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Acute non compressive myelopathies

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ACUTE NON COMPRESSIVE MYELOPATHIES

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Escribo esta tesis en tiempos revueltos; una época donde la pérdida de esperanza en este sistema galopante y apisonador parece ser el síntoma común de nuestra sociedad. Sistema que sacrifica el desarrollo social por el egocentrismo de unos pocos.
Al igual que en el deporte, al cual dediqué varios años de mi vida, en ciencia y en medicina, la plena constancia, dedicación y esfuerzo diario llevan al desarrollo personal y, por ende, al enriquecimiento de nuestra sociedad.
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,

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RESUMEN EN CASTELLANO

1 INTRODUCCIÓN

1.1 Mielitis transversa aguda idiopática: Definición y criterios según la Transverse Myelitis Consortium Working Group

La mielitis transversa aguda (MTA) no compresiva hace referencia a una inflamación de la médula espinal que deriva en manifestaciones neurológicas de comienzo agudo o subagudo en forma de pérdida de fuerza, alteración sensitiva o disfunción autonómica. Existen diversas causas que pueden ser el origen de una MTA. Las enfermedades desmielinizantes son la causa más frecuente de MTA, siendo la Esclerosis Múltiple (EM) su entidad más representativa. Otras entidades más infrecuentes como la Neuromielitis Óptica (NMO) o la Encefalomielitis Aguda Diseminada (ADEM) pueden comenzar en forma de mielitis longitudinalmente extensa (LETM), extendiéndose a lo largo de tres o más cuerpos vertebrales contiguos. Las enfermedades sistémicas autoinmunes como el Síndrome de Sjogren, el Lupus eritematoso sistémico, la Sarcoidosis, la Enfermedad de Behçet o el síndrome antifosfolípido son otro amplio grupo de enfermedades causante de MTA. Por último y con una incidencia menor, las MTA pueden ser secundarias a agentes infecciosos (entre ellos; herpes virus, Mycoplasma pneumoniae o Mybacterium tuberculosis), procesos vasculares (infartos espinales, fístulas durales o malformaciones arteriovenosas), embolismos fibrocartiloginosos, tumores intramedulares (ependinomas o astrocitomas) o síndromes paraneoplásicos (CRMP-5/CV-2, anfifisina, ANNA-2 o GAD) *(Jacob A, et al. 2008; Kitley J, et al. 2012).* *A pesar de un exhaustivo estudio etiológico, la causa no se llegará a identificar hasta en el 15,6% de los pacientes con un primer evento de MTA (MTAI). En el año 2002, la Transverse Myelitis Consortium Working Group (TMCWG) propuso unos criterios diagnósticos (**Tabla 1**), con el objetivo de unificar y homogeneizar este grupo de pacientes (TMCWG 2002).*

***Tabla 1**. Criterios diagnósticos de mielitis aguda transversa idiopática (MTAI)*

Inclusion criteria	Exclusion criteria
Development of sensory, motor, or autonomic dysfunction attributable to the spinal cord	History of previous radiation to the spine within the last 10 y
Bilateral signs and/or symptoms (though not necessarily symmetric)	Clear arterial distribution clinical deficit consistent with thrombosis of the anterior spinal artery
Clearly defined sensory level	Abnormal flow voids on the surface of the spinal cord c/w AVM
Exclusion of extra-axial compressive etiology by neuroimaging (MRI or myelography; CT of spine not adequate)	Serologic or clinical evidence of connective tissue disease (sarcoidosis, Behçet's disease, Sjögren's syndrome, SLE, mixed connective tissue disorder, etc.)*
Inflammation within the spinal cord demonstrated by CSF pleocytosis *or* elevated IgG index *or* gadolinium enhancement. If none of the inflammatory criteria is met at symptom onset, repeat MRI and lumbar puncture evaluation between 2 and 7 d following symptom onset meet criteria	CNS manifestations of syphilis, Lyme disease, HIV, HTLV-1, *Mycoplasma*, other viral infection (e.g. HSV-1, HSV-2, VZV, EBV, CMV, HHV-6, enteroviruses)*
Progression to nadir between 4 h and 21 d following the onset of symptoms (if patient awakens with symptoms, symptoms must become more pronounced from point of awakening)	Brain MRI abnormalities suggestive of MS*
	History of clinically apparent optic neuritis*

*Do not exclude disease-associated acute transverse myelitis.

AVM = arteriovenous malformation; SLE = systemic lupus erythematosus; HTLV-1 = human T-cell lymphotropic virus-1; HSV = herpes simplex virus; VZV = varicella zoster virus; EBV = Epstein–Barr virus; CMV = cytomegalovirus; HHV = human herpes virus.

1.2 Pronóstico funcional de los pacientes con una mielitis transversa aguda

Un tercio de los pacientes con un primer episodio de MTA no presentará secuelas o éstas serán ligeras, un tercio presentará un grado moderado de discapacidad y un tercio de los pacientes estarán confinados a una silla de ruedas según los estudios clásicos (Lipton HL, et al. 1973; Christensen PB, et al. 1990). La proporción de pacientes con un episodio de MTAI con mal pronóstico (incapacidad para la deambulación autónoma) se ha observado en el 35,8% de los pacientes en estudios que han evaluado mielitis bajo los criterios de la TMCWG (de Seze J, et al. 2005). Entre los factores asociados a un mal pronóstico funcional en pacientes con MTA se han descrito el dolor lumbar, el rápido comienzo de los síntomas, la alta frecuencia de recidivas, una mayor discapacidad o afectación motora al comienzo de los síntomas, la presencia radiológica de LETM y alteraciones neurofisiológicas como denervación en extremidades inferiores o anormalidad en los potenciales evocados sensitivo- motores. En pacientes con un primer episodio de MTAI según los criterios de la TMCWG 2002, una mayor discapacidad al comienzo de los síntomas, el shock medular y la presencia de LETM son los únicos factores descritos asociados a un mal pronóstico (de Seze J, et al. 2005; Bruna J, et al. 2006; Li R, et al. 2011) Otros factores moleculares como la proteína 14-3-3 o

la cistatina C han sido relacionados con mal pronóstico funcional en pacientes con un primer episodio de MTA (Irani D, et al. 2000; Gajofatto A, et al. 2010).

1.3 Esclerosis Múltiple y mielitis transversa aguda

La EM es la enfermedad crónica del Sistema Nervioso Central (SNC) más frecuente e invalidante en pacientes jóvenes de países occidentales. Se caracteriza por una afectación desmielinizante multifocal del SNC. En el 85% de los pacientes que desarrollarán EM, el comienzo clínico consiste en una afectación neurológica aguda o subaguda denominada síndrome neurológico aislado o " clinically isolated syndrome" (CIS) (Confavreux C, et al. 2000). La mielitis representa aproximadamente el 21% de los CIS y la manera de presentación más frecuente es en forma de inflamación medular parcheada e incompleta denominada mielitis transversa parcial aguda. El riesgo de conversión a EM en pacientes con un primer episodio medular varía entre 44 y 92%. Si se evalúan únicamente los pacientes sin lesiones cerebrales, la frecuencia disminuye hasta el 15-45% y, finalmente, hasta el 0-11% si se aplican los criterios de la TMCWG 2002 para IATM (de Seze J, et al. 2005; Bruna J, et al. 2006; Li R, et al. 2010). Los factores de conversión a EM descritos tras un primer episodio medular son la historia familiar de EM, el comienzo temprano de los síntomas, el género femenino, una mayor discapacidad o afectación sensitiva al inicio de los síntomas, la presencia de un índice IgG anormal (>0.7) o tener pleocitosis en líquido cefaloraquídeo (LCR), así como la localización posterolateral de la lesión medular por Resonancia magnética (RM). Sin embargo, los dos factores que mejor predicen la conversión a EM son la presencia de bandas oligoclonales (BOC) en LCR y la carga lesional en la RM cerebral (Sellner J, et al. 2008; Bourre B, et al. 2012; Ruet A, et al. 2011; Cordonnier C, et al. 2003).

La búsqueda de marcadores de conversión a EM es motivo de múltiples estudios. Sin embargo, estos marcadores continúan sin ser completamente dilucidados en pacientes con MTAI, debido en gran parte a su reducida incidencia y a la baja

probabilidad de conversión a EM tras los rigurosos criterios propuestos por la TMCW 2002.

1.4 Neuromielitis óptica y mielitis transversa aguda

La NMO es una rara enfermedad desmielinizante del SNC cuyos síntomas cardinales son la mielitis en forma de LETM y la neuritis óptica (NO). Entre estos pacientes, la LETM se observa hasta en el 45,6% como un primer episodio y hasta el 17,6% de los pacientes pueden presentar un primer episodio en forma de LETM y ON de manera simutanea. En 2004, el grupo de la Clínica Mayo describió el anticuerpo anti-aquaporina 4 (AQP4-ab) dirigido contra el canal AQP4 situado en los pies astrocitarios (Lennon V, et al. 2004). Hasta el 75% de los pacientes diagnosticados de NMO presentan este anticuerpo (Marignier R, et al. 2013). Desde su descripción, los pacientes con AQP4-ab y que presenten formas limitadas de NMO (episodios únicos o recurrentes de LETM y NO recurrentes o bilaterales simultáneas), formas óptico-espinales asiáticas de EM, NO o LETM asociadas a enfermedades sistémicas así como las NO o mielitis que presenten lesiones cerebrales típicas de NMO se engloban en el denominado espectro-NMO (NMOSD) (Wingerchuk D, et al. 2007).

La frecuencia de los AQP4-ab entre los pacientes con un primer episodio de LETM se ha descrito hasta en un 89% de pacientes, aunque dichas frecuencias son variables en función de los estudios (Kitley J, et al. 2013; Sepúlveda M, et al. 2013). Se han descrito ciertas diferencias entre los pacientes con un primer episodio de LETM positivos y negativos para AQP4-ab. Las principales se citan a continuación. Existe una predisposición hacia el género masculino, una edad de presentación más joven y una menor frecuencia de recidivas en los pacientes AQP4-ab negativos. Sin embargo, los pacientes AQP4-ab positivos presentan de manera más frecuente síntomas de tronco encefálico y una mayor discapacidad al inicio de los síntomas (Kitley J, et al. 2013; Sepúlveda M. et al. 2013; Hyun JW, et al. 2015; Iorio R, et al. 2013).

Los AQP4-ab son un importante marcador de recurrencia en pacientes con LETM y por tanto, de conversión a NMOSD (Weinshenker BG, et al. 2006). Aunque el índice de conversión a NMO es mayor en pacientes con LETM y AQP4-ab (83%), hasta el 25% de los pacientes negativos para AQP4-ab también convertirán a NMO (Iorio R, et al. 2013; Chang KH, et al. 2013).

1.5 Myelin oligodendrocyte glycoprotein (MOG) antibody y mielitis

La myelin oligodendrocyte glycoprotein (MOG) es una proteina transmembrana localizada en la vaina más externa de la capa de mielina. Esta proteína posee propiedades encefalitogénicas (Linington C, et al. 1988).

Actualmente y gracias a la utilización de técnicas de "Cell Based Assay", se puede detectar el anticuerpo contra la proteína MOG (MOG-ab) en su estado conformacional. Gracias a ello, los MOG-ab se han descrito fundamentalmente en pacientes pediátricos con ADEM así como en pacientes adultos diagnosticados de NMOSD (Baumann et al. 2015; Sato DW, et al. 2014; Höftberger R, et al. 2015). Entre estos últimos las frecuencias se han observados hasta en casi el 10%.

Los pacientes con NMOSD que presentan MOG-ab se caracterizan por ser más jóvenes al inicio de la enfermedad, tener una predominancia del sexo femenino y un comienzo de los síntomas en forma de NO y LETM de manera simultánea, comparado con aquellos pacientes con AQP4-ab o sin anticuerpos. Además, estos pacientes tendrán una enfermedad sin tendencia a la recidiva así como un mejor pronóstico funcional. Los pacientes con MOG-ab en suero presentan además una localización de la lesión más frecuente a nivel lumbar. Estos pacientes presentan, además, una tendencia a la resolución de la lesión medular objetivada por RM (Sato DW, et al. 2014; Höftberger R, et al. 2015).

Entre el 6 y el 7,5% de los pacientes diagnosticados de un primer episodio de LETM presentan MOG-ab en suero (Sato DW, et al. 2014; Höftberger R, et al. 2015; Hyun JW, et al. 2015). Un reciente estudio observó que estos pacientes eran más jóvenes y

con menor número de recidivas comparado con los pacientes con AQP4-ab. Los pacientes con MOG-ab tenían un mejor pronóstico funcional que los pacientes sin AQP4-ab ni MOG-ab en suero. Finalmente, una característica de estos pacientes fue la afectación de todos los segmentos medulares objetivada en la RM espinal (Höftberger R, et al. 2015).

2. HIPÓTESIS Y OBJETIVOS

Este estudio parte de la hipótesis de que existirían características específicas a nivel epidemiológico, clínico, de LCR y radiológico en pacientes con un primer episodio de MTAI que orientarían a predecir la conversión de estos pacientes a EM. Además, existirían algunas de ellas que ayudarían a identificar aquellos pacientes con evolución más tórpida y peor pronóstico funcional. La identificación de estas variables sería de vital interés para la realización de futuros ensayos terapéuticos en este tipo de pacientes.

Por otra parte, creemos que en pacientes con un primer episodio clínico de LETM existirían diferencias en las características epidemiológicas, clínicas, en LCR y radiológicas que permitirían su clasificación en los distintos subgrupos etiológicos. Además, el hallazgo de de estas características permitiría identificar aquellos pacientes que presentan un peor pronóstico en toda la cohorte y más específicamente en cada unos de los subgrupos etiológicos.

Finalmente, pensamos que una proporción de pacientes con un primer episodio de LETM seronegativa para AQP4-ab presentarían MOG-ab y podrían presentar hallazgos epidemiológicos, clínicos, de laboratorio y radiológicos diferentes de aquellos que son negativos para MOG-ab.

Los objetivos del estudio fueron, a) describir el ratio de conversión a EM y las variables asociadas a conversión en pacientes diagnosticados de MTAI según los criterios establecidos por la TMCWG, b) analizar los factores pronósticos y la discapacidad a largo plazo en pacientes con un primer evento de mielitis que cumplan los criterios de la TMCWG, 3) evaluar el espectro clínico de aquellos

pacientes que presentan un primer evento de LETM por RM y evaluar el pronóstico funcional de estos pacientes, 4) evaluar la frecuencia de MOG-ab en pacientes con un primer evento LETM seronegativa para AQP4-ab y describir las características clínicas de estos pacientes en comparación a aquellos que no presentan MOG-ab en suero.

3. METODOLOGÍA

El trabajo se divide en tres estudios; 1) Mielitis transversas agudas idiopáticas, 2) Mielitis longitudinalmente extensas y 3) MOG-ab en mielitis longitudinalmente extensas

La metodología de los dos primeros estudios es similar. Brevemente, se recogieron retrospectivamente los datos epidemiológicos (edad, género, estación de comienzo), clínicos (afectación de esfínteres, discapacidad al comienzo y al final del seguimiento), de LCR (BOC, índice IgG células, proteínas) y de RM craneal y espinal (número de lesiones localización, longitud de las lesiones, captación de gadolínio) de los enfermos que cumplían los criterios establecidos por la TMCWG 2002 entre los años 1989 y 2011 en el Hospital Universitario de Bellvitge. De ellos, se excluyeron aquellos que fueron positivos para AQP4-ab en suero. De la misma manera, se seleccionaron aquellos pacientes con un primer episodio de LETM independientemente de su enfermedad subyacente entre los años 1993 y 2011. Se definió LETM como sigue; 1) desarrollo de los síntomas durante no más de 21 días, 2) Hiperintensidad T2 en tres o más segmentos vertebrales contiguos, 3) síntomas bilaterales motores o sensitivos con o sin afectación de esfínteres, 4) RM cerebral disponible, 5) se excluyeron aquellos con irradiación espinal previa, compresión medular, historia de enfermedad neurológica y síntomas atribuidos a otra región distinta a la médula espinal. Para estos pacientes con LETM se definieron ocho variables etiológicas; 1) EM (definida y probable) de acuerdo con los criterios de Poser o McDonald, 2) ADEM, 3) NMO, 4) mielopatía parainfecciosa, definida por una prueba

serológica o de PCR de infección reciente en sangre o LCR, 5) enfermedad sistémica, definida por los criterios modificados de la American Rheumatism Association for Systemic Lupus Erythematosus y los criterios Vitali et al para Sjögren's syndrome, 6) infarto medular, definido por el comienzo agudo y anormalidades en la intensidad de la señal por RM correspondientes a un territorio vascular espinal sin otra etiología, 7) etiología tumoral o "tumor-related", 8) fístula dural, 9) idiopática con la presencia de ≥3 segmentos vertebrales demostrados en secuencias T2 por RM sin otra causa identificada tras un exhaustivo estudio.

Para la evaluación de la discapacidad se utilizó la modified Rankin Scale (mRS) con una categorización entre dos grupos: mRS < 2 y ≥ 2, para distinguir entre pacientes con buen y mal pronóstico, respectivamente. Los pacientes que conviertieron a EM fueron evaluados mediante la Expanded Disability Status Scale de Kurtzke (EDSS).

El tercer estudio es un estudio multicéntrico en el cual se incluyeron todos los pacientes diagnosticados de un primer episodio de LETM con AQP4-ab negativos en los hospitales universitarios de Toulouse, Lyon (Francia) y el Bellvitge (España). Los datos se introdujeron de manera prospectiva entre Enero del 2005 y Diciembre del 2014 en la "Database adapted from the EDMUS system" (Eugène Devic European Network, EDEN). Los criterios de inclusión se detallan en la ***Tabla 2****.*

Tabla 2*. Criterios de inclusión para LETM seronegativa para AQP4-ab*

1. Onset of symptoms between 4 hours and 21 days
2. Bilateral motor or sensory symptoms with or without sphincter dysfunction
3. Spinal cord T2 signal hyperintensity over three or more consecutive vertebral segments on MRI
4. Available brain magnetic resonance imaging study
5. Extensive work-up that reasonably exclude other diagnoses such as vascular, compressive, infectious, metabolic, paraneoplastic or radiation myelopathy
6. Tested for AQP4-ab in serum with a negative result

Se recogieron, al igual que en los dos primeros estudios, las variables epidemiológicas, clínicas, de laboratorio y de RM espinal y craneal. Se determimó los AQP4 y MOG-ab en los centros del Institut d'Investigació Biommèdica August Pi i Sunyer (IDIBAPS) de Barcelona y en el Centro de investigación de neurociencias de Lyon, como ya ha sido descrito (Höftberger R, et al. 2015; Marignier R, et al. 2013). Los pacientes se categorizaron en dos grupos EDSS ≤2,5 and EDSS ≥ 3 para la evaluación del pronóstico funcional.

Todos los estudios obtuvieron la aprobación de los comités de ética de los diferentes hospitales.

Para las variables categóricas se utilizaron X^2 o test de Fisher, para variables cuantitativas U de Mann-Whitney o t-test, según procediese. El análisis de las variables pronósticas se llevó a cabo con modelos de regresión logística y los análisis de supervivencia con análisis de Cox. Se utilizó el programa SPSS (versión 20.0) para los dos primeros estudios y STATA (64-bits) para el tercer estudio.

4. RESULTADOS

4.1 Primer estudio. Mielitis agudas transversas idiopáticas: pronóstico y conversión a Esclerosis Múltiple.

Se incluyeron 87 pacientes y dos de ellos fueron excluidos por presentar AQP4-ab. Ambos pacientes convirtieron a NMO. Tras un seguimiento de 2,9 años, el 13% de los 85 pacientes que cumplieron estrictamente los criterios de la TMCWG 2002 convirtieron a EM y el 87% permanecieron como MTAI. Se observó una LETM en el 30,6% de los pacientes y únicamente se objetivaron recidivas espinales en los pacientes del grupo de EM.

Al final del seguimiento, el 37% de los pacientes presentaron un mal pronóstico (mRS ≥ 2) y 9,4% fueron incapaces de deambular de manera independiente.

Los pacientes que convirtieron a EM presentaron un inicio de los síntomas a una edad más joven. Además, observamos que el 33% de los pacientes con una MTAI que presentaron BOC en LCR convirtieron a EM comparado con el 2% sin BOC, y que el valor predictivo negativo de la combinación de BOC negativas e índice IgG ≤ 0,7 en LCR era del 100%.

Los factores asociados a un mal pronóstico funcional fueron el presentar incontinencia urinaria y LETM por RM espinal al inicio del estudio.

4.2 Segundo estudio. Espectro etiológico y pronóstico de mielitis longitudinalmente extensas.

Tras la inclusión de 72 pacientes que cumplieron criterios de LETM y un seguimiento de 34 meses, la forma idiopática fue la etiología más frecuente (30,5%) seguido de la EM (25%). La etiología parainfeciosa se identificó en el 14,9% , Lupus Eritematoso Sistémico y Síndrome de Sjogren en el 12,2%. Otras etiologías como el infarto espinal y NMOSD se observaron en tres pacientes, y ADEM, fístula dural, y " tumour-related LETM" en dos pacientes cada uno.

Los pacientes con EM se caracterizaron por un inicio de los síntomas a edades más tempranas, con una menor discapacidad inicial y una menor frecuencia de afectación de esfínteres en comparación al resto de etiologías. Además, la presencia de BOC y una localización cervical en la RM espinal se relacionó con el diagnóstico de EM.

Al final del estudio, el 72,2% de los pacientes tenían un mRS ≥ 2, siendo la forma idiopática la más discapacitante. EL presentar una mayor discapacidad al inicio de los síntomas y una mayor edad fueron factores predictores de mal pronóstico funcional.

4.3 Tercer estudio. Anticuerpos anti-MOG en myelitis longitudinalmente extensa seronegativa para AQP4-ab: implicaciones clínicas y pronósticas

En el presente estudio, se incluyeron 56 pacientes diagnosticados de LETM seronegativa para AQP4-ab. Observamos que el 23% de los pacientes presentaron MOG-ab en suero. Los pacientes con MOG-ab positivos presentaron un inicio de síntomas más temprano, una mayor predisposición a NO y un mejor pronóstico funcional que aquellos con MOG-ab negativos. Además, una mayor proporción de pacientes con MOG-ab presentaron pleocitosis en LCR y una resolución completa de la lesión en la RM espinal comparado con los MOG-ab negativos.

Se objetivó que una mayor discapacidad al inicio del estudio se relacionó con peor pronóstico funcional y la presencia de MOG-ab se relacionó con un buen pronóstico funcional. Los pacientes con MOG-ab presentaron mayor riesgo de presentar NO y, por tanto, mayor probabilidad de convertir a NMO.

Al final del estudio, 10,7% convirtieron a NMO, 1,8% a EM, 16,1% presentaron recidivas de LETM y el 71,4% de los pacientes permanecieron como LETM monofásica.

5. DISCUSIÓN

5.1 Mielitis trasversa aguda idiopática

En el presente estudio observamos que únicamente el 9,4% de los pacientes fueron incapaces de deambular de manera independiente a diferencia de otros estudios donde la proporción es mayor (de Seze J, et al. 2005). Una de las posibles causas de esta diferencia puede ser que los pacientes fueron visitados en un centro de referencia produciéndose así un sesgo de selección. Una mayor discapacidad al inicio de los síntomas y la presencia de LETM se han relacionado a un peor pronóstico funcional en pacientes que cumplen los criterios de la TMCWG 2002 (de Seze J, et al.2005; Li R, et al 2011; Bruna J, et al.2006). En nuestro estudio, una mayor discapacidad al inicio de los síntomas se asoció a un peor pronóstico aunque perdió significación en el análisis multivariante.

La proporción de pacientes que convierten a EM en nuestro estudio es similar a lo descrito en otros estudio bajo los criterios de la TMCWG. Destacamos la utilidad de los parámetros de LCR en la predicción de conversión a EM ya que aquellos pacientes que no presenten ni BOC ni un índice IgG anormal en LCR muy probablemente no convertirán a EM. Al igual que lo descrito en otros estudios, el presentar los síntomas a edades menores se asoció a conversión a EM (Ruet A, et al. 2011).

En nuestra cohorte, dos pacientes presentaron un episodio de LETM y fueron exluidos al presentar AQP4-ab. Ambos pacientes convirtieron a NMO. Otros estudios señalan una mayor proporción de conversión a NMO tras un primer episodio de LETM (Chang KH, et al. 2013; Hyun JW, et al. 2014). De los pacientes que estrictamente cumplieron los criterios de la TMCWG, ninguno de ellos desarrolló una NMO, indicando que es una entidad rara en nuestro medio. Las técnicas de detección de los AQP4-ab, los criterios de inclusión de LETM así como las poblaciones genéticas incluidas entre los diferentes estudios pueden ser las causas de estas discrepancias.

En el presente estudio, nos llama la atención que únicamente aquellos pacientes que convierten a EM presentarán recidivas espinales. En nuestra opinión, es posible que diferentes mecanismos patogénicos aún no conocidos (ej, infecciones, anticuerpos patogénicos) sean los responsables de la presentación de LETM en forma monofásica.

5.2 Mielitis longitudinalmente extensas

La forma idiopática fue la etiología más frecuente al igual que se ha objetivado en diferentes estudios mediterráneos que describen frecuencias de entre el 40 y el 86% (Sepúlveda M, et al. 2013; Iorio R, et al. 2013). Otros estudios han descrito frecuencias menores (Kitley J, et al. 2013). Algunas causas que pueden explicar estas discrepancias son las diferencias entre los criterios de inclusión (algunos

pacientes incluidos presentaron episodios previos de afectación desmielinizante del SNC) o las diferencias proporciones en las poblaciones étnicas incluidas.

Pensamos que la alta prevalencia de EM en comparación a NMO en nuestra población puede ser el motivo por la cual la EM sea la segunda causa de LETM. Destacamos la edad temprana de comienzo de síntomas, la afectación cervical y la presencia de BOC en LCR como variables que nos deben hacer pensar en EM ante un primer episodio de LETM.

Como ya hemos mencionado, la presencia de NMOSD es rara en nuestra población. Aunque el test de AQP4 no se realizó a toda la población, ningún paciente presentó sucesivas recidivas de NO ni mielitis tras un seguimiento de tres años y por tanto no convirtieron a NMOSD.

Al final del estudio, el 72,2% de los pacientes tuvieron un mRS ≥ 2. Observamos una tendencia hacia un mejor pronóstico entre los pacientes cuya causa fue parainfecciosa como ha sido descrito en la literatura. Las mielitis secundarias a AQP4-ab o infartos medulares se han relacionado con un peor pronóstico (de Seze J, et al. 2001; Debette S, et al. 2009). Sin embargo, no fue posible comparar estos grupos dado el reducido número de pacientes

En nuestro estudio, una mayor discapacidad al comienzo de los síntomas y una mayor edad fueron factores de mal pronóstico funcional. El presentar una mayor discapacidad al comienzo de los síntomas se ha relacionado a un peor pronóstico en estudios centrados fundamentalmente ene LETM. Sin embargo, la mayoría de los pacientes incluidos en estos estudios presentaban una LETM idiopática y es por ello que no podemos directamente compararlos (de Seze J, et al. 2005; Sepúlveda M; et al. 2013).

5.3 Myelin oligodendrocyte glycoprotein en mielitis longitudinalmente extensas

Observamos que el 23% de los pacientes que presentaron un primer episodio de LETM seronegativa para AQP4-ab tenían MOG-ab en suero. Este porcentaje es

mayor que lo observado en la literaturas donde se han descrito frecuencias de hasta el 7,5% (Hyun JW, et al. 2015) La falta de consenso en la aplicación de criterios de LETM entre los diferentes estudios y el distinto perfil autoinmune que puede existir entre etnias, al igual que en los NMOSD y AQP4-ab, son las causas más probables de estas discrepancias (Marignier R, et al. 2013).

Al igual que en algunos experimentos en modelos animales donde se ha observado una resolución completa de las lesiones cerebrales después de dos semanas de la inmunización con MOG-ab, observamos que los pacientes con MOG-ab presentaron una resolución completa de las lesiones por RM espinal en comparación a aquellos que eran seronegativos para dicho anticuerpo (Saadoun S, et al. 2014).

Objetivamos que una mayor proporción de pacientes MOG-ab positivos presentaron pleocitosis en LCR, lo cual podría indicar una infección subyacente, al igual que ha sido observado en otras enfermedades con MOG-ab como el ADEM (Baumann M, et al. 2015).

El presentar una mayor discapacidad al inicio del estudio fue el único factor clínico asociado a un mal pronóstico funcional. Como se ha dicho con anterioridad, este dato se ha objetivado en algunos estudios que incluyen LETM (de Seze J, et al. 2005; Sepúlveda M, et al. 2013). Por otra parte, la presencia de MOG-ab en suero se asoció a un mejor pronóstico. Este últimos dato debe considerarse como preliminar y estudios prospectivos deben realizarse para confirmar nuestros resultados.

Por último, nos gustaría resaltar que cuatro pacientes presentaron un fenotipo clínico de NMO pero que sin embargo eran MOG-ab positivos. Este dato cuestiona la correcta clasificación de este tipo de pacientes bajo un fenotipo clínico y abre la puerta a una clasificación biológica en forma de "astrocitopatía" o "aquaporinopatía" y "oligodendrocitopatía" o "mogpatía", como ya han señalado otros autores (Zambil SS, et al. 2015).

6.CONCLUSIONES

Al final del primer estudio, el 37,6% de los pacientes diagnosticados de MTAI tuvieron un mRS ≥ 2 y el 9,4% no fueron capaces de deambular de manera independiente. El pronóstico funcional en los pacientes con MTAI fue peor en aquellos que presentaron afectación de esfínteres o LETM por RM espinal al inicio de los síntomas.

Objetivamos que hasta el 13% de los pacientes con diagnosticados de MTAI bajo los criterios de la TMCGW convirtieron a EM y que una edad de presentación menor se asocia a conversión a EM.

Hasta el 72,2% de los pacientes afectos de un primer episodio de LETM presentarán un mRS ≥ 2. Los factores que se asociaron a un peor pronóstico en pacientes con un primer episodio de LETM fueron una mayor discapacidad y una mayor edad al inicio de los síntomas. Mientras la causa más frecuente de LETM es la idiopática en nuestro medio, el diagnóstico de NMOSD entre estos pacientes es poco frecuente.

Los MOG-ab se encuentran hasta en el 23% de los pacientes que presentan un primer episodio de LETM seronegativa para AQP4-ab. Estos pacientes representan un subgrupo con hallazgos distintivos representados por una menor edad de presentación, mayor predisposición a NO y un mejor pronóstico funcional.

ABBREVIATIONS

Acute transverse myelitis (ATM)

Multiple Sclerosis (MS)

Cerebrospinal fluid (CSF).

Idiopathic ATM (IATM)

Transverse Myelitis Consortium Working Group (TMCWG).

Magnetic Resonance Imaging (MRI)

Neuromyelitis optica (NMO)

Aquaporin 4 antibody (AQP4-ab)

Acute partial transverse myelitis (APTM)

Acute complete transverse myelitis (ACTM).

Longitudinal extensive transverse myelitis (LETM)

NMO spectrum disorders (NMOSD)

Oligoclonal bands (OCB)

Clinically isolated syndrome (CIS)

Acute demyelinating encephalomyelitis (ADEM),

Plasma exchange (PLEX)

Central Nervous System (CNS)

Acute transverse myelitis associated with Multiple Sclerosis (ATM-MS).

Optic neuritis (ON)

Myelin oligodendrocyte glycoprotein (MOG)

Myelin oligodendrocyte glycoprotein antibody (MOG-ab)

Expanded Disability Status Scale (EDSS)

Sjogren's Syndrome (SS)

Systemic lupus erythematosus (SLE)

Behcet's disease (BD)

modified Rankin Scale (mRS)

Standard deviation (SD)

Interquartile range (IQR)

INDEX

1.- INTRODUCTION

1. INTRODUCTION

1.1 Historical aspects of acute transverse myelitis

1.1.1 First reports

Bastian HC (1837-1915, pathologist at St Mary's Hospital, London) was largely responsible for establishing and classifying the concept of transverse myelitis into two different nosologies; acute inflammatory myelitis and non-inflammatory acute myelitis. The former, he thought to be due to an infectious or an allergic mechanism, and the latter due to "blood changes and toxins often associated with feeble cardiac action, which may well act as causes of thrombosis in vessels of the spinal cord".[1,2] Vascular myelopathy was later confirmed by William Spiller when he reported the case of a patient who developed a tetraplegia within 24 hours after lifting 100-Ib. Spinal cord autopsy revealed a blood clot in the anterior spinal artery and a diagnosis of myelitis due to thrombosis was established.[3]

Spinal cord inflammation due to Smallpox vaccination was reported afterwards. Some authors hypothesized that a state dependent host susceptibility could be the initial cause of an immune mediated neurologic disease.[4] However, Frank Ford, in 1928, suggested that myelitis could be explained as a post infectious disease rather than as a direct attack of the virus to the spinal cord.[5] Over the next decades, several reports of post infectious myelitis due to measles or rubella were reported.[6-8] It was not until 1948 when the term "transverse myelitis" was proposed by an English

neurologist who described a case of rapidly progressive paraparesis with thoracic sensory level, occurring as a post infectious complication of pneumonia.[9]

1.1.2 Evolving concepts

Initial studies which established guidelines for diagnosis and prognosis of acute transverse myelitis (ATM) in a relatively large number of patients were reported in the seventies.[10,11] The authors' defined ATM as a progressive spinal cord dysfunction over a period of less than four weeks, with a well defined upper sensory level and without any compressive aetiologies or previous illness. At the end of the 20th century several criteria had already been proposed in order to clarify the ATM definition.[12-14] Others tried to identify factors related to functional outcome or to Multiple Sclerosis conversion (MS) after a first episode of ATM.[15-17]

The antecedent of the current criteria for ATM was proposed by the *de Seze J, et al*. who aimed to assess the different aetiologies comprising this entity as well as to report the prognosis.[18] Diagnosis criteria for ATM included acute or sub acute motor or sensory symptoms with or without sphincter dysfunction, a well defined sensory upper level, length of symptoms over no more than 3 weeks sustained at least 48 hours and no evidence of neither spinal compression by radiological imaging nor known history of neurological disease or symptoms. In this work, authors concluded that aetiologies could

be differentiated on the basis of clinical, brain and spinal cord imaging studies and cerebrospinal fluid (CSF). Most of the cases presenting with ATM were belong to the MS group (43%). Systemic disorders made up 16,5% of patients, spinal cord infarction 14%, infectious diseases 6%, delayed radiation myelopathy 4% and myelitis of unknown origin 16,5 %.

Soon thereafter, the current criteria for idiopathic ATM (IATM) were proposed by the Transverse Myelitis Consortium Working Group (TMCWG).[19]

1.2. Acute transverse myelitis

1.2.1 Transverse Myelitis Consortium Working Group Criteria

1.2.1.1 Proposed criteria

In 2002, the TMCWG proposed the diagnostic criteria for IATM in order to delimit and unify this group of patients (**Figure 1**).[19]

Figure 1. Idiopathic acute transverse myelitis criteria by the Transverse Myelitis Consortium Working Group. *(From the TMCGW 2002 criteria)*[19]

Inclusion criteria	Exclusion criteria
Development of sensory, motor, or autonomic dysfunction attributable to the spinal cord	History of previous radiation to the spine within the last 10 y
Bilateral signs and/or symptoms (though not necessarily symmetric)	Clear arterial distribution clinical deficit consistent with thrombosis of the anterior spinal artery
Clearly defined sensory level	Abnormal flow voids on the surface of the spinal cord c/w AVM
Exclusion of extra-axial compressive etiology by neuroimaging (MRI or myelography; CT of spine not adequate)	Serologic or clinical evidence of connective tissue disease (sarcoidosis, Behçet's disease, Sjögren's syndrome, SLE, mixed connective tissue disorder, etc.)*
Inflammation within the spinal cord demonstrated by CSF pleocytosis *or* elevated IgG index *or* gadolinium enhancement. If none of the inflammatory criteria is met at symptom onset, repeat MRI and lumbar puncture evaluation between 2 and 7 d following symptom onset meet criteria	CNS manifestations of syphilis, Lyme disease, HIV, HTLV-1, *Mycoplasma*, other viral infection (e.g. HSV-1, HSV-2, VZV, EBV, CMV, HHV-6, enteroviruses)*
Progression to nadir between 4 h and 21 d following the onset of symptoms (if patient awakens with symptoms, symptoms must become more pronounced from point of awakening)	Brain MRI abnormalities suggestive of MS*
	History of clinically apparent optic neuritis*

*Do not exclude disease-associated acute transverse myelitis.

AVM = arteriovenous malformation; SLE = systemic lupus erythematosus; HTLV-1 = human T-cell lymphotropic virus-1; HSV = herpes simplex virus; VZV = varicella zoster virus; EBV = Epstein–Barr virus; CMV = cytomegalovirus; HHV = human herpes virus.

1.2.1.2 Limitations in the current criteria

The TMCWG authors themselves noted several shortcomings regarding the elicited criteria.

Firstly, evidence of inflammation within the spinal cord was needed. The usefulness of Magnetic Resonance Imaging (MRI) and CSF in order to detect inflammation within the spinal cord was proposed by the authors as spinal cord biopsy was not a practical option. Gadolinium enhancement is a well known marker of blood barrier disruption,[20] and according to the authors, it should be present in patients with "definite IATM". Regarding CSF, pleocytosis (>5 cells/ml) or abnormal IgG index (>0,7) should be present, as well. In those patients who fulfill the IATM criteria with the exception of the inflammatory criteria, an MRI and lumbar puncture should be performed between two and seven days after the onset of symptoms. Nonetheless, the

spinal cord MRI of some patients fulfilling these criteria does not show gadolinium enhancement, having high signal T2-weight intensity instead. If it is not possible to demonstrate any evidence of CSF inflammation, patients should be classified as "possible IATM".

Secondly, the authors suggested that patients who develop symptoms over a period of less than four hours should be presumed to have an ischemic cause. However, as the authors pointed out, patients with ischemic myelitis could fulfill the time criterion for IATM and, therefore, they would be included.[21] Moreover, progressive myelopathies lasting less than 21 days could be included within the temporary range proposed by the TMCWG. The authors emphasized hereditary myelopathies, spinal cord tumors, dural arteriovenous fistules, or chronic forms of MS as main causes of progressive myelopathies.[22-24] TMCWG also noted that clinical history or gadolinium enhancement on MRI of spinal tumours could not differentiate them from IATM in some cases. Thus, they suggested starting with corticoids and to perform an imaging test shortly thereafter. If there is no decrease of gadolinium enhancement a biopsy should be done. Considering inflammatory myelopathies, some of them could clinically evolve over more or less than the time range proposed and they would be dismissed.

Thirdly, ATM could be the first symptom of a subsequent Neuromyelitis optica (NMO),[25] and a first episode of IATM could not be differentiated from NMO based on the current criteria. We must note that TMCWG proposed the

criteria before the aquaporin-4 antibody (AQP4-ab) marker to NMO was described.[26]

Finally, some authors have also criticized the proposed TMCWG criteria. *Scott TF, et al*. underlined the lack of distinction between acute partial (APTM) and acute complete transverse myelitis (ACTM). As the natural history between ACTM and APTM is significantly different, these authors defined alternative criteria to the current criteria proposed by the TMCGW.[27] They pointed out that ACTM refers to a complete o near complete disruption of function at the spinal cord level meanwhile APTM would be characterized by a patchy or grossly asymmetrical spinal cord dysfunction. The former would be associated to longitudinal extensive transverse myelitis (LETM) and would be related to the NMO spectrum disorders (NMOSD). The latter would be related to MS conversion, less frequency of oligoclonal bands (OCB) in CSF and less chance of relapse in the form of ATM.[28] The main difference between the Scott criteria and the TMCWG criteria is that in the former the evidence of CSF or MRI inflammation within the spinal cord is not mandatory compared to the latter. The authors also highlighted the lack of usefulness of the TMCWG criteria for characterizing patients from the outpatients neurology clinics. The criteria would exclude mild cases with APTM due to the fact that some of these patients will not undergo CSF or MRI in the clinical setting. Moreover, similar CSF or MRI results related to an inflammatory aetiology could be found between APTM and ACTM when prognosis and risk of MS conversion are significantly different between these two entities. Recently,

diagnosis and treatment guidelines of transverse myelitis have also emphasized the importance of classifying patients according to the complete or partial status in order to better identify the underlying aetiology and the relapse risk.[29]

1.2.2 Epidemiology

Reliable population-based studies estimating the incidence of ATM are limited. Two classical studies carried out in Israel and Albuquerque (New Mexico) yielded annual incidences for ATM ranging between 1,3 and 4,6 cases per million, respectively.[12,14] In the latter, the authors observed that IATM incidence was approximately 1,0 per million (21% among the whole ATM cohort). One study from the Kaiser Permanente Northern California (KPNC) patient database described an incidence of 3,1 per million (2,6-3,6 95% confidence interval).[30] Most recently, a multiethnic retrospective cohort study conducted by the same organization (KPNC) was performed in order to evaluate the incidence of clinically isolated syndrome (CIS) in a population of 9,0 million inhabitants. Herein, myelitis was observed in 34% of CIS cases (all ethnics included), corresponding to 22,6 per million in terms of annual incidence in Caucasians.[31] The only modern study focuses on IATM was carried out by a group from North Canterbury, New Zealand, in 2009. The overall incidence of ATM was 24,6 per million, decreasing to 6,2 per million in the group of IATM.[32]

Regarding gender, ATM was classically observed equal between men and women (ratios 1:1).[10,11,33] However, over the last few years, a trend towards female predominance has been observed in IATM studies fulfilling the TMCGW criteria (between 66% to 86%),[32,34,35] although some of them still disclose an equal proportion of cases.[36,37] Population-based health databases studying incidence of CIS reported that up to 65% of patients who develop ATM as a first manifestation of CIS were female.[31]

Bimodal peaks of distribution have been shown in older studies; ages between 10–19 and 30–39 years.[12-14] It seems that the mean age of the onset of the symptoms in patients with IATM ranges from 35 to 40 years, as has been observed in recent studies.[32,34,35,37] Only one study reported older ages of IATM with a mean of 59 years.[36]

1.2.3 Clinical management

The different ATM criteria applied through the last decades will mark clinical and prognostic aspects reported to date.

Transverse myelitis is characterized by a focal inflammation within the spinal cord resulting in acute and subacute clinical manifestations due to neural dysfunction of motor, sensory and autonomic pathways. In **Figure 2**, the clinical presentation of spinal cord disorders are represented.[38]

Figure 2. Clinical presentation of spinal cord disorders. *(From Jacob A, et al.)*[38]

Type of Lesion	Tracts Involved	Clinical Signs	Examples
Complete	All tracts	Pyramidal, sensory, and autonomic dysfunction* below lesion	Trauma or acute necrotizing viral myelitis
Brown-Séquard hemicord syndrome	Ipsilateral corticospinal, posterior columns; contralateral spinothalamic	Ipsilateral pyramidal weakness and loss of posterior column function; contralateral spinothalamic loss	Multiple sclerosis, compression
Anterior cord syndrome	Bilateral anterior horn cells corticospinal tracts, spinothalamic and autonomic	Acute bilateral flaccid weakness, loss of pain temperature and sphincter/ autonomic dysfunction; preservation of dorsal column modalities such as joint position sense	Anterior spinal artery occlusion
Posterior cord	Bilateral posterior columns	Bilateral loss of light touch, vibration and joint position	B_{12} or copper deficiency (usually chronic)
Central	Crossing spinothalamic, corticospinal, and autonomic fibers	Dissociated sensory loss (loss of pain and temperature with preserved vibration and joint position); pyramidal distribution weakness below lesion; autonomic dysfunction below the lesion	Syrinx, neuromyelitis optica
Conus medullaris	Autonomic outflow and sacral spinal cord segments	Early sphincter dysfunction, sacral sensory loss and relatively mild motor dysfunction	Post viral myelitis
Cauda equina	Spinal nerve roots of the cauda equina	Early often asymmetric flaccid weakness of the lower limbs, sensory loss in root distribution followed by autonomic dysfunction	Acute cytomegalovirus polyradiculitis, compression
Tractopathies	Selective tract involvement	Selective pyramidal, posterior column involvement	B_{12} deficiency, paraneoplastic myelopathy, multiple sclerosis

*Autonomic dysfunction: bladder, bowel, and sexual.

Prodromal symptoms often appears as the prelude of ATM within four weeks before the onset of ATM.[10-14,33,39] Studies carried out after the setting of TMCWG criteria point to a history of nonspecific previous infection or fever in 7,3-40% of patients,[37,40-42] and back pain up to 50%.[37]

Paresthesias or the sensation of numbness, both in the distal part of the lower extremities and the abdomen are usually described as the initial manifestation in ATM. A sensory level is documented in most of the cases and the thoracic level is affected in 50% to 80 % of patients.[10,32] Moreover,

studies performed after the TMCGW criteria have showed a wide range of variability in sensory impairment ranging from 17,5% up to 100%.[34,40,43]

Regarding pyramidal tract symptoms, a progressive ascending paraparesia starting in the lower limbs is usually observed and, although more uncommon, it could occasionally involve the arms. Spinal shock has being reported as an initial disabling symptom, as well. This severe state is characterized by lower limb arreflexia, flaccid paraparesia and spasticity developing 10 days after the onset.[11,13] The first study performed under TMCWG criteria observed that 37,8% of patients developed spinal shock after the first episode of ATM.[34] Tonic spasticity may follow the initial weakness and tonic involuntary spasms are often explained by patients. Motor symptoms in ATM range from 26,7% to 78%.[34,40]

Sphyncter dysfunction is a prominent symptom in ATM and is observed in a high proportion of patients (up to 94% in some series).[44] It comprises of a wide spectrum of symptoms; urge incontinence, incomplete retention, voiding difficulty or constipation are the main symptoms.[44,45] In the latest studies, between 26% and 67% of patients are reported to have sphincter dysfunction at the onset of ATM.[37,43] Sexual dysfunction is also observed in patients who develop an episode of ATM and includes erectile or ejaculatory dysfunction and difficulty to reach orgasm.[46]

It is usually observed that symptoms peak within the first ten days from onset. During this time, half of the patients are unable to develop any

movement in lower limbs and almost all patients present some degree of sensory or bladder dysfunction. However, symptoms may progressively worsen up to the first 21 days. These observations may vary depending on the criteria established.[13,16,37,39,43]

A moderate variety of depression could be a major neuropsychiatric symptom observed in patients with ATM (30%), although others such as anxiety, somatoform or neurotic disorders have also been reported.[47,48] Some authors have remarked on the importance of identifying depressive patients as suicide could represent up to 60% of deaths.[49] Moreover, cognitive impairment has been suggested in one study where a fifth of patients who suffer from ATM scored less than 23 in the Minimental Score Examination.[47]

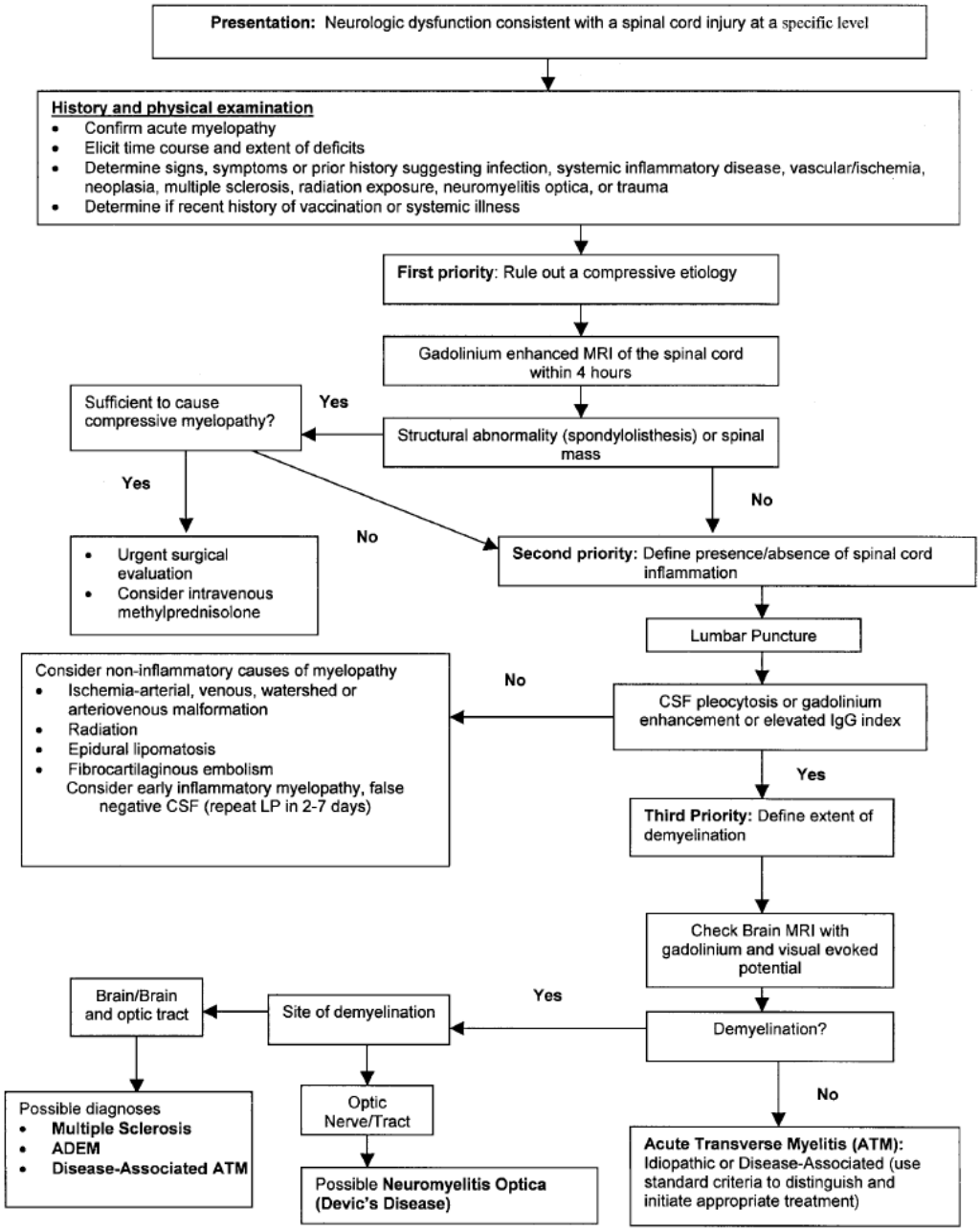
Finally, some patients may develop acute respiratory failure during the course of the disease due to upper cervical and brainstem affection. This affection may be potentially lethal for patients with ATM.[40]

1.2.4 Diagnosis

The diagnostic approach for evaluating patients with acute myelopathies specified herein is based on the TMCWG criteria. The differential diagnosis of ATM is wide and identification of the cause will inform us about the future clinical course as well as the prophylaxis treatment against future

neurological episodes. (**Figure 3** shows the diagnostic algorithm proposed by the TMCWG).[19]

Figure 3. Diagnostic algorithm proposed by the TMCWG. *(From the TMCWG 2002 criteria)*[19]



Before performing further additional medical tests, recognition of the clinical syndrome is the first step. The time scale of hours to days of neurological deficits, symmetric or asymmetric presentation along with a well defined truncal sensory level should promptly lead us to a spinal cord syndrome. Central signs of nervous system dysfunction such as hiperreflexia or Babinski sign are classically found in spinal cord syndromes. However, a flaccid weakness or global arreflexia could be observed as being part of spinal shock.

Ruling out compressive lesion is the priority in patients who develop a spinal cord syndrome. A spinal cord MRI with gadolinium contrast agent of the whole spinal cord should be performed within four hours from the onset of symptoms. Myelography Computerized Tomography is also recommended as a means to dismiss structural cause if no MRI techniques are available. As soon as the cause of compression is detected, neurosurgical evaluation should be carried out.

A lumbar puncture should be performed in order to document inflammation as a further step. The absence of pleocytosis or abnormal IgG index along with the absence of gadolinium enhancement in the spinal cord MRI leads to a non inflammatory aetiology. However, if any inflammatory data are present, a subsequent step is to determine whether demyelination extends beyond the spinal cord. Acute demyelinating encephalomyelitis (ADEM), MS and NMO are the main disorders to investigate and patients should undergo a brain MRI with gadolinium and visual evoked potentials.

If inflammation is confined to the spinal cord, ATM diagnosis is established and the underlying aetiology must be investigated. Medical, social and travel history as well as general examination are essential to identify the underlying disease (**Figure 4**).[19]

Figure 4. Work- up in suspected ATM. *(From the TMCWG 2002 criteria)*[19]

Indicative signs and symptoms	Suggested evaluation
Infectious etiology	
Fever	CSF Gram's stain and bacterial culture
Meningismus	CSF PCR: HSV-1, HSV-2, HHV-6, VZV, CMV, EBV, enteroviruses, HIV
Rash	CSF viral culture
Concurrent systemic infection	CSF acid-fast bacilli smear and tuberculous culture
Immunocompromised state	CSF HSV, VZV, and HTLV-1 antibodies
Recurrent genital infection	CSF anti-*Borrelia burgdorferi* antibodies
Symptoms of zoster radiculopathy	CSF VDRL
Adenopathy	CSF India ink and fungal culture
Residence in area endemic for parasitic infections	Chest radiograph
	Serology for antibodies to HSV, VZV, HTLV-1, *B. burgdorferi*
	Serology for hepatitis A, B, C, and *Mycoplasma*
	Consider serology for parasites
Systemic inflammatory disease (vasculitis, collagen vascular diseases, mixed connective tissue disease)	
Rash	Serum ACE
Oral or genital ulcers	Auto-antibodies: ANA, ds-DNA, SS-A (Ro), SS-B (La), Sm (Smith), RNP
Adenopathy	Complement levels
Livedo reticularis	Urinalysis with microscopic analysis for hematuria
Serositis	Lip/salivary gland biopsy
Photosensitivity	Chest CT
Inflammatory arthritis	Schirmer's test
Erythema nodosum	Chest radiograph
Xerostomia	Anti-phospholipid antibodies (anti-cardiolipin antibodies, Russel viper venom time, partial thromboplastin time)
Keratitis	
Conjunctivitis	
Contractures or thickening of skin	
Anemia/leukopenia/thrombocytopenia	
Raynaud's phenomenon	
History of arterial and venous thrombosis	
MS	
Previous demyelination event	Brain MRI
Incomplete deficit clinically with MRI abnormality ≤2 spinal segments and <50% of cord diameter	Evoked potentials
CSF oligoclonal bands	
Neuromyelitis optica (Devic's disease)	
Optic neuritis	Evoked potentials
Normal brain MRI	Brain MRI (usually negative)
	Presence of multiple autoantibodies, of the type listed above or others
Idiopathic transverse myelitis	
No clinical or paraclinical features suggestive of another diagnostic category	Evoked potentials Electromyography/nerve conduction velocity

HSV = herpes simplex virus; HHV = human herpes virus; VZV = varicella zoster virus; CMV = cytomegalovirus; EBV = Epstein–Barr virus; HTLV-1 = human T-cell lymphotropic virus-1; VDRL = Veneral Disease Research Laboratory; ACE = angiotensin-converting enzyme; ANA = anti-nuclear antibodies; ds = double-stranded; RNP = ribonucleoprotein.

1.2.5 Treatment

1.2.5.1 Goals of the treatment

ATM is a potentially severe disease with high rates of functional disability. Therefore, urgent treatment after the onset of symptoms is mandatory in order to halt the progression and initiate recovery from spinal cord inflammation.[50]

1.2.5.2 Corticosteroids

There are no placebo controlled trials and only few have evaluated the use of corticoids in patients presenting with ATM or spinal cord injury.[51,52] Thus, evidence of the use of these agents in myelitis derives from MS studies. Based assessment of corticoids in MS patients points out that corticoids shorten the recovery from attacks of MS without demonstrating long term benefits in the course of the disease.[53] Although common regimens use intravenous methylprednisolone (1g/24 h * 3 or 5 days), there is evidence that oral methylprednisolone could improve clinical and imaging parameters in a similar manner.[54,55]

Conflicting results have been reported in regards to corticoid treatment in ATM. Case series or retrospective studies have shown to be beneficial in pediatric populations.[56,57] The only prospective controlled based study performed in 21 patients (range of age between 12 and 70 years) revealed an apparently beneficial role of methylprednisolone in ATM (67% of patients in

the non- treated and 33% in the treated arm had poor outcome, respectively). However, such differences did not reach statistical significance.[51] Only Class IV existed concerning the utility of corticoids in treating ATM under the most recent based guidelines. It is concluded that although there is no sufficient evidence to determine the utility of corticosteroids in acute attacks of TM, they could be administrated in the clinical practice to hasten recovery, reduce disease activity and restore neurologic function.[29]

1.2.5.3 Plasma exchange

Plasma exchange (PLEX) has been proved to be a useful treatment in several antibody-mediated diseases. It has been implied in several immunological roles such as the non specific removal of toxins, antigens or humoral factors.[58] Meanwhile PLEX seem to have a potential beneficial effect in relapsing forms of neuroimmunological diseases such as MS or NMO,[59,60] it is not the case in progressive forms.[61]

A randomized double blind, placebo- controlled class II trial concluded that PLEX is a possible effective treatment for patients with acute Central Nervous System (CNS) demyelinating diseases that do not respond to a previous corticosteroids line.[62] However, this study did not conclude if PLEX was more or less effective in ATM patients due to the heterogeneity of the patients included. Recently, The Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology supported this

strategy in patients suffering ATM with a C level of evidence.[63] Others have noted that an early initiation of PLEX, better improvement on discharge, being male or preserved reflex increase the likelihood of improvement in response to PLEX in patients with CNS demyelinating diseases, including transverse myelitis.[64,65] Finally, only one retrospective un-controlled study regarding treatment has been carried out in patients who fulfill the current IATM criteria. This study included 122 patients with IATM and suggested that patients who do not reach the American Spinal Injury Association (ASIA) A level of disability at nadir will have a better outcome under a combination of PLEX and intravenous methylprednisolone, than intravenous corticoids alone.[66]

1.2.5.4 Intravenous immunoglobulins

Intravenous immunoglobulins have been widely used in neurological disorders as they are involved in the blocking of membranolytic attack complex, idiotypic antibodies or exert Fc region-mediated inhibition of antibody production, saturating Fc receptors and the suppression of inflammatory molecules such as metalloproteinasas and chemokines.[67]

There are no clinical trials concerning the use of intravenous immunoglobulins in ATM and most of the data come from MS or NMO trials. Considering MS, there are controversial results among randomized trials,[68,69] although it seems that intravenous immunoglobulins do not exert a beneficial effect in relapsing-remitting MS, as a multicentre double blind, placebo

controlled trial has showed.[70] No randomized placebo control studies have been performed in NMO patients although prospective studies and case series suggest a beneficial role in treating acute NMO relapses.[71,72]

1.2.5.5 Chronic complications and management

In the acute phase, physicians must carry out several stabilizing measures in order to avoid further acute or chronic complications. Mandatory approaches are respiratory or oropharingeal support derived from the bulbar damage. Rehabilitation is also important in order to improve tonic spasticity or motor weakness, as well as the placement of catheterism due to the urine retention or other symptoms derived from autonomic dysfunction such as constipation or bowel incontinence. Moreover, it is well known that neuropathic pain could be an initial uncomfortable symptom that deserves prior attention.[73]

In clinical practice, these interventions are based on observational studies coming from other neurological diseases. (Symptomatic treatment for ATM complications are shown in **Appendix 1**)

1.2.6 Prognosis

1.2.6.1 Functional outcome

Long term outcome varies widely from asymptomatic to wheel chair dependent or even death in a few proportions of patients. Classical studies reported that one third of patients had mild residual sequeale, one third had

a moderate degree of disability and lastly, one-third of patients were wheel chair dependent at the end of the follow-up.[10,13,39] In recent years, studies performed after the TMCWG criteria have shown similar prognostic rates. The proportion of IATM patients with poor outcome (inability to walk) has been observed up to 35,8%.[34-37,40]

Recovery usually begins within one to three months after the onset of symptoms and improvement can be observed up to two years.[74]

Fatal outcome has been classically reported in patients suffering from myelitis.[1] Death rates within the first year of the disease have decreased over the last decades from 14,7% to 4,8%.[10,40] Risk of death is most frequently a result from hospitalization itself and bed resting; namely pulmonary embolism or aspirative bronchopneumonia.[39] Less frequently, respiratory failure due to bulbar affection is reported in the acute phase.[40] The highest death rate has been related to myelopathies which are secondary to spinal cord infarction. However, deaths in this subgroup of patients have been reported after a long follow-up and are likely related to elderly and vascular risk factors than being directly related to the myelopathy.[75]

1.2.6.2 Prognostic factors associated with recovery

Clinical prognostic factors have been largely proposed in patients who present a first episode of ATM. Spinal shock, back pain, motor involvement, rapid progression of symptoms, relapse occurrence and severe functional deficit at nadir of symptoms have all been related to poor prognosis in older

studies.[10,11,13,39,43] Nonetheless, spinal shock and a higher Rankin score at the onset of symptoms have been the only independent factors related to poor outcome in patients who strictly fulfill the TMCWG criteria for IATM.[34,37]

Regarding MRI factors, an extensive spinal cord lesion over more than two vertebral segments has been related to a worse functional outcome both in classical and recent studies.[16,35,36,39]

Other studies have shown that neurophysiological findings could be implicated in ATM prognosis. Absence of motor or somatosensory evoked potentials and denervation in lower limbs muscles were proposed as the main variables indicating a worse outcome.[16,39,76]

Finally, molecular biomarkers suggesting a worse recovery after a first episode of ATM have also been described. CSF 14-3-3 protein was reported as a surrogate biomarker of short term to clinically defined MS conversion in patients with an initial demyelinating episode, including ATM.[77] Moreover, CSF 14-3-3 predicted little recovery and a higher disability at the end of the follow-up.[77,78] Others have failed to confirm the usefulness of the CSF 14-3-3 in both ATM and MS.[79] CSF Cistatyn C, a protease inhibitor of glial and neuronal cells, has been correlated to neurological disability in ATM patients who presented with at least one relapse of the disease.[43] Authors have suggested that CSF Cistatyn C might be an unfavorable prognostic factor of ATM. The same group did not replicate the findings regarding prognosis in a

further study although CSF Cistatyn C levels were significantly increased in IATM compared to CIS and non inflammatory disorders.[80]

1.2.7 Recurrent acute transverse myelitis

It is well known that recurrent ATM is related to demyelinating CNS conditions such as MS, NMO, ADEM or autoimmune systemic disorders.[18,81] Nonetheless, there are a proportion of ATM patients without an underlying cause who still develop further episodes of spinal cord inflammation. Relapsing forms of IATM were early reported on, suggesting a separate condition from ACTM or APTM.[17,82,83] Further on, some authors stated that idiopathic relapsing ATM forms underline differential findings from other CNS demyelinating disorders such ATM associated with MS (ATM-MS). Male predominance, absence of OCB in CSF and a higher number of relapses than ATM-MS were proposed to be distinctive features of idiopathic relapsing ATM.[84]

Serum AQP4-ab is a major risk of recurrence after an episode of ATM,[85,86] and most of the studies mentioned above were reported before this antibody was described. Therefore, idiopathic relapsing ATM patients could belong to NMOSD, as *Chan KH, et al.* suggested.[81] In the first study validating the current TMCWG criteria, *de Seze J, et al.* reported that up to 24% of patients fulfilling the TMCWG criteria for IATM followed a relapsing course (94,4% of them presented LETM on spinal cord MRI). However, the AQP4-ab test was

lacking in this study.[34] A subsequent study also carried out under the TMCWG criteria disclosed that 20 out of 29 patients (69%) diagnosed with IATM had a relapsing form. In this study, patients underwent the AQP4-ab test and six resulted in being positive.[35] A recent study analyzing 192 patients who initially presented with IATM under the current criteria revealed a 57% of recurrences after excluding AQP4-ab positive patients.[87]

Regarding relapsing risk factors, previous studies have identified some markers of recurrence. AQP4-ab is considered a consistent biomarker not only for recurrence but also for the diagnosis of NMOSD.[26,85] Moreover, relapsing ATM and, more specifically APTM, could be the beginning of a subsequent MS. OCB, abnormal IgG index in CSF and brain lesions on MRI at initial event of spinal cord inflammation are predisposing factors to develop MS and, therefore, a relapsing myelitis in this context.[88,89] A longer lesion extension at the first spinal cord MRI has been reported as an independent predictor for relapse in patients presenting with LETM.[90]

Serum biomarkers such as lower 25-hydroxivitamin D levels and the presence of anti-Ro (SSA) autoantibodies have also been significantly associated with recurrent spinal cord inflammation compared to the monophasic form.[91,92] Both biomarkers as well as OCB and an abnormal IgG index in CSF have been further confirmed as being risk factors for recurrent ATM in a recent study evaluating initial AQP4-ab seronegative IATM. In this study, authors described other variables associated with recurrence. Among demographic and clinical variables, African-American, female gender and

those presenting with LETM had a significant higher risk of myelitis recurrence. Regarding laboratory variables; pleocytosis and high titers (≥1:160) of antinuclear antibodies (ANAs) were also found to be related to recurrence.[92]

1.3 Acute transverse myelitis in demyelinating disorders

1.3.1 Multiple Sclerosis

1.3.1.1 Clinically isolated syndrome

MS is the most common chronic disabling disease of CNS in young adults in Western countries. This disorder is characterized by multifocal CNS demyelination whose diagnosis relies on objective dissemination in time and space.[93] In more than 85% of patients who later develop MS, clinical onset appears with an acute or subacute episode of neurological disturbance due to a single white-matter lesion. This presentation is known as CIS and usually consists of optic neuritis (ON), brainstem involvement or partial myelitis.[94] Patients who present with CIS are at a high risk of MS conversion. MRI and CSF findings have been shown to be the most valuable markers of MS conversion after CIS. Those patients with an initial abnormal brain MRI have a higher risk of conversion to MS than those with a normal brain MRI.[95] Moreover, the presence of OCB in CSF increases two-fold, the risk of having a second demyelinating attack.[96]

1.3.1.2 Clinical and paraclinical features

Myelitis represents up to 21% of CIS (spinal cord-CIS) and APTM is the major spinal expression of spinal cord lesions in MS.[97] Clinically, MS patients who develop an initial spinal cord demyelinating episode will present with clinical asymmetrical distribution.[17] Sensory disturbances are the most frequent symptoms described followed by motor weakness. Sphincter dysfunction is less frequent among spinal cord CIS patients.[17,89,98]

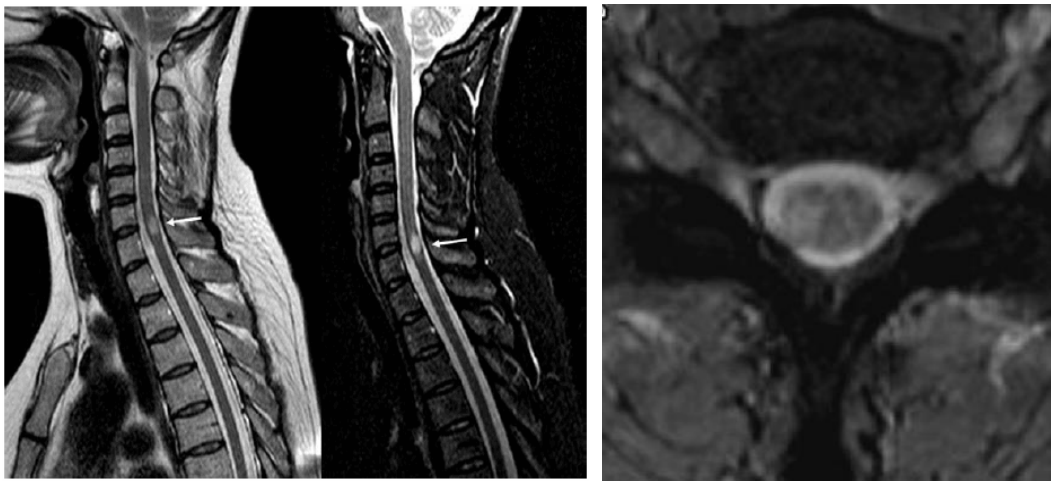
The presence of OCB in CSF has been described in the majority of spinal cord-CIS patients (57-92%).[17,88,89,99] One study described CSF inflammatory features (abnormal IgG index or OCB) in 74,8% of these patients.[98]

In one recent multicenter study, at least one brain MRI lesion was observed in up to 87% of patients who presented with spinal cord- CIS. This study and others have reported that up to 60% of these patients fulfilled the Barkhof criteria at first brain MRI.[89,99]

Spinal cord lesions in MS patients are characterized by a well– circumscribed focal T2 hyperintensity involving one to two contiguous vertebral segments (**Figure 5**). Spinal cord location in MS patients typically affects the cervical level (80%) the thoracic segment being less frequently involved (20%).[100] In the axial plane MS patients often present with lateral or posterolateral lesions. Moreover, MS lesions usually extend to less than one-half of the cross-sectional cord area.[101] Another distinctive radiological finding in MS patients is the trophy of the spinal cord, although this feature is usually

observed in progressive forms of MS and more rarely seen as a part of relapsing forms.[101] Moreover, at the time of the myelitis, some studies have shown that MS patients have more than one spinal cord lesion.[75,102]

Figure 5. Spinal demyelinating lesion in Multiple Sclerosis patient.



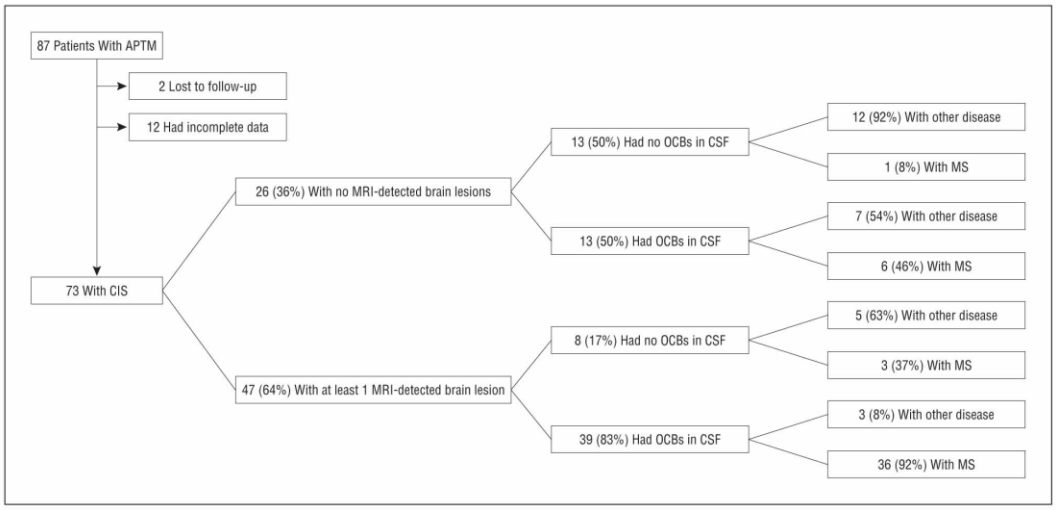
The conversion rate to MS after a first spinal cord demyelinating episode range between 43,8% and 92% in different studies.[17,88,89,98,99] The development of MS dramatically decreases to 15-45% if only ATM patients without brain lesions are evaluated.[28,88,99] Lastly, when the TMCWG 2002 criteria for IATM are applied, the conversion rate is even lower (0-11%).[32,34-37]

1.3.1.3 Prognostic factors of long term outcome

Some predictive factors for MS conversion from spinal cord- CIS have been identified. Among the demographic factors, family MS history, younger onset and female gender have been described.[37,88,98] Clinical features at onset of symptoms such as higher disability or sensory symptoms have also been reported.[88,99] Among CSF factors, the presence of OCB, abnormal IgG index or high cell count indicate a higher predisposition towards conversion to MS. Finally and considering MRI data, abnormal brain MRI and posterolateral location of lesions at first spinal cord MRI are described as predictive factors for conversion to MS in patients with a spinal cord CIS.[15,88,89,98,99,103]

Taken together, inflammatory CSF findings and brain lesions on MRI allow us to foresee MS conversion. One recent study evaluating MS conversion after a first event of APTM described conversion rates from 1,4% to 50% after a mean follow-up period of 8,7 years, when combining the presence of OCB in CSF and at least one brain lesion (**Figure 6**).[89]

Figure 6. Flow Chart of patients presenting with an initial acute transverse partial myelitis. *(From Bourre B, et al.)*[89]



Some studies have tried to find some variables associated with a poor term outcome in patients with a first spinal cord- CIS. One study found that a higher number of spinal cord lesions was related to higher disability.[99] However, another recent study was unable to identify any clinical, biological or MRI factors at onset of symptoms as predictive factors of long-term disability in spinal cord-CIS patients.[89]

1.3.2 Neuromyelitis optica spectrum disorders

1.3.2.1 Historical and evolving concepts in Neuromyelitis optica

NMO was originally described by Eugène Devic as a monophasic syndrome consisting of acute severe spinal cord inflammation and bilateral simultaneous or sequential ON in close temporal succession (1858-1930).[104] Eugene Devic and Fernand Gault reported another 17 patients with similar features soon thereafter.[105] Since then, a dilemma concerning the classification of NMO arose and NMO was regarded either as an MS subtype or as a separate entity. Several case reports came to light during the last century reporting patients with monophasic or a relapsing type of myelitis and simultaneous or subsequent ON.[106,107] NMO was classically recognized to evolve as a relapsing disorder that also included patients with unilateral ON and those with episodes of ON and myelitis occurring weeks or even years apart. The relapsing forms were related to a more severe disability than its monophasic counterparts. Regarding CSF findings, pleocytosis and the absence of OCB were frequently observed in NMO. In MRI studies, myelitis usually extends over three or more vertebral segments with diffuse abnormalities involving the cervical and thoracic spinal cord. Brain MRI was commonly reported as normal or nonspecific.[108,109]

A putative marker for NMO was described by the Mayo Clinic group in 2004. AQP4-ab were observed in patients with NMO diseases or at a higher risk of developing this disease such as monophasic LETM or recurrent LETM or ON. AQP4-ab reacts with the AQP4 channel at the astrocytic end-feet, the main channel regulating the water homeostasis in the CNS. The sensibility and specificity of this autoimmune maker was reported to be 73% and 91%,

respectively.[26] Building on this discovery, the same group proposed the current criteria for NMO (**Figure 7**).[25]

Figure 7. Neuromyelitis optica criteria*. (From Wingerchuk DM ,et al.)*[25]

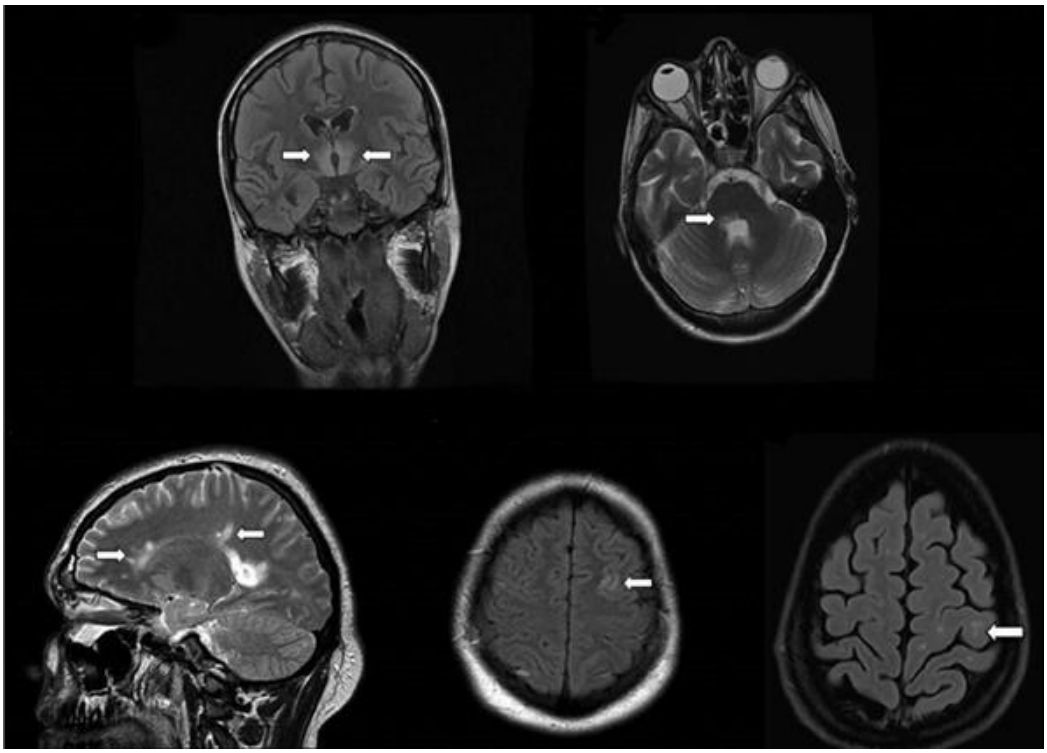
Definite NMO
- Optic neuritis
- Acute myelitis
- At least two of three supportive criteria
  1. Contiguous spinal cord MRI lesion extending over ≥3 vertebral segments
  2. Brain MRI not meeting diagnostic criteria for multiple sclerosis
  3. NMO-IgG seropositive status

Shortly thereafter, the clinical spectrum of NMO was proposed as follows: Idiopathic single or recurrent events of LETM, recurrent or simultaneous bilateral optic neuritis, optic neuritis of LETM associated with systemic autoimmune disease or myelitis associated with brain lesions typical of NMO. They also included the Asian optic-spinal form of MS.[110]

Substantial evidence, not only the discovery of AQP4-Ab but also clinical, laboratory and immunopathological data suggested that NMO disease is a distinctive entity from MS.[111,112] Although most of the classical features of NMO remain unchanged, subsequent extensive clinical experience revealed that MRI abnormalities may appear in up to 60% of NMOSD patients. New

findings may herald the onset of NMOSD and warrants particular emphasis such as hypothalamic disorders (narcolepsy and inappropriate antidiuretic hormone syndrome) and brainstem symptoms (intractable hiccup and nausea or vomiting).[113-117] (**Figure 8**)

Figure 8. Brain MRI findings in Neuromyelitis optic patients



A not depreciable proportion of patients who fulfill Wingerchuck criteria for NMO do not present serum AQP4-Ab despite the refinement of the methods.[118] Moreover, one study reported different epidemiological, clinical and radiological features in AQP4-Ab seronegative NMOSD from those who

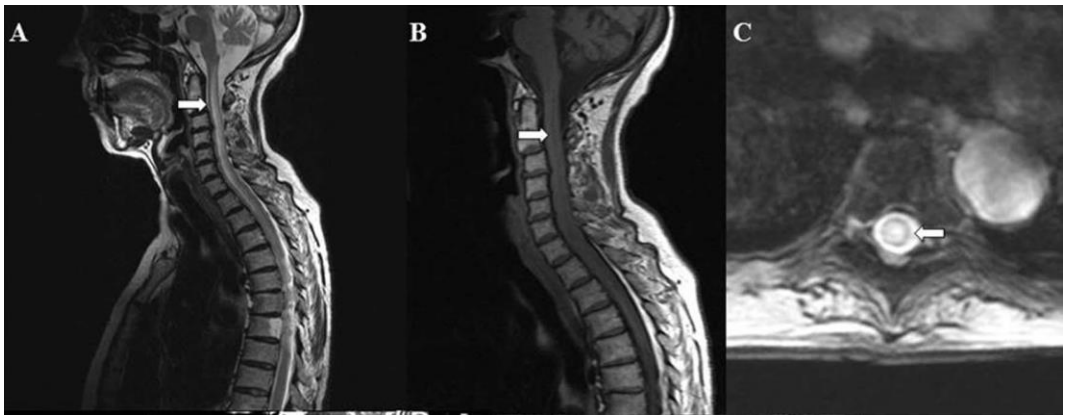
were seropositive. In seronegative NMO patients both genders were equally affected, Caucasians were the predominant ethnic group, concurrent ON and LETM at onset was more frequently observed and they developed a better visual acuity recovery compared to their seropositive counterparts.[119]

1.3.2.2 Myelitis as a first event of Neuromyelitis optica spectrum disorders

1.3.2.2.a Epidemiology and positivity for AQP4-ab

Myelitis, together with ON is a cardinal symptom in NMOSD. Although in the vast majority of cases the length of myelitis extends over three or more contiguous segments, at least 7,3% of patients could present with shorter lesions.[120] Among NMO patients, isolated LETM appears up to 45,6% as the initial manifestation and up to 17,6% of patients might present together with ON.[121] (**Figure 9**)

Figure 9. Longitudinal extensive transverse myelitis in NMO patient. A) T2-weighted hyperintensity, B) T1–weighted hypointensity, C) Centromedular NMO lesion



Divergent results have been obtained regarding the frequency of AQP4-ab seropositivity in LETM patients. Meanwhile some authors have reported AQP4-ab seropositivity up to 89%,[85,122-126] others have observed lower frequencies.[90,102,127,128] The causes of such discrepancies are still unclear although the most likely are selection bias (first-ever LETM vs LETM with history of ON or myelitis and collaborative multicentre studies vs hospital-based series), inclusion of different ethnic groups and different methods of AQP4-ab detection.

1.3.2.2.b Extensive myelitis with and without aquaporin- 4 antibodies (**Appendix 2**)

Different epidemiological data have been reported between those patients who present with a first AQP4-ab seronegative LETM and those who are seropositive; male predominance seems to be related to seronegative patients in most of the studies.[122,124,125,127] Moreover, contradictory results have been described regarding age of presentation; while some studies have described a younger age of presentation in AQP4-ab seronegative patients,[125] others have described an older onset.[124] Regarding clinical findings, brainstem symptoms such as nausea and vomiting or paroxismal tonic spasm were associated with the seropositive form.[115,125] These patients might also present with a more severe onset of symptoms.[124,128] Although a lower relapse rate is clearly related to AQP4-ab seronegative LETM, a better recovery at the end of follow-up has only been reported in one study.[123]

Among studies, other differences between both groups have been described with less consistent results. In relation to laboratory features, less proportion of abnormal IgG index and pleocytosis have been related to AQP4-ab seronegative LETM,[123,124] as well as less coexistence of autoimmune antibodies.[124,125] Considering MRI features, AQP4-ab seropositive patients have been found to show more white matter lesions on brain MRI.[122,124] After excluding myelin oligodendrocyte glycoprotein (MOG) antibody (MOG-ab) seropositive LETM, a recent study observed that AQP4-ab seropositive patients had more contiguous vertebral segments affected than seronegatives.[124] Moreover, this and another study observed that hypointense lesions on T1- weightened spinal cord MRI were related to the seropositive group.[122,124] Location of the spinal cord lesion may be another distinctive feature between groups. Central grey matter involvement has been related to AQP4-ab seropositive patients and a spinal cord involvement at a lower level (*conus medullaris*) to seronegatives.[122,123,125] Other paraclinical data such as visual evoked potentials have shown a delay latency in AQP4-ab seropositive patients compared to seronegatives.[128]

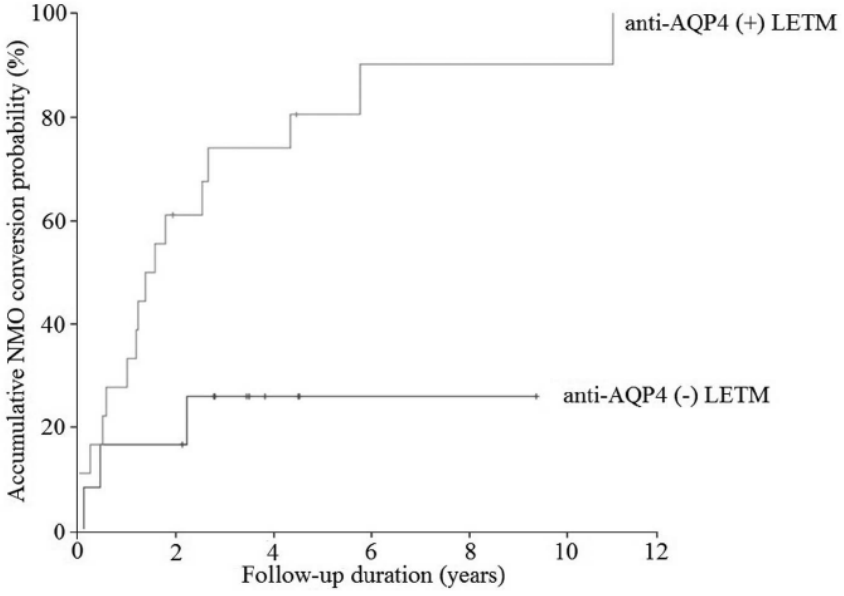
1.3.2.3 Conversion rate to Neuromyelitis optica after a first extensive myelitis

Patients who present with a first episode of LETM are at a high risk of recurrence and NMOSD conversion.[25] In a prospective study, 21,7% of patients who present with a first episode of LETM developed NMOSD.[85] Other

studies focused on LETM have reported between 20% and 60% of converters to NMOSD.[122,123,127] Importantly, AQP4-ab is a predictive marker of recurrence and therefore, a marker to NMO conversion. Although NMO conversion is higher in AQP4-ab seropositive LETM patients (up to 83%),[85,122,123] AQP4-ab seronegative LETM may also convert to NMO or develop recurrences in up to 25%.[85,122,123] (**Figure 10**)

Figure 10. Survival analysis comparison of the risk of developing NMO between AQP-4 and AQP-4negative LETM. (*From Chang HK, et al.)*[123]

AQP4-ab positive (n=18) vs negative (n=12), p=0,001



1.3.2.4 Treatment

Long-term treatment in limited forms of NMOSD remains unclear. A panel of experts has set up a scheme depending on the clinical course and the AQP4-ab serostatus. Hence, patients presenting with AQP4-ab seropositive LETM will need immunosuppressant due to the high risk of NMO conversion. However, it is not the case in AQP4-ab seronegative LETM where we should individualize the treatment. The panel do not recommend beginning with immunosuppressive agents unless the attack is severe or the recovery is poor.[129]

The overall rationale of NMO therapy is to decrease disability by improving acute events. Following this aim, several immunosupressants have been used in order to prevent or minimize further attacks of NMO.

The panel recommends Azathioprine as a first line therapy.[129] This purine synthesis inhibitor which interferes with lymphocyte proliferation, was analyzed in a retrospective study showing a reduction in the annual relapse rate over a median treatment of 22 months.[130] Azathioprine takes up to three months to exert its beneficial effect and an initial combination with oral prednisolone may be useful. One prospective study showed a sustained Expanded Disability Status Scale (EDSS) improvement and absence of relapses by combining Azathioprine and this corticoid.[131] Recommended doses of Azathioprine are 2,5-3 mg/kg/day and with prednisone being gradually reduced, should be considered after two or three months. A further

first line therapy is Rituximab.[129] Rituximab is a chimaeric anti-CD20 monoclonal antibody whose main function is to deplete naive and memory B cells. Multiple surrogate doses and time intervals have been used. The two most recommended options are four weekly doses of 375mg/m^2 or a 1000 mg infusion with a 2 week interval between the infusions followed by re-infusions after 6-12 months. However, in some studies Rituximab was administered depending on the circulating B-cell number. This treatment has shown to be very useful in NMO by reducing both the annualized relapse rate and the EDSS.[132,133]

As a second line therapy the panel recommends Cyclophosphamide (7-25 mg/kg every month over a period of 6 months), Mitoxantrone (12 mg/m^2 every three months for nine months) and Mycophenolate mofetil (1/3 g day). In addition to their use as an acute therapy, oral corticosteroids and plasma exchange may be used as a chronic treatment. Finally, intravenous immunoglobulins may be used as an additional treatment.[129]

1.3.2.5 Functional outcome

Functional outcome in patients with LETM largely depends on the final diagnosis.[125,127] Before the AQP4-ab description, *de Seze J, et al*. observed that 94% of patients diagnosed with IATM under the TMCWG criteria had an extensive lesion on MRI. This study reported that 35,5% of the whole cohort were unable to walk at the end of the follow-up.[34] After the discovery of AQP4-ab, few studies have focused on LETM prognosis. Although AQP4-ab

have been related to a higher risk of relapse, most of the studies did not show differences regarding disability between AQP4-ab seropositive and seronegative LETM.[124,125] Only one study reported a worse outcome in AQP4-ab seropositive LETM patients compared to seronegatives.[123]

Inability to walk independently was observed in 35% and 6% of patients among AQP4-ab seropositive and seronegative LETM, respectively.[125] Another recent study involving 23 LETM patients (only two patients tested positive for AQP4-ab) disclosed that 13% remained wheelchair dependent meanwhile more than half recovered with minimal disability.[90]

Although there is not much data regarding mortality in LETM patients, one study whose aim was to distinguish clinical and paraclinical features between AQP4-ab positive and negative LETM patients, reported that 5 (all of them were AQP4-ab positive) out of 76 patients died after a median follow- up of five years.[125]

1.3.2.6 Prognostic factors associated with recovery

Only one prospective study has focused on clinical factors associated with prognosis in LETM patients, so far. In this study, EDSS at nadir was predictive of the final functional outcome.[90] Another study also reported that EDSS at nadir was associated with a worse clinical outcome in most of the patients (94%) including those presenting with LETM.[34]

1.3.3 Acute demyelinating encephalomyelitis

1.3.3.1 Concept and current criteria

ADEM is a symptomatic diffuse or multifocal CNS inflammation typically observed in paediatric patients.[134]

ADEM is commonly preceded by a non-specific infection or febrile state in up to 74% of patients. In most of the cases, a precedent respiratory infection has been described. Moreover, ADEM can also develop after several different vaccines, namely measles, mumps or rubella vaccination. Latency between prodromal infectious symptoms or vaccine administration and ADEM onset may vary from any time between 14 days and three months.[135] On the basis of the above data, some authors suggest that molecular mimicry may be responsible for the acute demyelination observed in ADEM.[136]

ADEM patients presented with a polysymptomatic picture at onset of symptoms; headache and fever, ataxia, altered mental state or brainstem symptoms such as opthalmoplejia, dysartria or dysphagia are the most frequent ones observed.[134,137] However, other clinical symptoms may be observed such as ON or motor weakness (13 and 23% of patients, respectively).[137] The clinical course of ADEM is acute and symptoms peak over few days.[135] In **Table 1**, current ADEM criteria are shown.[138]

Table 1. International Pediatric Multiple Sclerosis Study Group criteria for ADEM.

Monophasic ADEM
• A first polyfocal, clinical CNS event with presumed inflammatory demyelinating cause • Encephalopathy that cannot be explained by fever • No new clinical and MRI findings emerge three months or more after the onset • Brain MRI is abnormal during the acute (three-month) phase. • Typical of brain MRI: - Diffuse, poorly demarcated, large (>1–2 cm) lesions involving predominantly the cerebral white matter - T1 hypointense lesions in the white matter are rare - Deep grey matter lesions (e.g. thalamus or basal ganglia) can be present

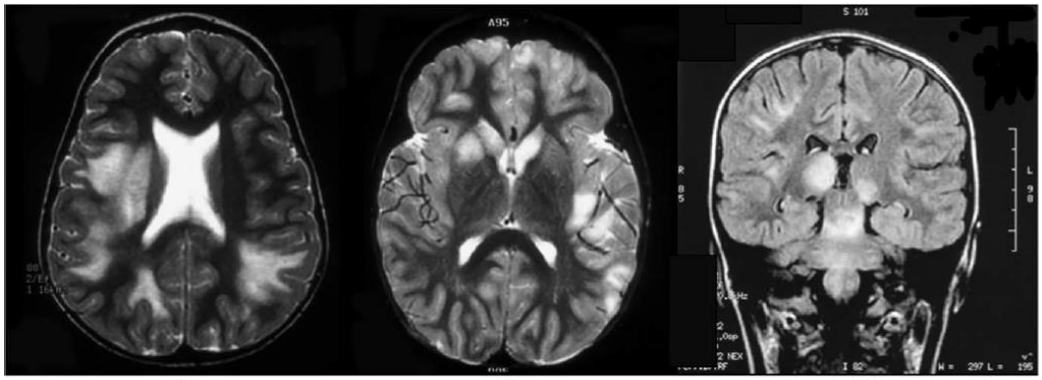
Multiphasic ADEM
• A new event of ADEM three months or more after the initial episode that can be associated with new or re-emergence of prior clinical and MRI findings. Timing in relation to steroids is no longer pertinent

Although there are some controversies about the possibility of recurrences in ADEM, there is a proportion of patients who will present further relapses (between 25-33%).[139,140] These patients will be considered as having multiphasic ADEM if the two episodes are separated by three months but no followed by further episodes. Moreover, if no alteration of consciousness is observed, MS or NMO will be considered as the probable cause.

1.3.3.2 Paraclinical features

Radiological features of ADEM are non specific although brain MRI usually shows both hemispheres asymmetrically affected by multifocal, widespread and extensive white matter lesions. In one study, thalamus, basal ganglia and brainstem lesions were often present (32,4% and 42%, respectively).[137] Although less frequently observed, spinal cord lesions are present in up to 28% of patients.[134] The length of the spinal cord lesion length is usually more extensive in ADEM patients than in IATM. One study reported that up to 92% of ADEM patients had extensive lesions on spinal MRI and 29% of them had gadolinium enhancing lesions.[141] (**Figure 11**)

Figure 11. Radiological lesions in ADEM patients



CSF findings reveal evidence of inflammation with pleocytosis or raised proteins in most of the cases. OCB and abnormal IgG index in CSF are usually absent.[134,135]

ADEM prognosis remains quite variable due to the differences in patient inclusion among different studies. If most of the studies are considered together, two thirds of patients have a complete recovery.[142] One recent study of 33 paediatric ADEM patients reported that 90,1% presented a recovery with minor neurological signs after a mean follow-up of 9,2 years.[140]

1.4 Acute transverse myelitis in connective disorders

1.4.1 Sjogren's syndrome

Sjogren's Syndrome (SS) is an autoimmune disorder characterized by mononuclear infiltration and predominantly the destruction of the lachrymal and salivary glands leading to xerostomia and xerophthalmia. However, this disorder may involve other visceral organs such as CNS. Pathology in SS could be produced by the disease itself or secondary to other connective diseases such as systemic lupus erythematosus (SLE) or arthritis.[143]

Neurological complications have been observed between 20-25% of SS cases.[144] Moreover, in the largest retrospective study performed to date reporting 82 SS patients with neurological symptoms, 56% of them had CNS involvement ranging from symptomatic white matter lesion on brain MRI to focal or multifocal neurological symptoms such as ON or transverse myelitis. In this study, myelitis was diagnosed in 35,4% of patients and for 61% of these patients the spinal cord involvement was the first SS manifestation.[144]

Clinically, myelitis in SS is often severe with sphincter dysfunction and para or tetraparesis.[144] Regarding radiological features, LETM has been observed in up to one third of cases. Cervical region was the most commonly affected (82% of myelitis patients) and half of them showed a centromedular location in the axial plane.[144] In contrast with these results, one South-Korean study described a higher frequency of extensive lesions with a mean length of 7,6 vertebral segments on MRI. In this study, all but one SS patients with myelitis also had NMO.[145]

1.4.2 Systemic lupus erythematosus and antiphospholipid syndrome

SLE is a multisystem autoimmune disorder of the connective tissue which involves CNS in 56% of patients.[146] Neurological deficits range from headache and visual alterations to seizures, psychosis and stroke. Myelitis is estimated to affect 1-2% of patients with SLE.[147] ATM often appears within five years from the diagnosis of SLE but may be the initial manifestation in up to half of them.[148] Typically, the spinal lesions extends to more than three contiguous vertebral segments.[149]

In one of the largest retrospective studies focussing on SLE with myelitis, sensory deficit was the most frequent initial symptom, followed by motor deficit and urinary sphincter dysfunction. Herein, almost 20% of patients presented with recurrences during the follow-up. Regarding the MRI findings, LETM was most frequently localized in the cervical and mid-lower thoracic spinal segments.[149]

Two different patterns of myelitis affection in SLE patients has been recently described;[150] a grey matter syndrome characterized by rapid and severe onset with poor recovery and a white matter syndrome with a mild paraparesis and better recovery. The former was mainly monophasic and AQP4-ab were present in 12,5% patients meanwhile the latter was relapsing with AQP4-ab in 57% of the cases.

Few studies have focused on prognostic factors in SLE with myelitis. One recent report described that one third of patients presenting with SLE and

myelitis had unfavorable outcome after six months of follow-up. The initial severity of symptoms was the main prognostic marker of the outcome.[151]

Antiphospholipid antibodies are target proteins that interact with phospholipids present in the plasma membrane of cells whose function is the blood clotting cascade regulation. Thus, antiphospholopid antibodies and in particular lupus anticoagulant, anticardiolipin and anti Beta-2 glicoprotein-1 antibodies could be potential direct contributors to CNS lesions. Some authors have suggested that these antibodies might play a critical role in ATM pathogenesis due to vascular injury secondary to vasculitis and hypercoagulablitiy.[152] Although ATM due to antiphospholopid syndrome is rare, one study observed that 73% of SLE patients who presented with myelitis, tested positive for antiphospholopid antibodies.[153]

1.4.3 Behçet's disease

Behcet's disease (BD) is a multisystemic chronic, relapsing inflammatory disorder of unknown etiology which may affect CNS, besides the mucocutaneous and ocular involvement. Although the prevalence of neurological affection in BD depends on geographical distribution, it has reported to be between 2-44%.[154] The most commonly affected CNS areas in BD are brainstem and basal ganglia whereas the spinal cord is less often involved. One recent study reported spinal cord lesions in 11% of BD patients.[154] Spinal lesions in BD are characteristically multifocal and may enhance gadolinium.[155] Some patients may develop extensive spinal lesions

which may even extend to the whole spinal cord.[156] The functional outcome in BD patients presenting with myelitis can lead to a bad prognosis and is even worse compared to those who present with involvement in other CNS regions.[155]

1.4.4 Sarcoidosis

Sarcoidosis is a multisystemic granulomatous disease of unknown aetiology affecting mainly the respiratory system. Sarcoidosis may be the cause of CNS affection in approximately 5% of cases. However, spinal cord involvement in Sarcoidosis is rarely observed. It may appear in the form of arachnoiditis, extradural or intradural lesions, and intramedullary involvement.[157]

In one of the largest retrospective series published on spinal cord involvement among Sarcoidosis patients, most of the lesions observed were extensive with a mean length of six vertebral contiguous segments. Lesions were heterogeneous with central distribution in the axial plane. During the follow-up, one third presented with relapses, one third remained monophasic and one third had a progressive course. In this study, most of patients presented sequelaes at the end of the follow-up.[158]

1.4.5 Neuromyelitis optica and connective diseases overlapping

NMOSD and connective disorders such as SLE or SS have been proposed to be overlapping disorders. Some authors have suggested that AQP4-ab might be the underlying pathogenesis of these autoimmune diseases. Moreover, the

fact that AQP4-ab positive NMO patients have a higher frequency of non-organ specific autoantibodies than seronegatives, supports the notion of an underlying autoimmune predisposition in the former group.[159]

AQP4-ab mediated NMOSD with AQP4-ab have also been related to other diseases such as Myasthenia Gravis or myopathy.[160,161]

1.5 Infectious diseases and postvacunal acute transverse myelitis

Infectious and parainfectious diseases may trigger demyelinating spinal cord lesions. Among them, the herpes virus family (virus herpes simplex, varizela herpes virus and Citomegalovirus) and VIH virus are the most commonly involved. Bacterial (*Treponema pallidum*, *Mycobarcterium tuberculosis* and *Borrelia burgdorferi*) or parasites such as *Schistosomiasis* are more rarely observed. Fever, meningismus, rash, an immunocompromised state or recurrent genital infections may suggest an specific aetiology.[162] (**Figure 12**)

Figure 12. Infectious agents involved in myelitis. (*From Jacob A, et al.*)[38]

	Specific Agents	
Viruses	**DNA Viruses**	**RNA viruses**
	Herpesviruses	**Flaviviruses**
	Herpes simplex virus-2*	Dengue virus
	Varicella-zoster virus*	Japanese encephalitis virus†
	Cytomegalovirus*	St. Louis encephalitis virus
	Human herpes viruses 6 and 7	Tick-borne encephalitis virus†
	Epstein-Barr virus[36]*	West Nile virus†
		Orthomyxoviruses
		Influenza A virus
		Paramyxoviruses
		Measles virus
		Mumps virus
		Picornaviruses
		Coxsackieviruses A and B†
		Echoviruses
		Enterovirus-70 and -71†
		Hepatitis A, C[37]
		Poliovirus types 1, 2, and 3†
Bacterial	Spinal cord abscess due to hematogenous spread of systemic infection	
	Mycoplasma, *Borrelia burgdorferi* (Lyme), *Treponema pallidum* (syphilis)	
	Mycobacterium tuberculosis	
Fungal	*Actinomyces*, *Blastomyces dermatitidis*, *Coccidioides*, *Aspergillus*	
Parasites	Neurocysticercosis, *Schistosoma*, *Gnathostoma*, angiostrongylosis (eosinophilic myelitis)	

*Common causes.
†Can cause acute poliomyelitis-like syndrome due to preferential, rather than selective, destruction of anterior horn cells and other motor pathways.
Note: HTLV-1 (human T-lymphotropic virus 1) and HIV can cause a chronic myelitis without brain involvement.

Vaccines have been related to an immunological reaction leading to myelitis. Smallpox, rabies, hepatitis B, typhoid or influenza have been implicated, among others.[38]

Finally, the term *parainfectious NMO* has been proposed for patients with viral or bacterial pathogens who fulfill NMO criteria. In one study attempting to characterize parainfectious NMO, varizella zoster virus and *Mycobacterium pneumoniae* were the most frequently observed agents.[163]

1.6 Other causes of acute transverse myelitis

Spinal infarctions may be a rare cause of spinal cord affection. Patients usually develop symptoms and reach nadir within minutes or within a few hours. Blockage or disruption of the anterior spinal cord lead to infarction of the anterior two thirds of the spinal cord.[164] Arteriovenous shunts or spinal arteriovenous fistulaes may also lead to spinal cord lesions spanning more than three vertebral segments.[165] Another cause of spinal cord infarction although less often observed is fibrocartilogenous embolisms which have been reported in up to 5%.[166] Prognosis in patients with spinal cord infarction is often poor with permanent and disabling sequelae.[167] CSF findings are characterized by proteinorraquia with an absence of pleocytosis and OCB.[29]

Although intramedullary tumours (ependymomas, astrocytomas, most commonly observed) or metastasis are the cause of a chronic myelopathy, some of them might be responsible for an acute onset and mimic the symptoms of myelitis.[168]

Paraneoplastic syndromes could be responsible for subacute myelopathies. Among the paraneoplastic antiibodies, collapsine response- mediator protein 5 (CRMP-5/CV-2) which has been also related to ON, seem to be the most frequent antibody related to myelopathies. Small cell lung cancer is the main underlying tumour associated with this antibody.[169] Amphiphysin antibodies have also been found in patients with myelopathy.[170] Other paraneoplastic

antibodies such as glutamic acid decarboxylase (GAD), antineuronal nuclear antibodies (ANNA-2), Purkinje cell antibodies have also been involved in myelopathies.[38,171]

Vitamin-B 12 deficiency is the cause of a predominantly subacute sensory myelopathy due to latero-dorsal affection of the spinal cord. Subacute combined degeneration due to vitamin- B 12 deficiency is usually observed in the context of chronic gastritis with the absence of intrinsic factor.[172] Acquired copper deficiency is a non-compressive myelopathy, clinically characterized by posterior column dysfunction which closely mimics subacute sensory myelopathy. The main causes are gastric surgery, zinc consumption or malabsortion.[173]

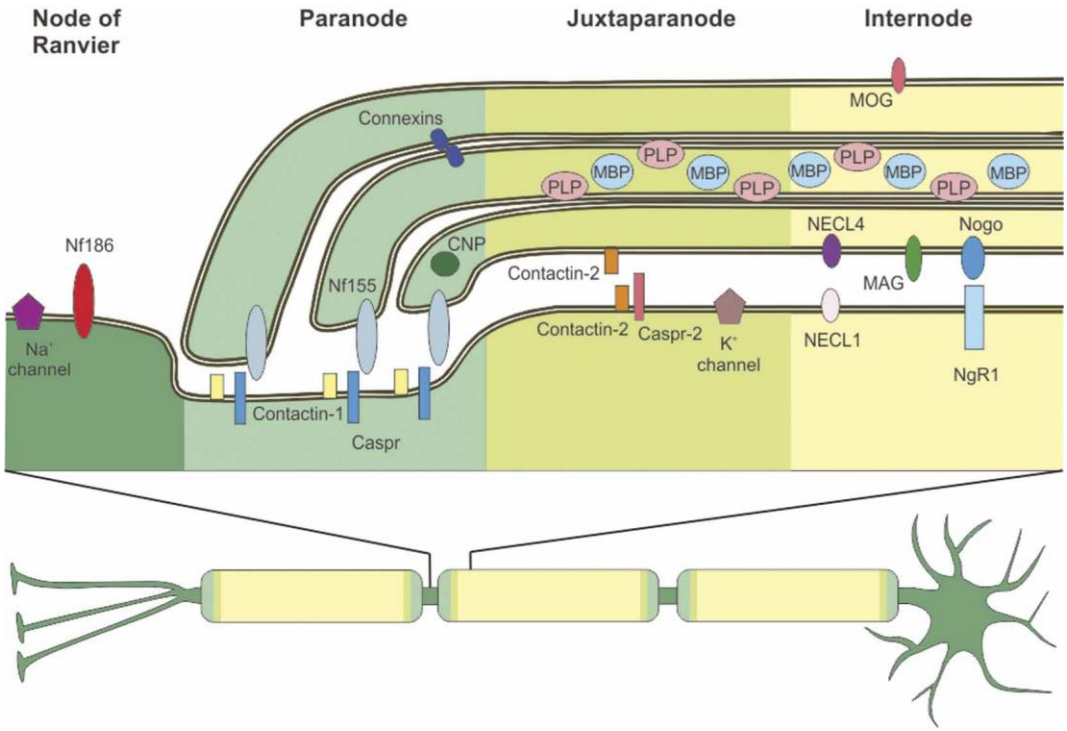
1.7 Myelin oligodendrocyte glycoprotein (MOG) antibody and myelitis

1.7.1 MOG protein and demyelinating disorders

MOG is a quantitatively minor type I transmembrane component of the myelin, comprising of 0,05% of the whole structure. Its IgV-like domain, located in the outer surface of myelin lamellae, seems to exert encephalitogenic properties.[174] **(Figure 13)** Both experimental allergic encephalomyelitis and "in vitro" studies have shown enhanced demyelination after MOG immunization.[175,176] Although the pathological relevance of MOG has been tried to be demonstrated in different studies, its potential role in the

process of the disease is still unknown. Meanwhile "in vitro" studies have remarked that only the antibodies against conformational MOG epitopes are pathogenic leading to demyelination and axonal damage,[177] others have suggested a pathologic effect via complement activation.[178]

Figure 13. Myelin oligodendrocyte glycoprotein location on the myelin sheath



MOG-ab have been increasingly recognized in pediatric patients with demyelinating conditions. Up to 57,6% and 14% of pediatric patients diagnosed with ADEM and MS were shown to have serum MOG-ab,

respectively.[178-185] High titers of MOG-ab have also been found in a lower proportion of pediatric patients reporting NMO or relapsing ON.[178,186,187]

Most of the data regarding serum kinetic of MOG-ab in demyelinating diseases comes from pediatric populations. It seems that MOG-ab kinetic depends on the underlying condition. They are present in serum after the initial episode and titers continuously decline over a period of time in pediatric patients with ADEM disease.[184,185] Some authors have associated the persistence of high titer MOG-ab in serum with poor recovery or relapses in ADEM pediatric patients.[182,185] Other chronic diseases such as MS or NMO seem to have a different kinetic profile and MOG-ab remain stable over time.[182,184,186] Few data are available regarding only adult patients. A recent study reported that only two among 14 MOG-ab positive patients diagnosed with NMOSD became seronegative after a median follow-up of 23 months. MOG-ab titers in these patients were related neither to prognosis nor to relapses.[188]

Association between MOG-ab and AQP4-ab in NMO patients has been rarely described. One pediatric and three adult NMO patients have been reported with double seropositivity for both antibodies.[178,188]

1.7.2 MOG antibodies and Neuromyelitis optica spectrum disorders

Considering NMOSD in adult populations, MOG-ab have been detected in up to 9,8%.[188,189] (**Table 2**)

Table 2. Different phenotypes according to MOG serostatus in NMOSD

	Sato DK, et al.[189]	Höfterberg R, et al.[188]	*Kitley J, et al.[190]
MOG-ab positive/NMOSD, n (%)	16/215 (7.4)	17/174 (9.8)	9/29 (30)
NMO, n (%)	1/16 (6,3)	4/17(24)	4/9 (44)
NMOSD- LETM, n (%)	5/16 (31.2)	5/17 (29)	3/9 (33)
NMOSD-ON, n (%)	10/16 (62.5)	7/17 (41)	0/9

n, number; MOG-ab, myelin oligodendrocyte glycoprotein; NMO, Neuromyelitis optica; NMOSD, Neuromyelitis optica spectrum disorders; LETM, longitudinally extensive transverse myelitis; ON, optic neuritis

**Comparison between AQP4-ab positive and MOG-ab positive NMOSD*

Different epidemiological, clinical and radiological features have been described between AQP4-ab and MOG-ab positive patients with NMOSD. The median age of onset of symptoms has been reported to range between 32 and 37,5 years in MOG-ab positive NMOSD patients compared with older range of ages in those with AQP4-ab.[188,190] In other data such differences were not found.[189] Moreover, a male predominance has also been observed ranging from 53% to 62,5% in MOG-ab positive NMOSD patients.[188-190]

MOG-ab have been associated with NMO patients with simultaneous ON and myelitis attacks at onset (classical Devic's Neuromyelitis optica) compared to those who have AQP4-ab.[189,190] However, other authors have reported no

differences between AQP4-ab and MOG-ab positive in patients who fulfilled Wingerchuck criteria for NMO regarding this clinical presentation.[188] Among NMOSD, MOG-ab are related to monophasic forms of the disease compared to those patients who report AQP4-ab. Up to 50% of these MOG-ab positive patients will not develop further relapses after a median follow-up of two years.[189] Among patients with recurrences, MOG-ab positive NMOSD patients seem to have a lower number of relapses than AQP4-ab and seronegative patients.[189] Moreover, MOG-ab positive NMOSD patients seem to have a better recovery compared to those with AQP4-ab or without either of them.[188,189]

Regarding the location of spinal cord lesion at onset of symptoms, some groups have suggested a predominance in the lower levels of the spinal cord (lumbar and *conus medullaris*) in the MOG-ab group compared with the AQP4-ab group.[189,190] *Kitley J, et al.* have also suggested that a transient abnormal spinal cord lesion on MRI could be another feature of MOG-ab positive NMOSD.[190] Moreover, antinuclear antibodies are reported in a higher proportion in MOG-ab positive patients.[189]

1.7.3 MOG antibodies in different clinical phenotypes of Neuromyelitis optica spectrum disorders

There are not many studies which detail distinctive clinical features of MOG-ab positive patients according to the clinical phenotype.[187-189,191]

1.7.3.1 Neuromyelitis optica and MOG antibodies

MOG-ab have been found in up to 8,7% of patients fulfilling Wingerchuck criteria for definite NMO.[178,188,189] MOG-ab positive NMO patients tend to be younger, to have a higher male: female ratio and higher pleocytosis than AQP4-ab patients. Moreover, they seem to have a better outcome.[188]

1.7.3.2 Optic neuritis and MOG

The frequency of MOG-ab in ON patients without AQP4-ab has been found to be 46% and 18% in children and adults, respectively.[187,188] Patients with MOG-ab who develop ON seem to have a good follow-up visual acuity.[188,189,191] A recent study has reported better visual acuity and visual field deficits at long term in this subgroup of patients than in AQP4-ab seronegative ON patients. In most of patients tested by optic computer tomography, authors also pointed out that their retinal nerve fiber layer thickness returned towards a normal range.[191] Moreover, MOG-ab positive patients will be more likely to develop a higher frequency of ON relapses than negatives. It has been recently observed that 38 out of 40 ON recurrences among a cohort of NMOSD patients belonged to the MOG-ab positive group.[188] In this study, bilateral ON attacks were more common in MOG-ab positive patients than in those seronegative both for AQP4 and MOG-ab.[188] Lastly and regarding treatment, MOG-ab positive patients with ON seem to have a faster recovery after steroid initiation. Nonetheless, they will be more

likely to relapse on steroid cessation, compared to MOG-ab negative patients.[191]

1.7.3.3 MOG and longitudinal extensive transverse myelitis

It has been described that between 6% to 7,5% of AQP4-ab seronegative patients who present with an isolated LETM had serum MOG-ab.[125,188,189] *Höftberger R, et al.* compared both subgroups of LETM patients.[188] MOG-ab positive patients presenting with an isolated episode of LETM appeared to have clinical distinctive findings than those who are seropositive for AQP4-ab or seronegative for both MOG and AQP4-ab. Compared to AQP4-ab positive LETM patients, MOG-ab positive were younger and presented with a monophasic form. However these differences were not observed between MOG-ab positive with AQP4-ab seronegative LETM patients. Patients presenting with MOG-ab positive isolated LETM were characterized by better prognosis than seronegatives. Moreover, the lesion extended over the whole spinal cord in a higher proportion of the MOG-ab positive group and a significant resolution or reduction of the lesion imaging was observed during the follow-up in comparison to the AQP4-ab positive group.[188]

2. -HYPOTHESIS AND OBJECTIVES

2. HYPOTHESIS AND OBJECTIVES

2.1 Hypothesis

1. IATM patients who fulfill the TMCWG criteria established in 2002 would present distinctive epidemiological, clinical, laboratory and radiological features at the acute phase of the disease which might lead to identify those with a worse functional long term outcome.

2. TMCWG criteria reliability to dismiss ATM as the initial event of a subsequent MS remains unclear in daily clinical practice. There might be a proportion of IATM patients who convert to MS, even though fulfilling the TMCWG criteria.

3. The functional outcome in LETM patients is highly variable depending on the aetiology. Patients presenting with a first episode of LETM might present initial distinctive epidemiological, clinical, laboratory and radiological features related to the functional long term outcome.

4. Although LETM is a characteristic clinical feature of NMO and part of the diagnostic criteria of the disease, LETM may encompass a heterogeneous group of disorders. The relative frequency of the different aetiologies causing a first LETM episode is not well known. We think that the idiopathic form is overrepresented and that unacknowledged underlying pathogenesis might be related to the demyelinating episode in this subgroup of these patients.

5. The underlying aetiology of a proportion of patients with a first event of AQP4-ab seronegative LETM remains unclear after a long workup and follow-up. MOG-ab might be present in the serum of these patients.

6. Patients with AQP4-ab seronegative LETM who have MOG-ab in serum might have epidemiological, clinical, laboratory and radiological features different from those who are MOG-ab seronegative.

2. 2 . Objectives

1. To analyze the functional long term outcome and prognostic factors associated with recovery in patients who fulfill the TMCWG criteria.

2. To describe the MS conversion rate and identify variables associated with MS conversion in patients who fulfill the TMCWG criteria for possible and definite IATM.

3. To describe the outcome, and to identify predictors of outcome in patients presenting with a first episode of LETM.

4. To describe the aetiologic spectrum of patients presenting with a first episode of LETM.

5. To investigate the frequency of MOG-ab in patients with a first episode of AQP4-ab seronegative LETM.

6. To describe the clinical features of patients with a first episode of AQP4-ab seronegative LETM who are seropositive and seronegative for MOG-ab in serum.

3.- MATERIALS AND METHODS

3. MATERIALS AND METHODS

3.1 Methodology

The present work is subdivided into three studies:

1. Idiopathic acute transverse myelitis

2. Longitudinal extensive transverse myelitis

3. Myelin oligodendricyte glycoprotein antibodies in longitudinally extensive transverse myelitis

In the first study, we included patients who fulfilled the definition for definite or possible IATM proposed by the TMCGW 2002 criteria.[19] We conducted a retrospective medical chart review from patients admitted to Internal Medicine, Neurosurgery and Neurological departments at Bellvitge University Hospital between January 1989 and December 2011.

Although the presence of AQP4-ab are not included in the TMCGW 2002 criteria, we excluded those patients who were positive for this antibody, as it has been shown to be a direct pathogenic cause of NMOSD.[26]

We noted epidemiological and clinical data as well as disability at onset and last visit based on the modified Rankin Scale (mRS) for IATM patients and the EDSS for patients who converted to MS. We categorized patients into mRS <2 or ≥ 2 to differentiate better and worse functional term outcome. CSF

characteristics were also analyzed. Baseline brain and spinal cord MRI were performed on a 1.5 Tesla system in all patients.

All patients were followed-up at 6 months intervals during the first year and once a year thereafter. MS diagnosis was based on the revised Poser or McDonald criteria.[93,192]

For the statistical analysis, we used Chi-square test and Mann-Whitney *U* test for categorical variables and Student *t* Test for continuous variables. Pearson's correlation coefficient performed correlations between ordinal variables. We performed a multivariate logistic regression in order to analyze predictive factors. Statistical analyses were performed by SPSS version 20.0.

In the second study, we reviewed medical histories from patients who presented with a first LETM episode at Bellvitge University Hospital (Internal Medicine, Neurosurgery and Neurological departments) between January 1993 and January 2011.

The inclusion criteria for LETM were: 1, onset of symptoms over no more than 21 days; 2, spinal cord T2 signal hyperintensity over three or more consecutive vertebral segments; 3, bilateral motor or sensory symptoms with or without sphincter dysfunction; 4, available brain MRI. The exclusion criteria were: 1, previous spinal irradiation; 2, evidence of spinal cord

compression; 3, history of neurological disease or symptoms; 4, no symptoms or signs attributable to involvement other than the spine.

Epidemiological and clinical data were noted. Disability was evaluated by mRS and patients were categorized into two groups, mRS<2 or ≥ 2 with the higher score indicating clinically significant functional disability.

CSF and MRI details were evaluated, as described in study 1. An extensive workup was performed in order to rule out infectious agents, connective, autoimmune, vascular or malignant disorders causative of LETM. AQP4-ab were no systematically sought as the technique was available at our centre in 2007.[193]

We defined eight aetiologies: 1, MS based on Poser or McDonald criteria;[93,192] 2, ADEM;[194] 3, NMOSD;[25,110] 4, parainfectious myelopathy;[75] 5, SLE;[195] 6, SS;[143] vascular aetiology differentiated in spinal cord infarction and dural fistula,[18]; 7, tumour related;[196] and 8, idiopathic LETM if the presence of LETM with no other cause is identified after an extensive workup and follow-up.

Statistical analysis was only performed in four subgroups (MS, PIM, systemic diseases and idiopathic LETM), as the patient number was too low in the rest of subgroups. Mann Whitney *U* test or Chi square test were used for quantitative variables or categorical variables, respectively. Univariate analysis followed by stepwise multivariate logistic regression was performed

to assess factors associated with functional outcome. SPSS version 20.0 program was used for the analysis.

For the third study, patients diagnosed with isolated AQP4-ab seronegative LETM from Lyon and Toulouse University Hospitals and Bellvitge University Hospital were included. We performed a retrospective analysis from data which were entered in a prospective way between January 2005 and December 2014 into the Database adapted from the EDMUS system (Eugène Devic European Network, EDEN).[197]

Inclusion criteria for isolated AQP4-ab seronegative LETM were: 1, onset of symptoms between 4 hours and 21 days; 2, bilateral or sensory symptoms with or without sphincter dysfunction; 3, spinal cord T2 signal hyperintensity over three or more consecutive vertebral segments on MRI; 4, available brain MRI; 5, extensive workup that reasonably excludes other diagnoses such as vascular, compressive, infectious, metabolic, paraneoplasic or radiation myelopathy; 6, tested for AQP4- ab in serum with a negative result.

Demographic and clinical data were collected. Disability was evaluated on admission and on the last visit based on the EDSS. Patients were categorized into two groups: EDSS ≤ 2,5 and EDSS ≥ 3 for functional outcome.

CSF and MRI data were also collected. AQP4-ab and MOG-ab were analyzed in two centres, the Lyon Neuroscience Research Centre of Lyon and the

Laboratory of the Neurommunolgy Programme, Institut d'Investigació Biommèdica August Pi i Sunyer (IDIBAPS) of Barcelona, by cell-based assays, as previously reported.[119,188,198]

All patients were followed-up every 6 months and when a relapse was suspected. MS and NMO diagnosis were based on revised McDonald criteria and Wingerchuk 2006 criteria, respectively.[25,93]

Categorical and continuous variables were compared with Fisher exact test and Mann- Whitney *U* test, respectively. The analysis of prognostic factors was carried out by multivariate logistic regression model. Cox regression analysis was performed to estimate cumulative survival probabilities. All statistical analyses were performed using STATA (64-bits) software.

3. 2 Ethical aspects

All the studies had the approval from the Clinical Research Ethic Committees of Bellvitge University Hospital, Lyon and Toulouse University Hospitals, and all data were collected in an anonymous fashion.

4.- RESULTS

4 RESULTS

4.1 Study 1. IDIOPATHIC ACUTE TRANSVERSE MYELITIS: OUTCOME AND CONVERSION TO MULTIPLE SCLEROSIS IN A LARGE SERIES.

Cobo- Calvo A, Mañé Martínez MA, Alentorn-Palau A, Bruna Escuer J, Romero Pinel L, Martínez- Yélamos S. BMC Neurology 2013, 13:135

In the first study, we included 85 patients who fulfilled the TMCWG 2002 criteria for IATM.

Demographic and general clinical features

We observed that IATM patients fulfilling the TMCWG 2002 criteria were represented by a slight increase in the female:male ratio (1:0,9) with a mean (Standard deviation, [SD]) age of presentation of 43 (16,2) years. After a median (interquartile range [IQR]) follow-up of 2,9 (1-4,8) years, 11 (13%) patients converted to MS and 74 (87%) remained as IATM.

Considering clinical aspects, the onset of IATM symptoms were preceded by back pain in up to 40% and 31,8% had previous symptoms related to infection. Moreover, urinary and anal sphincter dysfunction were presented in 55,3% and 13% of IATM patients at onset, respectively.

LETM was observed in 26 (30,6%) of patients; two (7,5%) patients were diagnosed as having MS and 24 (93,1%) remain as IATM. Those patients who presented spinal cord relapses were observed in the MS group and none of them presented an initial LETM.

On follow-up completion, 37% had moderate disability (mRS ≥ 2) and 9,4% were unable to walk unassisted. Moreover, 27% of patients with LETM were wheelchair dependent as compared to only 1,7% of patients without an extensive lesion on spinal MRI.

Variables associated to MS conversion

Onset of symptoms at an early stage was related to MS conversion. Patients from the MS group developed IATM symptoms at a mean (SD) of 28,2 (9,1) years compared to 45 (16) years in the IATM group.

CSF findings proved to be of high value when added to IATM prognosis. We found that 33,3% of IATM patients presenting with OCB in CSF had MS conversion compared to only 2% without OCB. This finding was significantly related to MS conversion, but lost strength after multiple comparison adjustement. Moreover, a negative OCB testing and IgG index ≤ 0,7 combination was proven to be useful to identify those IATM patients who will not develop MS conversion, as the negative predictive value was 100%.

Predictive factors associated with outcome

A higher mRS was related to a poorer outcome in univariate analysis ($p<0,001$). However, urinary sphincter dysfunction and LETM at baseline MRI were the only two independent risk factors associated with a worse functional outcome (mRS ≥ 2) in patients who presented with an episode of IATM fulfilling the TMCWG 2002 criteria.

Cobo Calvo *et al. BMC Neurology* 2013, **13**:135
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Idiopathic acute transverse myelitis: outcome and conversion to multiple sclerosis in a large series

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Abstract

Background: In 2002, the Transverse Myelitis Consortium Working Group (TMCWG) proposed the diagnostic criteria for idiopathic acute transverse myelitis (IATM) to delimit and unify this group of patients. This study aimed to describe the conversion rate to multiple sclerosis (MS) and variables associated with conversion, and to analyze functional outcome and prognostic factors associated with functional recovery in patients who fulfilled the current TMCWG criteria for definite and possible IATM.

Methods: Eighty-seven patients diagnosed with IATM between 1989 and 2011 were retrospectively reviewed. Two patients with positive neuromyelitis optica IgG serum antibodies were excluded. Epidemiological, clinical, laboratory, magnetic resonance imaging (MRI) data and outcome of 85 patients were analyzed.

Results: Eleven (13%) patients converted to MS after a median follow-up of 2.9 years (interquartile range 1.0-4.8). Early-age onset of symptoms was related to conversion to MS. Only 9.4% of patients with IATM were unable to walk unassisted at the end of follow-up. Urinary sphincter dysfunction (odds ratio [OR] 3.37, 95% confidence interval [CI] 1.04-10.92) and longitudinally extensive transverse myelitis (LETM) on MRI (OR 12.34, 95% CI 3.38-45.00) were associated with a poorer outcome (Rankin ≥ 2).

Conclusions: At least 13% of patients who fulfill the TMCWG criteria for definite and possible IATM will convert to MS. Functional recovery in IATM is poorer in patients with urinary sphincter dysfunction at admission or LETM on MRI.

Keywords: Transverse myelitis, Idiopathic, Multiple sclerosis, Prognosis, Neuromyelitis optica

Background

In 2002, the Transverse Myelitis Consortium Working Group (TMCWG) presented the proposed diagnostic criteria for idiopathic acute transverse myelitis (IATM) to delimit and unify this group of patients [1]. Since that time, identification of new diagnostic biomarkers, such as neuromyelitis optica (NMO) IgG antibodies has contributed to differentiate new conditions from the idiopathic group of acute transverse myelitis [2].

Another distinctive group of patients with an IATM event meeting the TMCWG criteria are individuals who present with a first attack of multiple sclerosis (MS) in the setting of an initially normal brain magnetic resonance imaging (MRI) study. The percentage of patients with TMCWG criteria for IATM who have a first demyelinating MS event remains to be clarified.

Individuals considered at a high risk of disability after a first IATM event may benefit from treatments that are more aggressive, such as plasma exchange. Hence, there is a need to identify this cohort of patients early in the course of the disease.

The aim of this study was 1) to describe the conversion rate to MS and identify variables associated with conversion, and 2) to analyze the functional outcome and prognostic factors associated with recovery in patients who fulfill the current TMCWG criteria for possible and definite IATM.

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Methods

Patients

The study was approved by the Clinical Research Ethics Committee of Bellvitge University Hospital and all data were collected in an anonymized fashion (ref PR228/12).

We reviewed 604 medical records from patients with neurological signs attributed to spinal cord inflammation assessed at Bellvitge University Hospital (Barcelona, Spain) between January 1989 and December 2011. Among them, we found 487 patients diagnosed with MS who presented a spinal cord inflammation or a first spinal cord inflammation with cranial MRI suggestive of MS, 11 due to parainfeccious disease, systemic disease in 9, spinal cord infarction in 3 patients and ADEM, dural fistula and tumoral-related spinal cord in 2 patients respectively. One patient had simultaneous myelitis and optic neuritis (ON) as a part of the classic Devic Syndrome. We found out 87 patients initially diagnosed with IATM and no history of previous neurological symptoms.

We then retrospectively studied these 87 patients. Patients who fulfilled the criteria for IATM proposed by the TMCWG (definite IATM) and those who met all criteria with the exception of 'objective documentation of inflammation within the spinal cord' (possible IATM) were included and analyzed in the present study. The current cohort includes the patients who were described in a previously published study [3].

In 38 of the 87 patients, serum samples were tested for NMO-IgG antibodies by immunohistochemistry, as described elsewhere [4]. NMO-IgG antibodies could not be systematically sought, as the technique became available in our hospital in 2007. This validated technique has shown a sensitivity (S) of 50-60% and a specificity (Sp) of more than 90%. Two patients showed positive reactivity and were excluded from the study. Both patients developed NMO disease, based on the diagnostic criteria for this condition [5].

The 85 patients fulfilling the criteria for definite and possible IATM were classified into two groups: the IATM group and the MS group. The diagnosis of MS was based on the revised Poser or McDonald criteria [6,7].

Epidemiological and clinical data

Sex, age at symptoms onset, season of onset and time to reach maximum functional deficit were recorded. Hypertension, hypercholesterolemia, diabetes mellitus, smoking habit, traumatic events, and symptoms related to infection (eg, flu, gastrointestinal, or urinary tract symptoms) within one month before the onset of IATM symptoms were also collected. Clinical findings were noted, such as urinary sphincter dysfunction or anal sphincter dysfunction, and the treatment received. None of the patients were receiving immunosuppressants or corticosteroids before the acute spinal event or at the time immunological studies were performed.

Disability was evaluated on admission and at last visit using the modified Rankin Scale [8]. Rankin scores were categorized into <2 and ≥2 to distinguish functional disability. Patients who converted to MS were further evaluated by the Expanded Disability Status Scale (EDSS) to determine the extent of the neurological disability at the last visit.

Laboratory data

A spinal tap was performed in all patients before treatment. CSF was analyzed for glucose concentration, cell count, and IgG index (positive, >0.7), and immunofixation electrophoresis was used for oligoclonal band (OCB) testing.

Imaging data

In all patients, baseline and follow-up MRI scans were performed on a 1.5-Tesla system. MRI study included axial and sagittal images of the brain and spinal cord obtained by T1, T2, FLAIR and T1 post-contrast sequences. All patients had normal brain MRI findings at the first episode of IATM. All underwent spinal MRI on admission, and the number, location, and length of lesions were noted. Longitudinally extensive transverse myelitis (LETM) was defined as extension over three or more vertebral segments on MRI study.

Follow-up

Patients were followed-up with a neurological evaluation every 6 months during the first year, and once a year thereafter. Follow-up time was established as the difference between the date of the last visit and the date of admission. Analysis of data was performed on December 2012. An additional neurological examination was performed when a relapse occurred. Relapse was defined as a second demyelinating event at the spinal cord (recurrence) or other central nervous system structure at least one month after the first event, sustained for a minimum of 24 hours. The date of MS conversion was noted in all patients in the MS group.

Statistical analysis

Categorical variables and ordinal variables were compared with the chi-square test and Mann–Whitney U test, respectively. Correlations between ordinal variables were analyzed with Pearson's correlation coefficient. Quantitative continuous variables were compared with the Student t test. Multivariate logistic regression analysis was performed using the forward stepwise method and including only those variables that were statistically different in the univariate analysis at a significance level of p-value < 0.05. After the Bonferroni correction the

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level of significance for multiple comparison was established at p-value < 0.001.

Results

Epidemiological and clinical data

Among the 85 IATM patients included in the study, 45 (53%) were women and mean age at onset was 43 ± 16.2 years. Seventy-four patients were ultimately classified in the IATM group (87%) and 11 (13%) in the MS group. Epidemiological and clinical data are shown in Table 1 and Table 2.

In the MS group, patients with a relapse after the first spinal cord event presented with typical symptoms of MS; three had ON, one sensory and sphincter dysfunction, one sensory and motor symptoms, two pure motor symptoms and three pure sensory symptoms. Nine patients had relapsing-remitting MS and two progressed to secondary progressive MS (SPMS). One SPMS patient experienced no further relapses after the first spinal attack.

At the end of follow-up, myelitis recurred in 5 patients, all in the MS group. No patients with LETM had recurrences. Two patients with a first LETM who converted to MS did so at one and seven months from the first attack, respectively.

Patients with onset of symptoms in summer reached nadir faster than the remaining patients (7.94 days, SD 7.5 *vs* 3.14 days, SD 3.08, $p < 0.001$).

Treatment with intravenous methylprednisolone (1 g daily for 5 days) was given to 67 patients. Three patients (two of whom presented as LETM) needed further treatment, such as plasma exchange, due to a poor response to corticosteroids and symptoms of impairment at admission (Rankin Score was 3, 5 and 4, respectively).

Among the MS group, seven patients were treated with disease modifying drugs during the follow up.

CSF findings

CSF cell count was determined in 77 patients and pleocytosis (total cellularity >5 cell/mm^3) was found in 18 (23.4%). Among the 10 MS group patients in whom cell count was performed, 5 had less than 5 cell/mm^3 and only 1 had more than 50 cell/mm^3.

Five out of 15 patients with OCB in CSF developed MS compared with only one out of 44 without OCB. The presence of OCB was associated with conversion to MS, but the results were not statistically significant after Bonferroni adjustment ($p = 0.003$) (S 83.3%, Sp 81.5%, positive predictive value [PPV] 33.3%, negative predictive value [NPV] 97.8%). The IgG index was not, however, related to MS conversion ($p = 0.800$) (S 60%, Sp 80%, PPV 23.1%, NPV 95%). The combination of positive OCB testing and IgG index >0.7 yielded a negative predictive value and sensitivity of 100% to MS conversion. (S 100%, Sp 68.6%, PPV 23.8%, NPV 100%) ($p = 0.011$). CSF data are shown in Table 3 and Table 4.

Table 1 Epidemiological and clinical characteristics of patients with low versus high Rankin Scores at the final of the follow up

	Outcome Rankin		*p*	Total
	<2	≥2		
N (%)	51 (60)	34 (40)		85
Age, mean (SD), y	38.9 (14)	49 (17.7)	*0.005*	43 (16.2)
Sex, male/female	21/30	19/15	*0.194*	40/45
Follow up, median (IQR), y	2.9 (1.5-4.1)	2.7 (0.3-7.4)	*0.683*	2.9 (1–4.8)
Time to maximum deficit, mean (SD), d	7.2 (7)	6.91 (7.6)	*0.821*	7.1 (7.1)
Admission Rankin Mean (SD)	2.27 (1)	3.65 (1.1)	*<0.001*[a]	2.82 (1.2)
Outcome Rankin Mean (SD)	——	——	——	1.4 (1.3)
Time onset-start treatment, mean (SD), d	9.7 (8.3)	8.5 (8)	*0.602*	9.2 (8.1)
Back pain, n (%)	19 (37.3)	16 (47.1)	*0.380*	35 (41.2)
Urinary sphincter dysfunction, n (%)	21 (41.2)	26 (76.5)	*0.001*[a]	47 (55.3)
Anal sphincter dysfunction, n (%)	2 (4)	9 (26.5)	*0.002*	11 (13)
Previous infection, n (%)	19 (37.3)	8 (23.5)	*0.237*	27 (31.8)
Summer season/Not summer season, n (%)	9/49 (18) /40/49 (81.6)	5/34 (14.7) / 29/34 (85.3)	*0.661*	14 (16.47) /69 (81.17)
TM relapses, n (%)	5/51 (9.8)	0/33 (0)	*0.085*	5/84 (6)
MS conversion, n (%)	8 (15.7)	3 (8.8)	*0.513*	11 (13)

IQR: Interquartile range.
SD: Standard deviation.
TM: Transverse myelitis.
[a]Significant after Bonferroni correction.

Table 2 Epidemiological and clinical characteristics comparing IATM versus MS group

	IATM group	MS group	*p*
N (%)	74 (87)	11 (13)	
Age, mean (SD), y	45 (16)	28.2 (9.1)	*0.001*[a]
Sex, male/female	36/38	4/7	*0.529*
Follow up, median (IQR), y	2.9 (0.9–3.9)	9.9 (2.7–17.8)	*<0.001*[a]
Time to maximum deficit, mean (SD), d	6.9 (7.2)	8.5 (7)	*0.487*
Admission Rankin, Mean (SD)	2.8 (1.2)	2.45 (1.1)	*0.284*
Outcome Rankin Mean (SD)	1.3 (1.3)	1.8 (1.2)	*0.290*
Time onset-start treatment, mean (SD), d	9 (8.1)	2 (2.2)	*0.553*
Back pain, n (%)	30 (40.5)	5 (45.5)	*0.755*
Urinary sphincter dysfunction, n (%)	41 (55.4)	6 (54.5)	*0.603*
Anal sphincter dysfunction, n (%)	10 (13.5)	1 (9.1)	*0.566*
Previous infection, n (%)	23 (31.1)	4 (36.4)	*0.485*
Summer season/Not summer season, n (%)	13/72(18.1)/59/72 (81.9)	1/11 (9.1)/10/11 (90.9)	*0.460*
TM relapses, n (%)	0/73 (0)	5/11 (45.5)	*<0.001*[a]

IATM: Idiopathic acute transverse myelitis.
MS: Multiple Sclerosis.
IQR: Interquartile range.
SD: Standard deviation.
TM: Transverse myelitis.
[a]Significant after Bonferroni correction.

MRI findings

Spinal cord MRI revealed a cervical lesion in 31 (36.5%), thoracic lesion in 33 (38.8%), and lumbar lesion in 11 (12.9%) of 85 patients. In 19 (22.5%) patients, no abnormalities were observed in the first spinal cord MRI. Five of these 19 patients showed abnormal CSF findings (positive IgG index and/or pleocytosis) and one patient had a cervical lesion in the second spinal cord MRI. The remainder showed no abnormal findings in the second MRI. All the patients with a normal first spinal cord MRI had abnormal neurological signs suggestive of transverse myelitis, as the TMCWG points out. There were no statistically significant differences between the IATM and MS groups with regard to the location of the MRI signal abnormality. None of the patients in the MS group developed lumbar myelitis.

Within the MS group, six patients fulfilled the Barkhof criteria in a subsequent brain MRI. The distributions of the lesions in the axial plane at the first spinal MRI were predominantly posterior (4/11) and lateral (2/11), and two patients had a lesion area that extended over more than 50% of the spinal cord section. In three MS patients, the first spinal MRI was normal and the subsequent spinal study revealed a single cervical lesion in one of them. Nine MS patients underwent a second spinal MRI; in three the lesion had resolved, three had new spinal lesions that extended over fewer than three vertebral segments, and three showed no changes.

Table 3 CSF and MRI characteristics with low versus high Rankin Scores at the final of the follow up

	Outcome Rankin		*p*	Total
	<2	≥2		
N (%)	51 (60)	34 (40)		85 (100)
CSF (mean, SD)				
Glucose, mmol/L	3.5 (1.1)	4 (1)	*0.035*	3.7 (n:78)
Cell count, n/mm^3	8.9 (24.1)	27.8 (125.4)	*0.321*	16.5 (n:77)
Protein, g/L	0.4 (0.2)	0.5 (0.2)	*0.389*	0.5 (n:78)
OCB+, n (%)	12/40 (30)	3/20 (15)	*0.343*	15/60 (25)
IgG index >0.7, n (%)	8/33 (24.2)	5 /22 (22.7)	*0.581*	13/ 55 (23.6)
MRI				
Vertebral segments, n, mean (SD)	1.7 (1.9)	3.8 (3.3)	*0.003*	2.5 (2.8)
LETM (%)	(9.8)	21 (61.8)	*<0.001*[a]	26 (30.6)
GD+, n (%)	14/30 (46.6)	8/21 (38.1)	*0.800*	22/51 (43.1)
Time onset-MRI, Mean (SD), d	9.84 (7.2)	8.37 (7.5)	*0.408*	9.26 (7.3)

CSF: Cerebrospinal fluid.
OCB+: Positive oligoclonal band test.
MRI: Magnetic resonance imaging.
LETM: Longitudinally extensive transverse myelitis.
GD+: Gadolinium enhancement.
SD: standard deviation.
[a]Significant after Bonferroni correction.

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Table 4 CSF and MRI characteristics comparing IATM versus MS group

	IATM group	MS group	p
N (%)	74 (87)	11 (13)	
CSF (mean, SD)			
Glucose, mmol/L	3.7 (1.1)	3.4 (0.6	*0.424*
Cell count, n/mm^3	17.4 (87.1)	10 (18.4)	*0.789*
Protein, g/L	0.5 (0.2)	0.35 (0.2)	*0.044*
OCB+, n (%)	10/54(18.5)	5/6 (83.3)	*0.003*
IgG index >0.7, n (%)	10/50 (20)	3/5 (60)	*0.800*
MRI			
Vertebral segments, n, mean (SD)	2.6 (2.8)	2 (2.2)	*0.403*
LETM (%)	24 (32.4)	2 (18.2)	*0.281*
GD+, n (%)	20/43 (46.5)	2/8 (25)	*0.309*
Time onset-MRI, Mean (SD), d	8.56 (7)	14.22 (8.1)	*0.029*

IATM: Idiopathic acute transverse myelitis.
MS: Multiple Sclerosis.
MRI: Magnetic resonance imaging.
CSF: Cerebrospinal fluid.
OCB+: Positive oligoclonal band test.
LETM: Longitudinally extensive transverse myelitis.
GD+: Gadolinium enhancement.
SD: Standard deviation.
[a]Significant after Bonferroni correction.

LETM was observed in 26 (30.6%) patients and was related to greater disability. In this group, 81% of patients had a Rankin score ≥2 at their last visit compared with 22% of patients without LETM ($p < 0.001$). The fact of having LETM did not rule out conversion to MS: two of 26 patients (7.5%) with LETM developed MS.

Twenty-two of 26 patients with LETM presenting as IATM were seronegative for NMO-IgG antibodies at presentation and during follow-up. In the four remaining LETM patients, NMO-IgG antibodies were not analyzed: two patients converted to MS and two died from myelopathy-unrelated etiology after two and three years of follow-up, respectively. Additional MRI data are shown in Table 3 and Table 4.

Follow-up and outcome

Among the whole cohort, the median follow-up time was 2.9 years (IQR 1.0-4.8). The median follow- up was quite long in the MS group, which had a median follow-up time of 9.9 years (IQR 2.7-17.8) compared to the IATM group with a median of 2.9 years (IQR 0.9-3.9). The patients converted to MS at a median of 1.2 years (IQR 0.37-1.87) after the first spinal cord event. At completion of follow-up, early age at onset of symptoms was related to conversion to MS in patients who fulfilled criteria for possible or definite IATM (Table 2). Data related to follow-up and outcome are shown in Figure 1.

Modified Rankin Score results at admission and end follow-up are shown in Table 5. A higher admission Rankin score was significantly related to a poorer outcome (Pearson correlation coefficient 0.65; $p < 0.001$). Thirty-three patients (97.1%) with functional disability at the last visit had an admission Rankin ≥2 ($p = 0.006$). Among 71 patients with a score ≥2 at admission, 33 (46.5%) had an outcome Rankin ≥2 ($p = 0.006$).

Urinary sphincter dysfunction was the only clinical symptom related to Rankin ≥2 at last visit ($p < 0.001$) (Table 1).

Independent risk factors associated with an outcome Rankin score ≥2 were urinary sphincter dysfunction (OR 3.37, 95% CI 1.04-10.92) and LETM (OR 12.34, 95% CI 3.38-45.00).

Discussion and conclusions

To the best of our knowledge, the 85 patients in the present study represent the largest series meeting the criteria for possible and definite IATM established by the TMCWG.

NMO spectrum disorders (NMOSD) are considered limited forms of NMO, such as single or recurrent LETM events or relapsing or simultaneous bilateral ON with positive serum NMO-IgG testing [9]. At onset of symptoms, NMO may not be easily distinguishable from IATM presenting as LETM, and NMO-IgG has been suggested as the most reliable marker to identify patients with this condition [2]. However, a recent report has indicated that positive NMO-IgG status may not be needed to reach a definite diagnosis in 90% of patients with clinically suspected NMO [10]. Among the idiopathic LETM patients presented here, all were seronegative, although in four patients, NMO-IgG were not analyzed. Two of these patients converted to MS and the other two died without presenting further relapses of either myelitis or ON. After excluding NMOSD and MS, recurrence of IATM or even LETM is rare in our experience. Monophasic isolated LETM might represent a distinct clinical syndrome, as others have suggested [11,12].

Studies analyzing CSF in IATM have reported pleocytosis in a high percentage of patients (42%-62%) [13-15]. Because patients with spinal cord ischemia show no CSF pleocytosis, it has been proposed that CSF leukocyte count could be a useful marker to differentiate inflammatory myelopathies from spinal cord infarcts [16]. In our series, however, a lower percentage of patients had pleocytosis (23.4%) than the reported rates. Because normal CSF cell counts can be found in both conditions, this marker would likely be of limited usefulness to identify IATM.

According to our findings, IATM presenting as LETM does not rule out a first demyelinating MS. These results are in agreement with a prospective study investigating

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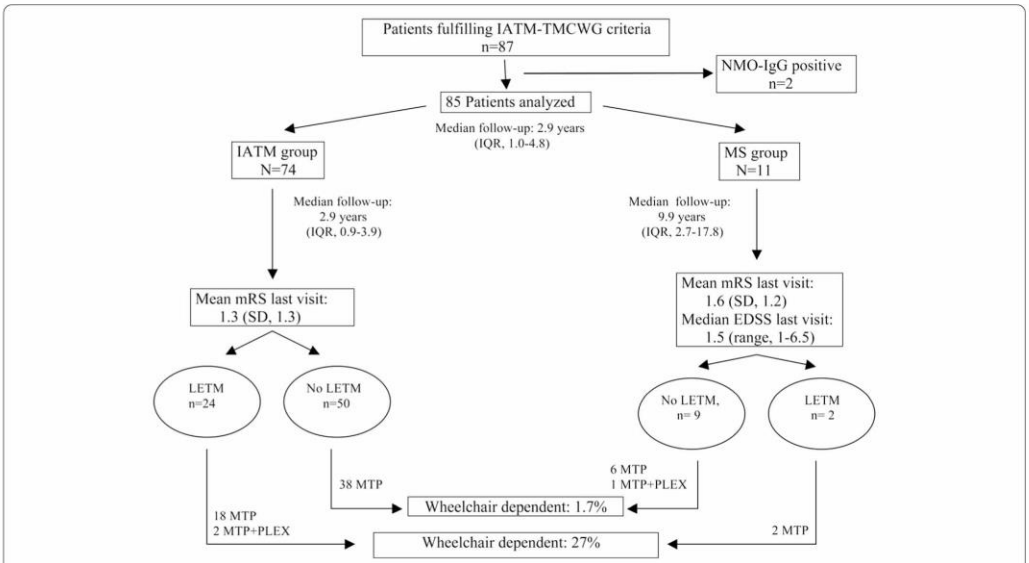

Figure 1 Diagram reflecting the prognosis of outcome in the different subgroups. *IATM* idiopathic acute transverse myelitis, *TMCWG* Transverse Myelitis Consortium Working Group, *LETM* longitudinally extensive transverse myelitis, *NMO-IgG* neuromyelitis optica IgG antibodies, *MTP* methylprednisolone, *PLEX*, plasma exchange, *EDSS* Expanded disability Status Scale, *mRS* modified Rankin Scale, *IQR* interquartile range.

LETM in white patients [17]. LETM has been associated with a poorer prognosis in patients with acute transverse myelitis [18,19] and recently, longer extension of LETM has been related to a higher number of relapses [17]. In our series, LETM was the most important independent risk factor for long-term disability.

Up to 50% of patients with neurological symptoms suggestive of spinal cord inflammation had normal spinal cord MRI [20]. In our study, 15.2% of patients neither showed evidence of lesions at first or subsequent spinal MRI nor revealed paraclinical data supporting inflammation within spinal cord. TMCWG criteria includes such a patients as 'possible ATM'.

Early studies reported that up to one third of patients with a first episode of acute transverse myelitis remained unable to walk [21,22]. Most studies carried out after establishment of the TMCWG criteria disclosed similar rates of poor outcome ranging from 11% to 35.8% [13,18,23]. In our series, only 9.4% of patients were unable to walk unassisted at completion of follow-up (Rankin ≥4). Differences in the length of follow-up, together with methodological aspects (collaborative multicenter studies *vs* hospital-based series), may have contributed to the better outcome in our cohort, compared to others [14,17].

Table 5 Disability at admission and last follow-up visit

mRS	Admission	Last visit
	n (%)	n (%)
0	0	27 (31.8)
1	14 (16.5)	26 (30.6)
2	22 (25.9)	11 (12.9)
3	21 (24.7)	13 (15.3)
4	21 (24.7)	7 (8.2)
5	7 (8.2)	1 (1.2)
6	0	0

mRS modified Rankin Scale.

Several clinical factors associated with a poor outcome have been described in patients with acute transverse myelitis, including back pain, severe functional deficit and motor involvement at onset of symptoms, symptoms progression within 24 hours, relapse occurrence, and spinal shock [3,14,21,22,24]. As was mentioned above, among the para-clinical factors, LETM has been associated with a poor prognosis in these patients [18,19]. The multivariate analysis in the present study showed that urinary sphincter dysfunction and LETM were independently associated with a poor prognosis in IATM.

Regarding patients with a first event involving an isolated spinal cord lesion, it is well recognized that partial myelitis is highly predictable of progression to MS [15,25]. Previous studies in IATM have reported a conversion rate of 0% [14,18] to 11.4% [23], with a mean follow-up ranging from 2 to 4.8 years. Therefore, in accordance with the results of our study, conversion to

MS may occur even after an appropriate follow-up of IATM patients. MS patients had a longer median follow-up compared with IATM patients. Although this difference might result in a lower conversion rate in the IATM group, MS patients showed a median time to conversion of 1.2 years (IQR 0.37-1.87) and the median follow-up time in the IATM group was 2.9 years. Therefore, IATM patients will unlikely convert to MS.

IATM patients testing positive for OCB in CSF had an increased risk of developing MS in the follow-up (33.3% vs 2% conversion rate). In contrast, the combination of negative OCB testing and IgG index ≤0.7 yielded a very low likelihood of converting to MS (NPV 100%). These data are in keeping with the results of previous studies investigating the utility of CSF findings in patients with a clinically isolated syndrome who convert to MS [26].

Age, family background, sensory symptoms, greater disability at onset of symptoms, brain MRI lesions, presence of OCB, and an abnormal CSF IgG index are reported predictive factors of conversion to MS in patients with a clinically isolated cord syndrome [27-29]. We found that in patients with an initial IATM, onset of symptoms at an early age is related to conversion to MS. In addition, patients with a normal IgG index and no evidence of OCB in CSF have a very low risk of converting to MS.

In addition to the retrospective nature of the case series, our study has other limitations. Firstly, our study was not designed to evaluate treatment response and therefore we could not consider therapeutic aspects when analyzing long term outcome. Secondly, a single centre design may be considered as a limitation although our hospital is a reference centre for patients with clinical symptoms suggestive of acute myelopathy in our sanitary district. Finally, we consider that the patients included herein will unlikely develop NMO: the seronegative status in LETM patients, the absence of other neurological signs such as ON, the relatively good final outcome and the absence of recurrence after almost 3 years of follow-up support the diagnosis of IATM [30,31].

In conclusion, our results indicate that at least 13% of patients who fulfill the TMCWG criteria for definite and possible IATM will convert to MS. Functional recovery in IATM is poorer in patients with urinary sphincter dysfunction at admission and findings of LETM on MRI study.

Consent

Written informed consent was obtained from all patients.

Abbreviations

TMCWG: Transverse myelitis consortium working group; IATM: Idiopathic acute transverse myelitis; NMO: Neuromyelitis optica; MS: Multiple sclerosis; MRI: Magnetic resonance imaging; ON: Optic neuritis; S: Sensitivity; Sp: Specificity; EDSS: Expanded disability status scale; CSF: Cerebrospinal fluid; OCB: Oligoclonal band; LETM: Longitudinal extensive transverse myelitis; SPMS: Secondary progressive multiple sclerosis; PPV: Positive predictive value; NPV: Negative predictive value; NMOSD: Neuromyelitis optica spectrum disorders.

Competing interest

Dr. Martínez Yélamos and Dra. Romero Pinel have received honoraria compensation for participating in AdvisoryBoards, acting as consultant and for speaking activities from Bayer Schering, Biogen idec, Merck-Serono and Teva.

Authors' contributions

AC designed the study, collected the data, participated in the statistical analysis and wrote the manuscript. AM and AA contributed to data collection and assisted with the writing manuscript. JB, LR and SMY participated in the design of the study, carry out the statistical analysis and reviewed the manuscript. All authors read and approved the final manuscript.

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Study 2. ETIOLOGIC SPECTRUM AND PROGNOSIS OF LONGITUDINALLY EXTENSIVE TRANSVERSE MYELOPATHIES.

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In this study we included 72 patients who fulfilled the criteria for the very first acute LETM.

Final diagnosis classification at follow-up completion

After a median (IQR) follow up of 34 (17,2-63) months, the most frequent diagnosis was the idiopathic form of LETM (30,5%) followed by MS (25%). A parainfectious aetiology was identified in 14,9% of patients; 4 viral, six bacterial and one patient due to *Mycobacterium tuberculosis.* SLE and SS were observed in 12,2% of patients. The other aetiologies identified, were spinal cord infarction and NMOSD in each of three patients and ADEM, dural fistula and tumour-related LETM in each of two patients.

Demographic and clinical relevant features

Among the whole cohort, LETM was diagnosed at a median (IQR) age of 41,5 (29-61,5) years and 45 (62,5%) patients were women. The median (IQR) length of contiguous vertebral segments in patients with a first episode of LETM was 5 (3-6,75).

MS patients were characterized by an onset of symptoms at an early age, a milder initial mRS score at onset and a lower frequency of sphincter

dysfunction compared to the rest of the aetiologies. Moreover, the presence of OCB and a cervical location on spinal cord MRI were related to MS patients.

In our population, we observed that only a small proportion of patients (5%) tested positive for AQP4-ab. The two patients who were positive for AQP4-ab were diagnosed with NMOSD at completion of follow-up.

Mortality is relatively frequent in LETM patients and 9,7% of them died at the end of the follow-up. Mortality was mainly observed in the vascular group. A high proportion of LETM patients had moderate disability and 72,2% of patients had an mRS ≥ 2. Idiophatic and systemic LETM were the most disabling aetiologies.

Predictive factors associated with outcome

Although sphincter dysfunction was related to poor outcome in the univariate analysis, the only two variables associated with unfavorable outcome in patients with a first episode of LETM after multivariate analysis were mRS ≥2 at admission and older age at onset.

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Etiologic Spectrum and Prognosis of Longitudinally Extensive Transverse Myelopathies

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Key Words
Longitudinal extensive transverse myelopathy · NMO-IgG · Multiple sclerosis, prognosis · Neuromyelitis optica

Abstract
Background: Patients with a first episode of longitudinal extensive transverse myelopathy (LETM) were reviewed with two objectives: to evaluate the clinical spectrum of LETM and to analyze the related clinical and laboratory variables that can be used as functional prognostic markers. ***Methods:*** A retrospective review was conducted of clinical, radiologic and biochemical data of patients admitted for LETM between 1993 and 2011. ***Results:*** Our cohort included 72 patients [median age 41 years, interquartile range (IQR) 29–61.5]. Median follow-up was 34 months (IQR 17.2–63). The modified Rankin Scale (mRS) score was ≥2 at the end of follow-up in 72.2%. The final diagnosis was idiopathic LETM in 22 patients, multiple sclerosis in 18, parainfectious disease in 11, systemic disease in 9, spinal cord infarction and neuromyelitis optica spectrum disorders in 3 patients each, and acute demyelinating encephalomyelitis, dural fistula, and tumor-related LETM in 2 patients each. Unfavorable outcome was associated with mRS ≥2 at admission [odds ratio (OR) 1.39, 95% confidence interval (CI) 1.16–1.66] and older age (OR 1.06, 95% CI 1.01–1.11). ***Conclusion:*** Idiopathic LETM was the most frequent diagnosis at the end of follow-up. Older age and clinically severe disease at onset were independent prognostic factors of poorer functional recovery.

Introduction

Longitudinal extensive transverse myelopathy (LETM) refers to a spinal cord lesion extending over three or more vertebral segments. This condition is classically associated with neuromyelitis optica (NMO) and NMO spectrum disorders (NMOsd) [1, 2]. NMO is also characterized by unilateral or bilateral optic neuritis (ON) and positive testing for an antibody targeting aquaporin-4 (NMO-IgG) [3] in serum. Traditionally, symptoms affecting regions other than the optic nerves and spinal cord exclude the diagnosis. However, asymptomatic lesions on brain magnetic resonance imaging (MRI) have been described in up to 60% of NMO patients [4, 5].

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The differential diagnosis of LETM includes a broad range of conditions, such as autoimmune inflammatory disease, infectious disease, neoplastic disease, nutritional deficiency, and traumatic injury [6]. Information on the existing etiologic and prognostic factors at the first clinical evidence of LETM is important for patient counseling, follow-up, and treatment. Nonetheless, most studies have investigated etiologic factors only in specific LETM subgroups, such as NMO or autoimmune-related NMO [7, 8]; very few have considered the entire etiologic spectrum of LETM [9].

The aim of this study is to assess the outcome of a large series of consecutive patients with a first ever LETM event, to establish the etiologic spectrum of this condition, and to identify predictors of outcome.

Table 1. Diagnostic criteria for LETM

Inclusion
1. Onset of symptoms over no more than 21 days
2. Spinal cord T2 signal hyperintensity over three or more consecutive vertebral segments
3. Bilateral motor or sensory symptoms with or without sphincter dysfunction
4. Available brain MRI study
Exclusion
1. Previous spine irradiation
2. Evidence of spinal compression
3. History of neurological disease or symptoms
4. No symptoms or signs attributable to involvement other than the spine

Table 2. NMO diagnostic criteria [3]

1. Optic neuritis
2. Acute myelitis
3. Two of three supportive criteria
3.1. Spinal cord MRI lesion extending over ≥3 contiguous vertebral segments
3.2. Brain MRI findings do not meet diagnostic criteria of MS
3.3. NMO-IgG-seropositive status

Materials and Methods

Ethics Statement

This study was approved by the Clinical Research Ethics Committee of Bellvitge University Hospital (IDIBELL, ref. PR277/12). Written consent was waived by the approving IRB.

Patients

Seventy-two patients older than 18 years, consecutively diagnosed with LETM at Bellvitge University Hospital (Barcelona, Spain) between January 1993 and January 2011, were evaluated. A retrospective medical chart review was conducted of relevant clinical, radiologic, and biochemical data.

Clinical Variables

The diagnostic criteria for LETM are described in table 1. ON was diagnosed based on the presence of at least two of the following criteria: reduced visual acuity, afferent pupillary defect, color vision loss, visual field abnormality, and/or pain on eye movement. Visual evoked potentials were performed when ON was suspected. The modified Rankin Scale (mRS) was used to evaluate disability at nadir of symptoms and at follow-up [10]. Rankin scores were categorized into two groups, mRS <2 and mRS ≥2, to distinguish two patient groups, with the higher score indicating clinically significant functional disability. Patients who converted to multiple sclerosis (MS) were evaluated by the Expanded Disability Status Scale (EDSS). Death during follow-up was recorded.

Imaging Data

Baseline (within 20 days from onset of symptoms) and follow-up MRI scans had been performed in all patients on a 1.5-Tesla system. Brain MRI studies included axial and sagittal images obtained with the following sequences: T1-weighted conventional spin-echo, T2-weighted fast spin-echo, fluid attenuated inversion recovery (FLAIR) spin-echo, and T1-weighted conventional spin-echo after a single dose of gadolinium (0.1 mg/kg).

MRI study included the cervical, thoracic, and lumbar spine. In the sagittal plane, T1-weighted sequences with and without gadolinium, T2-weighted sequences, and short tau inversion recovery (STIR) sequences were performed. We recorded the number of lesions, their extent (number of vertebral levels), and their location in the sagittal plane. In the MS group, we also recorded lesion location in the axial plane. Gadolinium contrast material was administered in 61 patients.

Laboratory Data

Information on cerebrospinal fluid (CSF) cell count, glucose concentration, and protein levels determined in lumbar puncture specimens was recorded, as well as oligoclonal bands (OCB) by immunofixation electrophoresis. In NMOsd, the CSF/serum albumin ratio (Q_{Alb}) – Alb_{CSF} [mg/l]/Alb_{serum} (g/l) – was performed to evaluate blood-brain barrier function. The upper limit was estimated as described elsewhere [11].

Antibodies against the following infectious agents were sought in serum analyses: *Borrelia burgdorferi*, human immunodeficiency virus (HIV) 1 and 2, hepatitis A, B and C, herpes simplex virus (HSV), adenovirus, cytomegalovirus (CMV), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6), enterovirus, chlamydia, and mycoplasma. Findings from polymerase chain reaction testing in CSF, performed when considered appropriate, were reviewed for HSV, CMV, VZV, EBV, HHV-6, adenovirus, and enterovirus. Fungal, parasite, and tuberculin testing had been carried out when these agents were suspected, and the results were included in the analysis. Autoantibodies were sought (anti-nuclear, anti-DNA, anti-Ro, anti-La,

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Table 3. Epidemiological and clinical features of LETM in the four main etiological subgroups

Etiology	Total (n = 72)	MS (n = 18)	PIM (n = 11)	Systemic disease (n = 9)	Idiopathic (n = 22)
Median age, years (IQR)	41.5 (29–61.5)	31.5 (24–40.5)[a]	35 (29–62)	55 (36–66.5)	55 (33.5–61)
Female, n (%)	45 (62.5)	15 (83.3)[b]	6 (54.5)	7 (77.8)	11 (50)
Sphincter dysfunction, n (%)	70.8 (51)	7 (38.9)[a]	10 (90.9)	7 (77.8)	17 (77.3)
Median initial functional score, mRS (IQR)	3.5 (2–4)	2 (2–3)[a]	4 (3–5)	3 (2.5–4)	4 (2–4.25)

[a] After Bonferroni correction $p < 0.001$. [b] $p < 0.05$ for comparison with the remaining etiologies.

lupus-like anticoagulant, anti-cardiolipin, anti-$\beta_2$gpI, and anti-neutrophil cytoplasmic antibodies), as well as cryoglobulins, complement, angiotensin-converting enzyme, rheumatoid factor, and anti-human globulin (Coombs' test). Lastly, we recorded onconeural antibodies [anti-Hu, anti-CV2 (CRMP5), anti-amphiphysin, and anti-Ma2], which had been determined based on clinical criteria.

Serum and CSF NMO-IgG antibodies could not be systematically sought, as the technique first became available in our hospital in 2007 [12]. This validated technique has a sensitivity of 50–60% and a specificity of more than 90%. Stored samples or samples obtained during follow-up were analyzed in idiopathic LETM patients diagnosed before 2007, seeking NMO-IgG antibodies.

Etiologies

Eight etiologic groups were defined: (1) MS, in accordance with the Poser or McDonald criteria [13, 14]. Patients previously diagnosed with MS at the time of LETM were excluded; (2) acute demyelinating encephalomyelitis (ADEM) [15]; (3) NMOsd [2] and NMO (table 2) [3]; (4) parainfectious myelopathy (PIM), defined by serological or polymerase chain reaction proof of recent infection [16]; (5) systemic disease, defined by the modified criteria of the American Rheumatism Association for systemic lupus erythematosus (SLE) and the revised Vitali et al. criteria for Sjögren's syndrome (SS) [17, 18]; (6) vascular etiology, differentiated into spinal cord infarction, defined by an acute onset, signal anomalies corresponding to a vascular territory on spinal cord MRI and no other etiology after an extensive work-up [19], and dural fistula; (7) tumor-related etiology (i.e. probable paraneoplastic-related myelopathy [20] or spinal cord tumor), and (8) idiopathic LETM, diagnosed on the presence of an extensive spinal cord lesion (≥3 consecutive vertebral segments) demonstrated by T2-weighted MRI when no other cause could be identified after an extensive work-up and follow-up.

Statistical Analysis

Data were expressed as the mean, median, or percentage, as appropriate. Statistical analysis was only performed in the main subgroups (MS, PIM, systemic, idiopathic), as patient number was too low in the other subgroups. Differences in clinical and demographic parameters between subgroups were evaluated using the Mann-Whitney U test (quantitative variables) or χ^2 test (categorical variables). All tests were bilateral, and a p value <0.001 was considered significant after Bonferroni correction.

Univariate analysis followed by stepwise multivariate logistic regression analysis was performed to assess factors associated with an unfavorable functional outcome. All variables with a p value <0.05 in the univariate analysis were entered in the multivariate model. All statistical analyses were performed by SPSS version 20.0.

Results

Epidemiological and Clinical Data

Seventy-two patients with a first ever acute LETM event were identified. The median age was 41.5 [interquartile range (IQR) 29–61.5] years and 45 (62.5%) were women. Median follow-up was 34 months (IQR 17.2–63). The epidemiological and clinical data of the four main subgroups are summarized in table 3.

Idiopathic LETM was diagnosed in 22 patients. The median follow-up in this group was 41 months (IQR 15–112). Demyelinating myelopathy was identified in 23 patients. Among them, 18 patients presented with MS. At the initial assessment, 2 patients fulfilled the McDonald criteria. The remaining patients were diagnosed during follow-up. Of 18 patients, 15 fulfilled the Barkhof criteria in the first brain MRI and 14 of 17 were OCB-positive on CSF testing (fig. 1; table 4).

Within the demyelinating syndromes other than MS, 2 men, aged 25 and 29 years, were diagnosed with ADEM and 3 women with NMOsd. Two of the women tested positive for NMO-IgG antibodies in serum and the third tested negative. One 41-year-old NMO-IgG-seropositive patient had recurrent LETM and recurrent bilateral ON (fig. 2), and the other (53 years old) had isolated LETM. The seronegative patient was 75 years old at onset of symptoms and presented with isolated LETM and bilateral recurrent ON. Clinical findings of NMOsd patients are shown in online supplementary table 1 (see www.karger.com/doi/10.1159/000358512 for all online suppl. material).

Table 4. MRI and CSF features of LETM in the four main etiological subgroups

Etiology	Total (n = 72)	MS (n = 18)	PIM (n = 11)	Systemic disease (n = 9)	Idiopathic (n = 22)
MRI characteristics					
Cervical lesion, n (%)	19 (26.4)	10 (55.6)[a]	1 (9.1)	1 (11.1)	6 (27.3)
Thoracic lesion, n (%)	56 (22.2)	4 (22.2)	3 (27.3)	2 (22.2)	3 (13.6)
MRI vertebral segments affected, median (IQR)	5 (3–6.8)	4 (3–6)	5 (3–10)	5 (4–5.5)	5 (3.8–7)
Contrast enhancement, n (%)	35/61 (57.4)	11/16 (68.7)	8/10 (80)	6/8 (75)	2/16 (12.5)[a]
Brain lesion features*, n = 71 (%)					
Normal	32/71 (45.0)	1 (5.6)	7 (63.6)	2 (22.2)	15 (68.2)
Non-specific white matter lesions	22/71 (31.0)	2 (11.1)	4 (36.4)	7 (77.8)	7 (31.8)
Barkhof criteria	17/71** (23.9)	15 (83.3)	0	0	0
CSF					
Proteins >0.45 g/l, n (%)	34/64 (53.1)	4/16 (25)[b]	10/10 (100)[b]	5/8 (62.5)	8/20 (40)
Cell count/mm^3 >5, n (%)	20/65 (30.8)	4/16 (25)	4/11 (36.4)	2/7 (28.6)	6/21 (28.6)
OCB positive, n (%)	15/48 (26.8)	14/17 (82)[a]	0/8 (0)	1/8 (13)	0/15 (0)[b]
Glucose >4 mmol/l, n (%)	15/60 (23.4)	4/18 (28.6)	2/11 (18.2)	1/9 (11.1)	7/22 (31.8)

[a] After Bonferroni correction, $p < 0.001$. [b] $p < 0.05$ for comparison with the remaining etiologies.
* The anti-Hu paraneoplastic patient with brain metastasis is not included. ** Two ADEM patients included.

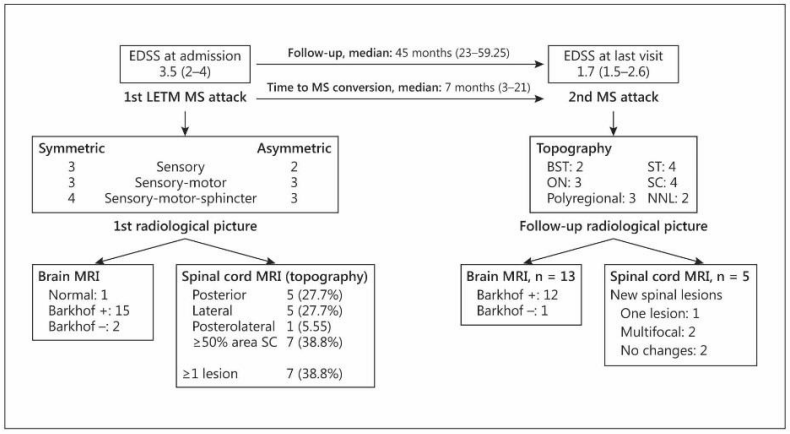

Fig. 1. Characteristics of the 18 MS patients. BST = Brainstem; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; MRI = magnetic resonance imaging; NNL = no new lesions; ON = optic neuritis; SC = spinal cord; ST = supratentorial.

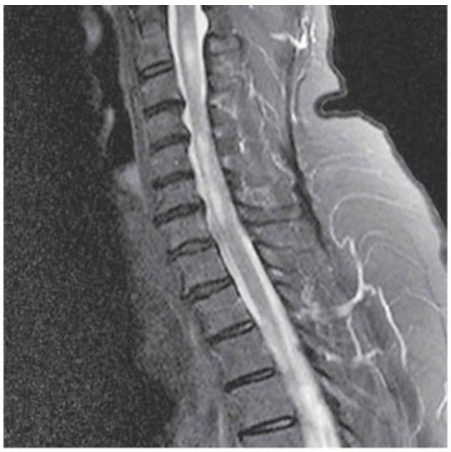

Fig. 2. Extensive T2 hyperintensity throughout the spinal cord in an NMO patient testing positive for NMO-IgG.

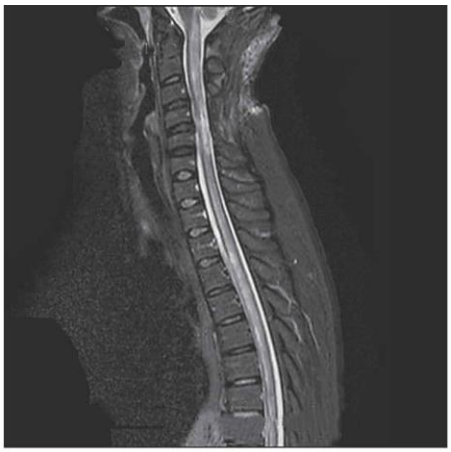

Fig. 3. Spinal cord magnetic resonance images from an MS patient presenting with LETM. Sagittal T2-weighted image shows extensive T2 hyperintensity from C5 to C7 and a patchy lesion from C1 to C2.

A parainfectious etiology was identified in 11 patients: 4 were classified as having viral-related myelopathy (2 VZV, 1 adenovirus, and 1 CMV), 6 as bacterial-related myelopathy (5 *Mycoplasma pneumoniae* and 1 *Chlamydia pneumoniae*), and 1 patient as *Mycobacterium tuberculosis*-related myelopathy.

Systemic disease was diagnosed in 9 patients; 5 had SLE (2 also had secondary SS) and 6 had SS (4 primary and 2 secondary).

Among the 4 main subgroups, early onset of symptoms and female sex were associated with MS, although the latter was not statistically significant after Bonferroni correction. The presence of sphincter dysfunction and disability at admission were less frequent in MS patients. There were no other differences between the groups regarding the other epidemiological or clinical variables (table 3).

Three women were diagnosed with spinal cord infarction at the age of 90, 71, and 62 years, respectively; the probable cause was aortic aneurysm in 1 patient, and unknown in the remaining 2 cases. Two men, aged 66 and 67 years, had a dural fistula.

Paraneoplastic myelopathy was present in a 64-year-old man (small-cell lung cancer and positive anti-Hu antibodies). Another 31-year-old man had a spinal cord tumor (astrocytoma).

Regarding treatment, 64 patients received intravenous methylprednisolone and 4 patients required further treatment (online suppl. table 2).

Laboratory Findings

NMO-IgG antibodies were determined in 41 (56.9%) patients, 6 of 9 in the systemic disease group, 5 of 11 in the PIM group, 4 of 18 in the MS group, all patients with NMOsd, and the 2 patients with a tumor-related etiology. Results were negative in all cases, with the exception of 2 NMOsd patients.

Among 22 patients with idiopathic LETM, NMO-IgG testing was negative in 21, and 1 patient died due to a myelopathy-unrelated condition before the technique was available. After 5 years of meticulous follow-up, no relapses had been observed in this patient. CSF features in patients with NMOsd are shown in online supplementary table 1.

The MS group had positive CSF OCB results and low protein levels more often than patients with the remaining etiologies. By contrast, in idiopathic LETM patients, there was a trend toward increased CSF protein levels and an absence of OCB (table 4).

Table 5. Factors associated with unfavorable outcome at the end of follow-up in the four main etiological subgroups

	Functional outcome (mRS)		Univariate analysis	Multivariate analysis	
	<2	≥2	p value	OR (95% CI)	p value
Number (%)	19 (31.6)	41 (68.3)			
Mean age, years ± SD	34.7±14.7	47.4±17.14	0.007	1.06 (1.01–1.11)	0.021
Male/female, %	36.8/63.2	34.1/65.9	1		
Sphincter dysfunction, %	47.4	78	0.035		
Median admission mRS (IQR)	2 (2–3)	4 (2.5–4.5)	<0.001	2.87 (1.52–5.39)	0.001
Cervical lesion on MRI, %	21.1	34.1	0.37		
Thoracic lesion on MRI, %	31.6	14.6	0.17		
Median MRI vertebral segments (IQR)	4 (3–6)	5 (4–6.5)	0.14		
Contrast enhancement, %	56.2	52.9	1		
CSF OCB-positive, %	29.4	32.3	1		
CSF glucose >4 mmol/l, %	17.6	21.6	1		
CSF proteins >0.45 g/l, %	52.9	48.6	0.7		
CSF cell count/mm^3 >5, %	33.3	27.02	0.7		
Autoantibodies in serum, %	26.3	28.9	1		
Etiology of LETM, %					
MS	36.9	61.1	0.36		
PIM	45.5	54.5	0.27		
Systemic disease	22.2	77.8	1.0		
Idiopathic	22.7	77.3	0.58		

MRI Findings

At baseline MRI analysis, a median of 5 (IQR 3–6.75) spinal cord vertebral segments were affected (table 4). LETM presenting in a cervical location was more common in the MS group (table 4; fig. 3). Gadolinium-enhancing lesions were less frequent in the idiopathic LETM group than in non-idiopathic patients. MS patients had a median of 9 brain lesions, whereas in the three other main groups, brain MRI was normal or showed non-specific white matter lesions (table 4). As to the less prevalent groups, brain MRI showed confluent supratentorial white matter lesions in the 2 ADEM patients, multiple supratentorial metastasis in the paraneoplastic LETM patient, and leukoaraiosis in 1 patient with vascular myelopathy. In the NMOsd group, the single NMO-IgG-seropositive patient with isolated LETM had 3 non-specific frontal white matter lesions. Brain MRI was normal in the remaining patients.

Outcome and Disability

Of the 72 patients with LETM, 7 (9.7%) died during follow-up after a median interval of 26 months (IQR 19–52) since the diagnosis. By etiology, mortality was greatest in the vascular myelopathy group, with 2 deaths (both due to spinal cord infarction). Two deaths occurred in patients with systemic disease and there was 1 death each in the MS group, idiopathic group, and anti-Hu paraneoplastic myelopathy. Death was due to LETM or LETM-related complications in 3 cases: 2 patients with spinal cord infarction died from bronchopneumonia, and the patient with paraneoplastic myelitis died from pneumonia complicating small-cell lung cancer. Of the non-LETM-related deaths, 1 patient in the systemic disease group died due to a complication of anaplastic lymphoma and the other to an undetermined cause. The MS patient died of high-grade glioma of the brain. The idiopathic patient developed respiratory failure after being diagnosed of non-small cell lung cancer at 5 years' follow-up.

At the end of follow-up, mRS was ≥2 in 52/72 (72.2%) patients. The final functional score was ≥2 in 11/18 MS, 6/11 PIM, 7/9 systemic, and 17/22 idiopathic LETM patients. The predictors of unfavorable functional score (mRS ≥2) are presented in table 5. On multivariate analysis, an unfavorable outcome was independently associated with mRS ≥2 at admission [odds ratio (OR) 1.39, 95% confidence interval (CI) 1.16–1.66] and older age at onset (OR 1.06, 95% CI 1.01–1.11).

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Discussion

In this study, we present the largest clinical series of patients with a first ever LETM event to better characterize the prognosis and etiologies related to this condition. The stratification of etiologies used in this study had been described in previous articles investigating non-longitudinally extensive acute and subacute myelopathies [16, 19]. In keeping with the results of these studies, we found that idiopathic LETM and MS were the most frequent etiologies in our patients.

Only 2 patients in our population were NMO-IgG-positive: 1 who fulfilled the NMO disease criteria and 1 with recurrent LETM. None of the seronegative LETM patients experienced a second relapse. Other authors have also reported a low percentage of positive NMO-IgG antibodies in patients presenting with LETM [21–23]. Nonetheless, a recent study evaluating LETM patients in an international reference center reported that almost 60% of cases presented antibodies against aquaporin-4 [9]. Referral bias, ethnicity, and technique sensitivity may be responsible for these differences.

Idiopathic LETM is reported to account for about 15% of all acute transverse myelitis cases [24]. In our LETM cohort, 30.5% of patients had an idiopathic etiology. In a recent study, we reported that 13% of patients with idiopathic myelitis will ultimately convert to MS [25]. To decrease potential misclassifications in this regard due to a short follow-up, the median duration of follow-up in our cohort was 3 years, a long enough period to detect conversions.

Although the onset of MS does not commonly manifest as LETM [21, 26], about 30% of patients presenting with LETM as their first neurological symptom will eventually develop MS [22]. In our cohort, MS was the second most frequent diagnosis at the end of follow-up (25%), and the patients had the typical features seen in MS. Of the 18 patients with MS, 15 fulfilled the Barkhof criteria on the first brain MRI and 7 had more than one spinal cord lesion on the first spinal cord MRI, results in keeping with those of other studies [16, 22, 27]. In the single patient with an initially normal brain MRI, spinal MRI revealed more than one cord lesion. Therefore, all MS patients presenting with LETM as the first neurological manifestation had more than one neuraxis lesion on MRI.

The third largest etiologic group was that of infectious disease. The term *parainfectious NMO syndrome* has been proposed for patients with an associated viral or bacterial agent, fulfilling NMO criteria [28]. Six of 11 patients in the PIM group were lacking NMO-IgG antibodies, hence we cannot strictly rule out the diagnosis of parainfectious NMO syndrome. Notwithstanding, the relatively good long-term outcome and the absence of subsequent ON or myelitis in this subgroup during a median follow-up of 58 months (IQR 16.8–95.3) suggest an etiology other than NMO. To the best of our knowledge, only 2 cases of LETM associated with *M. pneumoniae* infection have been reported [29].

The association between myelopathy and systemic diseases, such as SLE and SS, is well recognized [30, 31]. However, a recent study has suggested that NMOsd, SS, and SLE might be overlapping disorders that can coexist in some patients [8]. Within the systemic group, none of the 3 patients who were not tested for NMO-IgG presented further relapses after a mean follow-up of 102.3 months (SD 82.81); thus, we can reasonably dismiss the coexistence of other diseases, such as NMOsd.

Regarding the CSF features in NMOsd patients, it has been reported that up to 68% of NMO-IgG-seropositive NMO patients, but no -seronegative ones, are positive for NMO-IgG in CSF. The authors underlined the limited usefulness of testing NMO-IgG antibodies in CSF if it is not found in serum [11]. Despite the low prevalence of NMOsd in our study, all seropositive NMO patients were positive for NMO-IgG in CSF. A key unresolved issue in the pathogenesis of NMO is the mechanism by which serum NMO-IgG antibody enters the central nervous system to cause neuroinflammation. None of our patients had abnormal Q_{Alb} findings, which suggests an absence of blood-brain barrier disruption.

The other etiologic groups (vascular myelopathy, tumor-related myelopathy, ADEM, and NMOsd) were much less common and were not considered in the statistical analysis. Further studies focusing on these specific causes of LETM are needed to detect the singularities related with each cause.

The distribution of radiologic lesions in our cohort was heterogeneous. However, in the same line as reported in previous studies [32], the presence of cervical lesions on spinal MRI was more common in patients with MS. The number of affected spinal segments was not related to a poorer outcome in patients with a first LETM event, in accordance with the findings of a recent study [21].

Functional outcome has been assessed in patients with NMO [33, 34], and the single recent study focused on LETM reported a mortality rate of 6.5% [9]. The 9.7% mortality found in the present study is similar to the rates described for non-longitudinally extensive transverse myelitis [16]. It should be noted that some etiologies (e.g. vascular myelopathy) seem to be associated with higher

mortality, as has been suggested by others [35]. 72% of our cohort had an unfavorable functional outcome, with the PIM group showing a slightly better functional outcome than the other etiologies. This relatively good evolution has been previously described in herpes zoster myelitis [36].

We found that admission mRS ≥2 and older age were associated with a poorer prognosis in the multivariate analysis. Disability at admission was also found to be related to a worse prognosis in a recent prospective study of 23 LETM patients [21]. Authors investigating non-longitudinally extensive myelopathies have reported that admission functional score has an important impact on the final outcome [24].

The influence of immunosuppressive therapies on disability outcome in seronegative LETM remains elusive [37, 38]. In the absence of therapeutic guidelines, patients did not receive standardized treatment. Hence, we cannot make conclusions about therapeutic aspects related to outcome.

One possible limitation of this study is that patients were recruited in a single university hospital, although all departments were investigated to provide a more comprehensive representation of the etiologies. Second, NMO-IgG antibodies were not determined in the overall population. Since the medical chart review covered 19 years, the NMO-IgG technique was not available over the entire study period and some patients were not tested for these antibodies. We consider that the idiopathic LETM patients included here are not likely to develop NMO: the seronegative status, absence of other neurological signs such as ON, and absence of recurrence after almost 3 years of follow-up support the idiopathic form [33, 39]. Moreover, according to the revised criteria, positive NMO-IgG status is not currently required for the diagnosis of NMO, and is described to be mandatory for the diagnosis in only 10% of patients [3, 34]. Third, owing to the small number of patients fulfilling the revised NMOsd criteria, it was not possible to compare the clinical and radiological features or autoantibody status of this subgroup with that of the other etiologies, as others have done [9]. Finally, the long recruitment period may have affected the homogeneity of the criteria defining the different LETM etiologies, although for the final diagnosis the criteria available at the end of follow-up were applied. Given the long follow-up period, this is unlikely to be an important bias.

In conclusion, this study sheds light on the etiologic spectrum of LETM and the possible differential diagnoses related to this condition. In our cohort, idiopathic LETM was the most frequent etiology and less than 5% of patients had NMOsd. Older age and clinically severe disease at onset were independent prognostic factors of poorer functional recovery in patients with LETM.

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Study 3. ANTIBODIES TO MOG IN AQP4 ANTIBODIES SERONEGATIVE LONGITUDINALLY EXTENSIVE TRANSVERSE MYELITIS: CLINICAL AND PROGNOSTIC IMPLICATIONS.

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In the present study, we included 56 patients who met the diagnosis for AQP4-ab seronegative LETM.

Comparison between MOG-ab positive and negative patients

We observed that 13 (23%) of patients diagnosed with AQP4-ab seronegative LETM had MOG-ab present in serum.

Clinically, MOG-ab positive patients were characterized by an earlier onset of symptoms, higher predisposition to ON relapses, higher ON relapse rate and a better functional outcome than MOG-ab negatives.

Although there were no differences in length, lesion distribution or gadolinium enhancement at the spinal cord MRI, we identified 36,4% of MOG-ab positive patients who showed a complete resolution of the spinal cord lesion on MRI at the last follow-up, as compared to 6,9% of MOG-ab negatives.

One interesting finding was the relation between MOG-ab patients and the presence of CSF pleocytosis (92,3 % in MOG-ab positive group vs 45,2% in MOG-ab negative group).

Predictive factors associated with outcome

We identified two independent prognostic factors in AQP4-ab seronegative LETM patients. A higher disability at onset was related to a worse recovery and the presence of MOG-ab with a good outcome. Moreover, we observed that MOG-ab positive patients were at a higher risk to present an ON episode, and therefore, a higher chances of conversion to NMO, at the end of the follow-up.

Final diagnosis classification on completion of follow-up

The diagnostic distribution between MOG-ab positive and negative patients was different. Within the MOG-ab positive group, 30,8% of patients had NMO conversion, 15,4% presented LETM recurrences and 58,9% remained as monophasic LETM, after a median (IQR) follow-up of 43,8 (41,4-68,3) months. Only 4,7% of patients converted to NMO, 16,3% had recurrent LETM, 76,7% were monophasic LETM and 1,8% had MS conversion within the MOG-ab negative group after a median (IQR) follow-up of 38,4 (23,5-80,1) months.

MOG-ab temporal dynamics

In five out of 13 MOG-ab positive patients, the serum sample to analyze MOG-ab was collected in the acute phase (<30 days from onset) and during remission in the remainder after a median of 15 months (7-136) from onset. During the follow-up, we obtained serum from six patients after a median of 34 (range, 4-60) months. All but one patient (monophasic LETM) remained positive. The sample of the negative patient was collected after 43 months.

Antibodies to MOG in AQP4 antibodies seronegative longitudinally extensive transverse myelitis: clinical an prognostic implications

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Abstract

Objective: We aimed to investigate the frequency and clinical significance of antibodies to MOG (MOG-ab) in patients who presented with a first episode of seronegative AQP4 antibodies (AQP4-ab) longitudinally extensive transverse myelitis (LETM).

Methods: Epidemiological, clinical, and paraclinical data of 56 patients from three European centers were analyzed. Patients were retrospectively tested for MOG-ab and AQP4-ab, by cell-based assays.

Findings: Thirteen (23.2%) patients were MOG-ab positive. Among the 56 patients, 6 (10.7%) converted to neuromyelitis optica (NMO), 1 (1.8%) to MS, 9 (16.1%) had recurrent LETM, and 40 (71.4%) remained as monophasic LETM. Compared with seronegative patients, those with MOG-ab were younger (median: 32.5 vs 44 years; p=0.007), had more frequently

cerebrospinal fluid pleocytosis (94% vs 45%, *p*=0.003) and had better outcome (median EDSS 2.0 vs 3.0, *p*=0.027). MOG-ab positive patients also showed an increase risk of optic neuritis relapse and NMO conversion (*p*=0.010).

Conclusion: Patients with MOG-ab in AQP4-ab seronegative LETM have clinical distinctive features, higher risk of optic neuritis relapses, and better outcome than patients seronegative.

INTRODUCTION

Longitudinal extensive transverse myelitis (LETM) refers to an inflammation of the spinal cord extending at least three vertebral segments in length at spinal cord imaging.[1] Although LETM is a characteristic clinical feature of neuromyelitis optica (NMO) and part of the diagnostic criteria of the disease,[1] LETM at presentation may also be the prelude of a wide range of autoimmune or infectious diseases, and ischemic or metabolic disorders as well.[2]

Antibodies to aquaporin-4 (AQP4-ab) are the most valuable prognostic factor of recurrence or conversion to NMO after a first episode of isolated LETM.[3] However, up to 50% of patients presenting with isolated LETM remain seronegative for AQP4-ab, despite the refinement of detection methods,[4-6] and some of them will convert to NMO.[7] AQP4-ab seronegative LETM differs

from seropositive ones in several demographic and clinical features,[4] but whether AQP4-ab seronegative LETM represents a homogenous entity remains unclear. Hence, a first episode of AQP4-ab seronegative LETM is still a challenge in daily clinical practice and there is a need to identify further markers to predict the clinical course of this condition.

Humoral immune responses to native myelin oligodendrocyte glycoprotein (MOG), a transmembrane component of the outer surface of myelin lamellae with encephalitogenic properties,[8] have been detected specifically in patients with inflammatory central nervous system (CNS) demyelinating diseases using cell based assays.[9] These MOG-ab have been mainly described in paediatric patients with acute demyelinating encephalomyelitis (ADEM).[10,11] Interestingly, they have also been found in children and adults patients with NMO and suspected limited forms of the disease who are AQP4-ab seronegative.[12-16]

The aim of the present study was to investigate the frequency and clinical significance of MOG-ab after a first episode of AQP4-ab seronegative LETM.

METHODS

Patients

Fifty-six patients with a first episode of isolated LETM seronegative for AQP4-ab (inclusion criteria in **Table 1**) from three European

Neuroimmunology Centers (Universitary Hospital of Lyon, and Toulouse, France; and Universitary Hospital of Bellvitge, Spain) were included in the study. Data were prospectively collected from January 2005 through December 2014 and entered into the Database adapted from the EDMUS system (Eugène Devic European Network, EDEN)),[18] and retrospectively analyzed.

Demographic (gender, age, and ethnicity) and clinical data including topography and number of relapses were collected. Patients were followed every six months and additionally when relapses were suspected. Relapse was defined as a second inflammatory episode at the spinal cord or other CNS structure after one month from the first episode and sustained at least 24 hours in the absence of fever or infection.

Disability was evaluated on admission and last visit based on the Expanded Disability Status Scale (EDSS).[19] Multiple sclerosis (MS) and NMO conversion were based on McDonald and Wingerchuk 2006 criteria, respectively.[1,20] Date of conversion was noted.

Description of the number of levels affected on spinal cord magnetic resonance imaging (MRI) was determined in T2-weighted sequences in the sagittal plane, and brain MRI lesions were classified as normal and abnormal with or without Paty's criteria.[21] Follow-up spinal MRI were available in 40 patients. Results were classified as follows: normal imaging, decrease or increase lesion in length and atrophy.

Cerebrospinal fluid (CSF) was analyzed for cell count, protein content, IgG index and oligoclonal bands (OCB) by using immunofixation electrophoresis at the referring hospital for all patients.

Cell-based assays

Samples were tested for AQP4-ab and MOG-ab in two centers, Lyon Neuroscience Research Center of Lyon and laboratory of the Neuroimmunology Program, Institut d'Investigació Biomèdica August Pi iSunyer (IDIBAPS) of Barcelona, by live cell-based assays and using the same protocols and plasmids, as reported.[7,15,22] Briefly, for MOG-ab, HEK293 cells were transfected with the full- length MOG C-terminally fused to enhanced green fluorescence protein (the clone was a gift from Dr. M Reindl). After 24 hours, HEK293 transfected cells were incubated with patient's serum at 37 ºC for 30 minutes. They were fixed with 4% PFA for 10 minutes and permeabilized with 0.3% Triton X-100, thereafter. Alexa Fluor 594 was used as a secondary antibody against human IgG in order to immunolabeled the HEK cells. Transfected HEK293 cells were analyzed in Lyon by flow cytometry (BD, FACS Canto™; serum dilution 1:620), and in Barcelona by indirect immunofluorescence (serum dilution 1:160). All samples were investigated by two investigators blinded to the clinical data (R.M in Lyon, and A.S. in Barcelona). Previously, coded samples were exchanged between both centers and the results showed a complete agreement.

Samples used in this study were stored a -80 ºC at Biobank Institut d'Investigació Biomèdica de Bellvitge [IDIBELL] and Neurobiotec from Hospices Civils de Lyon. The study was approved by the ethics committee of the Hospital of Lyon, Toulouse and Hospital de Bellvitge. All patients gave their informed consent to participate in the study.

Statistical analysis

Categorical and continuous variables were compared with nonparametric test (Fisher exact and Mann–Whitney U test, respectively). Functional outcome was evaluated using the EDSS score at the last visit, and patients were categorized in two groups: good outcome for those with an EDSS $\leq$ 2.5 and moderate to severe disability for those with an EDSS $\geq$ 3.0 score. The analysis of prognostic factors was done by multivariate logistic regression model using the forward and backward stepwise method and including only those variables with a p-value < 0.20 in the univariate analysis. Cox regression analysis was performed to identify independent variables using the statistically significant variables from the bivariate study. Statistical significance was set at two-tailed *p*-value < 0.05. All statistical analyses were performed using STATA (64-bits) software.

RESULTS

Demographic and general clinical features

Clinical and demographic data of the series are shown in **Table 2 and 3**. The median age of presentation was 39.9 years (interquartile range [IQR]: 32.3-58.1); in 3 (5.4%) patients the onset was before 18 years. Patients were mainly Caucasian (94.6%), 30 (53.6%) were female with a female:male ratio 1:0.9 (30/26). The median EDSS score at nadir was 5.0 (IQR: 3.5-7.8). The majority of the patients were treated with intravenous methylprednisolone, nine patients (16.1%) additionally underwent plasma exchange and five (8.9%) intravenous immunoglobulins (**Table 2**). The findings of brain MRI at onset were normal in 38 patients (67.9%) and abnormal with Paty´s criteria in nine patients (16.1%) (**Table 3**). Spinal cord MRI performed at the acute phase showed a lesion extending over a median of 6 (range: 3-20) vertebral segments. The available CSF studies showed elevated cell count (>5/mm^3) in 31/53 patients (56.4%) and OCB in 7/47 patients (14.9%). Long-term immunosuppressive therapy was started in 19 patients (33.9%): azathioprine in six, rituximab in five, mycophenolate mofetil in six, metotrexate in one patient and beta-interferon in the unique patient who converted to MS. At the last follow-up (median 42.2 months; IQR: 25-79.5 months) the median EDSS score was 2.5 (IQR: 1.5-4.8), 49 patients remained as idiopathic isolated LETM (monophasic in 40 [71.4%], and recurrent in 9 [16.1%]), 6 (10.7%) patients had conversion to NMO and 1 (1.8%) patient had conversion to MS (**Figure 1**).

Frequency of MOG-ab detection and clinical course

Thirteen patients (23%) had MOG-ab. In five patients the serum sample was collected at disease onset, and in the other eight during remission after a median of 15 months from onset (range, 7-136 months). At the last follow-up, nine patients remained as idiopathic LETM (7 monophasic and 2 recurrent LETM), four converted to NMO (2 patients developed optic neuritis [ON] relapses, one had ON and myelitis, and one ON and brainstem symptoms with intractable hiccups and vomiting). Follow-up samples were obtained in six patients (46%), after a median follow-up of 34.8 months (range, 4-60). One patient with monophasic LETM became negative after 43 months, and 5 remained positive (three monopashic LETM, one recurrent LETM and one NMO).

Comparison between MOG-ab positive and negative patients

MOG-ab positive patients were younger at onset with a median age of 32.5 years (range, 6.8-70.7 years) compared to 44.1 years (range, 13.5-82.8 years) in the negative group (p=0.006). No differences regarding gender or ethnicity were found between both groups. One MOG-ab positive patient had been previously diagnosed with myasthenia gravis meanwhile three MOG-ab negative patients had the coexistence of other autoimmune diseases;

psoriasis, rheumatoid arthritis and autoimmune thyroiditis, respectively (*p*=1.0) (**Table 2**). Within the MOG-ab positive group, four out of 13 (30.8%) patients developed subsequent ON relapses compared to only 2 out of 43 (4.7%) in the negative group (*p*=0.022*)*. Similarly, MOG-ab positive patients had a higher frequency attacks of ON than those who were negative, *p*=0.008). However, no differences were found in the frequency of subsequent myelitis between both groups. At last follow-up, MOG-ab positive patients had a lower EDSS score (median 2.0; range, 0-5.5) than seronegative patients (median 3.0; range, 0-8.0) (**Figure 2**; *p*=0.027). In addition, 6 out of 43 (14.0%) seronegative patients were confined to a wheelchair but none of the MOG-ab positive patients.

Regarding paraclinical data, both MOG-ab positive and negative groups had similar length, lesion distribution and gadolinium enhancement on spinal cord MRI. But at the last follow-up, 4 out of 11 (36.4%) MOG-ab positive patients showed a normal spinal cord MRI as compared with 2 out of 29 (6.9%) negative patients (*p*=0.039). A higher proportion of MOG-ab positive patients had CSF pleocytosis compared to negative patients (92.3% vs 45.2%) (*p*=0.003) (**Table 3**).

Predictive factors associated with outcome

In the multivariate analysis after adjusting for age, higher disability at onset was the only prognostic factor associated with worse recovery (Odds Ratio [OR] 1.71 [95% CI 1.24-2.35]; *p*=0.001), and presence of MOG-ab with good

outcome (OR 0.17 95% CI 0.03-0.84]; *p*=0.030). In addition, seropositive MOG-ab patients showed an increased risk of ON relapse, and, therefore, a higher cumulative probability of conversion to NMO (Hazard Ratio 8.99; 95% CI 1.60-50.59; *p*=0.010).

DISCUSSION

In the present study, we show that MOG-abpositive LETM, as compare to AQP4-ab seronegative LETM, encompassed a distinctive and relatively frequent subgroup. Clinical features are younger age at onset,higher predisposition to ON relapses and better prognosis.

We found that 23% of patients who presented with a first episode of AQP4-ab seronegative LETM tested positive for MOG-ab**.** This higher frequency than previously described (6-14.3%)[4,15,16] may be explained by discrepancies in LETM definition, genetic predisposition and unintentional selection bias. Our study was unselected, based on a homogeneous ethnic background and following acknowledge definition for LETM. We also performed a large and comprehensive workup to rule out alternative diagnoses.

MOG-ab have been more closely related to pediatric than to adult populations with demyelinating diseases.[10-12,15,16,23] In line with previous studies, we observe that MOG-ab were more frequently in younger AQP4-ab seronegative LETM patients. Although we did not find significant gender

ratio differences between MOG-ab groups, up to 50% of MOG-ab positive patients were male. This finding underlines that female gender is not always overrepresented in autoimmune disorders and MOG-ab autoimmune phenotype appears in a higher proportion of male patients compared to other demyelinating diseases.[14-16]

MOG-ab patients seem to have a more benign course than AQP4-ab seropositive patients or seronegative forms of NMOSD.[14-16] We confirm that MOG-ab positive LETM patients were less disabled than negatives at long term outcome, despite the similar frequency of severe episode at onset and the higher relapse rate during the follow-up. We also observed a complete resolution of the spinal cord MRI lesions in a significant proportion of MOG-ab positive patients as reported in previous studies.[11,13-15] This good outcome could be related to a more sensitive response to steroids in MOG-ab positive patients leading to a more rapid recovery.[24] Another explanation might be the effect of the MOG-ab itself. Indeed, the intracerebral injection of human MOG-ab in mice causes only few and transient myelin changes and alteration of axonal proteins expression without leukocyte infiltration, and recover within two weeks.[25]

In the present study, four MOG-ab positive patients fulfilled the current criteria for clinical NMO.[1] Some studies have reported that NMOSD patients show distinctive clinical findings depending on the underlying biological profile (MOG vs AQP4 autoimmune phenotype).[14-16] Thus, in our opinion, if

NMOSD represent a homogeneous entity deserve to be clarified. Some authors have recently reinforced the idea of a different pathogenesis between MOG and AQP4-ab reporting a MOG-ab positive NMO patient with high myelin basic protein CSF level in the absence of glial fibrillary acidic protein during an acute attack.[26] The identification of new target autoantigens involving inflammatory CNS disorders raises the question of whether the proper classification of NMOSD patients should be based on the clinical or the biological phenotype.

Interestingly, we observed that most of the MOG-ab positive patients had CSF pleocytosis; this finding has also been described in ADEM patients with MOG-ab.[11] None of our patients, however, had clinical or MRI features of ADEM, but this fact along with the high prevalence of a preceding infectious prodrome in ADEM patients,[11] reinforce the interest to investigate the role of previous infection as a potential trigger of the immune response in these patients.

The retrospective nature of the present study entails methodological shortcomings. Some samples were obtained in remission or after treatment and one could argue about the existence of false negative results among the MOG-ab negative patients. However, this possibility appears to be overcome by the differences observed between both groups.

Taken together, our findings suggest that MOG-ab identify a subgroup of seronegative AQP4-ab LETM patients with demographic and clinical distinctive features. Their recognition has clinical and prognostic

implications and, therefore, testing of MOG-ab should be included in the workup of patients who present with LETM.

Acknowledgments

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Conflict of interest

Cobo-Calvo, Sepúlveda, Bernard-Valnet and Ruiz report no disclosures. Brassat have received travel grants, honoraria for teaching and participation to advisory boards from Bayer, Biogen Idec, Merck, Novartis, Sanofi Genzyme, Teva Pharma.; Sergio Martínez-Yélamos has received honoraria compensation to participate in advisory boards, collaborations as a consultant and scientific communications from Biogen Idec, Teva, Sanofi-Aventis, Merck Serono, Genzyme, Novartis and Bayer Schering pharmaceuticals; and received research support, funding for travel and congress expenses from Biogen Idec, Teva, Sanofi-Aventis, Merck Serono, Genzyme, Novartis and Bayer Schering pharmaceuticals. Saiz has received compensation for consulting services and speaking from Bayer-Schering, Merck-Serono, Biogen Idec, Sanofi-Aventis, Teva Pharmaceitical Industries Ltd, and Novartis. Marignier serves on scientific advisory board

for MedImmune and has received honoraria from Biogen Idec, Merck Serono, Novartis, Sanofi-Genzyme.

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Table 1. AQP4-ab seronegative LETM inclusion criteria

1. Onset of symptoms between 4 hours and 21 days
2. Bilateral motor or sensory symptoms with or without sphincter dysfunction
3. Spinal cord T2 signal hyperintensity over three or more consecutive vertebral segments on MRI
4. Available brain magnetic resonance imaging study
5. Extensive work-up that reasonably exclude other diagnoses such as vascular, compressive, infectious, metabolic, paraneoplastic or radiation myelopathy [17]
6. Tested for AQP4-ab in serum with a negative result

AQP4-ab: aquaporin 4 antibodies

Table 2. Comparison of epidemiological and clinical features between negative and MOG-ab positive LETM patients.

Patients characteristics n=56	All patients n= 56	Negative LETM n=43	MOG-ab+ LETM n=13	*p*-value
Age, median (IQR), y	39.9 (32.3-58.1)	44.1 (34.5-62.1)	32.5 (22.4-36.2)	**0.007**
Female, n (%)	30 (53.6)	23 (53.5)	7 (53.9)	0.617
Caucasian, n (%)	53(94.6)	40(93)	13 (100)	1.00
Other autoimmune diseases, n (%)	4 (7.1)	3 (7)	1 (7.7)	1.00
EDSS score at nadir, median (IQR):	5.0 (3.5-7.8)	4.5 (3.5-8.0)	5.5 (3.5-7.0)	0.790
<3.5, n (%) 3.5-7, n (%) ≥7.5, n (%)	8 (14.3) 30 (53.6) 18 (32.1)	6 (14.0) 22 (51.2) 15 (34.9)	2 (15.4) 8 (61.5) 3 (23.1)	0.683
Acute phase treatment, n (%): IVMP PLEX IVIG	 46 (82.1) 9 (16.1) 5 (8.9)	 34 (79.1) 7 (16.3) 2 (4.7)	 12 (92.3) 2 (15.4) 3 (23.1)	 0.420 1.00 0.076
Relapsing course, n (%)	16 (28.6)	10 (23.3)	6 (46.2)	0.160
LETM relapse	13 (23.2)	10 (23.3)	3 (23.1)	0.650
ON relapse Ratio ON Relapses, media (SD)	6 (10.7) 0.2 (0.6)	2 (4.7) 0.07 (0.38)	4 (30,8) 0.6 (1.12)	**0.022** **0.008**
Brainstem relapse	1 (1.8)	0	1 (7.7)	0.232
Time to first relapse, median (IQR), mo	5.2 (2.6-8.5)	5.3 (2.7-11.0)	4.7 (2.6-8.3)	0.560
Chronic treatment, n (%)	19 (33.9)	13 (30.2)	6 (46.2)	0.320
Last EDSS, median (IQR)	2.5 (1.5-4.8)	3 (2.0-5.5)	2 (0-2.5)	**0.027**
Follow-up, median (IQR), mo	42.2 (25-79.5)	38.4 (23.5-80.1)	43.8 (41.4-68.3)	0.370

MOG-ab: myelin oligodendrocyte glycoprotein antibodies; LETM: longitudinally extensive transverse myelitis; EDSS: Expanded Disability Status Scale; ON: optic neuritis; IQR: interquartile range; SD: standar desviation; IVMP: intravenous methylprednisolone; PLEX; plasma exchange; IVIG: intravenous immunoglobulins

Table 3. CSF and MRI findings in negative and MOG-ab positive LETM patients.

	All patients n= 56	Negative LETM n=43	MOG-ab+ LETM n=13	*p*-value
CSF:				
> 5 WBC/mm^3, n (%)	31/53 (56.4)	19/43 (45.2)	12/13 (92.3)	**0.003**
Protein (g/L), mean (SD)	0.62 (0.4)	0.63 (0.5)	0.63 (0.4)	0.700
OCB, n (%)	7/47 (14.9)	6/35 (17.1)	1/12 (8.3)	0.660
Brain MRI at onset, n (%)				
Normal	38 (67.9)	28 (65.1)	10 (76.92)	0.888
No Paty criteria	9 (16.1)	8 (18.6)	1 (7.7)	
Paty criteria	9 (16.1)	7 (16.3)	2 (15.4)	
Spinal MRI at onset:				
Length, median (range)	6 (3-20)	6 (3-20)	6 (3-20)	0.990
Gad enhancement, n (%)	28/48 (58.3)	23/36 (63.9)	5/12 (41.7)	0.198
Cord lesion location, n (%)				
Cervical	15 (26.8)	11 (25.6)	4 (30.8)	0.287
Cervical-thoracic	13 (23.2)	11 (25.6)	2 (15.4)	
Thoracic	15 (26.8)	11 (25.6)	4 (30.8)	
Thoracic-Lumbar	7 (12.5)	7 (16.3)	0	
All regions involved	6 (10.7)	3 (7.0)	3 (23.1)	
Spinal MRI at follow-up, n (%)				
Lesion decrease	21/40 (52.5)	17/29 (58.6)	4/11 (36.4)	0.107
Normal	6/40 (15.0)	2/29 (6.9)	4/11 (36.4)	
Atrophy	3/40 (7.5)	2/29 (6.9)	1/11 (9.1)	
No changes	10/40 (25)	8/29 (27.6)	2/11 (18.2)	

MOG-ab: myelin oligodendrocyte glycoprotein antibodies; LETM: longitudinally extensive transverse myelitis; CSF: cerebrospinal fluid; WBC: white blood cells; OCB: positive oligoclonal bands; Gad: gadolinium; SD: standar deviation

Figure 1. Final diagnosis classification in MOG-ab (1.a) positive and (1.b) negative patients.

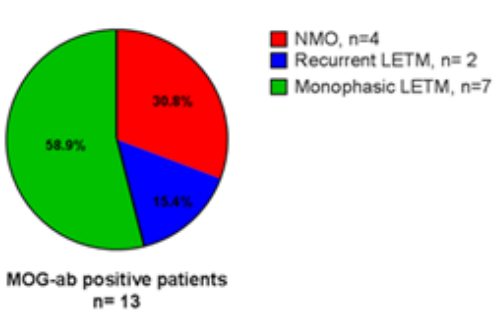


Figure 1.a

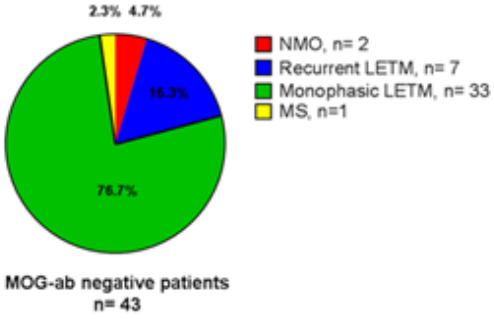


Figure 1.b

Figure 2. Expanded Disability Status Scale Scores at nadir and at last visit. (2.a). MOG-ab positive patients (2.b). MOG-ab negative patients. *Red line indicates mean EDSS

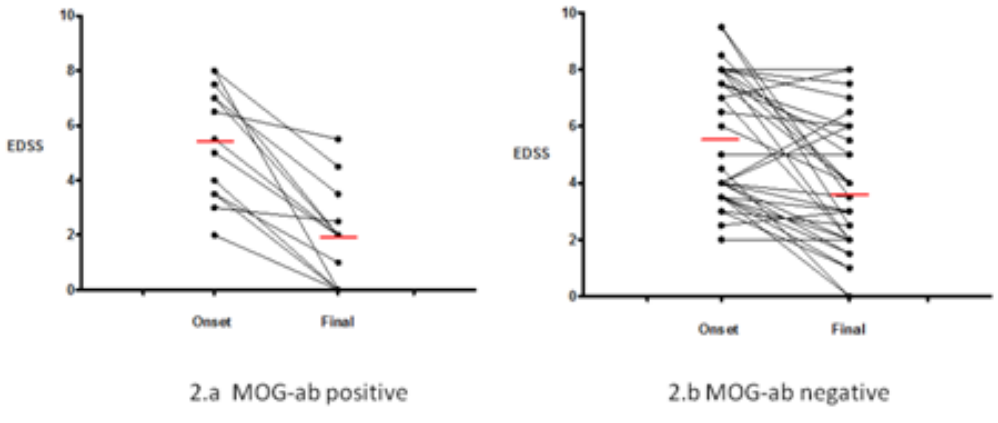


Figure 2

5.-DISCUSSION

5. DISCUSSION

5.1 General discussion

ATM may be the initial episode of a wide range of aetiologies, ranging from demyelinating diseases to systemic, vascular, metabolic or malignant disorders.[38,199] Prognosis may vary among underlying diseases leading to different degrees of disability. The lack of awareness about the clinical evolution in ATM patients at the time of the first episode make it still a challenge in clinical daily practice. Thus, the present work has been focused on the description of basal variables as well as on the identification of those which may lead us to foresee the clinical evolution and prognosis in ATM patients.In 2002, the TMCWG established a diagnostic workup panel in order to rule out the different aetiologies responsible for ATM. However, there is still a proportion of patients with a first episode of ATM whose underlying aetiology remains elusive.[19] It is likely that the cause of ATM in these patients might be an underlying unknown pathomechanism. Notwithstanding, the lack of robust diagnostic tools in order to identify the already known diseases, might be another possibility.

Moreover, ATM may be the prelude to a subsequent MS.[17] Hence, the identification of ATM patients who will develop MS at the time of the first episode is crucial for prognosis and therapeutic aspects.

On the other hand, an extensive spinal cord MRI lesion may be found in some patients presenting with ATM. Although this lesion has been classically

related to NMO, LETM is often found in other diseases, mainly systemic and autoimmune disorders.[200] The spectrum of diseases causing LETM has scarcely been studied and deserves further research. This is the reason why one section of the present work has tried to identify those disorders which are directly related to an extensive myelitis lesion on MRI.

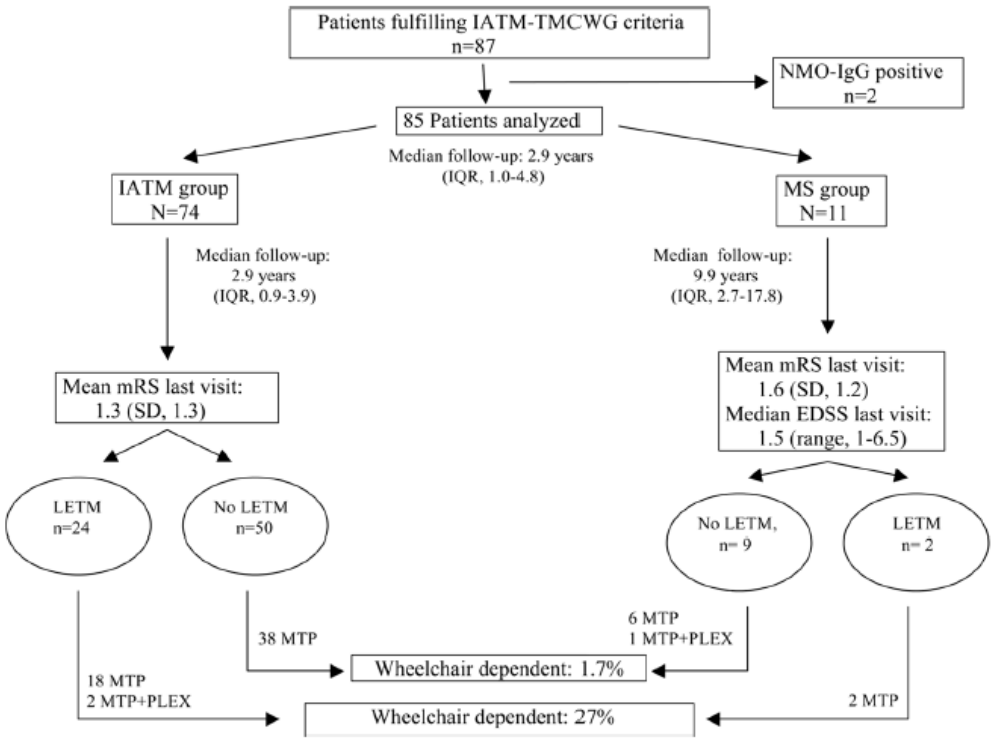
Recently, MOG-ab have been found in demyelinating diseases such as NMO or limited suspected forms and patients suffering from these disorders have shown to have distinctive clinical findings.[188-190] MOG-ab, whose pathogenicity is still under debate, have been mainly related to monophasic forms and a better prognosis compared to positive AQP4-ab NMOSD patients. MOG-ab might play a role in some forms of myelitis and more specifically in LETM with unknown aetiology, as it has been shown in NMOSD. The present work is an observational and retrospective study of patients with different subtypes of acute transverse myelitis, mainly IATM and LETM. We have searched for valuable clinical and biological markers to know the prognosis of patients at the time of the first myelitis episode. The identification of such markers will have relevant implications not only for a better comprehensive understanding of the disease, but also for a suitable patient counseling and treatment.

5.1.1 Idiopathic acute transverse myelitis

An acute spinal cord demyelinating attack is a potential disabling syndrome. In the present cohort of IATM patients, 37,6% of them had some degree of disability measured by the mRS at completion of follow-up (mRS ≥ 2). Studies performed under the TMCWG 2002 criteria have reported up to 36% of IATM patients having poor outcome.[35,40] These studies have used different methods to measure disability (mRS vs EDSS) as well as different criteria to define poor prognosis. Thus, a direct comparison among studies in terms of outcome is not completely feasible. We observed that 9,4% of patients remained wheel chair dependent at the end of the follow-up **(Figure 14).** This proportion is lower compared to 33,3% described in the French study performed under the TMCWG 2002 criteria.[34] One of the major causes of this discrepancy could be that the most severe cases are seen in tertiary referral centres leading to a selection bias. However, our center is the referral centre for our district for patients with any symptom suggestive of myelitis and, therefore, the cohort included herein would encompass all degrees of severity.

We searched for those variables leading us to identify patients with a worse outcome after a first IATM episode. Although a higher severity at onset was related to a worse prognosis in the univariate analysis, this variable was not significant in the multivariate analysis. The only independent variables associated to poor functional outcome were urinary sphincter dysfunction and an extensive lesion cord imaging on MRI.

Figure 14. Flow chart reflecting IATM subgroups



Only a few studies have focused on indentifying IATM prognostic factors under the TMCWG 2002 criteria. In line with our results, a higher disability at onset and LETM were the two main factors related to a worse functional outcome.[34,35,37]

Although the current TMCWG 2002 criteria for IATM diagnosis has tried to identify those patients who present with an initial episode of ATM and will remain idiopathic, there is a proportion of patients who will develop other pathologies during the follow-up, such as MS. In our cohort of 85 IATM patients fulfilling the above mentioned criteria, we identified 11 (13%)

patients who developed MS at completion of follow-up. Our finding is similar to other studies reporting MS conversion rates under the TMCWG criteria.[32,34-37] Taken together, these results underline that there is still a lack of consistent validated criteria to identify MS patients at the time of the first ATM.

The presence of OCB in CSF and a higher brain MRI lesion load have been strongly related to MS conversion after CIS.[96,201] According to these studies, OCB in CSF had a high predictive value for MS conversion in the present study. However, we did not evaluate brain MRI aspects, as an abnormal brain MRI was an exclusion criteria for the study. An interesting finding was the usefulness of combining OCB and IgG index results for MS prediction. Patients without CSF OCB and IgG index ≤ 0,7 will unlikely convert to MS. Some studies have reported the usefulness of both markers (OCB and IgG index ≥0,7) in MS conversion after spinal cord CIS.[88,89,98,99,103] However, none of these studies were carried out under the TMCWG 2002 criteria. Moreover, we observed that an early- onset of symptoms was associated with MS conversion after IATM, as previously described.[37,98] Other predictive epidemiological factors of MS conversion such as family MS background and female gender have been described.[88,98] Among the clinical predictive factors, a predominance of sensory symptoms and a higher severity at onset have been reported.[88,99] Finally, other paraclinical data such as spinal MRI lesion location or cell count in CSF have been related to MS conversion after spinal cord CIS.[99] On the basis of our results, IATM patiens who are young and have

OCB and abnormal IgG index in CSF will be at high risk of develop MS. Despite the lack of standardized protocols of follow-up, it would be reasonable to closely monitor these patients with a high risk of MS conversion. LETM may be the initial episode of NMO.[25] Meanwhile some studies have found low rates of NMO conversion after LETM,[90,102,127] others have reported higher rates, ranging from 45 to 60%.[123,125] We performed a retrospective chart review of all ATM patients admitted to our hospital from the last 22 years. During this period, only two (7%) out of 28 patients presenting with an initial isolated idiopathic LETM converted to NMO after a comprehensive long follow-up. Therefore, in our health district, NMO disease conversion after IATM in form of LETM is a rarely observed entity. We think that different technical approaches to measuring AQP4-ab, inclusion of LETM criteria and genetic background among different studies are probably the main causes of such discrepancies.

We also observed that all LETM patients remained as monophasic forms compared to five patients from the MS group who presented with recurrences. Although it is well known that LETM is related to a relapsing form of myelitis,[92] 22 out of 26 idiopathic LETM included in the study tested negative for AQP4-ab. Among the four patients whose samples were not analyzed for AQP4-ab, two converted to MS and the other two died without further relapses observed. As the presence of AQP4-ab is one of the major factors of myelitis relapse,[85] a negative result may explains the absence of relapses. According to our results, we believe that unknown mechanisms

could be related to isolated idiopathic LETM. In a proportion of IATM patients who initially present with prodromal infectious symptoms, the infectious agent is not identified either in serum or in CSF with the current techniques. In fact, we noted that almost one third of IATM patients included in our study had previous symptoms related to infections. We hypothesize that antigens could be directly involved in or inducing a cross- reactive immune responses in a process denominated “molecular mimicry”. Others, such as new target autoantigens involving demyelinating diseases deserve further investigations.

5.1.2 Longitudinal extensive transverse myelitis

LETM is a rare condition, which might be the first manifestation of a broad range of diseases. There are only a few studies reporting the spectrum of diseases causing LETM as a whole.[122,125]

In the present study, the underlying aetiology was not identified in almost one third of patients presenting with a first episode of LETM despite a long follow-up and workup. Thus, the term "idiopathic LETM" was applied to these patients. Our findings are in agreement with Mediterranean studies disclosing frequencies between 40 to 86% of idiopathic LETM among patients presenting with a first episode of LETM,[90,122] as compared to only 6,6% in one British study.[125] In this latter study, AQP4-ab seropositive LETM overcame all forms of LETM reaching a positivity of up to 58% of patients.

However, authors included patients with previous CNS attacks. This methodological aspect may likely explains the aetiological frequencies (eg, a higher rate of NMOSD as they included some patients with previous ON or LETM). Moreover, the ethnical background in the British study was heterogeneous compared to the present study, as 27% of the population were non-Caucasian. The ethnicity background may have led to a higher proportion of AQP4-ab positive patients, as it has been described that an AQP4-ab negative result is more likely to be found in Caucasian than non-Caucasian patients who fulfill NMO criteria.[119]

Although LETM is not commonly described in MS patients,[27] MS was the second cause of LETM in our cohort. The higher prevalence of MS in our population in comparison to other pathologies, such as NMO, might be one of the explanations for this finding. Our observation is supported by other groups describing that up to 30% of Caucasian patients presenting with LETM converted to MS.[102] The MS subgroup showed classical features; a younger onset, the presence of OCB in CSF and a cervical location at baseline spinal cord MRI. Moreover, when comparing to the rest of the subgroups, there were a lower proportion of sphincter dysfunction and milder disability at onset in MS patients. Therefore, some baseline findings may allow us to identify those patients who present with LETM and will likely convert to MS. We think that these features could be used as “red flags” for MS conversion in patients presenting with a first LETM.

The subsequent two overrepresented groups were secondary to parainfectious (15,3%) and systemic diseases (12,5%). Neither of the two groups showed distinctive findings at the onset of LETM. Moreover, when testing for AQP4-ab in both groups, a negative result was found. AQP4-ab mediated NMOSD have been related both to parainfectious and systemic disorders. In the former, the term *parainfectious NMO syndrome* has been proposed, referring to those patients fulfilling NMO criteria in which a previous infection may play a pathogenic role.[88] In the latter, the presence of AQP4-ab has been proposed to be the main cause of the spinal cord demyelinating episode despite a secondary vasculopathic or other complication of such systemic disorders.[159] After a comprehensive workup and follow-up, no further relapses were observed in any of the two groups and therefore, we could exclude NMOSD as a possible cause. Only 5% of LETM patients were diagnosed with NMOSD in our cohort. We have already mentioned that the diagnosis of NMOSD in our experience, is rare compared to other studies reporting higher percentages.[125] One could argue that the whole cohort was not tested for AQP4-ab, as the test was only performed in 56,9% of patients. However, none of the patients developed subsequent relapses in the form of ON or transverse myelitis after almost three years of follow-up and therefore, they did no convert to NMO. We would like to underline that the usefulness of AQP4-ab for NMO diagnosis is not mandatory and some authors have reported that a positive result for AQP4-ab is only necessary in 10% of cases.[121]

In the present study, among all LETM patients, 72,2% of them had a final mRS ≥ 2. Although there were not significant differences regarding outcome among the four major groups, the parainfectious group interestingly showed a trend towards a better functional outcome. Some studies reporting functional outcomes in ATM patients (not necessary LETM) have observed this trend in those secondary to parainfectious diseases.[18,75] ATM in the context of NMO or seropositive AQP4-ab and spinal cord infarction seems to lead to a poorer outcome compared to myelitis secondary to other diseases or seronegative AQP4-ab myelitis.[18,75,123] However, due to a low number of patients in the remaining groups, we could not perform a statistical analysis.

LETM may lead to relatively high rates of death and a tenth of the patients included in the present study died. Spinal cord infarction has been not only characterized as being highly disabling but also may lead to high rates of mortality.[167] In our population, spinal cord infarction was the first cause of LETM death related and two out of three LETM patients secondary to spinal cord infarction died. Nonetheless, it is difficult to extract from our study any conclusion regarding death due to the retrospective nature, differences in follow-up and the small number of patients in each group.

Interestingly, a higher disability and being elderly at onset were related to poor functional outcome at the end of the follow-up. One observational French study assessing the long term outcome in ATM patients identified both an increasing age and disability at onset to be related to a worse

functional outcome.[75] Another two studies, one French and one Spanish including idiopathic LETM myelitis in the majority of cases also found a higher disability at onset, as the only predictive factor of poor outcome.[34,90] Thus, our findings are in agreement with the previously reported data although they may not be directly comparable to the two last studies previously noted as they only included idiopathic LETM patients.

5.1.3 Myelin oligodendrocyte glycoprotein antibodies in longitudinally extensive transverse myelitis

Serum MOG-ab are very well- recognized in ADEM, especially in pediatric patients ranging from 35 to 58%,[179,180,182,184,185] and have now been described in other CNS autoimmune diseases affecting adult populations.[178,188-190,202] Two relevant studies (one Spanish and another Brazilian and Japanese collaborative study) have focused on the frequency and clinical characteristics of MOG-ab in NMOSD. Both studies discovered similar frequencies of 7,4% and 9,8%, respectively.[188,189] Moreover, one recent Japanese study comparing AQP4-ab positive and negative LETM patients reported that among those who were AQP4-ab negative, 7,5% had MOG-ab.[124] A higher frequency of MOG-ab positive patients is observed in our study. One possible explanation would be that the biological autoimmune profile may differ depending on the ethnical background, as we observe in NMOSD with AQP4-ab in NMOSD.[119] A lack of consensus in LETM definition

could also be another possibility to explain such differences. We performed an extensive workup and follow-up under the TMCWG 2002 recommendations in order to include a homogeneous cohort and to dismiss other potential underlying aetiologies.

Optic nerve inflammation in the absence of any signs of experimental autoimmune encephalomyelitis after MOG immunization has been successfully reproduced in animal models, suggesting that MOG responses may exert a direct role in ON pathogenesis.[203] In addition, immunization of rats with MOG induces lesions involving the optic nerve and the spinal cord, similar to human NMO,[204] and MOG-specific T and B cells cooperate to induce a NMO-like disease.[205] In the clinical setting, MOG-ab have been highly related to bilateral or recurrent ON in paediatric and adult patients.[187,188,191] In our study, MOG-ab positive patients were at a greater risk of ON relapse and presented higher ON relapse rates than those who were negative. A higher expression of MOG protein in the optic nerve than in the spinal cord or different blood barrier properties of the optic nerve may be some of the explanations for this specific predilection.

Recent animal model approaches have shown a complete resolution of brain damage within two weeks after MOG-ab immunization.[206] Compared to AQP4-ab treated mice where leukocyte infiltration, loss of astrocyte markers and subsequent gliosis were observed, MOG- ab mice had a reversible brain edema without inflammation.[206] MOG-ab may be involved in cytoskeletal

changes instead of brain inflammation and neuronal death.[206,207] In line with our results where there is a significant proportion of MOG-ab positive patients with transient abnormalities on spinal MRI, others have also observed the same tendency in MOG-ab diseases, such as recurrent ON, ADEM or NMOSD.[179,185,188,190]

Prodromal infectious symptoms such as fever, rash or meningismus before the onset of ATM are important clue points in suspecting an underlying infectious aetiology. Moreover, the presence of pleocytosis in CSF requires careful evaluation for infection. Even though a potential infection is suspected, the infectious agent cannot be demonstrated in CNS in a proportion of patients.[19] On the other hand, a previous infection has been observed in up to 72% of cases in ADEM patients,[135] and recently, pleocytosis has been related to ADEM patients with MOG-ab.[185] The fact that almost all MOG-ab patients showed pleocytosis in our study along with the high prevalence of a preceding infectious prodrome in MOG-ab patients with demyelinating CNS diseases,[185,191] makes us consider a previous infection as a potential trigger to be studied further. As with other neurological diseases such as Guillain Barré Syndrome, we hypothesize that T cells could be activated by molecular mimicry after infection, leading to an immune response against MOG. Moreover, the absence of intrathecal OCB synthesis in all but one of the MOG-ab positive LETM patients deserves to be highlighted. This observation has been previously reported in paediatric MOG-ab positive patients,[182,207] suggesting that the MOG-ab specific humoral immune process

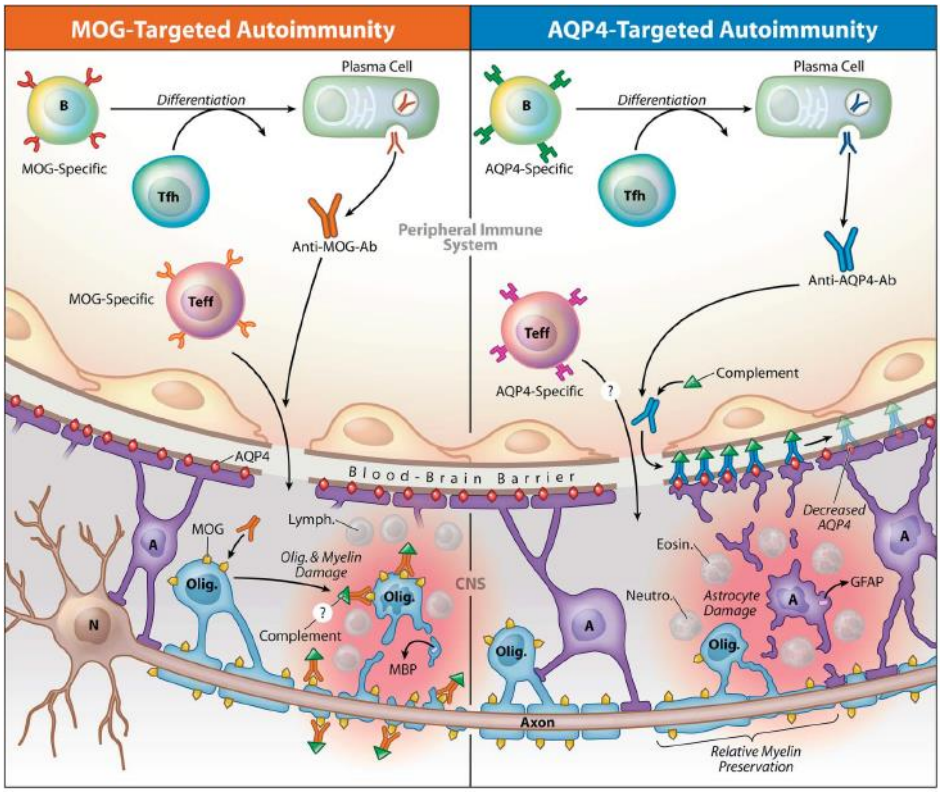
occurs predominantly outside the CNS. Some authors have supported this hypothesis by the fact that CSF MOG-ab were only detected in patients with high serum MOG-ab titres.[182]

The most consistent baseline clinical prognostic marker in patients with a first episode of idiopathic LETM is a higher disability at nadir.[34,90] We confirm previous studies and higher disability was the only clinical marker related to a worse long-term outcome. Moreover, when comparing outcome in NMOSD patients with and without MOG-ab, studies showed that patients with serum MOG-ab have a better clinical outcome. We found that MOG-ab seem to be a promising valuable marker of good prognosis in the clinical setting of patients suffering from LETM.[188-190] These data need to be considered as preliminary, and prospective studies with a larger number of patients should address this question.

MOG-ab have identified a subgroup of AQP4-ab seronegative NMOSD patients with distinctive clinical features who are currently encompassed under the umbrella of NMOSD. These patients not only seem to be different from a clinical point of view, but also from a pathological one. Recently, Japanese authors described one NMO patient disclosing high CSF levels of myelin basic protein at the time of an LETM attack. Nonetheless, CSF glial fibrillary acidic protein was not elevated. These findings suggest a myelin injury instead of astrocyte damage which is typically observed in AQP4-ab positive NMO patients.[208] Thus, two different biological phenotypes, "astrocytopathy or

AQP4-ab" and "oligodendrocitopathy or MOG-ab" would be part of the same clinical NMOSD syndrome. The fact that four MOG-ab positive LETM patients in our study were diagnosed as having NMO, leads us to the question of whether we should classify patients under a clinical or a biological phenotype. This classification may have important clinical and therapeutic implications and treatment response might depend on underlying biological phenotype. Thus, there are already some authors who suggest to differentiate the MOG-ab phenotype from NMOSD.[209] (**Figure 15**)

Figure 15. MOG-ab and AQP4-ab potential phisiopathological role in opticospinal inflammation. (*From Zambil SS, et al.)*[209]



5.2 Limitations

Our studies might involve diverse uncontrolled factors influencing the results due to the retrospective nature. We would like to highlight the most relevant shortcomings.

Firstly, one may wonder if treatment strategies could have played a role in disability outcomes. Our study was not designed to evaluate treatment responses in the clinical setting and the effect of both acute and chronic therapies regarding outcome cannot be ascertained. The role of acute and chronic immunotherapy related to outcome will only be answered with randomized clinical trials.

Secondly, when evaluating prognostic factors in patients presenting with the whole spectrum of LETM, we have only included the main four subgroups to perform statistical analysis due to the low number of patients in the remainder. Therefore, outcomes and prognostic factors could change if including other aetiologies. However, a higher disability at onset seems to be the most reliable clinical prognostic marker, as it has also been observed in previous studies.[34,90]

The target population of the two first studies should be representative of the general population from our region and, therefore, the evaluation of only a single referral centre could be a potential limitation. Our hospital is the referral centre for demyelinating disorders of the whole health area and, theoretically, all patients with potential spinal cord symptoms are evaluated.

In order to improve the myelitis spectrum, we searched for myelitis diagnosis not only in the neurology department but also in those where a patient with myelitis could be admitted. This procedure will invariably decrease the selection bias and most of the aetiologies will likely to be represented. In the third study, we performed a multicentre study due to the low prevalence of MOG-ab seropositivity in AQP4-ab seronegative LETM patients. In this study, we included in an unselected manner all patients who met the inclusion and exclusion criteria for LETM.

Regarding laboratory techniques, AQP4-ab test had a relatively low sensitivity (50-60%) in the two first studies. It is therefore likely that some real AQP4-ab positive patients were included in the idiopathic group. However, the absence of recurrences and NMOSD conversion support the correct classification of these patients. In the third study Cell Based Assays techniques were performed to analyze AQP4-ab and Sensitivity was increased to 75% meanwhile specificity remained unchanged at 100%, as it has been described.[119,198] Although these values may always lead to False Negative results, sensitivities are according to the highest sensitive methods used to date.[118] It is also important to underline that there is a proportion of MOG-ab patients whose serum samples were collected after the acute phase. The delay in serum collection could imply a loss of MOG-ab seropositivity, as some MOG-ab titers decrease through the time.[182]

5.3 New issues raised by the work and final considerations

In the present work we have tried to identify those IATM patients who are at high risk of disability and MS conversion when presenting a first episode of ATM. The identification of prognostic factors is essential to select those IATM patients who will profit from a more aggressive treatment, such as plasmapheresis. Moreover, baseline variables at the time of ATM to identify MS converters are needed and could be useful to develop new studies and clinical trials.

IATM patients who present with high severity, urinary dysfunction and LETM at onset are at high risk of long term disability and should be closely monitored. In the same vein, patients who present with IATM at an early age or OCB in CSF should be also closely followed in the outpatients clinics for a reasonable time in order to dismiss MS conversion. We have observed with a high negative predictive value that IATM patients who show neither abnormal IgG index nor OCB bands in CSF will unlikely develop MS. Hence, an extensive and indepth workup should be performed with the aim of finding out other underlying aetiologies or new unknown aetiological markers.

On the basis of our results, the current TMCWG 2002 criteria are not entirely able to identify patients who present with a first ATM and will remain as idiopathic. Some patients may evolve to MS or even NMOSD. Therefore, a new panel should be proposed to homogenize this subgroup of patients. Firstly, as those patients with negative OCB and IgG index in CSF will be unlikely to

convert to MS, one could question whether those patients with a positive result in both parameters should be classified under the criteria as IATM. However, the IATM criteria would increase in specificity to the detriment of sensibility. On the other hand, we think that the inclusion of surrogate markers such as AQP4-ab or MOG-ab in a new panel could orientate the underlying aetiology. Moreover, glial and neuronal markers have been related both to MS conversion and disability after CIS.[210,211] We think that these markers deserve further study as they might help not only to identify those IATM patient who will develop MS patients but also their long term disability.

We underline the relatively high proportion of idiopathic forms and the low proportion of NMSD found in our population among patients with a first episode of LETM. Even though the AQP4-ab technique sensitivity in the two first studies may be a possible explanation for false negatives, patients who tested negative for this antibody did not fulfill Wingerchuck 2006 criteria.[25] This is the reason why we think there must be other biological underlying mechanisms involved in idiopathic myelitis.

Following this observation, we aimed to investigate the role of MOG-ab in AQP4-ab seronegative LETM. This antibody has been proposed to be involved in different demyelinating CNS disorders.[188,189] Although the mechanism is not completely understood, MOG-ab could play a direct role in demyelination, it could reflect a secondary immune reaction, a bystander phenomenon or

even reflecting a beneficial effect.[212] We believe that a secondary immune reaction followed by a previous infection might be one of the most probable hypothesis. The high proportion of MOG-ab positive LETM patients with CSF pleocytosis in our study altogether with the link between MOG-ab and pleocytosis in other diseases which are likely triggered by previous infections, would support this notion. We not only identify MOG-ab in one fifth of idiopathic LETM patients, but also observe that MOG-ab positive patients share several distinctive features. This finding could open the door to new studies focussing on the role of MOG-ab in demyelinating disorders and also to evaluate whether a previous infection is directly related to the appearance of MOG-ab in the serum of patients with demyelinating disorders. As we have previously stated, an indepth understanding of this antibody could allow us to a better definition of the term IATM.

As the underlying pathomechanism is likely different, the identification of both AQP4-ab and MOG-ab biological phenotypes may be the basis to properly classify patients in different subgroups when clinical trials considering therapeutic options are performed. This categorization would be advantageous in order to detect the true benefit of treatments depending on the underlying biological phenotype.An important point to be highlighted is that some MOG-ab positive patients fulfilled the Wingerchuck 2006 criteria for NMO.[25] This observation raises the question of whether a positive MOG-ab result in patients presenting with ON or myelitis implies a diagnosis of NMOSD. We think we should be cautious in applying the term NMOSD in

MOG-ab positive patients, and we believe that new refinements of NMO diagnostic criteria should be performed.

6.-CONCLUSIONS

6. CONCLUSIONS

1. After a median follow-up of 2,9 years, 37,6% of IATM patients had a modified Rankin Score ≥ 2 and 9,4% of them were unable to walk unassisted.

2. Functional long term outcome in IATM was poorer in patients with urinary sphincter dysfunction at admission and LETM on spinal cord MRI.

3. At least 13% of patients who fulfill the TMCWG criteria for definite and possible IATM will convert to MS, after a median of three years of follow-up. An early-age onset of symptoms was related to MS conversion.

4. After a median follow-up of 2,7 years, 72% of patients presenting with a first episode of LETM had a modified Rankin Score ≥ 2.

5. An older age and clinically severe disease at onset were independent prognostic factors of poorer functional long term outcome in patients with LETM.

6. Whilst the idiopathic form was the most frequent aetiology in patients presenting with a first episode of LETM, less than 5% of patients ultimately were diagnosed as having NMOSD.

7. MOG-ab were present in 23% of patients presenting with a first episode of AQP4-ab seronegative LETM.

8. AQP4-ab seronegative LETM patients with serum MOG-ab, as compared to those MOG-ab seronegative, encompassed a distinctive subgroup clinically

represented by younger age at onset, higher predisposition to ON relapses and better long term outcome.

7.-REFERENCES

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8.-APPENDIX

8. APPENDIX

Appendix 1. Symptomatic treatment for Acute Transverse Myelitis complications. (*From Frohman EM, et al.*)[50]

Symptomatic Therapies for Transverse Myelitis and its Complications

Symptom	Pathophysiology/Cause	Investigations	Interventions	Purpose of Therapy/Comments
Respiratory weakness	Neurogenic muscle weakness	Bedside examination Pulmonary function tests Negative inspiratory force	Pulmonary toilet Incentive spirometry Postural percussion and drainage (PP&D) Mucus clearance vest	Prevent hypoxia, aspiration pneumonia, and infection
Swallowing and/or speech dysfunction	Oropharyngeal or lingual weakness with brainstem involvement	Bedside examination Modified barium swallowing study Speech evaluation	Prescribe appropriate diet (e.g. soft mechanical) Avoid thin liquids in those with dysphagia Feeding tube ifhigh risk of aspiration Speech therapy	Prevent aspiration pneumonia and dehydration Optimize nutritional status Enhance communication
Motor weakness	Pyramidal tract dysfunction	Neurological exam	Physical therapy Occupational therapy	Optimize upper and lower extremity voluntary motor function
Gait dysfunction	Pyramidal tract dysfunction: Circumduction, toe drag, pelvic obliquity (tilted pelvis while walking which may cause hip and muscle girdle pain), ataxia, trunk weakness, reduced righting reflexes, orthostasis	Examination	Ankle-foot orthotic (AFO) braces Functional electric stimulation (FES) Heel-cord stretching Assist devices (cane, walker, wheelchair, scooter) 4-aminopyridine (4-AP) increases walking speed in MS	Optimize gait mechanics, prevent falls, avoid deep vein thrombosis, minimize orthostasis Risk of 4-AP is seizures; do not use if prior seizure or significant renal impairment.

Spasticity and phasic motor events	Paroxysmal tonic spasms Hypertonia due to upper motor neuron injury. May be tonic or phasic.	Patient History Examination	Anticonvulsants, especially carbamazepine; baclofen Stretching, baclofen, tizanidine, ice therapy, benzodiazepines, botulinum toxin Intrathecal baclofen pump if severe and refractory	Purpose: enhance function and reduce pain. Risks: Pain during stretching; sedation with virtually all anti-spasticity agents. Pump risks: infection, overdose (causing hypotonia, sedation, and altered mental status), and interrupted dosing from catheter or pump failure or failure to refill (causing withdrawal, including seizures and coma).
Sensory symptoms/ Pain	L'hermitte's sign (symptom) Neuropathic (see text) Orthopedic, myofascial Rectal/genital pain	Patient History Examination	Usually resolves without requirement for therapy; when severe, anticonvulsants Anticonvulsants, muscle relaxants, tricyclic antidepressants, narcotics Physical therapy, acetaminophen, NSAIDS Belladonna & opium (B&O) supprettes, topical analgesics	Risks include sedation, reduced cognition, constipation and urinary retention (tricyclics and narcotics); anticholinergic side effects (tricyclics); also hyponatremia with carbamazepine.
Fatigue	Usually multifactorial: explore sleep hygiene, iatrogenic factors (drugs), depression, spasticity, anemia, hypothyroidism, vitamin deficiency (B12, D)	Patient History Sleep study Laboratory studies	Amantidine Modafinil? Methylphenidate? Acetyl-L-carnitine?	Risks include: livedo reticularis, peripheral edema, neuropsychiatric symptom (amantadine); agitation, elevated blood pressure, and appetite reduction (stimulants). Correct other medical disorders/adjust medications before adding medication.
Bladder	 Detrusor hyperreflexia Detrusor-sphincter dyssynergia (with high post void residual (>100cc)	History Post void urine residual (PVR) Urological consultation	 Anticholinergics Alpha antagonists Clean intermittent self catherization	Purpose: improve patient comfort, prevent infection and hydronephrosis. Risks: dry eyes and mouth, constipation, orthostatic hypotension, urinary retention. Avoid in glaucoma. Risks: hypotension, tachycardia, and bladder incontinence, particularly in those patients with coincident bladder spasms. Risks: urethral injury

	Nocturia Nocturnal enuresis		Antidiuretic hormone (DDAVP) Imipramine	Risks: hyponatremia (DDAVP), anticholinergic side effects (imipramine)
Bowel	Neurogastrointestinal signaling defects Dehydration Drug effects (e.g. anticholinergics) Poor evacuation	Patient History Stool Diary Review drug list	Fluids, fiber bulking, softeners, bowel stimulants Fluids Consider transcutaneous oxybutynin (Oxytrol®) Suppository, minidose enema (Enemeez®) Colostomy for severe cases	Risks: over-aggressive bowel care program can be associated with diarrhea, bloating, abdominal discomfort, and excessively large stools. Use of bowel stimulants, suppository, or minidose enema can be associated with bowel incontinence, particularly in those patients whose mobility limitations affect the ability to get to the toilet in a timely fashion.
Sexual dysfunction	Reduced libido Poor erection Reduced sensation Reduced lubrication	Patient History: Review drug list, depression, relationship issues Exclude non-neurogenic co-morbidities	Men: Eliminate offending agents Proerectile agents Women: High-intensity genital vibrators EROS device to enhance genital blood flow Water-soluble lubricating agents	Headache, lightheadedness, 'blue vision', and priapism have been associated with proerectile drugs
Venous thrombosis	Immobility and hypercoagulable state	Bedside exam Doppler studies	Prophylactic anticoagulation Compression boot Inferior vena cava filter (if necessary)	Risks: heparin-induced thrombocytopenia, hemorrhage
Edema	Immobility and weakness	Bedside exam	Compression socks Pneumatic compression pumps Lymphedema massage Fluid management	Purpose of therapy often cosmetic but may improve mobility in those with paraparesis
Skin Integrity	Immobility	Daily systematic examination of ventral and dorsal body surface	Increase mobility Scheduled repositioning Assess mattress and chair surface needs to avoid skin breakdown	Purpose: prevention of pressure sores which increase risk of sepsis and worsen symptoms such as spasticity

Appendix 2. Longitudinal extensive myeltis with and without aquaporin- 4 antibodies

2. 1Epidemiological and clinical features of AQP4-ab seropositive and seronegative LETM studies

2.1.1 AQP4-ab seropositive LETM patients

	Iorio R, et al.[122]	Chang K-H, et al.[123]	Kitley J, et al.[125]	Sung-Min K, et al.[128]	Hyun JW, et al.[124]	Jiao Y, et al.[126]
Number of patients	16	18	44	9	55	42
Female, n (%)	15 (94)	17 (94.4)	38 (86)	6 (66.6)	44 (80)	35 (83.3)
Age, years, mean (SD)	43 (11-71)*	40.6 (14.8)	45.3 (14.8)	50.3 (12.3)	37.4 (10.1)	50 (15-75)*
Clinical symptoms at onset, n (%)						
Motor	16 (100)	13 (72.2)	7 (18)	n.r	n.r	n.r
Sensory	16 (100)	13 (72.2)	13 (34)	n.r	n.r	n.r
Bladder and bowel	8 (50)	2 (11.1)	0 (0)	n.r	n.r	n.r
Nausea/Vomits	8 (56)	n.r	10 (29)	n.r	n.r	n.r
Hiccups	1 (6)	n.r	n.r	n.r	n.r	n.r
Tonic Spasm	6 (38)	n.r	n.r	n.r	n.r	n.r
EDSS at onset, mean (SD)	5.4 (1.8)	n.r	7.5 (0-9)**	6.1 (2.1)	8 (2.5-9.5)**	n.r
Final EDSS, mean (SD)	n.r	4.3 (22.2)	2 (0-7)**	n.r	3 (0-7.5)**	17 (41)****
Relapsing patients, n (%)	12 (75)	15 (83.3)	33 (74)	7 (77.8)	48 (87.3)	n.r
Relapse rate, mean (SD)	1.1 (0-3)	0.7 (0.3)	n.r	n.r	n.r	0.8 (0.4-1.8)**
Time to second attack, months, mean (range)	n.r	n.r	n.r	n.r	4.5 (1-41)	7 (3-34)**
Follow-up, months mean (SD)	53 (7-146)*	6.1(4.0)***	61.4 (2.3-260.2)**	n.r	7 (4.4)***	59 (10-318)**

2.1.2 AQP4-ab seronegative LETM patients

	Iorio R, et al.[122]	Chang K-H, et al.[123]	Kitley J, et al.[125]	Sung-Min K, et al.[128]	Hyun JW, et al.[124]	Jiao Y, et al.[126]
Number of patients	21	12	32	41	42	5
Female, n (%)	8 (38)	8 (66.6)	14 (44)	9 (22)	9 (21.4)	2 (40)
Age, y mean (SD)	48.9 (8-78)*	38.4 (14)	37.7 (16.1)	47.2 (12)	43.1 (9.8)	30 (3-52)*
Clinical symptoms at onset, n (%)						
Motor	17 (81)	11 (93.7)	5 (16)	n.r	n.r	n.r
Sensory	20 (95)	10 (83.3)	10 (32)	n.r	n.r	n.r
Bladder and bowel	6 (29)	4 (33.3)	5 (16)	n.r	n.r	n.r
Nausea/Vomits	0	n.r	3 (10)	n.r	n.r	n.r
Hiccups	0	n.r	n.r	n.r	n.r	n.r
Tonic Spasm	1 (5)	n.r	n.r	n.r	n.r	n.r
EDSS at onset, mean (SD)	5.5 (2.0)	n.r	8 (3-8)**	3.2 (1.9)	3 (3-8.5)**	n.r
Final EDSS, mean (SD)	n.r	2,67 (2,26)	3 (0-8)**	n.r	2,5 (1-6)**	1 (20)****
Relapsing patients, n (%)	5 (24)	5 (41.7)	10 (31)	8 (19.5)	30 (71.4)	n.r
Relapse rate, mean (SD)	0.4 (0-2)*	0.4 (0.2)	n.r	n.r	n.r	1.1 (0.5-2.2)
Time to second attack months (range)	n.r	n.r	n.r	n.r	11.5 (2-72)	3 (3-9)**
Follow-up, months mean (SD)	38 (12-199)*	4.9 (2.9)***	25.0 (1.9-169)**	n.r	5.4 (2.6)***	30 (11-152)**

n, number; SD, standard deviation; n.r, not registered; EDSS, Expanded Disability Status Scale; n.r, not reported.

*mean (range), ** median (range), *** years mean (SD), **** EDSS>6, n (%)

2.2 Laboratory features of AQP4-ab seropositive and seronegative LETM studies

2.2.1 AQP4-ab seropositive LETM patients

	Iorio R, et al.[122]	Chang K-H, et al.[123]	Kitley J, et al.[125]	Sung-Min K, et al.[128]	Hyun JW, et al.[124]	Jiao Y, et al.[126]
Number of patients	16	18	44	9	55	42
CSF Findings, n (%)						
OCB	3/16 (19)	0	3/19 (16)	n.r	3/43 (7)	5 (11.9)
Pleocitosis	n.r	3/25 (12)*	3/19 (16)*	7.13 (8,5)**	16/41 (39)	12 (28.6)
IgGIndex	n.r	8 (32)	n.r	0.6 (0.2)**	4/32 (12.5)	4 (9.5)
ANAs	n.r	6/15 (40)	nr	2 (2.2)	11/50(22)	n.r

2.2.2 AQP4-ab seronegative LETM patients

	Iorio R, et al.[122]	Chang K-H, et al.[123]	Kitley J, et al.[125]	Sung-Min K, et al.[128]	Hyun JW, et al.[124]	Jiao Y, et al.[126]
Number of patients	21	12	32	41	42	5
CSF Findings, n (%)						
OCB	5/21 (24)	1/12 (8.3)	0	n.r	4/30(13.3)	0(0)
Pleocitosis	n.r	0/13 (0)*	11/25 (44)*	8.6 (11.5)**	6/36(16.7)	2 (20)
IgG Index	n.r	0 (0)	n.r	0.6 (0.2)**	4/30(13.3)	n.r
ANAs	n.r	2/8 (25)	n.r	4 (11.8)	0(0)	n.r

CSF, cerebrospinal fluid; OCB, oligoclonal bands; ANAs, anti-nuclear antibodies; n.r, not reported

*pleocytoisis defined as >50 cells/ml ** Quantitative results, n (SD)

2.3 Radiological features of AQP4-ab seropositive and seronegative LETM studies

2. 3.1 AQP4-ab seropositive LETM patients

	Iorio R, et al.[122]	Chang K-H, et al.[123]	Kitley J, et al.[125]	Sung-Min K, et al.[128]	Hyun JW, et al.[124]	Jiao Y, et al.[126]
Number of patients	16	18	44	9	55	42
MRI findings				n.r		
Patients with brain Lesions, n (%)	8 (50)	9 (50)	32 (72.7)		55/55 (100)	32 (76.2)
Length spinal cord lesions, mean (SD)	5.5 (3)	5.6 (3)	7.5 (n.r)		7.4 (4.5)	n.r
Brainstem involvement, n (%)	10 (63.3)	n.r	n.r		n.r	n.r
Spinal cord involvement, n SD)						n.r
Cervical	15 (94.4)	91 (67)	n.r		13 (23.6)	n.r
Thoracic	8 (50)	42 (87.5)	n.r		19 (34.6)	n.r
Cervico-thoracic	9 (56)	n.r	n.r		23 (41,82)	n.r
Conus	n.r	n.r	2 (6)		0 (0)	n.r
Central grey matter involvement, n (%)	15 (94)	28 (58.3)	n.r		41/44 (93.2)	n.r
Hypointense T-1 lesion, n (%)	12 (75)	n.r	n.r		40/44 (90.9)	n.r
Gad, n (%)	15 (94)	n.r	n.r		21/31 (67.7)	n.r

2.3.2 AQP4-ab seronegative LETM patients

	Iorio R, et al.[122]	Chang K-H, et al.[123]	Kitley J, et al.[125]	Sung-Min K, et al.[128]	Hyun JW, et al.[124]	Jiao Y, et al.[126]
Number of patients	21	12	32	41	42	5
MRI findings				n.r		
Patients with brain Lesions, n (%)	7 (33)	1 (8.3)	3 (9.3)		37/42 (88.1)	3 (60)
Length spinal cord lesions, mean (SD)	4.6 (2.2)	4.9 (3.1)	7.6 (n.r)		4 (1.6)	n.r
Brainstem involvement, n (%)	0 (0)	n.r	n.r		n.r	n.r
Spinal cord involvement, n (SD)						n.r
Cervical	13 (62)	16 (59.3)	n.r		16 (38.1)	n.r
Thoracic	13 (62)	15 (55.6)	n.r		19 (45.2)	n.r
Cervico-thoracic	5 (24)	n.r	n.r		4 (9.5)	n.r
Conus	n.r	n.r	10 (34)		3 (7.1)**	n.r
Central grey matter involvement, n (%)	12 (57)	6 (22.2)	n.r		32/33 (97)	n.r
Hypointense T-1 lesion, n (%)	7 (33)	n.r	n.r		20/32 (62.5)	n.r
Gad, n (%)	15 (71)	n.r	n.r		20/26 (76.9)	n.r

n, number; SD, standard deviation; Gad, gadolinium enhancement; n.r, not reported.