Le malattie demielinizzanti in età pediatrica: diagnosi e terapia

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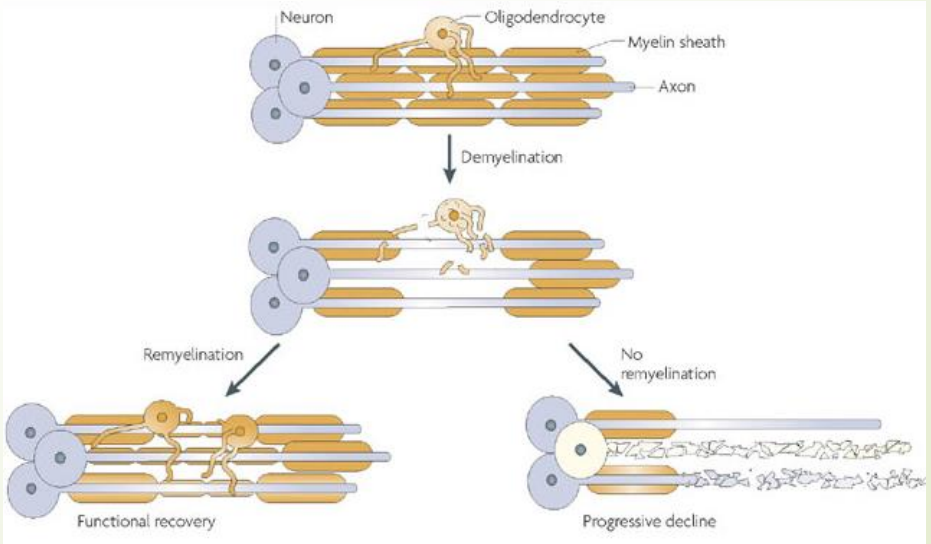
Malattie infiammatorie demielinizzanti del SNC

- **DEMIELINIZZAZIONE:** danno acquisito a carico della mielina di normale struttura, causato da diversi fattori eziopatogenetici (ischemico, autoimmune, infiammatorio, tossico, infettivo).

- **M. INFIAMMATORIE DEMIELINIZZANTI:** il danno della mielina è secondario ad un processo infiammatorio con possibile patogenesi autoimmune.

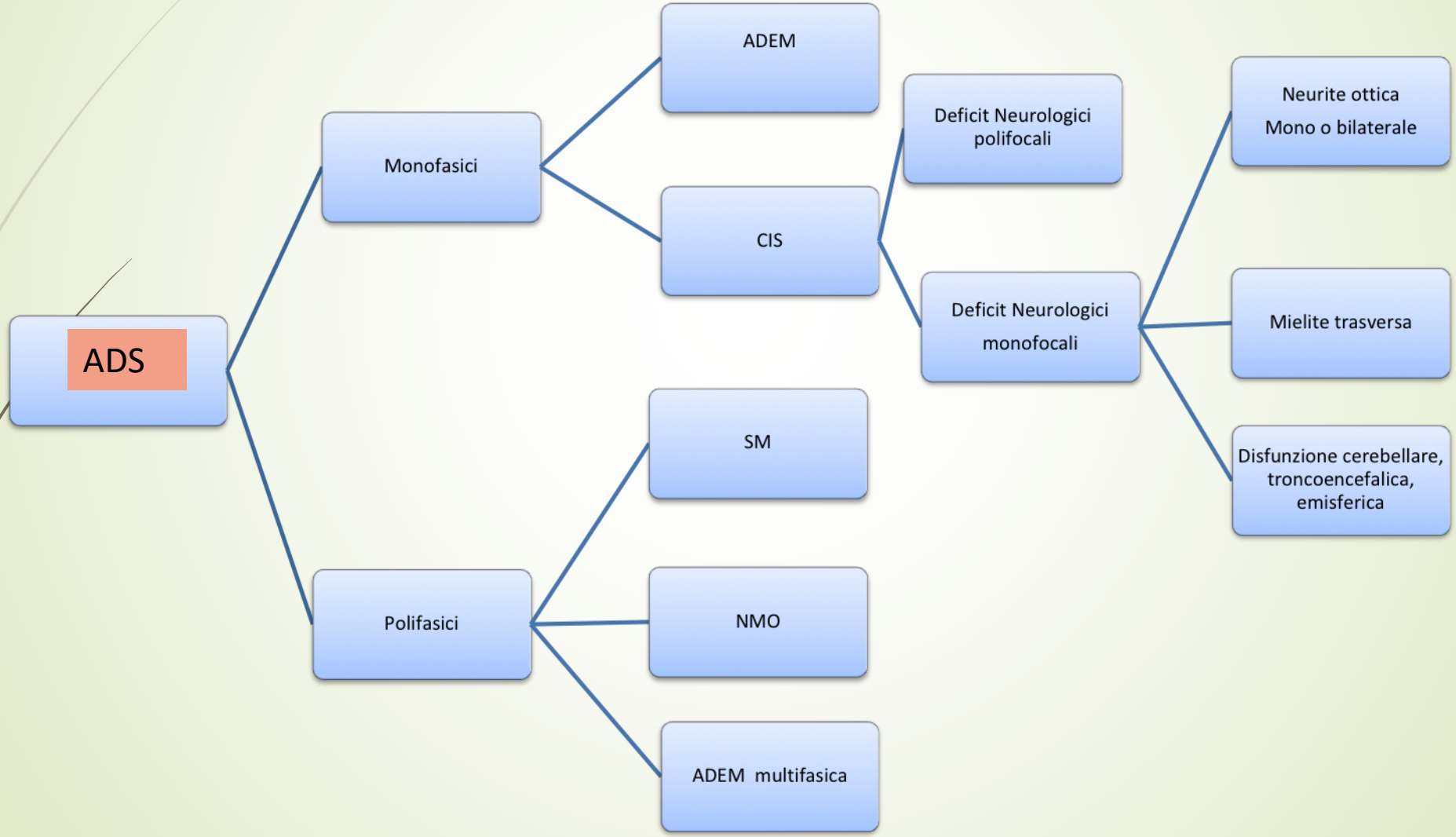


DEMIELINIZZANTI (ACQUISITE) *Danno a carico della mielina di* ***normale struttura***	***DISMIELINIZZANTI (EREDITARIE-METABOLICHE-MALFORMATIVE)*** *Errore geneticamente determinato nella costituzione della mielina.*
TOSSICHE: Mielinolisi centrale pontina ed extrapontina Alcool Farmaci DEFICIT NUTRIZIONALI: Mielinolisi centrale pontina Malattia di Marchiafava-Bignami Deficit di Vitamina B_{12} INFETTIVE: PESS Leucoencefalopatia progressiva multifocale HIV INFIAMMATORIE: Primitive (ADEM, NO, NMO, SM, MT) Secondarie (infezioni, m. autoimmuni, vasculiti)	DIFETTO DI STRUTTURA DELLA MIELINA Pelizaeus-Merzbacher (proteina proteolipidica) Sindrome 18q- (proteina basica della mielina) DIFETTO ENZIMATICO LISOSOMIALE: Krabbe, Leucodistrofia metacromatica MITOCONDRIALE: Melas, Leigh PEROSSISOMIALE: Refsum, Adrenoleucodistrofia X-L ALTRI DIFETTI ENZIMATICI: Galattosemia, Aciduria glutarica tipo 1, Deficit di piruvato carbossilasi SINDROMI MALFORMATIVE Walker-Warburg, Cockayne, Fukuyama

Malattie infiammatorie demielinizzanti idiopatiche Forme Classiche

- ADEM: encefalomielite acuta disseminata
- CIS: sindrome clinicamente isolata
- SM: sclerosi multipla
- NMO: neuromielite ottica

Disordini Infiammatori Demielinizzanti Idiopatici del SNC



CIS (Clinically Isolated Syndrome)

Pediatric CIS (all are required)

- A monofocal or polyfocal, clinical CNS event with presumed inflammatory demyelinating cause
- Absence of a prior clinical history of CNS demyelinating disease (e.g. absence of past optic neuritis (ON), transverse myelitis (TM) and hemispheric or brain-stem related syndromes)
- No encephalopathy (i.e. no alteration in consciousness or behavior) that cannot be explained by fever
- The diagnosis of MS based on baseline magnetic resonance imaging (MRI) features (as recently defined)[4] are not met

La sintomatologia deve avere durata superiore alle 24 ore

Krupp et al, 2012

CIS (Clinically Isolated Syndrome)

- ✓ Può manifestarsi con una singola lesione in una sola parte del sistema nervoso centrale (detta monofocale) oppure con lesioni multiple in diverse parte del sistema nervoso centrale (detta multifocale)
- ✓ I sintomi possono essere diversi in relazione alla sede della lesione o delle lesioni nel SNC.
- ✓ Le CIS possono avere delle manifestazioni "tipiche" con sintomi come la neurite ottica unilaterale (caratterizzata da un abbassamento della vista che tende a peggiorare rapidamente e che è accompagnato da dolore ad un occhio), disturbi di sensibilità ad un arto che possono evolvere coinvolgendo l'altro o estendersi al tronco, visione sdoppiata, deficit di sensibilità al volto o vertigini.
- ✓ Possono presentarsi anche in modo "atipico", con sintomi come neurite ottica bilaterale, declino cognitivo a rapida progressione, cefalea o fatica isolata. In questi casi risulta necessario prendere in considerazione altre possibili cause.

Mielite acuta trasversa (MT)

- L'infiammazione colpisce il midollo spinale.
- Debolezza e paralisi delle gambe e/o delle braccia, incontinenza e costipazione, perdita della sensibilità si sviluppano di solito dopo molte ore e possono aumentare fino a uno stato gravemente invalidante.
- La MT può essere anche un segno iniziale di una malattia cronica come la neuromielite ottica o la sclerosi multipla.
- Nella MT, le lesioni rilevate con RM tendono a interessare grandi segmenti del midollo spinale. Le lesioni cerebrali viste in RM che non causano sintomi si trovano in più di un terzo dei bambini con la MT e predicono la SM o la neuromielite ottica.
- I bambini di solito hanno esiti migliori rispetto agli adulti: il 5% guarisce completamente in due anni.

Neurite ottica

- L'infiammazione del nervo ottico porta a un peggioramento della vista, compreso il peggioramento dell'acuità visiva (chiarezza di visione), della visione dei colori e del campo visivo.
- Circa un terzo dei bambini con malattie demielinizzanti del sistema nervoso centrale può andare incontro a neurite ottica come primo sintomo.
- Nella maggior parte dei casi, la vista torna quasi normale ma con piccoli cambiamenti, compresi quelli nella visione dei colori e del contrasto. Questi cambiamenti possono accumularsi nel tempo.
- Non sono stati svolti studi clinici sulla neurite ottica pediatrica, quindi la pratica clinica nei bambini al momento segue questo protocollo: 20-30 mg/kg al giorno di metilprednisolone per via endovenosa, massimo 1g al giorno, per 3-5 giorni. Ancora non è nota la necessità di un ricorso prolungato a steroidi orali.

ADEM

Pediatric ADEM (all are required)

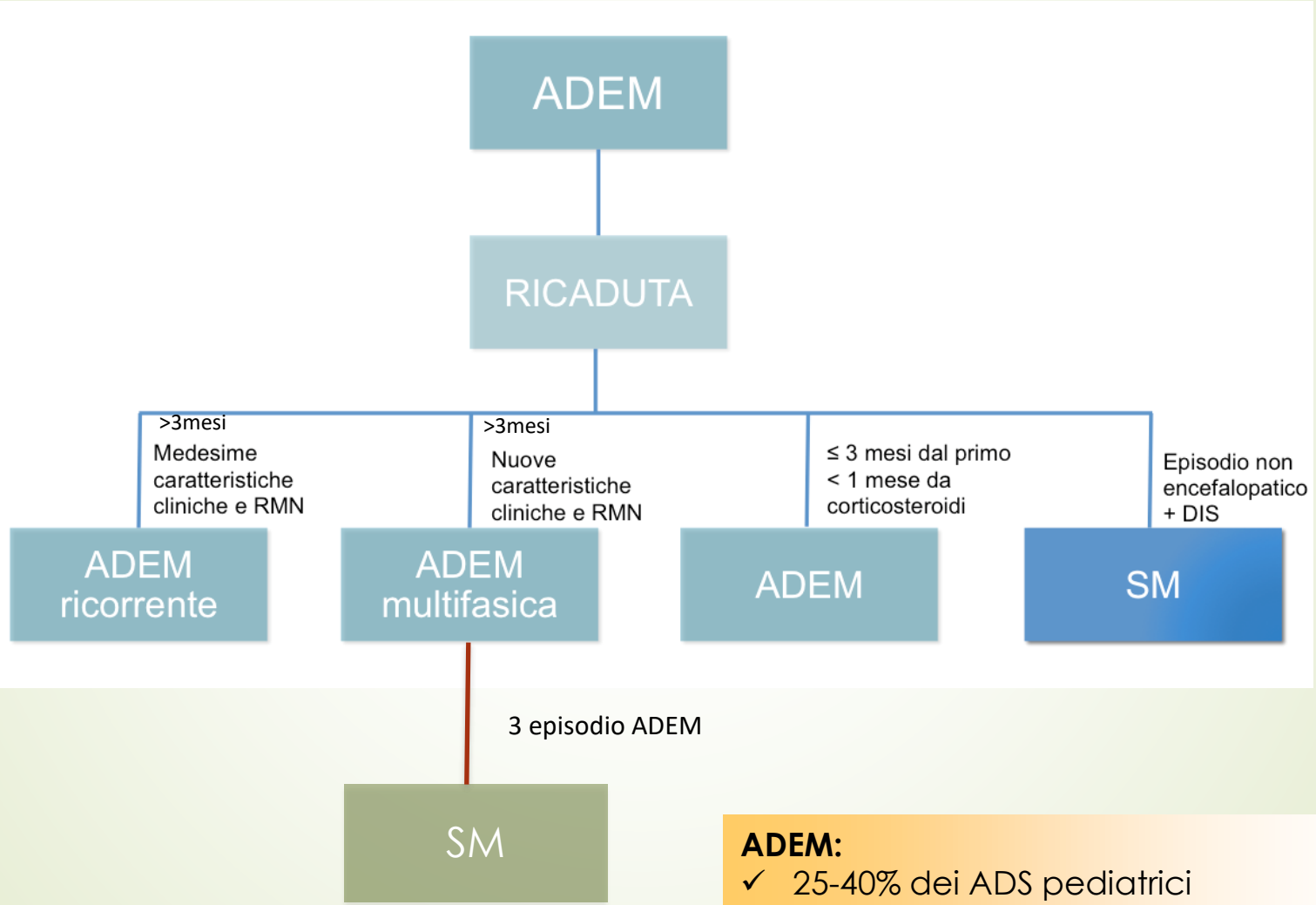
- A first polyfocal, clinical CNS event with presumed inflammatory demyelinating cause
- Encephalopathy that cannot be explained by fever
- No new clinical and MRI findings emerge three months or more after the onset
- Brain MRI is abnormal during the acute (three-month) phase.
- Typically on brain MRI:
  - 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

ENCEPHALOPATHY

- ✓ Behavioral change, e.g., confusion, excessive irritability
- ✓ Alteration in consciousness, e.g., lethargy, coma
- ✓ **unexplained by fever, systemic illness or postictal symptoms.**

Krupp et al, 2012

ADEM: decorso clinico



ADEM:

- ✓ 25-40% dei ADS pediatrici
- ✓ 80% dei casi decorso monofasico
- ✓ 20% SM presentano esordio ADEM - like

ADEM vs SM

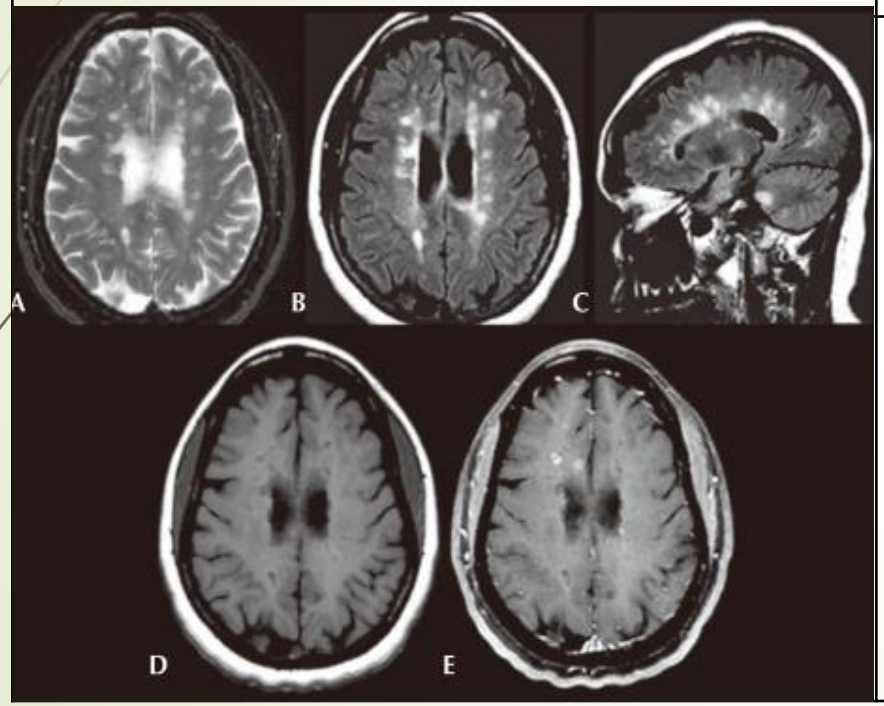
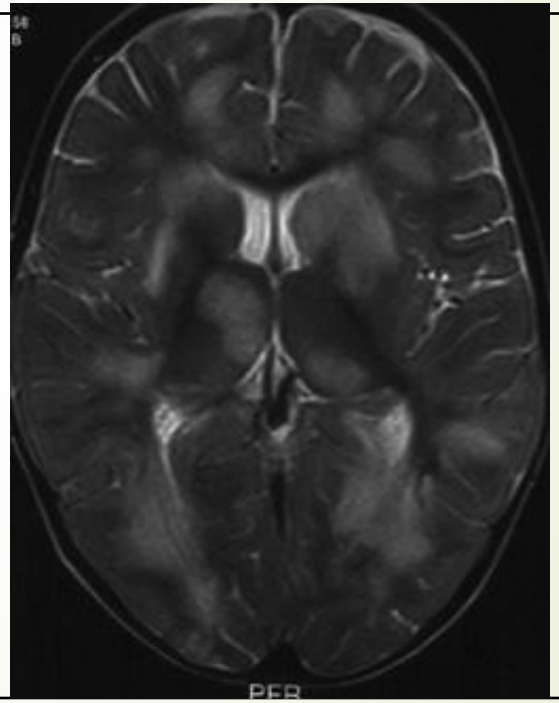
Table *Comparison of typical features of ADEM and MS*

Typical features	ADEM	MS
Demographic	More frequently younger age groups (<10 years); no gender predilection	More frequently adolescents; girls predisposed more than boys
Prior flu-like illness	Very frequent	Variable
Encephalopathy	Required in definition	Rare early in the disease
Seizures	Variable	Rare
Discrete event	A single event can fluctuate over the course of 12 weeks	Discrete events separated by at least 4 weeks
MRI shows large lesions involving gray and white matter	Frequent	Rare
MRI shows enhancement	Frequent	Frequent
Longitudinal MRI findings	Lesions typically either resolve or show only residual findings*	Typically associated with development of new lesions
CSF pleocytosis	Variable	Extremely rare, white blood cell count almost always <50
Oligoclonal bands	Variable	Frequent
Response to steroids	Appears favorable	Favorable

* A subset of patients with acute disseminated encephalomyelitis (ADEM) fail to have a self-limited disease course and instead experience additional relapses and accumulate lesions on neuroimaging. Subsequently, these patients are reclassified as multiple sclerosis (MS).

Krupp et al, 2007

SM vs ADEM

SM	ADEM
	

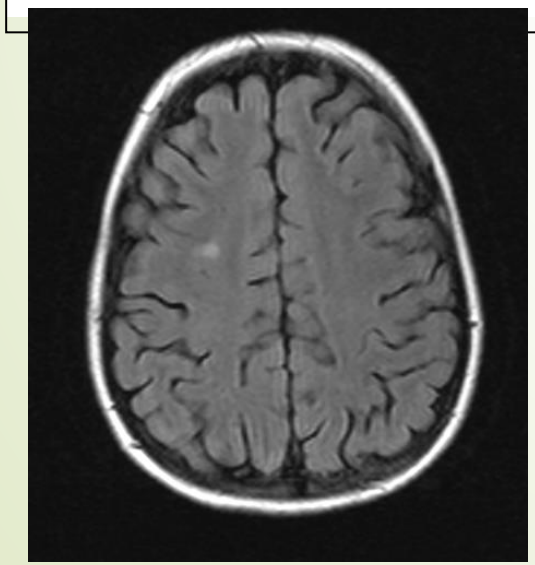
Terapia

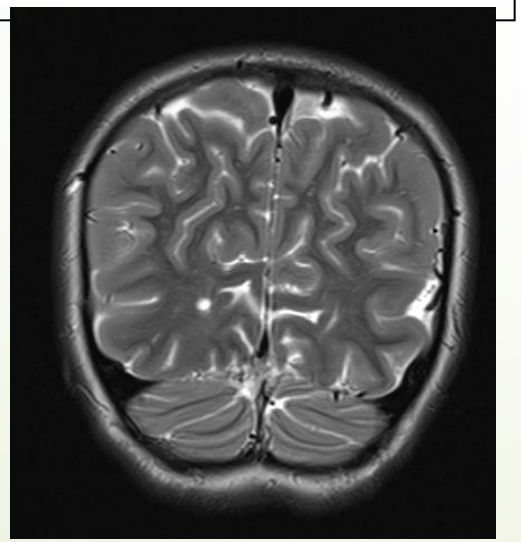
- Alte dosi di metilprednisolone (20-30 mg/Kg/die per 3-5 giorni)
- Proseguimento con prednisone per os 1.5-2 mg/Kg/die a scalare per un mese di terapia
- Terapia sintomatica (antiepilettica, fluidoterapia)

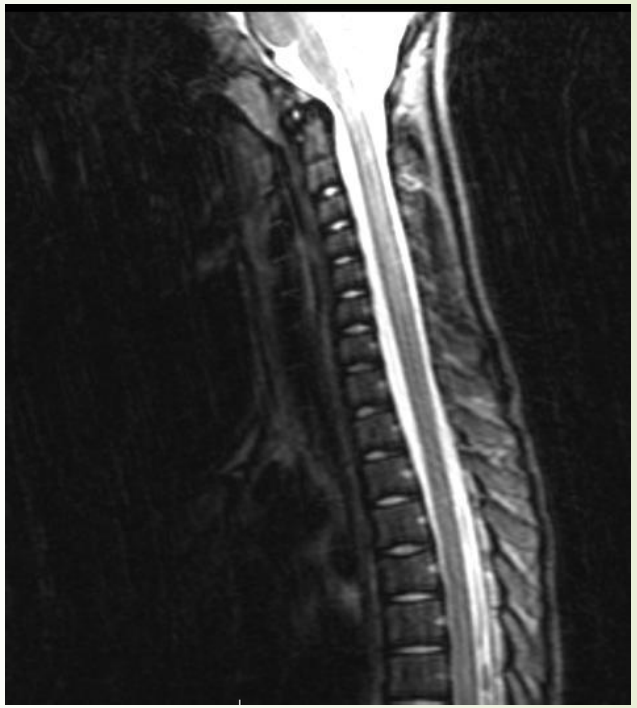
Neuromielite Ottica

Pediatric NMO[36] (all are required)

- Optic neuritis
- Acute myelitis
- At least two of three supportive criteria:
  - Contiguous spinal cord MRI lesion extending over three vertebral segments
  - Brain MRI not meeting diagnostic criteria for MS
  - Anti-aquaporin-4 IgG seropositive status





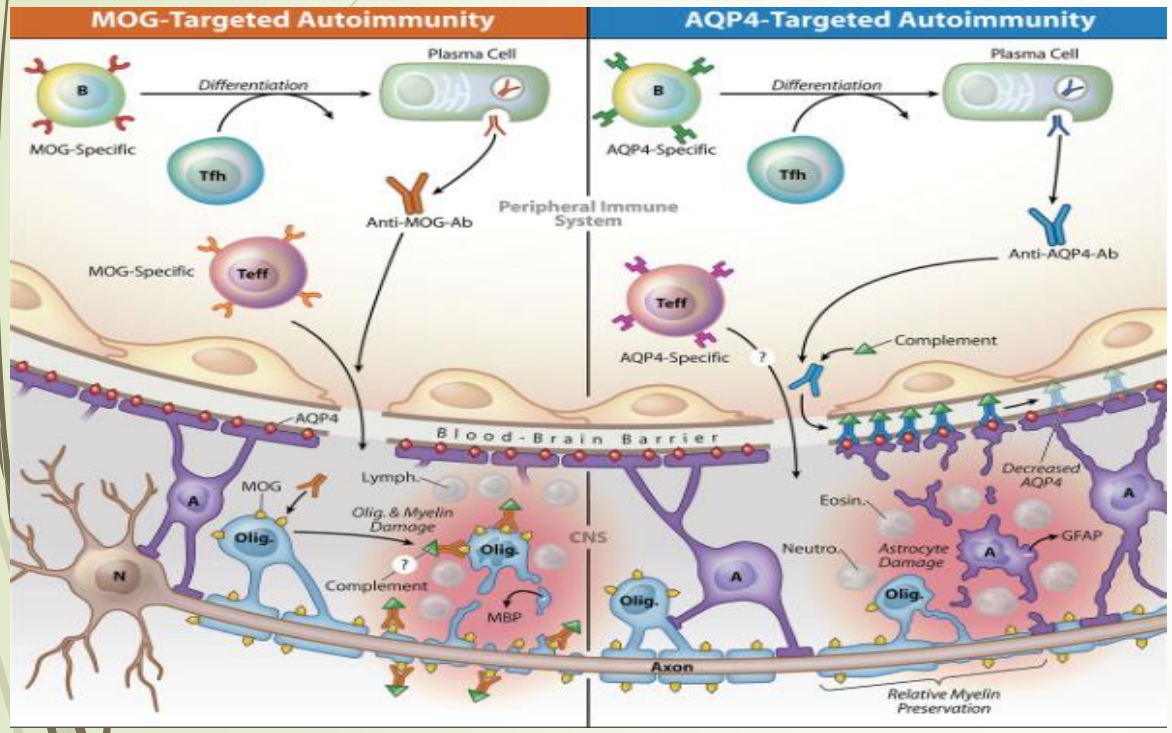


Altre cause: vasculopatie, infezioni, neoplasie, s. paraneoplastiche

Neuromielite ottica

- Nella NMO le cellule del sistema immunitario e gli anticorpi attaccano e distruggono la mielina nei nervi ottici e nel midollo spinale, causando la neurite ottica e mielite trasversa
- Siccome la NMO causa sintomi simili a quelli della sclerosi multipla, fino a tempi recenti è stata considerata una forma di SM. In realtà, la scoperta degli anticorpi (NMO-IgG) nel sangue di individui con la NMO adesso rende possibile distinguerla dalla SM.
- Gli attacchi di NMO sono più gravi di quelli della SM e all'inizio della malattia sono spesso confinati a nervi ottici e midollo spinale. Altri sintomi sono rari, anche se vomito incontrollabile e singhiozzo oggi sono riconosciuti come sintomi della NMO causati da danni al tronco encefalo.
- La NMO si tratta inizialmente con una combinazione di corticosteroidi e farmaci immunosoppressori. Alcuni pazienti hanno bisogno di essere trattati con corticosteroidi per un periodo più lungo e possono richiedere anche plasmaferesi
- I trattamenti che modificano il decorso della malattia usati per trattare la SM non sono efficaci per la NMO
- La terapia in cronico della NMOSD si basa su Ig ev, immunosoppressori (azatioprina, micofenolato), rituximab e, recentemente, satralizumab

Anticorpi anti MOG (Myelin oligodendrocyte glycoprotein)



- ✓ Ruolo patogenetico degli anti MOG nell'uomo non ancora definito
- ✓ La positività su siero degli anti MOG si può riscontrare in pazienti con diverse forme di malattie infiammatorie demielinizzanti all'esordio (SM, ADEM, NMO)
- ✓ Nella maggiorana dei casi si negativizzano entro 18 mesi dall'esordio
- ✓ Nell'ADEM e nella SM la positività è transitoria
- ✓ La persistenza di MOG + sembrerebbe fattore di rischio per evoluzione verso lo spettro della Neuromielite Ottica

DIFFERENZE CLINICHE, RADIOLOGICHE E DEMOGRAFICHE TRA NMOSD POSITIVA PER AQP4-IGG E MOG-IGG

	MOG ab+	NMO	MS
Demographics			
Women	63–74%	~90%	70–75%
Median age at onset (years)	31–37	35–45	20–30
Clinical presentation at onset			
Optic neuritis (ON)	60–74%	~45%	15–20%
Bilateral ON (of all ON)	35–41%	8–14%	0–1%
Myelitis	18–23%	~47%	rare
Brain stem encephalitis	8–14%	~3%	rare
Coexisting autoimmune disease	rare	frequent	rare
MRI			
Supratentorial MRI lesions (frequency at onset)	~35%	~50%	very high
Spinal MRI lesions (length, location)	2/3 LETM, 1/3 short; central/lateral	~94% LETM, central	short, lateral

Data summarized from several studies.[72,73,80,81–83]
LETM, longitudinally extensive transverse myelitis.

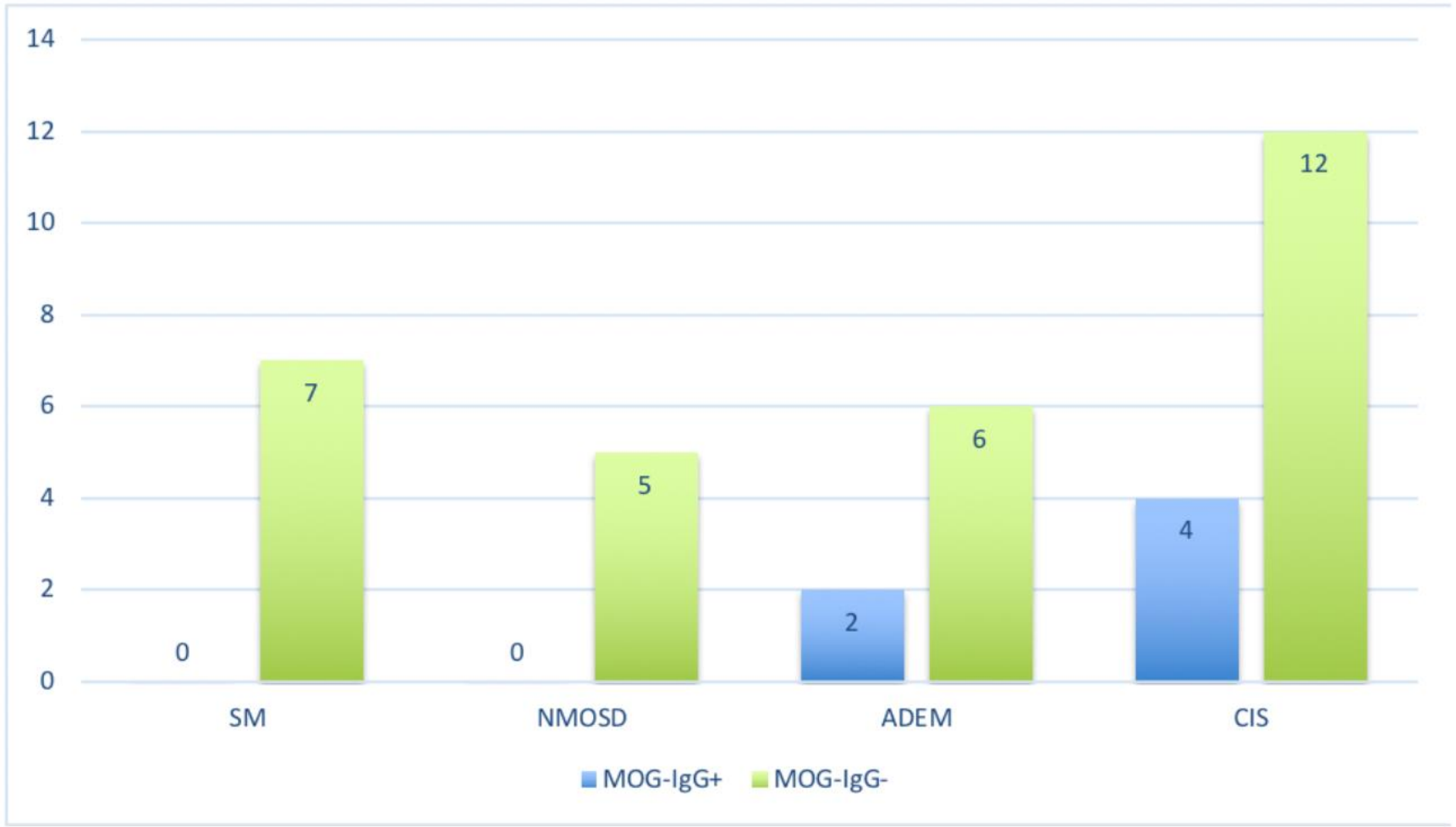


Diagramma 1. Pazienti arruolati presso il reparto di Neurologia dell'Ospedale Pediatrico Bambino Gesù.

Tabella 1. Caratteristiche cliniche dei pazienti MOG-IgG positivi.

	Pz 1	Pz 2	Pz 3	Pz 4	Pz 5	Pz 6	Pz 7	Pz 8	Pz 9	Pz 10
Età, sesso	8.3, F	3.6, M	4.8, F	10.3, M	10.9, M	3.6, M	37, M	36, M	35, M	21, F
Precedente infezione	SI	NO	SI	NO	NO	NO	SI	SI	NO	SI
Sintomi esordio	NORB dx	NORB bil. + midriasi	Sonnolenza, crisi epilettiche parziali sn, cefalea, astenia	Paraparesi, ROT assenti AAII	NORB bil. + papilledema	Atassia, cefalea, encefalopatia, tremore diffuso, andatura steppante, deficit di forza AI sn	Diplopia, nistagmo, sindrome midollare acuta con livello sensitivo D8	Vomito, cefalea, calo visus, sindrome midollare acuta con livello sensitivo D6	Cefalea, nistagmo, ipoestesia regione mentoniera, disturbo del visus OD	Afasia globale, stato confusionale, deficit VII n.c. dx, cefalea, vomito
LCR: BOC	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
LCR: pleiocitosi	NO	NO	SI	SI	NO	SI	SI	SI	SI	SI
EDSS fase acuta	2	3	4	7	3	8.5	8	8	3	8
EDSS ultimo FU	0	0	0	1	0	2	1	0	0	0
Ricadute	0	0	0	0	0	3	0	0	2	2
FU (mesi)	27	24	5	7	16	65	3	48	36	36
Diagnosi finale	NORB monol.	NORB bil.	ADEM	LETM	NORB bil.	MDEM	NMOSD	NMOSD	Clippers + lesione cono	MDEM

Tabella 2. Caratteristiche di RM dei pazienti MOG-IgG positivi.

	Pz 1	Pz 2	Pz 3	Pz 4	Pz 5	Pz 6	Pz 7	Pz 8	Pz 9	Pz 10
Lesioni del NO	Dx	Bil.			Bil.	Bil.				
Lesioni del chiasma						SI				
Lesioni cerebrali	Talamo bil., n. lenticolare sn, emisf. cerebellare sn	Parietale post. dx, temporale post. dx, talamo bil.	Parietale dx, sottocorticale bil., centri semiovali, talamo sn			Centro semiovale frontale sn e parietale bil., retrotrigonale bil (>sn), peduncoli cerebrali, corni occipitali dei ventricoli laterali	Peduncoli cerebellari medi	Corpo calloso, peduncolo cerebellare medio di sn	Alterazione corno occipitale sn	Alterazione talamo bil, peduncoli cerebellari, corticale frontale, giro temporale superiore sn
Lesioni del tronco encefalo			Ponte paramediale dx e tegmento pontino				Ponte e mesencefalo	Tegmento pontino in sede mediana dx, piramide bulbare dx	Ponte e bulbo	Ponte
LETM				D1-D8		C2-D2, D6, D8-D9	D1-D12	C4-C7, D5, D6, D10, D11		
Midollo cervicale						SI		SI		
Midollo toracico				SI		SI	SI	SI		SI
Cono			SI					SI	SI	

MOG quando cercarli?

- Pazienti con ADEM
- Pazienti con NMOSD
- Neurite Ottica
- Mielite trasversa
- RMN encefalo non mostra lesioni compatibili con SM

The numbers of pediatric multiple sclerosis

- Approximately 3–5% of all patients with MS have pediatric-onset[1]
- MS in pediatric population is a rare disease
  - The incidence ranges from 0.18 to 0.64 per 100,000 children per year[2,3] except in countries with higher incidence of >2.6 per 100,000 children[4,5]
- Defined as onset of MS symptoms in patients aged less than 18 years[1]
- The median age of onset of MS in children is 14.5 years[6]

DMTs, disease-modifying therapies; MS, multiple sclerosis

1. Simone M, et al. *Curr Treat Options Neurol*. 2016;18:36.
2. Chitnis T, et al. *Neurology*. 2013;80:1161–1168.
3. Alroughani R, et al. *BMC Neurol.* 2018;18: 27.
4. Dell'Avvento S, et al. *Eur J Pediatr.* 2016;175:19–29.
5. Reinhardt K, et al. *Eur J Neurol.* 2014;21:654–659.
6. Renoux C, et al. *N Engl J Med*. 2007;356:2603–2613.

Diagnostic criteria

Table 2 Comparison of the International Pediatric Multiple Sclerosis Study Group (IPMSSG) definitions for pediatric multiple sclerosis (MS) and the 2017 revised McDonald criteria (for adults)

2007 IPMSSG	2013 IPMSSG	2017 Revised McDonald criteria
Any of the following • Multiple clinical episodes of central nervous system (CNS) demyelination separated in time and space • Single clinical event that is associated with 2001 McDonald brain magnetic resonance imaging (MRI) criteria[a] for dissemination in space and subsequent changes on MRI consistent with criteria for 2001 McDonald criteria for dissemination in time – An episode consistent with the clinical features of acute disseminated encephalomyelitis (ADEM) cannot be considered as the first event of MS	*Any of the following* • Two or more non-encephalopathic CNS clinical events separated by more than 30 days, involving more than one area of the CNS – The development of new symptoms must occur at least 3 months after the incident illness irrespective of steroid use for the second event to be considered • Single clinical event and MRI features rely on 2010 revised McDonald criteria[b] for dissemination in space and dissemination in time – Criteria relative for dissemination in time for a single attack and single MRI only apply to children ≥12 years and only apply to cases without an ADEM onset • ADEM followed 3 months later by a non-encephalopathic clinical event with new lesions on brain MRI consistent with MS	*Addition to the 2010 McDonald criteria* • Cerebrospinal fluid-specific oligoclonal bands (in the absence of other cerebrospinal fluid findings atypical of multiple sclerosis) allow the diagnosis of MS in a patient with a typical clinically isolated syndrome + fulfillment of clinical or MRI criteria[c] for dissemination in space + no better explanation for the clinical presentation • Symptomatic and asymptomatic MRI lesions can be considered in the determination of dissemination in space or in time – Symptomatic brainstem or spinal cord syndrome were not included as MRI evidence of dissemination in space or in time on 2010 McDonald criteria • Cortical and juxtacortical lesions can be used in fulfilling MRI criteria for dissemination in space

Padilha et al., 2020

frontiers in Neurology

ORIGINAL RESEARCH
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Predictors of Evolution Into Multiple Sclerosis After a First Acute Demyelinating Syndrome in Children and Adolescents

Laura Papetti[1], Lorenzo Figà Talamanca[2], Alberto Spalice[3], Federico Vigevano[1], Diego Centonze[4] and Massimiliano Valeriani[1,5]

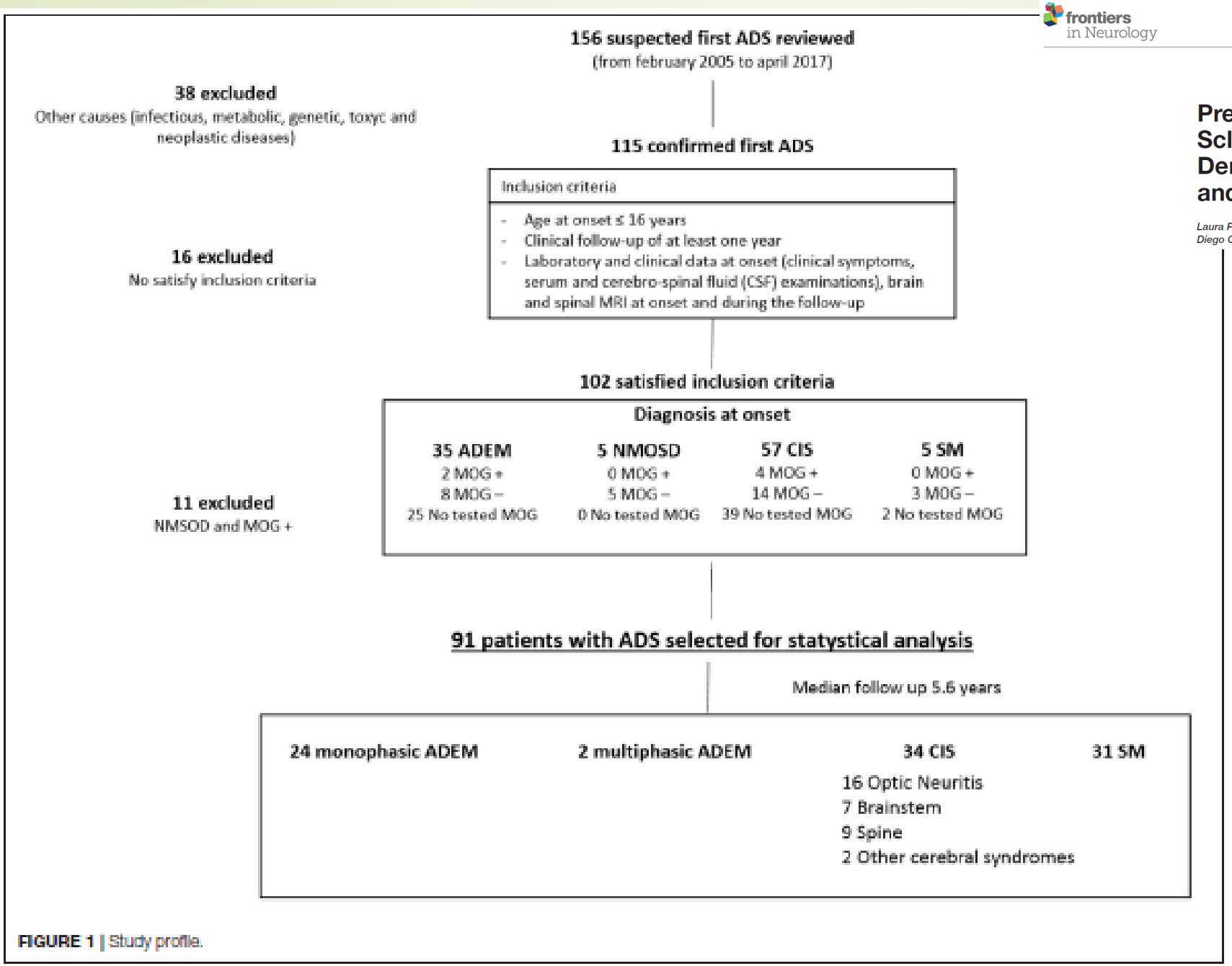
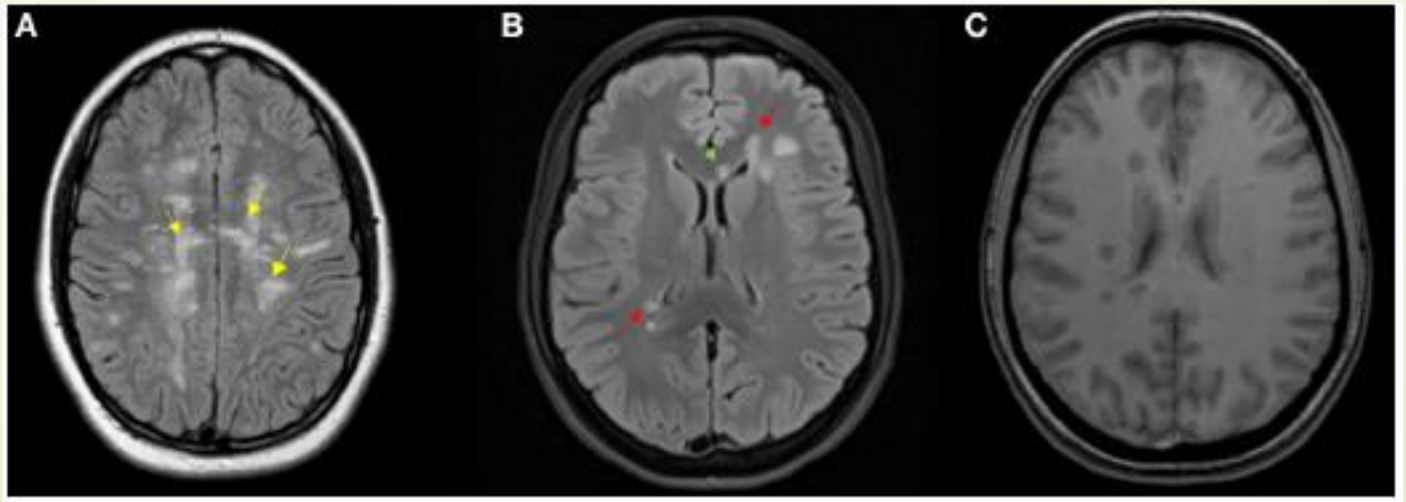


FIGURE 1 | Study profile.

TABLE 4 | Current criteria compared with our models in our cohort.

Criteria	KIDMUS 2004	McDonald2005 (Barkhof)	Callen per MS 2009	Callen MS vs. ADEM 2009	McDonald 2010 DIS	Verhey 2011	I model	II model
Features	Two of two: -lesions perpendicular to the long axis of the corpus callosum - well-defined lesions	Three of four: ≥9 T2 lesions o 1 gad + lesion ≥3 periventricular ≥1 subtentorial ≥1 subcortical	Two of three: ≥5 T2 lesion ≥2 periventricular ≥1 brainstem	Two of three -no diffuse bilateral lesions - black holes ->1 brainstem lesion	Two of four ≥1 periventricular ≥1 subcortical ≥1 subtentorial ≥ 1spine	Two of two: ≥1 periventricular ≥1 T1 hypointhense	Dawson Finger ≥1 periventricular lesion ≥1 T1 hypointhense lesion	≥1 Periventricular lesion ≥1 Corpus callosum lesion ≥1 T1 hypointhense lesion
Sensibility	21–47%	56–91%	26–74%	95%	85–100%	70–84%		
95% CI	**38.5%**	**56%**	**45%**	**16%**	**85%**	**80%**	**76%**	**80%**
Specificity	98-100%	30-100 %	68-100%	90%	80–86%*	90–93%		
95% CI	**100%**	**85%**	**90%**	**100%**	**61%**	**91.4%**	**100%**	**96%**
PPV	82–100%	34–69%	37-97%	71%	76%*	76%		
95% CI	**100%**	**70%**	**60%**	**100%**	**58%**	**85%**	**100%**	**92%**
NPV	61–87%	40–98%	90–91%	99%	100%*	96%		
95%CI	**74%**	**77%**	**70%**	**76%**	**88%**	**91%**	**87%**	**90%**

Bold figures refer to criteria applied to our cohort.
**Children under the age of 12.*



1.1 vs 0.4 in adults

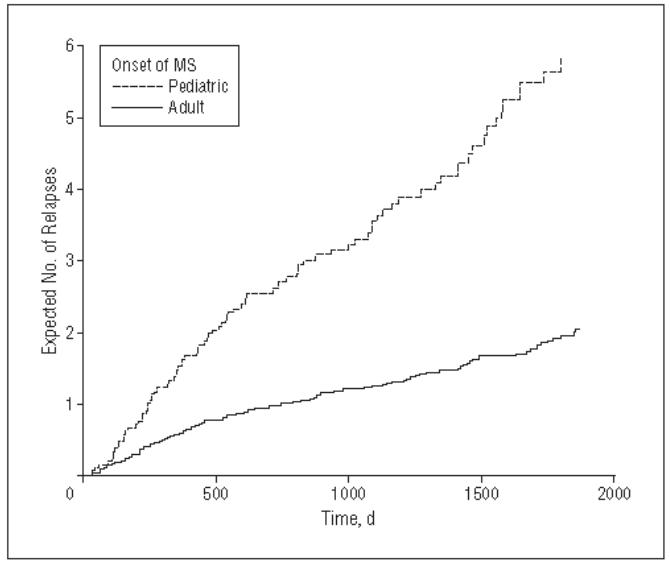
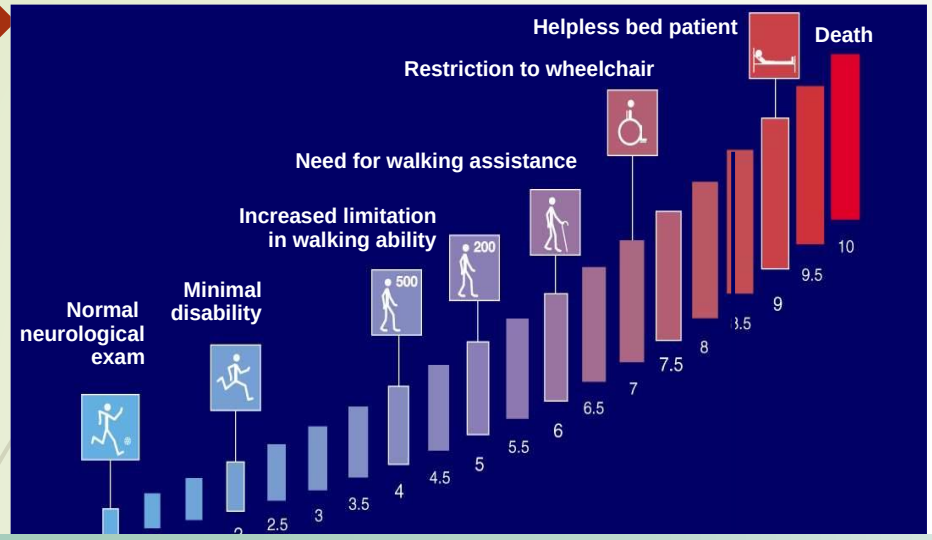


Figure. Cumulative number of multiple sclerosis (MS) relapses (excluding the first relapse).

Relapsing rate in pediatric patients is higher than in adults and the interval between the first and second relapse is shorter in pediatric age

Gorman et al., Arch Neurol 2009

Clinical course



Negative prognostic factors

- ✓ sub-tentorial lesions
- ✓ incomplete recovery after relapse
- ✓ high relapse frequency

- ✓ ARR in paediatrc patients with MS is almost twice that in adulthood.
- ✓ In paediatric patients, MS duration to reach unreversible disability is 10 years longer than in adults.
- ✓ **However, when MS starts in paediatric age, unreversible disability is reached at an age lower by 10 years, as compared to adult patients with MS.**
- ✓ The transformation from RR to SP form occurs at a younger age.

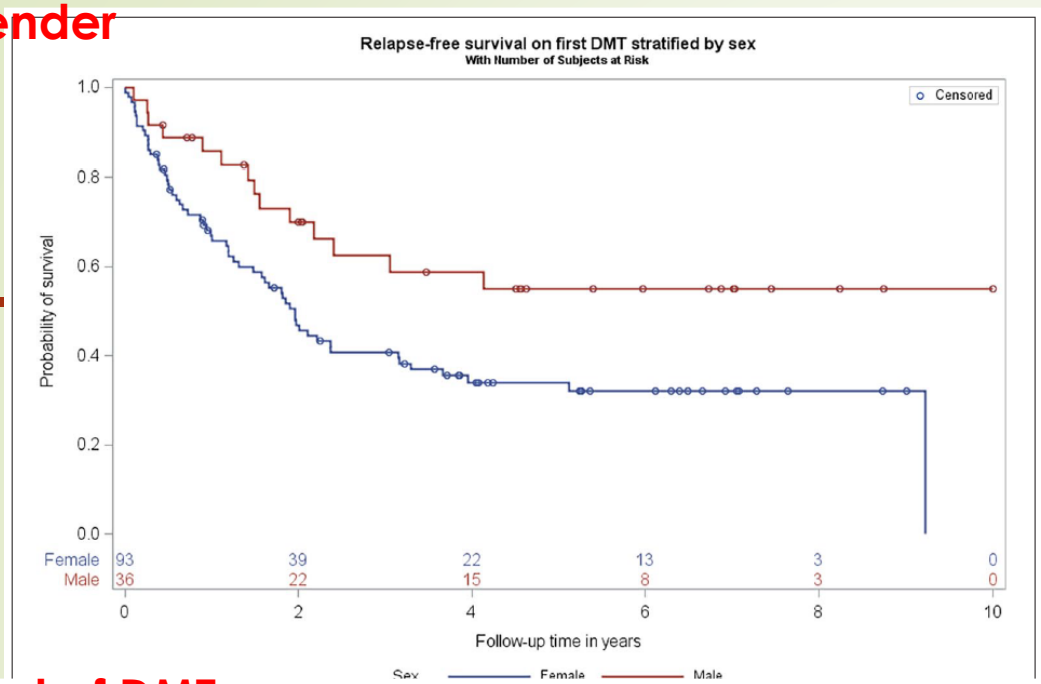
Unmet medical and treatment needs for the pediatric population

1. Lack of pharmacokinetic or pharmacodynamic data in pediatric population with MS makes dose selection difficult[1]
2. No evidence-based strategies in case of sub-optimal response to IFN/GA[1]
3. Data on DMTs are only available from open-label observational studies and many studies have a small sample size[1]
4. Medication adherence decreases with time to approximately 50% in the 3rd year of treatment. Issues include injection site reaction and needle phobia[2]
5. More than 40% of patients on injectable DMT need switching to high efficacy DMT due to suboptimal response[3]

DMTs, disease-modifying therapies; GA, glatiramer acetate; IFN, interferon; MS, multiple sclerosis

1. Ghezzi A, et al. *Neurology*. 2016;87:S97–S102.
2. Mah JK, et al. *Adolesc Health Med Ther*. 2010;1:31–43
3. Yeh EA et al. *Arch Neurol*. 2011;68:437–444.

1) gender



MULTIPLE SCLEROSIS JOURNAL | MSJ

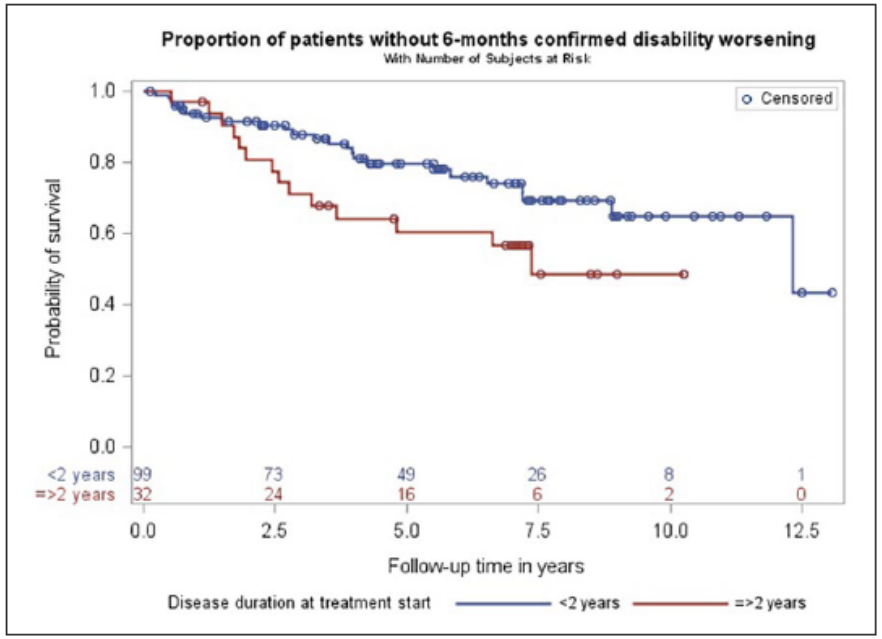
Original Research Paper

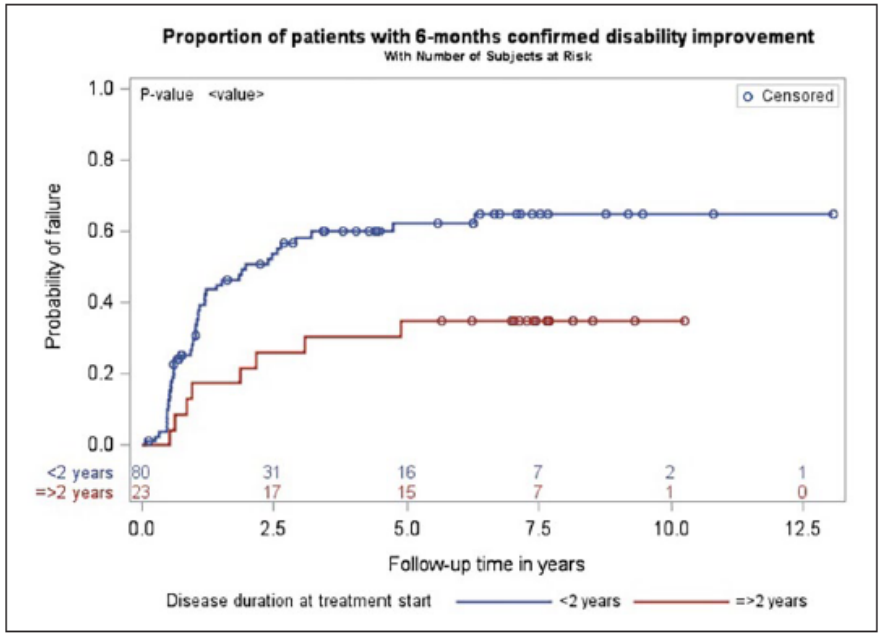
Predictors of treatment outcome in patients with paediatric onset multiple sclerosis

Tine Iskov Kopp, Morten Blinkenberg, Thor Ameri Chalmer, Thor Petersen, Mads Henrik Ravnborg, Per Soelberg Sørensen and Melinda Magyari

No difference between older and younger patients

2) Start of DMT



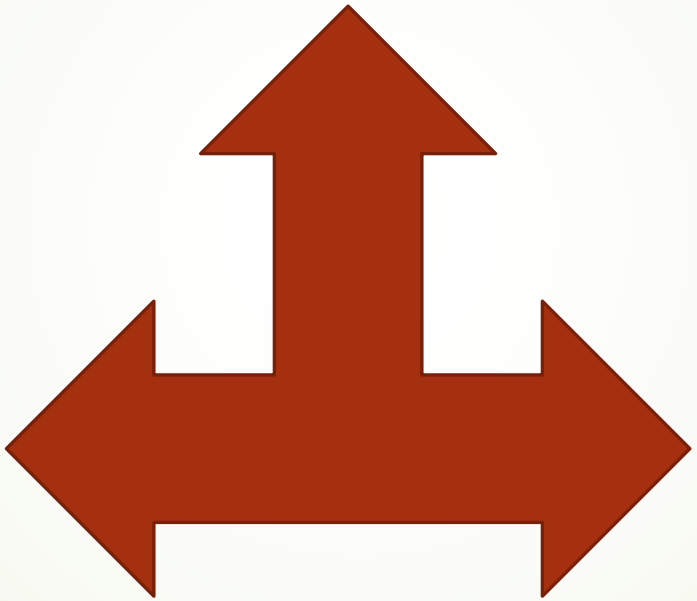


Patients treated earlier have a better prognosis

What are the therapeutic possibilities for children with MS (in Europe)?

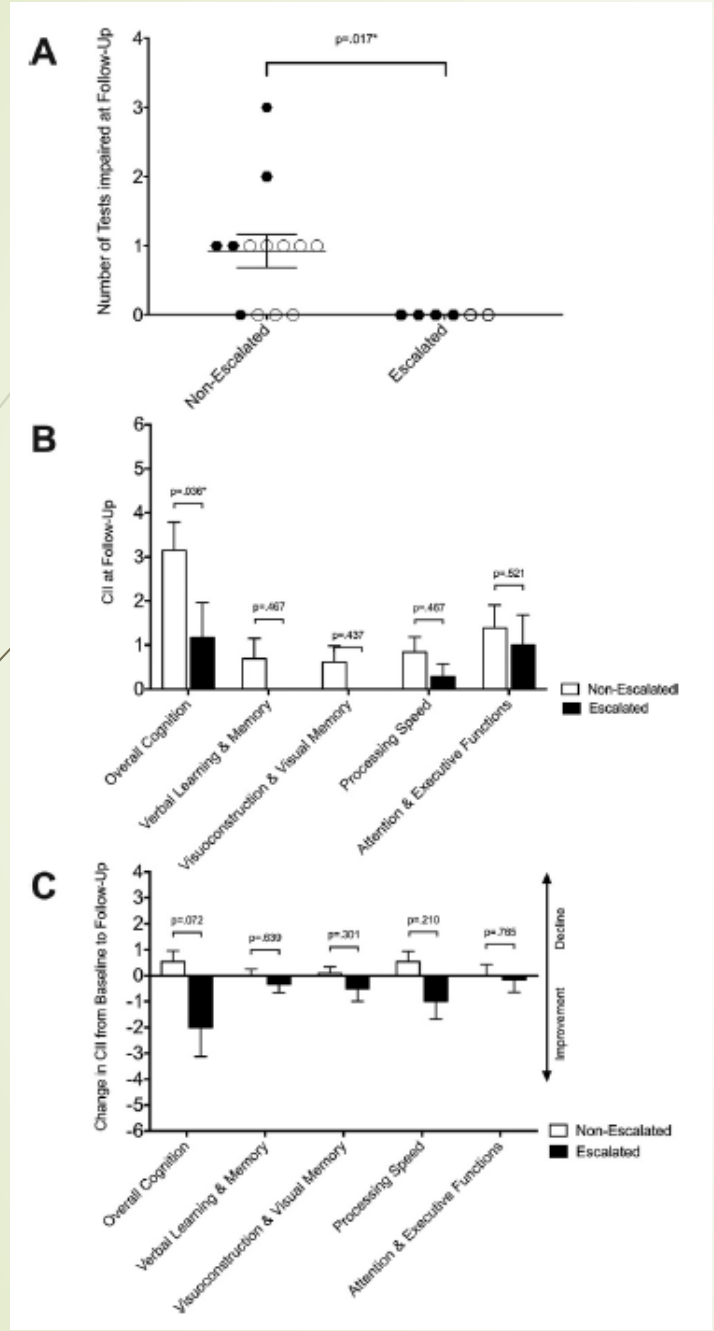
First line:

- Glatiramer acetate
- Interferons
- (Dimethyl fumarate)
- (Teriflunomide)



Second line:

- Fingolimod
- Natalizumab
- (Rituximab)



EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY 23 (2019) 783–791

ELSEVIER

Official Journal of the European Paediatric Neurology Society

Original article

Early effective treatment may protect from cognitive decline in paediatric multiple sclerosis

A. Johnen [a,*,1], C. Elpers [b,1], E. Riepl [a], N.C. Landmeyer [a], J. Krämer [a], P. Polzer [c], H. Lohmann [d], H. Omran [b], H. Wiendl [a], K. Göbel [a,2], S.G. Meuth [a,2]

[a] University of Münster, Department of Neurology with Institute of Translational Neurology, Germany
[b] University of Münster, University Children's Hospital Münster, General Pediatrics – Neuropediatric Department, Germany
[c] University of Münster, Institute of Clinical Radiology, Germany
[d] Herz-Jesu-Hospital, Münster-Hiltrup, Germany

Cognitive impairment in patients treated with first line therapies was higher than that of patients shifted to secon line treatments

TABLE 2. Distribution of DMTs, Follow-up Duration, and Annualized Relapse Rate (N = 718) on Newer Compared to Injectable DMTs during Treatment with Initial Therapy

Outcomes	Treatment Group: Newer DMT, n = 197	Treatment Group: Injectable DMT, n = 544	p
Distribution of DMTs			—
Interferon-β	—	296	
Interferon-β1a IM		143	
Interferon-β1a SC		111	
Interferon-β1b SC		30	
Peginterferon-β1a		12	
Glatiramer acetate	—	248	
Dimethyl fumarate	56	—	
Natalizumab	56	—	
Rituximab	56	—	
Fingolimod	26	—	
Teriflunomide	2	—	
Ocrelizumab	1	—	
Alemtuzumab	0	—	
Follow-up			0.63
Follow-up duration during first DMT, mean yr (SD)	1.5 (1.5)	1.8 (1.8)	
Follow-up duration during first DMT, median yr (IQR)	1.1 (0.4–2.3)	1.1 (0.5–2.5)	
Clinical relapse, n = 718			
Patients contributing to relapse analysis, n[a]	195	523	—
Patients with relapse, n (%)	38 (19%)	227 (43%)	—
Number of relapses, n	48	400	—
Person-years	305.1	958.9	—
Unadjusted annualized relapse rate	0.17 (95% CI = 0.12–0.24)	0.56 (95% CI = 0.48–0.66)	<0.001
PS-adjusted annualized relapse rate[b]	0.22 (95% CI = 0.15–0.33)	0.49 (95% CI = 0.41–0.59)	<0.001
Unadjusted rate ratio	0.30 (95% CI = 0.20–0.44)	1 (reference)	<0.001
PS-adjusted rate ratio[b]	0.45 (95% CI = 0.29–0.70)	1 (reference)	<0.001
Unadjusted rate difference	0.39 (95% CI = 0.29–0.50)	0 (reference)	0.003
PS-adjusted rate difference[b]	0.27 (95% CI = 0.14–0.40)	0 (reference)	0.004
Unadjusted number needed to treat	2.56 (95% CI = 2.00–3.45)	—	—
Adjusted number needed to treat[b]	3.70 (95% CI = 2.50–7.14)	—	—

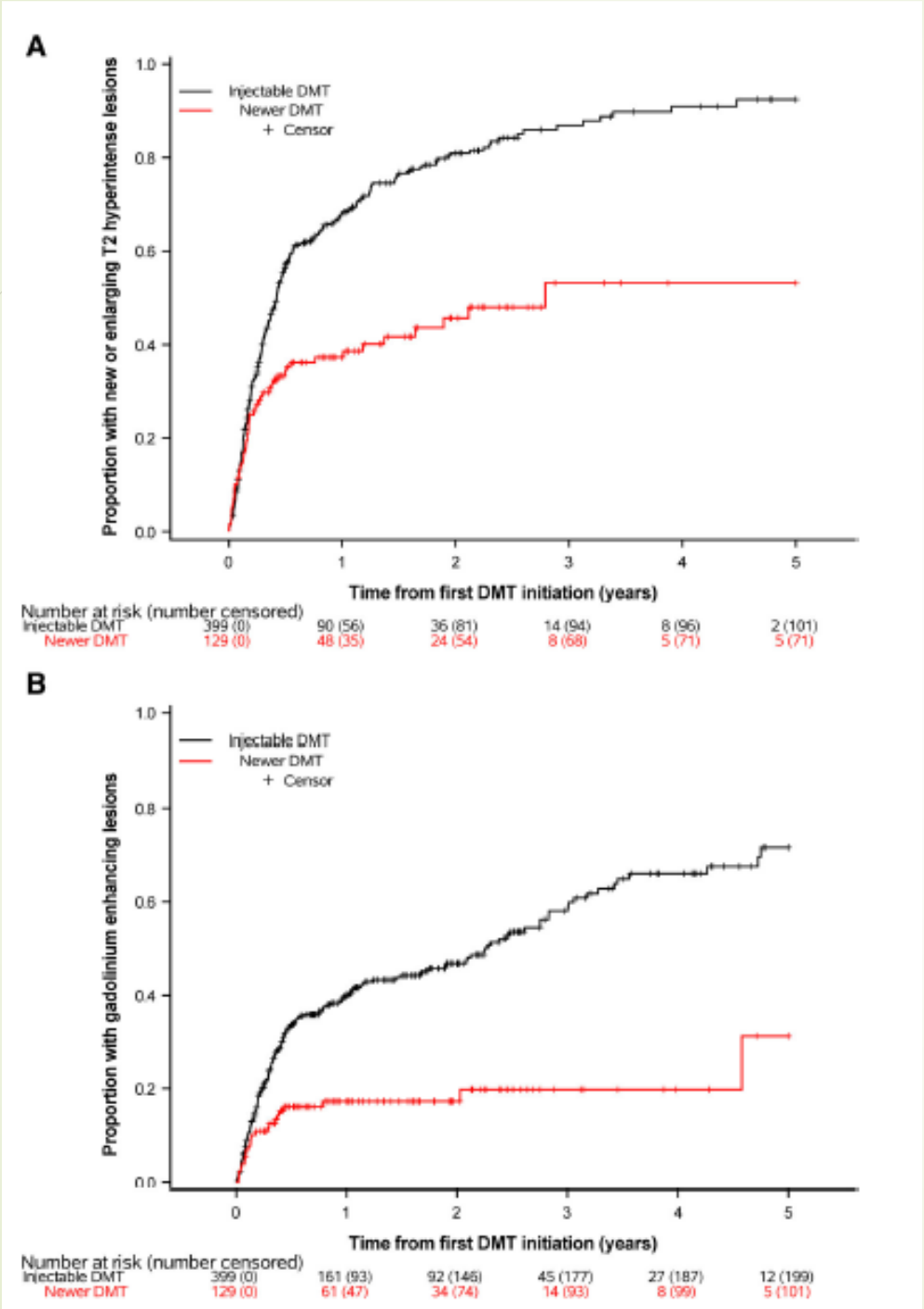
[a]Individuals were not included in the relapse analysis if they were missing either number of relapses or follow-up time during initial DMT.
[b]Adjusted for PS-quintile. PS includes baseline sex, race, ethnicity, Network site, age at onset and at first DMT initiation, first event characteristics (monofocal, optic nerve localization, severity), height, weight, diagnosis, number of relapses in the prior 6 months, new T2 hyperintense or gadolinium-enhancing lesions in the prior 6 months, and baseline Expanded Disability Status Scale.
CI = confidence interval; DMT = disease-modifying therapy; IM = intramuscular; IQR = interquartile range; PS = propensity score; SC = subcutaneous; SD = standard deviation.

Real-World Effectiveness of Initial Disease-Modifying Therapies in Pediatric Multiple Sclerosis

Kristen M. Krysko, MD, MAS,[1] Jennifer S. Graves, MD, PhD, MAS,[1,2] Mary Rensel, MD,[3] Bianca Weinstock-Guttman, MD,[4] Alice Rutatangwa, DO, MSc,[1] Gregory Aaen, MD,[5] Anita Belman, MD,[6] Leslie Benson, MD,[7] Tanuja Chitnis, MD,[8] Mark Gorman, MD,[7] Manu S. Goyal, MD, MSc,[9] Yolanda Harris, PhD,[10] Lauren Krupp, MD,[6] Timothy Lotze, MD,[11] Soe Mar, MD,[12] Manikum Moodley, MBCHB,[13] Jayne Ness, MD,[14] Moses Rodriguez, MD,[15] John Rose, MD,[16] Teri Schreiner, MD, MPH,[17] Jan-Mendelt Tillema, MD,[15] Michael Waltz, MAS,[18] T. Charles Casper, MStat, PhD,[18] and Emmanuelle Waubant, MD, PhD,[1] on behalf of the US Network of Pediatric MS Centers

ANN NEUROL 2020;88:42–55

Newer treatments proved to be far more effective than injectable ones



MRI worsening is faster with the injectable than newer DMTs

MULTIPLE SCLEROSIS JOURNAL | MSJ

Topical Review

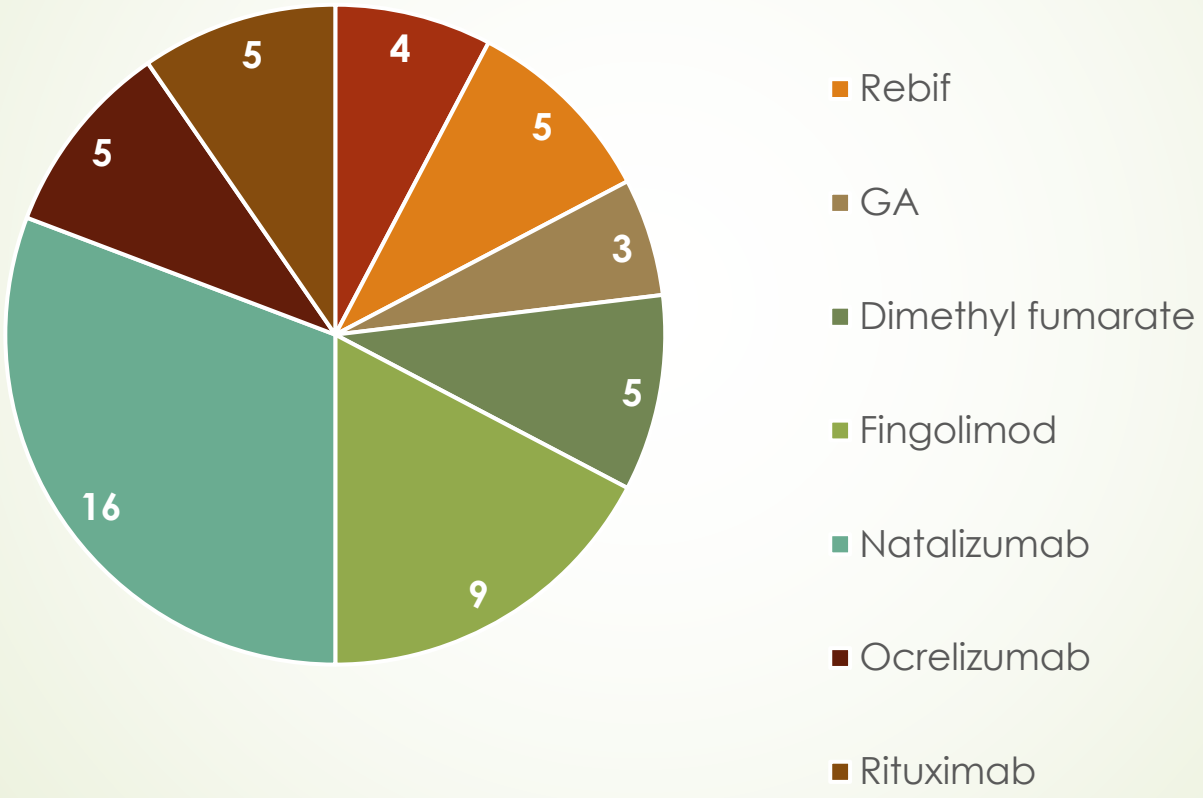
What does first-line therapy mean for paediatric multiple sclerosis in the current era?

Multiple Sclerosis Journal
1–7
DOI: 10.1177/1352458520937644

Yael Hacohen, Brenda Banwell and Olga Ciccarelli

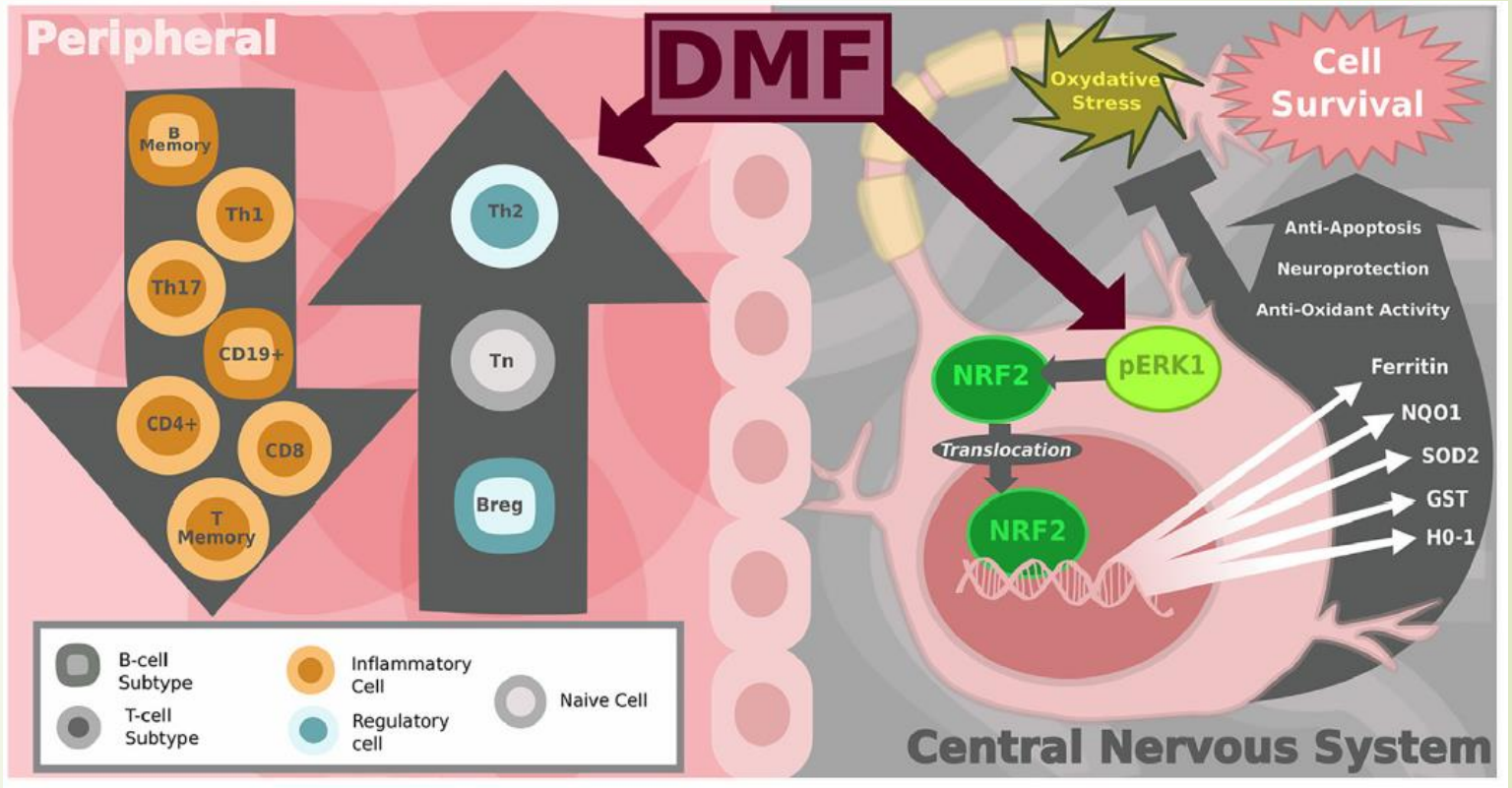
Abstract: Paediatric multiple sclerosis (MS) is associated with higher relapse rate, rapid magnetic resonance imaging lesion accrual early in the disease course and worse cognitive outcome and physical disability in the long term compared to adult-onset disease. Current treatment strategies are largely centre-specific and reliant on adult protocols. The aim of this review is to examine which treatment options should be considered first line for paediatric MS and we attempt to answer the question if injectable first-line disease-modifying therapies (DMTs) are still an optimal option. To answer this question, we review the effects of early onset disease on clinical course and outcomes, with specific considerations on risks and benefits of treatments for paediatric MS. Considering the impact of disease activity on brain atrophy, cognitive impairment and development of secondary progressive MS at a younger age, we would recommend treating paediatric MS as a highly active disease, favouring the early use of highly effective DMTs rather than injectable DMTs.

Our patients



DIMETHYL FUMARATE

FIGURE 2 | Diagram of peripheral immune and central nervous system (CNS) effects of dimethyl fumarate (DMF) in multiple sclerosis (MS). On the left: the shift in the balance toward anti-inflammatory immune cells in the peripheral blood. DMF-treated MS patients show a reduction in $CD8^+$ and to lesser extent $CD4^+$ T-cells as well as a decrease in the number of $CD19^+$ B-cells. Subset analysis reveals that total B and T memory cells decline while the number of naïve T-cells increases. Pro-inflammatory T helper subsets Th1 and Th17 decrease, shifting the balance toward more anti-inflammatory Th2, T-regulatory and B-regulatory subsets. On the right: within the CNS, DMF and its metabolites are activators of the Nrf2-dependent intracellular pathway, which protects neurons from oxidative stress. Nrf2 translocates from the cytoplasm to the nucleus to increase transcription of genes encoding antioxidant enzymes, including: heme oxygenase-1 (HO-1), NAD(P)H quinone dehydrogenase 1 (NQO1), GSTP1 (others glutathione-S-transferase), superoxide dismutase-2 (SOD2), Sulfiredoxin-1 (SRXN1), ferritin heavy chain 1 (FTH1).



JAMA Network | Open

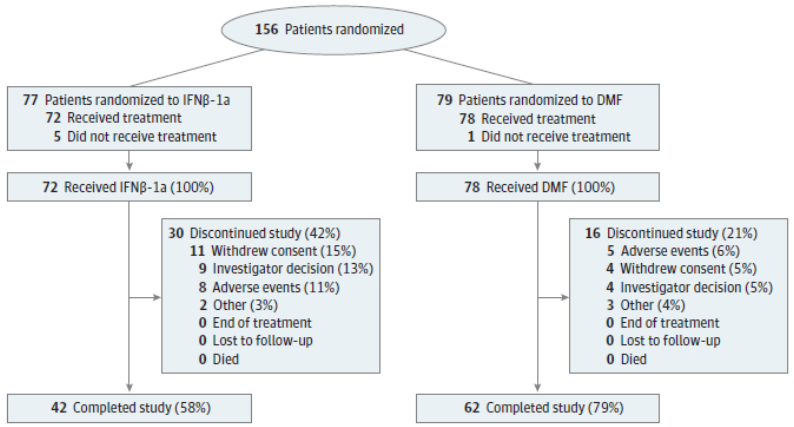
Original Investigation | Neurology

Effect of Dimethyl Fumarate vs Interferon β-1a in Patients With Pediatric-Onset Multiple Sclerosis

The CONNECT Randomized Clinical Trial

Patrick Vermersch, MD, PhD; Matthew Scaramozza, MS; Seth Levin, MD; Raed Alroughani, MD; Kumaran Deiva, MD, PhD; Carlo Pozzilli, MD, PhD; Jennifer Lyons, MD; Oksana Mokliatchouk, PhD; Joe Pultz, PhD; Fatou N'Dure, MBA; Shifang Liu, PhD; Runda Badwan, PharmD; Filipe Branco, MSc; Valencia Hood-Humphrey, MS; Nathalie Franchimont, MD, PhD; Jerome Hanna, MBBCh, BAO; Amir-Hadi Maghzi, MD

Figure 1. Patient Disposition



The number of individuals screened and excluded prior to randomization is not available.

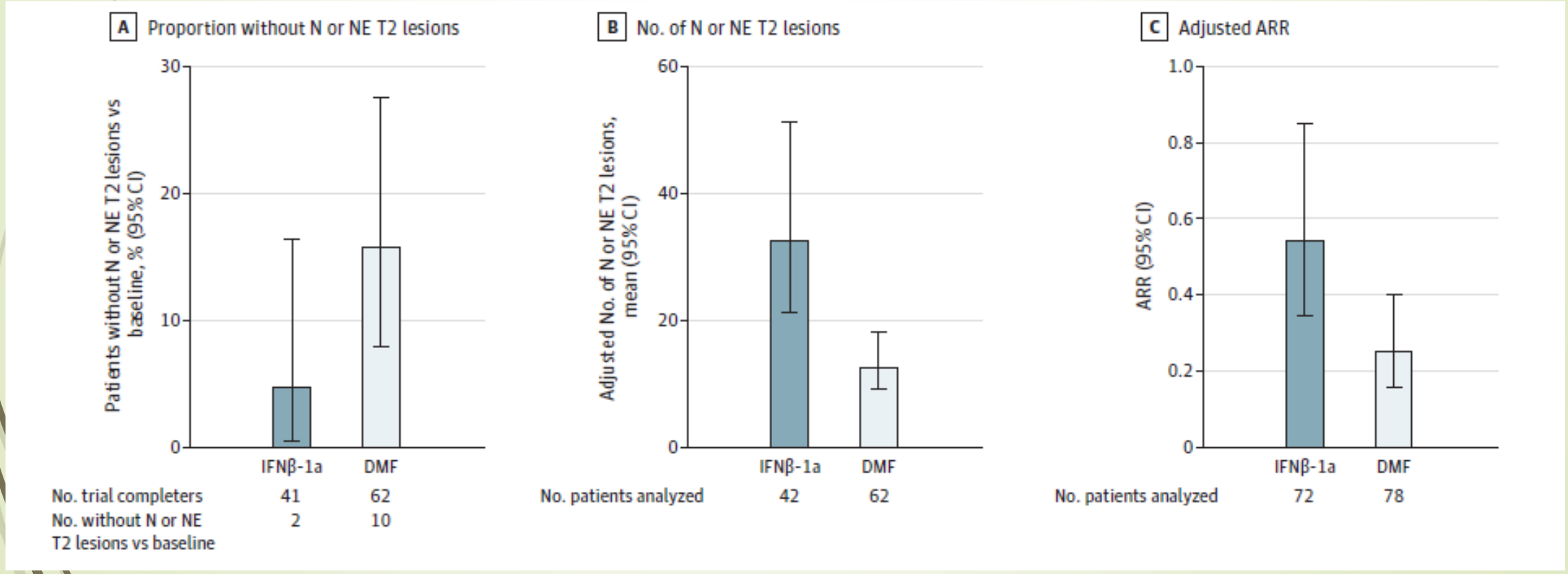
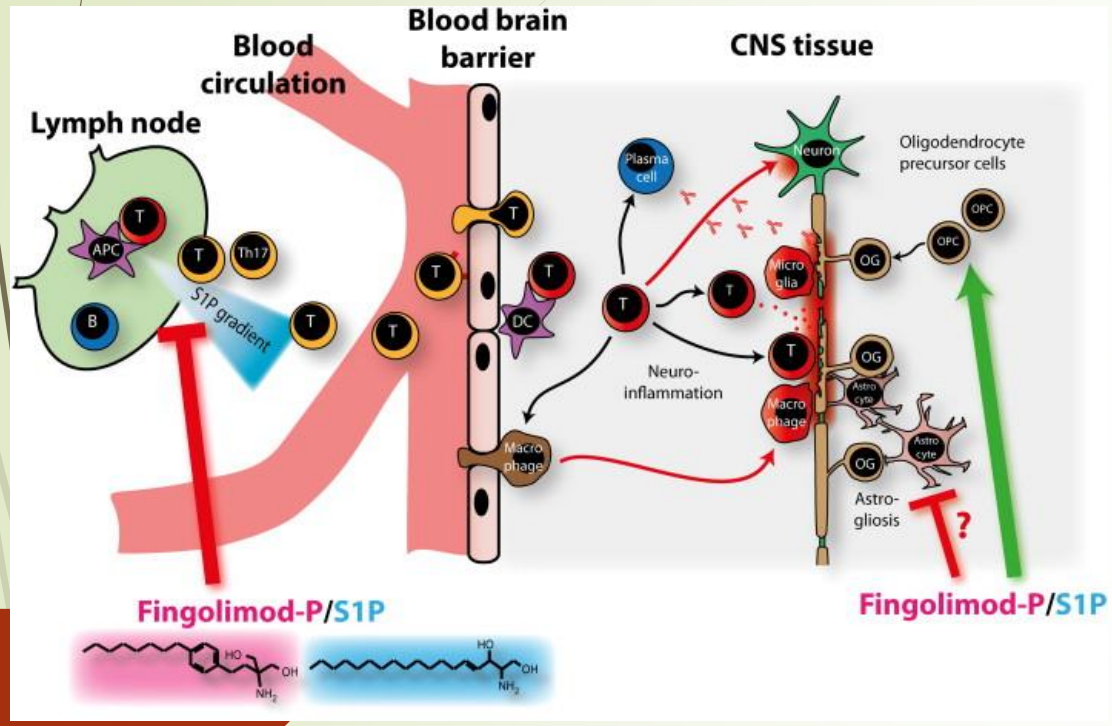


Table 3. Most Common TEAEs Occurring in ≥20% of Patients and TEAEs of Special Interest

Event[a]	Patients, No. (%)		
	IFNβ-1a (n = 72)	DMF (n = 78)	Total (N = 150)
TEAE[b]			
MS relapse	33 (45.8)	27 (34.6)	60 (40.0)
Headache	26 (36.1)	22 (28.2)	48 (32.0)
Influenza-like illness	37 (51.4)	2 (2.6)	39 (26.0)
Abdominal pain	5 (6.9)	32 (41.0)	37 (24.7)
Flushing	1 (1.4)	30 (38.5)	31 (20.7)
TEAE of special interest[b]			
Flushing or other related symptom	1 (1.4)	30 (38.5)	31 (20.7)
GI tolerability[c]	22 (30.6)	58 (74.4)	80 (53.3)
Hepatic disorder	1 (1.4)	1 (1.3)	2 (1.3)
Infection or infestation	30 (41.7)	41 (52.6)	71 (47.3)
Vascular disorder	5 (6.9)	36 (46.2)	41 (27.3)
Leukopenia	0	0	0
Lymphopenia	0	2 (2.6)	2 (1.3)
Malignant neoplasm	0	0	0
Kidney disorder	7 (9.7)	4 (5.1)	11 (7.3)

FINGOLIMOD



Fingolimod is a sphingosine 1-phosphate receptor modulator used to treat patients with the relapsing-remitting form of multiple sclerosis (MS).

Oral fingolimod is thought to provide therapeutic benefit by preventing normal lymphocyte egress from lymphoid tissues, thus reducing the infiltration of autoaggressive lymphocytes into the CNS, where they would cause inflammation and tissue damage.

REVIEW

Fingolimod in multiple sclerosis: Mechanisms of action and clinical efficacy

Jens Ingwersen [a], Orhan Aktas [a] ✉, Patrick Kuery [a], Bernd Kieseier [a], Alexey Boyko [b], Hans-Peter Hartung [a] ✉

FDA and EMA approval of fingolimod in pediatric MS

Novartis announces FDA approval of Gilenya® as the first disease-modifying therapy for pediatric relapsing multiple sclerosis

May 2018

Novartis announces EU approval of Gilenya® for children and adolescents with MS, making it the first and only oral disease-modifying treatment for these patients in Europe

Nov 2018

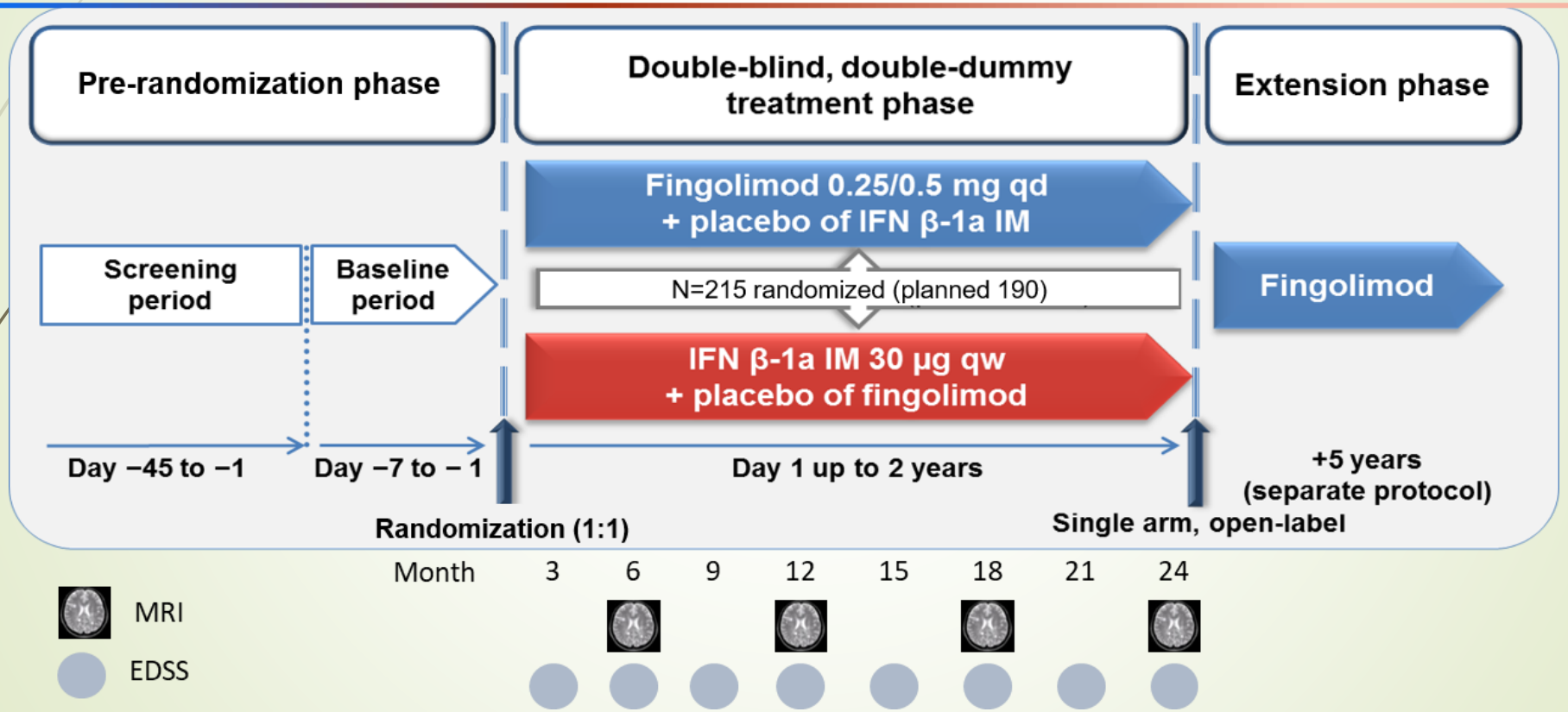
https://www.novartis.com/news/media-releases/novartis-announces-fda-approval-gilenya-first-disease-modifying-therapy-pediatric-relapsing-multiple-sclerosis
https://www.novartis.com/news/media-releases/novartis-announces-eu-approval-gilenya-children-and-adolescents-ms-making-it-first-and-only-oral-disease-modifying-treatment-these-patients-europe

PARADIGMS: study objective and design

Randomized, multicenter, double-blind, controlled, parallel-group study

Objective

To evaluate the efficacy and safety of fingolimod (0.5 mg once-daily or 0.25 mg once-daily for ≤40 kg) versus IFN β-1a IM (30 µg once weekly up to 2 years) in pediatric patients with relapsing MS

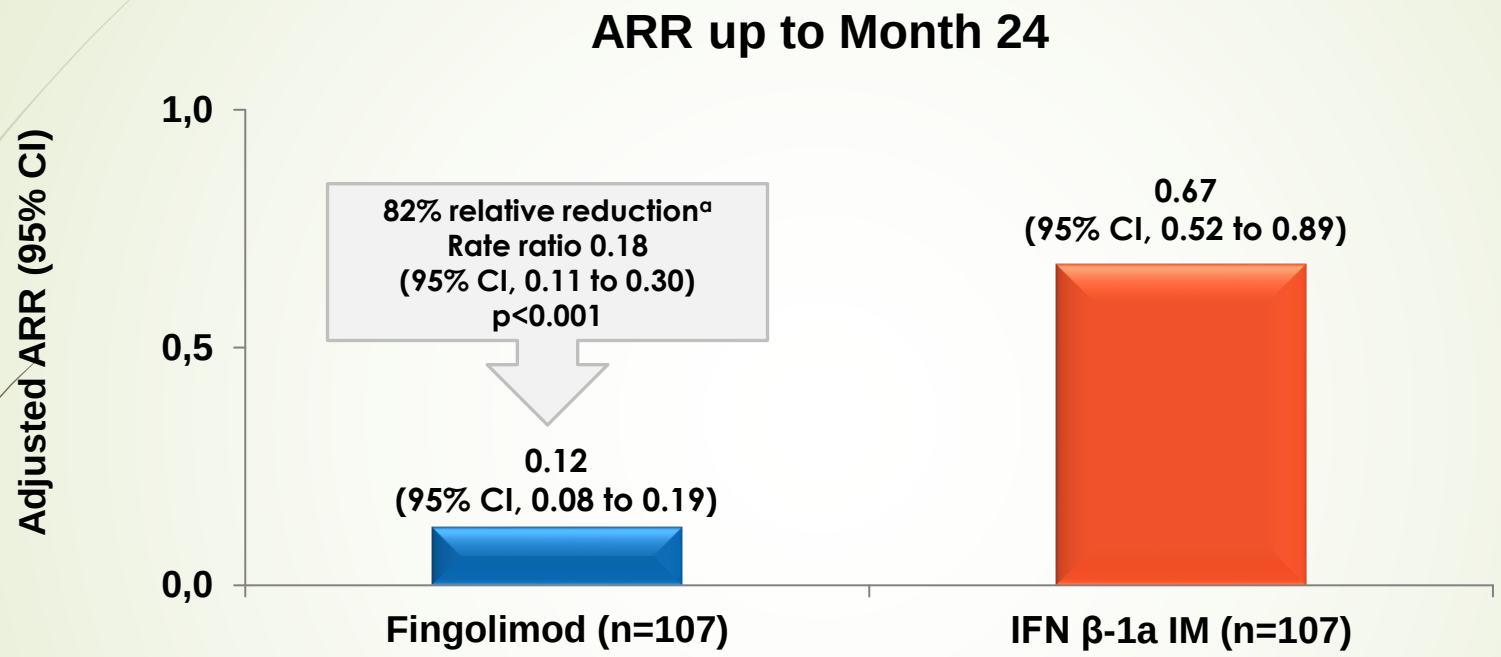


Double-dummy design was performed using matching placebo capsules and placebo prefilled syringes for IM injection

EDSS, Expanded Disability Status Scale; IFN β-1a, interferon beta-1a; IM, intramuscular; MRI, magnetic resonance imaging; MS, multiple sclerosis; qd, once-daily; qw, once weekly

Chitnis T, et al. *N Engl J Med* 2018;379:1017–1027.

Fingolimod significantly reduced ARR versus IFN β-1a

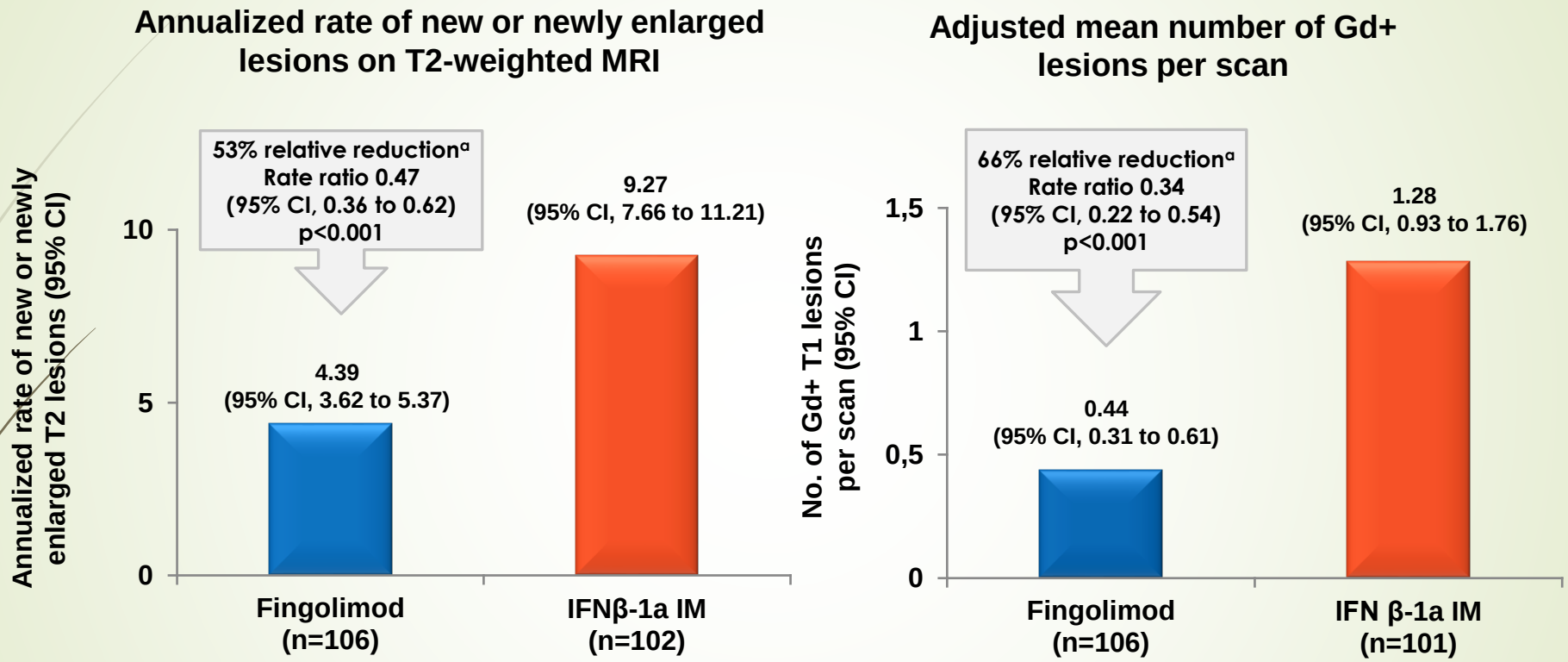


Fingolimod was superior to IFN β-1a IM in reducing ARR (confirmed relapses) up to Month 24 in paediatric patients with MS

[a]Negative binomial regression model with a log link, adjusted for trial regimen, the number of relapses in the 2 years before randomization, pubertal
status, and geographic region

ARR, annualized relapse rate; CI, confidence interval; IFN β-1a, interferon beta-1a; IM, intramuscular; MS, multiple sclerosis
Chitnis T, et al. *N Engl J Med* 2018;379:1017–1027.

Significantly better MRI outcomes with fingolimod vs IFN β-1a

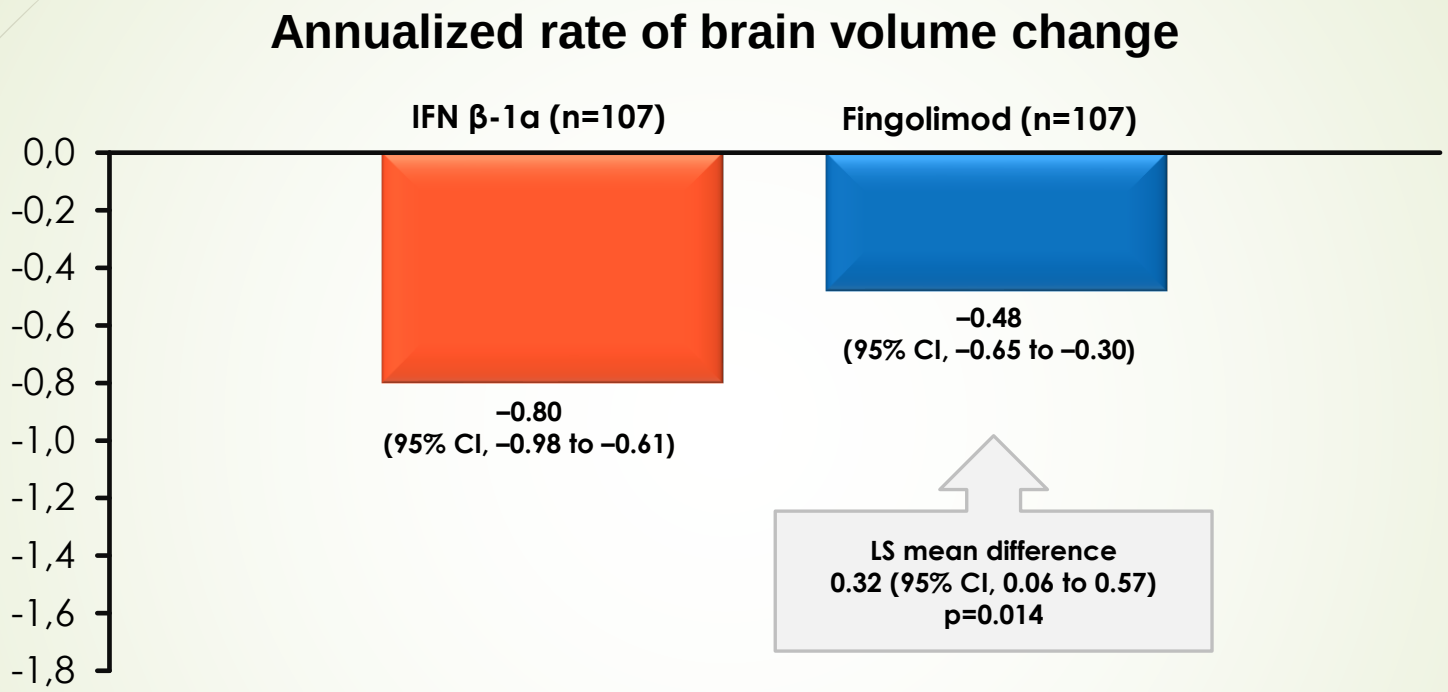


Fingolimod significantly reduced MRI activity in paediatric patients with MS for up to 24 months compared with IFN β-1a

[a]Negative binomial regression model adjusted for treatment, pubertal status, geographical region, and relevant baseline value if applicable. There was no prespecified plan for adjustment for multiple comparisons for other secondary end points, and results are reported as point estimates with unadjusted confidence intervals only.

CI, confidence interval; Gd+, gadolinium-enhancing; IFN β-1a, interferon beta-1a; IM, intramuscular; MRI, magnetic resonance imaging
Chitnis T, et al. *N Engl J Med* 2018;379:1017–1027.

Fingolimod significantly reduced BVL vs IFN β-1a



In pre-specified exploratory analyses, the rate of BVL with fingolimod was –0.48 and –0.80 with IFN β-1a IM

P values are obtained from ANCOVA model adjusted for treatment, region, pubertal status, and baseline normalized brain volume as covariates. There was no prespecified plan for adjustment for multiple comparisons for other secondary end points, and results are reported as point estimates with unadjusted confidence intervals only.
ANCOVA, analysis of covariance; BVL, brain volume loss; IFN, interferon; LS, least square; n, number of patients with available result for the corresponding time point and included in the analysis
Chitnis T, et al. *N Engl J Med* 2018;379:1017–1027.

Adverse events

The overall incidence of AEs was lower in fingolimod treatment group than in IFN β-1a treatment group (88.8% vs. 95.3%)

	Fingolimod (N=107)	IFN β-1a IM (N=107)
All events	n (%)	n (%)
Any AEs	95 (88.8)	102 (95.3)
AE leading to interruption of study drug	12 (11.2)	3 (2.8)
AE leading to discontinuation of study drug	5 (4.7)	3 (2.8)
Any serious AE[a]	18 (16.8)	7 (6.5)
Frequent AEs by PT (>10% of patients receiving fingolimod or IFN β-1a IM)		
Headache	34 (31.8)	32 (29.9)
Viral URTI	23 (21.5)	26 (24.3)
URTI	17 (15.9)	5 (4.7)
Leukopenia	15 (14.0)	3 (2.8)
Influenza	12 (11.2)	4 (3.7)
Influenza-like illness	5 (4.7)	40 (37.4)
Cough	10 (9.3)	12 (11.2)
Chills	1 (0.9)	11 (10.3)
Pyrexia	8 (7.5)	22 (20.6)

[a]For further details on SAEs, please refer to slide #48 (Back-up)
AEs, adverse events; IFN β-1a, interferon beta-1a; IM, intramuscular; PT, preferred term; URTI, upper respiratory tract infections
Chitnis T, et al. *N Engl J Med* 2018;379:1017–1027.

NATALIZUMAB

- **Reduced relapsing rate**
- **Reduced neuroradiological progression of the disease**

Warning!

Progressive multifocal leukoencephalopathy (PML) → following JCV reactivaction (1:500 treated pts)

Risk factors for PML:
AntiJCV Ab
Treatment duration(> 24 months)
Previous immunosuppressive treatments

AntiJCV Ab can be found in 37% of paediatric population

Ghezzi *et al. BMC Neurology* (2015) 15:174
DOI 10.1186/s12883-015-0433-y

BMC Neurology

RESEARCH ARTICLE Open Access

Natalizumab in the pediatric MS population: results of the Italian registry

Angelo Ghezzi[1*], Lucia Moiola[2], Carlo Pozzilli[3], Vincenzo Brescia-Morra[4], Paolo Gallo[5], Luigi Maria Edoardo Grimaldi[6], Massimo Filippi[7], Giancarlo Comi G.[2] and the MS Study Group-Italian Society of Neurology

Table 1 Demographic and baseline clinical characteristics

	Mean (SD)
Age at MS onset (years)	12.9 (2.7)
Pre-NA disease duration (months)	25.6 (23.3)
Age at NA initiation (years)	14.7 (2.4)
Weight (Kg)	62.0 (13.3)
Height (cm)	163.5 (12.3)
Number of relapses prior NA initiation	4.0 (2.2)
Number of relapses in the year prior NA initiation	2.3 (1.3)
Number of Gd + MRI lesions prior NA initiation	3.3 (4.4)
EDSS at NA initiation	2.6 (1.3)

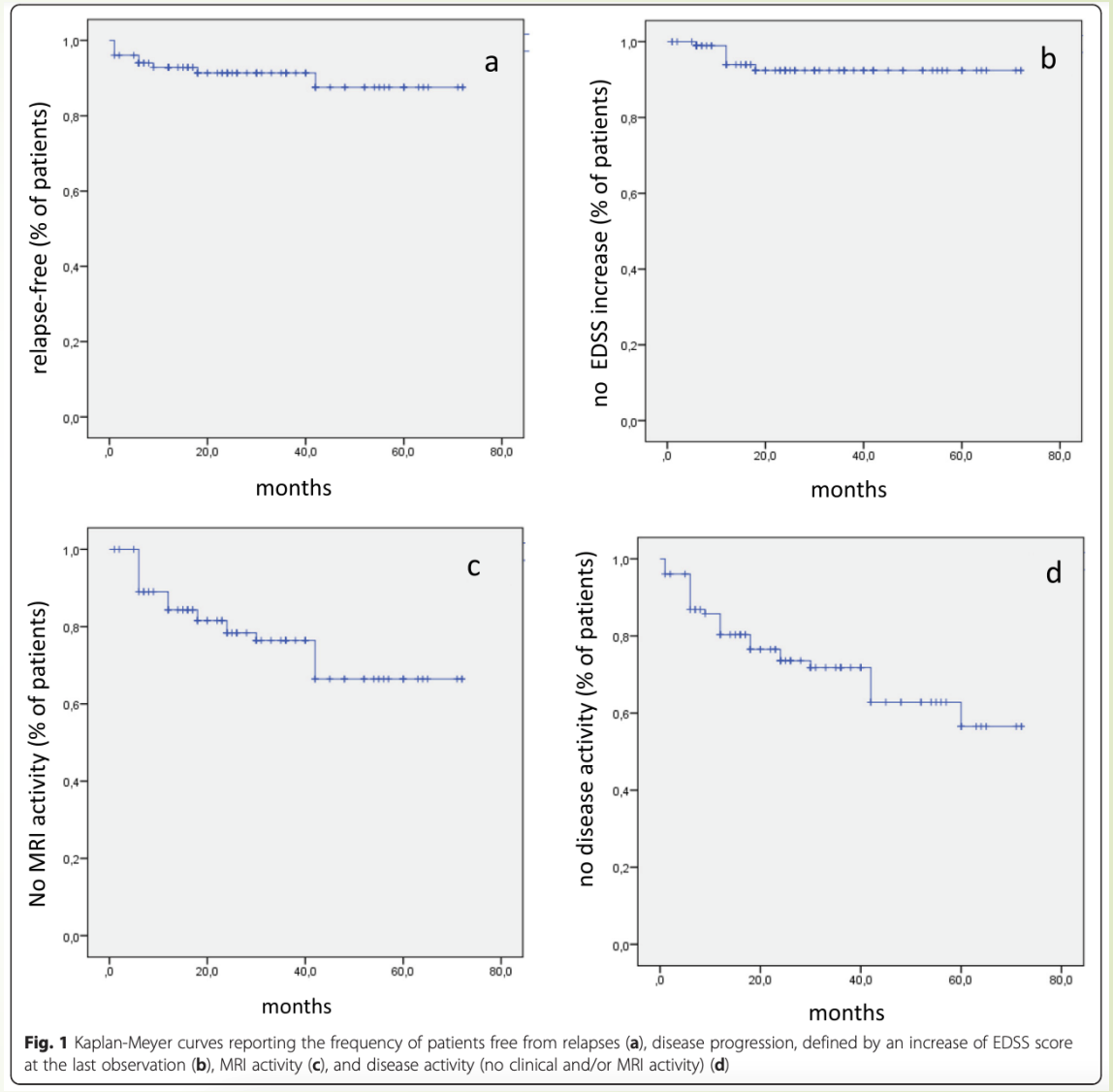


Fig. 1 Kaplan-Meyer curves reporting the frequency of patients free from relapses (**a**), disease progression, defined by an increase of EDSS score at the last observation (**b**), MRI activity (**c**), and disease activity (no clinical and/or MRI activity) (**d**)

RITUXIMAB

Rituximab is antiCD20 monoclonal antibody

Targeting CD20 has proved effective in breaking the inflammatory mechanisms leading to the neurological damage

JAMA Neurology | Original Investigation

Comparative Effectiveness of Rituximab and Other Initial Treatment Choices for Multiple Sclerosis

Mathias Granqvist, MD; Malin Boremalm; Amyar Poorghobad, MD; Anders Svenningsson, MD, PhD; Jonatan Salzer, MD, PhD; Thomas Frisell, PhD; Fredrik Piehl, MD, PhD

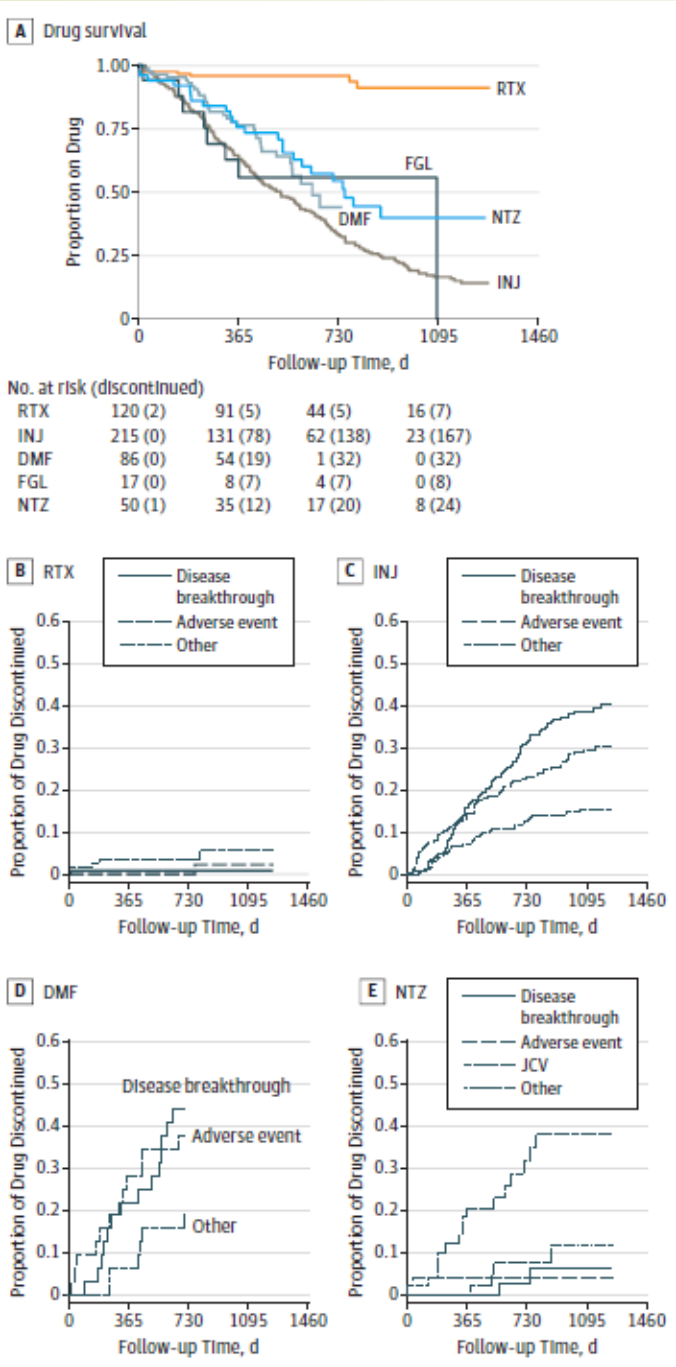


Figure 1. Cohort Selection and Treatment Groups

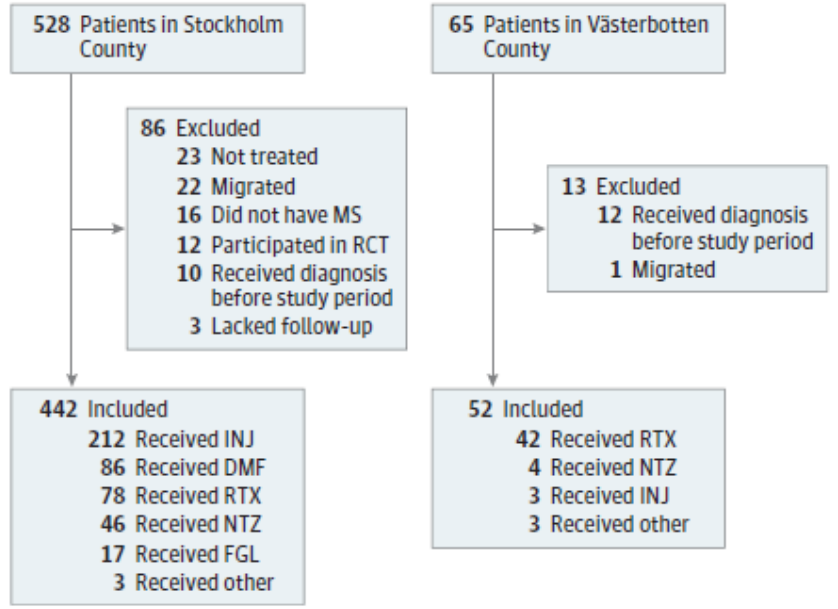


Table 1. Distribution of Outcomes for Treatment Groups

Outcomes	Treatment Group RTX (n = 120)	INJ (n = 215)	DMF (n = 86)	FGL (n = 17)	NTZ (n = 50)
Drug discontinuation					
Patients who discontinued therapy, No. (%)	7 (5.8)	173 (80.5)	32 (37.2)	8 (47.1)	24 (48.0)
Person-years	206.9	326.9	99.6	21.0	83.6
Annual drug discontinuation rate	0.03	0.53	0.32	0.38	0.29
HR, crude (95% CI)	NA	16.0 (7.5-34.1)	14.5 (5.1-41.4)	10.3 (3.7-28.6)	8.7 (3.7-20.2)
HR, adjusted (95% CI)	NA	14.4 (4.9-42.3)	12.4 (3.1-49.4)	8.7 (2.0-38.0)	13.9 (3.8-50.6)
HR, propensity score (95% CI)	NA	11.4 (4.7-27.4)	15.1 (3.9-58.0)	5.9 (1.5-23.4)	11.3 (3.2-39.4)
Clinical relapse					
Patients with clinical relapse, No. (%)	6 (5.0)	58 (27.0)	10 (11.6)	3 (17.6)	10 (20.0)
Person-years	183.9	275.6	78.8	19.1	73.7
Annual rate of clinical relapses	0.03	0.21	0.12	0.16	0.14
HR, crude (95% CI)	NA	7.1 (3.1-16.6)	3.8 (1.3-11.2)	5.3 (1.3-21.4)	4.9 (1.8-13.4)
HR, adjusted (95% CI)	NA	4.3 (1.6-11.2)	3.2 (0.9-10.6)	6.0 (0.8-44.1)	5.1 (1.2-22.2)
HR, propensity score (95% CI)	NA	7.0 (2.5-19.6)	3.4 (1.0-11.8)	3.8 (0.6-24.2)	4.1 (1.0-17.2)
Gd+ lesions					
Patients with positive scan, No. (%)	2 (1.7)	27 (12.6)	11 (12.8)	1 (5.9)	3 (6.0)
Patients with valid scan, No. (%)[a]	104 (86.7)	159 (74.0)	73 (84.9)	15 (88.2)	43 (86.0)
Patients with positive scan/patients with valid scan	0.02	0.17	0.15	0.07	0.07
OR, crude (95% CI)	NA	10.5 (3.0-65.8)	9.1 (2.3-59.7)	3.7 (0.2-40.9)	3.8 (0.6-30.2)
OR, adjusted (95% CI)	NA	9.3 (2.0-87.0)	8.8 (1.5-168.2)	2.7 (0.1-116.3)	6.6 (0.1-94.7)
OR, propensity score (95% CI)	NA	10.1 (2.3-73.0)	8.4 (1.7-72.1)	3.0 (0.1-85.0)	8.5 (0.9-109.1)
AE					
Patients with AE, No. (%)	28 (23.3)	93 (43.3)	43 (50.0)	5 (29.4)	19 (38.0)
Person-years	173.0	218.0	55.6	19.3	57.3
Incidence of AE/y	0.16	0.43	0.77	0.26	0.33
First-dosing AEs					
Patients with first-dosing AE, No. (%)	25 (20.8)	91 (42.3)	52 (60.5)	3 (17.6)	2 (4.0)

Abbreviations: AE, adverse event; DMF, dimethyl fumarate; FGL, fingolimod; Gd+, gadolinium enhancing magnetic resonance imaging scan; HR, Hazard Ratio; INJ, interferon beta and glatiramer acetate; NA, not applicable; NTZ, natalizumab; OR, odds ratio; RTX, rituximab.

[a] A magnetic resonance imaging scan done at least 3 months after treatment started and before treatment ended.

Conclusions

1. Paediatric MS in not more benign than the adult form of the disease

2. An early disease-modifying treatment is mandatory in order to prevent an early disability

3. Newer drugs have proved more effective than injectable ones in reducing the disease progression

4. A careful DMT choice is mandatory to guarantee a good QoL to children and adolescents with MS

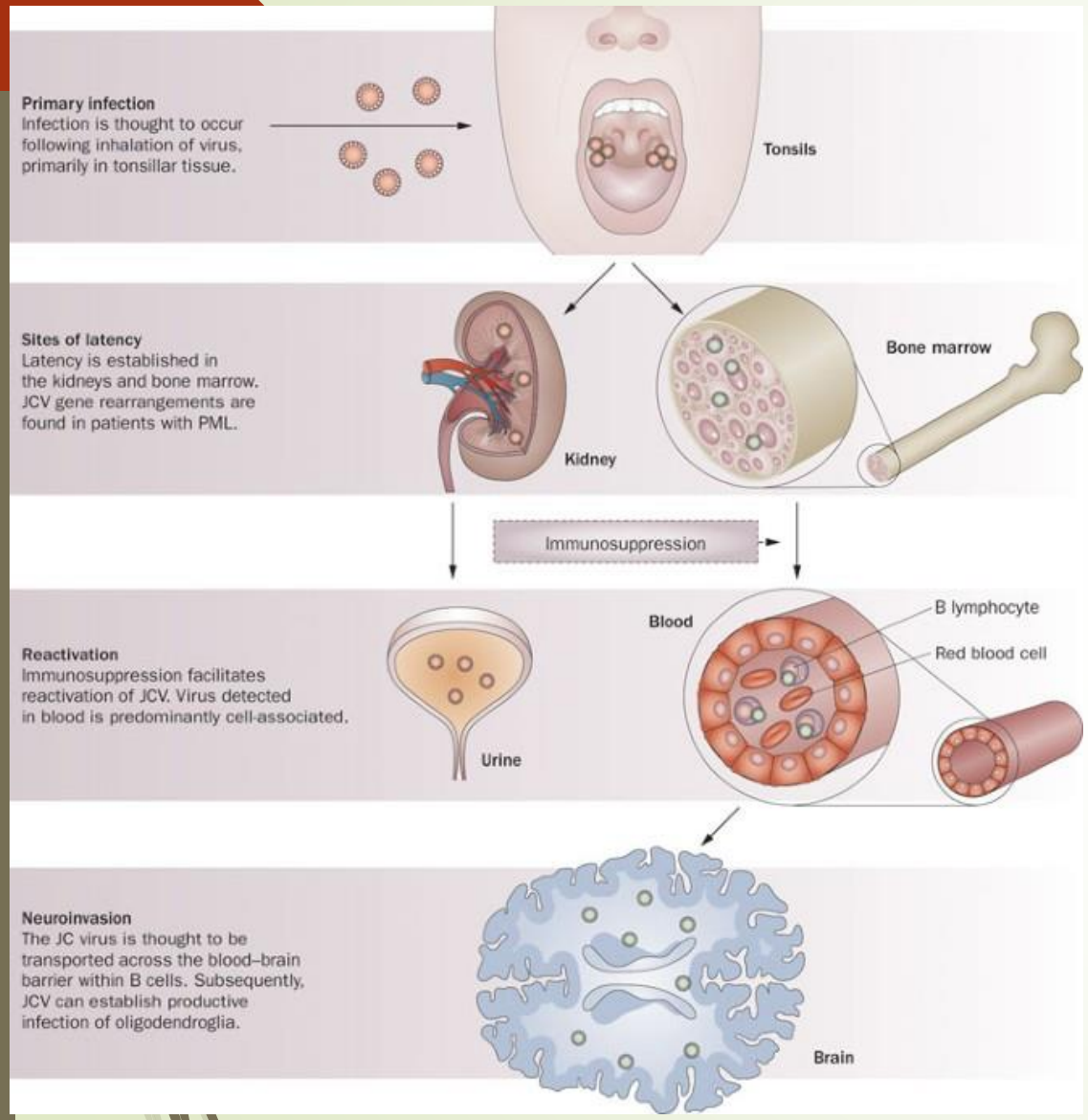
leucoencefalopatia multifocale progressiva

La PML è una malattia demielinizzante segnalata per la prima volta nel 1958 come complicanza della leucemia linfocitica cronica e del morbo di Hodgkin

Nel 1970, il virus che causa la malattia è stato isolato dal cervello di un paziente e ha preso il nome dalle sue iniziali (virus John Cunningham, JCV)

A metà degli anni '80, quando la pandemia di HIV/AIDS si intensificò, l'incidenza della PML aumentò rapidamente

EZIOLOGIA



- Grave malattia demielinizzante del SNC associata ad un alto tasso di mortalità
- È legata alla riattivazione del JCV. Il virus una volta riattivato presenta tropismo per gli oligodendrociti
- Questo virus è presente nell'86% della popolazione, tipicamente si contrae durante l'infanzia e rimane latente nei reni e probabilmente in altre sedi (p. es., cellule mononucleate e SNC)
- Essa compare nei soggetti con sistema immunitario compromesso, come nei pz affetti da HIV, trapiantati in terapia con immunosoppressori, pz affetti da malattie ematologiche e in terapia con immunomodulanti in particolare con anticorpi monoclonali
- In particolare la PML può verificarsi in pz affetti da SM in terapia con Natalizumab, Rituximab, Fingolimod ecc.

Natalizumab e PML

Natalizumab-Related Progressive Multifocal Leukoencephalopathy in Multiple Sclerosis: Findings from an Italian Independent Registry

Luca Prosperini,[1,*] Nicola de Rossi,[2] Cristina Scarpazza,[2] Lucia Moiola,[3] Mirco Cosottini,[4] Simonetta Gerevini,[5] Ruggero Capra,[2] and on behalf of the Italian PML study group[¶]

Conclusion

Our findings support that early PML diagnosis, limited CNS involvement and initial signs of immune restoration are associated with a better outcome and higher survival rate, and confirm the utility of MRI as a surveillance tool for NTZ-treated patients.

PML risk is the main factor driving the choice of discontinuing natalizumab in a large multiple sclerosis population: results from an Italian multicenter retrospective study

Background: Natalizumab (NTZ) is an effective treatment for relapsing-remitting multiple sclerosis (RRMS). However, patients and physicians may consider discontinuing NTZ therapy due to safety or efficacy issues. The aim of our study was to evaluate the NTZ discontinuation rate and reasons of discontinuation in a large Italian population of RRMS patients.

Materials and methods: The data were extracted from the Italian MS registry in May 2018 and were collected from 51,845 patients in 69 Italian multiple sclerosis centers. MS patients with at least one NTZ infusion in the period between June 1st 2012 to May 15th 2018 were included. Discontinuation rates at each time point were calculated. Reasons for NTZ discontinuation were classified as "lack of efficacy", "progressive multifocal leukoencephalopathy (PML) risk" or "other".

Results: Out of 51,845, 5151 patients, 3019 (58.6%) females, with a mean age of 43.6 ± 10.1 years (median 40), were analyzed. Out of 2037 (39.5%) who discontinued NTZ, a significantly higher percentage suspended NTZ because of PML risk compared to lack of efficacy [1682 (32.7% of 5151) vs 221 (4.3%), p < 0.001]; other reasons were identified for 99 (1.9%) patients. Patients discontinuing treatment were older, had longer disease duration and worse EDSS at the time of NTZ initiation and at last follow-up on NTZ treatment. The JCV index and EDSS at baseline were predictors for stopping therapy (HR 2.94, 95% CI 1.22-4.75; p = 0.02; HR 1.36, 95% CI 1.18-5.41; p = 0.04).

Conclusions: Roughly 60% of MS patients stayed on NTZ treatment during the observation period. For those patients in whom NTZ discontinuation was required, it was mainly due to PML concerns.

Risk of natalizumab-associated PML in patients with MS is reduced with extended interval dosing

Abstract

Objective

To use the large dataset from the Tysabri Outreach: Unified Commitment to Health (TOUCH) program to compare progressive multifocal leukoencephalopathy (PML) risk with natalizumab extended interval dosing (EID) vs standard interval dosing (SID) in patients with multiple sclerosis (MS).

Methods

This retrospective cohort study included anti-JC virus antibody-positive patients (n = 35,521) in the TOUCH database as of June 1, 2017. The effect of EID on PML risk was evaluated with 3 planned analyses using Kaplan-Meier methods stratified by prior immunosuppressant use. Risk of PML was analyzed by Cox regression adjusted for age, sex, prior immunosuppressants, time since natalizumab initiation, and cumulative number of infusions.

Results

This study included 35,521 patients (primary analysis: 1,988 EID, 13,132 SID; secondary analysis: 3,331 EID, 15,424 SID; tertiary analysis: 815 EID, 23,168 SID). Mean average dosing intervals were 35.0 to 43.0 and 29.8 to 30.5 days for the EID and SID cohorts, respectively. Hazard ratios (95% confidence intervals) of PML risk for EID vs SID were 0.06 (0.01–0.22, $p < 0.001$) and 0.12 (0.05–0.29, $p < 0.001$) for the primary and secondary analyses, respectively. Relative risk reductions were 94% and 88% in favor of EID for the primary and secondary analyses, respectively. The tertiary analysis included no cases of PML with EID.

Conclusion

Natalizumab EID is associated with clinically and statistically significantly lower PML risk than SID.

MANIFESTAZIONI CLINICHE

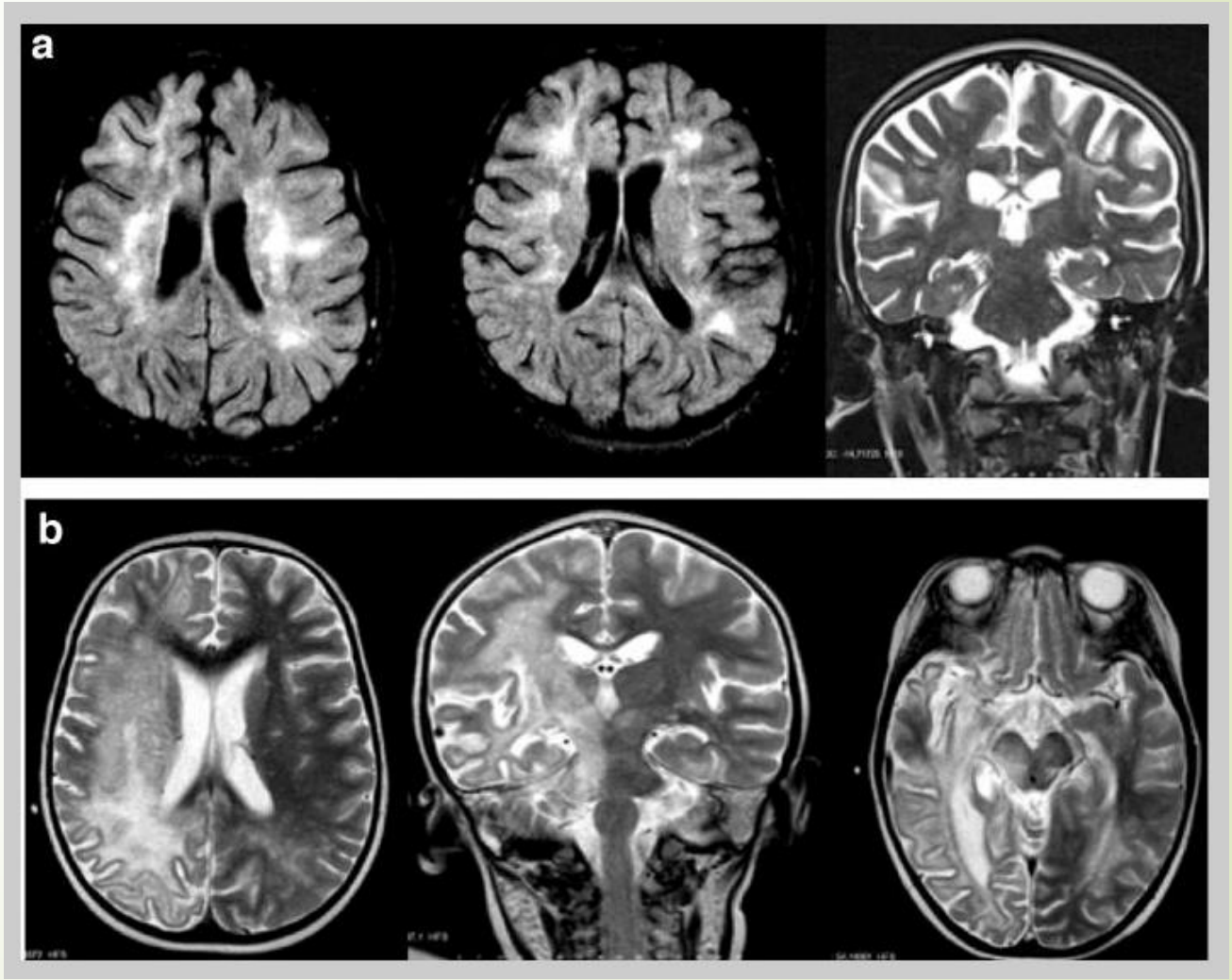
- DEFICIT MOTORI
- DETERIORAMENTO COGNITIVO
- DISTURBO DEL LINGUAGGIO
- CAMBIAMENTI DI UMORE O DEL COMPORTAMENTO
- DISTURBI VISIVI
- ATASSIA
- COINVOLGIMENTO DEL TRONCO DELL'ENCEFALO

DIAGNOSI

RISONANZA MAGNETICA: tipico è il coinvolgimento multifocale, sottocorticale e periventricolare. Le lesioni tendono ad interessare la sostanza bianca sopratentoriale. Appaiono confluenti, bilaterali e asimmetriche. Vi può essere un coinvolgimento talamico. Possono tuttavia essere coinvolti anche i gangli della base, il tronco cerebrale e il cervelletto. Comune è l'interessamento delle regioni frontali sottocorticali e parieto-occipitali.

Progressive Multifocal Leukoencephalopathy in Children with Primary and Secondary Immune Deficiency

Asuman Demirbuğa, MD, [1] Ozge Kaba, MD, [1] Selda Hançerli Törün, MD, [1] Edibe Pembegül Yıldız, MD, [2] Esra Yücel, MD, [3] and Ayper Somer [1]



(a) Radiological findings of case 1. Findings of cranial MRI lesions of a 13-year-old male with primary immune deficiency. Patch lesions in the subcortical deep *white matter* in both frontoparietal lobes. There are also T2WI flair hyperintense lesions in the *right half* of the pons, both cerebellar hemispheres. **(b)** Radiological findings of case 1. A 6-year-old patient with HIV encephalopathy and progressive multifocal leukoencephalopathy; brain MRI from a patient with PML, showing on FLAIR-weighted images and T2-weighted MRI sequences, we can see PV area and subcortical–cortical involvement of the *left* frontoparietal lobe adjacent to the WM lesion. FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging; PML, progressive multifocal leukoencephalopathy; PV, periventricular; T2WI, weighted imagine; WM, white matter.

DIAGNOSI

La malattia viene diagnosticata con l'esame del DNA del JCV nel liquor

Una positività del risultato con studio di neuroimaging suggestivo è praticamente patognomonica della malattia

La biopsia cerebrale può fornire una diagnosi definitiva ma è raramente necessaria

TERAPIA PROGNOSI

Nessun trattamento specifico ha dimostrato un’efficacia clinica contro il JCV

Un ripristino del sistema immunitario può associarsi a un controllo della PML

Tuttavia, i pazienti che interrompono l'assunzione di questi farmaci sono anche a rischio di sviluppare la *immune reconstitution inflammatory syndrome*

La prognosi è spesso fatale o può portare a gravi danni neurologici

ANGIOITE PRIMITIVA DEL SISTEMA NERVOSO CENTRALE (PACNS)

- rara forma di vasculite del SNC con esclusivo interessamento cerebrale e del midollo spinale
- incidenza stimata di 2,4 casi per 1.000.000 di persone / anno
- rappresenta la forma più frequente di vasculite del SNC
- il solo dato istopatologico può darne una conferma definitiva
- risulta fondamentale escludere condizioni che possano mimare la PACNS, quali le sindromi da vasocostrizione reversibile, le vasculiti cerebrali secondarie, infezioni, patologie neoplastiche

ITER DIAGNOSTICO

- Valutazione neurologia con EON
- Esami del sangue di routine
- Screening trombofilico e autoimmune
- Screening infettivologico su sangue
- Rachicentesi con esame chimico-fisico, ricerca bande oligoclonali, esame batterioscopico, citologico, esami virali
- Valutazione immunologica, reumatologica, oculistica con FOO
- Valutazione cardiologica con ECG, ecocardiogramma e Holter ECG
- Angio TAC total body
- Angio RM encefalo
- Angiografia (in caso di negatività della Angio RM encefalo)
- Biopsia cerebrale (in caso di negatività della angiografia)

ITER TERAPEUTICO

Fase acuta

Eparina a basso peso molecolare 100 UI/kg x 2 per due settimane e poi aspirina 1-2 mg/kg (max 100 mg)

Metilprednisolone 20 mg x 5 giorni o 30 mg x 3 giorni

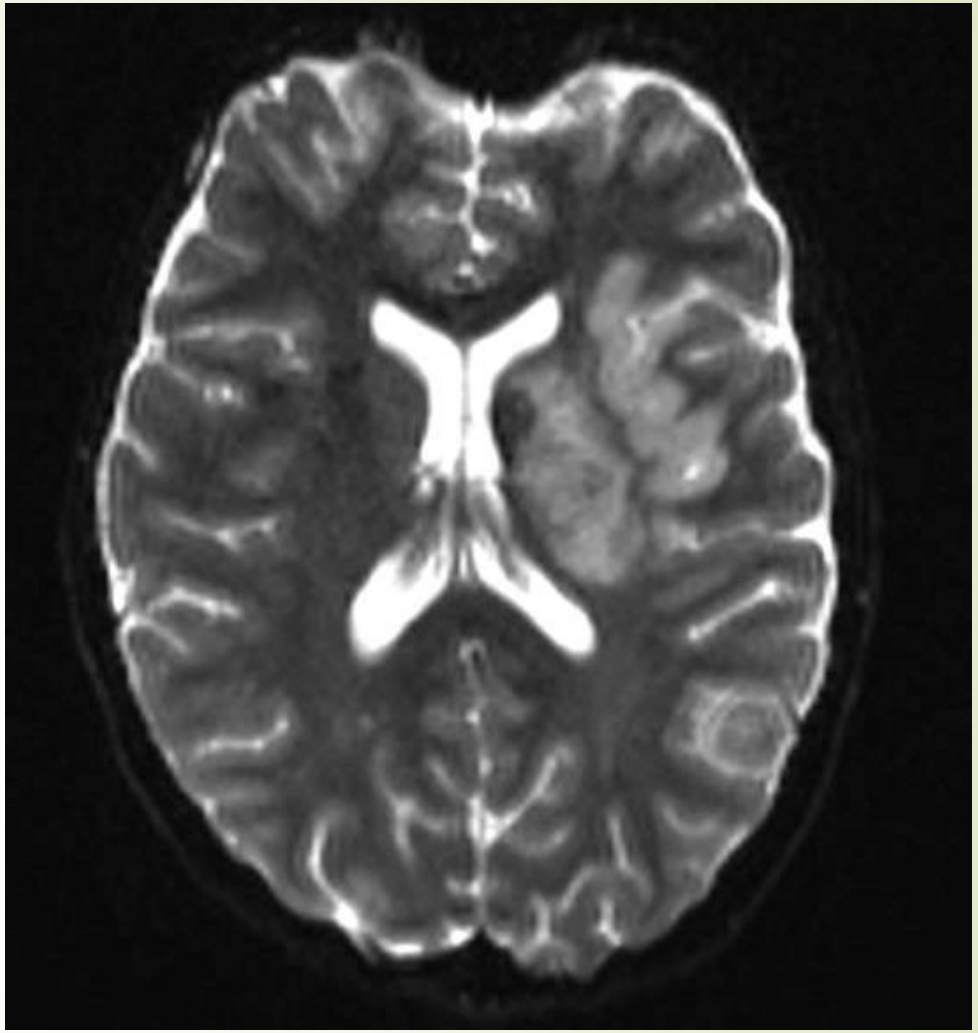
Fase cronica

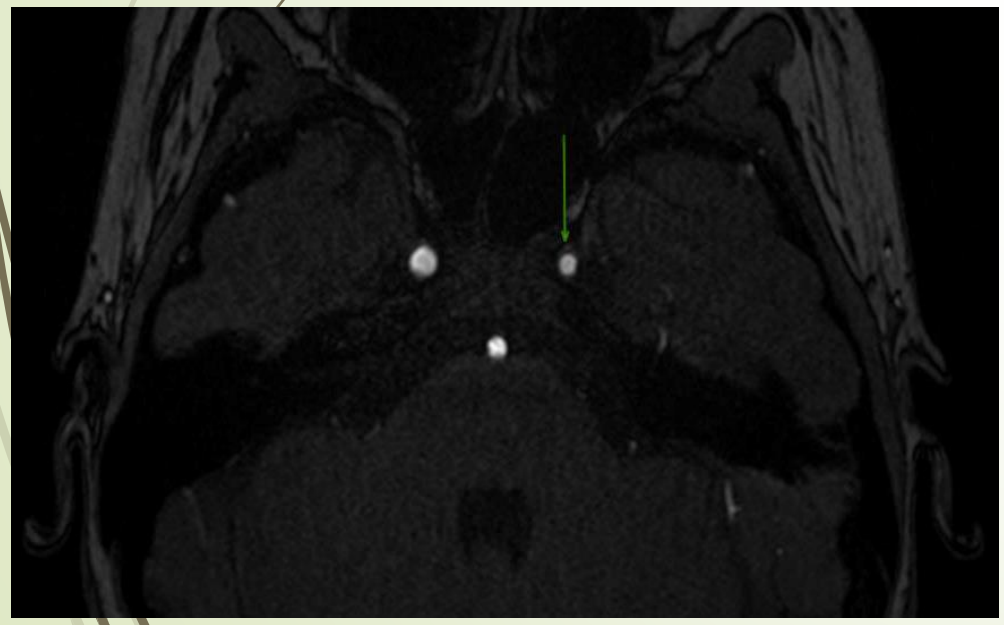
Terapia steroidea per OS 2 mg/kg per un mese, poi 1,5 mg/kg per un mese, 1 mg/kg per un altro mese e poi a scalare

Nelle forme progressive ciclofosfamide per 6 mesi e mantenimento con micofenolato mofetile o azatioprina. In caso di mancata efficacia valutare Rituximab

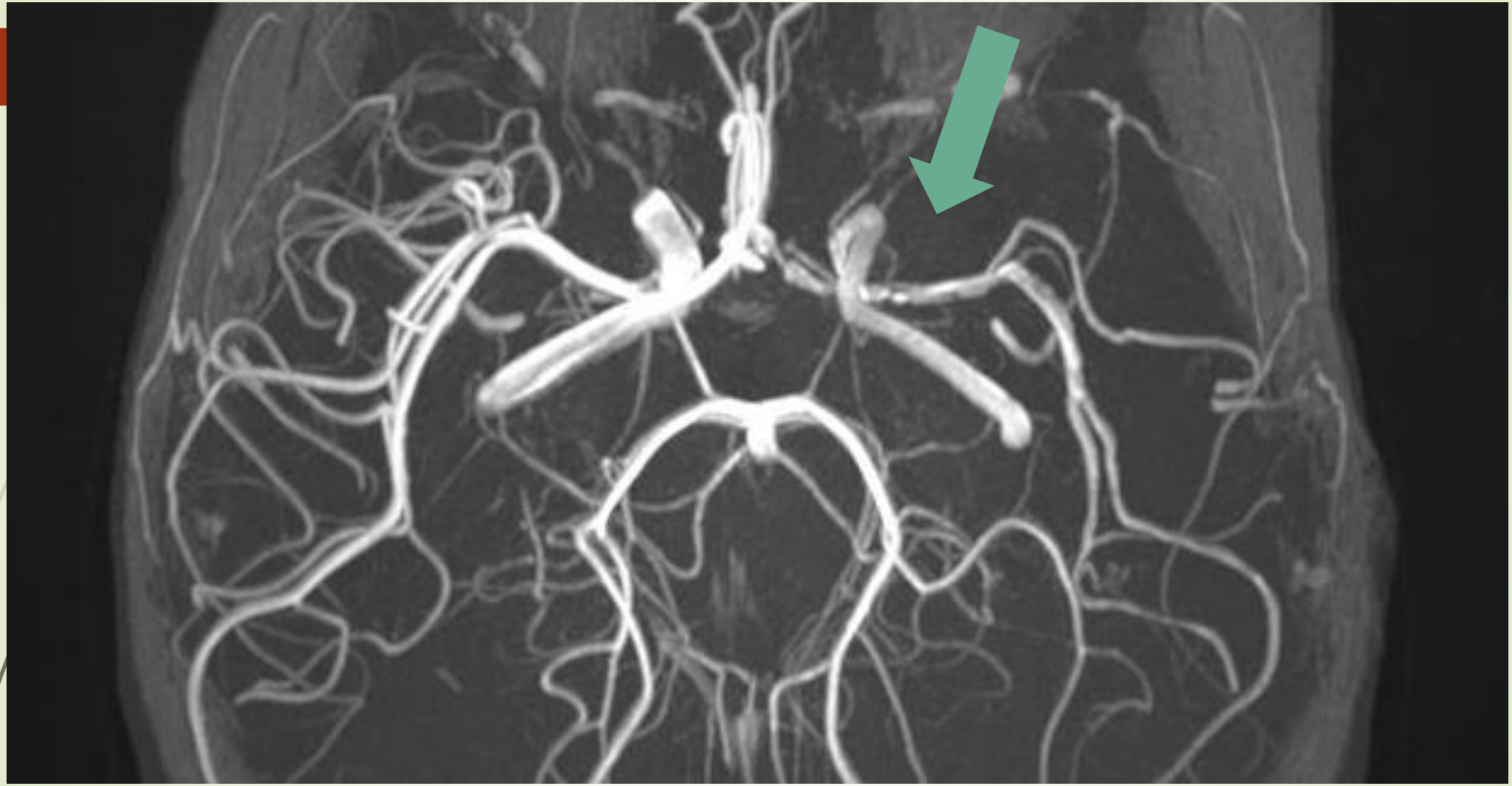
Sofia, 10 anni

Presentazione clinica: emiparesi dx insorta acutamente





Angio-RM encefalo: lesioni ischemiche recenti nel territorio dell'ACM di sinistra cui si associa riduzione di calibro dell'ACI sn.



Angio RM encefalo: le sequenze TOF mostrano aspetto a corona di rosario dei tratti A1, M1-M2 di sinistra nonchè la riduzione di calibro del tratto intracranico della carotide interna di sinistra rispetto al controlato.

Monoarterite post-varicella

- Da considerare sempre nei casi di stroke insorti entro un anno dalla malattia infettiva
- Il VZV è una delle cause più frequenti di stroke in età pediatrica
- Ricerca degli Ab antiVZV nel liquor

MALATTIA DI BEHÇET

Si tratta di una vasculite multisistemica recidivante cronica caratterizzata da lesioni mucocutanee, articolari, vascolari, oculari e sintomi a carico del SNC

E’ caratterizzata da afte orali, genitali, uveite, tromboflebite che frequentemente coinvolge le articolazioni, la cute, il SNC e il tratto gastrointestinale

L'esordio avviene di solito nella vita adulta, ma sono stati descritti casi pediatrici

Sono frequenti (> 20%) i segni neurologici sporadici (neuro-BD), che spesso insorgono 1-10 anni dopo l'esordio dei primi sintomi

NEURO- BEHÇET

Nella maggioranza dei casi, le lesioni cutanee precedono il coinvolgimento neurologico, favorendo la diagnosi

Nel 3% dei casi, le manifestazioni del SNC si verificano per prime, rendendo la diagnosi significativamente più difficile

Segni e sintomi neurologici:

Cefalea

Deficit motori

Alterazioni della sensibilità

Cambiamenti del comportamento

Disturbo del linguaggio

Segni cerebellari

Caratteristiche radiologiche:

Lesioni focali o multifocali

Meningoencefalite

Trombosi venose cerebrali

Ipertensione endocranica

Risonanza magnetica:

Tronco encefalo: molto comune, in particolare il ponte

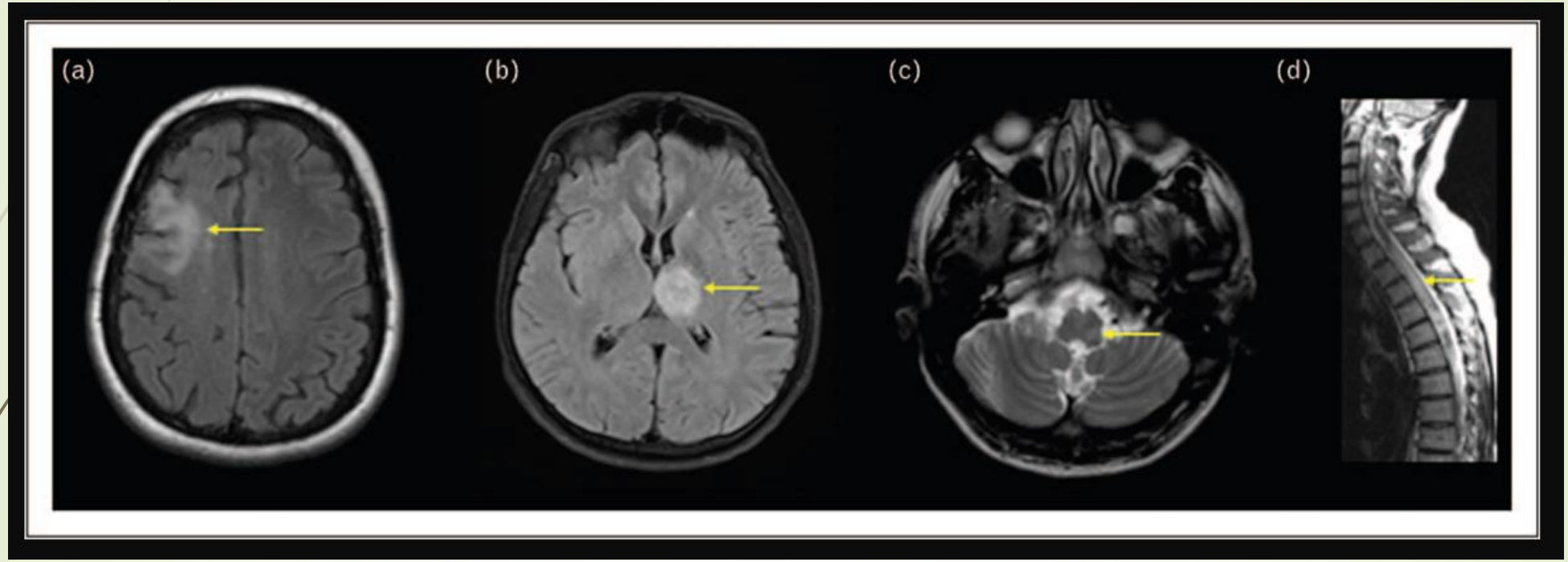
Gangli della base: interessamento bilaterale in 1/3 dei casi

Talami

Lesioni della SB sottocorticali e midollo spinale meno comuni

Nervous system involvement in Behçet's syndrome

Uğur Uygunoğlu [1], Aksel Siva



Brain magnetic resonance and spinal cord MRI of typical parenchymal patterns during the parenchymal neuro-Behçet's syndrome episodes are shown. (a) Axial FLAIR image shows the telencephalic involvement. (b) Axial FLAIR image shows the diencephalic involvement. (c) Axial T2-weighted image shows the brainstem involvement. (d) Sagittal T2-weighted image shows the longitudinally extensive (≥3 sagittal spinal cord segments) involvement.

TERAPIA, PROGNOSI E DIAGNOSI DIFFERENZIALE

Table 1 – Summary table for neuro-Behcet's disease.

Etiology	• Underlying cause is unknown • Autoimmune vasculitis, involving arteries and veins of all sizes • Associated with molecular mimicry of mycobacterial heat shock proteins [7] • Associated with HLA-B51/B5 [6]
Clinical Symptoms	• NBD occurs in less than 10% of BD cases [1] • Motor dysfunction • Memory Impairment • Personality changes • Wide range of other potential symptoms
MRI Findings	• T2-weighted hyperintense foci • Acute/subacute lesions enhance with contrast • Common and can be diffuse in the brainstem and basal ganglia [18]
Treatment	• Azathioprine as first-line agent, with cyclophosphamide, mycophenolate, and methotrexate as alternatives • With severe manifestation, include high dose corticosteroids and a TNF-alpha inhibitor [22] • Anticoagulation may be considered with ischemic vascular symptoms
Prognosis	• Disease activity declines over time, but cumulative disease burden increases, as neurological damage is mostly irreversible • One-third of patients with NBD suffer relapse [23]

Neuro-Behcet's syndrome: Case report and literature review☆

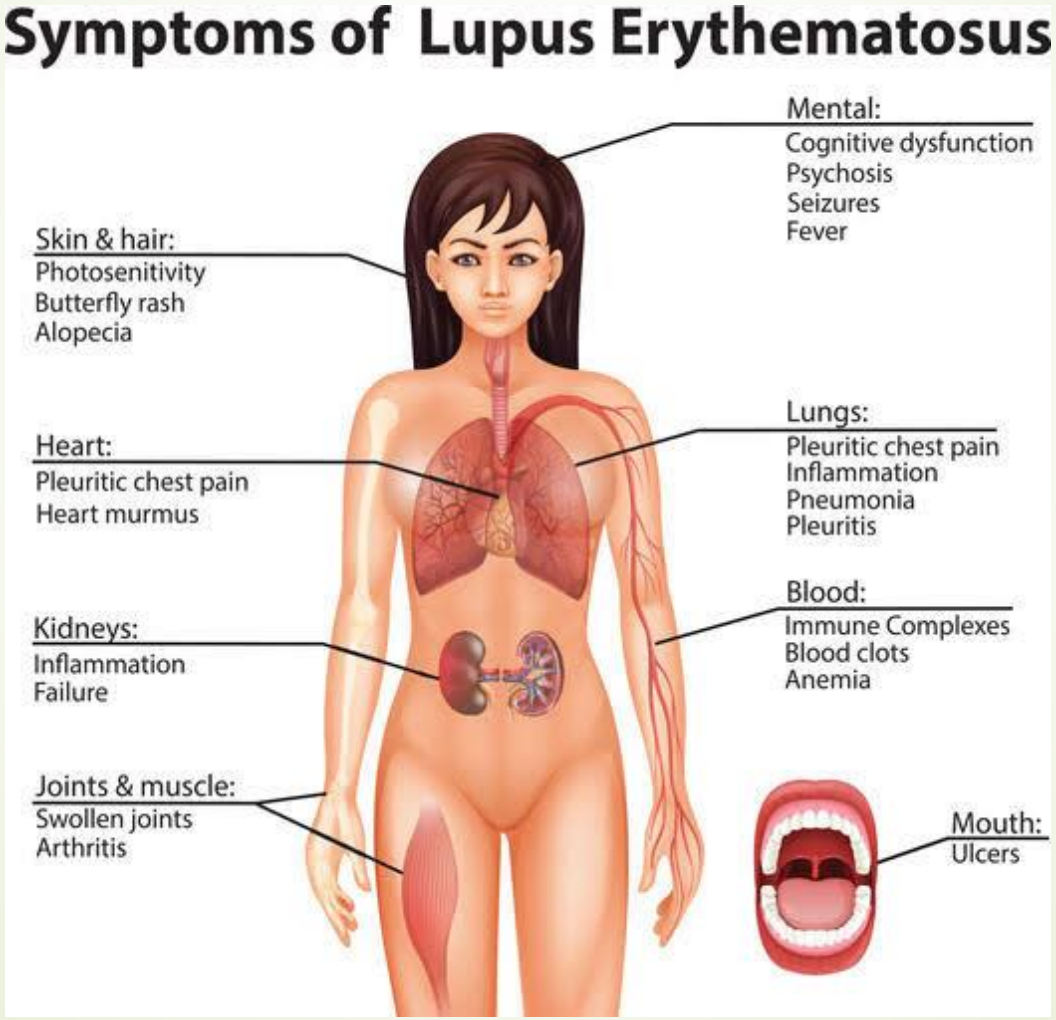
Brian Peine, BS[a,], Christian Figueroa, MD[b], Natasha Robinette, MD[b,c]*

Table 2 – Differential diagnosis table for neuro-Behcet's disease.

	Clinical findings	MRI
Neuro-Behcet's disease	Motor dysfunction, dementia, personality changes	T2-weighted hyperintense foci, predilection for brainstem, basal ganglia, and thalamus [18]
Multiple sclerosis	Optic neuritis, numbness, weakness, paresthesia	T2-weighted hyperintense periventricular lesions that vary by location over time [24]
Thromboembolic infarction	Acute, unilateral focal deficits	Increased intracellular water demonstrated by DWI in ischemic area [25]
RCVS	Headache, seizures, bilateral focal deficits	"Sausage on a string" appearance of arteries in Circle of Willis and its branches [26]

LUPUS ERITEMATOSO SISTEMICO

Il LES è una malattia autoimmune complessa con interessamento multisistemico



MANIFESTAZIONI NEUROPSICHIATRICHE

- Il coinvolgimento neuropsichiatrico nel LES è una complicanza che può coinvolgere sia il sistema nerovoso centrale che periferico
- I sintomi variano da cefalea, manifestazioni cerebrovascolari, epilessia, alterazioni della coscienza, psicosi
- A causa della eterogeneità dei diversi studi, la prevalenza varia dal 12 al 95%
- Si associa ad una prognosi sfavoevole e una alta mortalità

TABLE 1 Clinical symptoms in NPSLE.

	Focal	Diffuse
Central Nervous System	Headache	Psychosis Mood disorders Anxiety disorders Cognitive dysfunction Acute confusional state
	Myelopathy	Mood disorders
	Seizure disorder	Anxiety disorders
	Movement disorders	Cognitive dysfunction
	Cerebrovascular disease	Acute confusional state
	Aseptic meningitis	—
	Demyelinating syndromes	—
Peripheral Nervous System	Acute inflammatory demyelinating lesions (Grimm-Barré syndrome)	—
	Autonomic neuropathy	
	Myasthenia gravis	
	Polyneuropathy	
	Mononeuropathy	
	Cranial neuropathy	
	Plexopathy	

Pathogenesis and treatment of neuropsychiatric systemic lupus erythematosus: A review

Yuhong Liu[1†], Zhihua Tu[2†], Xi Zhang[1], Keqian Du[1], Zhengquan Xie[2*] and Zhiming Lin[1*]

[1]Department of Rheumatology, Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, [2]Department of Rheumatology, Panyu Hospital of Chinese Medicine, Guangzhou, China

MANIFESTAZIONI NEUROLOGICHE

Le crisi epilettiche sono la manifestazione neurologica più comune del LES, e si verificano fino al 20% di tutti i pazienti, la presentazione può essere con crisi generalizzate o focali

Lo stroke è una caratteristica relativamente comune del LES, fino al 19% dei casi. Può manifestarsi come stroke ischemico, attacco ischemico transitorio (TIA), trombosi venosa, emorragia cerebrale

Fattori di rischio per stroke dovuto al LES includono anticorpi anti-fosfolipidi (presenti fino al 55% dei pazienti con LES), vasculite, ipertensione, aterosclerosi (ad es. a causa dell'uso prolungato di corticosteroidi), malattie delle valvolari cardiache

I disturbi del movimento sono descritti raramente. La manifestazione più comune è la corea, che è stata riscontrata in circa l'1% dei casi

La mielopatia è una rara complicanza e si manifesta in circa l'1% dei casi. Si pensa che l'eziologia sia legata ad un meccanismo di tipo vascultico

La cefalea nel LES può essere di tipo emicranico o legata ad ipertensione cerebrale idiopatica

La meningite asettica si manifesta con i classici sintomi di irritazione meningea, in assenza di positività batterica o virale sul liquor

MANIFESTAZIONI PSICHIATRICHE

La psicosi è una classica manifestazione psichiatrica del LES ma si verifica solo in circa il 5% dei pazienti ad eziologia incerta e si manifesta con allucinazioni e delirio.

Lo stato confusionale acuto ha una eziologia multifattoriale. Può essere manifestazione di demenza vascolare dei piccoli vasi o vasculite. Può variare da lievi disturbi della coscienza fino al coma

I disturbi cognitivi sono molto comune nel LES e si verifica fino all'80% dei pazienti

Sindrome ansioso-depressiva è spesso di natura reattiva alla malattia

DIAGNOSI

Update on the diagnosis and management of systemic lupus erythematosus

Antonis Fanouriakis [1], Nikolaos Tziolos,[2] George Bertsias [3,4], Dimitrios T Boumpas [2,5,6,7]

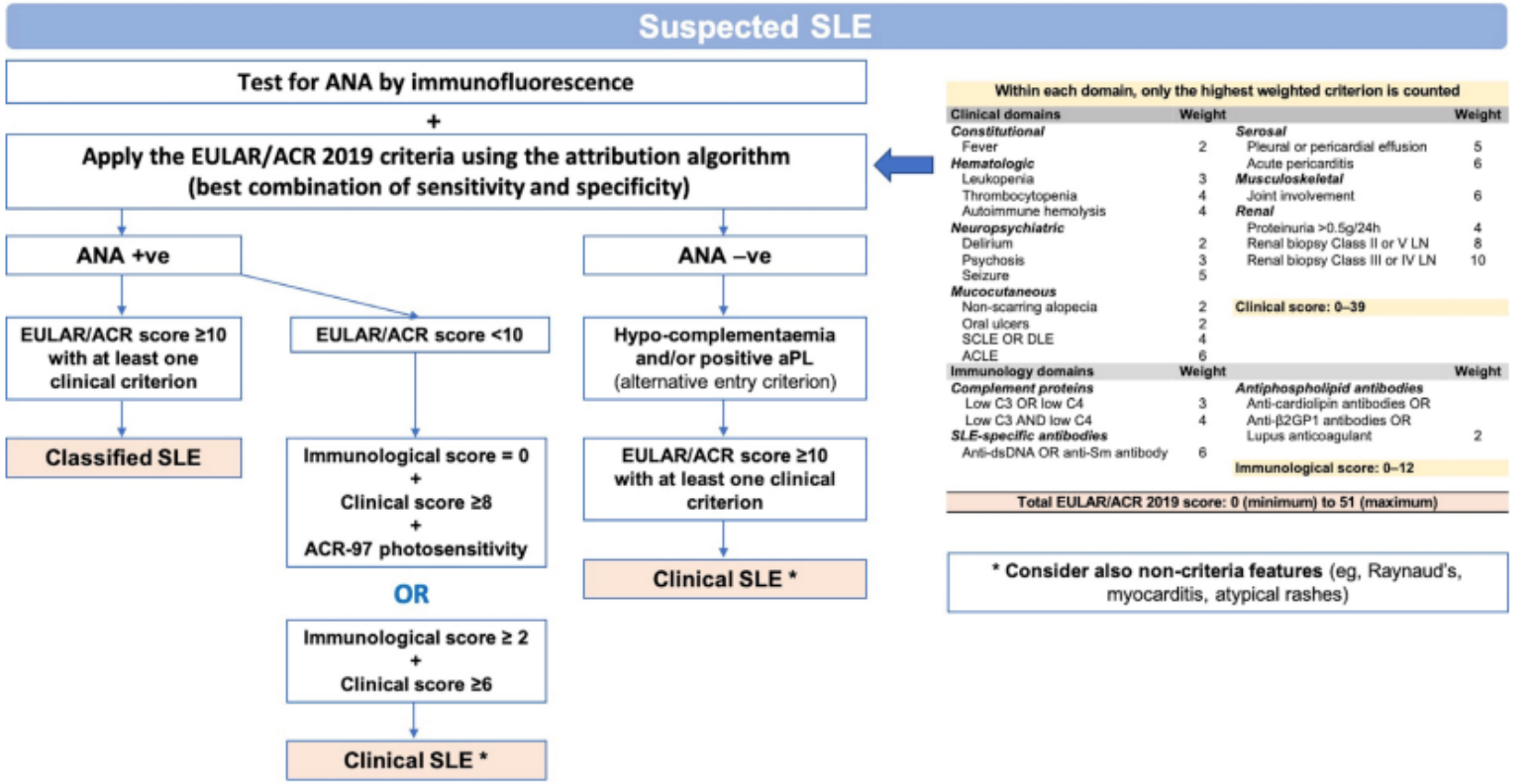
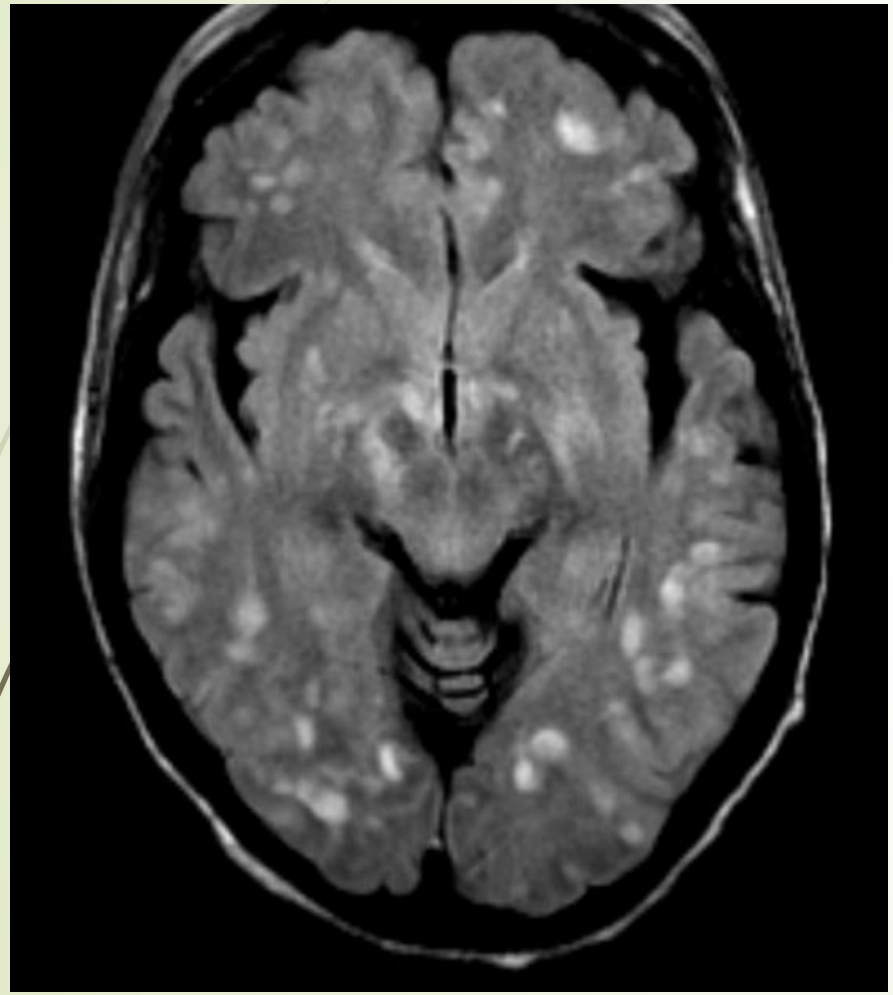
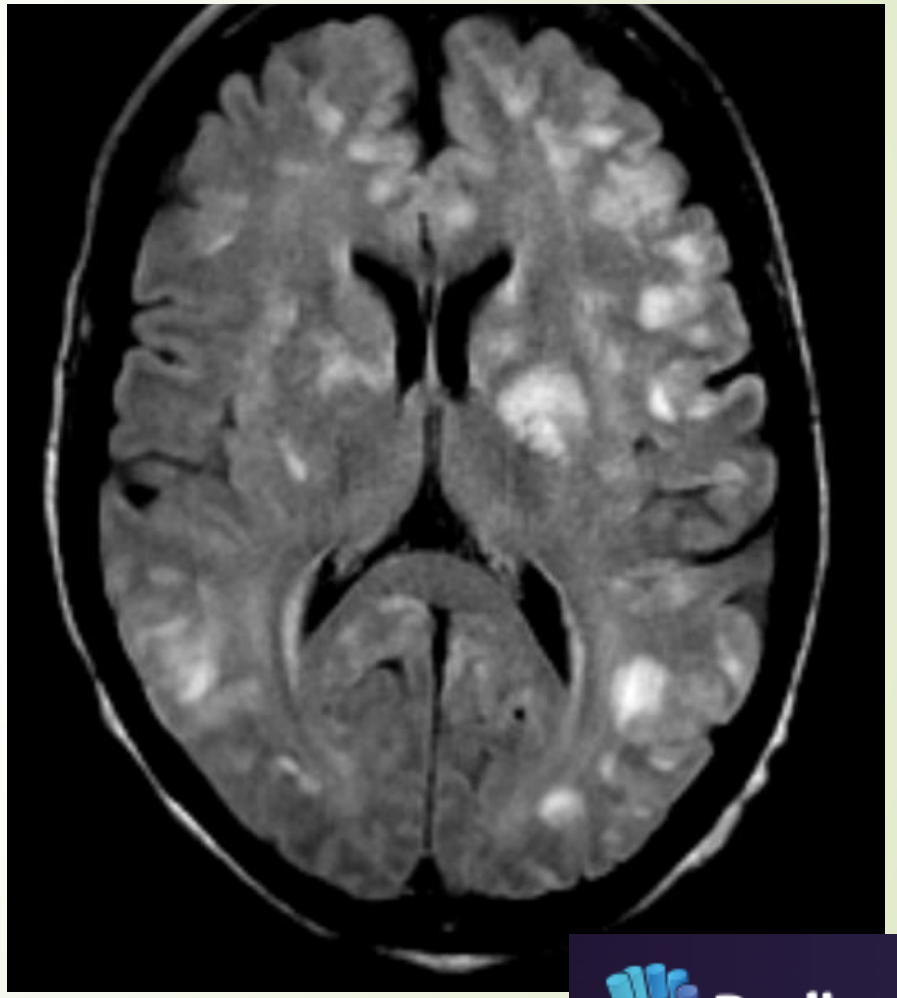


Figure 4 Diagnostic approach to a patient with suspected SLE and the use of classification criteria to aid clinical diagnosis. The diagnosis of SLE is clinical, supported by laboratory abnormalities including serologic assays. Diagnostic criteria are not available for SLE and classification criteria are often used as such, but with several caveats. Among classification criteria, the EULAR/ACR-2019 have the best combination of sensitivity and specificity but require positive ANA as an entry criterion. However, for diagnosis, some patients may be ANA-negative; in such cases, low complement levels and/or positive anti-phospholipid antibodies could be used as an alternative entry criterion in the classification algorithm. For patients who fall short of the classification threshold (ie, EULAR/ACR score <10), inclusion of photosensitivity (defined as in the ACR-1997 criteria) or a combination of immunological and clinical features can still be used for SLE diagnosis. ACR, American College of Rheumatology; ANA,antinuclear antibody; EULAR, European League Against Rheumatism; SLE,systemic lupus erythematosus.

Systemic lupus erythematosus - CNS vasculitis





Radiopaedia

PATOGENESI E TERAPIA

Management of Neuropsychiatric Systemic Lupus Erythematosus: Current Approaches and Future Perspectives

César Magro-Checa[1] · Elisabeth J. Zirkzee[1,2] · Tom W. Huizinga[1] · Gerda M. Steup-Beekman[1]