UNIVERSITAT DE BARCELONA

Afectación neurológica en el lupus eritematoso sistémico: Alteraciones en la neuroimagen y caracterización de la afectación del sistema nervioso periférico

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TESIS DOCTORAL

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Afectación neurológica en el lupus eritematoso sistémico: Alteraciones en la neuroimagen y caracterización de la afectación del sistema nervioso periférico

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y

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Certificamos que la memoria titulada **"Afectación neurológica en el lupus eritematoso sistémico: Alteraciones en la neuroimagen y caracterización de la afectación del sistema nervioso periférico"** presentada por **Pilar Toledano Sierra**, se ha realizado bajo nuestra dirección y consideramos que reúne las condiciones necesarias para ser defendida delante del tribunal correspondiente para optar al grado de Doctor en Medicina.

Dr. Gerard Espinosa Garriga Dr. Ricard Cervera Segura

Dedicatoria

A mis padres, por ser el pilar fundamental en todo lo que soy y por su incondicional apoyo en todas las circunstancias.

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Abreviaturas

ACR: American College of Rheumatology

EULAR: European League Against Rheumatism

LCR: líquido cefalorraquídeo

LES: lupus eritematoso sistémico

LESNP: lupus neuropsiquiátrico

NMDA: N-metil-D- aspartato

NMO: neuromielitis óptica

NP: neuropsiquiátrico

PDIA: polirradiculopatía desmielinizante inflamatoria aguda

PET: tomografía por emisión de positrones

RM: resonancia magnética

SLEDAI: Systemic Lupus Disease Activity

SLICC: The Systemic Lupus International Collaborating Clinics

SNC: sistema nervioso central

SNP: sistema nervioso periférico

SPECT: tomografía computarizada por emisión de fotón único

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I. INTRODUCCIÓN

Introducción

El lupus eritematoso sistémico (LES) es una enfermedad crónica autoinmune de etiología desconocida y con afectación multisistémica, que cursa con una gran variedad de manifestaciones clínicas con curso heterogéneo y pronóstico incierto (1,2). Con la introducción de los criterios clasificatorios establecidos por la *American Rheumatism Association* (actualmente *American College of Rheumatology* [ACR]) en la década de los años setenta del siglo pasado, se han podido efectuar estudios epidemiológicos que han permitido conocer mejor la incidencia y la prevalencia de esta enfermedad, así como de sus principales manifestaciones clínicas y serológicas y su tasa de supervivencia. Estos criterios fueron modificados en 1982 por la ACR para mejorar su sensibilidad y especificidad diagnóstica (3,4). De forma reciente, el grupo colaborativo SLICC (*Systemic Lupus International Collaborating Clinics*) ha elaborado unos nuevos criterios de clasificación del LES que mejoran la sensibilidad de los criterios ACR, a expensas de disminuir su especificidad (5).

Desde el punto de vista epidemiológico, el LES afecta con mayor frecuencia a mujeres (9:1), con un pico de máxima incidencia entre la adolescencia tardía y el comienzo de la quinta década de la vida y es más frecuente y más grave en las etnias africana y oriental respecto a la población caucásica (6–9).

La etiopatogenia de la enfermedad no está claramente establecida, aunque se han descrito factores ambientales, hormonales, agentes infecciosos, trastornos en la apoptosis (deficiencias del complemento y en la presentación de antígenos al sistema inmunitario), anomalías de la transducción de señales (receptores *toll-like*) y factores relacionados con citocinas y genéticos, asociados todos ellos con el desarrollo de esta enfermedad (10). Probablemente, la conjunción de estos factores ocasione una respuesta inmune dirigida contra los antígenos nucleares endógenos y los anticuerpos producidos sean los responsables de las lesiones tisulares.

Clásicamente se han descrito varias fases en el desarrollo de la enfermedad, con la predisposición genética inicial, la producción asintomática de autoanticuerpos, los síntomas prodrómicos y, por último, la enfermedad clínica con la aparición de la inflamación, la disfunción de órganos y las lesiones (11).

La complejidad del LES queda reflejada por las diversas manifestaciones

clínicas que incluyen la afectación articular, cutánea, neurológica, renal, hematológica y gastrointestinal, entre otras, y las alteraciones del laboratorio, como las hematológicas y los cambios serológicos, tales como la disminución de los niveles de complemento y el aumento de anticuerpos (12).

Desde el punto de vista inmunológico, el LES se caracteriza por la producción de una enorme cantidad de autoanticuerpos, entre los que destacan los dirigidos frente al ADN de doble cadena, nucleosomas, Sm, C1q y la alfa-actina, implicados en la nefritis lúpica (6,13–18), frente a los antígenos Ro y La en el lupus neonatal y el lupus cutáneo (19,20), frente a las proteínas de unión a los fosfolípidos en el síndrome antifosfolipídico (21) y contra los receptores de N-metil-D-aspartato (NMDA) en las manifestaciones del sistema nervioso central (SNC) (22).

El diagnóstico del LES se basa en las manifestaciones clínicas y las pruebas de laboratorio que incluyen la detección de autoanticuerpos. No obstante, el diagnóstico de esta enfermedad continua siendo un desafío (12). Existen una serie de criterios (3,4,5) que en la práctica clínica se usan para el diagnóstico pero que se han desarrollado originalmente para la clasificación del LES.

En cuanto al tratamiento del LES, se deben tener en cuenta tres objetivos principales: a) el control de los síntomas de los pacientes que permite la prevención de las complicaciones inmediatas y, por tanto, la mejora en la calidad de vida; b) minimizar el daño causado por la actividad de la enfermedad; y c) la prevención de la morbilidad y la mortalidad. Los tratamientos disponibles en la actualidad no siempre nos permiten alcanzar estos objetivos al mismo tiempo, pero el uso juicioso y un enfoque específico puede lograr buenos resultados en la mayoría de los pacientes (23).

El arsenal terapéutico disponible se ha ido ampliando progresivamente y, en la actualidad, se dispone de distintas opciones terapéuticas tales como los antiinflamatorios no esteroideos (AINE), los glucocorticoides, los antipalúdicos, los inmunodepresores convencionales y las terapias biológicas.

Los AINE estarían indicados en el tratamiento de las manifestaciones musculo-esqueléticas y la fiebre durante periodos cortos de tiempo. Los glucocorticoides constituyen el tratamiento de base de la mayoría de manifestaciones clínicas del LES (12,24). En los últimos años cada vez son mayores las evidencias acerca de la conveniencia de mantener la dosis más

baja posible de glucocorticoides (igual o inferior a 5 mg/día de prednisona (25)) en el tratamiento crónico y, si es posible, intentar suspenderlos dado su perfil de efectos secundarios (23).

El papel de los antipalúdicos, especialmente la hidroxicloroquina, está bien establecido a través de su acción inmunomoduladora. Se ha demostrado que reducen la aparición de brotes de la enfermedad, el daño acumulado y la mortalidad relacionada con el proceso (26–28). Además, existen evidencias acerca de su papel en la reducción del riesgo cardiovascular, del síndrome metabólico y de las trombosis (29,30).

Los inmunodepresores convencionales se deben usar en casos de afectación orgánica grave como la nefritis lúpica, pero también como ahorradores de glucocorticoides en aquellos pacientes que, debido a sus manifestaciones lúpicas, no pueden disminuir la dosis de corticoides por debajo de 10 mg/día. El metotrexato ha demostrado su eficacia en los casos de afectación musculoesquelética, la azatioprina como tratamiento de mantenimiento en varias afectaciones orgánicas (31) y el micofenolato y la ciclofosfamida en los ensayos clínicos de tratamiento de la nefritis lúpica proliferativa y membranosa (32).

Respecto a las terapias biológicas, el rituximab y el belimumab son los dos fármacos más empleados. El primero es un anticuerpo monoclonal anti-CD20 que, en ensayos clínicos, su adición al tratamiento convencional no ha mostrado beneficio en casos de afectación moderada y de nefritis lúpica (33,34). Sin embargo, numerosos estudios observacionales han descrito que su uso *off-label* obtiene respuestas efectivas en pacientes con manifestaciones graves (35). El belimumab es un anticuerpo monoclonal completamente humanizado que se une a la forma soluble de la proteína estimuladora de los linfocitos B (BLYS) e inhibe su supervivencia y reduce su diferenciación. Dos ensayos clínicos (36,37) han mostrado su efecto beneficioso al añadirlo al tratamiento convencional y es el único fármaco biológico que ha obtenido la indicación para el tratamiento del LES en su ficha técnica.

Entre las nuevas terapias emergentes cabe destacar otras terapias biológicas como el atacicept, el bortezomib, el anifrolumab y el epratuzumab, dirigidos frente a diversas moléculas que intervienen en los procesos de respuesta inmunológica de la enfermedad (38).

A lo largo de los últimos 40 años la supervivencia de los pacientes con LES ha aumentado de forma significativa, de forma que se ha pasado de una tasa inferior al 50% a los 5 años en 1955, a más de un 90% en la década de 1990 (39). No obstante, esta mejora en la supervivencia alcanzó una meseta entre los años 1980 y 1990, a pesar de las mejoras en el diagnóstico y el tratamiento. Esto puede ser debido al aumento del daño acumulado y, por tanto, de la morbilidad asociada a la enfermedad (40). Las causas de mortalidad en los pacientes con LES son de naturaleza dispar y varían en función de las fases del proceso. En las iniciales, la mortalidad suele estar relacionada con la actividad de la enfermedad en forma de afectación renal, cardiovascular o neurológica y con procesos infecciosos asociados a la inmunodepresión necesaria. En las fases avanzadas del cuadro, la mortalidad tiene sus principales causas en procesos cardiovasculares (accidentes vasculares cerebrales o cardiacos) y neoplásicos (carcinoma pulmonar, linfoma no Hodgkin) (41).

Las comorbilidades en el LES pueden ser consecuencia directa de la enfermedad (sobre todo la enfermedad renal crónica y la ateroesclerosis acelerada) o de la medicación empleada para el control de la enfermedad, especialmente los glucocorticoides con su amplio repertorio de efectos secundarios. Tanto una como los otros pueden originar un proceso de aterosclerosis acelerada. Por lo tanto, los paciente con LES tienen mayor riesgo de desarrollar enfermedad cardiovascular precoz (42), incremento de cáncer, particularmente hematológico, de cuello de útero, de mama y de pulmón (43), osteonecrosis (44) y complicaciones neuropsiquiatricas (45), entre otras.

En la presente tesis se analiza la afectación del sistema nervioso, tanto SNC como periférico (SNP), en el LES, mediante el estudio de la cohorte de pacientes con esta enfermedad controlados en el Servicio de Enfermedades Autoinmunes del Hospital Clínic de Barcelona. En el apartado siguiente se realiza una revisión bibliográfica acerca de la afectación neurológica del LES con especial énfasis en aspectos del diagnóstico y de la utilidad de la resonancia magnética (RM) cerebral. Además, se revisa el conocimiento actual de la afectación del SNP en el LES. A continuación se presentan la hipótesis y

los objetivos, los estudios publicados que conforman el cuerpo principal de la tesis, con un breve comentario de cada uno de ellos y se exponen las conclusiones que de ellos se desprenden. Al final, se ha añadido una discusión y en el anexo, se incluyen dos artículos sobre la misma temática en los que la doctoranda ha participado como coautora pero que no forman parte del cuerpo de la presente tesis.

II. REVISIÓN BIBLIOGRÁFICA

2.1. Afectación del sistema nervioso en el LES

La afectación neurológica del LES se conoce como lupus neuropsiquiátrico (LESNP). Los síndromes neuropsiquiátricos en el LES se definen como síndromes neurológicos del SNC, SNP, autonómico y los síndromes psiquiátricos observados en pacientes con LES, una vez descartada otras etiologías (farmacológicas, infecciones, alteraciones metabólicas u otras manifestaciones sistémicas como uremia o hipertensión) (46).

La primera manifestación neuropsiquiátrica en el LES fue descrita por Kaposi y Osler en el siglo XIX, en una mujer joven con pleuresía, neumonía, función neurológica alterada y rápida evolución hasta la muerte (47,48). Hoy en día, estas manifestaciones continúan siendo una de las principales causas de morbimortalidad en estos pacientes (49,50). Estudios recientes han mostrado un aumento de la mortalidad en los pacientes con manifestaciones neuropsiquiátricas en comparación con la población general o pacientes con LES sin este tipo de manifestaciones (51,52).

En 1999, la ACR publicó el documento de consenso para la clasificación, nomenclatura y tratamiento del LESNP que se utiliza hasta la fecha. En ésta se definieron 12 síndromes del SNC y 7 del SNP (tabla 1) (46). Aunque este enfoque estandarizado para clasificar el LESNP ha mejorado la descripción y clasificación de estas manifestaciones en estudios clínicos, su utilidad en la práctica clínica es limitada.

Tabla 1. Síndromes neuropsiquiátricos observados en el LES (46)

Sistema Nervioso Central	**Sistema Nervioso Periférico**
Meningitis aséptica	Polirradiculopatía desmielinizante Inflamatoria aguda (Síndrome Guillain Barré)
Enfermedad cerebrovascular	Neuropatía autonómica
Síndrome desmielinizante	Mononeuropatía (simple o múltiple)
Cefalea (incluyendo la migraña y la hipertensión intracraneal benigna)	Mistenia Gravis
Alteración motriz (corea)	Neuropatía craneal
Mielopatía	Plexopatía
Convulsiones	Polineuropatía
Estado confusional agudo	
Trastorno de ansiedad	
Disfunción cognitiva	
Desórdenes del humor	
Psicosis	

2.2. Prevalencia y epidemiología del LES neuropsiquiátrico

El primer punto importante a tener en cuenta es la variabilidad de la prevalencia del LESNP entre los diferentes estudios, que va desde el 14 al 90% (tabla 2), aunque sólo el 40% de los mismos se pueden atribuir directamente a la enfermedad activa (LESNP primario) (53–62). Este es el principal problema a la hora de afrontar un paciente con LES y manifestaciones neurológicas; en otras palabras, decidir si lo que le ocurre al enfermo está relacionado o no con su enfermedad. La decisión que se tome es crucial en términos de tratamiento. En la mayoría de ocasiones es difícil establecer la causalidad de los síndromes neuropsiquiátricos al LES y, por ello, se han propuesto diferentes modelos de atribución en un intento de diferenciar estas manifestaciones. En un estudio que luego ha sido la base de la mayoría de las series en este campo, Ainala y cols (63) señalan que si se excluyeran las manifestaciones neuropsiquiátricas menores y más comunes en la población general (cefalea, depresión leve, ansiedad, quejas cognitivas leves y polineuropatía con electromiografía negativa), la prevalencia del LESNP disminuiría del 91% al 46%. Estos criterios se conocen como los “criterios de inclusión de Ainala” y, como se ha comentado, se han utilizado como criterios de exclusión en los modelos de atribución más relevantes (64,65).

La cohorte de LESNP del grupo SLICC definió mediante dos modelos de atribución los factores que hacen más probable que la manifestación neuropsiquiátrica esté relacionada con el LES. En el Modelo A la manifestación se atribuye a la enfermedad si: a) ocurre en los 6 meses previos al diagnóstico del LES o en los 15 meses siguientes al mismo, b) no presenta ninguno de los factores de confusión que probablemente fueran la causa o un contribuyente importante (tal como se define en la nomenclatura ACR) y c) no es uno de los “criterios de Ainala”. En el Modelo B, la manifestación se atribuye al LES si: a) ocurre dentro de los 10 primeros años del diagnóstico del LES, b) no presenta ninguno de los factores de confusión (tal como se define en la nomenclatura ACR) y c) no es uno de los “criterios de Ainala“ (65).

Tabla 2: Prevalencia de los síndromes de LESNP en los diferentes estudios

	Ainala 2001 (n=46)	**Brey 2002 (n=128)**	**Zhou 2008 (n=1965)**	**Hanly 2010 (n=1206)**		**Kampylafka 2013 (n=370)**	**Hajighaemi 2013 (n=556)**
Tipo de estudio	Prospectivo	Prospectivo	Retrospectivo	Prospectivo		Prospectivo	Retrospectivo
Duración del estudio (años)	17	ND	14	9		3	6
Etnia:							
Caucásicos	46 (100)	42 (30)	0	572 (47.4)		ND	ND
Asiáticos	0	0	1965 (100)	199 (16.5)			
Afroamericanos	0	10 (8)	0	188 (15.6)			
Hispanos	0	72 (56)	0	199 (16.5)			
Otras	0	4 (3)	0	5 (3.9)			
Edad* (años)(media ± DE)	45 ± 13	43	31.1 ± 11.8	34.5 ± 13.2		32 ± 14	33.9 ± 14.1
Modelo de atribución	NME†	NME	NME	SLICC		Criterios Ainala¶	NME
Prevalencia LESNP	42 (91.3)	102 (79.7)	240 (12.2)	486 (40.3)		16 (4.3)	121 (21.7)
				Modelo A	Modelo B		
				149 (17.7)	258 (30.6)		
Tipos de LESNP							
Sistema Nervioso Central							
Meningitis asépitca	1 (2)	0	34 (1.7)	4 (2.7)	4 (1.6)	1 (0.3)	1 (0.2)
Enfermedad cerebrovascular	7 (15)	2 (2)	37 (1.9)	18 (12.1)	40 (15.5)	5 (1.4)	47 (8.4)
Síndrome desmielinizante	1 (2)	0	6 (0.3)	1 (0.7)	3 (1.2)	0	9 (1.6)
Cefalea	25 (54)	73 (57)	70 (3.6)	0	0	0	47 (8.4)
Desórdenes de movimiento	1 (2)	1 (1)	9 (0.5)	4 (2.7)	5 (1.9)	0	4 (0.7)
Mielopatía	0	0	8 (0.4)	5 (3.4)	10 (3.9)	4 (1.1)	7 (1.2)
Convulsiones	4 (9)	21 (16)	62 (3.1)	39 (26.2)	54 (20.9)	6 (1.6)	32 (5.7)
Estado confusional agudo	3 (7)	0	38 (1.9)	11 (7.4)	17 (6.6)	0	0
Ansiedad	6 (13)	27 (21)	5 (0.3)	0	0	0	10 (1.8)
Deterioro cognitivo	37 (80)	53 (41)	25 (1.3)	8 (4.4)	22 (8.5)	0	14 (2.5)
Desórdenes del humor	20 (44)	25 (20)	40 (2)	18 (12.1)	47 (18.2)	0	6 (1.1)
Psicosis	0	6 (5)	31 (1.6)	8 (5.4)	13 (5)	1 (0.3)	32 (5.7)
Sistema nervioso periférico							
PDIA	0	0	0	2 (1.3)	2 (0.8)	0	0
Desórdenes autonómicos	0	0	0	2 (1.3)	2 (0.8)	0	3 (0.5)
Mononeuropatía	0	9 (7)	7 (0.4)	10 (6.7)	18 (6.9)	0	7 (1.3)
Miastenia Gravis	1 (2)	0	0	0	0	0	10 (1.8)
Neuropatía craneal	3 (7)	2 (2)	9 (0.5)	11 (7.4)	11 (4.3)	1 (0.3)	20 (3.6)
Plexopatía	0	0	0	0	0	0	7(1.3)
Polineuropatía	13 (28)	29 (23)	11 (0.6)	8 (5.4)	10 (3.9)	0	6 (1.1)

Los resultados se expresan como n (%)

* Edad a la inclusión en el estudio
† En el estudio inicial todos los eventos NP fueron atribuidos al LES. Posteriormente al utilizar los "criterios de Ainala" la prevalencia de NPLES disminuyó hasta el 46%.
¶ El modelo de atribución se basó en los "criterios de Ainala" y también se excluyeron todos los LESNP del SNP salvo la neuropatía craneal.

Abreviaturas: NME: ningún modelo específico de atribución salvo la exclusión de pacientes con causas secundarias o factores de confusión para el desarrollo de manifestaciones neuropsiquiátricas, de acuerdo con lo propuesto por la ACR (articulo ACR 1999); ND: No disponible; LESNP: lupus neuropsiquiátrico; PDIA: polirradiculopatía desmielinizante inflamatoria aguda.

Por su parte, Bortoluzziet y cols. (64) desarrollaron un nuevo algoritmo que añade tres ventajas a los modelos de atribución del SLICC: 1) una serie de factores favorecedores que apoyan la atribución de la manifestación

neuropsiquiátrica al LES (basados en las recomendaciones de la *European League Against Rheumatism* [EULAR] del año 2010) (66), 2) una lista de factores de confusión y factores favorecedores para cada uno de los 19 síndromes de LESNP establecidos por la ACR y 3) un sistema de puntuación que proporcionó un valor predictivo positivo del 86,3%, un valor predictivo negativo del 85,7% y un error de clasificación errónea menor del 10%. Este algoritmo de atribución se ha aplicado en 2016 en la cohorte de pacientes con LES de la Universidad de Heraklion. En este estudio se recogieron un total de 242 episodios de manifestaciones neuropsiquiátricas en 191 pacientes. Según el criterio del médico tratante, 136 (56,2%) se atribuyeron al LES. Los dos modelos, A y B del SLICC mostraron una elevada especificidad (96,2% y 79,2%, respectivamente), pero un baja sensibilidad (22,8% y 34,6%, respectivamente) frente al criterio del médico. Cuando se excluyeron las manifestaciones recogidas en los criterios de Ainala, la sensibilidad aumentó ligeramente (27,2% y 42,0% para el modelo A y B, respectivamente) con reducción de la especificidad (94,8% y 65,5%, respectivamente). Finalmente, cuando se aplicó el algoritmo del grupo italiano, mostró una mejor precisión en la atribución al LES con un área bajo la curva ROC de 0,862, de manera que valores ≥7 fueron los que obtuvieron la mejor combinación de sensibilidad (82,4%) y especificidad (82,9%) (67).

No obstante, en esta disparidad en la prevalencia contribuyen otros factores además de los criterios de atribución al LES, como son la población estudiada, los diferentes criterios de inclusión, los métodos diagnósticos utilizados y el periodo de observación (53–62). Unterman y cols. (56), realizaron un metaanálisis agrupando todos los estudios disponibles hasta la fecha. Incluyeron una población de 5057 pacientes con LES con una prevalencia de LESNP de 44,5% en los estudios prospectivos frente al 7,6% en los estudios retrospectivos. Por su parte, la menor prevalencia observada en los estudios de Zhou y cols. (68) y Kampylafka y cols. (69) quizás se deba a que en el primer estudio la población incluida era asiática y en esta población se describe una menor prevalencia de síntomas menores como ansiedad, dolor de cabeza o deterioro cognitivo leve (70), mientras que la baja prevalencia del segundo estudio podría estar justificada por la utilización de los criterios de Ainala, junto con la exclusión de los síndromes del SNP, salvo las neuropatías craneales.

El LESNP puede ocurrir en cualquier momento del curso de la enfermedad, aunque cerca de la mitad de los casos ocurren en su inicio o en los dos primeros años después del diagnóstico del LES (54,65,71). Como factores de riesgo para su desarrollo se han descrito una mayor actividad de la enfermedad, haber sufrido manifestaciones neuropsiquiátricas con anterioridad o la presencia de anticuerpos antifosfolipídicos (66).

Los estudios epidemiológicos han sugerido diferencias en la prevalencia del LESNP según el sexo y el origen étnico. Se ha descrito una mayor incidencia del compromiso neurológico en las mujeres y un mayor riesgo de sufrir convulsiones en los varones; no obstante, la evidencia para apoyar la asociación entre el sexo y los distintos síndromes de LESNP es limitada, ya que la mayoría de los estudios no realizan corrección de los posibles factores de confusión (72–74). Las manifestaciones neuropsiquiátricas son más frecuentes en descendientes de africanos, mestizos y asiáticos que en individuos caucásicos (75–77). Sin embargo, estas manifestaciones son más graves en la población caucásica tal como se describe en las cohortes LUMINA y de Maryland (78,79).

2.3. Patogenia del LES neuropsiquiátrico

La patogenia del LESNP continúa siendo controvertida en el momento actual. Se han implicado múltiples factores de riesgo en su desarrollo, entre los que destacan factores genéticos (polimorfismos del gen TREX1 o alelos HLA-DRB1*04) (80–82), la presencia de distintos autoanticuerpos, como los anticuerpos antifosfolipídicos (relacionados con trombosis) (83), los anticuerpos antiribosoma P (relacionados con el desarrollo de depresión y psicosis) (71,84,85) o los anti-ADN/NR2 (relacionados con el deterioro cognitivo) (86), factores inflamatorios relacionados con niveles elevados de diferentes citocinas (45,87) o la aterosclerosis acelerada (88–91), entre otros.

Actualmente, existen dos hipótesis para explicar los principales mecanismos patogénicos que conducen al desarrollo del LESNP (92–94). Por un lado, la autoinmune o inflamatoria, que se caracteriza por la disfunción cerebral secundaria a la presencia de autoanticuerpos o mediadores inflamatorios o la

formación intratecal de complejos inmunes con una barrera hematoencefálica interrumpida. En este caso, la disfunción neuronal puede ser inducida directamente por estos mediadores o indirectamente mediante la activación de células neuronales. Por otra parte, la hipótesis vascular en la que la lesión vascular y la oclusión trombótica de los vasos intratecales de pequeño y gran tamaño sería la causante de la clínica neurológica. Esta afección vascular estaría mediada por autoanticuerpos, complejos inmunes, deposición de complemento, leucoaglutinación y ateroesclerosis acelerada

Es probable que según la naturaleza del síndrome de LESNP la causa sea una u otra. En general, se reconocen dos tipos de afectación, los síndromes focales y los difusos. Entre los primeros estarían la enfermedad cerebrovascular, las convulsiones, la corea, la mielitis y las neuropatías craneales. En el segundo grupo se encuadrarían el estado confusional agudo, la meningitis aséptica, la enfermedad desmielinizante, la disfunción cognitiva y la psicosis grave. Se asume que, probablemente, la afectación vascular sería la causante en mayor medida de los síndromes focales, mientras que la disfunción inflamatoria sería la etiología dominante en los difusos. Sin embargo, en la práctica clínica es muy difícil encuadrar en un grupo u otro ciertas manifestaciones. En otras palabras, algunas de estas pueden ser debidas a una causa vascular e inflamatoria como el estado confusional agudo, la mielitis, la disfunción cognitiva o las convulsiones refractarias (93).

2.4. Diagnóstico del LES neuropsiquiátrico

La variedad de posibles manifestaciones neuropsiquiátricas en el LES, así como la falta de biomarcadores diagnósticos precisos hacen que el diagnóstico del LESNP sea una desafío (66). Actualmente, la decisión de atribuir una manifestación neuropsiquiátrica al LES se basa en gran parte en el juicio médico, los resultados clínicos, de laboratorio y la neuroimagen, a menudo a través del consenso entre distintas especialidades médicas (92). Ante la aparición de una clínica neurológica en un paciente con LES se debe establecer el diagnóstico diferencial entre la propia enfermedad, una enfermedad infecciosa concomitante, la comorbilidad del paciente y un efecto adverso del tratamiento seguido. Por todo ello, el diagnóstico de LESNP se

establece mediante un proceso de exclusión y se considera que ante un paciente con LES con signos o síntomas neuropsiquiátricos de nueva aparición, el protocolo diagnóstico debería ser similar al de un paciente sin LES (66,95).

Dependiendo de los hallazgos de la historia clínica y la exploración física, existen una serie de exploraciones complementarias que pueden ayudar a realizar el diagnóstico diferencial. En general, el resultado de todas ellas permitirá excluir otras opciones diagnósticas.

El examen del líquido cefalorraquídeo (LCR) se debe realizar de forma precoz para descartar procesos infecciosos. La utilidad de la determinación en el LCR de autoanticuerpos, citocinas, factores de crecimiento, así como de biomarcadores de lesión cerebral es controvertida. Existe consenso en no recomendar su determinación en la práctica clínica por la ausencia de especificidad (93,96–98). Además, en un 40-50% de los pacientes con LESNP se detectan alteraciones leves en el LCR pero no son específicas de estas manifestaciones (66).

Respecto a los autoanticuerpos circulantes, los que tienen un posible valor diagnóstico más importante son los anticuerpos antifosfolipídicos (99). El valor de los anticuerpos contra la proteína P ribosómica y el de los anticuerpos contra el receptor NR2 es, por el momento, incierto (84,87,100–103), aunque algunos estudios y un metaanálisis reciente ya los relacionan con el desarrollo de síndromes de LESNP específicos (84,104–106). Por su parte, los autoanticuerpos anti-NMO (neuromielitis óptica o IgG antiacuaporina-4) pueden ayudar en el proceso diagnóstico de un paciente con mielopatía o neuritis óptica (93). De hecho, su determinación es obligada en caso de sospecha de neuromielitis óptica asociada al LES.

Los estudios electrofisiológicos están indicados cuando se sospecha clínica comicial o neuropatías (107,108). Sin embargo, estas pruebas no presentan tampoco signos específicos para LESNP (107,109,110).

Las pruebas de neuroimagen deben valorar, por un lado, la estructura cerebral y, por otro, los mecanismos fisiopatológicos. La RM, la tomografía por emisión de positrones (PET) y la tomografía computarizada por emisión de fotón único (SPECT) siguen siendo las técnicas de imagen de elección (111–113), aunque la relevancia clínica de estas pruebas en pacientes individuales requiere

prueba de validación adicionales.

Las pruebas neuropsicológicas resultan de utilidad para valorar la habilidad cognitiva, aunque la detección de pequeñas deficiencias subclínicas pueden tener escasa relevancia clínica (95,114,115).

No obstante, a pesar de las distintas pruebas disponibles y de los avances que se han realizado, el diagnóstico de las manifestaciones neuropsiquiátricas del LES sigue siendo un desafío, dada la ausencia de una prueba de oro para su diagnóstico.

2.5. Resonancia magnética en el diagnóstico del LES neuropsiquiátrico

La RM se considera actualmente como el método de referencia para la evaluación de los pacientes con LES y afectación neurológica central, al tratarse de una prueba ampliamente disponible y que permite la exclusión de otras enfermedades causantes de síntomas neuropsiquiátricos (54,59,95,116). Se pueden apreciar alteraciones en la RM en el 19-70% de los pacientes con LES (53,117).

En general, su sensibilidad para la detección de lesiones focales como la enfermedad cerebrovascular aguda, tanto isquémicas como hemorrágicas, y la mielitis es elevada (80-90%), aunque disminuye hasta un 50% para las lesiones en la sustancia blanca, la sustancia gris y la atrofia cerebral (88,118–120). Dicha sensibilidad puede aumentar con las secuencias T2 (66). Además, las anomalías de la RM causadas por el LESNP primario carecen de especificidad, lo que dificulta el diagnóstico diferencial de las manifestaciones causadas por el LES o las asociadas a otras causas (121).

Las lesiones de la sustancia blanca están presentes en el 18-40% de los pacientes con manifestaciones neuropsiquiátricas no relacionados con el LES (122). Varios estudios han demostrado que estas lesiones también se asocian con la edad, la duración de la enfermedad, la presencia de valvulopatías, otros factores de riesgo cardiovascular y la positividad de anticuerpos antifosfolipídicos (123–125).

Los hallazgos anormales en la RM pueden dividirse en tres grupos, de acuerdo con su fisiopatología y las características de la imagen: enfermedad de vasos pequeños, enfermedad de vasos grandes y lesiones inflamatorias (Figura 1).

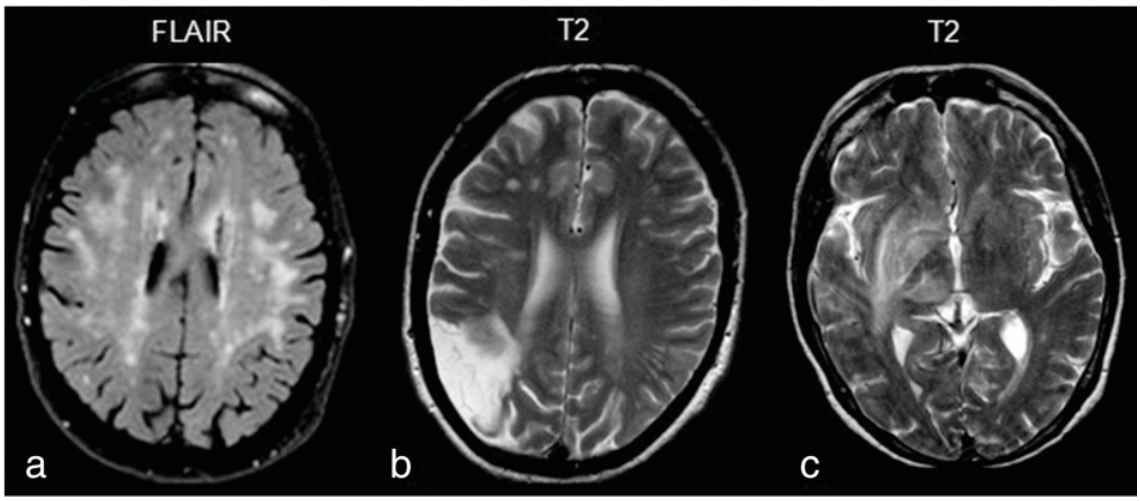
- Enfermedad de vasos pequeños: Representa del 30-70% de los hallazgos e

incluye hiperintensidades de color blanco, atrofia cerebral cortical e infartos lacunares y subcorticales. Estas lesiones se consideran inespecíficas, aunque se han relacionado con la disfunción cognitiva, las convulsiones y la enfermedad cerebrovascular (126,127). La atrofia cerebral parece correlacionarse con la duración de la enfermedad, la disfunción cognitiva, la enfermedad cerebrovascular, las convulsiones, la terapia con glucocorticoides, el complemento bajo y el anticoagulante lúpico (57,128).

• Afectación de grandes vasos: Es menos frecuente que las anteriores, representa entre 10-15% de los hallazgos de la RM en el LESNP (128) y se asocia con infartos de mediano y gran tamaño (127).

• Lesiones inflamatorias: Son las menos frecuentes (5-10%). En estos casos la RM es de ayuda en el diagnóstico diferencial de los trastornos desmielinizantes, así como en la evaluación de la neuropatía craneal (54).

Figura 1: Imágenes de RM cerebral mostrando las lesiones descritas en el LES neuropsiquiátrico.



a) secuencia FLAIR que muestra lesiones hiperintensas confluentes en sustancia blanca clasificadas como enfermedad de pequeño vaso; b) imagen ponderada en T2 que muestra infarto crónico en el territorio posterior de la arteria cerebral media junto a hiperintensidades focales en sustancia blanca que indican enfermedad de gran y pequeño vaso, respectivamente y c) imagen ponderada en T2 que muestra imágenes de hiperintensidades en ganglios basales, tálamo y cápsula interna y externa derechas.
Tomado de Sarbu N, et al. Autoimmun Rev 2015;14:153-9.

Por otra parte, la diferenciación entre enfermedad activa y las lesiones crónicas a través de la RM es difícil. La presencia de lesiones con bordes mal definidos e intensidad media en las imágenes potenciadas en T2, así como las lesiones que afectan a la sustancia gris, sugieren la presencia de un proceso activo (59). El uso de gadolinio y la cuantificación de los valores potenciados en T2 (FLAIR) han demostrado su utilidad para definir las lesiones inflamatorias activas (128–130). Como consecuencia de lo comentado, la especificidad de la RM para la detección de las lesiones agudas en la sustancia blanca asociada al LESNP se estima entre 60-80% (122). Por otra parte, Arinuma y cols. (131) objetivaron que los pacientes con LESNP difuso con anomalías en la RM cerebral tenían una enfermedad más grave y, por tanto, una mortalidad más elevada.

Se han utilizado diferentes técnicas de RM en el diagnóstico del LESNP. La RM espectroscópica permite la cuantificación de metabolitos en los tejidos cerebrales implicados en las manifestaciones neuropsiquiátricas del LES, al objetivar anomalías en la sustancia blanca y gris, no detectadas en la RM convencional (132–134). El estudio de difusión es una técnica de RM que mide la difusión de agua en el cerebro y, por tanto, permite diferenciar las lesiones inflamatorias de las isquémicas. Esta técnica ha demostrado que, en los pacientes con LESNP con síntomas agudos, existe un incremento de la difusión generalizada en el cerebro, lo que indica que en estos pacientes se produce una pérdida de la integridad cerebral. La transferencia de magnetización permite cuantificar el cambio de protones entre aquéllos unidos a macromoléculas, lo que permite diferenciar las lesiones crónicas en los pacientes con LESNP (135).

Algunos estudios han utilizado el análisis multimodal de varias técnicas de RM, incluyendo FLAIR, imágenes ponderadas en T1, T2, transferencia de magnetización y técnica de tensor de difusión (136,137). No obstante, estos estudios se han limitado a mostrar solamente cambios globales cerebrales.

Pese a todo, la validez e importancia de la RM en el diagnóstico del LESNP está todavía por determinar (138). No obstante, a pesar de sus limitaciones, la RM podría ser útil para explorar los mecanismos patológicos (126), facilitar el diagnóstico diferencial (54,139,140), cuantificar la actividad de la enfermedad y determinar el pronóstico de los síndromes LESNP (58,121,126).

2.6. Afectación del sistema nervioso periférico en el LES

La afectación del SNP en el LES ha sido poco investigada, pese a asociarse a una morbilidad significativa y un empeoramiento de la calidad de vida de los pacientes (3). En la literatura, existen pocos estudios controlados (4,141) y la mayoría de las publicaciones son series de casos o estudios con un número limitado de pacientes (142,143).

Su prevalencia se estima en un 5-27%, aunque los estudios que utilizan criterios electrofisiológicos para el diagnóstico de neuropatías a menudo describen prevalencias más altas, ya que incluyen pacientes asintomáticos con anomalías en la conducción nerviosa (61,144–148).

La afectación del SNP en el LES se caracteriza fundamentalmente por una polineuropatía sensorial o sensitivo-motora, aunque también se describen mononeuropatías, neuropatías craneales, alteraciones del sistema nervioso autónomo o neuropatías desmielinizantes como el síndrome de Guillain-Barré (46,149). Las neuropatías craneales más frecuentes implican al octavo, tercer, cuarto y sexto par craneal, mientras que la afectación del quinto y del séptimo par craneal son menos frecuentes (66). Además, en los últimos años, la neuropatía de fibra fina y la polirradiculopatía desmielinizante crónica se han relacionado con el LES (150–153), aunque estas manifestaciones no están incluidas en la clasificación de síndromes LESNP establecida por la ACR (46) .

Su patogenia no está clara, aunque se ha asociado con una vasculopatía de las pequeñas arterias que irrigan los nervios afectados, produciendo isquemia y, por tanto, degeneración axonal y desmielinización segmentaria (154,155). La actividad de la enfermedad y la presencia de algunos marcadores serológicos, como los anticuerpos anti-Sm, también se han relacionado con la presencia de este tipo de afectación (116,146).

El diagnóstico del LES se suele realizar antes de la aparición de los síntomas neurológicos, pero en ocasiones la afectación del SNP puede ser la primera manifestación de la enfermedad (146,147,156). El diagnóstico suele ser clínico, en ocasiones apoyado por métodos electrofisiológicos y biopsia de nervio (152). El hallazgo más frecuente en la biopsia de nervio es una degeneración axonal con pérdida de fibras mielinínicas y no mielínicas; la infiltración perivascular es un hallazgo menos frecuente (156). En el caso de las neuropatías craneales, la

RM, el fondo de ojo y los potenciales evocados son de ayuda en el diagnóstico; en los casos de polineuropatía y mononeuropatía, los estudios de conducción nerviosa permiten diferenciar las mononeuropatías múltiples de las polineuropatías y distinguir las neuropatías axonales de las desmielinizantes. Por otra parte, el análisis de LCR está indicado ante la sospecha de enfermedad desmielinizante y la biopsia de piel en los casos en los que se sospeche neuropatía de fibra fina con estudios de conducción normales (66).

Aunque la afectación del SNP en el LES produce un empeoramiento de la calidad de vida de los pacientes, rara vez aumenta el riesgo de muerte (157).

Dadas todas las limitaciones comentadas, la afectación del SNP aún no ha sido bien caracterizada en el LES en términos de prevalencia, inicio, gravedad y asociaciones clínicas y electrofisiológicas.

2.7. Tratamiento del LES neuropsiquiátrico

Una vez establecido el diagnóstico de LESNP, los primeros pasos terapéuticos deben dirigirse a identificar y tratar los factores potencialmente agravantes, como hipertensión arterial, anormalidades metabólicas o infecciones intercurrentes (66), así como a tratar las manifestaciones clínicas de forma sintomática (agentes anticomiciales, antidepresivos, neurolépticos o AINE en función de las necesidades del caso) (66,158,159). En la misma línea, también se han utilizado programas de rehabilitación cognitiva para pacientes con disfunción cognitiva para que se puedan adaptar a sus limitaciones y mantener cierto grado de independencia (160–162).

Aunque no se ha estudiado de forma especifica la hidroxicloroquina y los fármacos antipalúdicos en el tratamiento del LESNP, se ha sugerido un papel preventivo de estos fármacos en las afectaciones del SNC (163,164). En la cohorte LUMINA se puso de manifiesto su efecto protector frente a las convulsiones (165), efecto que se ha comprobado también en el estudio de Magro-Checa y cols. (158) aunque el mecanismo por el que se produce esta protección es desconocido (166).

El tratamiento inmunodepresor, representado por glucocorticoides, azatioprina, metotrexato, ciclofosfamida y micofenolato mofetilo, estaría indicado en los casos en los que se sospeche origen inflamatorio (síndrome orgánico cerebral, meningitis aséptica, neuropatías craneales y periféricas y psicosis), proceso

neurotóxico o presencia de actividad del LES (95), una vez excluidas otras causas no relacionadas con la enfermedad (167,168). Los glucocorticoides, aunque se usan de forma frecuente en los pacientes con LESNP, también se han relacionado precisamente con el desarrollo de manifestaciones neuropsiquiátricas como la depresión, la psicosis y la hipomanía (169,170). Los bolos endovenosos de ciclofosfamida se han utilizado con buenos resultados en las manifestaciones graves del LESNP, sobre todo, en los que existe participación del SNC (171,172). Un estudio aleatorizado (167) objetivó mejores resultados al utilizar como terapia de mantenimiento ciclofosfamida respecto a bolos de glucocorticoides; este hecho también se objetivó en el estudio de Fanouriakis y cols. (173). Actualmente, se considera el tratamiento de primera línea en LESNP grave. Por su parte, la azatioprina y el micofenolato de mofetilo han sido poco estudiados en el tratamiento del LESNP (70,174–178). Una reciente revisión sistemática apunta a que la eficacia del micofenolato mofetilo en el LESNP parece modesta y recomienda que su uso se restrinja a los pacientes refractarios o intolerantes al tratamiento con ciclofosfamida (179).

Respecto al rituximab, existen cinco estudios de cohortes en LESNP en los que se observó un 73-100% de mejoría clínica o de respuesta de las manifestaciones neuropsiquiátricas (180). Aunque los resultados no han sido concluyentes, diversas revisiones de series de casos han alcanzado resultados muy prometedores, con índices de respuesta a rituximab del 85% en pacientes refractarios a tratamiento inmunodepresor convencional (181).

Otro tratamiento a considerar en el caso de manifestaciones graves de LESNP o refractarias al tratamiento convencional son los recambios plasmáticos, aunque deben realizarse en combinación con inmunodepresión por el posible incremento de los anticuerpos circulantes al suspender el procedimiento (182,183). Además, no están indicados en caso de infarto cerebral o tromboflebitis por el tratamiento anticoagulante que se debe administrar con los recambios (184).

En los casos en los que el LESNP se relacione con la presencia de anticuerpos antifosfolipídicos, especialmente en casos de enfermedad trombótica, se recomienda la terapia antiagregante y/o anticoagulante (185–188). Este tratamiento también es el aconsejado en los casos de isquemia asociada a neuropatía óptica, corea y mielopatía refractaria al tratamiento inmunodepresor

(189–191). El tratamiento antiagregante se debe considerar como prevención primaria en los pacientes con LES con títulos moderados o altos de anticuerpos antifosfolipídicos (66).

Entre las terapias futuras para el tratamiento del LESNP se encuentran los anticuerpos monoclonales, como el belimumab, aunque en los ensayos de este fármaco los pacientes con LESNP se excluyeron de forma específica. Otros biológicos potencialmente útiles serían el tabalumab, el epratuzumab, el sifalimumab, el rontalizumab, el blisibimod y la proteína de fusión atacicept, entre otros, aunque la mayoría de ellos aún deben evaluarse en los ensayos en fase III.

Atendiendo a las manifestaciones del SNP en el LES, se recomienda el tratamiento con bolos intravenosos de glucocorticoides en combinación con ciclofosfamida intravenosa en los casos de neuropatía craneal. La anticogulación se puede considerar si la neuropatía craneal se asocia con anticuerpos antifosfolipídicos positivos y existe una falta de respuesta al tratamiento inmunodepresor (66,167). Los glucocorticoides solos o en combinación con terapia inmunodepresora se han utilizado con buenos resultados en la polineuropatía, la mononeuropatía, la polirradiculopatía inflamatoria aguda, la miastenia gravis, la plexopatía y la neuropatía autonómica. Las inmunoglobulinas intravenosas, los recambios plasmáticos y el rituximab están indicados para los casos graves y refractarios al tratamiento convencional (66,192).

III. HIPÓTESIS

Los síndromes neuropsiquiátricos son una complicación grave del LES que contribuyen de forma considerable a una disminución de la calidad de vida y a un aumento de la morbilidad y mortalidad de dichos pacientes. No obstante, su diagnóstico continúa siendo un desafío por la ausencia de una prueba de oro que permita la atribución correcta de estas manifestaciones a la enfermedad.

La RM es la prueba de imagen de elección en los casos de afectación neuropsiquiática de localización central, pero su validez e importancia en el diagnóstico del LESNP está todavía por determinar. Además, no se ha establecido aún una correlación entre la localización de las lesiones de RM y el tipo concreto de LESNP. No obstante, esta prueba puede ser de utilidad para mejorar el conocimiento etiopatogénico de los síndromes neuropsiquiátricos de localización central, facilitar el diagnóstico diferencial, identificar la anatomía de los focos patológicos, cuantificar la actividad de la enfermedad y determinar las consecuencias funcionales y el pronóstico de los mismos.

La afectación del SNP en pacientes con LES es una complicación importante. Sin embargo, aún no ha sido bien caracterizada en el LES en términos de prevalencia, inicio, gravedad y asociaciones clínicas, inmunológicas y electrofisiológicas. Mejorar el conocimiento de estos aspectos podría posibilitar un diagnóstico precoz y un tratamiento más específico que repercuta en el pronóstico y calidad de vida de estos pacientes.

En este contexto, la presente tesis plantea las hipótesis de que la afectación neuropsiquiátrica del SNC en el LES podría tener un patrón característico desde el punto de vista de los hallazgos de la RM cerebral que se relacionase con características clínicas e inmunológicas de los pacientes. Por otra parte, la afectación del SNP en el LES podría estar asociado a diferentes factores clínicos e inmunológicos de los pacientes.

IV. OBJETIVOS

Objetivos generales

1. Mejorar el conocimiento de la afectación neuropsiquiátrica del LES.
2. Determinar la utilidad clínica de la RM cerebral en la afectación del SNC en los pacientes con LES.
3. Caracterizar la afectación de SNP en pacientes con LES respecto a las manifestaciones clínicas, marcadores serológicos y hallazgos en los estudios electrofisiológicos.

Objetivos particulares

Primer estudio

1. Describir las anomalías cerebrales halladas en la RM convencional en pacientes con LES con un primer episodio de LESNP.
2. Investigar la posible correlación entre los hallazgos radiológicos en la RM cerebral y las características clínicas e inmunológicas de los pacientes con LES con un primer episodio de LESNP.

Segundo estudio

1. Conocer la prevalencia de la afectación de SNP en los pacientes con LES.
2. Describir las características clínicas y electromiográficas de la afectación del SNP en pacientes con LES.
3. Analizar si existe un patrón inmunológico característico de la afectación del SNP.
4. Describir los tratamientos administrados y la evolución de los pacientes con LES y afectación del SNP.
5. Identificar los factores clínicos e inmunológicos asociados al desarrollo de la afectación del SNP en pacientes con LES.

V. ARTÍCULOS PUBLICADOS

Neuropsychiatric systemic lupus erythematosus: Magnetic resonance imaging findings and correlation with clinical and immunological features

Lupus neuropsiquiátrico: Hallazgos en la resonancia magnética y su correlación con características clínicas e inmunológicas

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Review

Neuropsychiatric systemic lupus erythematosus: Magnetic resonance imaging findings and correlation with clinical and immunological features

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ABSTRACT

Neuropsychiatric (NP) syndromes are a major cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE). The aims of this work were to describe the brain abnormalities in a group of SLE patients during their first episode of NP manifestations using a conventional magnetic resonance imaging (MRI) technique and to investigate the possible correlation between these findings and the clinical and immunological characteristics of these patients.

We performed an observational retrospective cross-sectional study that included all patients with NP symptoms who underwent MRI at the Hospital Clinic of Barcelona between the years 2003 and 2012 because of suspecting NP syndromes due to SLE (NPSLE).

We studied 43 patients in which 11 types of NPSLE were present, being headache the most frequent, followed by cerebrovascular disease, epileptic crises and cranial neuropathy. A statistically significant association was found between myelopathy and low complement (C4) levels ($p = 0.035$) and disease activity measured as SLE Disease Activity Index (SLEDAI) >4 ($p = 0.00006$). Eighteen (41.9%) patients presented MRI abnormalities. We found an association between myelopathy and the presence of inflammatory or mixed (vascular and inflammatory) type lesions ($p = 0.003$). This pattern was also associated with a high SLEDAI score ($p = 0.002$) and low complement (CH50) levels ($p = 0.032$). We found no relationship between MRI changes and age, time of evolution, or the presence of antiphospholipid or anti-dsDNA antibodies.

These results suggest that MRI, although it is the imaging modality of choice in the present moment, by itself does not establish or exclude the diagnosis of NPSLE. In addition, the presence of certain disease activity features (SLEDAI and low complement levels) seems to be associated with the presence of an inflammatory pattern on MRI.

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1. Introduction

Prognosis of patients with systemic lupus erythematosus (SLE) has improved considerably in recent decades. However, neuropsychiatric (NP) complications remain one of the main causes of morbidity and mortality in these patients [1,2]. In 1999, the American College of Rheumatology (ACR) published the consensus for the classification, nomenclature and management of NP syndromes in SLE (NPSLE), defining 19 NPSLE, 12 of the central nervous system (CNS) and 7 of the peripheral nervous system (PNS) [3].

Although the prevalence of NPSLE ranges between 14% and 90%, depending on the population studied, inclusion criteria, the diagnostic methods used and the period of observation [4–15], only 40% of them can be attributed directly to active disease (primary NPSLE) [5].

Primary NPSLE can occur at any time during the course of the disease, although they occur at the beginning or in the first two years after the diagnosis of SLE nearly in half of the patients [5,7,16]. Their pathogenesis still remains controversial at the present time and multiple pathogenetic mechanisms have been implicated in their development, including neuronal or vascular damage mediated by antibodies (antiphospholipid, antiribosomal P, anti endothelial cells, anti N-methyl-D-aspartate receptor), intrathecal production of inflammatory cytokines and accelerated atherosclerosis [5,17–20]. In addition, it seems that SLE activity, the previous background of NP manifestations and the presence of antiphospholipid antibodies are risk factors for CNS involvement in SLE patients [5,17].

The correct attribution of the NP events to SLE or to an alternative etiology is a challenge for clinicians, given the absence of "gold standard tests" for their diagnosis. Magnetic resonance imaging (MRI) is the preferred imaging procedure because it is a widely available test and allows the exclusion of other conditions causing NP symptoms [5,11,21]. Its sensitivity for the detection of acute vascular lesions, both ischemic and hemorrhagic, is high (80–90%), while it decreases for lesions in the white matter (50%) [5,22]. In addition, these white matter lesions are present in 18–40% of patients with NP events not related to SLE [23–25]. Several studies have shown that they are also associated with age, duration of the disease, the presence of valvular heart disease, other cardiovascular risk factors, and the positivity of antiphospholipid antibodies [26–28]. The specificity of MRI for the detection of acute lesions in the white matter associated with NPSLE is estimated between 60 and 80% [5].

Therefore, despite the fact that MRI abnormalities can be found in 19–70% of patients with SLE, its validity and importance in the diagnosis of the NPSLE are still not clear [7]. Furthermore, a correlation between the location of MRI lesions and the particular type of NP syndrome has not been established [29,30]. However, this imaging procedure could be useful to improve our knowledge on the etiopathogenesis of NPSLE, to facilitate the differential diagnosis, to identify the spotlight pathological anatomy, to quantify the disease activity, and to determine the functional consequences and prognosis of NPSLE [10,22,31].

In this context, the main objectives of our study were to describe the brain abnormalities found on conventional MRI in a group of patients during their first episode of NPSLE, and to investigate whether there is a correlation between the MRI findings and the clinical and immunological characteristics of patients with NPSLE.

2. Material and methods

2.1. Design and target population

This is an observational retrospective cross-sectional study that included all SLE patients with NP symptoms who underwent an MRI procedure at the Hospital Clínic of Barcelona between the years 2003 and 2012 as a result of NPSLE suspicion. All patients met at least 4 of the 11 ACR revised criteria for the classification of SLE [32,33] and were followed by an experienced internist at the Department of Autoimmune Diseases from this hospital. Patients with NPSLE were identified according to the ACR criteria [3]. Those patients with NP symptoms that could be attributed to causes other than SLE were excluded. None of the patients had a previous history of neurological or psychiatric symptoms. A final decision about the attribution of each NP event to SLE was reached through a clinical judgment. Furthermore, MRI should have been conducted in the first episode of NPSLE with less than 6 months between the onset of symptoms and the MRI procedure.

2.2. Study variables

2.2.1. Demographic and disease variables

Besides classic sociodemographic variables, we collected the time of evolution and the scores of SLE activity (Systemic Lupus Erythematosus Disease Activity, SLEDAI) and the accumulated damage (Systemic Lupus International Collaborating Clinic, SLICC). Regarding the immunological features, we reviewed the presence of anti-dsDNA and antiphospholipid antibodies.

2.2.2. MRI

MRI studies were performed in all patients with three different systems of 1.5 T and T1, T2 and FLAIR sequences included in the axial plane with 5 mm of thickness. In addition, 38 patients underwent diffusion sequences and 21 also T1 + contrast sequences. All MRI procedures were read by an experienced neuroradiologist. The lesions were classified into three types: small vessel, large vessel and an inflammatory injury. Small vessel lesions were classified by scoring the Age-Related White-Matter Changes (ARWMC) European working group taking into account the number and location [34]. Large-vessel lesions were classified by vascular territories and the type of inflammatory injury by locating and characterizing images. The distribution of small vessel lesions was divided into supratentorial and infratentorial regions. Fazekas scale was used to determine the extent of involvement of the white matter [35]. The number of small focal hyperintensity lesions was divided into <5, 5–15, 16–25 and >25.

2.3. Statistical analysis

The data collected were introduced into a SPSS 15.0 database designed specifically for the study. Statistical analysis was performed using tools of descriptive and analytical statistics (Mann–Whitney test for continuous variables and Fisher's exact test for categorical variables).

3. Results

A total of 43 patients were included. The sociodemographic and clinical characteristics of these patients are shown in Table 1. Most of the patients were women aged 18 to 73 years, although only 3 (7%) were older than 60 years. Twelve (27.9%) patients were diagnosed as having hypertension, but all cases had controlled blood pressure at the time of the onset of NP symptoms. Of the total patients on steroid therapy, only 3 patients received doses above 30 mg/day and none had steroid psychosis. None of the 2 patients who were treated with methotrexate showed clinical or radiological signs of leukoencephalopathy. Five patients had a history of hypothyroidism that was well controlled.

Eleven of the 19 NPSLE described by the ACR were present in our patients, being headache the most frequent, followed by cerebrovascular disease, epileptic crises and cranial neuropathy (Table 2). No statistically significant association was found between the different NPSLE and the sociodemographic variables. There was no significant relationship with the time of evolution. Regarding the relationship between NPSLE and the immunological features, a statistically significant association was found between myelopathy and low C4 complement levels ($p = 0.035$) and disease activity (SLEDAI > 4) ($p = 0.0006$).

Table 1
Demographic and clinical features of the 43 NPSLE patients.

Demographic and clinical features	Number of patients (%)
Female/male	40/3 (93/7%)
Age, mean ± SD (range) years	41.80 ± 12.42 (18–73)
Ethnicity	
Caucasian	43 (100%)
ACR SLE criteria	
1. Malar rash	21 (48.8%)
2. Discoid lupus	3 (7%)
3. Photosensitivity	12 (27.9%)
4. Oral ulcers	7 (16.3%)
5. Arthritis	32 (74.4%)
6. Pleuritis or pericarditis	11 (25.6%)
7. Renal disorders	13 (30.2%)
8. Neurologic disorder (psicosis/seizures)	1 (2.3%)
9. Hematologic disorder	18 (42.9%)
10. Immunologic disorder (antiDNA, antiSm, antiphospholipid)	34 (79.1%)
11. ANA positive	42 (97.7%)
SLE duration, mean ± SD (range) weeks	399.26 ± 392.65 (337–1380)
Cardiovascular risk factors[a]	
Hypertension	12 (27.9%)
Diabetes Mellitus	2 (4.7%)
Dyslipidemia	4 (9.3%)
Smoke	8 (18.6%)
Treatment at Diagnosis—NPSLE	
Antimalarials	20 (46.5%)
Corticosteroids	26 (60.5%)
(2.5–7.5 mg/day)	18
(7.6–29 mg/day)	5
(>30 mg/day)	3
Methotrexate	2 (4.7%)
Azathioprine	3 (7%)
Mycophenolate mofetil	8 (18.6%)
Cyclophosphamide	1 (2.3%)
Rituximab	0
Anticoagulants	9 (20.9%)
Antiplatelet	11 (25.6%)
Immunological data	
AntiDNA	13 (30.2%)
Rheumatoid factor	5 (11.6%)
C3 (low)	12 (27.9%)
C4 (low)	8 (18.6%)
CH50 (low)	6 (14%)
Antiphospholipid antibodies[b]	
Anticardiolipin IgG	9 (20.9%)
Anticardiolipin IgM	4 (9.3%)
Lupus anticoagulant	9 (20.9%)
AntiRo	11 (25.6%)
AntiLa	7 (16.3%)
AntiRNP	7 (16.3%)
AntiSm	3 (7%)
Anti ribosomal P[c]	2 (4.7%)
SLEDAI, mean ± SD (range)	11.30 ± 4.70 (1–25)
2–4 points	3 (7%)
5–7 points	1 (2.3%)
≥8 points	39 (90.7%)
SLICC, mean ± SD (range)	1.53 ± 2.20 (0–12)

ACR: American College of Rheumatology; ANA: antinuclear antibody; C: complement; RNP: ribonucleoprotein.
[a] Four patients had two or more cardiovascular risk factors.
[b] Three patients had both lupus anticoagulant and anticardiolipin antibodies.
[c] Antiribosomal P was not determined in 90.7% of cases.

MRI findings are detailed in Table 3. Twenty-five (58.1%) patients showed normal MRI. Of these, 40% had headache as the main symptom. In the 18 (41.9%) patients who presented MRI abnormalities, the mean age was 45.5 years. Only 3 patients were over 60 years and 16 (88.9%) were women. There was an association between NPSLE and the presence of MRI abnormalities ($p = 0.005$) (Table 3), although when the analysis was stratified by specific NPSLE, this association was only confirmed for myelopathy and the presence of inflammatory or mixed type lesions in MRI ($p = 0.003$). The presence of a high SLEDAI (SLEDAI > 8) ($p = 0.002$) and low CH50 levels ($p = 0.032$) was associated with an inflammatory pattern. We found no relationship between MRI changes and age, time of evolution, or the presence of antiphospholipid or anti-dsDNA antibodies.

Table 2
NPSLE manifestations and correlation with magnetic resonance imaging (MRI) findings.

Manifestations of NPSLE	Number (%) of patients	MRI				p
		Normal (n)	Vascular (n)	Inflammatory (n)	Both (n)	
Headache	13 (30.2%)	10	3	0	0	0.504
Cerebrovascular disease	8 (18.6)	3	5	0	0	0.380
Seizure disorder	4 (9.3%)	1	3	0	0	0.370
Cognitive dysfunction	3 (7%)	1	2	0	0	0.638
Mood disorder	3 (7%)	2	1	0	0	1.0
Anxiety disorder	2 (4.7%)	2	0	0	0	0.584
Myelopathy	2 (4.7%)	0	0	1	1	0.003
Aseptic meningitis	1 (2.3%)	0	0	0	1	0.067
Acute confusional state	1 (2.3%)	0	1	0	0	0.414
Plexopathy	2 (4.7%)	2	0	0	0	0.584
Cranial neuropathy	4 (9.3%)	4	0	0	0	0.468
Total	43 (100%)	25	15	1	2	0.005

White matter lesions were the most frequent finding, being observed in 17 (94.4%) of the 18 patients with abnormal brain MRI signal: 15 (88.2%) of them had focal involvement, one (5.9%) beginning confluent and one (5.9%) diffuse involvement. A statistically significant association was detected between myelopathy and the presence of focal lesions in the white matter ($p = 0.036$). Regarding clinical and immunological parameters, high SLEDAI (SLEDAI > 8) and the presence of lupus anticoagulant were associated with white matter lesions ($p = 0.002$ and $p = 0.035$, respectively).

Regarding the location of the lesions, supratentorial involvement was present in 16 of the 17 (94.1%) patients with MRI abnormalities, and infratentorial involvement in 5 (29.4%). Within the supratentorial lesions, they were located in the corpus callosum in 2 patients, in the cortico-subcortical region in other 2, and in the periventricular and deep white matter in 12. A statistically significant association was observed between myelopathy and infratentorial lesions ($p = 0.004$).

Twelve (70.6%) patients had less than 16 lesions, 2 patients (11.8%) had 16–25 lesions and 3 (17.6%) more than 25. No relationship was found between the number of lesions observed on MRI and the NPSLE.

Of the 18 patients with brain signal abnormalities, in 6 (33.3%) the lesion size was greater than 1 cm, 4 had lesions between 1 and 5 cm, and 2 had extensive lesions, both in the posterior fossa.

Two patients had large vessel injury, affecting one of them in the right middle cerebral artery and another patient in the left middle cerebral artery. Both patients presented also small vessel lesions.

Three patients had inflammatory like lesions, in two of them the lesion was located in the infratentorial region (pontomedullary) and in

Table 3
Magnetic resonance imaging of 43 patients with NPSLE.

Finding	Number (%)
Normal MRI	25 (58.1%)
Abnormal MRI	18 (41.9%)
White-matter lesions	17
Vascular involvement	15
Small vessel	13
Small and large vessel	2
Inflammatory	1
Both (vascular and inflammatory)	2
Microscopical bleeding	3
Contrast enhancement	3/21 (14.3%)
Diffusion abnormality	3/38 (7.9%)

another patient the lesion affected the right basal nuclei, thalamus, midbrain and hypothalamus.

4. Discussion

Our observations are in accordance with the data from previous studies showing white matter lesions as the most common finding in patients with NPSLE [11,31,36–40]. However, their role in relation to the NPSLE is unclear. Similar abnormalities are found in patients with active NPSLE, in patients with previous NPSLE, and in SLE patients with no NP history [11,22,29,36,39,41–46]. In addition, this type of MRI lesions has also been associated with hypertension, diabetes, antiphospholipid antibodies, valvular heart disease, and even found in healthy individuals, probably related to age [26–28,47]. In most studies in which MRI quantified lesions in the white matter, they were most common in NPSLE patients than in SLE patients without NP symptoms [9,36,37,39,41]. Furthermore, some studies have observed a correlation between accumulated SLE damage and the time of evolution of the disease with the presence of white matter lesions [10,27,37,41,42,48]. Conversely, our study has not found this association between NPSLE and white matter lesions on MRI. Additionally, we have not observed any association between accumulated damage and the time of evolution of the disease with the presence of MRI lesions.

Our stratified analysis found a statistically significant association between myelopathy and white matter lesions. These results are in agreement with other published studies [49,50]. A recent study [51] described two subtypes of myelopathy related with SLE: The first subtype is related to the presence of gray matter lesions and presents irreversible paraplegia and cerebrospinal fluid profile similar to bacterial meningitis; and the second subtype is associated with white matter involvement and presents with less SLE activity. The patients in our study seem to correspond to the second subtype of myelopathy.

Our study found an association between low complement levels and high SLEDAI with the presence of an inflammatory pattern on MRI. This is the pattern mainly associated with antibody-mediated damage and cytokines [5].

Around 60% of the MRI of our patients was normal. These data are consistent with the majority of published studies [9,36,39,52,53]. These results probably are due to the limitations of conventional MRI. Several studies show that patients with normal MRI can present pathological abnormalities. This could be minimized with the application of new imaging techniques in the assessment of NPSLE [11,54].

As in other publications [55,56], headache was the most common neurological syndrome in our study. This syndrome, along with anxiety, depression and mild cognitive impairment is common in healthy patients, mainly in those with chronic diseases [57,58]. In this sense, Katsiari et al. [59] even suggest that migraine should not be considered as a neurological manifestation of systemic or organ-specific autoimmunity, since the higher prevalence of migraine in patients with SLE may be due to methodological deficiencies. In this sense, the data also supported the evidence that the presence of headache was not associated with any parameters of SLE activity in our series.

Clinically, the presence of antiphospholipid antibodies has been associated with a variety of NP syndromes such as stroke, transient ischemic attacks, chorea, dementia and transverse myelitis [60,61]. In our study, we have found a statistically significant association between the presence of lupus anticoagulant and focal lesions on MRI.

We found no correlation between NPSLE, age of patients and duration of SLE, supporting the idea that CNS involvement can occur at any time during the course of the disease [10,11,62–64]. However, other publications found that CNS injury was associated with age and duration of the disease [62,65,66], but in these studies patients were younger, and with shorter duration of SLE.

5. Conclusions

The results obtained from our study suggest that MRI, although it is the imaging modality of choice in the present moment, by itself does not establish or exclude the diagnosis of NPSLE. In addition, our data also suggest that the presence of certain abnormalities (SLEDAI and low complement levels) seems to correlate with the presence of an inflammatory pattern on MRI; and the myelopathy syndrome with inflammatory lesions, with focal pattern and with infratentorial lesions on MRI.

Take-home messages

- The NP complications remain one of the main morbidity and mortality causes in patients with SLE.
- There is no "gold standard" test for the diagnosis of NPSLE.
- The MRI is normal in more than half of the patients diagnosed with NPSLE.
- Although MRI is the imaging modality of choice at the present moment, it cannot confirm or exclude the diagnosis of NPSLE by itself.

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Comentario

En este primer estudio se describen las anomalías cerebrales halladas en la RM convencional en una serie de 43 pacientes durante su primer episodio de LESNP y se analizan las correlaciones entre los hallazgos radiológicos y las características clínicas e inmunológicas de estos pacientes.

En todos los casos se realizaron estudios de RM con tres sistemas diferentes de 1,5 T, que incluían secuencias en T1, T2 y FLAIR. Además, en 38 pacientes se realizaron secuencias de difusión y en 21 en T1 con contraste.

En primer lugar, cabe mencionar que se diagnosticaron 11 de los 19 síndromes de LESNP descritos por la ACR, siendo la cefalea el más frecuente (30,2%), seguido de la enfermedad cerebrovascular (18,6%), las crisis comiciales (9,3%) y la neuropatía craneal (9,3%).

El 58,1% de los pacientes presentaron una RM cerebral normal (el 40% de ellos fueron diagnosticados de cefalea). No obstante, es importante destacar que, salvo los casos de meningitis aséptica, mielopatía y síndrome confusional agudo, en todos los demás, la RM no presentó hallazgos patológicos.

La afectación de la sustancia blanca (94,4%), el patrón focal (88,2%), la localización supratentorial (94,1%), la presencia de menos de 26 lesiones (70,6%) y el tamaño mayor de un centímetro (33,3%) fueron los hallazgos más frecuentes en la RM.

A nivel global, las distintas manifestaciones de LESNP se asociaron de forma significativa con los diferentes tipos de alteraciones en la RM, aunque en el análisis estratificado por síndromes esta asociación sólo se confirmó para la mielopatía y la presencia de lesiones inflamatorias o mixtas.

De forma más específica, la mielopatía se asoció con niveles de complemento C4 bajos, con puntuación de actividad lúpica moderada (SLEDAI>4), con la presencia de lesiones de tipo inflamatorio o mixto, con patrón focal en la sustancia blanca y con la localización infratentorial.

Finalmente, la presencia de lesiones en la sustancia blanca se relacionó con un SLEDAI alto (SLEDAI>8) y con la presencia de anticoagulante lúpico mientras que el patrón inflamatorio se relacionó con la presencia de un SLEDAI alto (SLEDAI>8) y los niveles de complemento CH50 bajos.

Por tanto, y a la luz de estos resultados, la RM cerebral puede ayudar en el diagnóstico de manifestaciones de LESNP, especialmente en el caso de la mielopatía. Además, los parámetros serológicos y de actividad lúpica pueden apoyar la atribución de los hallazgos en la RM a los síndromes de LESNP.

Peripheral nervous system involvement in systemic lupus erythematosus: Prevalence, clinical and immunological characteristics, treatment and outcome of a large cohort from a single centre

Afectación del sistema nervioso periférico en el lupus eritematoso sistémico: Prevalencia, características clínicas e inmunológicas, tratamiento y resultado de una cohorte amplia de un solo centro.

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Review

Peripheral nervous system involvement in systemic lupus erythematosus: Prevalence, clinical and immunological characteristics, treatment and outcome of a large cohort from a single centre

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ABSTRACT

Disorders of peripheral nervous system in patients with systemic lupus erythematosus (PNS-SLE) are a major cause of morbidity. The aims of the present study were to determine the prevalence of PNS-SLE involvement in a large cohort of SLE patients from a single centre, to characterize such involvement, treatment modalities and outcome, and to identify the possible variables that may be associated with its presence.

We performed an observational cross-sectional study that included all SLE patients being followed in our department between March and December 2015 who met at least one of the PNS-SLE case definitions proposed in 1999 by the American College of Rheumatology.

Overall, 93 out of 524 (17,7%) patients presented with PNS-SLE syndrome; 90 (96.8%) of them were women with a mean age at PNS-SLE syndrome diagnosis was 44.8 ± 14.1 years and the average time from diagnosis of SLE to PNS-SLE diagnosis was 88 (range, 541–400) months. The most frequent manifestation was polyneuropathy (36.6%), followed by non-compression mononeuropathy (23.7%), cranial neuropathy and myasthenia gravis (7.5%, each), and Guillain-Barré syndrome (1.1%). The most frequent electrodiagnostic tests (EDX) pattern was axonal degeneration, present in 49 patients that corresponded to 80.3% of the overall EDX patterns. Mixed sensory-motor neuropathy was the most common type of involvement accounted for 56% of cases. Thirty-six out of 90 (40%) received glucocorticoids and/or immunosuppressant agents. Overall, global response (complete and/or partial) to treatments was achieved in 77.4% of patients without differences between the types of PNS-SLE involvement. Older age at SLE diagnosis (37.3 ± 14.8 versus 30.8 ± 12; $p = 0.001$) and absence of hematologic involvement as cumulative SLE manifestation (11.8% versus 21.5%; $p = 0.034$) had independent statistical significant associations with PNS-SLE development.

The PNS-SLE involvement is not uncommon. Its most frequent manifestation is sensory-motor axonal polyneuropathy. The involvement occurs more frequently in patients who are diagnosed with SLE at older age. Prospective studies are needed to establish the incidence of PNS-SLE syndromes and the role of hematological manifestations in their development.

1. Introduction

Neuropsychiatric involvement is one of the leading causes of morbidity and mortality in patients with systemic lupus erythematosus (SLE) [1–4]. In 1999 the American College of Rheumatology (ACR) defined 19 neuropsychiatric syndromes in SLE from which 12 involve the central nervous system (CNS-SLE) and 7 the peripheral nervous system (PNS-SLE) [5].

In the last decade, CNS-SLE involvement has been the focus of numerous studies, thus allowing to its clinical characterization, association with immunological markers or their relationship with SLE activity [6–11]. In contrast, PNS-SLE has been scarcely studied [12–15], despite its association with significant morbidity and a worsen quality of life [16]. Its prevalence is estimated to be between 5 and 27% [7–9,16–18] and it is fundamentally characterized by sensory or sensory-motor neuropathy. The pathogenesis is unclear, although it has been linked to vascular disease of the small arteries that supply the affected nerves [13,19]. However, PNS-SLE involvement has not been well characterized in terms of manifestations at onset, severity, and clinical and electrophysiological associations.

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The present study aims to determine the prevalence of PNS-SLE involvement in a large cohort of SLE patients from a single centre, and to characterize such involvement regarding clinical features, serological markers and electrophysiological findings. In addition, we describe the different treatment modalities and the outcome, and study the possible variables that may be associated with the development of PNS-SLE.

2. Material and methods

2.1. Design and target population

This is an observational cross-sectional study that included all SLE patients with active monitoring between March 2014 and December 2015 at the Department of Autoimmune Diseases, Hospital Clínic, Barcelona, Catalonia, Spain. All patients fulfilled at least 4 of the 11 ACR criteria for SLE classification [20,21]. The case group target population included patients with PNS-SLE who met at least one of the PNS-SLE case definitions proposed in 1999 by the ACR [5]. Attribution to SLE was considered when PNS was present in the absence of other common etiologies. Those patients with PNS involvement that could be attributed to other diseases than SLE (diabetes mellitus, thyroid disease, primary vasculitis including anti-neutrophil cytoplasmic antibody-associated vasculitis, drugs or metabolic diseases with potential side effects on PNS) were excluded. Initially, compression neuropathy was not excluded due to the difficulty in consider its relationship with SLE activity. However, we performed the analysis taken and not into account this type of PNS involvement. The control group target population included SLE patients without PNS-SLE.

2.2. Study variables

The following variables were collected from medical records of each patient and entered into a database designed specifically for the present study by the same person (PT) to avoid bias in the collection: a) demographic variables such as sex and mean age at the SLE diagnosis and at the time of PNS-SLE appearance; b) time between SLE diagnosis and the appearance of PNS-SLE; c) time of follow-up defined as the time (in months) from the diagnosis of PNS-SLE to the last medical visit for the patients with PNS-SLE and from the SLE diagnosis to the last medical visit for the remaining SLE patients; d) associated SLE manifestations at the time of PNS-SLE development; e) characteristics of neurological involvement, including syndromic and topographic characteristics of the involvement; f) data from electrodiagnostic tests (EDX) in patients in which they were performed; g) immunological parameters, such as profile of antibodies against extractable nuclear antigens and antiphospholipid antibodies, from SLE diagnosis to the appearance of PNS-SLE, and anti-dsDNA antibody and complement levels at the time of PNS-SLE development; h) SLE disease activity index (SLEDAI) at the time of SLE diagnosis; i) SLEDAI and Systemic Lupus International Collaborating Clinics (SLICC) chronicity index at the time of appearance of PNS-SLE; and j) treatment at the time of PNS-SLE syndrome and treatment of PNS-SLE and outcome. Complete remission (CR) was considered when all the signs and symptoms had completely disappeared, partial remission (PR) when they had improved, but at least one persisted (sign and/or symptom), and no response (NR) when the clinical manifestations remained unchanged or deteriorating.

2.3. Statistical analysis

Categorical data are summarised as percentages; significant differences or associations were analysed using the χ^2 test or Fisher's exact tests. Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range, IQR) depending on normality demonstrated by Kolmogorov-Smirnov test.

Associations of quantitative data were analysed with Student's *t*-test and with the non-parametric Mann-Whitney *U* test. A two-tailed value of $p < 0.05$ was taken to indicate statistical significance. When independent variables appeared to have statistical significance in the univariate analysis ($p < 0.05$), they were included in a multivariate logistic regression analysis using a backward stepwise method. To avoid possible bias due to different follow-up time between two groups of patients, we included this variable in the regression model. The odds ratios (OR) and their 95% confidence interval (CI) obtained in the adjusted regression analysis were calculated. Statistical analysis was performed using the SPSS program (SPSS Statistics 22.0).

3. Results

3.1. General characteristics

The overall series comprised 529 SLE patients but 5 of them were excluded due to the lack of complete information. From 524 patients, 487 (93% [CI95 90.9%–94.8%]) were females and the mean age at SLE diagnosis was 31.9 ± 13.4 (range, 8–85) years and the median follow-up was 174 (1–570) months.

One hundred (19.1% [CI95 15.9%–22.7%]) patients developed some type of PNS-SLE syndrome. Seven of them were excluded due to other causes such as anti-neutrophil cytoplasmic antibody-associated vasculitis (n = 3), diabetic peripheral neuropathy (n = 3) and vitamin B12 severe deficiency (n = 1). Overall, 93 out of 524 (17.7% [CI95 14.7%–21.3%]) patients presented with PNS-SLE syndrome; 90 (96.8% [CI95 90.9%–99.0%]) of them were women and they had a mean age at SLE diagnosis of 36.8.3 ± 14.8 years and a median follow-up of 198 (1–462) months. The mean age at PNS-SLE syndrome diagnosis was 44.7 ± 13.8 years and the average time from diagnosis of SLE to PNS-SLE diagnosis was 88 (41–400) months. Excluding patients with carpal tunnel syndrome (n = 22), the prevalence of PNS-SLE involvement in our cohort was 13.5% (CI95 10.9%–16.7%).

In 9 (1.7% [CI95 0.9%–3.2%]) patients, PNS-SLE was the presenting manifestation of SLE. The main demographic data, clinical characteristics, immunological features and treatment at the moment of PNS-SLE diagnosis are described in Table 1.

From the clinical point of view, PNS-SLE syndrome was the only manifestation of SLE flare in 42 (45.2%) patients, whereas in those patients with other SLE-associated clinical manifestations at the time of PNS-SLE syndrome, articular and cutaneous involvements were the most frequent features. Interestingly, 5 (5.4%) patients had concomitantly CNS-SLE and PNS-SLE involvement. Specifically, the CNS-SLE manifestations in these patients were seizures (n = 2), psychosis (n = 2) and lupus headache (n = 1). Considering disease activity, 10 (10.7% [CI 10.8%–18.7%]) patients had low (SLEDAI ≤ 4), 23 (24.7% [CI 17%–34.4%]) moderate (SLEDAI 5–7), and 60 (64.5% [CI95 54.4%–73.5%]) high (SLEDAI ≥ 8) disease activity at the time of PNS-SLE diagnosis. The median SLICC value at the time of PNS-SLE involvement was 1 (range 0–5) (Table 1). Regarding immunological parameters of disease activity, 56 (60.2% [50.0%–

Table 1
Demographic data, clinical characteristics, immunological parameters and treatment modalities at the time of PNS-SLE diagnosis in 93 patients with PNS-SLE.

	n (%)[a]
Ethnicity	
Caucasian	91(97.8)
Asian	2 (2.2)
Other	0
Sex (female)	90 (96.8)
Age at SLE diagnosis, mean ± SD (years)	36.8 ± 14.8
Age at PNS-SLE diagnosis, mean ± SD (years)	44.7 ± 13.9
Time between diagnosis of SLE and PNS-SLE, median (IQR) (months)	85.5 (− 541–400)
SLEDAI at SLE diagnosis, median (range)	8 (2 − 32)
SLEDAI at PNS-SLE diagnosis, median (range)	4 (0–36)
Associated SLE manifestations at the time of PNS-SLE	
Arthritis	19 (20.4)
Cutaneous involvement	18 (19.4)
Kidney involvement	15 (16.1)
Hematological involvement	8 (8.6)
Central nervous system involvement	5 (5.4)
Serositis	3 (3.2)
Thrombosis	0
Immunological features at the time of PNS-SLE	
Elevated levels of anti-dsDNA antibodies	43 (46.2)
Low levels of C3	27 (29.0)
Low levels of C4	18 (19.4)
Low levels of CH50	21 (22.6)
Antiphospholipid antibodies	14 (15.1)
Lupus anticoagulant	17 (18.3)
IgG anticardiolipin	21 (22.6)
IgM anticardiolipin	4 (4.3)
Treatment at the time of PNS-SLE diagnosis	
Antimalarials	33 (35.5)
Corticosteroids	30 (32.3)
(≤ 7.5 mg/day)	19 (20.4)
(7.6–30 mg/day)	11 (12)
(> 30 mg/day)	0
Methotrexate	4 (4.3)
Azathioprine	2 (2.2)
Rituximab	2 (2.2)

Abbreviations: ACR: American College of Rheumatology; PNS-SLE: peripheral nervous system-SLE syndrome; SD: standard deviation; SLE: systemic lupus erythematosus; SLEDAI: SLE disease activity index; IQR: interquartile range.

[a] Unless otherwise indicated in the text for this variable.

Table 2
Types of neurological involvement and electrodiagnostic tests patterns in patients with PNS-SLE.

Type of PNS-SLE syndrome	n (%)
Mononeuropathy	44 (47.3)
Electrodiagnostic tests pattern (n = 37)	
Axonal degeneration	36 (97.3)
Fine fiber	0
Demyelination	1 (2.7)
Type of involvement (n = 37)	
Motor	2 (5.4)
Sensory	14 (37.8)
Both	21 (56.8)
Distribution of involvement (n = 37)	
Distal	10 (27)
Proximal	23 (62.2)
Both	4 (10.8)
Symmetrical	6 (16.2)
Asymmetrical	31 (83.8)
Polyneuropathy	34 (36.6)
Electrodiagnostic tests pattern (n = 20)	
Axonal degeneration	13 (65)
Fine fiber	4 (20)
Demyelination	3 (15)
Type of involvement (n = 20)	
Motor	0
Sensory	9 (45)
Both	11 (55)
Distribution of involvement (n = 20)	
Distal	15 (75)
Proximal	2 (10)
Both	3 (15)
Symmetrical	16 (80)
Asymmetrical	4 (20)
Cranial neuropathy	7 (7.5)
II cranial nerve	4 (57.1)
V cranial nerve	1 (14.3)
VII cranial nerve	1 (14.3)
XII cranial nerve	1 (14.3)
Myasthenia gravis	7 (7.5)
Guillain-Barré syndrome	1 (1.1)

Abbreviations: SLE: systemic lupus erythematosus; PNS-SLE: peripheral nervous system-SLE.

69.6%]) patients had high levels of anti-dsDNA antibody and/or low levels of complement at the moment of PNS-SLE diagnosis.

3.2. Types of PNS-SLE involvement

The different types of PNS-SLE are described in Table 2. A symmetric distribution of the involvement, in the form of distal polyneuropathy was present in 34 (36.6% [CI95 27.5%–46.7%]) patients. Overall, mononeuropathy was present in 44 (47.3% [CI 37.5%–57.4%]) patients but in 13 (14.0% [CI 8.3%–22.5%]) patients mononeuropathy affected more than one nerve and could be considered as mononeuritis multiplex. Excluding the 22 patients with carpal tunnel syndrome (defined as mononeuropathy due to compression), non-compression mononeuropathy (isolated or multiple) was present in 22 (23.7% [CI95 16.2%–33.2%]) patients. Cranial nerve involvement was found in 7 (7.5% [CI95 3.7%–14–7%]) patients, myasthenia gravis also in 7 (7.5% [CI95 3.7%–14–7%]) patients, and Guillain-Barré syndrome in one (1.1% [CI95 0.2%–5.8%]) patient. No cases of autonomic dysfunction or plexopathy were identified.

EDX was performed in 79 of the 93 patients (84.9%). Abnormalities were found in 61 (77.2% [CI95 66.8%–85.1%]) of them: 37 with mononeuropathy and 20 with polyneuropathy (Table 2). The four remaining reports of abnormal EDX corresponded to two patients with myasthenia gravis, a patient with cranial neuropathy and a patient with Guillain-Barré syndrome. The most frequent EDX finding was axonal degeneration, present in 49 patient' EDX (80.3% of all pathological EDX studies). Mixed sensory-motor neuropathy was the most common type of neuropathy, as per EDX findings (56% of cases). The most frequent cranial neuropathy was optic neuritis, present in 4 (57.1% [CI95 25.0%–84.2%]) out of the 7 patients with cranial neuropathy. In one of them, the anti-aquaporin 4 antibody was positive four years after the initial diagnosis.

A peripheral nerve biopsy was performed in 9 patients. In 3 of them, biopsy described non-necrotizing small vessel vasculitis (in two patients EDX findings were of axonal polyneuropathy and in one of mononeuritis multiplex). In 3 patients, axonal degeneration was found in the nerve biopsy (with axonal polyneuropathy in two of them and demyelinated polyneuropathy in the remaining). Finally, in 3 patients with axonal polyneuropathy (n = 1) and mononeuritis multiplex (n = 2) in EDX studies, biopsy was described as normal.

3.3. Treatment and outcome

Table 3 describes the treatment according to the type of PNS-SLE syndrome. Information regarding treatment was available in 90 patients. In 36 (40.0%) patients, the dose of prednisone was increased

Table 3
Treatment according to the type of PNS-SLE involvement.

Type of PNS-SLE syndrome	Treatment	n (%)
Mononeuropathy (n = 41)[a]	Unmodified treatment	13 (31.7)
	Gabapentin	10 (24.3)
	Increased corticosteroids	10 (24.3)
	IV pulses of corticosteroids	3 (7.3)
	IV pulses of cyclophosphamide	3 (7.3)
	Intravenous immunoglobulin	1 (2.4)
	Surgery[b]	8 (19.5)
Polyneuropathy (n = 32)[a]	Unmodified treatment	5 (15.6)
	Gabapentin	9 (28.1)
	Increased corticosteroids	19 (59.4)
	IV pulses of corticosteroids	3 (9.4)
	IV pulses of cyclophosphamide	1 (3.1)
	Intravenous immunoglobulin	2 (6.2)
	Mycophenolate mofetil	2 (6.2)
Cranial neuropathy (n = 6)[a]	Unmodified treatment	1 (16.7)
	Gabapentin	2 (33.3)
	Increased corticosteroids	4 (66.7)
	IV pulses of corticosteroids	1 (16.7)
Myasthenia gravis (n = 7)	Pyridostigmine	6 (85.7)
	Increased corticosteroids	2 (28.6)
	Surgery[c]	2 (28.6)
Guillain-Barré syndrome (n = 1)	Increased corticosteroids	1 (100)
	IV pulses of cyclophosphamide	1 (100)

Some patients received more than one treatment.
Abbreviations: SLE: systemic lupus erythematosus; PNS-SLE: peripheral nervous system-SLE; CTS: carpal tunnel syndrome.

[a] In three patients with mononeuropathy, two with polyneuropathy and one patient with cranial neuropathy, data of the treatment were not available.

[b] Due to carpal tunnel syndrome.

[c] Due to thymectomy.

(mean increase of oral prednisone, 29.3 ± 22.3 mg/day; range 2.5–80), 7 of them received intravenous pulses of methylprednisolone, 5 (5.6%) intravenous pulses of cyclophosphamide, 3 (3.3%) intravenous immunoglobulins and 2 (2.2%) mycophenolate mofetil. Additionally, 21 (23.3%) patients were treated with gabapentin. Surgery was performed in 10 (10.7%) patients, 8 of them with compression mononeuropathy because of carpal tunnel syndrome. Data on treatment was not available in 6 (6.5%) patients.

Overall, the response to the treatments was complete in 48 (55.1%) patients, partial in 24 (27.6%), and no response was obtained in 15 (17.2%). In 6 patients, outcome was not reported. According to the type of PNS-SLE syndrome, the percentages of CR, PR and NR were 36.4%, 34.1%, and 22.7% in patients with mononeuropathy (data was not available in two patients), and 55.9%, 23.5%, and 14.7% in those with polyneuropathy (data was not available in 2 patients). Regarding the 7 patients with cranial neuropathy, outcome was available in 5, with CR in 3 and PR in 2, respectively. Finally, the response was complete in all patients with myasthenia gravis and the patient with Guillain-Barré.

3.4. Factors related with the development of PNS-SLE syndrome

We performed a comparative analysis of epidemiological and clinical characteristics of patients with and without PNS-SLE (Table 4). Patients with PNS-SLE syndrome were older (37.3 ± 14.8 vs 30.8 ± 12.7; $p = 0.001$), had lower SLEDAI score and lower prevalence of kidney involvement (13.0% vs 23.6%; $p = 0.042$) at the time of SLE diagnosis.

Considering the cumulative SLE manifestations, they exhibited lower prevalence of kidney and hematological manifestations. No statistically significant differences were found in terms of immunological parameters at SLE diagnosis or during SLE course. All these findings remained unchanged when we excluded patients with carpal tunnel syndrome.

Table 4
Univariate analysis between SLE patients according to the presence or absence of PNS-SLE involvement.

	With PNS-SLE	Without PNS-SLE	P
	n = 93	n = 424	
Mean age at SLE diagnosis (years)	37.3 ± 14.8	30.8 ± 12.7	0.001
Sex (female)	90 (96.8)	391 (92.2)	0.118
Time of follow-up (months) (median; IQR)	198.5 (93.8–278)	162.7 (85.6–258.5)	0.149
ACR criteria at SLE diagnosis			
Malar rash	49 (52.7)	225 (53.1)	0.947
Discoid lupus	8 (8.6)	38 (9.0)	0.912
Photosensitivity	45 (48.4)	176 (41.5)	0.225
Oral ulcers	22 (23.7)	123 (29.0)	0.298
Arthritis	73 (78.5)	316 (74.5)	0.422
Pleuritis o pericarditis	22 (23.7)	84 (19.8)	0.406
Kidney involvement	13 (14.0)	100 (23.6)	0.042
Neurological involvement	2 (2.2)	11 (2.6)	0.804
Hematological involvement	28 (30.1)	138 (32.5)	0.648
Immunological criteria	82 (88.2)	358 (84.4)	0.359
Antinuclear antibodies	93 (100)	422 (99.5)	0.507
SLEDAI at SLE diagnosis (median; IQR)	8 (6–10)	8 (6–12)	0.006
Cumulative SLE manifestations[a]			
Arthritis	76 (81.7)	323 (76.2)	0.249
Cutaneous involvement	76 (81.7)	348 (82.1)	0.936
Serositis	25 (26.9)	99 (23.4)	0.477
Kidney involvement	23 (24.7)	163 (38.4)	0.013
Central nervous system involvement	14 (15.1)	43 (10.1)	0.171
Hematological involvement	11 (11.8)	91 (21.5)	0.034
Thrombosis	4 (4.3)	32 (7.5)	0.265
Immunological features[a]			
Anti-SSA/Ro antibody	30 (34.1)	149 (37.9)	0.503
Anti-SSB/La antibody	18 (20.5)	62 (15.8)	0.291
Anti-RNP antibody	16 (18.4)	91 (23.6)	0.296
Anti-Sm antibody	16 (18.4)	83 (21.7)	0.498
Antiphospholipid antibodies			
Lupus anticoagulant	17 (18.7)	82 (19.9)	0.791
IgG anticardiolipin	21 (22.6)	85 (20.0)	0.817
IgM anticardiolipin	4 (4.3)	35 (8.2)	0.345

Percentages in (%).
Abbreviations: ACR: American College of Rheumatology; PNS-SLE: peripheral nervous system-SLE syndrome; SLE: systemic lupus erythematosus; SLEDAI: SLE disease activity index.

[a] Cumulative SLE manifestations and immunological features present from SLE onset to PNS-SLE diagnosis.

The multivariate analysis performed by a logistic regression model with PNS-SLE as dependent variable and those that appeared to have significant statistical significance in the univariate analysis (Table 4) as independent variables showed that older age at SLE diagnosis (37.3 ± 14.8 versus 30.8 ± 12; $p = 0.001$) and absence of hematologic involvement as cumulative SLE manifestation (11.8% versus 21.5%; $p = 0.034$) had independent statistical significant associations with PNS-SLE development.

4. Discussion

In the present study, we found an overall prevalence of PNS involvement of 17.7% (CI95 14.7%–21.3%), and of 13.5% (CI95 10.9%–16.7%) if patients with carpal tunnel syndrome were excluded. In nearly half of them, PNS-SLE involvement was the only manifestation of the SLE flare when it appeared. Mixed sensory-motor axonal polyneuropathy was the most frequent type of PNS-SLE in EDX tests. Complete and partial response to treatment was achieved

in up to 80% of patients. Older age at SLE diagnosis and absence of hematologic involvement were significantly associated with the presence of PNS-SLE.

Although the overall prevalence of PNS-SLE in our study was similar to that reported by other authors [16,22,23], higher prevalences ranging from 20% to 50% have been described in previous series that analysed it as part of SLE neuropsychiatric syndromes [12,13,17,24–29]. In studies focused on peripheral neuropathy, the prevalence ranged from 1.5% to 12% (Table 5). There are various explanations for these discrepancies, such as the different number of patients analysed in each study and their ethnic origin. In the same way that occurs in renal involvement, the prevalence and severity of PNS- SLE might be influenced by the ethnic origin of the patients. The study of Xianbin et al. [27], which included only Chinese patients presented the lowest prevalence of PNS-SLE involvement. In addition, the case definition of PNS-SLE was different between studies. For example, Oomatia et al. [18] used definitions of peripheral neuropathies provided from the American Academy of Neurology and the American Academy of Physical Medicine and Rehabilitation instead of the 1999 ACR case definition for neuropsychiatric SLE. In addition, they excluded patients having cranial neuropathies and included small-fiber neuropathy diagnosed with skin biopsy. Otherwise, Florica et al. [16] included patients with chronic inflammatory demyelinating polyradiculoneuropathy, which was not included in the 1999 ACR case definition for neuropsychiatric SLE and that can increase the prevalence of PNS-SLE involvement. Finally, exclusion criteria and the attribution of neuropathy to SLE differed among studies [9,13,16,30,31].

Table 5
Main demographic and clinical characteristics of different cohorts of patients that analysed the PNS-SLE involvement.

Type of PNS-SLE syndrome	Present series (n = 524)	Florica et al.[a] (n = 1533)	Xianbin et al. (n = 4924)	Oomatia et al.[b] (n = 2097)
Type of study	Retrospective	Retrospective	Retrospective	Retrospective
Duration of study (yrs)	31	40	18	25
Prevalence of PNS-SLE	13.5	12	1.5	3.9
Sex (female)	96.8	86	91.8	92.7
Ethnicity				
Caucasian	97.8	81	0	62.2
Asian	2.2	7	100	3.7
Black	0	9	0	31.7
Age at SLE onset (mean ± SD) (yrs)	37.3 ± 14.8	36.5 ± 14.9	36.9 ± 1.4	34.0 ± 14.7
Age at PNS-SLE (mean ± SD) (yrs)	44.4 ± 14.1	35.2 ± 14.4	NA	NA
SLEDAI score (median; IQR)	4 (2–8)	8 (4–14)	12 (10.5)	2.2 ± 2.0[d]
Type of PNS-SLE				
Polyneuropathy	43.7	62.5	59.5	84.3
Mononeuropathy	35.2	22.8	13.9	NA
Mononeuritis multiplex	17.2	10.3	NA	13.9
Cranial neuropathy	9.9	14.1	12.7	0
Myasthenia gravis	9.9	0	10.1	0
Guillain-Barré syndrome	1.4	0.5	1.3	1.9
Plexopathy	0	0	0	1.9
Autonomic neuropathy	0	0	2.5	0
Electrodiagnostic tests patterns				
Axonal neuropathy	80.3	71.4	NA	56.1
Demyelination	6.8	23.8	NA	7.6
Immunologic features				
Anti-dsDNA antibodies	47.3	39	49.3	63.4
Low C3	30.1	20	54.8	57.3
Low C4	20.3	23	43.8	46.3
Antiphospholipid antibodies	15.1	22	23.4[c]	NA

Qualitative variables are presented in percentages.
Abbreviations: IQR: interquartile range; NA: not available; PNS-SLE: peripheral nervous system-SLE syndrome; SD: standard deviation; SLE: systemic lupus erythematosus; yrs: years.

[a] 11 (5.3%) patients were diagnosed with chronic inflammatory demyelinating polyradiculoneuropathy.

[b] 16 patients were diagnosed with small-fiber neuropathy.

[c] Referred as lupus anticoagulant positive.

[d] Referred as mean ± SD.

The characteristics of the involvement in the PNS-SLE cases reported in the current studies are very similar to those described in previous studies (Table 5) [13,16,18,27,28]. In general, sensory-motor axonal polyneuropathy was the most frequent manifestation, described in more than half of patients with PNS-SLE. Regarding cranial neuropathies, optic neuritis is the most frequent manifestation in most studies [27]. Conversely, the prevalence of Guillain-Barré syndrome, plexopathy, and autonomic neuropathy is very low in all series [7–9,16,22,32–34].

The prevalence of carpal tunnel syndrome in our study was 4.2% and it is similar to that found in the general population (3.8–4.9%) [35], thus suggesting that SLE is not, probably, a direct cause of this compression syndrome in the majority of cases. However, the results did not change when we excluded these patients.

The pathogenesis of PNS-SLE is not fully understood. Several factors have been described such as vasculitis involvement small vessels, deposits of immune complexes, and lesions due to production of antibodies or hyperfunction of B-lymphocytes [36–38]. In our series, a peripheral nerve biopsy was performed in 9 patients showing non- necrotizing small vessel vasculitis in 3 of them.

In the majority of series, patients with PNS were older at the time of SLE diagnosis than those without PNS involvement [13,25,27,28]. In our series, SLEDAI at the time of diagnosis of SLE was low (SLEDAI ≤ 4) in more than half of the patients that developed PNS involvement, as in the study by Oomatia et al. [18]. However, contradictory results have been published regarding disease activity at the moment of PNS development. Some studies described higher disease activity [16,27] whereas others found that patients with PNS-SLE had lower values of SLEDAI [18,30]. In our series, hematologic involvement as cumulative SLE manifestation was associated with a lower prevalence of PNS-SLE involvement. In the study of Jasmin et al. [30], there were non-significant trends to have less hematological disease in SLE patients with polyneuropathy (34.8% versus 54.3%; $p = 0.084$). Of note, no statistically significant differences were found in terms of immunological parameters at SLE diagnosis or during SLE course. Similar results were reported in other studies [21,23,25,28]. Some authors have described an association of PNS-SLE with the presence of anti-Sm antibody [13,27] whereas others did not [16,28]. This association and the pathogenic role of this antibody must be taken with caution, since the pathogenesis of PNS-SLE is still not well defined. Although there is no clear recommendation on the treatment of PNS-SLE syndrome, induction treatment with glucocorticoids with or without immunosuppressant agents are indicated if the PNS-SLE appears in the context of lupus activity [39]. Overall, global response (complete and/or partial) to treatments was achieved in 77.4% of patients in our study without differences between the types of PNS-SLE involvement. This result is similar to

previous studies such as Florica et al. which described a response rate of 65.6% [16]. However, the definitions of response are different between studies precluding direct comparative analysis.

Limitations of the present study include its retrospective and cross-sectional design with the potential loss of information. However, a single author (PT) reviewed all medical records and entered into the database all variables without previous knowledge of EDX data, to avoid bias in the collection. In addition, two investigators (RC, GE) were in charge of all included patients and one investigator (JV-S) performed the great majority of EDX studies. The restriction of definitions of PNS-SLE established by the ACR may have excluded other forms of PNS-SLE disease, such as small fiber neuropathy. Finally, our study was restricted to patients with symptomatic PNS-SLE and this might have underestimated the prevalence of the nerve involvement in EDX in asymptomatic SLE patients [24,29,40]. The main strength of our study comes from the large sample size giving a strong robustness to our findings.

5. Conclusions

PNS-SLE involvement is not uncommon and sensory-motor axonal polyneuropathy is the most frequent manifestation. It occurs more frequently in patients who are diagnosed with SLE at older age. Prospective studies are needed to establish the true incidence of PNS-SLE syndromes and the role of hematological manifestations to their generation.

Take-home messages

- Peripheral nervous system involvement in SLE (PNS-SLE) patients is associated with significant morbidity and a worsen quality of life.
- PNS-SLE involvement is not uncommon and sensory-motor axonal polyneuropathy is the most frequent manifestation.
- Glucocorticoids with or without immunosuppressant agents are used if the PNS-SLE appears in the context of lupus activity.

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Comentario

En este segundo trabajo se determinó la prevalencia de la afectación del SNP en una cohorte de 524 pacientes diagnosticados de LES y con seguimiento activo en el momento de la realización del estudio. Además, se analizaron las posibles variables que pueden estar asociadas con el desarrollo de esta afectación.

Como resultados más destacados cabe resaltar que 93 pacientes (17,7%) habían presentado alguna manifestación de SNP a lo largo de la evolución de su enfermedad, disminuyendo hasta el 13.5% al excluir a los pacientes con síndrome de túnel carpiano. En casi la mitad (45,2%) de los pacientes, la afectación neurológica periférica fue la única manifestación de LES y en el 5,4% de los casos se asoció a afectación del SNC.

La polineuropatía axonal sensitivo-motora fue la neuropatía más frecuente objetivada en las pruebas electrofisiológicas, presente en más de la mitad de los casos (56%). La neuropatía de fibra fina se detectó en 6,6% de los electromiogramas, pese a no estar incluida en los criterios clasificatorios de la ACR de 1999.

Respecto al tratamiento recibido para esta afectación, en el 40% de los pacientes se aumentó la dosis basal de glucocorticoides, el 5,6% recibió bolos intravenosos de ciclofosfamida, el 3,3% inmunoglobulinas intravenosas y el 2,2% micofenolato de mofetilo. Un 23,3% de los pacientes fueron tratados con gabapentina. La respuesta global (completa y/o parcial) a los tratamientos se logró en el 77,4% de los pacientes, sin diferencias entre los tipos de afectación.

La edad avanzada al diagnóstico del LES (37,3 ± 14,8 años versus 30,8 ± 12,7 años) y una menor puntuación en el SLEDAI en el momento del diagnóstico del LES se asociaron de forma significativa con la presencia de manifestaciones del SNP; asimismo, la ausencia de afectación renal en dicho momento disminuyó la frecuencia de desarrollo ulterior del SNP. Además, considerando las manifestaciones acumuladas del LES, los pacientes con afectación del SNP presentaron una menor prevalencia de manifestaciones hematológicas (11.8% versus 21.5%) y renales (24.7% versus 38.4%). Sin embargo, no se encontraron diferencias estadísticamente significativas en términos de

parámetros inmunológicos en el momento del diagnóstico del LES o durante el curso de dicha enfermedad. Estos resultados no se modificaron al excluir a los pacientes con síndrome del túnel carpiano.

En base a todos los resultados obtenidos, se puede afirmar que la afectación del SNP en el LES no es infrecuente y ocurre con mayor frecuencia en pacientes diagnosticados de LES a una edad más avanzada. La asociación entre la afectación del SNP y la menor presencia de manifestaciones hematológicas del LES debe comprobarse en otros estudios.

VI. DISCUSIÓN

Las complicaciones neuropsiquiatricas del LES están presentes en un porcentaje importante de los pacientes y, aunque el pronóstico general del cuadro ha mejorado en las últimas décadas, la presencia de dichas complicaciones empeora el pronóstico, con disminución de la calidad de vida y aumento de la mortalidad. Pese a ello, el manejo de esta afectación en el LES continúa presentado limitaciones entre las que se puede destacar la ausencia de una prueba diagnóstica especifica que permita una correcta atribución de las manfestaciones neuropsiquiatricos a la enfermedad (LESNP) o a otra etiología concurrente.

Los resultados del primer estudio ponen de manifiesto que la RM cerebral, además de contribuir en el diagnóstico diferencial al excluir otras enfermedades neuropsiquiátricas, podría ser de utilidad para la atribución de las manifestaciones neuropsiquiátricas al LES y la caracterización de algunos cuadros como en el caso de la mielopatía. Los pacientes diagnosticados de mielopatía presentan con más frecuencia lesiones focales en la sustancia blanca, localización infratentorial y son de tipo inflamatorio o mixto en la RM. Al contrario, no se encontró asociación entre los hallazgos de la RM cerebral y el resto de tipos de manifestaciones de LESNP.

La presencia de un patrón inflamatorio en la RM cerebral se asoció con unos parámetros de actividad más elevados y niveles bajos de complemento CH50. Esto apoya el hecho de que este patrón se relacione con el daño mediado por anticuerpos y citocinas y estos datos sugieren que en estos casos se debería valorar, como tratamiento de elección, la administración de inmunodepresores.

La presencia de lesiones en la sustancia blanca se asoció con una actividad lúpica más elevada, lo que sugiere que estas lesiones podrían ser una manifestación de la actividad del LES en el cerebro, dando lugar a los signos y síntomas neuropsiquiátricos. Por otra parte, en el análisis estratificado por síndromes, las lesiones en la sustancia blanca únicamente se relacionaron con la mielopatía. Pese a todo ello, en la actualidad, el significado de las lesiones en la sustancia blanca en los pacientes con LESNP aún está por dilucidar ya que muchos estudios las han relacionado con la presencia de hipertensión arterial, diabetes mellitus, enfermedad cardiovascular valvular e, incluso, se han descrito en pacientes sanos en relación con la edad.

Desde el punto de vista clínico la presencia de anticuerpos antifosfolipídicos se ha asociado con una variedad de síndromes neuropsiquiátricos, como los accidentes cerebrovasculares, la corea, la demencia y la mielitis transversa. Sin embargo, en nuestro estudio, aunque no se evidenció la relación entre estos anticuerpos y los distintos tipos de LESNP, sí se encontró asociación entre la presencia del anticoagulante lúpico y las lesiones focales en la RM cerebral, lo que podría corresponder a pequeñas lesiones isquémicas descritas en otros trabajos.

Por otro lado, la RM cerebral ayuda a una mejor caracterización de las lesiones cerebrales y a determinar su localización, siendo en nuestro estudio las lesiones focales y de localización supratentorial las más frecuentes. Todo ello contribuye a determinar las consecuencias funcionales y el pronóstico de las manifestaciones neuropsiquiátricas.

No obstante, pese a estos hallazgos, cerca del 60% de las RM de los pacientes del primer estudio fueron normales y correspondieron a prácticamente todos los tipos de LESNP. Estos datos están en consonancia con la mayoría de estudios. Probablemente, estos resultados se deban a las limitaciones de la RM convencional. Existen varios trabajos que evidencian que imágenes de RM normales presentaban alteraciones histológicas; este hecho podría ser minimizado con la aplicación de nuevas técnicas de imagen en la valoración de estos pacientes.

La cefalea fue la manifestación neuropsiquiátrica que con más frecuencia se asoció con una RM cerebral normal. Además, en nuestra serie tampoco se asoció con ningún parámetro de actividad, lo que está de acuerdo con diversos estudios que sugieren que este síntoma no debe ser considerado una manifestación neurológica de autoinmunidad sistémica u órgano específica.

Este estudio presenta algunas limitaciones. El número de pacientes es bajo y en el futuro estos resultados se deberían confirmar en series con mayor número de pacientes. En segundo lugar, no se investigó la atrofia cerebral a través de la RM y existen datos que ponen de manifiesto que los pacientes con LESNP presentan más atrofia cerebral que los pacientes sin afectación neurológica y que esta diferencia es aún mayor respecto a los pacientes sin LES. Por último, al no estar determinados en un alto porcentaje de los pacientes y no siendo posible su determinación por el carácter retrospectivo del

estudio, no pudo estudiarse la presencia de anticuerpos antineuronales y su posible relación con las manifestaciones neuropsiquiátricas. En este sentido, distintos trabajos establecen una relación entre la presencia de estos anticuerpos y los distintos síndromes de LESNP.

Los resultados del segundo estudio demuestran que la afectación del SNP en pacientes con LES no es infrecuente. No obstante, continúan existiendo muchas discrepancias respecto a la prevalencia entre los distintos estudios, que se deben en parte a diferencias metodológicas. En esta línea, la inclusión de los pacientes con síndrome de túnel carpiano en el grupo de pacientes con afectación de SNP es un tema controvertido. Los datos de nuestro estudio ponen de manifiesto que la prevalencia de este síndrome en los pacientes con LES es similar a la encontrada en la población general, lo que sugiere que el LES no es, probablemente, una causa directa de este síndrome de compresión en la mayoría de los casos.

En nuestro estudio, al igual que en la mayoría de las series publicadas, los pacientes con afectación del SNP presentaron mayor edad en el momento del diagnóstico del LES que los pacientes sin afectación neurológica. Quizás este retraso en el diagnóstico del LES y por tanto en el inicio de tratamiento, favorezca el desarrollo de esta afectación.

Respecto a la patogénesis de la alteración del SNP en el LES, se han involucrado varios factores, como la vasculitis de pequeños vasos, los depósitos de complejos inmunes y las lesiones secundarias a la producción de anticuerpos o hiperfunción de los linfocitos B. Sin embargo, en la mayoría de series publicadas no se han descrito asociaciones estadísticamente significativas en términos de parámetros inmunológicos en el momento del diagnóstico del LES o durante el curso de la enfermedad. Sólo dos estudios han descrito una asociación entre la afectación del SNP y la presencia de anticuerpos anti-Sm. No obstante, esta asociación y el papel patogénico de este anticuerpo debe tomarse con precaución, ya que la patogénesis de la alteración del SNP en el LES, como se ha comentado, no está bien definida.

Por otra parte, se han publicado resultados contradictorios con respecto a la actividad de la enfermedad en el momento del desarrollo de la alteración del SNP. Mientras que algunos estudios describen una mayor actividad de la

enfermedad, otros, incluido el nuestro, describen que los pacientes con esta afectación presentan valores más bajos.

Los datos de nuestra serie muestran que la presencia de afectación hematológica como manifestación acumulada del LES se asocia con una menor prevalencia de la afectación del SNP. Este dato es concordante con el obtenido en el estudio de Jasmin y cols. No obstante, el papel desempeñado por las manifestaciones hematológicas en el desarrollo de la alteración del SNP, al igual que el jugado por la actividad lúpica, esta todavía por determinar.

Los interrogantes existentes en referencia a los factores etiopatogénicos que pueden intervenir en la aparición de los síndromes de LES en el SNP ponen de manifiesto la necesidad de investigaciones futuras que contribuyan a profundizar en el conocimiento de estos factores. Todo ello contribuirá, sin duda, a mejorar el abordaje terapéutico de estos pacientes, ya que actualmente no existe una clara recomendación al respecto. Hoy en día y en presencia de actividad lúpica, el tratamiento de inducción se basa en los glucocorticoides, con o sin agentes inmunodepresores. Con esta estrategia, la respuesta global al tratamiento (completa y/o parcial) en nuestro estudio fue mayor del 70%, sin diferencias entre los tipos de LES en el SNP. Este nivel de respuesta es difícil de comparar de forma directa con el obtenido por otros autores ya que la definición de respuesta al tratamiento difiere entre los distintos estudios publicados.

Nuestro estudio presenta alguna limitación que debe ser comentada. En primer lugar, su diseño retrospectivo y transversal que puede favorecer la pérdida de información. Además, la restricción de las definiciones de las manifestaciones del SNP a las establecidas por la ACR en 1999 pudo haber excluído otras formas de enfermedad, como la neuropatía de fibra fina. Por último, nuestro estudio se limitó a los pacientes con síndrome clínico y esto podría haber subestimado la prevalencia de la participación de los nervios objetivada en los estudios electrofisiológicos en pacientes con LES asintomáticos. Por el contrario, la amplitud de la serie, superior a la de otros trabajos publicados, puede considerarse como una fortaleza del mismo.

Los síndromes de LESNP son, por tanto, una complicación frecuente en los pacientes con LES. Una mejor caracterización de los mismos en términos de

prevalencia, inicio, gravedad y asociaciones clínicas, inmunológicas, electrofisiológicas y radiológicas puede contribuir a mejorar el conocimiento de estos aspectos y, por tanto, posibilitar un diagnóstico precoz y un tratamiento más específico que repercuta en el pronóstico y calidad de vida de estos pacientes. Es importante conseguir una mejora en los sistemas de atribución de estos síndromes a la enfermedad lúpica y a una caracterización de los hallazgos de la RM cerebral para que se pueda convertir en la prueba de oro para el diagnóstico de estos síndromes.

En este sentido, los dos trabajos que componen esta tesis sirven para ampliar el conocimiento sobre las manifestaciones del LESNP y pueden contribuir a un mejor control de los mismos.

VII. CONCLUSIONES

Conclusiones del primer estudio

1. Las manifestaciones más frecuentes del LESNP son la cefalea, la enfermedad cerebrovascular, las crisis comiciales y la neuropatía craneal.
2. Los hallazgos en la RM más frecuentemente encontados en los pacientes afectos de LESNP son la afectación de la sustancia blanca, el patrón focal, la localización supratentorial, la presencia de menos de 26 lesiones y el tamaño mayor de un centímetro.
3. La presencia de determinadas alteraciones (SLEDAI más elevado y niveles bajos de complemento) parece asociarse con la presencia de un patrón inflamatorio en la RM cerebral.
4. El síndrome de mielopatía se relaciona con lesiones inflamatorias o mixtas, con un patrón focal y con lesiones de localización infratentorial en la RM cerebral.
5. La presencia de lesiones en la sustancia blanca objetivadas en la RM cerebral podría estar relacionada con las manifestaciones de LESNP; no obstante, su significado concreto está aún por dilucidar.
6. La cefalea se relaciona con frecuencia con ausencia de lesiones en la RM cerebral y de alteraciones de los parámetros de actividad lúpica, lo que hace que se reconsidere como manifestación de LESNP.

Conclusiones del segundo estudio

1. La prevalencia de afectación del SNP en los pacientes con LES es significativa, aproximándose a uno de cada cinco pacientes.
2. La polineuropatía sensitivo-motora es la manifestación del SNP más frecuente en los pacientes con LES.
3. La prevalencia del síndrome de túnel carpiano en los pacientes con LES es similar a la de la población general, lo que puede sugerir que el LES no es causa directa de esta alteración.
4. La afectación del SNP es la primera manifestación de LES en la mitad de los pacientes con esta complicación.
5. Los pacientes afectos de SNP en el LES reciben un tratamiento heterogéneo

para dicha afectación, por lo que son necesarios estudios controlados para determinar el correcto tratamiento de las distintas manifestaciones del SNP en el LES.

6. La edad avanzada en el momento del diagnóstico del LES y la ausencia de compromiso hematológico a lo largo de la evolución de la enfermedad se asociaron con la presencia de manifestaciones de SNP.

7. No existe un patrón immunológico característico de la afectación del SNP en el LES.

Conclusiones globales

1. La afectación neuropsiquiatrica en el LES no es infrecuente, ya sea a través de afectación del SNC o del SNP. No obstante, se precisa de estudios prospectivos para establecer la verdadera incidencia de dicha afectación.

2. Los actuales criterios clasificatorios de la ACR de 1999 del LESNP incluyen algunas manifestaciones del SNC como la cefalea, el deterioro cognitivo leve, la ansiedad y los trastornos del ánimo que no se relacionan con la actividad lúpica ni se ha encontrado asociación con parámetros inmunológicos en la mayoría de trabajos. Sin embargo, no incluye otras manifestaciones neurológicas como el síndrome de encefalopatía reversible posterior y la neuropatía de fibra fina, vinculadas cada vez más al LES. Esto pone de manifiesto la necesidad de revisión de dichos criterios clasificatorios.

3. La RM cerebral es, en el momento actual, la técnica de imagen de elección en los pacientes con sospecha de LESNP. Pese a que la prueba no permite por si sola establecer o descartar dicho diagnóstico, sí que posibilita una aproximación diagnóstica al proceso.

4. Tampoco existen patrones de actividad o inmunológicos que permitan confirmar o descartar el diagnóstico de LESNP, pero algunas alteraciones se asocian con un aumento de su incidencia.

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Review

Brain abnormalities in newly diagnosed neuropsychiatric lupus: Systematic MRI approach and correlation with clinical and laboratory data in a large multicenter cohort

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ABSTRACT

Objectives: To describe brain magnetic resonance imaging (MRI) abnormalities in newly diagnosed neuropsychiatric lupus (NPSLE). To correlate them with clinical and laboratory data.
Methods: This retrospective cross-sectional study included patients presenting NPSLE undergoing brain MRI within 6 months after onset between 2003 and 2012. Clinical and laboratory data were recorded. MRI findings were defined as inflammatory-like, large-vessel disease (LVD), and small-vessel disease (SVD); SVD was classified as white-matter hyperintensities (WMH), recent small subcortical infarcts, lacunes, microbleeds, and brain atrophy.
Results: We included 108 patients (mean 40.6 ± 14.2 years; range 14–77), 91.7% women. The most frequent syndromes were headache (28.5%), cerebrovascular disease (15.5%), seizure (15.5%), and cognitive dysfunction (11.4%). Brain abnormalities were found in 59.3%. SVD was the most common (55.6%), followed by LVD (13%) and inflammatory-like lesions (6.5%). The most frequent SVD findings were WMH (53.7%), atrophy (18.5%), microbleeds (13.7%) and lacunes (11.1%). Cerebrovascular syndrome correlated with LVD ($p = 0.001$) and microbleeds ($p = 0.002$), cognitive dysfunction with WMH ($p = 0.045$) and myelopathy with inflammatory-like lesions ($p = 0.020$). Low C4 and CH50 correlated with inflammatory-like lesions ($p < 0.001$, $p = 0.019$) and lupus anticoagulant with WMH ($p = 0.018$), microbleeds ($p = 0.002$) and atrophy ($p = 0.008$).
Conclusions: Vascular disease is the hallmark of NPSLE. Certain syndromes and immunological patterns are prone to more extensive brain damage. MRI could provide significant clinical information and insights into the pathological substrate.

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1. Introduction

Although the prognosis of systemic lupus erythematosus (SLE) has improved significantly in recent years, neuropsychiatric SLE (NPSLE) remains a major cause of morbidity and mortality [1,2], representing the cause of death in up to 19% of patients with SLE [3,4]. The prevalence of NPSLE varies widely among studies, ranging from 14% to 95% with an average of about 50%, depending on the population studied, inclusion criteria, and period of observation [5–7]. The cause of NPSLE is unknown, and several mechanisms seem to be involved: accelerated atherosclerosis, infarcts, embolisms and immune-mediated alterations [6,8–13].

No specific tests to diagnose NPSLE are available, and numerous investigations are required, mainly to rule out secondary causes [5]. Therefore, NPSLE is essentially a diagnosis of exclusion, yet the correct diagnosis is critical for therapeutic decisions and outcome. A prospective multicenter study of 1206 patients with SLE showed that neuropsychiatric events occurred in 40.3% but that the majority were not due to active inflammation [14]. The events due to active SLE however, were more likely to resolve with treatment than those not due to active SLE. This finding shows the importance of accurately distinguishing neuropsychiatric events due to SLE from those caused by other factors.

Magnetic resonance imaging (MRI) is the neuroimaging technique of choice in SLE and NPSLE [15], although a wide range of nonspecific abnormalities have been reported [16,17]. The most prevalent findings are white-matter hyperintensities (WMH, 8%–75%) [18–23] and brain atrophy (9%–67%) [8,23–29]. The wide range of reported frequencies of MRI abnormalities could be explained by difficulties in recruiting large cohorts while applying stringent inclusion criteria. Many publications include in the same analysis patients with SLE without NPSLE or MRI performed in different disease periods and using different field strengths (0.5 T–3 T) [22,28,30,31]. In a previous retrospective single-center study, our group found correlations between radiological findings and certain clinical parameters indicating disease severity [16]. These results motivated this multicenter study to use standardized international radiological terminology to describe the brain MRI abnormalities in a large cohort of newly diagnosed NPSLE and to correlate these findings with the clinical and laboratory data.

2. Materials and methods

2.1. Patients and study design

This retrospective cross-sectional study included all patients presenting NPSLE who underwent brain MRI between 2003 and 2012 at one of three national referral institutions for SLE and NPSLE: University College Hospital London, The National Hospital of Neurology and Neurosurgery London, and Hospital Clinic Barcelona. Each center's institutional review board approved the study.

SLE and neuropsychiatric syndromes were diagnosed and classified by specialists with experience in SLE and NPSLE using the American College of Rheumatology (ACR) revised nomenclature [32–34]. The patients fulfilled at least 4 ACR criteria for SLE [32,33]. Only 8 patients were referred from other hospitals, with the diagnosis of SLE also confirmed by rheumatologists. All patients presented at least one classified neuropsychiatric syndrome [34] when the diagnosis of NPSLE was established. NPSLE was considered newly diagnosed when the patient presented a neuropsychiatric syndrome for the first time. Only newly diagnosed NPSLE patients undergoing MRI within 6 months after the onset of the neuropsychiatric manifestations were included.

We excluded patients with uncertain neuropsychiatric syndromes, with manifestations that could be attributed to causes unrelated to SLE, and with other concomitant systemic autoimmune diseases.

2.2. Clinical and immunological data

Demographic (age, sex) and clinical data (classification of NPSLE syndromes and cardiovascular risk factors such as hypertension, hypercholesterolaemia, diabetes and smoking) were recorded. Corticosteroid treatment was classified in three dosage groups (low: 2.5–7.5 mg/day; medium: 7.6–29 mg/day; high: >30 mg/day).

Immunological data included complement (C3, C4, and CH50) levels and positivity for antiphospholipid (lupus anticoagulant and anticardiolipin), anti-DNA, anti-Ro, anti-La, anti-Sm, and anti-RNP antibodies obtained within six months after the onset of the neuropsychiatric manifestations.

2.3. Neuroradiological data

All MRI studies were acquired on 1.5 T systems and included T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) sequences. We also analyzed diffusion (DWI), gradient-recalled echo (GRE), susceptibility-weighted imaging (SWI), and contrast-enhanced T1-weighted sequences when available.

MRI studies were read by 3 neuroradiologists blinded to the clinical and immunological data. Double-blind reading was used to assess inter-rater (3 centers) and intra-rater (1 center) reliability.

Three types of MRI findings were defined: inflammatory-like lesions, large-vessel disease (LVD), and lesions classified as small-vessel disease (SVD). Inflammatory-like lesions were defined as T2/FLAIR hyperintense lesions involving gray- or white-matter, generally medium-large, ill defined, without vascular territory distribution, with possible mass effect. LVD was defined as brain infarcts in a large-artery territory and classified by number (single/multiple), presumed arterial territory, and evolution (acute/chronic). SVD was classified according to STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) [35] as WMH (including also basal ganglia and infratentorial involvement), recent small subcortical infarcts, lacunes, microbleeds, and brain atrophy. WMH were graded on FLAIR images, using the European Task Force's Age-Related White Matter Changes (ARWMC) score, described elsewhere [36], which takes into account the location and degree of white-matter involvement. We also defined the lesion burden according to the number of WMH as low (<5), medium (5–25), or high (>25). We recorded the location of recent small subcortical infarcts and lacunes, defined following the STRIVE recommendations, in the territory of perforating arterioles [35]. Cerebral microbleeds were assessed on GRE or SWI sequences; as SWI identifies more microbleeds than GRE, they were classified only as present or absent. Brain atrophy was evaluated on FLAIR images, using the global cortical atrophy (GCA) scale, described elsewhere [37], which has 4 scores ranging from 0 = no atrophy to 3 = severe atrophy.

2.4. Statistical analysis

We did a descriptive analysis, summarizing categorical variables as percentages and continuous variables as means ± standard deviations (SD). We correlated MRI findings with clinical and immunologic findings, using chi-square statistics, corrected by Fisher's exact test for subgroups, for categorical variables, and Student's t-test for continuous variables; p values < 0.05 were considered

significant. Inter-and intra-rater reproducibility was assessed using kappa statistics: we considered $k < 0.4$ poor agreement, $0.4 < k < 0.6$ moderate, $0.6 < k < 0.8$ good, and $k > 0.8$ excellent agreement. We used the Statistical Package for Social Sciences version 17.0 (SPSS, Chicago, IL, USA).

3. Results

3.1. Clinical and immunological data

A total of 108 of the 163 NPSLE patients initially screened fulfilled the inclusion criteria. Of 55 patients excluded, 30 (54.5%) had no MRI study within six months of NPSLE onset; 10 (18.2%) had uncertain neuropsychiatric syndromes; 8 (14.5%) had neuropsychiatric manifestations that could be attributed to other causes unrelated to SLE; and 7 (12.7%) had other concomitant systemic autoimmune diseases.

Table 1 reports the demographic and clinical data. The mean age of the 108 patients was 40.6 years, only 6.5% being older than 60 years; 91.7% were women. The 108 patients had 123 NPSLE syndromes, 87% classified as central. Headache was the most frequent (28.5%), followed by cerebrovascular disease (15.5%), seizure (15.5%), and cognitive dysfunction (11.4%).

The only NPSLE syndrome associated with demographic was cerebrovascular disease, with these patients presenting a higher mean age (49.7 ± 16.4 years, $p = 0.002$). One third of all patients had at least one cardiovascular risk factor, most commonly hypertension (22.2%), but they were not correlated with NPSLE syndromes.

Table 1
Demographic and clinical features of 108 patients with newly diagnosed neuropsychiatric lupus (NPSLE) studied by magnetic resonance imaging (MRI).

	NPSLE patients studied by MRI, *N* (%)
Age (years), mean ± standard deviation (range)	40.6 ± 14.2 (14–77)
Sex (female)	99 (91.7)
Vascular risk factors	36 (33.3)
Hypertension	24 (22.2)
Diabetes mellitus	8 (7.4)
Hypercholesterolaemia	7 (6.5)
Smoking	7 (6.5)
Corticosteroid treatment	75 (69.4)
2.5–7.5 mg/day	39
7.6–29 mg/day	28
>30 mg/day	8
Central nervous system syndromes[a]	107 (87)
Headache	35 (28.5)
Cerebrovascular syndrome	19 (15.5)
Seizure disorder	19 (15.5)
Cognitive dysfunction	14 (11.4)
Mood disorder	5 (4.1)
Myelopathy	4 (3.3)
Anxiety disorder	3 (2.4)
Acute confusional state	3 (2.4)
Psychosis	3 (2.4)
Aseptic meningitis	1 (0.8)
Demyelinating syndrome	1 (0.8)
Movement disorder (chorea)	0
Peripheral nervous system syndromes[a]	16 (13)
Cranial neuropathy	5 (4.1)
Mononeuropathy	5 (4.1)
Polyneuropathy	4 (3.3)
Plexopathy	2 (1.6)
Acute inflammatory demyelinating polyradiculopathy	0
Autonomic disorder	0
Myasthenia gravis	0
Patients with single/two or more NPSLE syndromes	94/14 (87%/13%)

[a] For central and peripheral nervous system syndromes, data refer to 123 NPSLE syndromes.

Table 2 reports the immunological findings from the 93 (86.1%) patients for whom the data were available. The most commonly detected antibody was anti-DNA (43%), followed by anticardiolipin IgG (30.1%), anti-Ro (30.1%), and lupus anticoagulant (LA, 21.5%). C3 levels were low in 31.2%.

3.2. Neuroradiological data

Table 3 reports the MRI findings. MRI was normal in 40.7% of patients. Abnormalities were found in the remaining 59.3%, and consisted of SVD in 55.6% of all patients, LVD in 13%, and inflammatory-like lesions in 6.5%. Fig. 1 shows typical SVD, LVD, and inflammatory-like lesions. Most MRI findings were related to SVD. More than half of all patients presented WMH (53.7%). Lacunes were present in 11.1% and recent small subcortical infarcts in 1.9%. Microbleeds were identified in 13.7% of 73 patients with GRE/SWI. Cortical atrophy was observed in 18.5% of patients. Of the 14 patients with LVD, 6 had multiple infarcts. Middle cerebral artery (8 patients) was most frequently involved. Only 2 patients showed restricted diffusion (DWI) indicating acute stroke. Of 7 patients with inflammatory-like lesions, 3 had both infratentorial and supratentorial involvement, 2 only infratentorial and 2 only supratentorial lesions. Contrast enhancement was observed in 5 patients and restricted diffusion in only 1.

Inter-rater agreement was excellent for 2 variables ($k = 1$, $p < 0.001$), good for 12 variables (k ranges 0.608–0.783, $p < 0.007$) and moderate for 2 variables, which were the temporal lobe WMH and lesion burden ($k = 0.459$ and 0.509, $p < 0.015$). Intra-rater agreement was excellent for 10 variables (k ranges 0.810–1, $p < 0.001$), good for 4 variables (k ranges 0.644–0.788, $p < 0.001$) and moderate for 2, which were lesion burden and the infratentorial WMH ($k = 0.556$ and 0.585, $p < 0.001$).

3.3. Correlations between clinical and immunological data and MRI findings (Tables 4 and 5)

Hypertension correlated with microbleeds ($p = 0.008$) and LVD ($p = 0.002$). No other relationships between vascular risk factors and radiological findings were observed.

Cranial neuropathy correlated with normal MRI ($p = 0.010$), while cerebrovascular syndrome was associated with LVD ($p = 0.001$), microbleeds ($p = 0.002$) and myelopathy with inflammatory-like lesions ($p = 0.020$). Cognitive dysfunction was associated with WMH ($p = 0.045$) but there was no correlation with corticosteroid treatment. Cortical atrophy was associated with other patterns of SVD such as WMH ($p = 0.002$), high lesion burden ($p < 0.001$), microbleeds ($p = 0.008$) and lacunes ($p = 0.044$).

Low CH50 correlated with inflammatory-like lesions ($p = 0.019$), WMH ($p = 0.010$) and cortical atrophy ($p = 0.003$). Low C4 correlated with inflammatory-like lesions ($p < 0.001$). LA correlated with WMH ($p = 0.018$), high lesion burden ($p = 0.005$), microbleeds ($p = 0.002$),

Table 2
Immunological profile of 93 patients (out of 108) with available immunological data.

	NPSLE patients studied by MRI, *N* (%)
Low levels of C3	29 (31.2)
Low levels of C4	16 (17.2)
Low levels of CH50	13 (14)
Antiphospholipid antibodies	37 (39.8)
Lupus anticoagulant	20 (21.5)
Anticardiolipin IgG	28 (30.1)
Anticardiolipin IgM	12 (12.9)
Anti-DNA antibodies	40 (43)
Anti-Sm antibodies	14 (15.1)
Anti-Ro antibodies	28 (30.1)
Anti-La antibodies	17 (18.3)
Anti-RNP antibodies	18 (19.4)

Table 3
Brain MRI findings in 108 patients with neuropsychiatric lupus.

Normal MRI	44 (40.7%)
Abnormal MRI	64 (59.3%)
Inflammatory-like lesions	7 (6.5%)
Vascular lesions	63 (58.3%) (6 both inflammatory-like and vascular)
Large-vessel disease	14
Small-vessel disease	60 (11 both large and small vessel disease)
Inflammatory-like lesions	7
Supratentorial/Infratentorial	5/5 (3 both supra- and infratentorial)
Contrast-enhancement	5
Diffusion restriction	1
Large-vessel disease	14 (13%)
Single/multiple	8/6
Acute/chronic	2/13 (1 both acute and chronic)
Vascular territory	MCA 8, PICA 3, cortical border zone 4, striatocapsular (>2 cm) 2, PCA 1, ACA 1, AICA 1
Small-vessel disease	60 (55.6%)
White-matter hyperintensities	58 (53.7%)
Location:	
Frontal	48 (44.4%)
Parieto-occipital	42 (38.9%)
Temporal	8 (7.4%)
Basal ganglia	6 (5.6%)
Infratentorial	8 (7.4%)
Degree of involvement	
Focal	48 (44.4%)
Beginning confluence	7 (6.5%)
Diffuse	3 (2.8%)
Lesion burden:	
Low (<5)	25 (23.1%)
Medium (5–25)	21 (19.4%)
5–15	16 (14.8%)
16–25	5 (4.6%)
High (>25)	12 (11.1%)
Lacunes[a]	12 (11.1%)
Recent small subcortical infarcts	2 (1.9%)
Microbleeds[a]	10 (13.7%)
Brain atrophy (GCA scale)[a]	20 (18.5%)
GCA 1 (mild)	17
GCA 2 (moderate)	3
GCA 3 (severe)	-

Abbreviations: GCA—Global Cortical Atrophy scale, MCA—middle cerebral artery, PICA—posterior inferior cerebellar artery, PCA—posterior cerebral artery, ACA—anterior cerebral artery, AICA—anterior inferior cerebellar artery.
[a] Microbleeds: all with other signs of small-vessel disease (SVD); lacunes and cortical atrophy: all but 1 patient with other signs of SVD.

cortical atrophy ($p = 0.008$) and it tended to associate lacunes ($p = 0.069$) and LVD ($p = 0.069$). No relationships between other antibodies and the radiological manifestations were found.

4. Discussion

Our study is one of the largest cohorts of clearly defined patients with newly diagnosed NPSLE, describing MRI findings using standard international terminology and analysing their correlation with clinical and immunological data. Despite recent onset of neuropsychiatric syndromes, many of our patients had either a normal MRI or only focal WMH with low lesion burden. Importantly, we found a correlation between inflammatory and immunological biomarkers and radiological patterns, implicating their role in the brain damage.

The most common neuropsychiatric syndromes in our cohort were headache, cerebrovascular syndrome, seizure and cognitive dysfunction, being also the most described syndromes in previous MRI studies [38,39]. A recent meta-analysis showed in a subanalysis of the highest qualitative studies (2049 patients) that the most frequent syndromes were headache with 28.3% (18.2%–44.1%), followed by mood disorders, cognitive dysfunction, seizures and cerebrovascular disease [7].

In around 40% of our patients, no abnormalities were found on brain MRI at the onset of NPSLE. No patients presenting with headache showed major injuries such as LVD or inflammatory-like lesions. These data are consistent with former studies in patients with SLE with or without neuropsychiatric manifestations [18,20,22,31]. In addition, a recent study showed that most headaches in SLE patients are not due to active disease. The prevalence of headache was 18% at enrollment and rose to 58% after 10 years yet only 1.5% were identified as having headache due to active disease. There were no associations between headache and disease activity, medications or autoantibodies [40]. The absence however, of abnormalities in many patients could be partially explained by limitations of conventional MRI. Advanced techniques in NPSLE revealed abnormalities in patients with normal findings on standard sequences [27,41–43].

In this study, the most frequent MRI abnormalities were vascular lesions, commonly related to SVD. Approximately half of the patients had WMH, mostly in frontal and parieto-occipital regions, similar to other studies [21]. The presence of WMH in our patients correlated with cognitive dysfunction, low CH50 and LA. Other authors also found an association between WMH and antiphospholipid antibodies [21], cognitive impairment [21,24] and cerebrovascular disease [24]. Although the etiopathology of cerebral SVD is most frequently caused by arteriolosclerosis (age-related and vascular risk factor-related), inflammatory and immunologically mediated small-vessel inflammation can present with indistinguishable WMH radiological pattern. The absence of correlation between WMH and vascular risk factors and age and the association with markers of inflammatory activity such as CH50 could support the inflammatory origin of certain of these WMH.

We found microbleeds in 13.7% of the patients, and lacunes in 11.1%, in line with a previous report in NPSLE that found a prevalence of lacunes

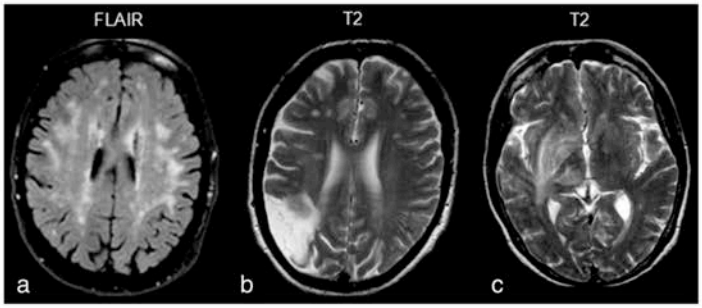

Fig. 1. (a) Axial FLAIR sequence at the level of the lateral ventricle shows beginning confluent white-matter hyperintensities, classified as small-vessel disease. (b) Axial T2-weighted at the level of the lateral ventricle demonstrates a chronic infarct in the posterior superficial territory of the right middle cerebral artery together with focal white-matter hyperintensities, indicating both large- and small-vessel disease. (c) Axial T2-weighted at the level of the basal ganglia in a patient with aseptic meningitis shows an ill-defined T2-hyperintensity involving the right basal ganglia, thalamus, and external and internal capsule.

Table 4
Relationship between neuropsychiatric syndromes and brain MRI findings.

NPSLE syndrome	Patients *N*	Normal MRI, *N* (%)	Abnormal MRI, *N* (%)	Inflammatory-Like	LVD	SVD	SVD Classification				
							WMH	Lacunes	Rrecent small subcortical infarcts	Microbleeds[a]	Atrophy
Central síndromes											
Headache	35	18 (51.4%) $p = 0.118$	17 (48.6%)	–	–	17 (48.6%) $p = 0.312$	17 (48.6%) $p = 0.459$	1 (2.9%) $p = 0.059$	–	1 (4.5%) $p = 0.135$	3 (8.6%) $p = 0.065$
Cerebrovascular syndrome	19	4 (21.1%)	15 (78.9%) $p = 0.054$	1 (5.3%) $p = 0.812$	7 (36.8%) $\mathbf{p = 0.001}$	15 (78.9%) $\mathbf{p = 0.024}$	14 (73.7%) $p = 0.054$	3 (15.8%) $p = 0.475$	1 (5.3%) $p = 0.224$	5 (41.7%) $\mathbf{p = 0.002}$	5 (26.3%) $p = 0.335$
Seizure	19	7 (36.8%)	12 (63.2%) $p = 0.703$	1 (5.3%) $p = 0.812$	5 (26.3%) $p = 0.056$	10 (52.6%) $p = 0.778$	10 (52.6%) $p = 0.918$	4 (21.1%) $p = 0.129$	–	1 (9.1%) $p = 0.630$	5 (26.3%) $p = 0.335$
Cognitive dysfunction	14	3 (21.4%)	11 (78.6%) $p = 0.115$	–	2 (14.3%) $p = 0.875$	11 (78.6%) $p = 0.063$	11 (78.6%) $p = \mathbf{0.045}$	2 (14.3%) $p = 0.685$	–	1 (11.1%) $p = 0.809$	3 (21.4%) $p = 0.764$
Mood disorder	5	4 (80%) $p = 0.067$	1 (20%)	–	–	1 (20%) $p = 0.101$	1 (20%) $p = 0.122$	–	–	–	–
Myelopathy	4	–	4 (100%) $p = 0.091$	2 (50%) $\mathbf{p = 0.020}$	–	3 (75%) $p = 0.425$	3 (75%) $p = 0.384$	1 (25%) $p = 0.368$	–	1 (25%) $p = 0.499$	–
Anxiety disorder	3	2 (66.7%) $p = 0.354$	1 (33.3%)	–	–	1 (33.3%) $p = 0.432$	–	–	–	–	1 (33.3%) $p = 0.503$
Acute confusional state	3	1 (33.3%)	2 (66.7%) $p = 0.791$	1 (33.3%) $p = 0.055$	–	2 (66.7%) $p = 0.694$	2 (66.7%) $p = 0.648$	–	1 (33.3%) $p = 0.055$	–	–
Psychosis	3	3 (100%) $p = 0.065$	–	–	–	–	–	–	–	–	–
Aseptic meningitis	1	–	1 (100%)	1 (100%)	–	1 (100%)	1 (100%)	–	–	–	–
Demyelinating syndrome	1	–	1 (100%)	1 (100%)	–	1 (100%)	1 (100%)	–	–	–	1 (100%)
Peripheral síndromes											
Cranial neuropathy	5	5 (100%) $\mathbf{p = 0.010}$	–	–	–	–	–	–	–	–	–
Mononeuropathy	5	1 (20%)	4 (80%) $p = 0.334$	–	1 (20%) $p = 0.631$	4 (80%) $p = 0.260$	4 (80%) $p = 0.227$	2 (40%) $p = 0.094$	–	1 (33.3%) $p = 0.312$	1 (20%) $p = 0.930$
Polyneuropathy	4	1 (25%)	3 (75%) $p = 0.514$	1 (25%) $p = 0.125$	2 (50%) $p = 0.081$	2 (50%) $p = 0.820$	2 (50%) $p = 0.880$	1 (25%) $p = 0.368$	–	–	2 (50%) $p = 0.099$
Plexopathy	2	2 (100%) $p = 0.159$	–	–	–	–	–	–	–	–	–
Single syndrome	94	37 (39.4%)	57 (60.6%) $p = 0.450$	7 (7.4%) $p = 0.291$	11 (11.7%) $p = 0.312$	53 (56.4%) $p = 0.654$	51 (54.3%) $p = 0.766$	10 (10.6%) $p = 0.685$	2 (2.1%) $p = 0.582$	10 (14.5%) $p = 0.412$	19 (20.2%) $p = 0.240$
More than 1 syndrome	14	7 (50%)	7 (50%) $p = 0.450$	–	3 (21.4%) $p = 0.312$	7 (50%) $p = 0.654$	7 (50%) $p = 0.766$	2 (14.3%) $p = 0.685$	–	–	1 (7.1%) $p = 0.240$

Abbreviations: LVD-large-vessel disease, SVD-small-vessel disease, WMH-white-matter hyperintensities. Significant *p*-values are highlighted.
[a] Percentages for microbleeds are calculated from a total of 73 patients with available T2*/SWI sequences.

Table 5
Immunological profile and brain MRI findings in 93 NPSLE patients with available immunological data.

Immunology	Patients *N*	Normal MRI, N (%)	Abnormal MRI, *N* (%)	Inflammatory-like	LVD	SVD	SVD classification				
							WMH	Lacunes	Recent small subcortical infarcts	Microbleeds	Atrophy
C3 (low)	29	12 (41.4%)	17 (58.6%) $p = 0.831$	3 (10.3%) $p = 0.153$	5 (17.2%) $p = 0.401$	16 (55.2%) $p = 0.854$	16 (55.2%) $p = 0.644$	3 (10.3%) $p = 0.620$	–	5 (23.8%) $p = 0.092$	7 (24.1%) $p = 0.432$
C4 (low)	16	6 (37.5%)	10 (62.5%) $p = 0.625$	5 (31.3%) $\mathbf{p < 0.001}$	4 (25%) $p = 0.113$	8 (50%) $p = 0.740$	8 (50%) $p = 0.887$	1 (6.3%) $p = 0.383$	–	3 (23.1%) $p = 0.256$	5 (31.3%) $p = 0.186$
CH50 (low)	13	2 (15.4%)	11 (84.6%) $\mathbf{p = 0.030}$	3 (23.1%) $\mathbf{p = 0.019}$	3 (23.1%) $p = 0.238$	11 (84.6%) $\mathbf{p = 0.015}$	11 (84.6%) $\mathbf{p = 0.010}$	3 (23.1%) $p = 0.238$	–	3 (30%) $p = 0.125$	7 (53.8%) $\mathbf{p = 0.003}$
aPL											
aCL IgM	12	6 (50%)	6 (50%) $p = 0.600$	1 (8.3%) $p = 0.627$	–	6 (50%) $p = 0.779$	6 (50%) $p = 0.905$	2 (16.7%) $p = 0.677$	–	2 (22.2%) $p = 0.406$	1 (8.3%) $p = 0.300$
aCL IgG	28	10 (35.7%)	18 (64.3%) $p = 0.351$	2 (7.1%) $p = 0.27$	2 (7.1%) $p = 0.500$	18 (64.3%) $p = 0.182$	16 (57.1%) $p = 0.484$	5 (17.9%) $p = 0.350$	1 (3.6%) $p = 0.535$	4 (21.1%) $p = 0.250$	8 (28.6%) $p = 0.140$
LA	20	5 (25%)	15 (75%) $p = 0.066$	2 (10%) $p = 0.301$	5 (25%) $p = 0.069$	15 (75%) $\mathbf{p = 0.032}$	15 (75%) $\mathbf{p = 0.018}$	5 (25%) $p = 0.069$	–	6 (35.3%) $\mathbf{p = 0.002}$	8 (40%) $\mathbf{p = 0.008}$
Anti–DNA	40	14 (35%)	26 (65%) $p = 0.175$	2 (5%) $p = 0.889$	5 (12.5%) $p = 0.920$	24 (60%) $p = 0.295$	23 (57.5%) $p = 0.324$	4 (10%) $p = 0.468$	–	7 (22.6%) $p = 0.070$	9 (22.5%) $p = 0.505$
Anti-Sm	14	5 (35.7%)	9 (64.3%) $p = 0.550$	1 (7.1%) $p = 0.751$	2 (14.3%) $p = 0.867$	9 (64.3%) $p = 0.392$	9 (64.3%) $p = 0.303$	1 (7.1%) $p = 0.485$	–	3 (30%) $p = 0.096$	4 (28.6%) $p = 0.344$
Anti-Ro	28	14 (50%) $p = 0.372$	14 (50%)	2 (7.1%) $p = 0.620$	4 (14.3%) $p = 0.794$	12 (42.9%) $p = 0.166$	12 (42.9%) $p = 0.267$	3 (10.7%) $p = 0.679$	1 (3.6%) $p = 0.535$	4 (19%) $p = 0.362$	4 (14.3%) $p = 0.417$
Anti-La	17	6 (35.3%)	11 (64.7%) $p = 0.477$	1 (5.9%) $p = 0.919$	2 (11.8%) $p = 0.877$	10 (58.8%) $p = 0.643$	10 (58.8%) $p = 0.510$	3 (17.6%) $p = 0.519$	1 (5.9%) $p = 0.241$	3 (21.4%) $p = 0.324$	3 (17.6%) $p = 0.844$
Anti-RNP	18	10 (55.6%) $p = 0.231$	8 (44.4%)	1 (5.6%) $p = 0.970$	3 (16.7%) $p = 0.596$	7 (38.9%) $p = 0.159$	7 (38.9%) $p = 0.229$	3 (16.7%) $p = 0.596$	–	3 (27.3%) $p = 0.141$	1 (5.6%) $p = 0.099$

Abbreviations: aPL—antiphospholipid antibodies, aCL IgM—anticardiolipin IgM, aCL IgG—anticardiolipin IgG, LA—lupus anticoagulant, LVD—large-vessel disease, SVD—small-vessel disease, WMH—white-matter hyperintensities. Significant *p*-values are highlighted.

of 16% [22]. Microhemorrhages on MRI have not yet been formally assessed in large series of NPSLE. We observed an association between microbleeds and LA and a trend toward association between lacunes and LA. The association between LA, lacunes and microbleeds may provide an explanation for the thrombotic activity observed with focal acute ischemia of small vessels leading to complete tissue necrosis (lacunes) or vessel rupture (microhemorrhages) [44]. In our sample microbleeds were also associated with hypertension, as previously reported [45].

Brain atrophy has often been reported in NPSLE and SLE, although the reported frequencies vary widely, probably reflecting the heterogeneity of the radiological language and inclusion criteria. In the present study, we used the GCA scale to assess brain atrophy, finding atrophy in a significant number of young subjects (mean age, 42.5 years), in agreement with other publications [8,27–29]. In our patients, cortical atrophy correlated with LA and low CH50. Previous studies related atrophy with disease duration [24–26], antiphospholipid antibodies [25,26] and cerebrovascular disease [24]. Many authors suggested cerebral atrophy might result from prednisone use [24,46], while others found no association [20,23,27]. In this study, brain atrophy correlated with patterns consistent with SVD suggesting that global microangiopathy in NPSLE could be partially responsible for brain atrophy.

LVD, one of the most important complications of SLE [19], was present in 13% of our cohort, with a mean age of 40 years, similar to other studies [19,28,47]. Most notably, almost half of our patients with LVD had more than one large-vessel infarct, indicating a high recurrence rate. LVD correlated with cerebrovascular syndrome, hypertension and there was a trend to associate LA. The association between LA and recurrent stroke involving LVD in young adults has been repeatedly described, in the presence and absence of SLE [28,48]. Conversely, SLE has an underlying inflammatory and immune-mediated etiopathogenesis similar to that of atherosclerosis which may also provide clues to understanding premature vascular disease in SLE patients [12].

Only 6.5% of this NPSLE sample presented with an inflammatory-like pattern. This radiological pattern has been related to primary cerebral vasculitis, which is considered to be rare in SLE. Cerebral vasculitis can be widespread or restricted to one region, involving small cerebral vessels or predominantly large arteries [13]. In our series the inflammatory-like pattern was associated with low complement supporting an immune-mediated complement consumption pathogenesis.

Conventional MRI findings in NPSLE are non-specific, reflecting the various underlying pathogenic mechanisms involving different cerebral vessels at different stages of the disease. The capability of new advanced MRI techniques such as diffusion-tensor or spectroscopy to detect microstructural and metabolic abnormalities should help to understand further the pathology and time course of this disease. New-longitudinal studies using these advanced MRI techniques must be performed to demonstrate the value of neuroimaging as a biomarker in disease monitoring.

The present study has several potential limitations, mostly inherent to retrospective studies. As the inclusion criteria were based on referral for brain MRI in the early period of NPSLE, our sample may be biased because not all subjects were referred for MRI; thus, our cohort probably contains a higher proportion of patients with more severe symptoms. We did not include data about disease activity because our institutions used different activity scores, nor did we include the quantification of antibodies and complement. No data about additional therapies such as acetylsalicylic acid or anticoagulation were available, so we could not analyze their relationship with LVD and SVD. We did not include data about the time of evolution of SLE prior to the onset of NPSLE, which may be important for a better understanding of the evolution of MRI lesions. Furthermore, we had no control group of healthy individuals or SLE patients. Despite these limitations, this study can be representative in current clinical settings.

In conclusion, although nonspecific, vascular disease is the hallmark of NPSLE. Certain syndromes and immunological patterns are prone to more extensive brain damage. A systematic approach combining radiological, clinical and laboratory data could provide important clinical and prognostic information, and important insights into disease pathology.

Take-home messages

- Many newly diagnosed NPSLE patients had normal MRI or focal WMH.
- Low levels of complement are associated with inflammatory-like lesions.
- Lupus anticoagulant is correlated with findings related to small vessel disease.
- Cerebrovascular syndrome, cognitive dysfunction and myelopathy are related to radiological abnormalities.
- A systematic radiological approach could provide important insights into disease pathology.

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SPECIAL ARTICLE

Advanced MRI techniques: biomarkers in neuropsychiatric lupus

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Objectives: The objective of this study was to determine whether advanced MRI could provide biomarkers for diagnosis and prognosis in neuropsychiatric systemic lupus erythematosus (NPSLE). **Methods:** Our prospective study included 28 systemic lupus erythematosus (SLE) patients with primary central NPSLE, 22 patients without NPSLE and 20 healthy controls. We used visual scales to evaluate atrophy and white matter hyperintensities, voxel-based morphometry and Freesurfer to measure brain volume, plus diffusion-tensor imaging (DTI) to assess white matter (WM) and gray matter (GM) damage. We compared the groups and correlated MRI abnormalities with clinical data. **Results:** NPSLE patients had less GM and WM than controls ($p = 0.042$) in the fronto-temporal regions and corpus callosum. They also had increased diffusivities in the temporal lobe WM ($p < 0.010$) and reduced fractional anisotropy in the right frontal lobe WM ($p = 0.018$). High clinical scores, longstanding disease, and low serum C3 were associated with atrophy, lower fractional anisotropy and higher diffusivity in the fronto-temporal lobes. Antimalarial treatment correlated negatively with atrophy in the frontal cortex and thalamus; it was also associated with lower diffusivity in the fronto-temporal WM clusters. **Conclusions:** Atrophy and microstructural damage in fronto-temporal WM and GM in NPSLE correlate with severity, activity and the time from disease onset. Antimalarial treatment seems to give some brain-protective effects. *Lupus* (2017) **26,** 510–516.

Key words: Anti-malarial treatment; atrophy; brain; lupus; magnetic resonance imaging; malaria; neuropsychiatric systemic lupus erythematosus; systemic lupus erythematosus

Introduction

Although the systemic lupus erythematosus (SLE) prognosis has improved in recent decades, neuropsychiatric SLE (NPSLE) remains an important cause of morbidity and mortality.[1,2] The pathogenesis of NPSLE is unknown, with several mechanisms being implicated, including: vascular and neuronal damage, precocious atherosclerosis and embolisms.[3–5] The 1999 American College of Rheumatology (ACR) Case Definitions classify NPSLE into central and peripheral syndromes.[6] An accurate diagnosis is essential, and algorithms have been developed to attribute neuropsychiatric events to SLE.[7] MRI is the imaging technique of choice for NPSLE, although up to 50% of patients have no apparent abnormalities.[8] MRI findings in NPSLE are nonspecific, reflecting the diversity of underlying mechanisms.[4,9–15] The most common findings are: white-matter hyperintensities (WMH), occurring in 30–75% of patients; and atrophy, occurring in 15–20%.[1] The role of advanced MRI has yet to be defined. A few studies applying diffusion tensor imaging (DTI), morphometry or spectroscopy have demonstrated underlying abnormalities even in normal-appearing brains.[16–18] Volumetric studies show gray matter (GM) atrophy in NPSLE and SLE non-NPSLE patients.[19–21] DTI findings may serve as biomarkers of NPSLE,[22] as studies have found there is decreased fractional anisotropy (FA) and increased mean and axial diffusivity (MD, AD) in frontal white matter (WM), the corpus callosum and thalamus.[16,17,19,23–26] Localized damage to WM tracts has also been reported in the limbic system, internal capsule and corona radiate.[18,27,28] Few efforts to correlate advanced MRI findings with clinical data have been reported: brain volume loss has been correlated with the time from disease onset[19]

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and the SLE Disease Activity Index (SLEDAI).[29] One study found atrophy correlated with corticosteroids and antiphospholipid antibodies,[19] but another did not.[30] Another study reported decreased FA associated with antiphospholipid antibodies.[31]

We aimed to determine whether combining different MRI techniques (voxel-based morphometry (VBM), Freesurfer, DTI and WMH volumetry) could define biomarkers for the diagnosis and prognosis of NPSLE in a way that could be used in trials and clinical practice. To this end, we designed a prospective study with stringent inclusion criteria to determine brain abnormalities in three groups of subjects: primary central NPSLE, non-NPSLE and healthy controls. Finally, we also looked for correlations between MRI findings with clinical and laboratory data.

Materials and methods

Patients

We recruited 28 SLE patients with primary central NPSLE, 22 SLE patients without NPSLE and 20 healthy controls: these were matched for age and socio-professional category. Subjects were studied at a national referral institution for NPSLE between 2014 and 2015. The institutional review board approved the study, and subjects provided written informed consent. All patients were recruited and classified using ACR nomenclature by a clinician with a large amount of experience in lupus. All patients fulfilled at least four ACR criteria for SLE,[32,33] and the patients with NPSLE were identified according to ACR criteria.[6] All NPSLE patients had primary central NPSLE with at least one classified neuropsychiatric syndrome. We excluded patients with peripheral, secondary or uncertain NPSLE syndromes, or manifestations attributable to other causes.

Clinical and laboratory data

We recorded demographics (ethnicity, age), clinical data (NPSLE syndromes, vascular risk factors, time since disease onset, SLEDAI score, and Systemic Lupus International Collaborating Clinic (SLICC) score), treatment and immunological data.

MRI acquisition and processing

See the Supplementary Data for the protocols. For the conventional MRI analysis, an experienced neuroradiologist who was blinded to all data interpreted the MRI studies, classifying the inflammatory-like lesions, large-vessel disease and small-vessel disease.[4,9] Small-vessel disease was classified according to the STandards for ReportIng Vascular changes in nEuroimaging (STRIVE) criteria[34] as WMH, recent small infarcts, lacunae, microbleeding and/or atrophy. WMH were graded on FLAIR images, using the European Task Force's Age-Related White Matter Changes score.[35] Brain atrophy was evaluated using the global cortical atrophy visual scale,[36] which has four scores ranging from 0 (no atrophy) to 3 (severe atrophy).

Statistical analyses

The details (SPM and SPSS analysis) are described in the Supplementary Data.

Results

Comparison between groups

Clinical characteristics, laboratory data and treatment
Table 1 reports the clinical data. All subjects were female Caucasians, and there were no significant differences between groups. Patients with NPSLE had higher SLICC scores than those with non-NPSLE ($p < 0.001$).

Neuroimaging data
Conventional MRI Table S2 (Supplementry Data) reports the findings. An abnormal MRI was present in 57.1% of NPSLE, 27.3% of non-NPSLE and 30% of healthy controls. The most common abnormalities were related to small-vessel disease. A greater proportion of atrophy was found in NPSLE ($p = 0.005$).

Brain volumetry: VBM and the Freesurfer analysis
Table S3 (Supplementry Data) reports differences in WM and GM volumes; and in DTI parameters. WM volume in the left frontal region was lower in the NPSLE patients than in healthy controls ($p = 0.002$, Figure 1).

DTI analysis Compared to healthy controls, NPSLE had lower FA in the WM of the right frontal lobe ($p = 0.018$); and higher MD, AD, RD in the WM of both superior temporal lobes ($p < 0.010$ for all the clusters, Figure 1).

WMH volumetry No significant differences between groups were observed (mean values were 110.6 mm^3/person in NPSLE subjects, 58.9 mm^3 in

Table 1 Clinical and laboratory findings in patients with neuropsychiatric SLE and in those with non-neuropsychiatric SLE

Patient characteristics	*NPSLE patients* n = *28* n *(%)*	*SLE patients* n = *22* n *(%)*	p-*value*
Age, mean years ± SD (range)	39.5 ± 12.6 (21–71)	41.1 ± 13.3 (19–72)	0.918
Gender (female)	28 (100%)	22 (100%)	0.639
SLE duration, mean weeks ± SD (range)	591.8 ± 562.4 (16–2199)	563.6 ± 416.2 (86–1900)	< **0.001**
NPSLE duration,			
1. mean weeks ± SD (range)	198.7 ± 338.9 (1–1650)	–	< **0.001**
2. SLEDAI, mean ± SD (range)	11.5 ± 6.6 (0–28)	3.8 ± 2.8 (0–10)	0.616
0–1 points	2 (7.1%)	3 (13.6%)	
2–4 points	1 (3.6%)	12 (54.5%)	
5–7 points	1 (3.6%)	4 (18.2%)	
≥ 8 points	24 (85.7%)	3 (13.6%)	
3. SLICC, mean ± SD (range)	1.2 ± 0.8 (0–4)	0.3 ± 0.5 (0–2)	0.44
Vascular risk factors			0.591
Hypertension	3 (10.7%)	2 (9.1%)	
Diabetes mellitus	–	1 (4.5%)	
Hypercholesterolemia	2 (7.1%)	1 (4.5%)	
Smoking	5 (17.9%)	2 (9.1%)	0.332
ACR criteria			
Malar rash	15 (53.6%)	13 (59.1%)	
Discoid lupus	1 (3.6%)	2 (9.1%)	
Photosensitivity	8 (28.6%)	11 (50%)	
Aphthosis	10 (35.7%)	7 (31.8%)	
Arthritis	25 (89.3%)	21 (95.4%)	
Serositis	7 (25%)	2 (9.1%)	
Nephritis	7 (25%)	4 (18.2%)	
Neurologic disorder (psychosis, seizures)	8 (28.6%)	–	
Hematologic disorder	11 (39.3%)	8 (36.3%)	
Immunologic disorder	25 (89.3%)	15 (68.2%)	
Antinuclear antibodies	28 (100%)	21 (94.4%)	
Treatments			
Antimalarials	15 (53.6%)	18 (81.8%)	**0.035**
Corticosteroids	9 (32.1%)	7 (31.8%)	0.612
2.5–7.5 mg/day	6 (21.4%)	5 (22.7%)	0.691
7.6–29 mg/day	3 (10.7%)	2 (9.1%)	0.167
>30 mg/day	–	–	0.309
Methotrexate	1 (3.6%)	1 (4.5%)	0.616
Azathioprine	3 (10.7%)	–	0.457
Cyclophosphamide	2 (7.1%)	–	0.322
Mycophenolate mofetil	3 (10.7%)	2 (9.1%)	0.134
Rituximab	–	–	0.216
Anticoagulants	4 (14.3%)	2 (9.1%)	0.371
Antiplatelet	5 (17.9%)	2 (9.1%)	0.208
Immunological data			
C3 (low)	11 (39.3%)	13 (59.1%)	0.638
C4 (low)	4 (14.3%)	6 (27.3%)	0.223
CH50 (low)	6 (21.4%)	3 (13.6%)	0.309
Antiphospholipid antibodies	5 (17.9%)	7 (31.8%)	0.119
Lupus anticoagulant	4 (14.3%)	3 (13.6%)	0.208
Anticardiolipin IgG	3 (10.7%)	5 (22.7%)	0.137
Anticardiolipin IgM	2 (7.1%)	–	0.179
Anti-DNA antibodies	22 (78.6%)	13 (59.1%)	0.323
Anti-Sm antibodies	5 (17.9%)	7 (31.8%)	0.56
Anti-Ro antibodies	13 (46.4%)	6 (26.3%)	
Anti-La antibodies	8 (28.6%)	3 (13.6%)	
Anti-RNP antibodies	5 (17.9%)	6 (27.3%)	
Rheumatoid factor	1 (3.6%)	–	

ACR: American College of Rheumatology; IgG: immunoglobulin G; IgM: immunoglobulin M; NPSLE: neuropsychiatric SLE; SLE: systemic lupus erythematosus; SLEDAI: systemic lupus erythematosus disease activity index; SLICC: Systemic Lupus International Collaborating Clinic

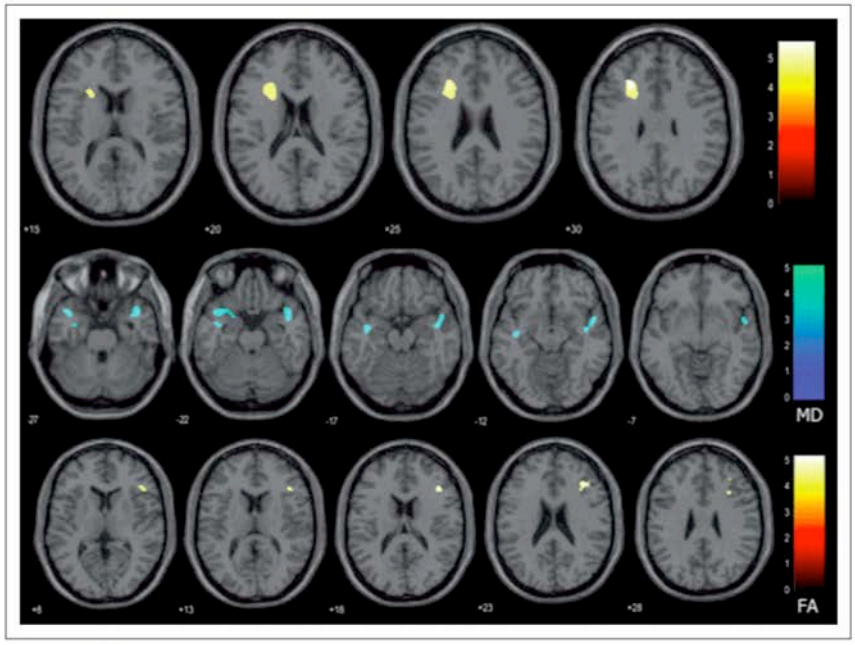

Figure 1 VBM and DTI differences between NPSLE and controls.
The first row shows the white matter volume differences between both groups. There is a significant decrease in the left frontal sublobar white matter in NPSLE patients. The second row and the third row demonstrate the changes observed in MD and FA, respectively. NPSLE patients have a significantly increased mean diffusivity in both temporal lobes and decreased fractional anisotropy in the right frontal lobe.
DTI: diffusion tensor imaging; FA: fractional anisotropy; MD: mean diffusivity; NPSLE: systemic lupus erythematosus; VBM: voxel-based morphometry

the non-NPSLE subjects and 61.8 mm^3 in the healthy controls).

Correlations between neuroimaging findings and clinical and laboratory data and among MRI analyses

Correlations between MRI findings in patients and clinical and laboratory data

SLEDAI correlated positively (Figure 2) with atrophy on conventional MRI ($p = 0.046$) and negatively with left superior temporal cortex volume ($p = 0.029$) in NPSLE patients. SLEDAI also correlated negatively with FA in the WM of left hippocampal, parahippocampal and lingual regions (left side, $p = 0.002$). SLICC correlated negatively with FA in WM of left hippocampal and parahippocampal regions ($p < 0.001$) and positively with RD in right frontal WM ($p = 0.005$). The time from SLE onset correlated negatively with FA in WM of right frontal WM ($p < 0.0005$). Serum levels of C4 and CH50 correlated negatively with left superior temporal cortex volume ($p = 0.003$ and $p = 0.002$, respectively). Brain atrophy was less common in patients receiving antimalarial drugs (Results: 2 (6.1%) out of 33 versus 7 (41.2%) out of 17 not receiving antimalarials, $p = 0.004$). Patients on antimalarial drugs also had lower diffusivity parameters in the superior temporal WM (MD (right) $p = 0.006$, (left) $p = 0.004$; AD (bilateral) $p = 0.007$ and RD (bilateral) $p = 0.005$). No correlations were found between the MRI findings and vascular risk factors, NPSLE syndromes, corticosteroid or immunosuppressive treatment.

Correlations between conventional MRI imaging, brain volumetry and DTI analysis

As expected, atrophy on conventional MRI correlated negatively with cortical volume ($p = 0.003$) and positively with diffusivity ($p < 0.001$ for all

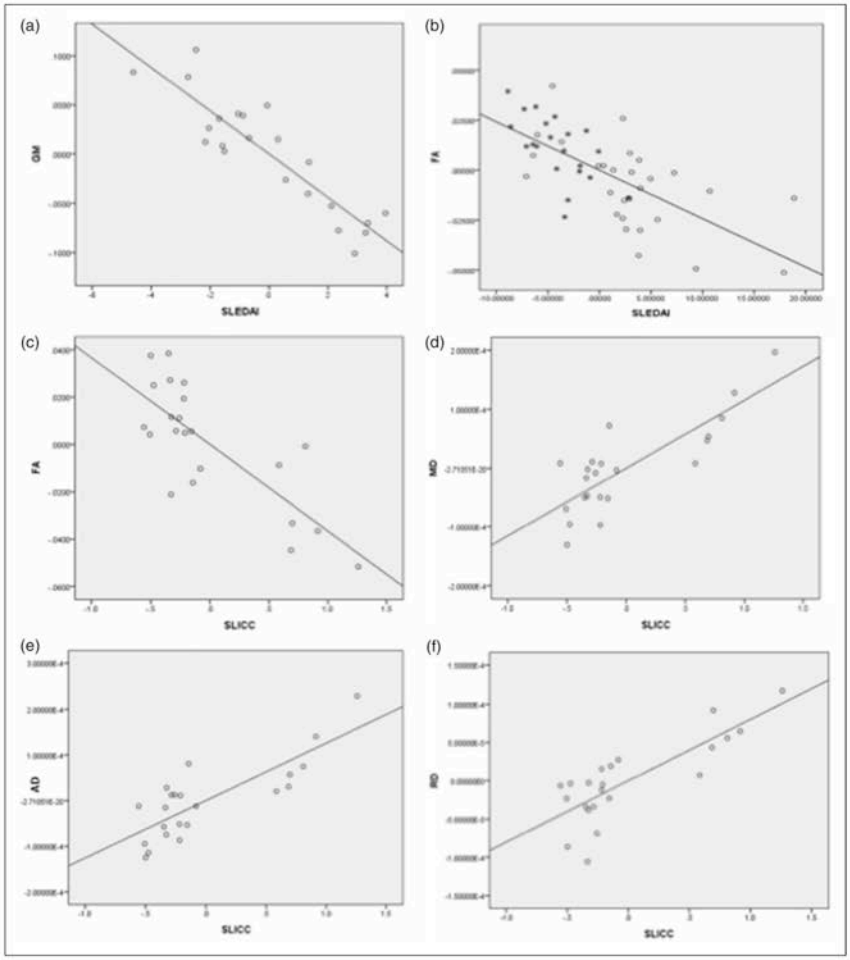

Figure 2 Correlations between VBM and DTI findings and clinical data. (a) Inverse correlation between GM mean volume in the significant clusters and the SLEDAI score in NPSLE patients after controlling for total intracranial volume and age ($r = -0.896$; $p < 0.001$). (b) Inverse correlation between the FA mean value in the significant clusters and the SLEDAI score in NPSLE and non-NPSLE patients, after controlling for total intracranial volume and age ($r = -0.685$; $p < 0.001$). (c) Inverse correlation between FA mean value in the significant clusters and SLICC score in NPSLE and non-NPSLE patients after controlling for total intracranial volume and age ($r = -0.779$; $p < 0.001$). (d) Positive correlation between the MD mean value in the significant clusters and the SLICC score in the NPSLE and non-NPSLE patients after controlling for total intracranial volume and age ($r = 0.817$; $p < 0.001$). (e) and (f) Positive correlation between the AD and RD mean values in the significant clusters and the SLICC score in NPSLE and non-NPSLE patients after controlling for total intracranial volume ($r = 0.809$; $p < 0.001$) and age ($r = 0.807$; $p < 0.001$).
AD: axial diffusivity; DTI: diffusion-tensor imaging; FA: fractional anisotropy; GM: gray matter; MD: mean diffusivity; NPSLE: neuro-psychiatric systemic lupus erythematosus; RD: radial diffusivity; SLEDAI: SLE Disease Activity Index; SLICC: Systemic Lupus Erythematosus International Collaborating Clinic; VBM: Voxel-based morphometry

DTI parameters). WMH did not correlate with atrophy. FA correlated positively with global cortical volume ($p < 0.001$). High MD, AD, RD and low FA correlated with cortical volume loss (right superior temporal WM: all DTI parameters ($p < 0.001$); right frontal WM: RD ($p = 0.003$); and left superior temporal WM: MD ($p = 0.008$); AD ($p < 0.001$) and RD ($p = 0.006$)).

Discussion

This prospective study correlating multimodal MRI findings with clinical data in NPSLE, non-NPSLE and healthy subjects found that NPSLE patients had brain volume loss, as well as increased diffusivity and decreased anisotropy. Moreover, the brain volume loss and DTI changes correlated with clinical parameters related to the activity, severity and time from disease onset. Interestingly, antimalarial drugs seem to confer protection against these brain changes.

We found no association between WMH and atrophy, suggesting probably different underlying mechanisms for them. Furthermore, we found no significant differences in WMH between the groups; this result contradicts those of some studies,[37,38] but agrees with another, more recent study.[16] WMH are nonspecific, and are frequently related to age, vascular risk factors and chronic diseases, including NPSLE, and are reported in up to 47% of healthy populations.[38]

Our results corroborate the findings of other studies, where atrophy involving the frontal and temporal GM or WM was a hallmark of NPSLE.[19,21,23] Previous studies also found that atrophy correlated with the time from onset.[19,30] Like Xu et al.,[29] we found that there was a correlation between WM volume and SLEDAI; however, we did not find greater WM volume in the patients treated with immunosuppressive drugs. In our data, atrophy correlated with complement deficiency (low C4 and low CH50), and this probably reflects complement consumption, supporting the immune-mediated pathogenesis mechanism put forth by other authors.[14,18] Thus, atrophy is probably the most important imaging biomarker for the diagnosis and prognosis of NPSLE.

Our results also corroborate the findings of other studies where DTI showed NPSLE patients having microstructural changes; with a higher MD, AD and RD, and lower FA, than healthy controls.[16–18,21,23,39] DTI abnormalities reflect a loss of WM density[40] and structural network.[41] In our study, DTI abnormalities were associated with atrophy and decreased cortical volume. The correlation between DTI abnormalities in WM and the regional loss of volume of adjacent GM suggested that the mechanism underlying atrophy could also induce the loss of axons and myelin, compromising white matter integrity. DTI parameters were also associated with time from SLE onset, SLEDAI and SLICC, so they could be useful for diagnosis and prognosis. Because the time from SLE onset, SLEDAI and SLICC correlate with volumetric and DTI data, these parameters could be considered risk factors for developing neuropsychiatric involvement in SLE and for greater severity in NPSLE. Another interesting finding was that patients on antimalarial drugs had lower diffusivity and less atrophy in some regions, suggesting that the antimalarials could have a protective effect. Clinical trials should be undertaken to explore this possible protective effect.

The potential limitations of this study included the size of the sample. Our strict inclusion criteria ensured a degree of homogeneity in each group, but did not preclude a mixture of treatment regimens in the SLE and NPSLE groups, making it difficult to directly compare those who had received antimalarial drugs and those who did not. Moreover, including neuropsychological tests might have helped us reach a better understanding of the clinical repercussions of the MRI findings.

In conclusion, brain atrophy and microstructural breakdown in WM and GM are the most important imaging biomarkers for the diagnosis and prognosis of NPSLE. Clinical trials should determine whether antimalarial drugs could prevent brain atrophy and WM damage.

Declaration of conflicting interests

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