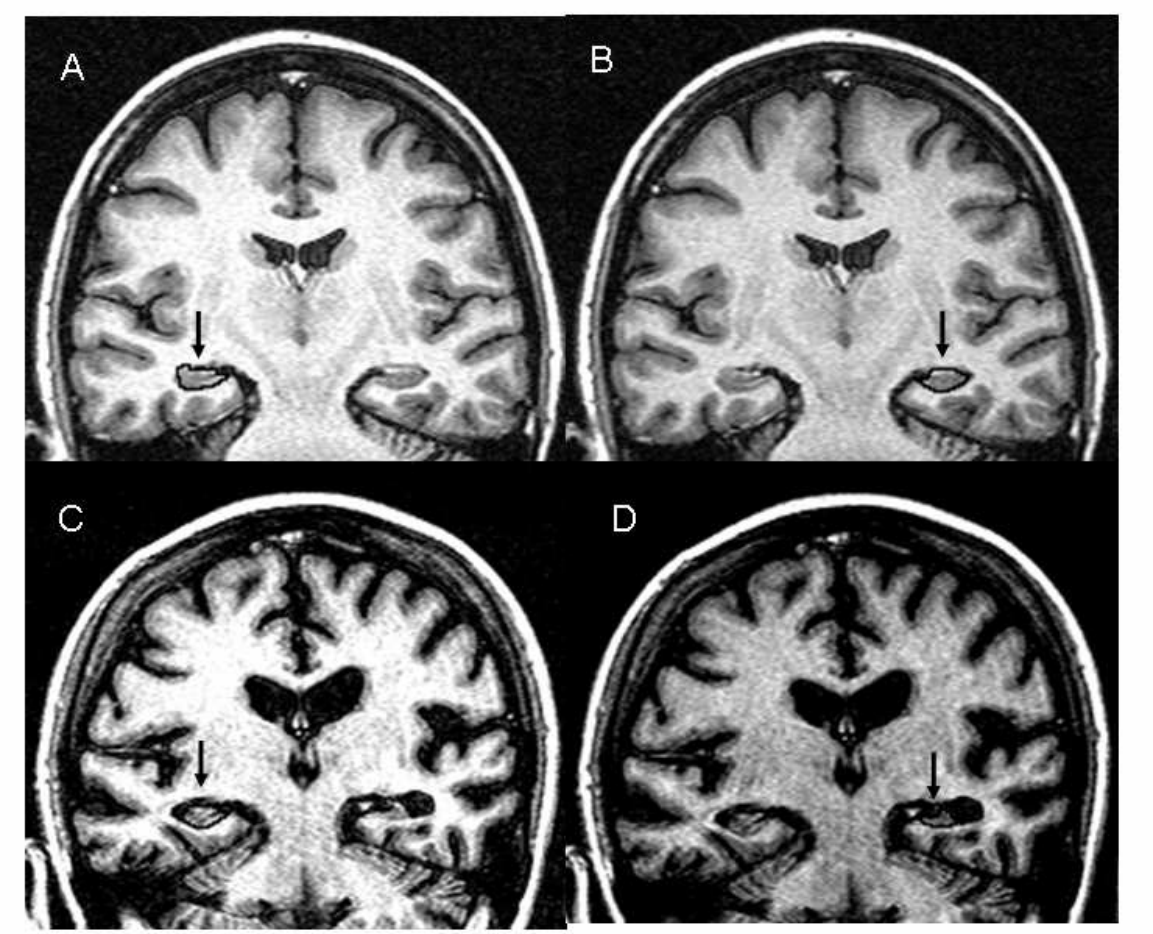


Figure 2. Mean right and left hippocampal volumes in controls, SLE patients at baseline and at follow-up. Line with tick above each bar represents 1 standard deviation.

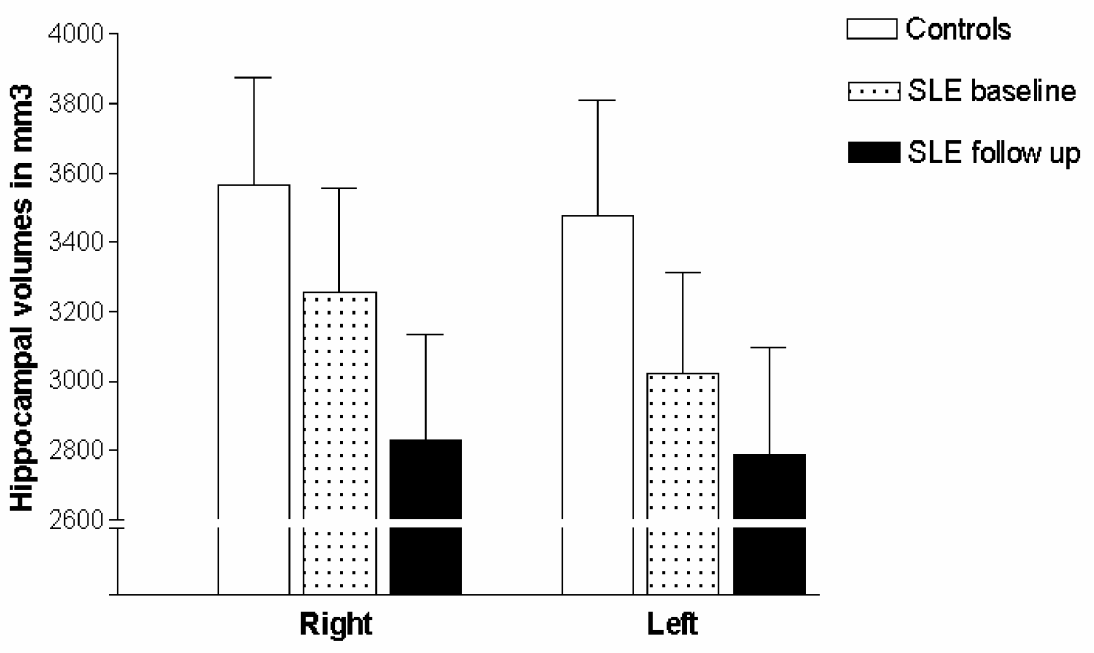
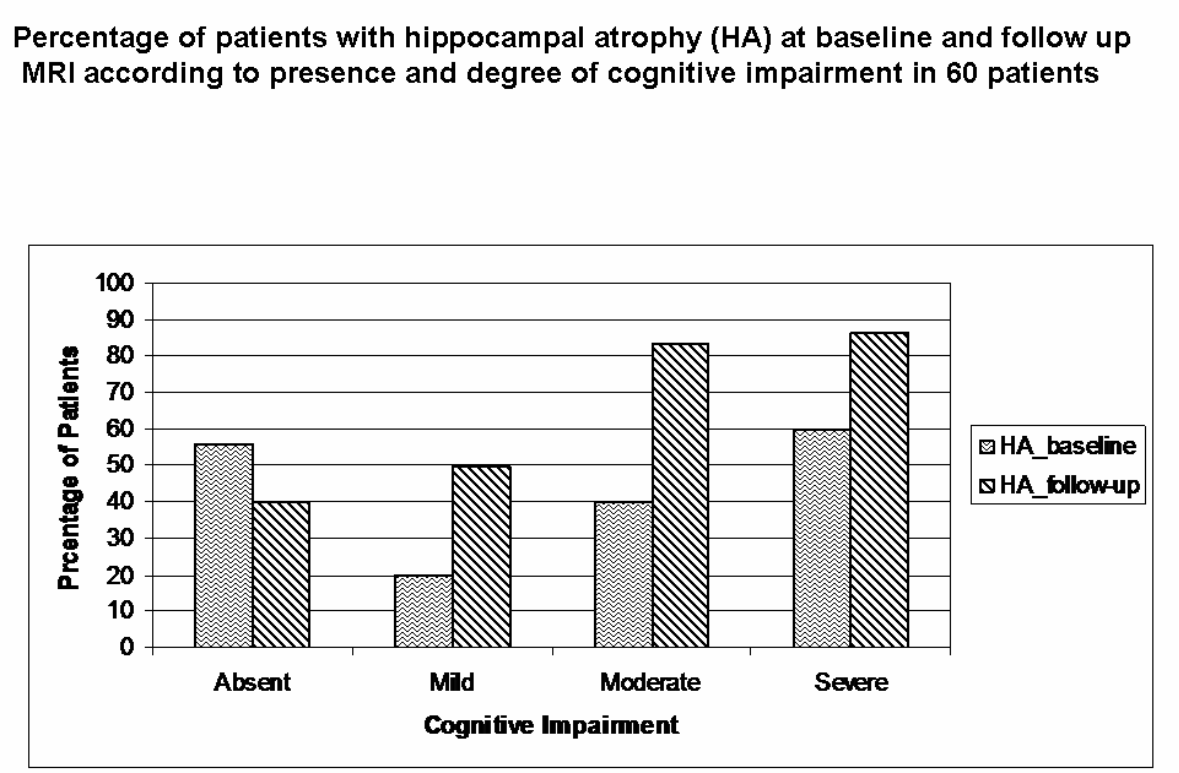


Figure 3. Percentages of patients with hippocampal atrophy (HA) at baseline and follow up MRI according to presence and degree of cognitive impairment in 60 patients



ARTIGO 11

Voxel-based morphometry of brain SPECT can detect the presence of active central nervous system involvement in systemic lupus erythematosus

Simone Appenzeller; Bárbara Juarez Amorim; Celso Dario Ramos; Pablo A Rio; Elba Cristina Sá de Camargo Etchebehere; Edwaldo Eduardo Camargo; Fernando Cendes, Lilian TL Costallat

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Voxel-based morphometry of brain SPECT can detect the presence of active central nervous system involvement in systemic lupus erythematosus

S. Appenzeller[1,2], B. J. Amorim[3], C. D. Ramos[3], P. A. Rio[2], E. C. S. de C. Etchebehere[3], E. E. Camargo[3], F. Cendes[2,4] and L. T. L. Costallat[1]

Objective. **To determine the value of voxel-based morphometry (VBM) of brain SPECT (single-photon emission computed tomography) images (BSI) in discriminating active central nervous system (CNS) manifestations in systemic lupus erythematosus (SLE) patients.**

Patients and Methods. **Forty SLE patients (mean age 33 yrs) and 33 normal volunteers were submitted to BSI. SLE patients were screened for the presence of CNS involvement following the American College of Rheumatology (ACR) case definition. Patients with CNS infections, uraemia, diabetes and previous ischaemic or haemorrhagic stroke were excluded. Magnetic resonance imaging (MRI) scans were obtained in a 2T scanner (Elscint Prestige) with T1- and T2-weighted images. BSI were performed after injection of 1110 MBq (30 mCi) of ^{99m}Tc-ECD (ethyl-cysteinate-dimer). BSI were analysed using the statistical parametric mapping. After normalization, segmentation and smoothing the groups of SLE patients with active and inactive CNS manifestations and healthy volunteers were compared using VBM. Post-processed images were compared voxel-by-voxel using *t*-test in order to determine differences of intensity between groups. This analysis included grand mean scaling, proportional threshold masking (set to 0.4) and implicit masking. A *P*-value of 0.001 and cluster size of 32 were taken into consideration.**

Results. **VBM analyses of BSI did not show any differences between SLE patients with inactive CNS involvement and normal controls. However, the group of SLE patients with active CNS involvement had a global hypoperfusion, more intense in the frontal, dorsolateral and medial temporal lobe when compared with SLE patients without CNS involvement ($P = 0.001$) and healthy volunteers ($P = 0.001$).**

Conclusion. **VBM of BSI is a useful and objective method for detecting perfusion abnormalities in SLE patients, which is indicative of active CNS involvement. However, it is not helpful in differentiating the clinical sub-types of CNS involvement according to the ACR classification.**

KEY WORDS: SPECT, VBM, SLE.

Introduction

Central nervous system (CNS) involvement is seen in as many as 11–60% of systemic lupus erythematosus (SLE) patients and may cause transient neurological manifestations or chronic brain injury [1, 2]. The diagnosis of CNS involvement of SLE is difficult because of the need to differentiate primary from secondary causes of neurological involvement such as CNS infections and metabolic encephalopathy. In addition, the absence of reliable serum markers and an ideal imaging modality increases this difficulty [3].

Magnetic resonance imaging (MRI) is the preferred anatomic imaging modality [3]. MRI is more likely to show abnormalities if there are focal neurological deficits, seizures, chronic cognitive dysfunction or the antiphospholipid syndrome. However, in many patients with obvious CNS involvement, MRI may not show abnormalities, especially in patients with affective disorders, confusional states or headaches [3, 4]. Another drawback of MRI is the difficulty in differentiating lesions of active CNS manifestations from old lesions [5, 6]. MRI frequently (25–50%) reveals chronic lesions in patients with and without active disease, and the incidence of these lesions increases with age, disease severity and past history of CNS involvement [3, 6, 7]. Therefore, techniques for detecting functional brain abnormalities may be useful. Several functional techniques have been used in SLE, including positron emission tomography (PET), magnetic resonance spectroscopy (MRS), and single-photon emission computed tomography (SPECT). PET with 18-fluoro-2-deoxyglucose (FDG) shows cerebral involvement in patients with NP-SLE who have no morphological changes detectable by CT and MRI. PET is considered to be a sensitive and reliable method for evaluating SLE patients with CNS involvement. However, it is not yet established in routine clinical use because it is expensive and not available in most hospitals [8]. MRS is another functional method that may be used for detecting CNS manifestations in SLE. Although it

[1]Rheumatology Unit, State University of Campinas, [2]Neuroimaging Lab, State University of Campinas, [3]Division of Nuclear Medicine, Department of Radiology and [4]Department of Neurology, FCM, State University of Campinas (UNICAMP), Campinas, Brazil.

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Correspondence to: Dr. F. Cendes, Department of Neurology, State University of Campinas (UNICAMP), Cidade Universitaria Zeferino Vaz CEP 13083-970 Campinas-SP, Brazil. E-mail: fcendes@unicamp.br

is more frequently used than PET, most studies use single-voxel MRS, and so only a predetermined volume of the brain may be analysed [9]. Multi-voxel MRS is still rare in clinical practice [9]. Therefore, brain SPECT may be an alternative functional method for detecting functional abnormalities in CNS manifestations in clinical practice, providing important clinical information by imaging regional blood flow changes. Several studies used brain SPECT images (BSI) to investigate patients with SLE [3, 8, 10–20]. Hypoperfusion, suggesting decreased regional blood flow, were identified in SLE patients with neuropsychiatric manifestations [10, 12–17], although others have also found perfusion abnormalities in SLE patients without neuropsychiatric manifestations [18–20]. Most studies use visual analysis with regional quantification of perfusion abnormalities. Semi-quantitative analysis of BSI have increased diagnostic yield of BSI in other diseases [21–23]. Statistical parametric mapping (SPM) is an increasingly established form of neuroimaging analysis to detect statistically significant differences in spatially normalized images on a voxel-by-voxel basis [24–26]. The use of SPM eliminates observer subjectivity inherent in visual analysis [27–29]. The purpose of this study was to determine the value of voxel-based morphometry (VBM) of brain SPECT images (BSI) in discriminating active CNS manifestations in SLE patients.

Subjects and method

Subjects

Sixty consecutive SLE patients fulfilling four or more criteria for classification of SLE [30] with CNS involvement were invited to participate in the study. All patients had active or past history of CNS involvement as defined by the American College of Rheumatology (ACR) case definition [31]. Active CNS disease, as defined by the new onset or persistence of a CNS manifestation at the time of examination, was identified in 27 patients. The remaining 33 patients had inactive (past history) CNS involvement. Patients were followed-up prospectively in the Rheumatology Unit of the State University of Campinas (UNICAMP).

We excluded patients with associated clinical conditions that could cause cerebral atrophy, such as stroke (10 patients), arterial hypertension (one patient), diabetes mellitus, alcohol and drug abuse and malignancy. Patients satisfying the ACR criteria for rheumatoid arthritis, systemic sclerosis, Sjögren syndrome (two patients) or other connective tissue disease and with drug-induced SLE were also excluded.

Total dose of corticosteroids and other immunosuppressant medications used since the onset of disease were estimated using the data obtained by careful review of the medical charts. Seven patients with incomplete charts were excluded from the analysis.

Therefore, 40 patients (20 with active and 20 with inactive CNS manifestations) were submitted to BSI. The control group consisted of 50 healthy age- and sex-matched volunteers.

This study was approved by the Ethical Committee of our institution and informed, written consent was obtained from each subject.

Clinical, serological and treatment features of SLE patients

Clinical manifestations. Data on gender and age at disease onset and disease duration were collected for each patient. Disease duration was defined as the initial manifestation clearly attributable to SLE until the day of BSI acquisition. All clinical manifestations and laboratory test findings were recorded according to ACR criteria [30, 31]. Disease activity was measured in all visits using the systemic lupus erythematosus disease activity index (SLEDAI), which is a standardized score for SLE patients and includes 24 items [32]. The SLEDAI score is calculated by summing the predetermined weights for the items that are present. Items that are life-threatening have higher weights, with possible scores ranging from 0 to 105. Cumulative organ damage was analysed by validated damage index (SLICC/ACR-DI) [33]. SLICC/ACR-DI is an unweighted index composed of 41 items grouped in 12 domains, with a maximum possible score of 47. As previously established, damage was considered when the irreversible lesions were present for at least 6 months unrelated to active inflammation and had occurred after SLE diagnosis [33].

CNS involvement. A complete neurological examination, as well as cognitive and psychiatric charts, was prospectively applied to all patients during their clinical visit in order to identify active CNS involvement [31]. Mini Mental State Examination [34] was applied to all participants. All patients were submitted to a battery of standardized neuropsychological tests in order to screen for possible impairment in one or more of the subsequent cognitive domains: simple attention, complex attention, memory, visuospatial processing, language, reasoning/problem solving, psychomotor speed and executive functions [35–38]. These tests have not been validated for SLE patients, but are widely used for patients with CNS disorders in clinical practice and research. The individual test results were converted into standard scores, which were compared with the available normative data [35–38]. Regarding any of the eight cognitive domains, subjects with a total score of $\geq$2 S.D. below the normative value were considered to be impaired. Cognitive dysfunction was classified as mild if there were deficits in less than three dimensions, as moderate if there were deficits in three or four dimensions and as severe if there were deficits in at least five dimensions [38, 39].

Assessment of depression was based on clinical interview and the Beck Depression Inventory (BDI) [40, 41]. On BDI, scores from 10 to 17 were considered to indicate mild depression, from 18 to 24 moderate depression and greater than 24 severe depression. Anxiety was evaluated by anxiety through the Hospital Anxiety and Depression scale [42]. The presence of psychosis was determined through the Brief Psychiatry Rating Scale (aBPRS) [43].

For past history of CNS involvement we reviewed the medical charts of patients.

Laboratory features. Antinuclear antibodies (ANA) were determined by indirect immunofluorescence using mouse liver as the substrate, and were regarded as positive if higher than 1:40. Anti-double-stranded DNA (AdsDNA) antibodies were determined by indirect immunofluorescence using Chrithidia as substrate, and were considered positive if higher than 1:10. Precipitating antibodies to extractable nuclear antigens (ENA), including Ro (SSA), La (SSB) and Sm were detected by immunodiffusion and/or microhaemagglutination. Anticardiolipin antibodies (aCL) of the IgG and IgM isotypes were measured by the ELISA method [44]. Lupus anticoagulant (LA) activity was detected by coagulation assays in platelet-free plasma obtained by double centrifugation, following the recommendation of the subcommittee on LA of the Scientific and Standardization Committee of the International Society of Thrombosis and Homeostasis [45].

BSI acquisition. After completing inclusion and exclusion criteria, 40 patients (20 with active and 20 with inactive CNS manifestations) were required to remain resting in a dark, quiet room for 15 min, with a permanent intravenous access through a *butterfly* connected to a catheter with saline solution. While at rest, 1110 MBq (30 mCi) of ^{99m}Tc-ECD (ethyl-cysteinate-dimer) was injected. The patients remained resting for another 10 min. BSI was performed in a computed scintillation camera with a *fan-beam* collimator. Sixty images were acquired in a 64×64 matrix, every 6°, in a total of 360°. Raw data were reconstructed by filtered backprojection, and attenuation correction was

performed using Chang's method with a 0.115 attenuation coefficient.

BSI analysis. The reconstructed BSI were converted into Analyze format using MRIcro software (www.mricro.com). Voxel-based analysis was performed using SPM2 (Wellcome Department of Cognitive Neurology, London)

To allow group comparisons, the size and shape of each individual's scan were normalized to sterotaxic space by estimating the optimum 12-parameter affine transformation [46–48]. The ^{99m}Tc-ECD uptake was standardized to the mean global uptake using a proportional scaling. At this point, standard VBM protocols include segmentation of brain tissues, but because BSI signals are acquired from radio tracers dispersed in blood flow and most of blood vessels are in the GM portion of brain, this step was not necessary and is not recommended for nuclear medicine images to avoid spatial resolution worsening. The images were subsequently smoothed by convolving its voxels with an isotropic Gaussian kernel (IGK) of 10 mm in order to minimize border effects caused by gyral inter-individual variability and create images that can be spatially compared with a good correspondence of analogous tissues.

MRI acquisition protocol and analysis. MRI scans were obtained in a 2T Elscint Prestige scanner. T1-weighted gradient-echo sequence with 1 mm thickness (TR = 22 ms, TE = 9 ms, flip angle = 35° and matrix = 256 × 220) was used for voxel-based morphometry (VBM) analysis. Images were normalized to the standard space using 12 linear parameters and 7 × 8 × 7 nonlinear basis functions, using a brain mask. Spatially normalized images were re-sliced to isotropic voxels of 1.5 mm and underwent segmentation of white and gray matter. The images were smoothed by convolution with an IGK of 10 mm in order to minimize inter-individual gyral variability. The resulting images were then compared voxel-by-voxel by using *t*-test to determine differences in gray matter between patients with active and inactive CNS involvement and controls using statistical parametric mapping (SPM 2). This analysis included grand mean scaling and proportional threshold masking (set to 0.4) and implicit masking. A *P*-value of 0.001 was taken into analysis, and the minimum cluster size taken into account was 32.

Statistical analysis. Group differences for age were assessed using one-way ANOVA, and the gender distribution was evaluated with the chi-square test.

The statistical analysis of the normalized and smoothed BSI data was performed using the SPM2. Statistical analysis was performed by comparing both groups of patients (with and without CNS manifestations) with the control group. It was also performed a comparison between the group of patients with CNS manifestation and the group of patients without manifestation. These comparisons between these groups were performed using a non-paired two-sample *t*-test. Only voxels with signal intensity above a threshold of 0.4 were entered in each analysis. It was used with a *P*-value of 0.001 with false discovery rate (FDR) and a cluster size of 32. The tool FDRs minimize errors from multiple comparisons and eliminates, from the final statistical *t*-map, all values with a probability of being a false positive discovery. This step is important since the natural variability can produce false discoveries and lead to incorrect results [49]. The areas of hypoperfusion on BSI were compared with areas of reduced voxel number (atrophy) on MRI in order to determine if the hypoperfusion is due to cerebral atrophy in SLE patients.

In order to determine the relationship between specific clinical manifestation and pattern of reduced blood flow assessment, multiple regression was used.

Results

Demographic data

We included 40 SLE patients with mean age of 33.3 yrs (range 18–45 yrs, S.D. = 12.46). Thirty-eight were women. The mean duration of disease was 31.5 months (range 1–150, S.D. = 58.50) (Table 1).

The control group consisted of 33 healthy volunteers (29 women and 4 men) with mean age 30.6 yrs (range 20–53 yrs; S.D. = 8.65 yrs).

Clinical, laboratory and treatment features

Clinical features are summarized in Table 2. Mean SLEDAI scores was 4.7 points (S.D. = 0.74). Mean SLICC score was 3.9 (S.D. = 2.3) (Table 1). Of 48 CNS manifestations observed in SLE patients, 27 manifestations were active in 20 patients (Table 3). Although headache is the most frequently observed CNS manifestation, it occurred isolated only in two patients with inactive CNS manifestations. The other patients had other CNS manifestations, especially cognitive dysfunction, associated.

All patients were on corticosteroid dose with doses ranging from 5 to 60 mg/day. Fifteen patients were on chloroquine and eight patients (three with active and five with inactive CNS manifestations) were receiving azathioprine.

MRI findings

Areas of abnormal T2 signal, identified as small white matter lesions, were observed in 10 (25%) patients. Five of these patients had cognitive impairment, four had seizures and one patient had aseptic meningitis. All patients with MRI abnormalities had active (four patients) or past history (six patients) of CNS manifestations. On visual analysis, no further abnormalities

TABLE 1. Demographic characteristics in groups[a]

Data	SLE with active CNS disease	SLE with past history of CNS disease	Healthy controls
Age (mean ± S.D. yrs)	32.4 ± 11.8	32.6 ± 13.1	30.6 ± 8.6
Female: male ratio	18/2	20/0	29/4
Disease duration (mean months ± S.D.)	30.2 ± 10.2	33 ± 8.4	–
SLEDAI (mean ± S.D.)	5.1 ± 0.6	4.8 ± 0.9	–
SLICC (mean ± S.D.)	4.1 ± 1.5	3.9 ± 1.9	–

[a] $P > 0.05$ in all comparisons.

TABLE 2. Clinical manifestations in SLE patients with active and inactive CNS involvement

Manifestations	SLE patients with active CNS involvement, *n* (%)	SLE patients with inactive CNS involvement, *n* (%)
Arthritis	16 (80)	15 (75)
Avascular necrosis	1 (5)	2 (10)
Discoid rash	6 (30)	7 (35)
Fever	18 (90)	18 (20)
Hemolytic anaemia	4 (20)	3 (15)
Leucopenia	10 (50)	12 (60)
Malar rash	12 (60.0)	10 (50)
Nephropathy	6 (30)	7 (35)
Oral Ulcers	4 (20)	4 (20)
Photosensitivity	14 (70)	15 (75)
Raynaud's phenomenon	6 (30)	7 (35)
Serositis	7 (35)	5 (25)
Thrombocytopenia	3 (15)	4 (20)

TABLE 3. CNS manifestations in patients with active CNS involvement

CNS manifestations	CNS involvement, *n* (%)	Active CNS involvement, *n* (%)
Headache	10 (50)	4
Seizures	4 (20)	2
Acute confusional state	4 (20)	2
Psychosis	2 (10)	2
Myelopathy	2 (10)	0
Aseptic meningitis	1 (5)	1
Movement disorder	1 (5)	0
Cognitive impairment	13 (65)	10
Anxiety disorder	5 (25)	2
Mood disorder	6 (30)	4
Total number of events	48	27

TABLE 4. Brain sites where patients with active CNS involvement have less perfusion than patients with inactive CNS involvement[a]

Spatial coordinates			Anatomical location	
X	*Y*	*Z*	Side	Lobe
−42	−63	9	Left	Temporal
41	−65	−9	Right	Occipital
−39	−71	11	Left	Temporal
−50	−71	−3	Left	Occipital
−48	−17	36	Left	Frontal
−50	−26	36	Left	Parietal
33	21	42	Right	Frontal
−15	45	−23	Left	Frontal

[a]Height threshold: $T = 3.50$, cluster ≥ 20 voxels, FDR corrected ($P < 0.05$).

were detected. Applying VBM to MRI, we observed that SLE patients had a reduced voxel volumes in frontal, dorsolateral and medial temporal lobe when compared with controls ($P = 0.001$). However, there was no difference in gray matter concentration between patients with inactive and active CNS SLE manifestations ($P < 0.005$).

Brain SPECT images

We found a significant hypoperfusion, especially in frontal ($P < 0.001$), parietal ($P < 0.001$) and medial temporal lobes ($P < 0.001$), in patients with active CNS involvement when compared with patients with past history of CNS involvement, as well as when comparing SLE patients with active CNS manifestations to healthy volunteers ($P = 0.001$) (Table 4). These perfusion abnormalities occurred in areas without structural abnormalities on MRI. No difference between SLE patients without CNS manifestations and healthy volunteers was observed ($P > 0.05$).

No relation between a specific clinical manifestation, active or inactive, and pattern of reduced blood flow was observed ($P = 0.45$). There was no relationship between areas of hyperintense T2 signals on MRI and BSI hypoperfusion ($P > 0.05$).

Discussion

This is the first study using VBM analysis of SPECT images in SLE. Furthermore, using this method, we were able to differentiate active form inactive CNS manifestations in SLE patients.

SPM is an increasingly established form of neuroimaging analysis to localize statistically significant changes in spatially normalized images on a voxel-by-voxel basis [24–26]. This method does not have the subjectivity inherent in visual analysis. SPM has been applied to BSI in several studies [27–29].

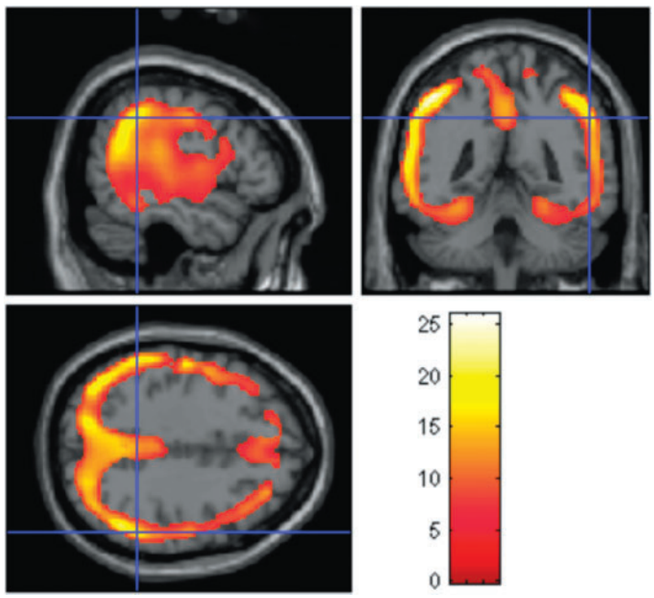

FIG. 1. The parametric map depicting the location and the statistical significance of voxels with a significant probability of reduced tracer uptake and, therefore, reduced blood flow in SLE when compared with controls. The map is illustrated over a MRI template in radiological convention ($P = 0.001$). Colour scale indicates standard deviation from controls.

SPECT scanning has been used in the assessment of CNS involvement in SLE [3, 8, 10–20, 50–61] and has proved highly sensitive, detecting abnormalities in up to 90% of patients with clinical neuropsychiatric involvement [10, 12–17, 51–53]. However, SPECT has low specificity and abnormalities are also seen in up to 20% of patients without CNS involvement [18–20]. In our study, using group analysis, we were able to detect perfusion changes only in patients with active CNS involvement. Our study revealed that patients with active CNS involvement had a global hypoperfusion, especially in the frontal, parietal and medial temporal regions when compared with SLE patients with inactive CNS involvement and controls. We did not observe a difference between patients with inactive CNS involvement and healthy controls, suggesting that the hypoperfusion was directly related to disease activity in the CNS. Comparing MRI of patients with active CNS to patients with inactive CNS, we could also demonstrate that these abnormalities are not due to cerebral atrophy in these regions.

Using the VBM method, we compared voxel-by-voxel the perfusion pattern of SLE patients with and without CNS involvement and were able to detect statistically difference in patients with active CNS involvement. These changes were not evident on visual analysis. However, it is not helpful in differentiating the different clinical sub-types of CNS involvement.

BSI hypoperfusion abnormalities have been reported in the middle cerebral artery distribution, parietal (65–80%), frontal (57–65%) and temporal lobes (46–57%) in SLE patients. Basal ganglia hypoperfusion is much less common (12–30%) [15, 59]. In neuropathological analysis, the most frequent findings in brains of SLE patients are multiple microinfarcts, which are related to vasculopathy with small vessels presenting thickening of the intima and fibrinoid degeneration [58]. Therefore, in patients with CNS manifestations, decrease cerebral blood flow due to loss

of cerebral perfusion reserve occurs earlier than detected on structural MRI. This explains why our patients with active CNS manifestations presented hypoperfusion on BSI images.

In agreement with previous data [10, 13, 15], we did not find a relationship between the type of CNS manifestations and the pattern of perfusion abnormalities. Thus, BSI scanning may be used mainly to support a clinical diagnosis of active neuropsychiatric involvement as a syndrome and not to differentiate between different types of manifestations. Perhaps the inclusion of a greater number of individual manifestations could differentiate different patterns of hypoperfusion on BSI. In order to determine if hypoperfusion could be secondary to cerebral atrophy, we analysed the MRI data of patients and controls. Although we observed a statistical difference in relation to gray matter volume reduction in patients when compared with controls, there was no difference in gray matter volume between patients with active and inactive CNS involvement. These findings support the idea that hypoperfusion could be secondary to disease activity in the CNS and not only due to the cortical atrophy.

The absence of SLE patients with quiescent SLE and SLE patients with active disease without CNS involvement is a limitation of this study. Further studies are necessary to determine the relationships between structural and functional abnormalities in these groups of patients.

Because functional abnormalities may precede anatomic abnormalities, perfusion and metabolic studies employing BSI are complementary to MRI in diagnosing CNS involvement. Qualitative analysis of BSI has an interobserver variability and the importance of combining neuroimaging studies has been emphasized in order to assess both brain structure and function.

Rheumatology	Key message
	• VBM of BSI is a useful and objective method for detecting perfusion abnormalities. • VBM was able to differentiate active from inactive CNS manifestations in SLE patients. • It is not helpful in differentiating the clinical sub-types of CNS involvement.

The authors have declared no conflicts of interest.

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ARTIGO 12

Evidence of reversible axonal dysfunction in systemic lupus erythematosus: a proton MRS study

Appenzeller S, Li LM, Costallat LT, Cendes F.

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Evidence of reversible axonal dysfunction in systemic lupus erythematosus: a proton MRS study

Simone Appenzeller,[1,3] Li Min Li,[2,3] Lilian T. L. Costallat[1] and Fernando Cendes[2,3]

[1]Departments of Rheumatology and [2]Neurology and [3]Neuroimaging Laboratory, University of Campinas, São Paulo, Brazil

Correspondence to: Dr Fernando Cendes, MD, PhD, Department of Neurology, FCM–UNICAMP, Cidade Universitária Zeferino Vaz, Campinas, São Paulo, Brazil, CEP 13083-970
E-mail: fcendes@unicamp.br

Our objective was to investigate axonal dysfunction in patients with systemic lupus erythematosus (SLE) using proton magnetic resonance spectroscopy (^{1}H-MRS).We studied prospectively 90 SLE patients (mean age of 32.5 years) and 23 normal volunteers (mean age of 33.8 years). We performed single voxel proton MRS using point resolved spectroscopy sequence over the superior–posterior region of the corpus callosum. We measured signals from *N*-acetyl compounds [*N*-acetylaspartate (NAA)] at 2.01 p.p.m., choline-based compounds (Cho) at 3.2 p.p.m. and creatine and phosphocreatine containing compounds (Cr) at 3.0 p.p.m. and determined NAA/Cr ratios. After 12 months, MRI and MRS were repeated in 50 patients and 9 volunteers. Patients were divided according to disease activity (measured by SLE disease activity index) during initial and follow-up MRS. We performed paired *t*-test and ANOVA with Tukey's *post hoc* comparisons to evaluate group differences. At study entry, 29 patients had active SLE with involvement of central nervous system (CNS) and 28 patients had active SLE without CNS manifestations. A total of 14 patients had inactive SLE with past CNS presentation, and 19 had inactive SLE without history of CNS involvement. NAA/Cr ratios were significant lower in patients with active SLE, independently of CNS involvement, when compared with patients with inactive SLE ($P = 0.005$) and controls ($P = 0.01$). We observed a significant increase in NAA/Cr ratio in 15 patients who had active SLE at initial MRS and inactive SLE at follow-up ($P = 0.04$). In 10 patients with active SLE both at initial and at follow-up MRS we observed a reduction in NAA/Cr ratio ($P = 0.02$). By contrast, there was a significant reduction of NAA/Cr ratio in 15 patients who had inactive SLE at initial MRS and active SLE at follow-up ($P = 0.001$). In 10 patients with inactive SLE both at initial and at follow-up MRS NAA/Cr ratio did not change ($P = 0.2$). This study shows evidence of axonal dysfunction in patients with active SLE, independently of CNS manifestations that may be reversible, at least in part, during periods of inactivity of disease.

Keywords: axonal dysfunction; magnetic resonance spectroscopy; *N*-acetylaspartate; systemic lupus erythematosus

Abbreviations: ACR = American College of Rheumatology; Cho = choline-based compounds; CNS = central nervous system; Cr = creatine and phosphocreatine containing compounds; LA = lupus anticoagulant; MRS = magnetic resonance spectroscopy; NAA = *N*-acetylaspartate; PRESS = point resolved spectroscopy; ^{1}H-MRS = proton magnetic spectroscopy; ROI = region of interest; SLE = systemic lupus erythematosus; SLEDAI = SLE disease activity index

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that is frequently manifested by involvement of the central nervous system (CNS) (Omdal *et al.*, 1988; Adelmann *et al.*, 1986). The neuropsychiatric symptoms vary from overt neurological and psychiatric disorders to more subtle signs such as headache, mood disorders and defects in cognitive function (Adelmann *et al.*, 1986; Omdal *et al.*, 1988; Carbotte *et al.*, 1992; West, 1994; Chinn *et al.*, 1997; Sanna *et al.*, 2003; Sibbitt *et al.*, 2003). Although clinical assessment is still the cornerstone in the diagnosis of neuropsychiatric SLE, the diagnosis is often difficult and remains presumptive in some patients.

Proton magnetic spectroscopy (^{1}H-MRS) of human brain *in vivo* allows non-invasive quantification of biological compounds. It contains a large signal from *N*-acetyl groups that originates largely from *N*-acetyl aspartate (NAA), a compound localized exclusively in neurons and neuronal

processes (Moffett *et al.*, 1991; Simmons *et al.*, 1991). The neuronal marker NAA is reduced in certain diseases with neuronal loss or dysfunction, including cerebrovascular and neurodegenerative diseases, tumours, multiple sclerosis and epilepsy (Miller *et al.*, 1993; Sibbitt and Sibbitt, 1993; Lanfermann *et al.*, 1995; Tien *et al.*, 1996; Wang *et al.*, 1996; Cendes *et al.*, 1997*a*, 2002). In addition, NAA abnormalities may be reversible in certain conditions (De Stefano *et al.*, 1995; Cendes *et al.*, 1997*b*)

In SLE, ^{1}H-MRS has been performed in an attempt to detect early CNS involvement (Sibbitt and Sibbitt, 1993; Sibbitt *et al.*, 1994, 1997; Davie *et al.*, 1995; Passe *et al.*, 1995; Brooks *et al.*, 1997; Colamussi *et al.*, 1997) or to demonstrate abnormalities in some patients with neuropsychiatric SLE in whom structural MRI failed to show any focal changes (Sibbitt *et al.*, 1994, 1997; Davie *et al.*, 1995; Friedman *et al.*, 1998).

The purpose of this study was to determine the presence of axonal dysfunction in SLE patients with and without evidence of CNS involvement. We also performed follow-up studies in these patients in order to determine if these abnormalities are transient or permanent.

Subjects and methods

Subjects

In this prospective study, we evaluated 150 consecutive patients (138 women) with four or more criteria for SLE (Tan *et al.*, 1982) seen regularly at our Rheumatology Unit. We excluded patients who were not able to undergo MRI, such as patients with claustrophobia, pacemaker and prosthetic valves, and patients with previous clinical conditions that could influence cerebral atrophy, such as stroke, arterial hypertension, diabetes mellitus, alcohol and drug abuse, and malignancy. Patients satisfying the American College of Rheumatology (ACR) criteria for rheumatoid arthritis, systemic sclerosis, Sjögren syndrome (primary or secondary) or other connective tissue disease and with drug-induced SLE were also excluded. After initial evaluation a total of 10 patients have been excluded. We used the classification proposed by the ACR to analyse neuropsychiatric involvement (ACR, Ad Hoc Committee on Neuropsychiatric Lupus, 1999). We considered only primary involvement of the CNS by SLE.

The control group consisted of 23 healthy volunteers with similar age and gender distribution. The study was approved by the Ethical Committee of our institution and informed written consent was obtained from each subject.

Clinical, serologic and treatment features of SLE patients

Data on age at disease onset and disease duration were collected for each patient. Disease duration was defined as the initial manifestation clearly attributable to SLE until the day of magnetic resonance spectroscopy (MRS) acquisition. Disease activity was measured through SLE disease activity index (SLEDAI) (Bombardier *et al.*, 1992) and considered active if scores were >8 points.

All clinical manifestations and laboratory test findings were obtained at baseline visit by careful chart review. Data are systematically recorded in special database on quarterly basis visits by the same investigators using a structured questionnaire (SA and LTLC). The following clinical manifestations were analysed: malar rash, discoid lesions, subacute cutaneous lesions, photosensitivity, oral ulcers, arthritis, serositis, nephritis, neurological and psychiatric involvement, thrombocytopenia, haemolytic anaemia, Raynaud's phenomenon, thrombosis, myositis, lung involvement and lymphadenopathy.

Nephritis was diagnosed on the basis of proteinuria exceeding 0.5 g/l with abnormal urinary sediment and/or histological findings. Nephrotic syndrome was defined as proteinuria in excess of 3.5 g/day. Haematological alterations were ascribed to lupus only in the absence of bone marrow suppression (leukopenia <4000 cells/mm^3; thrombocytopenia <100 000/mm^3; haemolytic anaemia with positive Coombs test). Antinuclear antibodies (ANA) were determined by indirect immunofluorescence using Hep 2 as the substrate and regarded as positive if >1:40. Anti-double-stranded DNA (AdsDNA) antibodies were determined by indirect immunofluorescence using Chrithidia as substrate and considered positive if >1:10. Precipitating antibodies to extractable nuclear antigens (ENA), including Ro (SSA), La (SSB) and Sm were detected by immunodiffusion and/or microhaemagglutination. Anticardiolipin antibodies (aCL) of the IgG and IgM isotypes were measured by the enzyme-linked immunosorbent assay (ELISA) method as described (Brandt *et al.*, 1995). Lupus anticoagulant (LA) activity was detected by coagulation assays in platelet free plasma obtained by double centrifugation, following the recommendation of the subcommittee on LA of the Scientific and Standardization Committee of the International Society of Thrombosis and Homeostasis (Harris *et al.*, 1987).

CNS manifestations were recorded following ACR case definitions (ACR Ad Hoc Committee on Neuropsychiatric Lupus, 1999) and considered active when present at the day of MRI/MRS acquisition.

Patients had clinical and laboratory evaluation at the time of their first MRI/MRS examination and were divided in groups, according to their disease activity, as follows: Group A, active SLE and CNS involvement; Group B, active SLE without evidence of CNS involvement; Group C, inactive SLE and history of CNS manifestations; and Group D, inactive SLE without previous history of CNS involvement. Group E consisted of normal volunteers. At the time of the second MRI/MRS patients were also divided into groups, considering their disease activity at study entry and at follow-up: Group F, active SLE at initial MRS and inactive SLE at follow-up; Group G, inactive SLE at initial MRS and active SLE at follow-up; Group H, inactive SLE both at initial and at follow-up; and Group I, active SLE both at initial and at follow-up MRS. A subgroup of nine normal volunteers had repeated MRS with an interval of 21 months on average (Group J).

Group A had SLEDAI scores indicating active SLE disease even after excluding CNS manifestations from the SLEDAI.

Total doses of corticosteroids and other immunosuppressant medications used since the onset of disease were calculated by careful review of the medical charts. A total of 10 patients with incomplete charts were excluded from this analysis. Doses of oral and parenteral corticosteroids were analysed and converted to the equivalent doses of prednisone. The cumulative dose of corticosteroids used was calculated by the sum of daily dosages versus time (days) of treatment.

MRI and MRS protocol

All subjects had MRI and MRS examination for the purpose of this study, using an Escint 2Tesla scanner (Prestige, Haifa, Israel).

Our MRI protocol consisted of:

(i) Sagittal T1 spin echo = 6 mm thick, flip angle = 180°, repetition time (TR) = 430, echo time (TE) = 12, matrix 200 × 350, field of view (FOV) = 25 × 25 cm;
(ii) Coronal images, perpendicular to long axis of hippocampus, defined by the sagittal images:
  (a) T2-weighted 'fast-spin echo' (FSE) = 3 mm thick, flip angle = 120°, TR = 4800, TE = 129, matrix 252 × 320, FOV = 18 × 18 cm;
  (b) T1-weighted inversion recovery (IR) = 3 mm thick, flip angle = 200°, TR = 2800–3000, TE = 14, inversion time (TI) = 840, matrix 130 × 256, FOV = 16 × 18 cm;
(iii) Axial images parallel to the long axis of the hippocampi:
  (a) T1-weighted gradient echo = 3 mm thick, flip angle = 70°, TR = 200, TE = 5, matrix 180 × 232, FOV = 22 × 22 cm;
  (b) Fluid attenuated inversion recovery (FLAIR) = 4 mm thick, flip angle = 120°, TR = 6800, TE = 129, matrix 252 × 328, FOV = 21 × 23 cm;
(iv) T1-weighted 3D gradient echo, acquired in the sagittal plane for multiplanar and reconstruction: 1 mm thick, flip angle = 35°, TR = 22, TE = 9, matrix 256 × 220, FOV = 23 × 25 cm.

Single voxel ^{1}H-MRS was acquired using point resolved spectroscopy (PRESS) sequence (Bottomley, 1987) (TR = 1500 ms, TE = 135 ms, NEX = 200) over the superior–posterior region of the left hemisphere at the level of corpus callosum. This area was previously analysed using T1-weighted, T2-weighted and FLAIR sequences. Patients with white matter lesions in this region were not included (n = 30). Therefore, all patients evaluated in this study had normal appearing white matter within the MRS region of interest (ROI). After the acquisition of scout anatomical images in sagittal planes for localization of corpus callosum, one single voxel (2 × 5 × 1 cm) was placed over the ROI (Fig. 1). Prior to the acquisition, a localized shimming at the ROI was performed to ensure adequate field homogeneity followed by water suppression adjustment.

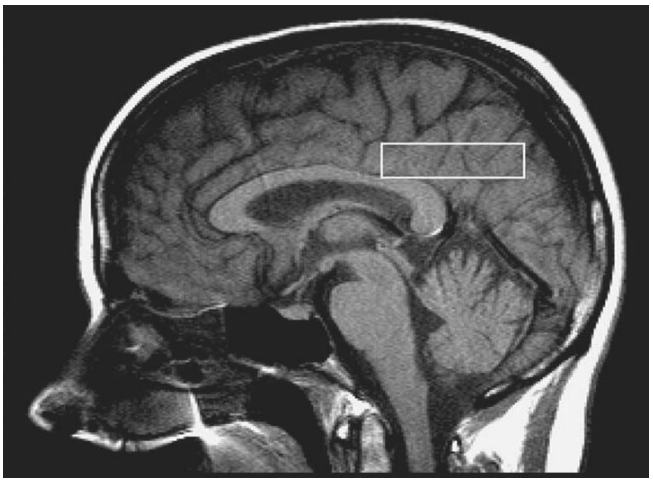

Fig. 1 Placement of region of interest (ROI).

The spectra were post-processed using software supplied by the machine manufacturer (Elscint 2T Prestige, Haifa, Israel). After zero-filling and baseline correction we determined peak areas by integration of the corresponding signals from *N*-acetyl compounds (NAA) at 2.01 p.p.m., choline-base compounds (Cho) at 3.2 p.p.m. and creatine and phosphocreatine containing compounds (Cr) at 3.0 p.p.m.. The spectra were scaled in relation to creatine values. Ratios of NAA/Cr were used for analyses.

Spectral acquisition, quantification and analysis were performed by one investigator (S.A.). The evaluation was cross-checked by two spectroscopists (L.M.L. and F.C.), blinded to the name and clinical data of patients and volunteers. The quality of the spectral analysis was judged independently by these two investigators from the parameters linewidth and signal-to-noise ratio (Fig. 2) and spectra with broad peaks and poor separation of individual peaks were excluded from analysis. Values <2 SD from the mean of controls were considered abnormal. A total of 10 patients were excluded because of bad quality spectra.

Therefore, 90 patients (88 women) with mean age of 32.5 years (range 18–59 years, SD = 13.1) were available for evaluation for this study. We repeated MRI and MRS exams in 50 of these patients (48 women) and in 9 volunteers after a minimum interval of 1 year.

Statistics

We performed analysis of variance (ANOVA) to test differences among the groups, followed by *post hoc* Tukey's HSD for pairwise comparison if necessary. Follow-up MRS results were analysed using paired *t*-test with Bonferroni's correction for multiple comparisons. Statistical significance was considered to be present for $P < 0.05$.

Results

Demographic data

We analysed MRS data of 90 SLE patients. In relation to the different patients groups at study entry, we observed

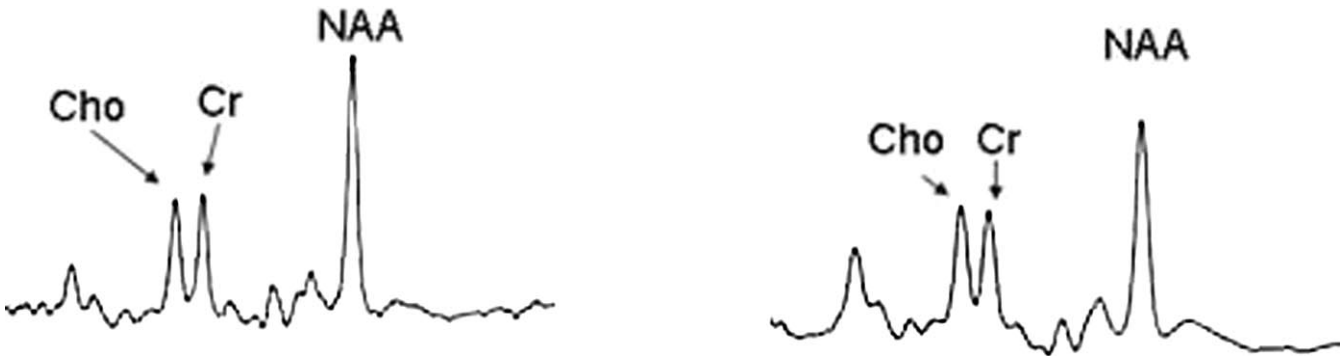

Fig. 2 Illustrative proton magnetic spectra from posterior supraventricular region from a volunteer (left) and one SLE patient (right).

the following age and gender distribution: Group A: 29 patients (28 women) with mean age of 32.2 (range 18–56; SD = 12.9); Group B: 28 patients (27 women) with mean age of 33.0 (range 18–59; SD = 13.1); Group C: 14 patients (14 women) with mean age of 31.9 (range 18–50; SD = 13.7); Group D: 19 patients (19 women) with mean age of 33.5 (range 18–56; SD = 12.9).

The control group (Group E) consisted of 23 healthy volunteers (19 women) with mean age of 33.8 years (range 20–60, SD = 13.7 years)

MRI and ^{1}H-MRS studies were repeated in 50 SLE patients (48 women) with mean age of 33.3 years (ranging from 18 to 57 years; SD = 12.2) at study entry. In relation to the different patients groups at follow-up, we observed the following gender and age distribution: Group F, 15 patients (14 women) with mean age of 32.5 (range 18–55; SD = 12); Group G, 15 patients (14 women) with mean of age 33.0 (range 18–57; SD = 13.1); Group H, 10 patients (10 women) with mean age of 32.3 (range 18–50; SD = 13); Group I, 10 patients (10 women) with mean age of 33.6 (range 18–50; SD = 13).

The mean interval between the two ^{1}H-MRS of SLE patients was 19 months (range 12–24 months; SD = 2.3)

MRS studies were repeated in 9 volunteers (7 women) of Group J with mean age of 32.1 (range 20–60; SD = 14.1) at study entry. The mean interval between MRS examinations was 21 months (range 18–24 months; SD = 1.8).

There was no statistical difference between the age and gender distribution among the different groups of patients (Groups A–D and F–I) and volunteers (Groups E and J).

Clinical, laboratory and treatment features

The mean disease duration was 64.5 months (range 1–362 months, SD = 48.50) at study entry and 93 months (range 12–421 months, SD = 45.45) at follow-up MRS. At baseline, 65 episodes of CNS manifestations had occurred in 43 patients (29 patients with active and 14 with inactive CNS manifestations) (Table 1). At the time of MRS scans, 57 patients had active SLE, with SLEDAI scores ranging between 10 and 20 (mean 14.56, SD = 6.52). Active CNS manifestations at the first MRS scan were observed in 29 of 57 patients with active SLE. Number of patients who had inactive SLE at the time of first MRS was 33 and 14 of them had past history of CNS involvement and 19 did not. All patients were on steroid use on the day of MRS study, with doses ranging from 5 to 80 mg/day (mean 43 mg/day). IgG antiphospholipid antibodies were positive in 32 patients.

Table 1 Summary of cumulative neuropsychiatric manifestations that occurred in 43 patients at study entry

Neuropsychiatric manifestations	Number of CNS events (%)
Headache	18 (27.7)
Cognitive impairment	20 (30.8)
Mood disorder	10 (15.4)
Seizures	7 (10.8)
Acute confusional state	5 (7.7)
Psychosis	2 (3.1)
Mononeuropathy	1 (1.5)
Cranial neuropathy	1 (1.5)
Aseptic meningitis	1 (1.5)
Total number of events	65

Disease activity and MRS

Median NAA/Cr values for each group of patients were: (A), active SLE and CNS involvement, 1.65 (SD = 0.25); (B), active SLE without evidence of CNS involvement, 1.67 (SD = 0.27); (C), inactive SLE and history of CNS manifestations, 1.82 (SD = 0.23); (D), inactive SLE without previous history of CNS involvement, 1.98 (SD = 0.21); (E), volunteers, 1.86 (SD = 0.15) (Table 2).

Median NAA/Cr ratios were significantly lower in patients with active SLE (Groups A and B), when compared with patients with inactive SLE (Groups C and D) (P = 0.005) and volunteers (Group E) (P = 0.01) (Fig. 3).

We did not find a correlation between daily corticosteroid dose or cumulative corticosteroid dose and median NAA/Cr value (r = 0.4).

Follow-up study

Patients were divided, according to their disease activity at study entry and at follow-up MRS, into four groups. Group F (n = 15) with active SLE at initial MRS (median NAA/Cr = 1.6; SD = 0.36) and inactive SLE at follow-up (median NAA/Cr = 2.1; SD = 0.31); P = 0.04. Group G (n = 15) with inactive SLE at initial MRS (median NAA/Cr = 1.9; SD = 0.12) and active SLE at follow-up (median NAA/Cr = 1.3; SD = 0.21); P = 0.001. Group H (n = 10) with inactive SLE both at initial (median NAA/Cr = 2.0; SD = 0.48) and at follow-up (median NAA/Cr = 2.1; SD = 0.42) MRS; P = 0.2. Group I (n = 10) with active SLE both at initial (median NAA/Cr = 1.7; SD = 0.21) and at follow-up (median NAA/Cr = 1.38; SD = 0.48) MRS; P = 0.02 (Fig. 4). The NAA/Cr ratios remained constant in

Table 2 Median NAA/Cr and Cho/Cr values

Groups	Median NAA/Cr at initial MRS (±SD)	Median Cho/Cr at initial MRS (±SD)
A	1.65 (0.25) ↓	1.03 (0.3)
B	1.67 (0.27) ↓	0.98 (0.4)
C	1.82 (0.23)	1.1 (0.2)
D	1.98 (0.21)	1.0 (0.3)
E	1.86 (0.15)	0.96 (0.2)

Values in 90 patients and 23 normal volunteers at study entry. Groups: (A), Active SLE and CNS involvement; (B), active SLE without evidence of CNS involvement; (C), inactive SLE and history of CNS manifestations; (D), inactive SLE without previous history of CNS involvement; and (E), normal volunteers.
↓: Significantly lower than normal volunteers.

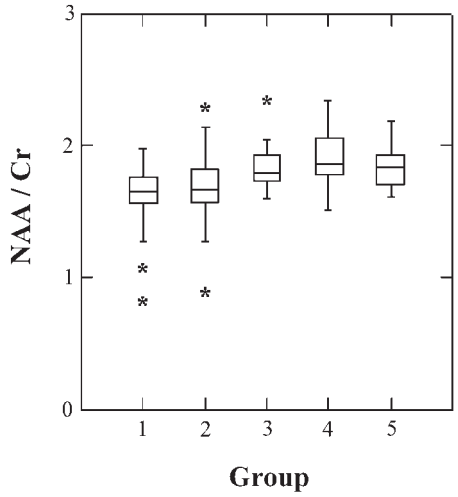

Fig. 3 Box-and-whiskers plot showing median NAA/Cr ratio in SLE patients with active SLE and CNS manifestations. No. 1 represents Group A, patients with active SLE without CNS manifestations; No. 2 represents Group B, inactive SLE patients with past history of CNS involvement; No. 3 represents Group C, inactive patients without history of CNS involvement; No. 4 represents Group D and No. 5 represents volunteers, Group E. The box extends from the 25th percentile to the 75th percentile, with a horizontal line at the median (50th percentile). Whiskers extend down to the smallest value and up to the largest. Outliers are represented by an asterisk (*).

normal volunteers (initial median NAA/Cr = 1.86; SD = 0.17; follow-up MRS: median NAA/Cr = 1.89; SD = 0.18. Cho and Cr values remained stable during follow-up periods in patients and controls (Table 3).

MRI findings and MRS

Subtle abnormal MRI findings, in areas outside and far from the MRS ROI, (hyperintense areas suggestive of cerebral microinfarcts) in cortical and subcortical regions were observed in 53 patients at baseline study. These MRI abnormalities were more frequently observed in patients with antiphospholipid antibodies ($P = 0.04$). The number of lesions was counted in all MRI scans. Visual analysis of MRI did not demonstrate significant increase in the number of these lesions during the follow-up study as compared with baseline study.

NAA/Cr ratios were lower in SLE patients with MRI abnormalities when compared with patients with normal MRI ($P = 0.028$). No difference in Cho/Cr values between patients with and without MRI abnormalities was observed.

Antiphospholipid antibodies and MRS

SLE patients with positive antiphospholipid antibodies had lower NAA/Cr ($P = 0.021$) values when compared with patients without antiphospholipid antibodies. The frequency of antiphospholipid antibodies was distributed equally among these groups.

Discussion

Although several studies (Sibbitt *et al.*, 1994, 1997; Davie *et al.*, 1995; Friedman *et al.*, 1998, Castellino *et al.*, 2005) showed the usefulness of ^{1}H-MRS in CNS manifestations in SLE, only one previous study (Castellino *et al.*, 2005) analysed SLE patients without CNS manifestations. In our study we observed that SLE patients with active disease had low relative NAA signal intensity, indicating axonal dysfunction, when compared with SLE patients with inactive disease and volunteers. This occurred independently of clinical CNS involvement as defined by the ACR criteria (ACR Ad Hoc Committee on Neuropsychiatric Lupus, 1999).

Cerebrovascular abnormalities may be the basis of diffuse cerebral injury in SLE. Small-vessel injury is primarily associated with decreased NAA/Cr ratio, while medium-vessel injury is primarily associated with increased Cho/Cr ratio (Davie *et al.*, 1995). In our study we observed that patients with white matter abnormalities in regions outside the MRS ROI and patients with antiphospholipid antibodies had more pronounced decreased NAA/Cr ratios, supporting the theory of small vessel involvement in SLE. We did not observe differences in Cho/Cr ratio among the subgroups of SLE patients and normal volunteers.

The ROI for MRS examination in patients with SLE should best reflect the area where the metabolic changes might precede the morphological changes. MRS studies have already been performed in the supraventricular and subcortical white matter (Sibbitt and Sibbitt, 1993; Sibbitt *et al.*, 1994; Friedman *et al.*, 1998; Lim *et al.*, 2000) and in the basal ganglia (Lim *et al.*, 2000). In this study the normal appearing white matter was chosen, despite the presence of small hyperintense lesions in other areas of the brain, because most of the time these MRI abnormalities are referred to as non-specific findings. MRS abnormalities in these regions would support the idea that MRS could precede the appearance of hyperintense lesions in T2 or FLAIR sequences due to CNS involvement of SLE (Castellino *et al.*, 2005). Other studies (Sanna *et al.*, 2003; Sibbitt *et al.*, 2003) have shown the association of non-specific white matter abnormalities and signs and symptoms of CNS manifestations in SLE. The specific susceptibility of the white matter to small vascular lesions is thought to be due to unique vascularization of this tissue. Blood is supplied to the white matter by means of single sources, rendering the deep white matter more vulnerable to vascular insults. In SLE the precise biochemical mechanism that explains the basis of CNS involvement is still unknown (Lim *et al.*, 2000). We therefore choose the supraventricular region, in order to test the hypothesis that early NAA changes might occur in this area in patients with overt CNS manifestations. Our results confirm previous findings (Sibbitt and Sibbitt, 1993; Sibbitt *et al.*,1994, Castellino *et al.*, 2005) and support this hypothesis. However, in the present study, after 19 months of follow-up, we did not observe that low NAA/Cr ratio predisposed to the appearance of structural lesions detectable by MRI. Perhaps longer periods of observation are necessary to

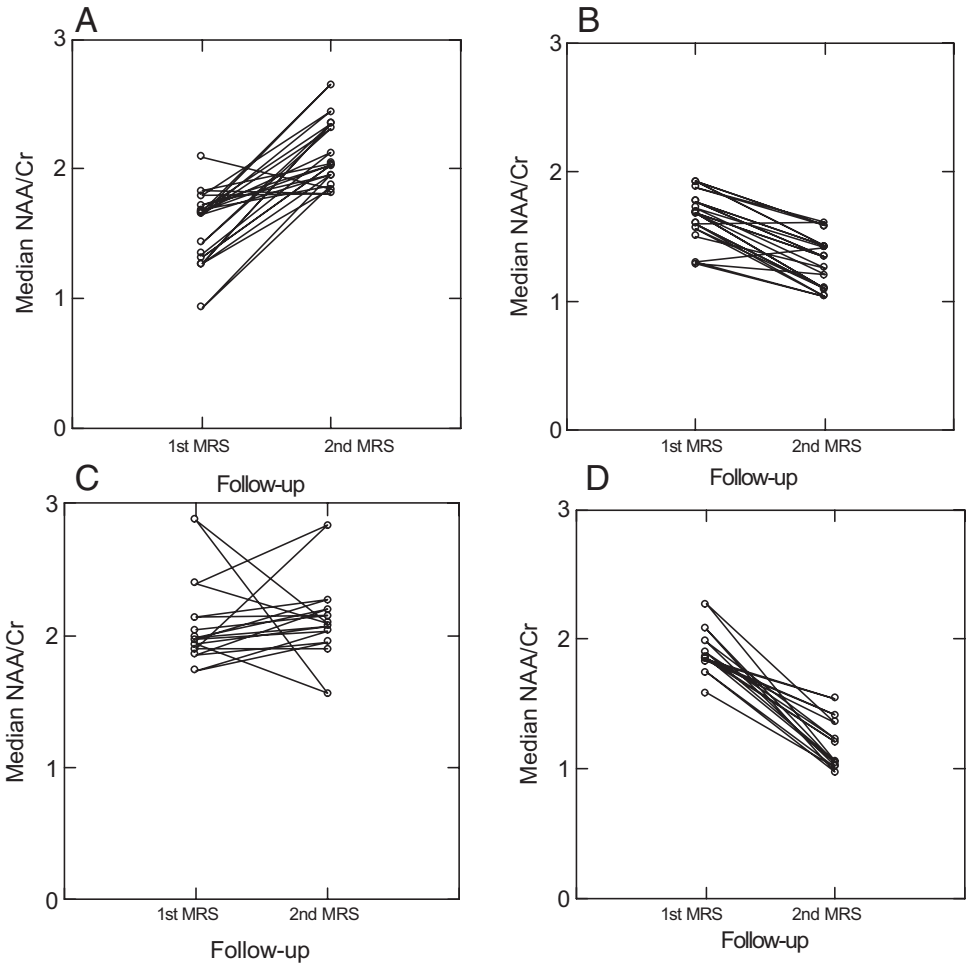

Fig. 4 Paired *t*-test comparing MRS finding at study entry and at follow-up. Panel (**A**), 15 patients (Group F) with active SLE at initial MRS and inactive SLE at follow-up ($P = 0.04$). Panel (**B**), 15 patients (Group G) with inactive disease at initial MRS and active disease at follow-up ($P = 0.001$). Panel (**C**), 10 patients (Group H) with inactive SLE both at initial MRS and at follow-up ($P = 0.2$). Panel (**D**), 10 patients (Group I) with active disease both at initial MRS and at follow-up ($P = 0.02$).

Table 3 Median NAA/Cr and Cho/Cr values

Groups	Median NAA/Cr at initial MRS (±SD)	Median NAA/Cr at follow-up MRS (±SD)	*P*-value	Median Cho/Cr at initial MRS (±SD)	Median Cho/Cr at follow-up MRS (±SD)	*P*-value
F	1.6 (0.36)	2.1 (0.31)	0.04	1.09 (0.4)	0.98 (0.37)	0.4
G	1.9 (0.12)	1.3 (0.21)	0.001	1.1 (0.3)	1.0 (0.3)	0.7
H	2.0 (0.48)	2.1 (0.42)	0.2	0.93 (0.2)	0.93 (0.2)	0.9
I	1.76 (0.17)	1.38 (0.48)	0.02	0.96 (0.2)	0.91 (0.26)	0.4
J	1.86 (0.17)	1.89 (0.18)	0.12	0.95 (0.16)	0.94 (0.17)	0.2

Values in 50 patients and 9 normal volunteers at follow-up. Groups: (F), with active SLE at initial MRS and inactive SLE at follow-up; (G), with inactive SLE at initial MRS and active SLE at follow-up; (H), with inactive SLE both at initial and at follow-up; (I), with active SLE both at initial and at follow-up MRS; and (J), follow-up volunteers.

detect the appearance of these lesions as suggested by a previous study (Castellino *et al.*, 2005).

^{1}H-MRS may be more sensitive in the detection of early CNS involvement in SLE patients. A decrease in NAA level, as shown in this study, indicates not only loss of neurons or neuronal activity, but also neuronal dysfunction secondary to myelin breakdown (Sibbitt and Sibbitt, 1993; Sibbitt *et al.*, 1994; Lim *et al.*, 2000). Decreased NAA/Cr ratio in supraventricular region suggests axonal dysfunction due to extensive small-vessel injury in normal appearing white matter. In our study we also observed that patients with active SLE, independently of CNS manifestations, also had decreased NAA/Cr ratio. We also demonstrated for the first time that the relative NAA reduction in SLE is transient and it is

probably dependent on disease activity. We observed that SLE patients with active disease had low relative NAA signal intensity that returned to normal range after disease remission. In the group of patients with inactive disease both at baseline and follow-up MRS, there was no difference in NAA values as compared with the control group. On the other hand, in the group of patients with active disease both at baseline and follow-up MRS, there was a progressive decrease in NAA values. These findings suggest that axonal dysfunction in SLE patients may be transient and related to disease activity, independently of the presence of CNS involvement or corticosteroid use.

In the follow-up graphs (Fig. 4) we observed that not all patients had the same pattern of NAA/Cr increase or reduction. Further studies are necessary to determine the factors associated with the intensity and rate of NAA/Cr loss or recovery. These factors may help to explain the outliers in Fig. 4. It is possible that the NAA reduction precedes the clinical signs and symptoms of SLE disease activity, among other factors. This could explain the drop of relative NAA/Cr values in the three patients who had inactive SLE disease at both initial and follow-up MRS. However, it is difficult to explain the two outlier patients in Group H who had a more pronounced increase in NAA/Cr values.

The fall of NAA reflects neuronal loss or dysfunction (Passe *et al.*, 1995; Tsai and Coyle, 1995). Previous studies have correlated NAA loss with cerebral atrophy (Sibbitt *et al.*, 1994), cognitive dysfunction and damage index (Brooks *et al.*, 1999). NAA recovery, after initial reduction, has not been reported in SLE before, but was observed in multiple sclerosis (Wolinsky and Narayana, 2002), stroke (Saunders *et al.*, 1995), schizophrenia (Haussinger *et al.*, 1994) and epilepsy (Cendes *et al.*, 1997b)

Cho concentrations, on the other hand, are reported to rise in SLE patients with CNS involvement (Brooks *et al.*, 1997, 1999; Sibbitt *et al.*, 1997; Castellino *et al.*, 2005), but the cause has not been determined, although it may be due to myelin breakdown secondary to neuronal loss or due to inflammatory process (Brooks *et al.*, 1997; Brooks *et al.*, 1999).

In this study we used Cr values as an internal reference, although it has not been demonstrated that Cr is stable in SLE. The facts that we performed MRS in normal appearing white matter and that Cho/Cr ratios were not different among groups give support to the assumption that eventual changes in Cr were minimal and did not produce a great influence in our results.

In conclusion, our findings suggest that SLE activity, independently of CNS involvement, is associated with white matter insult, often not evident by structural MRI or by clinical manifestations. The relative NAA decrease may be a surrogate marker for disease activity in SLE patients and may be useful for follow-up of disease activity. These findings are limited to the area in the brain studied here, and further studies are necessary to confirm these findings.

Acknowledgements

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ARTIGO 13

Increased choline/creatinine ratio on MRS may predict appearance of white matter lesions in systemic lupus erythematosus

Appenzeller S, Li LM, Costallat LT, Cendes F.

Increased choline/creatinine ratio on MRS may predict appearance of white matter lesions in systemic lupus erythematosus

Submetido

Increased choline/creatinine ratio on MRS may predict appearance of white matter lesions in systemic lupus erythematosus

Simone Appenzeller[1,3], MD, Li Min Li[2,3], MD, PhD, Lilian TL Costallat[1], MD, PhD, Fernando Cendes[2,3], MD, PhD

Departments of Rheumatology[1] and Neurology[2], and Neuroimaging Laboratory[3]

University of Campinas, São Paulo – Brazil

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Correspondence to: *Fernando Cendes, MD, PhD*

Department of Neurology,

FCM – UNICAMP

Cidade Universitária Zeferino Vaz

Campinas SP, Brazil, CEP 13083-970

FAX: +55 19 3289-1818

Email: fcendes@unicamp.br

Abstract

Objective: To investigate proton magnetic resonance spectroscopy (MRS) in patients with systemic lupus erythematosus (SLE) with small hyperintense lesions on T2-weithed MRI.

Methods: We studied 30 SLE patients who had lesions in MRS ROI and 23 controls. We performed single voxel proton MRS over the superior-posterior region of the corpus callosum. We measured signals from *N*-acetyl-compounds (NAA), choline (Cho) and creatine+phosphocreatine (Cr) and determined NAA/Cr and Cho/Cr ratios. After a minimum of 12 months, MRI and MRS were repeated in all patients and 9 volunteers. We performed paired T-test and Anova with Tukey´s post hoc comparisons to evaluate group differences.

Results: Ten patients had MRI hyperintense lesions in the MRS-ROI at baseline, and 20 had lesions in follow-up MRI but no lesions at baseline MRI. They had increased Cho/Cr values at both MRS when compared to normal controls (p=0.001). In addition, there was an increase in Cho/Cr values when patients' baseline and follow up MRS were compared (p=0.001). Controls had no change in Cho/Cr between scans (p=0.56). NAA/Cr was lower in patients with active disease and returned to normal range in patients with inactivity.

Conclusion: Increased Cho/Cr in normal appearing white matter may be indicative of future appearance of hyperintense T2-weighet MRI lesions.

Introduction

Magnetic resonance imaging (MRI) is currently considered the standard technique for determination of morphological brain abnormalities in systemic lupus erythematosus (SLE) patients (Castellino et al., 2005; Stimmler et al., 1993). Reported prevalence of detectable lesions varies from 62% to 100% (Stimmler et al., 1993; McCune et al., 1998; Bell et al., 1991; Sibbitt et al., 1989; Aisen et al., 1985; West et al., 1995; Karassa et al., 2000). Imaging findings in SLE patients vary from ischemic lesion to frequently found small hyperintense lesions in deep white matter. These lesions often referred to as nonspecific lesion, may be related to small foci of ischemia and may be

associated with CNS manifestations (West et al., 1995; Karassa et al., 2000) and with the presence of antiphospholipid antibodies (Karassa et al., 2000; Sanna et al., 2000).

Proton magnetic resonance spectroscopy (^{1}H-MRS) has proved to be a non-invasive tool for detecting neuronal metabolic dysfunction in several neurological diseases, including SLE (Colamussi et al., 1995; Nossent et al., 1991; Rubbert et al., 1993; Sibbitt et al., 1993; Castillo et al., 1996). This technique shows four major spectra, depending of the echo time used during acquisition, corresponding to different metabolites: N-acetylaspartate (NAA), choline (Cho), and creatine (Cr). Altered metabolite ratios have been observed even in the absence of MRI lesions; however, few studies have been carried out in SLE patients with and without overt neurological involvement (Sibbitt et al., 1994; Handa et al., 2003; Lim et al., 2000; Axford et al., 2001; Peterson et al., 2003; Appenzeller et al., 2005).

In a previous study (Appenzeller et al., 2005), we demonstrated that patients with active SLE without white matter lesions in the MRS region of interest (ROI) had a decrease in NAA/Cr values, independently of the presence of CNS manifestations. Furthermore, there was a recover in NAA/Cr values after disease control. In the present study we analyzed only patients who had lesions in MRS ROI in order to determine if MRS may be helpful to predict the appearance of new white matter lesions in patients with SLE.

Subjects and Methods

Subjects

We selected 30 patients who had follow-up MRIs and white matter lesions inside the MRS region of interest (ROI) in at least one MRI. The presence of these lesions was determined by visual analysis of MRI using FLAIR and T2-wheighted sequences. None of them were included in a previous study (Appenzeller et al., 2005) in which we did evaluate patients with normal appearing white matter in both baseline and follow up MRS ROI. These patients were selected among a group of 150 consecutive patients (138 women) with four or more criteria for SLE (Tan et al., 1982) seen regularly at our Rheumatology Unit. From this initial group, we excluded patients that were not able to undergo MRI, such as patients with claustrophobia, pacemaker and prosthetic valves, and patients with previous clinical conditions that could influence cerebral atrophy, such as stroke, arterial hypertension, diabetes mellitus, alcohol and drug abuse, and malignancy. Patients satisfying

the American College of Rheumatology (ACR) criteria for rheumatoid arthritis, systemic sclerosis, Sjögren syndrome (primary or secondary) or other connective tissue disease and with drug-induced SLE were also excluded (Appenzeller et al., 2005).

The control group consisted of 23 healthy volunteers with similar age and gender distribution. The study was approved by Ethical Committee of our institution and informed written consent was obtained from each subject.

Clinical, serologic and treatment features of SLE patients

Data on age at disease onset and disease duration were collected for each patient. Disease duration was defined as the initial manifestation clearly attributable to SLE until the day of MRS acquisition. Disease activity was measured through SLE disease activity index (SLEDAI) (Bombardier et al., 1992) and considered active if scores were higher than eight points.

All clinical manifestations and laboratory test findings were obtained at baseline visit by careful chart review. Data are systematically recorded in special database on quarterly basis visits by the same investigators using a structured questionnaire (SA and LTLC). The following clinical manifestations were analyzed: malar rash, discoid lesions, subacute cutaneous lesions, photosensitivity, oral ulcers, arthritis, serositis, nephritis, neurological and psychiatric involvement, thrombocytopenia, hemolytic anemia, Raynaud's phenomenon, thrombosis, myositis, lung involvement and lymphadenopathy.

Nephritis was diagnosed on the basis of proteinuria exceeding 0.5 g/L with abnormal urinary sediment and/or histological findings. Nephrotic syndrome was defined as proteinuria in excess of 3.5 g/day. Hematologic alterations were ascribed to lupus only in the absence of bone marrow suppression (leukopenia <4000 cells/mm3; thrombocytopenia <100.000/mm3; hemolytic anemia with positive Coombs test). Antinuclear antibodies (ANA) were determined by indirect immunofluorescence using Hep 2 as the substrate and regarded as positive if higher than 1:40. Anti-double-stranded DNA (AdsDNA) antibodies were determined by indirect immunofluorescence using Chrithidia as substrate and considered positive if higher than 1:10. Precipitating antibodies to extractable nuclear antigens (ENA), including Ro (SSA), La (SSB) and Sm were detected by immunodiffusion and/or microhemagglutination. Anticardiolipin antibodies (aCL) of the IgG and IgM isotypes were measured by the ELISA method as described (Harris et al., 1987). Lupus

anticoagulant (LA) activity was detected by coagulation assays in platelet free plasma obtained by double centrifugation, following the recommendation of the subcommittee on LA of the Scientific and Standardization Committee of the International Society of Thrombosis and Homeostasis (Brandt et al., 1995).

CNS manifestations were recorded following ACR case definitions (ACR 1999) and considered active, when present at the day of MRI/MRS acquisition.

Patients had clinical and laboratory evaluation at time of their first MRI/MRS examination and were divided in groups, according to the presence of white matter lesions in the ROI, as follows: (A) 10 patients with white matter lesions at study entry; (B) 20 patients without white matter lesions at study entry, but with white matter lesions at follow-up study.

Total doses of corticosteroids and other immunosuppressant medications used since the onset of disease were calculated by careful review of the medical charts.

MRI and MRS Protocol

All subjects had MRI and MRS examination for the purpose of this study, using an Escint 2Tesla scanner (Prestige, Haifa, Israel). Our MRI protocol consisted of: (*1*) Sagittal T1 spin echo, 6 millimeters (mm) thick, flip angle= 180^{o}; repetition time (TR)=430, echo time (TE)=12, matrix 200X350, field of view (FOV)=25X25 centimeters (cm); (*2*) Coronal images, perpendicular to long axis of hippocampus, defined by the sagittal images; (*2.a*) T2-weighted "fast spin echo" (FSE), 3mm thick, flip angle= 120^{o}; TR=4800, TE=129, matrix 252X320, FOV=18X18cm; (*2.b*) T1-weighted inversion recovery (IR), 3mm thick, flip angle=200^{o}; TR=2800-3000, TE=14, inversion time (TI)=840, matrix 130X256, FOV=16X18cm; (*3*) Axial images (*3.a*) T1-weighted gradient echo, 3mm thick, flip angle=70^{o}, TR=200, TE=5, matrix 180X232, FOV=22X22 cm; (*3.b*) Fluid attenuated inversion recovery (FLAIR), 4mm thick, flip angle=120^{o}, TR=6800, TE=129, matrix 252X328, FOV=21X23cm (*4*) T1-weighted 3D gradient echo, acquired in the sagittal plane for multiplanar and reconstruction (1mm thick, flip angle=$35^{o;}$ TR=22, TE=9, matrix 256X220, FOV=23X25cm).

Single voxel 1H-MRS was acquired using point resolved spectroscopy (PRESS) sequence (26) (TR= 1500 ms, TE=135ms, NEX=200) over the superior-posterior region of the left hemisphere at the level of corpus callosum. This area was previously

analyzed using T1-weighted, T2-weighted and FLAIR sequences. After the acquisition of scout anatomical images in sagittal planes for localization of corpus callosum, one single voxel (2x5x1cm) was placed over the ROI (Appenzeller et al., 2005). Prior to the acquisition, a localized shimming at the ROI was performed to ensure adequate field homogeneity followed by water suppression adjustment.

The spectra were post-processed using software supplied by the machine manufacturer (Elscint 2T Prestige, Haifa, Israel). After zero-filling and baseline correction we determined peak areas by integration of the corresponding signals from *N*-acetyl compounds (NAA) at 2.01 parts per million (ppm), choline-base compounds (Cho) at 3.2 ppm and creatine and phosphocreatine contained compounds (Cr) at 3.0 ppm. The spectra were scaled in relation to creatine values. Ratios of NAA/Cr and Cho/Cr were used for analyses.

Spectral acquisition, quantification and analysis were performed by one investigator (SA). The evaluation was cross-checked by two spectroscopists (LML and FC), blinded to the name and clinical data of patients and volunteers. The quality of the spectral analysis was judged independently by these two investigators from the parameters linewidth and signal-to-noise ratio and spectra with broad peaks and poor separation of individual peaks were excluded from analysis. None of these patients or controls was excluded because of poor quality spectra.

Statistics

We performed analysis of variance (ANOVA) to test differences among the groups, followed by post hoc Tukey's test for pairwise comparisons if necessary. Follow-up MRS results were analyzed using paired t-test with Bonferroni's correction for multiple comparisons.

Results

Demographic data

We analyzed MRS data of 30 SLE patients. The age and gender distribution was: group (A): 10 patients (10 women) with mean age of 32.2 (range 18-56; SD=12.9); group (B): 20 patients (18 women) with mean of age 33.0 (range 18-59; SD=13.1).

The mean interval between the two proton MRS of SLE patients was 19 months (range 12-24 months; SD=2.3).

The control group consisted of 23 healthy volunteers (19 women) with mean age of 33.8 years (range 20-60, SD=13.7 years) (Group C). MRS studies were repeated in 9 volunteers (7 women) with mean age of 32.1 (range 20-60; SD=14.1) at study entry (Group D). The mean interval between MRS examinations was 21 months (range 18-24 months; SD= 1.8).

There was no statistical difference between the age and gender distribution among the different groups of patients (groups A and B) and volunteers (groups C and D).

Clinical, laboratory and treatment features

The mean disease duration was 59 months (range 1-312 months, SD=20.2) at study entry and 79 months (range 12-331 months, SD=20.45) at follow-up MRS. At baseline, 39 episodes of CNS manifestations had occurred in 20 patients (12 patients with active and 8 with inactive CNS manifestations) (Table 1). At the time of MRS scans, 15 patients had active SLE, with SLEDAI scores ranging between 10 and 20 (mean 12.6, SD=4.6). Active CNS manifestations at the first MRS scan were observed in 12 of 15 patients with active SLE. Fifteen patients had inactive SLE at the time of first MRS. Eight of them had past history of CNS involvement and 7 did not. All patients were on steroid use at the day of MRS study, with doses ranging from 5 to 60 mg/day (mean 38 mg/day). IgG antiphospholipid antibodies were positive in 10 patients.

MRI findings

Subtle abnormal MRI findings, inside the MRS ROI, (areas of hyperintense signal on T2-weighted images) in subcortical regions were observed in 10 patients at baseline study. Visual analysis of MRI demonstrated a significant increase in the number of these lesions during the follow-up study as compared to baseline study (p=0.03).

Follow-up MRI demonstrated white matter lesions inside the ROI in all 30 patients. A greater number of white matter lesions were observed in patients with antiphospholipid antibodies (p=0.04). We observed a significant correlation between the presence of CNS involvement and white matter lesions (r=0.7; p=0.01).

MRS findings

Group A had increased Cho/Cr ratios (median Cho/Cr=1.13; SD=0.11) when compared normal controls (median Cho/Cr=0.95; SD=0.15; p=0.008). Group B had similar

Cho/Cr ratios when compared to group A (median Cho/Cr=1.07; SD=0.12; p=0.19) and increased in relation to controls (p=0.001) (Table 2 and 3).

After 19 months follow-up, we observed a significant increase in median Cho/Cr ratio in patients of group A (median Cho/Cr=1.6; SD=0.2; p=0.001) and B (median Cho/Cr=1.2; SD=0.2; p=0.006) (Table 2). We observed a correlation between Cho/Cr ratios and number of white matter lesions (p=0.001). Patients with antiphospholipid antibodies had more pronounced Cho/Cr increase than patients without this antibody (p=0.01). Patients with CNS manifestations had an increase in Cho/Cr ratios. Controls who had follow up MRS had no change in Cho/Cr values (median Cho/Cr=0.94; SD=0.15; p=0.88) (Figure 1).

NAA/Cr ratios were lower in patients with active disease at study entry when compared to controls. No difference in NAA/Cr values of patients with and without CNS involvement could be observed. In patients with active disease at study entry and inactive at follow-up we observed that NAA/Cr ratios returned to normal range, similar to controls. In patients with active disease at study entry and at follow-up MRS we observed a reduction in NAA/Cr ratios, although not statistically significant. In patients with inactive disease at both initial and follow-up MRS, constant NAA/Cr ratios were observed. NAA/Cr ratios were lower in SLE patients with MRI abnormalities when compared to patients with normal MRI at study entry (p=0.03).No difference in relation to individual clinical or laboratory variables could be observed.

Discussion

MRI is currently considered the neuroimaging method of choice for morphological brain evaluation SLE, being capable of detecting a large proportion of the brain lesions, which are frequently represented by small focal T2-weighted hyperintense lesions in the white matter (Castellino et al., 2005; Stimmler et al., 1993). Although MRI appears sensitive for detecting abnormalities in patients with major clinical manifestations such as focal neurological defects, seizures, and cerebrovascular disease, its sensitivity is very low in SLE patients with neuropsychiatric disturbances such as headache, cognitive dysfunction, affective disorders, or confusional states (Castellino et al., 2005; Stimmler et al., 1993; West et al., 1995; Sibbitt et al., 1995; Rozell et al., 1998; Sabet et al., 1998). In these patients functional or metabolic brain imaging may reveal abnormalities before the

appearance in conventional MRI. Furthermore the interpretation of small hyperintense MRI lesions which are often observed even in normal subjects is still debated, as is the normal MRI found in SLE patients with CNS involvement.

Although neuro-metabolic abnormalities in SLE have been described in several studies (1, 5, 10, 13-18, 30-32), there are few follow-up studies (Castellino et al., 2005). Castellino et al (Castellino et al., 2005) observed the appearance of white matter lesions 3 of 5 patients in areas of normal appearing white matter with hypoperfusion in SPECT images and increase in Cho/Cr ratios.

In this study we observed that Cho/Cr ratios were increased in patients with white matter lesions inside the MRS ROI when compared to controls and this increase correlated independently with the presence of antiphospholipid antibodies. At follow-up MRS Cho/Cr ratios increased further and were associated with an increase in the number of white matter lesions inside the ROI. We further observed that patients with normal appearing white matter at baseline MRS who presented with white matter lesions in the follow-up MRI also had an increased Cho/Cr ratio at both MRS studies. In our previous study, SLE patients with normal appearing white matter inside the ROI both at baseline and follow up MRS had Cho/Cr ratios similar to normal controls (Appenzeller et al., 2005).

Cho concentrations is reported to rise in SLE patients with CNS involvement (Castellino et al., 2005; Sibbitt et al., 1997; Brooks et al., 1974; Brooks et al., 1999), but its cause has not been determined, although it may be due to myelin breakdown secondary to neuronal loss or due to inflammatory process (Brooks et al., 1974; Brooks et al., 1999). We observed that patients with CNS involvement had higher Cho/Cr ratios than patients without CNS involvement. The reduction of NAA/Cr ratios observed in the present series, is similar as in our previous study (Appenzeller et al., 2005). We used Cr values as an internal reference, although it has not been demonstrated that Cr is stable in SLE (Appenzeller et al., 2005).

In conclusion, we demonstrated a progressive increase of Cho/Cr ratios associated with the number of white matter lesions and the presence of antiphospholipid antibodies. In addition, increased Cho/Cr ratios in normal appearing white matter may predict the appearance of white matter lesions in patients with SLE. Cho/Cr and NAA/Cr ratios may be used as a surrogate marker in follow-up studies of SLE.

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Table 1. Summary of cumulative neuropsychiatric manifestations which occurred in 20 patients at study entry

Neuropsychiatric manifestations	Number of CNS events (%)
Headache	12 (30.8)
Cognitive impairment	11 (28.2)
Mood disorder	6 (15.4)
Seizures	4 (10.2)
Acute confusional state	2 (5.1)
Psychosis	3 (7.7)
Aseptic meningitis	1 (2.6)
Total number of events	39

Table 2. Median Cho/Cr values in 30 patients and 9 controls.

Groups	Median Cho/Cr at initial MRS (±SD)	Median Cho/Cr at follow-up MRS (±SD)	p-value
A	1.13 (0.11)↑	1.6 (0.2)↑	<0.001
B	1.07 (0.12)↑	1.2 (0.2)↑	0.006
D	0.95 (0.15)	0.94 (0.15)	0.88

(A) SLE patients with WM lesions in MRS ROI initial MRS

(B) SLE patients without WM lesions at initial MRI but with WM lesions at follow-up MRI within MRS ROI

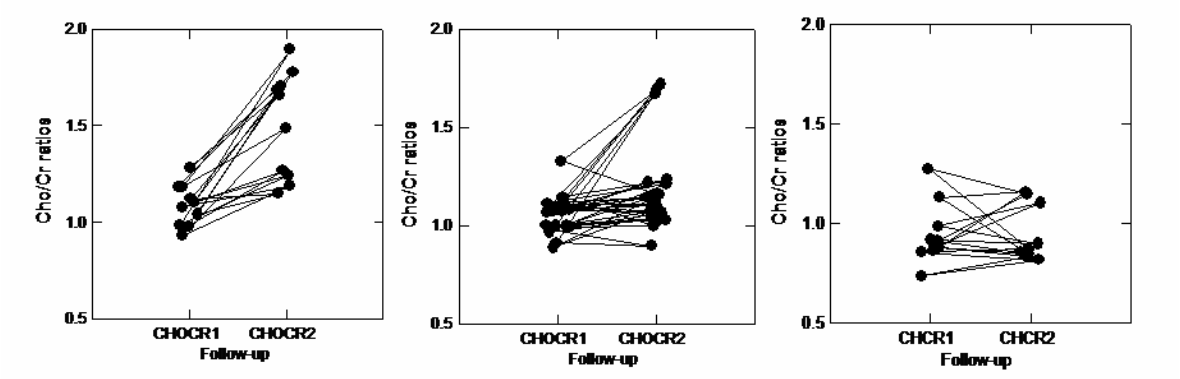
(C) Controls at follow-up

Table 3: Individual Cho/Cr ratios at study entry and during follow-up period with clinical and radiological findngs

Patient	Age	Presence of CNS manifestations	Lesions in MRS ROI at study entry	Lesions in MRS ROI at follow-up	Initial Cho/Cr ratio	Follow-up Cho/Cr ratio
#1	26	+, inactive	+	+↑	1.24	1.82
#2	19	+, active	+	+↑	1.03	1.32
#3	65	-	+	+↑	1.07	1.34
#4	26	-	+	+↑	1.28	1.51
#5	37	+, inactive	+	+↑	1.13	1.93
#6	30	-	+	+↑	1.02	1.24
#7	43	-	+	+↑	1.08	1.70
#8	39	+, active	+	+↑	1.02	1.34
#9	44	+, inactive	+	+↑	1.10	1.69
#10	18	+, inactive	+	+↑	1.32	1.72
#11	38	-	-	+	1.02	1.09
#12	43	+, inactive	-	+	1.08	1.70
#13	39	-	-	+	1.02	1.19
#14	44	+, inactive	-	+	1.10	1.69
#15	47	+, active	-	+	1.05	1.18
#16	41	+, active	-	+	0.86	1.19
#17	18	+, inactive	-	+	1.32	1.72
#18	45	-	-	+	0.89	1.29
#19	49	+, active	-	+	1.02	1.17
#20	28	+, active	-	+	1.11	1.39
#21	20	-	-	+	1.13	1.24
#22	29	+, active	-	+	1.10	1.28
#23	18	+, active	-	+	1.01	1.22
#24	28	+, inactive	-	+	1.10	1.29
#25	25	+, active	-	+	1.09	1.36
#26	25	+, active	-	+	1.09	1.17
#27	35	-	-	+	1.05	1.13
#28	19	+, active	-	+	1.15	1.35
#29	18	-	-	+	0.95	1.21
#30	26	+	-	+	1.04	1.45

+: present; -: absent; +↑: increased number

Figure 1. Paired T-test comparing MRS finding at study entry and at follow-up. Panel A: 10 patients (#A) with lesions in MRS ROI at study entry (p=0.001). Panel B: 20 patients (#B) with normal appearing white matter at study entry and white matter lesions at follow-up MRS (p=0.03). Panel C: 9 controls (#D) (p=0.56).



5. DISCUSSÃO

Os três primeiros artigos da tese são trabalhos de revisão. O artigo Neurolupus (artigo #1) é uma revisão histórica sobre as primeiras menções do LES na literatura e as primeiras descrições clínicas, mostrando que há muito tempo tinha sido reconhecida uma variedade destas manifestações e um pior prognóstico de cada uma delas. Neste artigo também enfatiza-se a importância da uniformização dos critérios diagnósticos e do tratamento, ressaltando o fato interessante que os antimaláricos (quinina) serem utilizados para o tratamento do LES desde o século 19. Ainda com relação ao tratamento, o uso de corticosteróides e imunosupressores melhorou muito a sobrevida dos pacientes (Urowitz et al., 1997), apesar de ainda observarmos uma elevada morbi-mortalidade naqueles com manifestações do SNC (Blanco et al., 1998; Kasitanon et al., 2002; Jonsen et al., 2002).

No artigo sobre as manifestações do SNC no LES (artigo #2) apresentamos uma revisão mais ampla, enfatizando além da dificuldade diagnóstica, a patogênese, a investigação clínica e neuroimagem das manifestações do SNC. Comparamos os diferentes estudos que utilizam os critérios diagnósticos do Colégio Americano de Reumatologia (1999) e observamos que, apesar de uma tentativa de uniformização, ainda ocorrem diferentes freqüências das manifestações. Isto pode ser explicado por diferenças loco-regionais ou por viés na inclusão dos pacientes nos trabalhos (Hanly, 2005). Enfatizamos também a importância do diagnóstico diferencial, visto que até 40% das manifestações do SNC no LES podem ser atribuídas a outras causas, e não a doença propriamente dita (Hanly et al., 2004).

Juntamente com a RM, a ERM (artigo #3) é uma ferramenta que pode ser utilizada na investigação do comprometimento do SNC no LES. Ela permite uma avaliação das alterações estruturais e pode ser realizada juntamente com a RM. Uma revisão sobre os mecanismos físicos, dificuldades de aquisição e os resultados obtidos, muitas vezes por diferentes técnicas de aquisição, é discutido neste trabalho. A maioria dos autores concorda que há dano neuronal no LES (Axford et al., 2001; Handa et al., 2003), porém, a associação destes achados com as manifestações do SNC (Sibbitt et al., 1997; Brooks et al., 1999; Lim et al., 2000), o uso de corticsteróides (Chinn et al., 1997) ou alterações estruturais (Davie et al., 1995; Lim et al., 2000) ainda é controversa.

A maioria dos estudos envolvendo as manifestações NP no LES, mesmo os mais atuais, (Sabbadini et al., 1999; Sanna et al., 2000; Ainiala et al., 2001; Mok et al., 2001; Kasitanon et al., 2002; Sanna et al., 2003; Hanly et al., 2004; Mikdashi et al., 2004; Hanly et al., 2005; Shimojima et al., 2005; Robert et al., 2006) apresenta uma descrição generalizada destas manifestações, dificultando muitas vezes a sua análise individual. Assim, ao estudar algumas destas manifestações isoladamente, pudemos avaliar melhor a relação entre estas e outras variáveis clínicas e laboratoriais e de neuroimagem.

Ao estudar a freqüência de epilepsia em 519 pacientes (artigo #4), observamos que a prevalência de crises epilépticas em nossa casuística (11,6%) é similar (8,3-28%) ao que foi previamente descrito (Mackworth-Young et al., 1985; Herranz et al., 1994; Jennekens e Kater, 2002; Brey et al., 2002; Kassitanon et al., 2002; Sanna et al., 2003; Cimaz et al., 2006; Robert et al., 2006). A maioria destes pacientes (88,3%) apresentou crises únicas e somente 11,7% apresentaram crises recorrentes, caracterizando, assim, epilepsia. Crises tônico-clônicas generalizadas e crises parciais complexas foram mais freqüentemente observadas em nossa casuística. A ocorrência de crises epilépticas no início do LES ocorreu em 19 de 60 pacientes (31,7%) e esteve associada à presença de acidente vascular cerebral (AVC) e aos anticorpos antifosfolípides, em títulos moderados a elevados. Ambos os fatores devem estar associados à gênese das crises epilépticas, sejam secundárias a eventos isquêmicos (Bresninhan et al., 1979; Cocito et al., 1982; Asherson et al., 1989; Kumeral et al., 2002) ou ao aumento da excitabilidade neuronal (Liou et al., 1994). No entanto, por se tratar de um estudo retrospectivo, não foi possível definir as causas de crises em nossa casuística. Assim, como observado em nossos pacientes com crises epilépticas, que apresentaram mais freqüentemente AVC, outros estudos demonstraram a associação de crises epilépticas com outras manifestações NP no LES (Futrell et al., 1992; Mok et al., 2001; Brey et al., 2002; Sanna et al., 2003).Estes achados, portanto, sugerem que, na presença de manifestação NP, outras manifestações NP devam ser pesquisadas. Embora tinha sido observada uma associação entre a ocorrência de crises epilépticas e nefrite, a atividade da doença não parece ser responsável pela crise, visto que outras manifestações clínicas não estavam associadas à presença de crises nesta casuística. A associação de crises epilépticas com a presença de AVC e de sinais de doença de pequenos vasos à RM, reforça a importância deste exame na investigação destes pacientes. O eletroencefalograma (EEG)

foi útil na identificação de pacientes com maior risco de recorrência de crises, pois estes apresentaram atividade epileptiforme interictal ao exame. Contudo, a recorrência das crises foi rara, e ocorreu somente em pacientes com anticorpos antifosfolípides. O tratamento com drogas antiepiléticas, não necessitaria, portanto, ser iniciado para todos os pacientes com LES crises epilépticas isoladas. No entanto, pacientes com EEG demonstrando atividade epileptiforme interictal e pacientes com anticorpos antifosfolípides poderiam ser medicados com drogas antiepilépticas precocemente, mesmo após crises isoladas, visto que apresentam maior risco de recorrência de crises.

Ainda há controvérsias se existe associação entre migrânea e o LES (Glanz et al., 2001;Whitelaw et al., 2004), ou trata-se de ocorrência fortuita (Sfikakis et al., 1998; Fernandez-Nebro et al., 1999; Mitsikostas et al., 2004). Realizamos um estudo prospectivo de pacientes com LES com e sem migrânea comparando-os a dois grupos controles (indivíduos normais e pacientes com artrite reumatóide) com objetivo de analisar a importância clínica desta manifestação no LES (artigo #5). Optou-se por incluir um grupo de pacientes com artrite reumatóide, com o intuito de excluir o fator doença crônica na presença de cefaléia.Neste trabalho, pacientes com LES apresentaram migrânea com freqüência significativamente maior do que aqueles com artrite reumatóide e controles. Observamos ainda que na vigência da migrânea, os pacientes com LES apresentavam mais frequentemente atividade da doença e piora do fenômeno de Raynaud. Desta forma, a atividade de doença deve ser suspeitada naqueles que apresentam piora do quadro de migrânea. A associação do fenômeno de Raynaud com migrânea no LES também foi observada por outros autores (Cervera et al., 2002; Lessa et al., 2006), assim como na população geral (Heslop et al., 1983; Silman et al., 1990; O'Keeffe et al., 1993), sugerindo mecanismos patogênicos comuns, como reação vascular (Heslop et al., 1983; Silman et al., 1990) e disfunção endotelial (Spierings, 2003; Hanly, 2003). A presença de migrânea relacionou-se também a presença dos anticorpos antifosfolípides. Vários estudos analisaram a interação entre a presença deste anticorpo e a disfunção endotelial. O anticorpo antifosfolípide ao se ligar à superfície endotelial, levaria a uma ativação celular, que, por sua vez, promoveria um aumento das moléculas de adesão e um aumento da secreção de interleucina 6 e prostaglandinas. Isto, por sua vez, levaria a uma lesão endotelial induzida por complemento ou por citotoxicidade induzida por anticorpos. Portanto, a disfunção

endotelial é um dos mecanismos patogênicos que explicaria a associação entre migrânea, anticorpos antifosfolípides e fenômeno de Raynaud (Del Papa et al., 1992; Del Papa et al., 1997; Simantov et al., 1995; Hanly et al., 1996). Analisando o índice de dano nestes pacientes, observamos uma associação positiva com a história pregressa de migrânea. Uma possibilidade plausível é que, como se observou associação entre atividade de doença e migrânea, esta atividade, juntamente com uma possível dose maior de corticosteróides e outras drogas, poderiam levar a um maior dano permanente nestes pacientes. A importância da RM neste grupo de pacientes não foi avaliada neste trabalho, fazendo parte de um estudo já em andamento.

A freqüência de psicose, avaliada em 537 pacientes com LES (artigo #6) também foi semelhante à publicações prévias, ou seja 17,5% (Mok et al., 2001, Brey et al., 2002, Kasitanon et al., 2002, Sanna et al., 2003). A ocorrência da psicose no início do LES apresentou associação positiva com atividade de doença, mas uma associação negativa com lesões cutâneas, ou seja, pacientes com psicose apresentaram menor freqüência de comprometimento de pele. Pacientes com psicose, no início do LES, provavelmente são encaminhados inicialmente ao psiquiatra, o que pode levar a uma subestimação deste sintoma no início do LES.

Uma das questões mais frequentes na prática clínica e durante a evolução da doença, é se a psicose apresentada pelos pacientes com LES é primária ou secundária ao uso de corticosteróides. Observou-se que pacientes com psicose primária apresentavam mais frequentemente anticorpos antifosfolípides e outras manifestações do SNC, como depressão, AVC, crise epilépticas e distúrbios cognitivos. Isto pode ser devido à interação dos anticorpos antifosfolípides com a membrana neuronal, não necessariamente secundários a fenômenos trombóticos (Wysenbeek et al., 1999, Mok et al., 2001, Sanna et al., 2003). Apesar do anticorpo anti-P ser de grande utilidade para o diagnóstico da psicose no LES (Bonfa et al., 1987), sua realização de rotina ainda não ocorre na maioria dos centros de atendimento. Por isso é importante determinar outros fatores que possam diferenciar psicose primária daquela induzida por corticosteróides, além das evidências clínicas e sua relação temporal com o uso da droga. Um dado interessante neste trabalho (artigo #6) foi a associação da psicose induzida por corticosteróides com a

hipoalbuminemia. Por se tratar de um estudo retrospectivo, não foi possível determinar um nível crítico de albumina a partir do qual os pacientes teriam uma maior chance de desenvolver psicose. Como os corticosteróides sintéticos ligam-se a albumina para o transporte, tornando-se assim inativos, a hipoalbuminemia estaria relacionada a níveis mais elevados de corticosteróides livres circulantes, o que pode justificar o maior efeito colateral nestes pacientes, incluíndo-se a psicose (Kohen et al., 1993; Patten &Neutel 2000, Lopez-Medrano et al., 2002; Sirois, 2003).

Quando se estudou a recorrência da psicose nestes pacientes, observou-se que esta ocorreu mais frequentemente em pacientes com atividade de doença e outras manifestações do SNC. No entanto, não foi possível identificar substratos anatômicos na RM associados à recorrência de psicose nestes pacientes.

A trombose venosa central (TVC) é considerada rara no LES (Vidailhet et al., 1990; Flusser et al., 1994; Laversuch et al., 1995; Lee et al., 2001; Uthman et al., 2004). Em nosso estudo analisando 24 pacientes com TVC de diferentes etiologias (artigo #7), somente três pacientes apresentaram síndrome do anticorpo antifosfolípide e destes, somente um tinha também o diagnóstico de LES. Os principais sintomas dos pacientes com TVC foram, em freqüência decrescente, cefaléia, vômitos e alterações do nível de consciência. Portanto, é recomendável que pacientes com LES, principalmente aqueles com anticorpos antifosfolípides associados, que apresentem cefaléia intensa de início recente e aqueles com distúrbios cognitivos progressivos, sejam avaliados por método de imagem para afastar a presença de TVC.

Estes trabalhos acima descritos, ao analisarem algumas manifestações do SNC no LES puderam destacar a utilidade da RM estrutural como método de investigação complementar. A partir destes trabalhos procurou-se estudar de forma mais minuciosa o papel de diferentes métodos de neuroimagem aplicados à pacientes com LES para avaliar, do ponto de vista estrutural e funcional, o envolvimento do SNC.

Analisando a RM estrutural de 115 pacientes com LES, 72 com manifestações do SNC (artigo #8), observamos que pacientes com LES apresentavam mais frequentemente atrofia de corpo caloso e do volume cerebral do que controles normais. Observamos atrofia cerebral grave em 8,7% dos casos, inferior ao previamente relatado

(Bilaniuk et al., 1977; Killian et al., 1979; Gonzalez-Scarano et al., 1979; Gayliset al., 1982; Carette et al., 1982; Kaell et al., 1986; McCune e Golbus, 1988; McCune et al., 1988; Omdal et al., 1989; Ostrov et al., 1982; Waterloo et al., 1999). Isto decorre, possivelmente, do método utilizado para análise, pois a maioria dos estudos descritos acima utilizou uma análise visual ou medição manual em imagens bidimensionais (Tabelas 4 e 5), enquanto que, em nosso trabalho, com a utilização de um método de segmentação semi-automática e a elaboração de protocolos de segmentação bem definidos, pode-se obter resultados mais fidedignos e reproduzíveis. A atrofia cerebral no LES não estava associada aos diferentes tipos de manifestações do SNC, nem a dose cumulativa de corticosteróides, como sugerido por alguns autores (Carette et al., 1982; Ostrov et al., 1982; Zanardi et al., 2001), porém correlacionou-se ao número de manifestações pregressas do SNC e ao maior tempo de doença.

Apesar da atrofia cerebral ter sido estudada por vários autores (Bilaniuk et al., 1977; Killian et al., 1979; Gonzalez-Scarano et al., 1979; Gayliset al., 1982; Carette et al., 1982; Ostrov et al., 1982; Kaell et al., 1986; McCune e Golbus, 1988; McCune et al., 1988; Omdal et al., 1989; Waterloo et al., 1999; Zanardi et al., 2001;), apenas um trabalho (Steens et al., 2004) procurou determinar se há uma região cerebral predominantemente acometida. Nossos trabalhos permitiram observar, através de dois métodos distintos [VBM (artigo #9) e segmentação semi-automática (artigo #8)], que o corpo caloso é a região de substância branca mais freqüentemente afetada. Na análise semi-automática a atrofia do corpo caloso esteve associada à história pregressa de manifestações do SNC, ao número total destas manifestações e ao maior tempo de doença. A atrofia do corpo caloso é frequentemente observada em RM estrutural de idosos (Janowsky et al., 1996; Hampel et al., 1988; Black et al., 2000; Bjartmar et al., 2001). A explicação é que a maioria dos neurônios projetados para o corpo caloso são das células piramidais gigantes das camadas corticais III e IV do hemisfério contralateral (Hampel et al., 1998) e a isquemia cerebral resulta em lesão da camada III (Innocenti et al., 1986), levando a degeneração Walleriana do corpo caloso (Grahm et al., 1992). Portanto, a atrofia do corpo caloso pode ser considerada um marcador de perda neuronal em idosos (Grahm et al., 1992). Esta hipótese foi testada pelo método de VBM, e uma maior perda de substância branca foi também observada na região frontal e occipital, além do corpo caloso, em nossos pacientes. Este achado poderia representar um

substrato anatômico para a presença de distúrbios cognitivos no LES, que envolve principalmente funções subcorticais frontais (Leritz et al., 2000). Entre os fatores associados observados, além da história pregressa de manifestações NP e maior tempo de doença, já descritas, observamos também uma correlação entre atrofia de substância branca e presença dos anticorpos antifosfolípides pela técnica de VBM. As lesões de substância branca que ocorrem frequentemente em idosos (Awald et al., 1986; Katzman t al., 1999), assim como em pacientes lúpicos (Chinn et al., 1997; Walcki et al., 2002; Cotton et al., 2004), ainda que muitas vezes consideradas inespecíficas, podem ser decorrentes de vasculopatia (Wen et al., 2004). Na etiologia da vasculopatia, parece haver a participação dos anticorpos antifosfolípides, observada mais frequentemente naqueles pacientes com lesões de substância branca, embora estudos anátomopatológicos devam confirmar esta hipótese. A vasculopatia, por sua vez, leva a atrofia de substância branca que por sua vez leva a atrofia de corpo caloso.

Em relação à substância cinzenta, a análise pela técnica de VBM (artigo #9) demonstrou, principalmente a redução do volume dos lobos temporais e outras áreas límbicas, associada à dose total de corticosteróides utilizada, entre outros fatores. Analisando os volumes dos hipocampos, isoladamente, (artigo #10) observamos, no início do estudo, 43,9% de atrofia hipocampal, associada ao maior tempo de doença, dose cumulativa de corticosteroides e ao número de manifestações do SNC, indicando que o hipocampo parece ser uma estrutura muito sensível aos insultos sistêmicos. A presença da atrofia hipocampal esteve associada à presença e ao grau dos distúrbios cognitivos no LES.

A partir da padronização destas técnicas, pode-se avaliar, no artigo #9 e #10, se a atrofia cerebral no LES é progressiva e qual os fatores associados à sua progressão. Observamos que, após um tempo médio de 19 meses de seguimento ocorreu progressão significativa da perda tanto de substância branca como de cinzenta. Pela técnica de VBM (artigo #9), observamos também uma redução do volume cortical em pacientes com LES, ocorrendo predominantemente em lobos frontal, dorsolateral e temporal medial.

Já a progressão da atrofia hipocampal (artigo #10) esteve associada não somente ao número de manifestações NP, mas também à dose cumulativa de corticosteróides. Clinicamente, a progressão da atrofia hipocampal esteve associada à piora

do distúrbio cognitivo. Estudos prévios demonstraram que no LES, grande parte dos pacientes com distúrbios cognitivos não piora ao longo da doença (Karassa et al., 2000; Carlomagno et al., 2000). Isto sugere que pacientes com flutuações na cognição provavelmente não apresentam alteração estrutural, enquanto que aqueles com persistência e progressão de distúrbios cognitivos provavelmente apresentam atrofia hipocampal. Portanto, a análise volumétrica dos hipocampos pode ser uma importante ferramenta para predizer o curso clínico dos distúrbios cognitivos no LES.

Observamos também que a atrofia hipocampal progressiva esteve associada à presença pregressa de manifestações do SNC e não à atividade do LES, indicando que o dano estrutural causado pelo envolvimento do SNC ocorre de forma gradual e lenta. Além disto, nossos resultados mostram que a dose cumulativa de corticosteróides esteve associada com a perda de substância cinzenta, como o hipocampo, enquanto o tempo de doença influenciou a progressão de atrofia tanto de substância branca como cinzenta. A piora do distúrbio cognitivo nos pacientes com LES esteve claramente associada à perda de substância cinzenta (atrofia hipocampal) neste estudo (artigo #10).

A aplicação de técnicas de neuroimagem funcional revelou que as alterações funcionais observadas ocorrem mais precocemente que as alterações estruturais e parecem estar relacionados mais à presença de atividade sistêmica de doença do que com manifestações do SNC isoladamente, indicando que o cérebro é mais amplamente afetado pela doença ativa do que se supunha.

O estudo com SPECT cerebral foi realizado em 40 pacientes, sendo que 20 apresentavam manifestações NP ativas e 20 pacientes história pregressa de comprometimento do SNC (artigo #11). Analisando-se as imagens do SPECT cerebral através da técnica do VBM, foi possível identificar alterações em pacientes com manifestações NP ativas, não identificadas visualmente. Estes apresentavam uma hipoperfusão cerebral difusa, independentemente do tipo da manifestação apresentada. Pacientes sem manifestações neuropsiquiátricas ativas apresentavam um padrão de perfusão cerebral semelhante aos controles. Para determinar se os achados de hipoperfusão cerebral não são decorrentes da presença da atrofia, as RM destes pacientes foram analisadas pela técnica do VBM. Como não foi observada diferença quanto à atrofia nos

dois grupos de pacientes, podemos considerar o hipofluxo secundário a presença de manifestações NP ativas. Utilizando-se, portanto, a técnica do VBM para análise de SPECT cerebral, foi possível identificar alterações de hipoperfusão em pacientes com manifestações NP ativas, porém pelo pequeno número de pacientes, não foi possível avaliar se esta alteração foi decorrente da atividade sistêmica da doença ou da manifestação do SNC propriamente dita. Para responder a esta pergunta, utilizamos outro método funcional, a ERM. Neste estudo (artigo #12) foram incluídos 90 pacientes, sendo 29 com doença ativa e comprometimento do SNC ativo, 28 pacientes com doença ativa sem evidência de envolvimento do SNC, 14 pacientes com doença inativa e história pregressa de manifestações NP e 19 pacientes com doença inativa sem evidências de comprometimento do SNC. Observamos uma redução significativa do marcador neuronal NAA (relativo ao sinal de cratina -NAA/Cr) em pacientes com doença ativa, independentemente da presença do comprometimento do SNC. O fato da redução relativa do NAA ser semelhante em pacientes com e sem história pregressa de comprometimento do SNC, sugeriu que a perda neuronal poderia ser, até certo ponto, transitória e relacionada à presença de atividade sistêmica do LES, fato demonstrado no estudo de seguimento destes pacientes. A normalização da relação NAA/Cr em pacientes que apresentaram doença ativa no início do estudo e doença inativa no seguimento e a piora da relação NAA/Cr em pacientes com doença inativa que se tornou ativa, indica a transitoriedade destes achados. Em pacientes com doença ativa tanto no início como na evolução observou-se uma progressiva piora da relação NAA/Cr. Não observamos elevação da relação cholina/creatina nos pacientes com substância branca normal. Em outro estudo (artigo #13) em que a ERM foi realizada em regiões com grande número de lesões de substância branca observamos um aumento na relação Cho/Cr em relação aos controles. Neste mesmo estudo também observamos que houve um aumento do número de lesões de substância branca após uma média de 19 meses de seguimento, assim como um aumento da relação Cho/Cr nesta mesma região. Em pacientes que, no início do estudo, não apresentavam lesões de substância branca, mas apresentavam aumento da relação Cho/Cr, a RM realizada após 19 meses evidenciou a presença de lesões de substância branca, demonstrando que o aumento da relação Cho/Cr em substância branca normal pode predizer o aparecimento de lesões de substância branca. Este achado, além de ressaltar a importância da ERM no acompanhamento destes pacientes,

contribui para que se valorize as lesões de substância branca no LES, muitas vezes consideradas inespecíficas, porém, como demonstrado, associadas a alterações neurometabólicas.

Pelos resultados dos nossos trabalhos, podemos concluir que a padronização de técnicas de neuroimagem estrutural e funcional pode, portanto, acrescentar informações valiosas quanto ao comprometimento do SNC no LES e auxiliar a correlação entre a RM e a clínica destes pacientes, influenciando na conduta terapêutica e no prognóstico destes pacientes.

6. CONCLUSÕES

1. Crises epilépticas em pacientes com LES são geralmente únicas e, quando há recorrência,o EEG e a RM são ferramentas úteis para identificar estes casos.

2. Os anticorpos antifosfolípides estão associados a manifestações do SNC no LES, em especial a ocorrência e recorrência de crises epilépticas, a migrânea, e a psicose na evolução.

3. A migrânea está associada à atividade de doença, à presença de anticorpos antifosfolípides e à presença do Fenômeno de Raynaud. Pacientes com história pregressa de migrânea apresentaram mais dano, avaliado pelo SLICC, que pacientes sem migrânea.

4. A trombose venosa central é rara no LES, mas, quando ocorre, pode estar associada à presença de distúrbios cognitivos.

5. A atrofia cerebral, tanto de substância branca como de substância cinzenta, é mais freqüente no LES que em controles e ocorre de forma progressiva. A atrofia está associada ao número e a história pregressa de manifestações do SNC e não ocorre na vigência da manifestação ativa. O uso de corticosteróides está associado à atrofia de substância cinzenta e não à atrofia de substância branca.

6. A presença e o grau de atrofia do corpo caloso e do hipocampo estão associados à presença e a gravidade dos distúrbios cognitivos.

7. A análise do SPECT cerebral pela técnica de VBM é capaz de diferenciar pacientes com manifestações do SNC ativas de inativas.

8. A ERM demonstra disfunção axonal na substância branca normal, associada à atividade de doença, independentemente do comprometimento do SNC. Estes achados são transitórios, melhorando com controle da atividade da doença.

9. Pacientes com lesões de substância branca apresentam elevação da relação Cho/Cr. A elevação da Cho/Cr na substância branca normal pode predizer o aparecimento de lesões de substância branca.

10. A padronização de técnicas de neuroimagem é importante para avaliação da presença e da progressão da atrofia cerebral. Métodos de neuroimagem estruturais e funcionais são úteis na identificação do comprometimento do SNC no LES e podem demonstrar um maior envolvimento, independentemente da presença de manifestações do SNC.

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