Paediatric Multiple Sclerosis: Faster diagnosis and more effective treatments but are we making a difference?

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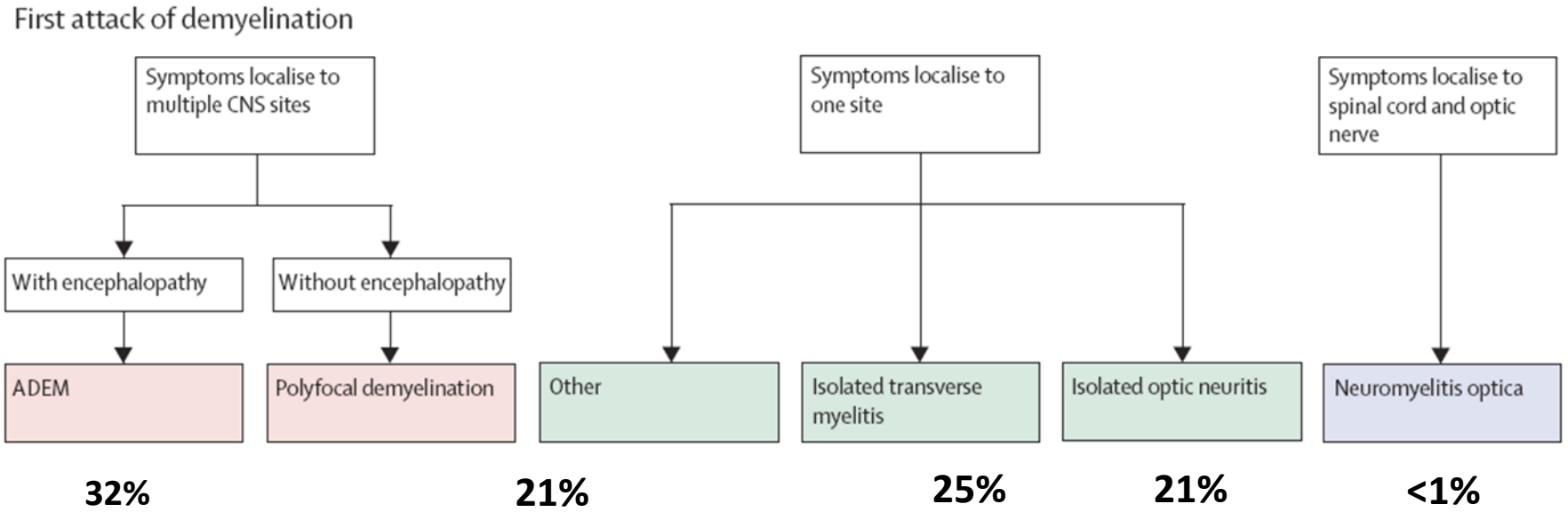
Summary

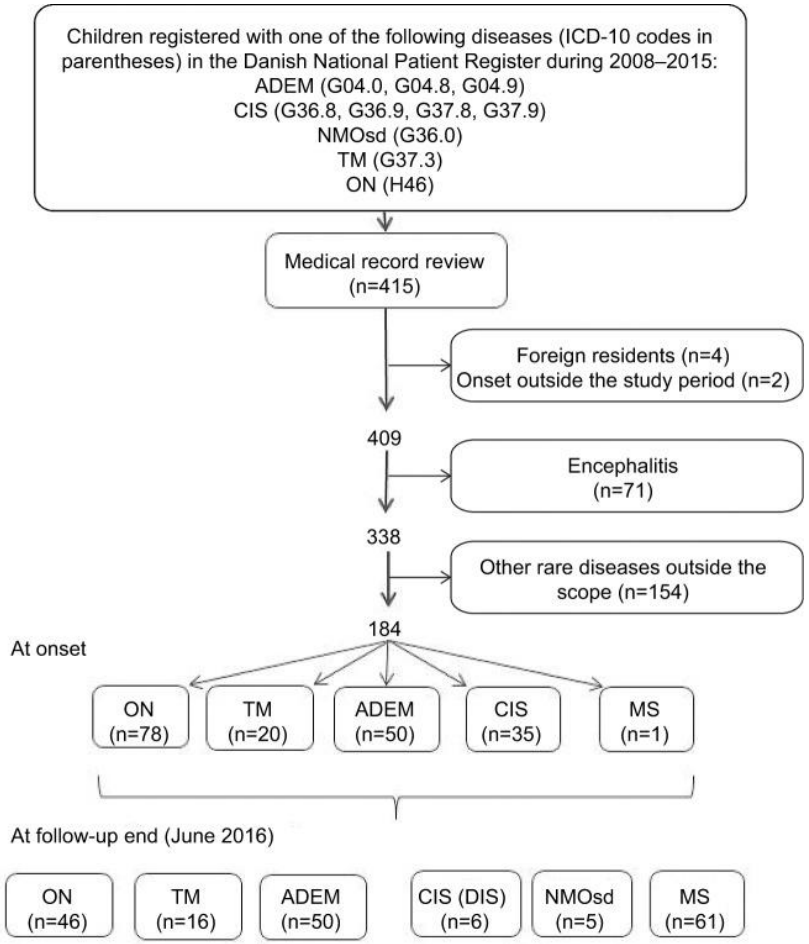
- Evolving diagnosis of childhood MS
- How effective (and available) are the treatments
- Future proofing

Acute/Inflammatory demyelination syndrome/event

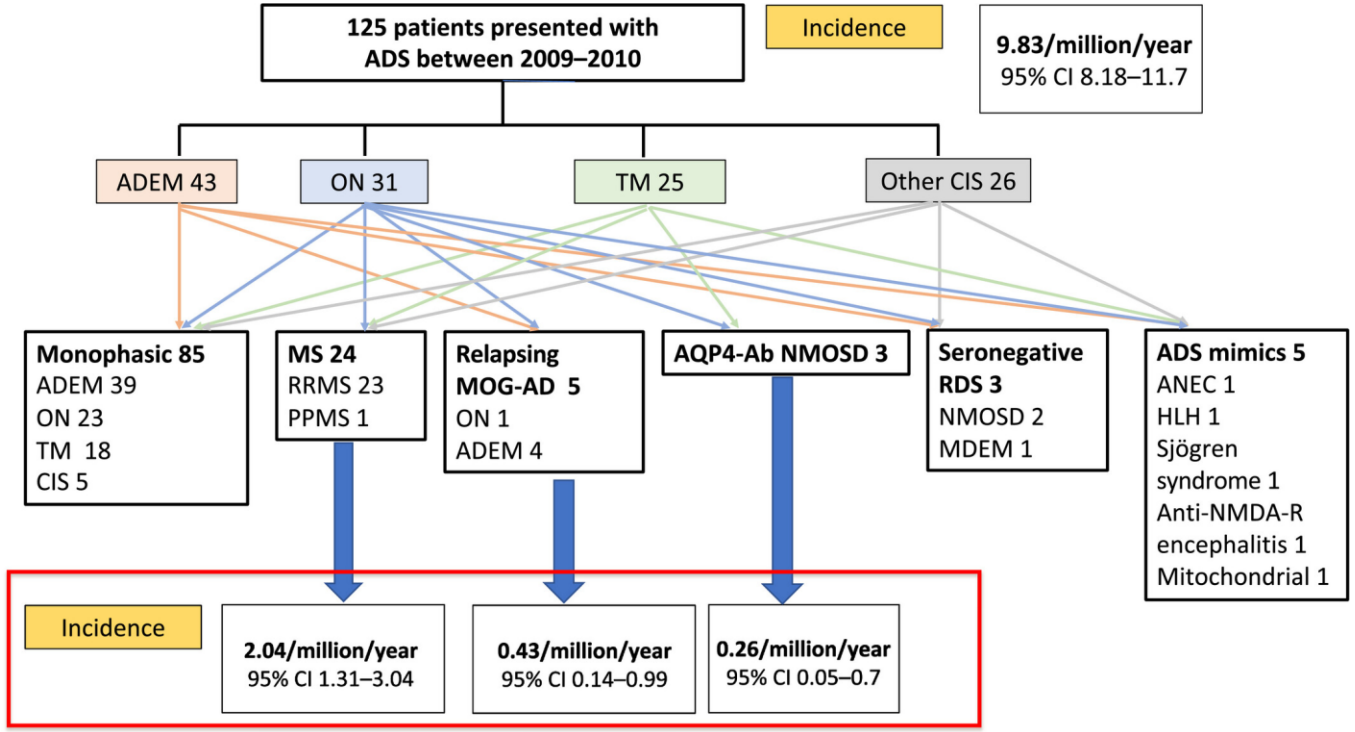


Up to 10 per million

Mikaeloff et al., 2004 ***J Pediatr*** 144 246-52; Banwell et al., 2007 ***Lancet Neurol*** 6 887-902; Neuteboom et al., 2008 ***Neurology*** 71 967-973; Absoud et al., 2013 ***Mult Scler.*** 19(1):76-86; Yamaguchi et al., 2016 ***Neurology***. 2016 Nov 8;87(19):2006-2015; Boesen et al., 2018 ***Clin Epidemiol*** 10:391-399



Boesen et al., 2018 ***Clin Epidemiol*** 10:391-399



Abdel-Mannan et al., 2022 ***Dev Med Child Neurol.*** 64(4):502-508

58-73% Monophasic

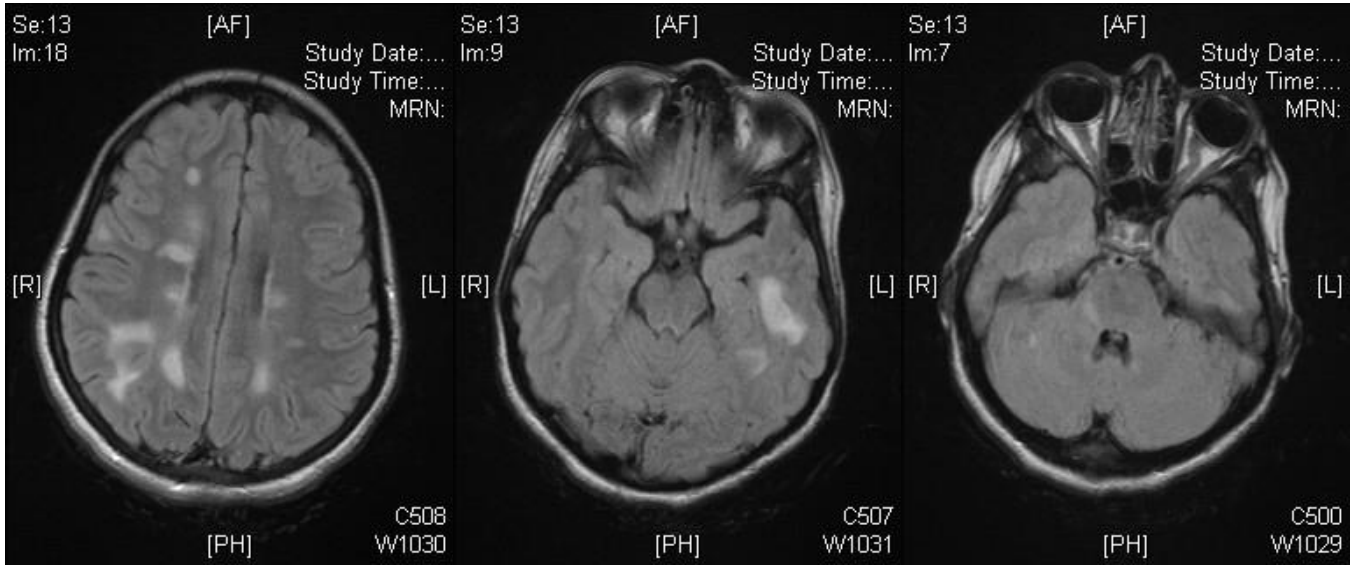
MS still the most prevalent RDS phenotype

Case 14Y F

2 weeks right weakness

Fatigue lasting months

Clinically long tract signs



Clinically **I**solated **S**yndrome

Presenting features of paediatric MS

Table 3 Clinical features of pediatric multiple sclerosis (MS) in prospective studies published in English since 2007

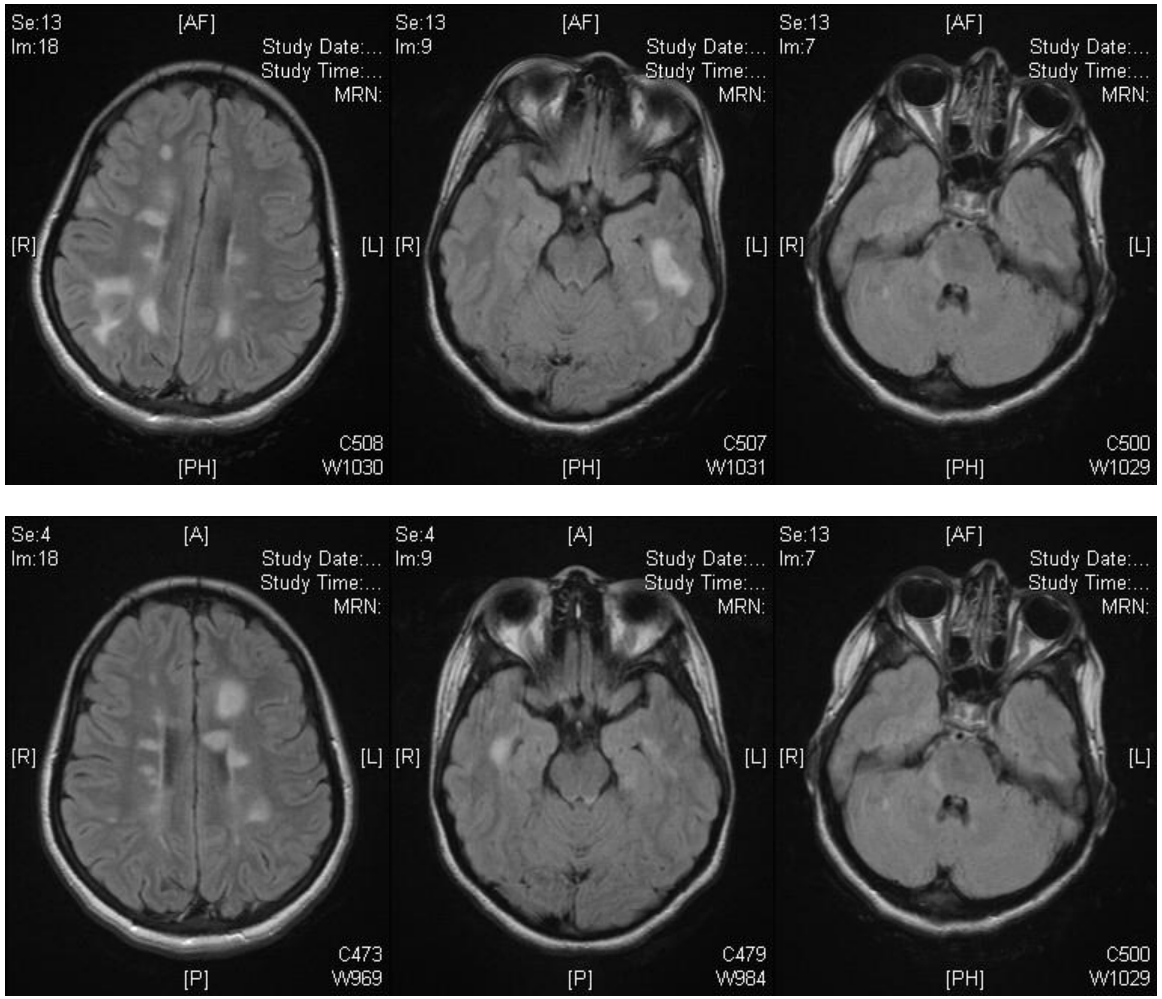
Year of publication and ref.	Study design, country	No.	Mean age, y (range)	Sex ratio, F:M	Clinical symptoms of the initial demyelinating attack in pediatric MS, % (n)							
					Visual loss	Paresthesias	Weakness	Coordination difficulties	Oculomotor or cranial nerve deficits	Urinary or bowel	Altered mental status or Sz	Polyfocal
2007[5]	Prospective cohort, France, Belgium	394	13.7	3.2	23 (92)	38 (149 with long tract symptoms)		NS	17 (66)	NS	7 (29)	22 (87)
2007[e1]	Prospective survey, Germany	132	13 (3-15)	1.2	36 (47)	39 (51)	29 (38)	44 (58)	30 (40)	NS	22 (29)	67 (88)
2007[e17]	Prospective cohort, Isfahan, Iran	82	14.1 (5-16)	4.5	28 (23)	10 (8)	12 (10)	6 (5)	9 (7)	1 (1)	16 (13 Sz)	35 (27)
2009[e14]	Prospective cohort, Italy	48	14.4	2.8	19 (9)	38 (18)	52 (25)	13 (6)	29 (10)	NS	0	27 (13)
2011[e18]	Prospective cohort, Canada	63	12.0	1.8	19 (12)	NS	NS	NS	NS	9 (6)	5 (3)	44 (27)
2012[6]	Prospective cohort, South Wales	49	NS (4-15)	4.4	12 (6)	18 (9)	40 (20)	6 (3)	12 (6)	6 (3)	0 (0)	10 (5)
2013[e7]	Prospective survey, Germany	126	13.1 (7-15)	2.1	43 (54)	55 (69)	25 (32)	26 (33)	23 (29)	NS	NS	46 (58)
2013[10]	Prospective cohort, Southeast Wales	111	15.9 (4-17)	2.8	26 (29)	NS	53 (59)	NS	NS	NS	1.8 (2)	23 (26)
2014[9]	Prospective cohort, Northeast USA	88	14.4 (3.3-17.9)	2.8	41 (34)	57 (48)	38 (32)	19 (16)	NS	1 (1)	5 (4)	48 (40)
2014[e8]	Prospective cohort, Shiraz, Iran	32	13.8	3.0	63 (20)	34 (11)	44 (14)	38 (12)	3 (1)	9 (3)	13 (4)	NS
2015[36]	Prospective cohort, Russia	47	13.9 (11-17)	0.88	38 (18)	15 (7)	17 (8)	34 (16)	34 (16)	NS	NS	NS

Clinical Message 1: Visual, sensory, pyramidal and cerebellar symptoms are key presenting features of MS

Waldman et al., 2016 ***Neurology*** 87(9 Suppl 2):S74-81

Case 4 14Y F

2 weeks history of right sided weakness
Fatigue lasting months
Clinically long tract signs in right



Right sided visual failure

3 years ago had a cerebellar syndrome

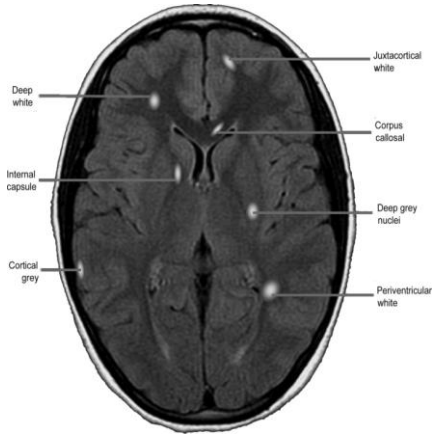
Strong family history of neuro-inflammatory condition (MS and cerebral lupus)

Normal neurological examination

Clinical Message 2: Normal neurological examination is not uncommon in MS

Diagnosis multiple sclerosis

McDonald 2010



DIS Can Be Demonstrated by ≥1 T2 Lesion[a] in at Least 2 of 4 Areas of the CNS:
Periventricular
Juxtacortical
Infratentorial
Spinal cord[b]

DIT Can Be Demonstrated by:
1. A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI
2. Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time

Sedani et al., 2012 ***Mult Scler.*** 18(5):679-82; Sadaka et al., 2012 ***Ann Neurol***. 72(2):211-23; Kornek et al., 2012 ***Mult Scler*** J.18: 1768-74; Bigi et al., 2013 ***Mult Scler*** 18: 1359-62; Heussinger et al., 2013 ***Eur J Neurol***. 20: 1292-1296 ; Hummel et al., 2013 ***Mult Scler*** 19: 1330-1335 ; Tansis et al., 2013 ***Mult Scler*** 19: 1749-1759; Williams et al., 2014 ***Pediatr Neurol.*** 51: 826-830

Can be applied to children

McDonald 2017

- DIS and OCB sufficient
  - No need to demonstrate DIT
- Symptomatic lesions count equally
  - Brainstem and spinal cord
- Juxtacortical/intracortical lesions
- RIS with DIS becomes MS at first symptom

Lancet Neurol 2018 17(2): 162–173

	MS ≤11years at onset (n=26)	MS > 11years at onset (n=68)	P value ≤11rs vs >11yrs
Age at presentation median IQR	10.1 (8.723-11.23)	14.23(13.42-15.0)	<0.001
Sex (M: F)	1:1.17	1:3.53	0.0395
Ethnicity (white: other)	1:1.17	1:1.94	1.0
McD 2010 at onset	12 (46.2%)	32 (47.1%)	1.0
McD 2017 at onset	22 (84.6%)	57 (83.8%)	1.0
OCB	23/25 (92%)	58/61(95.1%)	1.0

Fadda et al., 2018 ***Lancet Child Adolesc Health.*** 2(3):191-204
Wong et al., 2018 ***Neurol Neuroimmunol Neuroinflamm.*** 6(2):e528
Hacohen et al., 2020 ***Mult Scler.*** 26(11):1372-80
Boesen et al., 2022 ***Mult Scler Relat Disord***. 57:103443

2024 proposed revisions of the McDonald criteria - September 2024 ECTRIMS

Prof Xavier Montalban *International Advisory Committee on Clinical Trials in MS*

Signs or Symptoms suggestive of MS

↓

Initial workup suggestive of MS?

- Medical history and clinical examination
- Imaging and laboratory tests
- Differential diagnosis

→ No → **MS diagnosis should only be considered after ruling out better explanations**

↓ Yes

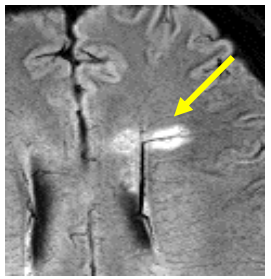
Lesions present in ≥2 CNS topographies
or
Patients with ≥ 12 months progression and ≥2 spinal cord lesions[1]

↓

Multiple Sclerosis may be diagnosed if one or more of the following are also demonstrated:

- CSF+[2]
- CVS+[3]
- Dissemination in Time[4]
- Lesions are present in 4 or 5 CNS topographies

≥6 CVS lesions



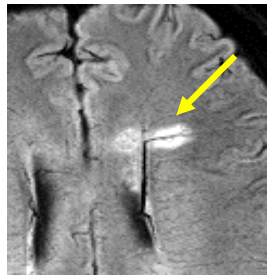
Lesions present in 1 CNS topography (including patients with ≥ 12 months progression)

↓

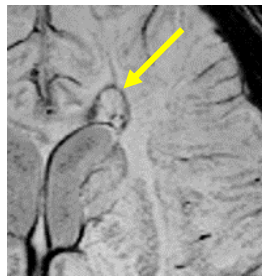
Multiple Sclerosis may be diagnosed if one or more of the following are also demonstrated:

- CSF+ and CVS+
- CSF+ and PRL+[5]
- Dissemination in Time and CVS+
- Dissemination in Time and PRL+

≥6 CVS lesions

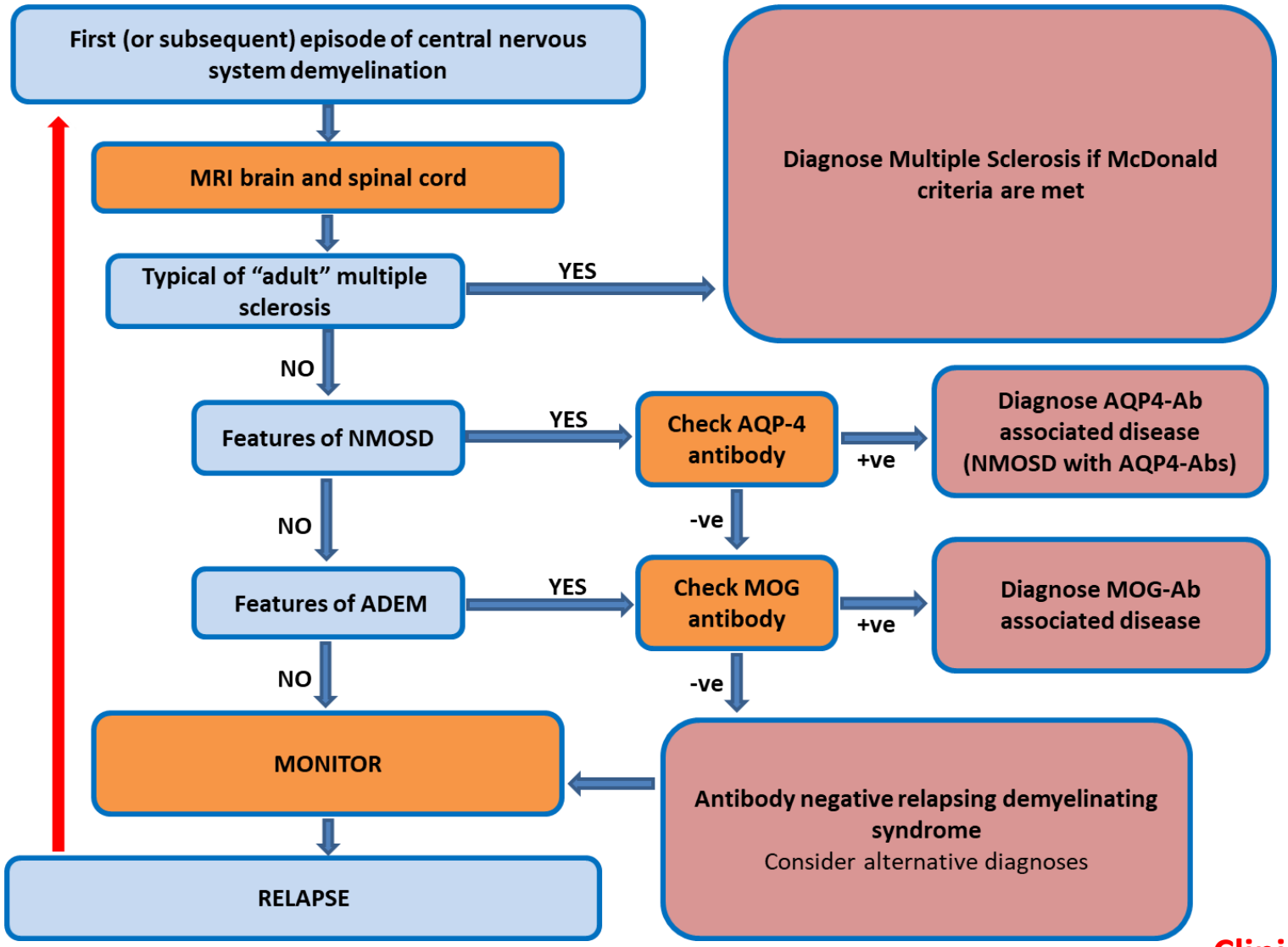


≥1 PRL



International Advisory Committee on Clinical Trials in MS | ECTRIMS European Committee for Treatment and Research in Multiple Sclerosis | MS National Multiple Sclerosis Society

https://ectrims.eu/mcdonald-diagnostic-criteria



56%

7%

26%

11%

Hacohen et al., 2017
Neurology. 89(3):269-278

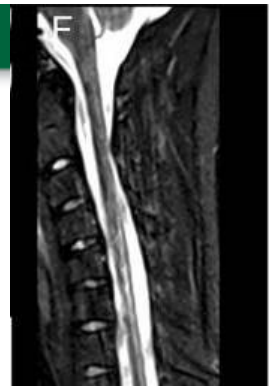
NMOSD
3MOG:1AQP4

50% RION
Mitochondrial,
HLH, Biotinidase

Clinical Message 3: Simple once you think of it

ARTICLES

DARS-associated leukoencephalopathy can mimic a steroid-responsive neuroinflammatory disorder



Wolf et al., 2015
Neurology 84(3):226-30

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Section Editor
John J. Millichap, MD

Teaching Neuro*Images*: Neuroradiologic evolution of Leigh disease

OPEN

Ng et al., 2016
Neurology 87(14):e159-e160

Isolated central nervous system familial hemophagocytic lymphohistiocytosis (fHLH) presenting as a mimic of demyelination in children

Multiple Sclerosis Journal
1–7
DOI: 10.1177/13524585211053565

Parida et al., 2021 ***Mult Scler***
doi: 10.1177/13524585211053565

Clinical Message 4: If does not fit criteria it is something else

Higher disease activity

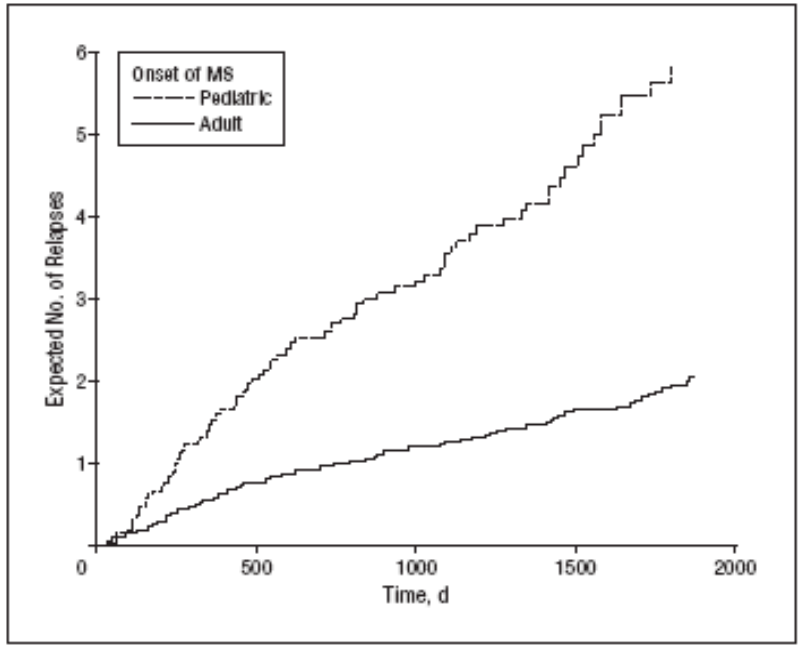


Figure. Cumulative number of multiple sclerosis (MS) relapses (excluding the first relapse).

Benson et al., 2014 ***Mult Scler Relat Disord.*** 3(2):186-93

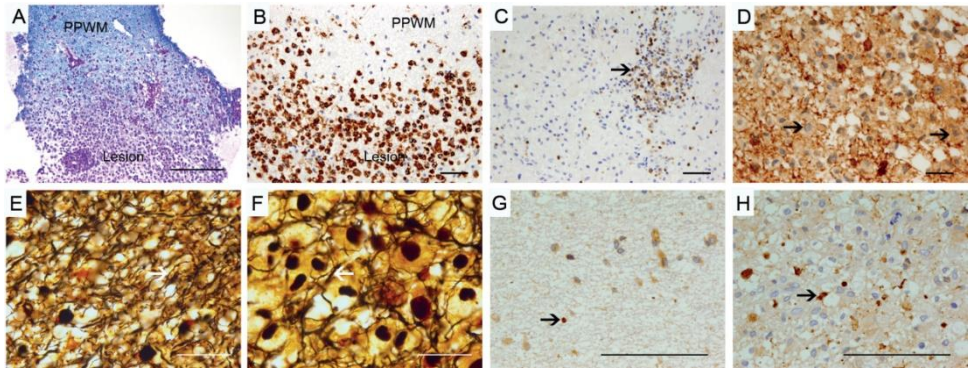
Table 2. MRI Characteristics on the First Brain Scans[a]

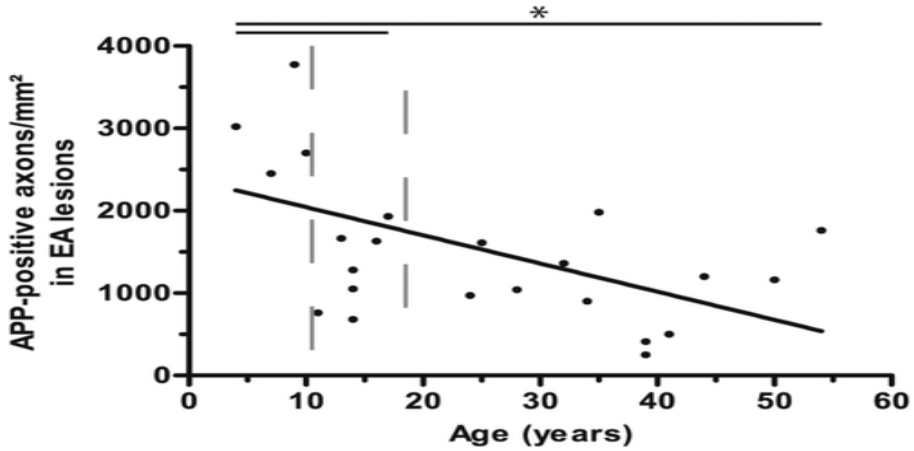
Characteristic	No. of Lesions, Median (Range)		*P* Value
	Pediatric MS (n=41)	Adult MS (n=35)	
Total number of T2-bright foci	21 (0-74)	6 (0-76)	<.001
Nonovoid, poorly defined T2-bright foci	3 (0-55)	0 (0-4)	<.001
Ovoid, well-defined T2-bright foci	12 (0-69)	5 (0-75)	.006
Large (≥1 cm) T2-bright foci	4 (0-26)	0 (0-5)	<.001
Gadolinium-enhancing lesions	2 (0-60)	0 (0-5)	<.001
Juxtacortical lesions	9 (0-48)	1 (0-8)	<.001
Periventricular lesions	6 (0-21)	2 (0-12)	<.001
Cerebellar lesions	0 (0-8)	0 (0-2)	.01
Brainstem lesions	1 (0-6)	0 (0-3)	.002
Corpus callosum lesions	1 (0-8)	0 (0-3)	.07

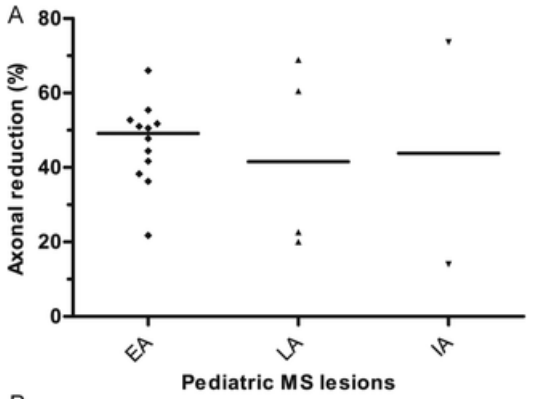
Abbreviations: See Table 1.
[a]The Mann-Whitney test was used to compare groups because the distribution of lesions was not normal.

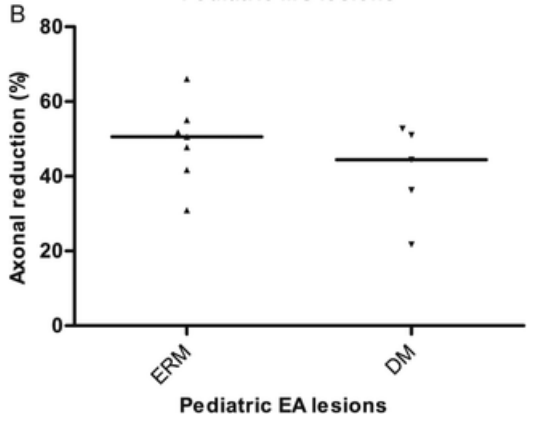
Waubant et al., 2009 ***Arch Neurol***. 66(8):967-971

Extensive acute axonal damage in pediatric lesions



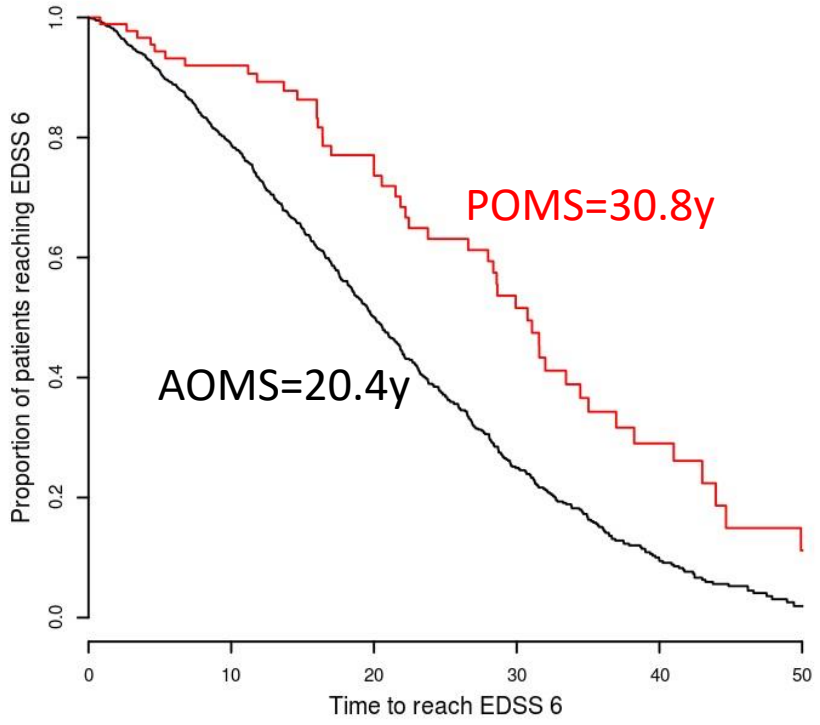


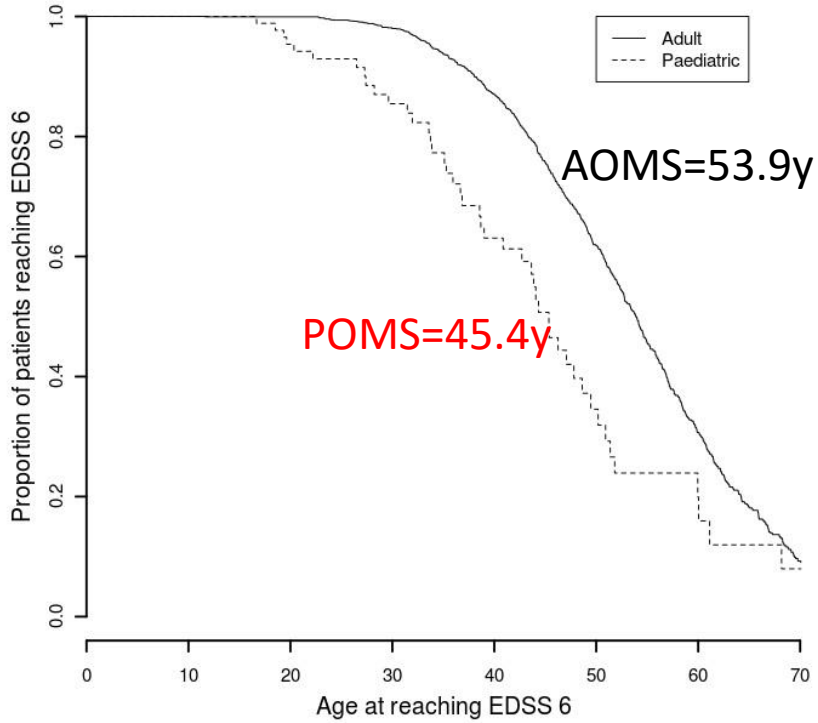




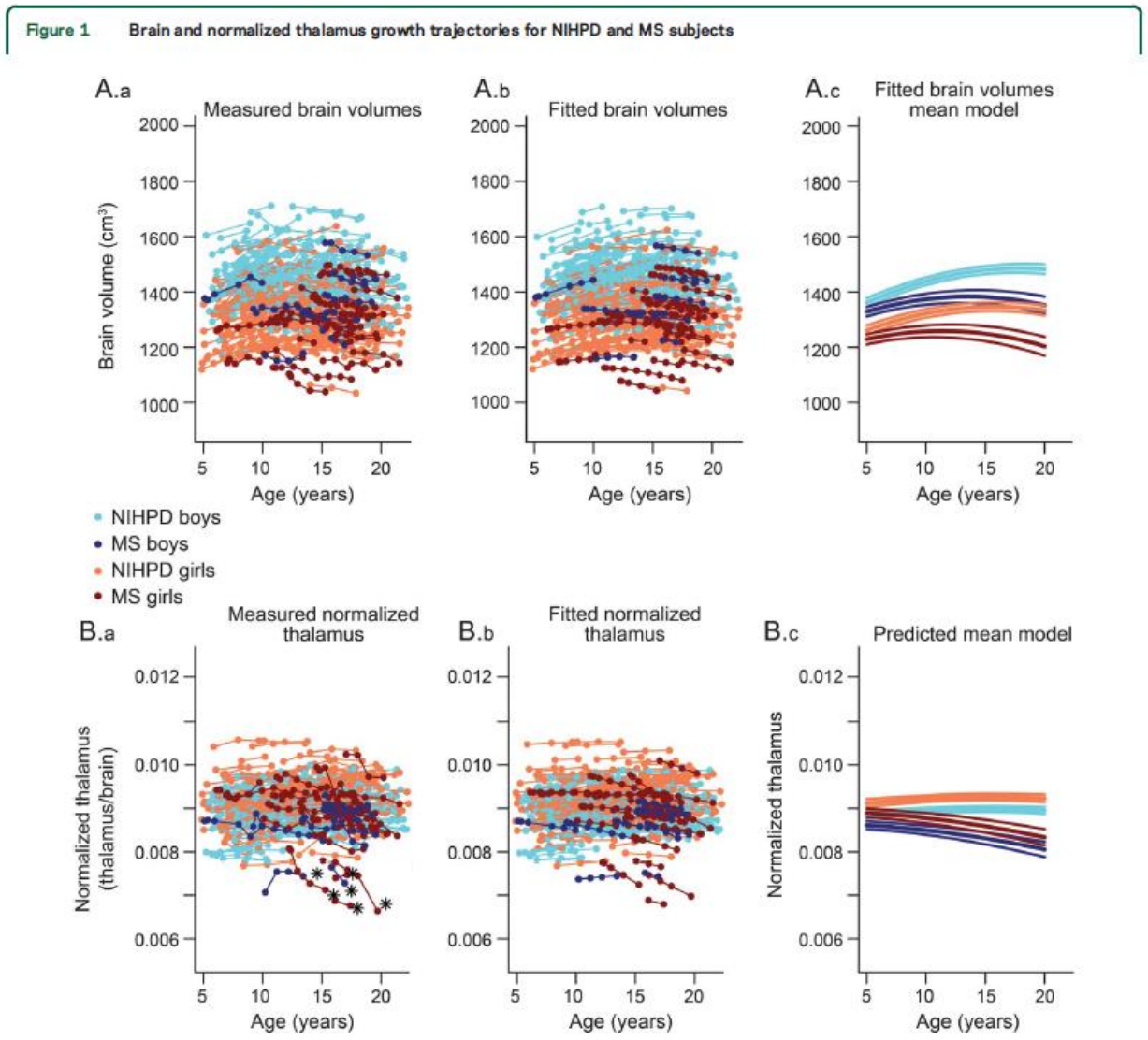
Pfeifenbring et al., 2015
Ann Neurol 77(4); 655-667

Time to EDSS 6.0





Renoux et al., 2007 ***NEJM*** 356: 2603-13
Harding et al 2013 ***J Neurol Neurosurg Psychiatry*** 84(2):141-7



Onset of multiple sclerosis before adulthood leads to failure of age-expected brain growth

- Significant cognitive impairment in 31% (failure on at least 3 tests)
- 53% failure on 2 tests
- 75% showed worsening of CI at 2 years follow up

Amato et al., 2008 ***Neurology*** 70(20):1891-7

Aubert Broche et al., 2014 ***Neurology***83:2140-2146

Corticosteroids in acute MS attack

- **Acute treatment**

  Methylprednisolone IV/PO 30mg/kg or 500mg/m^2

- **Maintenance treatment**

  Oral prednisolone 1-2mg/kg

  Dexamethasone 20mg/m2 for 3 days

Dale et al., 2017 ***Curr Opin Neurol***. 30(3):334-344

	Equivalent Glucocorticoid Dose (mg)	Potency relative to Hydrocortisone: Anti-Inflammatory	Potency relative to Hydrocortisone: Mineral-Corticoid	Half-Life: Plasma (minutes)	Half-Life: Duration of Action (hours)
Short Acting					
Hydrocortisone (Cortef, Cortisol)	20	1	1	90	8-12
Cortisone Acetate	25	0.8	0.8	30	8-12
Intermediate Acting					
Prednisone	5	4	0.8	60	12-36
Prednisolone	5	4	0.8	200	12-36
Triamcinolone	4	5	0	300	12-36
Methylprednisolone	4	5	0.5	180	12-36
Long Acting					
Dexamethasone	0.75	30	0	200	36-54
Betamethasone	.6	30	0	300	36-54
Mineralocorticoid					
Fludrocortisone	0	15	150	240	24-36
Aldosterone	0	0	400 +	20	- -

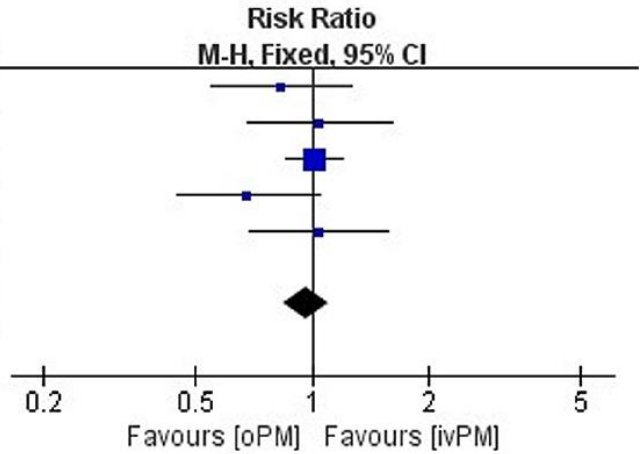
Reference: Adrenal Cortical Steroids. In Drug Facts and Comparisons. 5th ed. St. Louis, Facts and Comparisons, Inc.:122-128, 1997

Adapted from Lui et al 2013
Allergy, Asthma & Clinical Immunology 9(1):30

Oral as good as IV

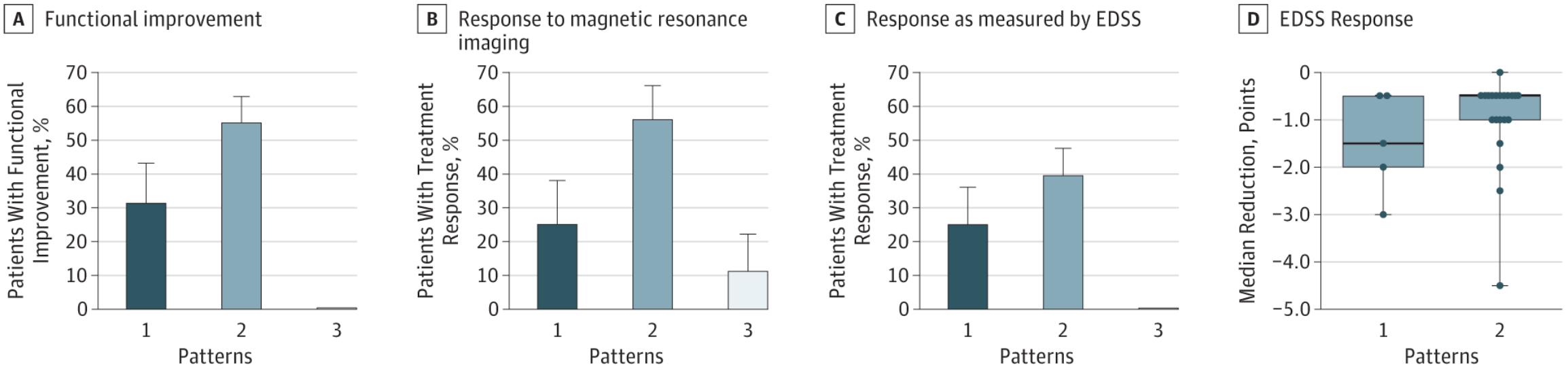
Study or Subgroup	oPM Events	oPM Total	ivPM Events	ivPM Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alam 1993	10	15	16	20	10.6%	0.83 [0.55, 1.27]
Barnes 1997	22	42	18	36	15.0%	1.05 [0.68, 1.62]
Le Page 2015	63	82	68	90	50.2%	1.02 [0.86, 1.20]
Martinelli 2009	11	19	17	20	12.8%	0.68 [0.45, 1.04]
Ramo-Tello 2014	15	22	15	23	11.4%	1.05 [0.69, 1.58]
Total (95% CI)		**180**		**189**	**100.0%**	**0.96 [0.84, 1.10]**
Total events	121		134			

Heterogeneity: Chi² = 3.71, df = 4 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.56 (P = 0.58)



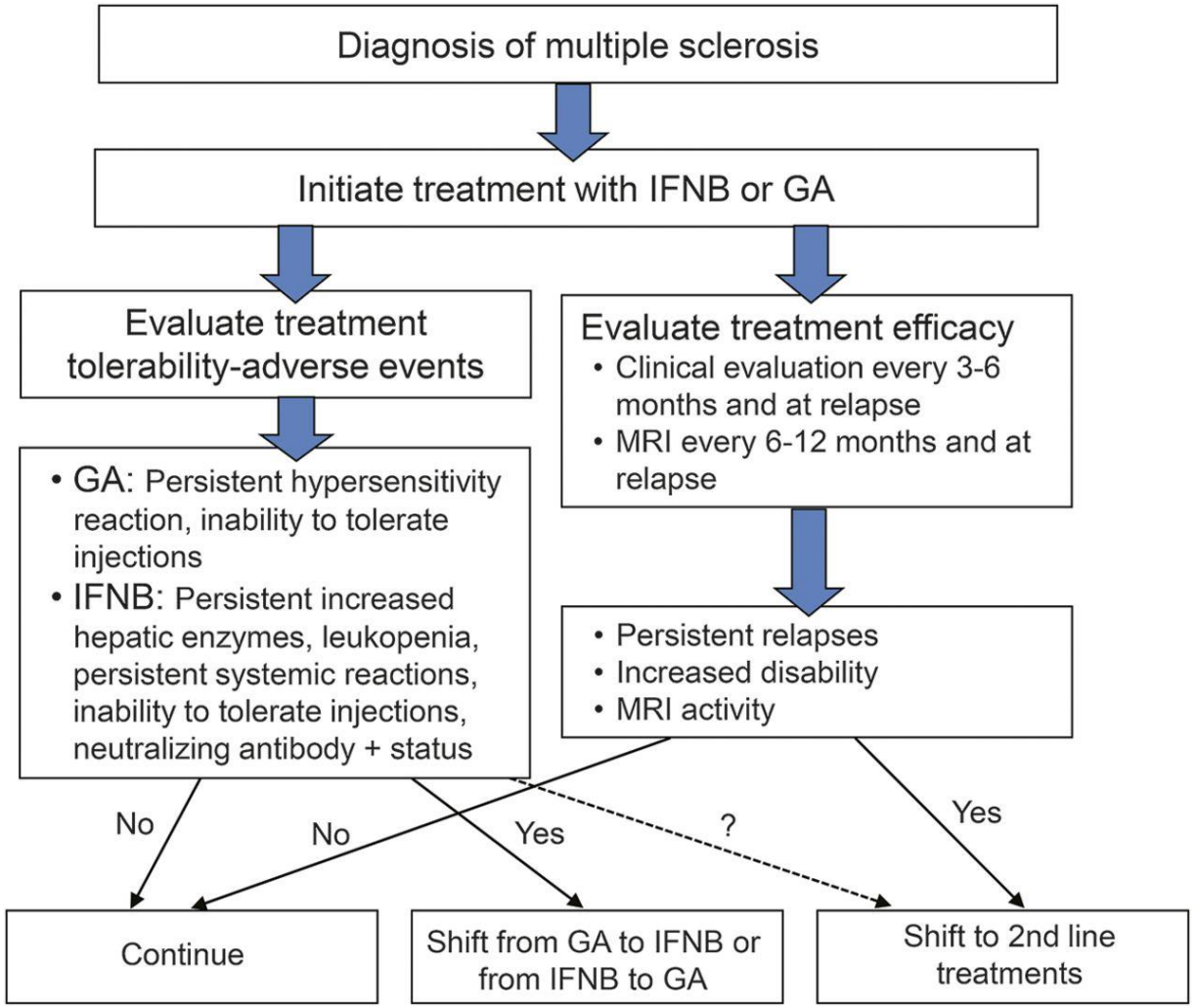
Liu et al., 2017 ***PLoS One.*** 12(11):e0188644

Differences in the responses to apheresis therapy in patients with different immuno-pathological patterns of multiple sclerosis



Stork et al., 2018 ***JAMA Neurol.*** 75(4): 428–435

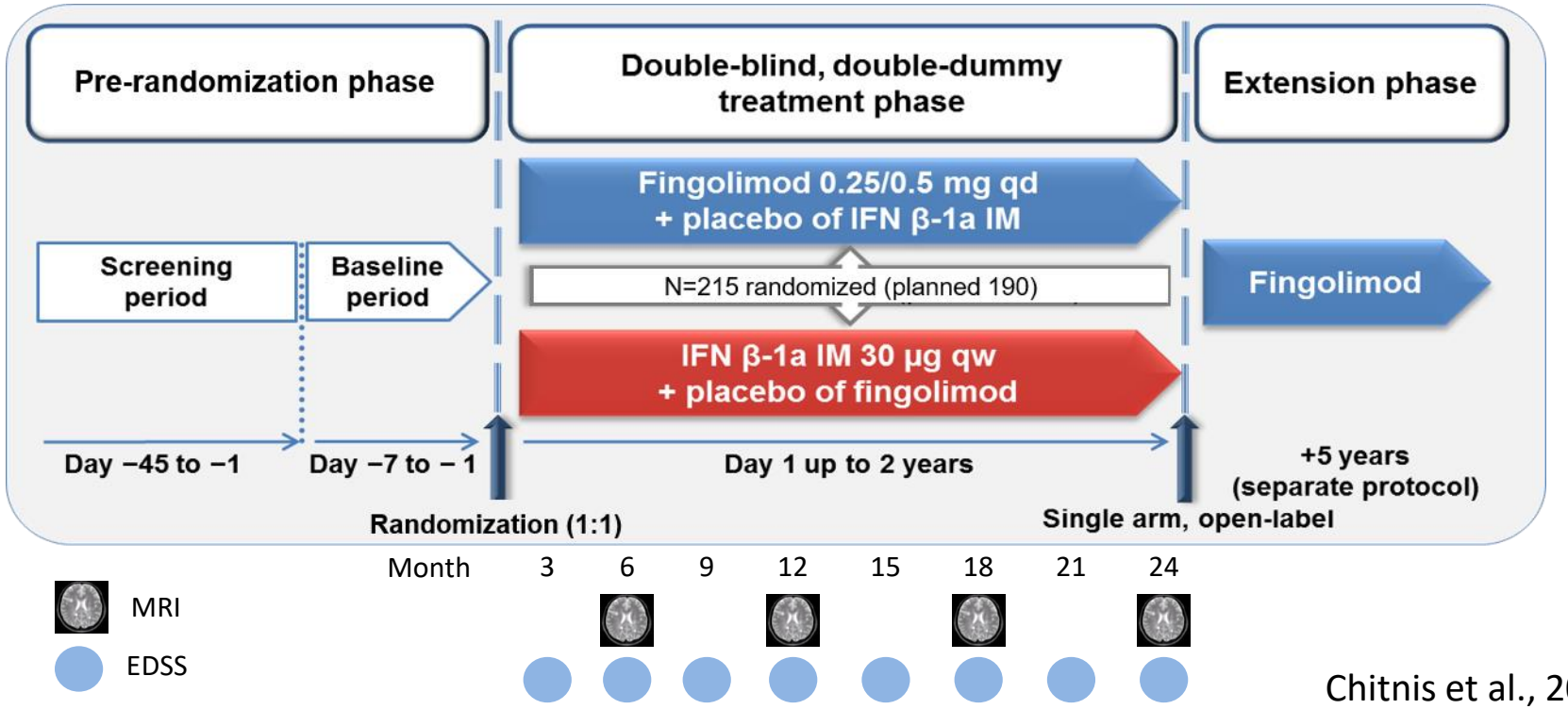
Clinical Message 5: Do not forget acute treatment



Disease modifying therapy in paediatric MS: What it used to be

Ghezzi et al. 2016
Neurology 2016;87:S97-S102

First RCT specifically designed for pediatric MS



Chitnis et al., 2018 ***N Engl J Med.*** 379(11):1017-1027

Superiority of Fingolimod over IFN β-1a

Table 2. Primary and Secondary End Points at Month 24 (Full Analysis Set).

End Point	Fingolimod	Interferon Beta-1a	Rate Ratio (95% CI)	Between-Group Difference (95% CI)
Primary end point				
Patients evaluated	107	107		
Annualized relapse rate (95% CI)*	0.12 (0.08–0.19)	0.67 (0.52–0.89)	0.18 (0.11–0.30)†	0.55 (0.36–0.74)†‡
Key secondary end point				
Patients evaluated	106	102		
Annualized rate of new or newly enlarged lesions on T_2-weighted MRI (95% CI)*	4.39 (3.62–5.37)	9.27 (7.66–11.21)	0.47 (0.36–0.62)†	4.88 (2.91–6.84)†‡
Secondary clinical end point				
Patients evaluated	107	107		
Patients free of relapse — % (95% CI)§	85.7 (79.0–92.4)	38.8 (27.4–50.3)		46.9 (33.7–60.1)
Secondary MRI-related end point				
Patients evaluated	106	101		
Adjusted mean no. of gadolinium-enhancing lesions per scan (95% CI)*	0.44 (0.31–0.61)	1.28 (0.93–1.76)	0.34 (0.22–0.54)	

Chitnis et al., 2018
N Engl J Med. 379(11):1017-27

More treatments in the pipeline

Table 1 Completed and ongoing clinical trials in pediatric multiple sclerosis (MS) as of January 2018 (based on clinicaltrials.gov)

	Medication	Type	Randomized	Controlled	Target n	Duration	Primary endpoint	Status
Completed								
NA: NCT02137109	Tysabri	Open-label	0	0	13	16 wk	PK/PD	Completed in 2014
FOCUS: NCT02410200	Dimethyl fumaric acid	Open-label	0	0	22	6 mo	• PK • Number of new/newly enlarging T2 foci	Completed in 2016 Early ECTRIMS 2017
PARADIGMS: NCT01892722	Fingolimod	Phase 3	+	IM IFN-β-1a	210	Up to 2 y	Relapse rate	Completed in 2017 Chitnis 2018
Ongoing								
TERIKIDS: NCT02201108	Teriflunomide	Phase 3	+	Placebo	165	2 y	Time to first relapse	Enrollment complete
CONNECT: NCT02283853	Dimethyl fumaric acid	Phase 3, open-label	+	IM IFN-β-1a	142	2 y	% Free of new/enlarging T2-bright lesions	Enrollment ongoing
LEMKIDS: NCT03368664	Alemtuzumab	Open-label	0	0	50	8 mo/2 y	New or enlarging T2-bright foci	Enrollment ongoing

Abbreviations: PD = pharmacodynamic; PK = pharmacokinetic.

Neurology 2019 May 28; 92(22): e2538–e2549

Lancet Neurol. 2021 Dec;20(12):1001-1011

JAMA Netw Open. 2022;5(9):e2230439

TABLE 2.
Descriptions of all DMTs (EDSS 0 to 5.5 With Active MS)

	DMT					Overall (N = 367)
	Fingolimod (N = 61)	Natalizumab (N = 87)	Rituximab (N = 97)	Dimethyl Fumarate (N = 100)	Ocrevus (N = 22)	
Age at start of DMT: mean (S.D.)	15.7 (1.8)	15.1 (2.2)	15.2 (2.1)	15.7 (2.0)	16.3 (1.4)	15.5 (2.0)
Sex	39 (64%)	64 (74%)	66 (68%)	66 (66%)	15 (68%)	250 (68%)
Race						
White	35 (64%)	51 (61%)	50 (58%)	64 (68%)	12 (63%)	212 (63%)
Black	13 (24%)	16 (19%)	29 (34%)	13 (14%)	3 (16%)	74 (22%)
Asian	3 (5%)	6 (7%)	3 (3%)	5 (5%)	1 (5%)	18 (5%)
Other	4 (7%)	10 (12%)	4 (5%)	12 (13%)	3 (16%)	33 (10%)
Ethnicity						
Hispanic or Latino	21 (35%)	32 (37%)	45 (49%)	41 (43%)	6 (27%)	145 (41%)
Not Hispanic or Latino	39 (65%)	55 (63%)	47 (51%)	55 (57%)	16 (73%)	212 (59%)
Body mass index: mean (S.D.)	25.0 (4.7)	26.0 (6.6)	26.0 (6.9)	26.7 (6.8)	26.6 (5.5)	26.1 (6.4)
EDSS before starting DMT						
N	61	87	97	100	22	367
Mean (S.D.)	1.2 (1.1)	1.8 (1.2)	1.8 (1.2)	1.2 (0.9)	1.4 (1.1)	1.5 (1.1)
Median (q1-q3)	1.0 (0.0-2.0)	2.0 (1.0-2.5)	1.5 (1.0-2.5)	1.5 (1.0-2.0)	1.5 (0.0-2.0)	1.5 (1.0-2.0)
(min-max)	(0.0-3.5)	(0.0-5.5)	(0.0-4.5)	(0.0-3.5)	(0.0-3.5)	(0.0-5.5)
Relapse rate in past year*	0.57 (0.35,0.92)	1.04 (0.79,1.36)	1.14 (0.86,1.52)	1.00 (0.77,1.30)	1.08 (0.64,1.82)	0.99 (0.86,1.13)
Relapse rate while on DMT*	0.11 (0.04,0.29)	0.14 (0.06,032)	0.15 (0.08,0.28)	0.22 (0.16,0.31)	0.08 (0.00,1.57)	0.15 (0.12,0.21)
MRI in past 12 months	60/61 (98%)	81/87 (93%)	96/97 (99%)	96/100 (96%)	21/22 (95%)	354/367 (96%)
New T2 lesion in past 12 months	57/60 (95%)	77/81 (95%)	93/96 (97%)	89/96 (93%)	21/21 (100%)	337/354 (95%)
MRI while on DMT (at least 2 MRI)	26/61 (43%)	46/87 (53%)	49/97 (51%)	49/100 49%)	4/22 (18%)	174/367 (47%)
New T2 lesion while on DMT	11/26 (42%)	9/46 (20%)	6/49 (12%)	28/49 (57%)	0/4 (0%)	54/174 (31%)
Gadolinium used in past 12 months	58/61 (95%)	80/87 (92%)	92/97 (95%)	95/100 (95%)	21/22 (95%)	346/367 (94%)
New Gd lesion in past 12 months	44/58 (76%)	66/80 (83%)	70/92 (76%)	64/95 (67%)	17/21 (81%)	261/346 (75%)
Gadolinium used while on DMT	35/61 (57%)	59/87 (68%)	63/97 (65%)	69/100 (69%)	9/22 (41%)	235/367 (64%)
New Gd lesion while on DMT	8/35 (23%)	9/59 (15%)	7/63 (11%)	23/69 (33%)	1/9 (11%)	48/235 (20%)
NEDA-2	33/51 (65%)	53/71 (75%)	68/87 (78%)	39/86 (45%)	15/17 (88%)	208/312 (67%)
NEDA-2 in first 6 months on DMT	41/50 (82%)	60/73 (82%)	70/82 (85%)	60/78 (77%)	12/12 (100%)	243/295 (82%)
NEDA-2 in first 12 months on DMT	37/48 (77%)	54/72 (75%)	64/76 (84%)	55/82 (67%)	10/10 (100%)	220/288 (76%)

Real world data of effectiveness of highly effect in paediatric MS

Rituximab had good efficacy

Krysko et al., 2020 ***Ann Neurol*** 88(1):42-55
Shukla et al., 2023 ***Pediatr Neurol*** 145:125-13
Etemadifar et al. 2024 ***Mult Scler Relat Disord*** 91:105849

Evelina London
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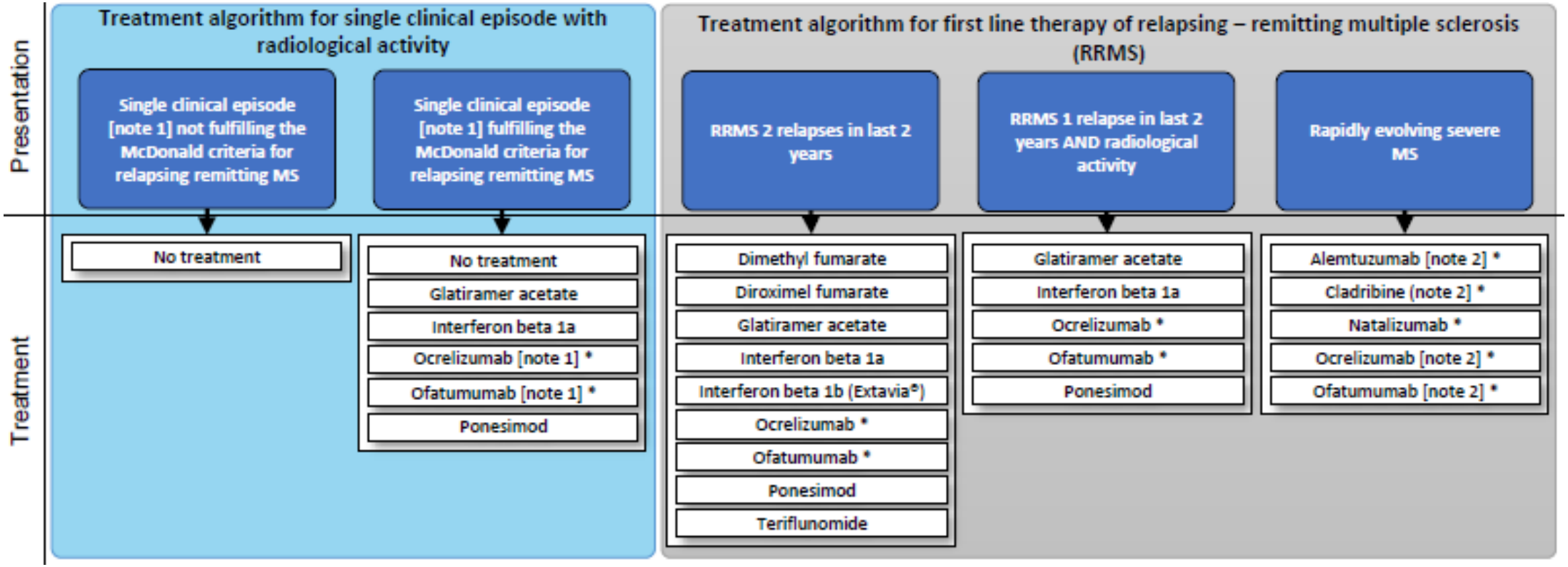


Children may receive disease-modifying therapies (DMTs) that are[2]

- Licensed for children
- Have a recognised dose for children (for instance are cited in the British National Formulary) or—if neither of the previous two criteria apply—
- **The child is post-pubescent**

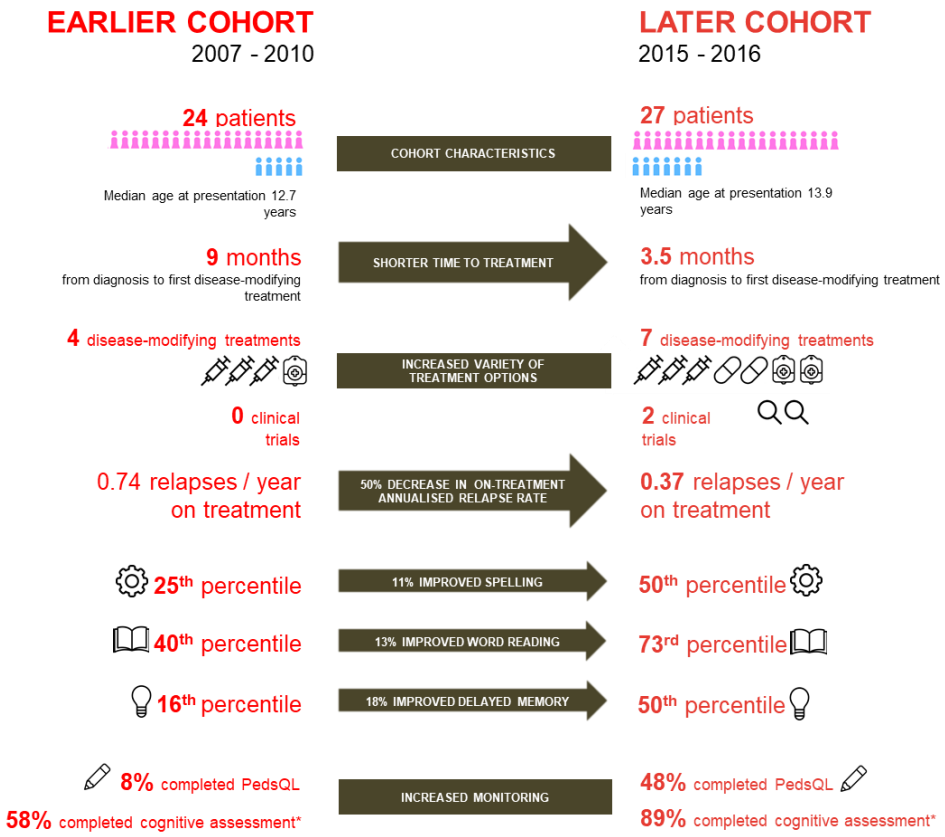
Rapidly evolving severe (RES) MS

- ≥2 disabling relapses in 1 year
- ≥1 gadolinium-enhancing lesions or significant increase in T2 lesion load compared with a previous MRI

UK NHS England MS treatment algorithm

https://www.england.nhs.uk/publication/treatment-algorithm-for-multiple-sclerosis-disease-modifying-therapies/

Progress in management of MS in children



Luchesa-Smith et al, 2020 ***Children*** 7(11):222

Brain atrophy

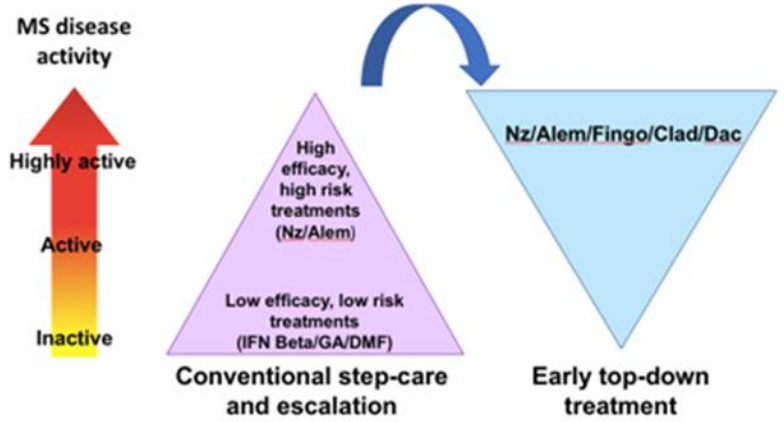
Disability progression

Imaging

Clinical Relapse

No Evidence of Disease Activity

Curr Treat Options Neurol 2017 19(5):20



Curr Opin Neurol. 2018 31(3):233-243

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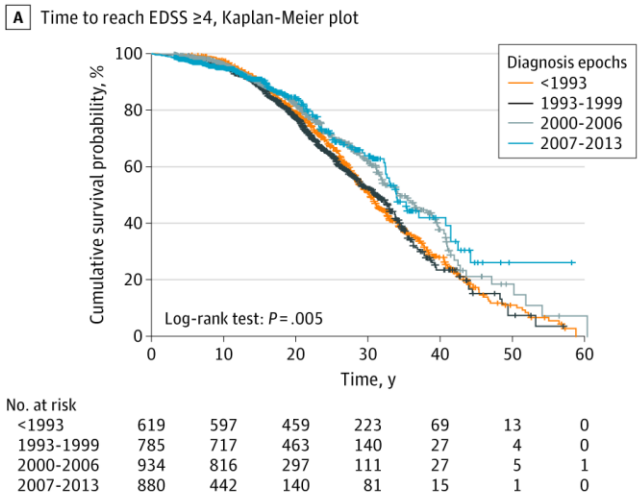
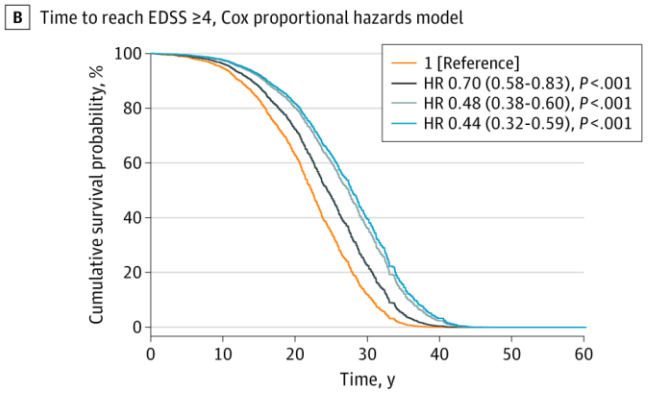
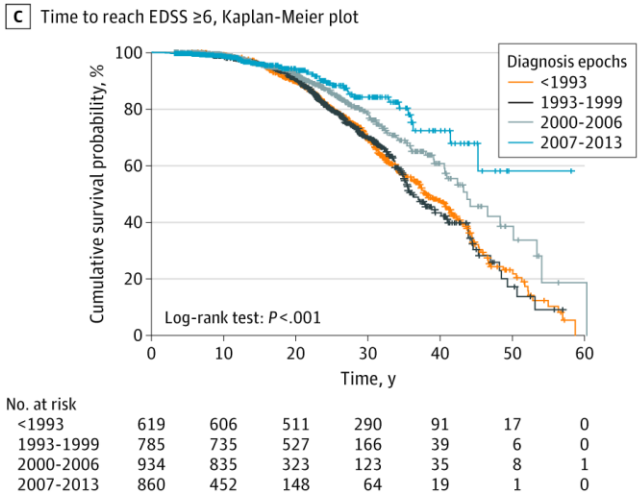
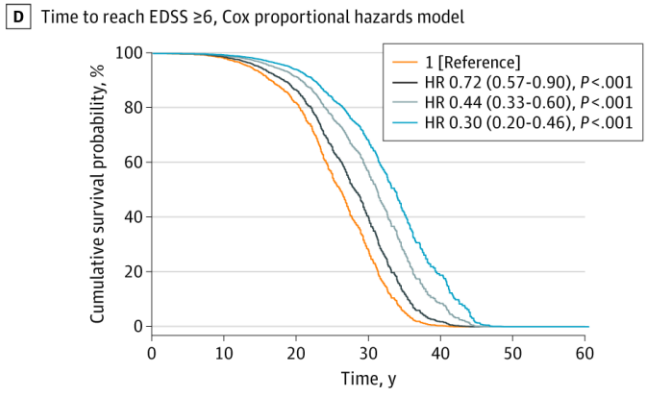
Progress in management of childhood MS



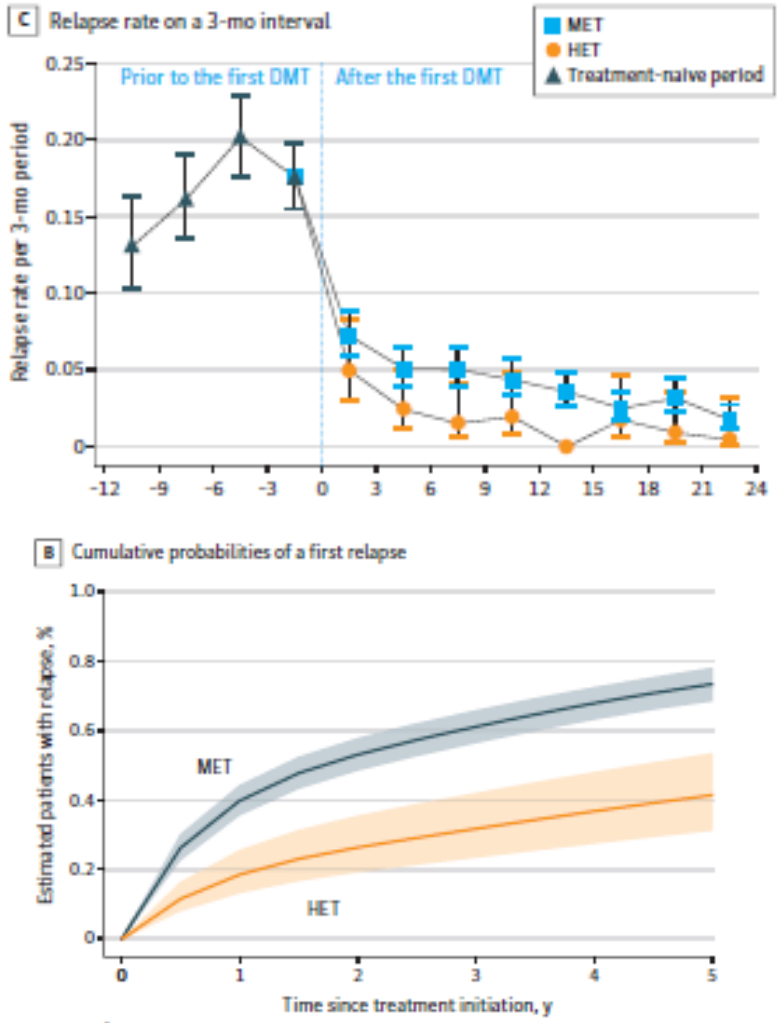






Baroncini et al., 2021 ***JAMA Neurol*** 78(6):726-735

Highly Effective Therapies as First-Line Treatment for Pediatric-Onset Multiple Sclerosis



530 patients (mean 16.0 [SD1.8] years; 364 female)

- HET dampened disease activity with a 54% reduction in first relapse risk (adjusted hazard ratio [HR], 0.46; 95% CI, 0.31-0.67; P < .001) sustained over 5 years, confirmed on MRI activity (adjusted odds ratio [OR], 0.34; 95% CI, 0.18-0.66; P = .001), and with a better tolerability pattern than MET.
- Index treatment was not associated with EDSS progression or tertiary education attainment (adjusted OR, 0.51; 95% CI, 0.24-1.10; P = .09).

Benallegue et al., 2024 ***JAMA Neurol*** 81(3):273-282

Effects of DMT on disease progression

	Number (%)* of people treated	Median (IQR) recorded time on therapy, years	Number (%)* of people treated before age 18 years
Alemtuzumab	84 (1·6%)	2·65 (1·34–3·77)	1 (<0·1%)
Autologous haematopoietic stem cell transplantation	10 (0·2%)	..	0
Cladribine	104 (2·0%)	1·03 (0·72–1·72)	3 (0·1%)
Daclizumab	9 (0·2%)	0·63 (0·40–2·35)	0
Fingolimod	1116 (21·4%)	2·03 (0·94–3·77)	88 (1·7%)
Mitoxantrone	340 (6·5%)	0·78 (0·52–1·71)	25 (0·5%)
Natalizumab	1377 (26·4%)	2·11 (1·15–3·62)	262 (5·0%)
Ocrelizumab	351 (6·7%)	1·55 (0·73–2·42)	7 (0·1%)
Ofatumumab	1 (<0·1%)	..	0
Rituximab	126 (2·4%)	1·56 (0·74–2·95)	19 (0·4%)
Siponimod	3 (0·1%)	..†	0
Interferon beta	3615 (69·2%)	2·60 (1·09–5·30)	1191 (22·8%)
Glatiramer acetate	1207 (23·1%)	1·58 (0·56–3·45)	167 (3·2%)
Dimethyl fumarate	622 (11·9%)	1·16 (0·35–2·39)	57 (1·1%)
Teriflunomide	233 (4·5%)	1·17 (0·43–2·14)	14 (0·3%)

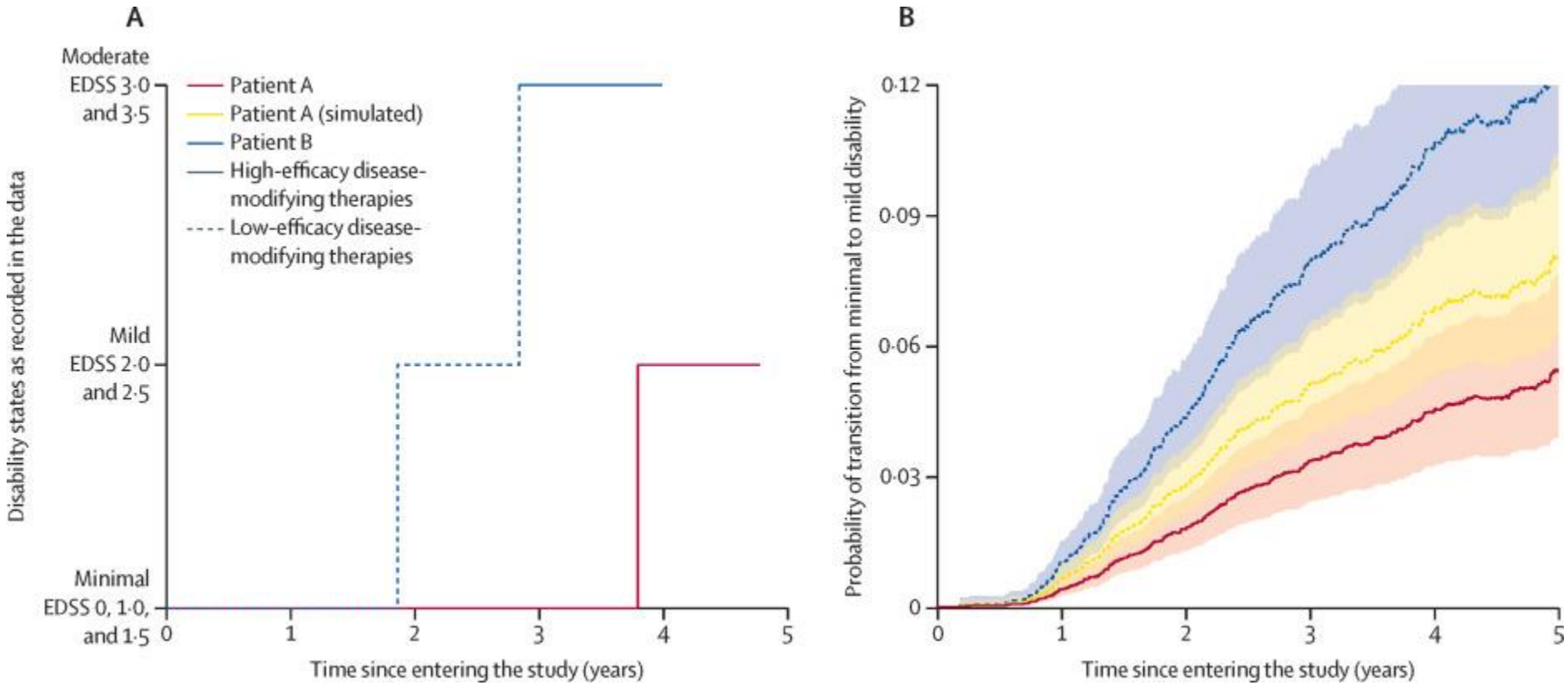
*Denominator is 5224 people included in the study. †Complete data available for one person.

Table 2: **Treatment with disease-modifying therapies during the study follow-up**

5224 people (3686 female; mean age 15.2)

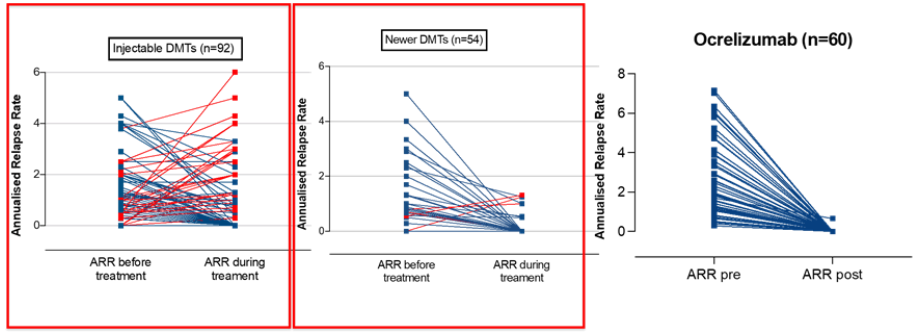
- High-efficacy therapies reduced the hazard of disability worsening across the disability states.
- The largest reduction (hazard ratio 0·41 [95% CI 0·31–0·53]) was observed in participants who were treated with high-efficacy therapies while in the minimal disability state, compared with those remained untreated.
- Young people with minimal disability who received low-efficacy therapy also experienced a reduced hazard (hazard ratio 0·65 [95% CI 0·54–0·77])

Sharmin et al., 2024 ***Lancet Child Adolesc Health*** 8(5):348-357



Sharmin et al., 2024 ***Lancet Child Adolesc Health*** 8(5):348-357

Real world data



Hacohen et al., 2017 ***Neurology*** 89(3):269-278

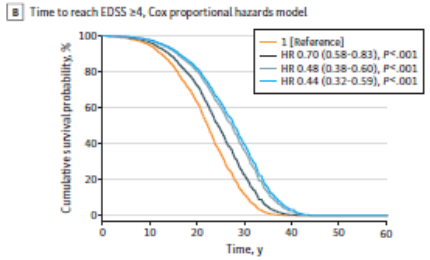
Abdel-Mannan et al., 2021 ***N2*** 8 (4) e1008

Abdel-Mannan et al., 2023

9 year EDSS score predicted by:-

- Base line EDSS, brain stem lesion, cervical spine lesions (+/- GAD), brain (GAD+)
- On going GAD lesion brain

Ann Neurol 2021;89:1011–1022



Baroncini et al., 2021 ***JAMA Neurol*** 78(6) 726-35

Long-term Socioeconomic Outcomes Associated With Pediatric-Onset Multiple Sclerosis

	Childhood-onset PoMS	Adolescent-onset PoMS
Outcome	Adjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
High School or higher (vs elementary)	0.60 (0.27 – 1.34)	0.91 (0.66 – 1.28)
University (vs high school or elementary)	0.69 (0.38 – 1.25)	0.82 (0.66 – 1.00)

JAMA Neurol. 2021 78(4):478-482

Usage of range of DMTs
N=1019 total
Krysko et al., 2018
Neurology 91: e1778-87

New superior to injectables (197vs 544)
Krysko et al., 2020 ***Ann Neurol*** 88: 42-55

Effectiveness of HET N=1218 total
Spleman et al., 2024 ***Neurology*** 102: e208114

HET effective up to 5 years (N=530)
Benallegue et al., 2024 ***JAMA Neurol*** 81(3) 273-82

DMT exposure[a]	Q4[b]
Never treated	7.06 (2.05–24.34)*
Q1	4.76 (1.35–16.76)*
Q2	3.86 (1.07–13.97)*
Q3	3.17 (0.87–11.58)

Amato et al., 2020 ***Brain 143*** 3013-3024

2-5 years **10 years** **20+ years**

RCT data

PARADIGMS

TERIKIDS

CONNECT

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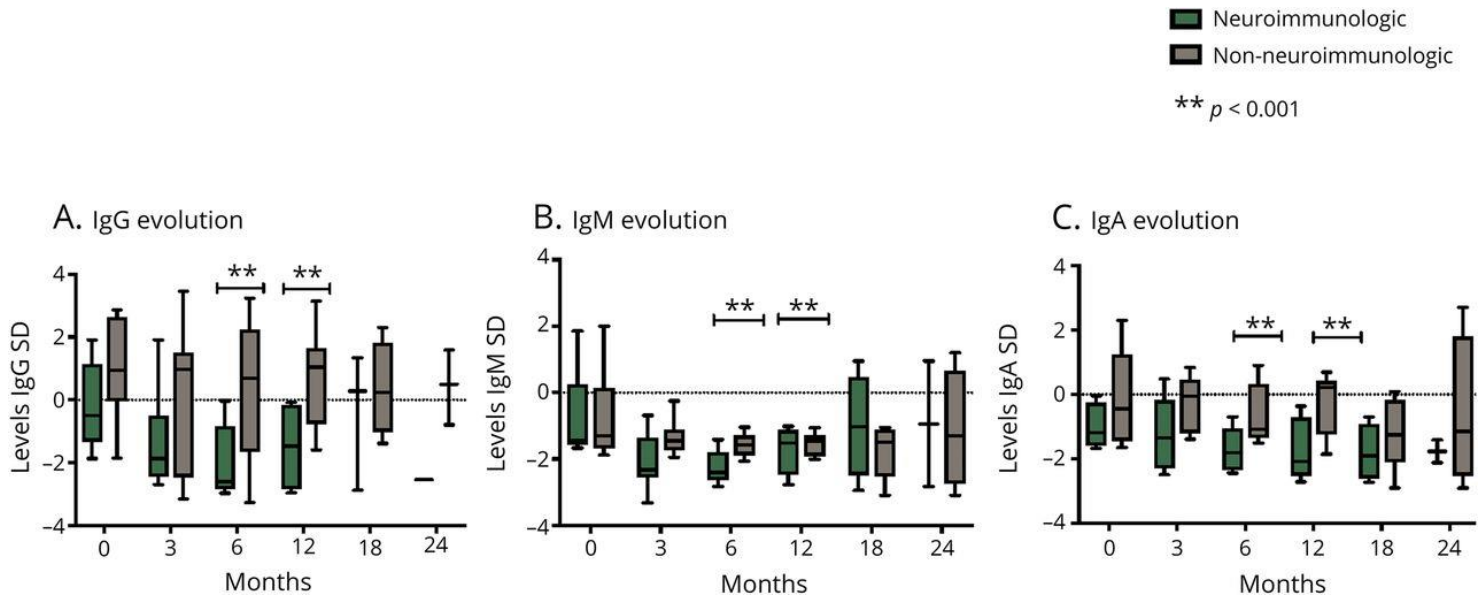
Long lasting immunologic changes in children

More intense immunotherapy and rituximab dosing regime

Younger age

Even a single dose



Long terms effect of immune treatment

Infection
Growth
Bone health
Tumour checking

Dale et al., 2014 ***Neurology*** 83(2):142-50

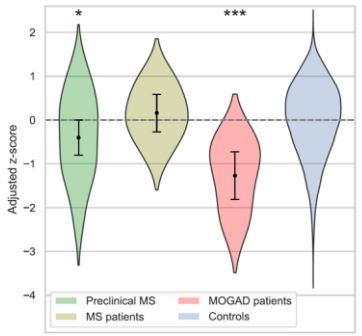
Deya-Martinez et al., 2020 ***N2*** 7(4):e724

Anderson et al., 2017 ***Pediatr Blood Cancer.*** e26548

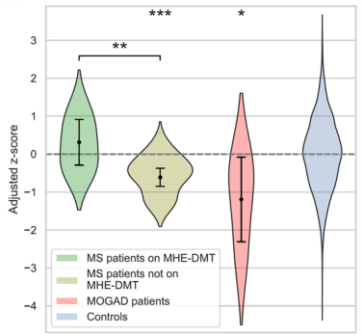
The MS PRODROME

Makhani & Tremlett 2021
Nat Rev Neurol 17(8):515-521

SAT performance at ages 10-11



Performance in final academic assessments (GCSE/A-level)



60 (38 MS, 22 MOGAD) vs 449,553 controls

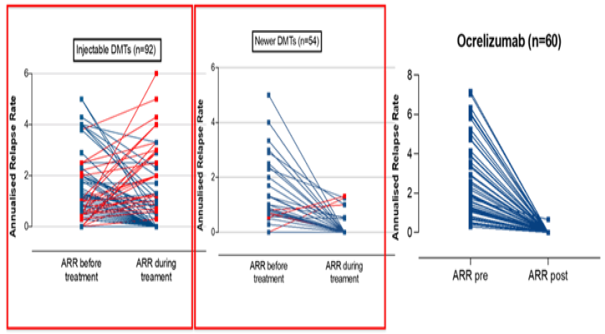
Eyre et al., 2024
Ann Clin Transl Neurol 11(11):3025-30

2-5 years

Academic performance

	Prior to the first clinical event	Following the first clinical event
MOGAD		Significantly worse (z -1.3 = 10th centile)
MS	Mildly worse (z -0.4 = 35th centile)	Not on MHE-DMT: moderately worse (z -0.6 = 27th centile)
		MHE-DMT: normal

Real world data



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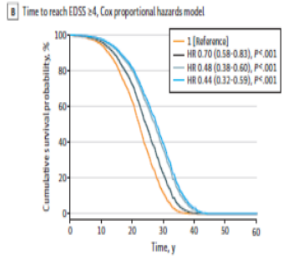

Baroncini et al., 2021 ***JAMA Neurol*** 78(6) 726-35

DMT exposure[a]	Q4[b]
Never treated	7.06 (2.05–24.34)*
Q1	4.76 (1.35–16.76)*
Q2	3.86 (1.07–13.97)*
Q3	3.17 (0.87–11.58)

Amato et al., 2020 ***Brain 143*** 3013-3024

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University (vs high school or elementary)	0.69 (0.38 – 1.25)	0.82 (0.66 – 1.00)

JAMA Neurol. 2021 78(4):478-482

2-5 years | **10 years** | **20+ years**

RCT data

- PARADIGMS
- TERIKIDS
- CONNECT

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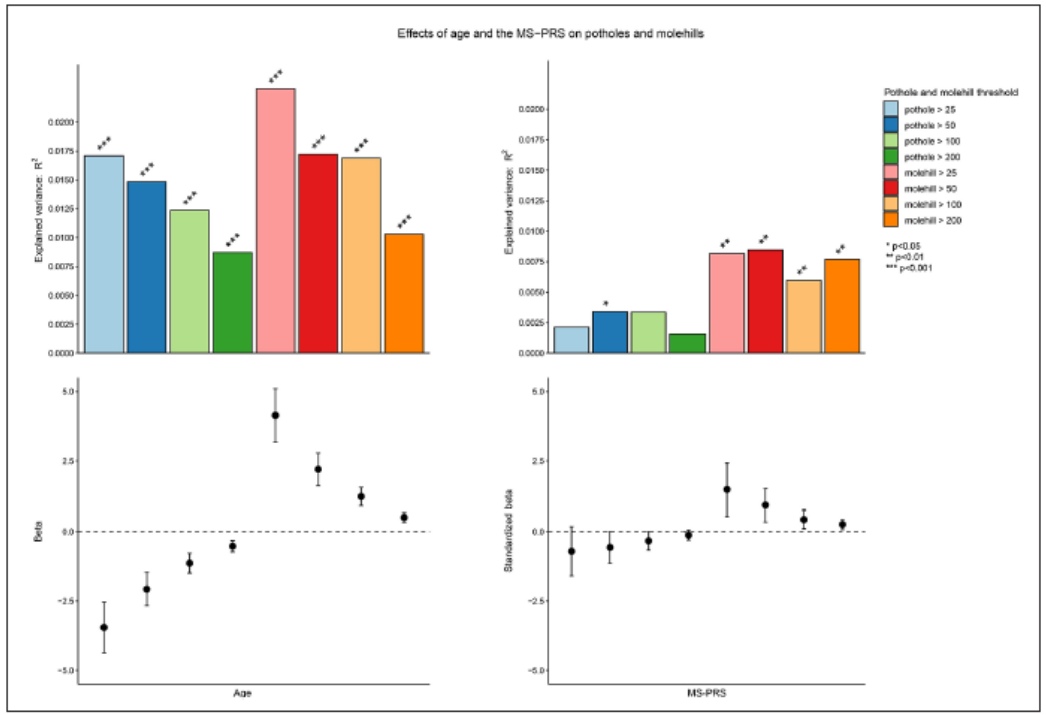
MS risk scores influences brain growth in normal children



Louk de Mol et al., 2022 ***Mult Scler*** 28(5):730-741

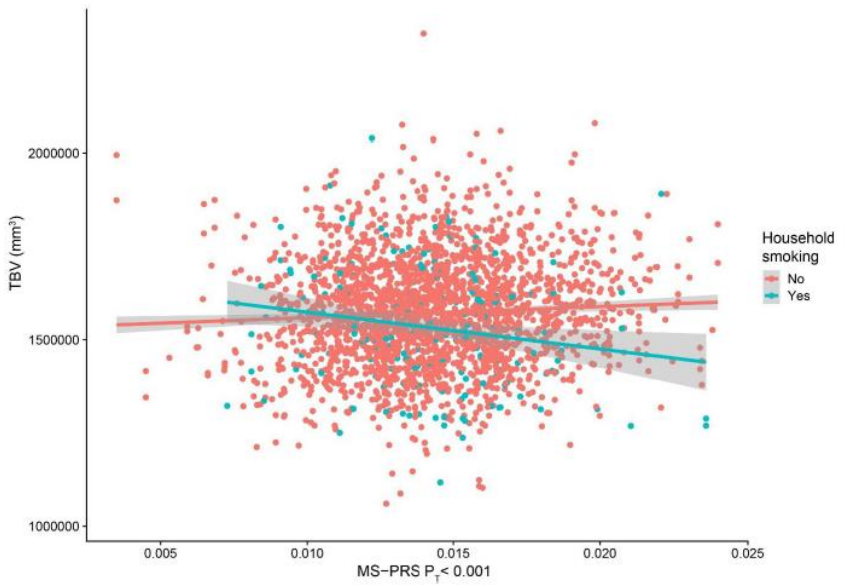


Table 3 Interaction effects between MS-PRS and parental smoking on brain volumes

Determinant	Outcome	β	SE	P value
P_T<0.001 * Parental smoking	TBV	−0.21	0.095	**0.02**
P_T<0.001 * Parental smoking	Subcortical GM volume	−0.17	0.070	**0.01**
P_T<0.001 * Parental smoking	Thalamus volume	−0.22	0.075	**3.19×10^{-3}**

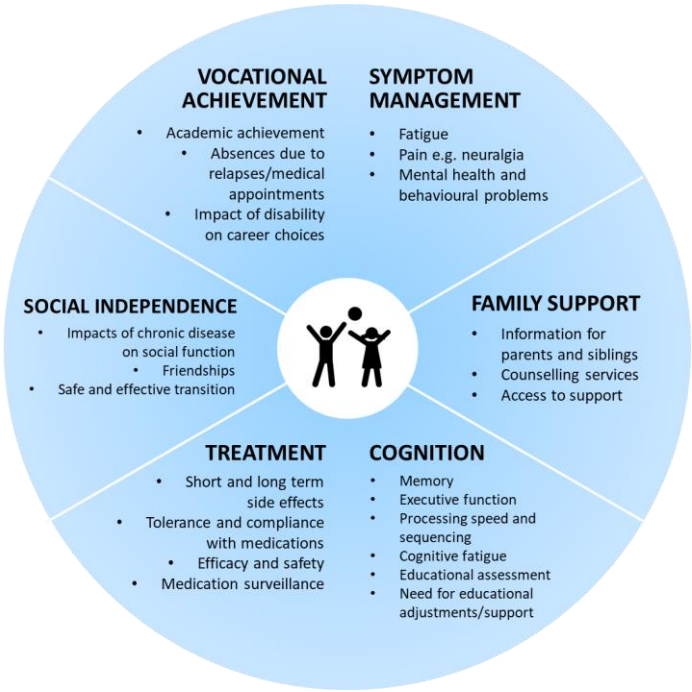
Louk de Mol et al., 2024 J Neurol Neurosurg Psychiatry Dec 10:jnnp-2024-335053

Environmental factors influencing chronic inflammation?

Table 1 | **Established and possible lifestyle and environmental risk factors for MS**

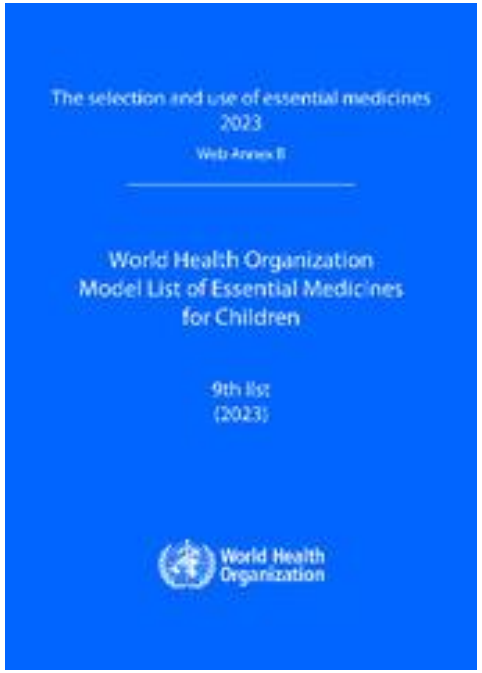
Factor	OR	HLA gene interaction	Combined OR (nongenetic factor + HLA allele)	Effect during adolescence	Immune system implied	Level of evidence
Smoking	~1.6	Yes	14	No	Yes	+++
EBV infection (seropositivity) ★	~3.6	Yes	~15	Yes	Yes	+++
Vitamin D level <50 nM ★	~1.4	No	NA	Probably	Yes	+++
Adolescent obesity (BMI >27 at age 20 years) ★	~2	Yes	~15	Yes	Yes	+++
CMV infection (seropositivity) ★	0.7	No	NA	Unknown	Yes	++
Night work	~1.7	No	NA	Yes	Yes	++
Low sun exposure ★	~2	No	NA	Probably	Yes	++
Infectious mononucleosis ★	~2	Yes	7	Yes	Yes	++
Passive smoking	~1.3	Yes	6	No	Yes	+
Organic solvent exposure	~1.5	Unknown	Unknown	Unknown	Unknown	+
Oral tobacco/nicotine	0.5	No	NA	Unknown	Yes	+
Alcohol	~0.6	No	NA	Unknown	Yes	+
Coffee	~0.7	No	NA	Unknown	Yes	+

Olsson et al., 2017 ***Nat Rev Neurol.*** 13(1):25-36



Luchesa-Smith et al ., 2022
Arch Dis Child 107(3):216-222

Global impact of paediatric MS



Barriers to diagnosis

- Lack of awareness MS symptoms among the public and healthcare professionals
- Access to specialist
  - 1 vs 0.007 per 100,000 population
- Access to health care technology
  - 55 Vs 0.3 MRI scanners per million population

Barriers to treatment

- Cladribine, Rituximab, Glatiramer acetate on essential medicines list
- Limitations of licensing
- Cost and expertise

Ann Yeh, Helen Tremlett, Rabporn Suntornlohanakul, Daniela Castillo-Villagran, Beyza Ciftci, Silvia Tenembaum, Andrea Savaransky, Lekha Pandit, Ming Lim (In Press ***Lancet Child Adolesc Health***)

Conclusion

- MS care has change significantly in the last decade
- Treatment in children should be initiated as quickly as possible using highly effective treatments
- Newer strategies can be employed to improve outcome better
- We are not reaching many children globally

Brain and Spine Inflammation

Hock Sin Heng
Yaiza Hernandez
Rahul Singh
John Gadian
Ani Almoyan
Giulia Bravar
Sarah Rudeback
Renata Paolilo
Aphra Luchesa Smith
Susan Byrne
Tatia Gakharia
Sonia Khamis

Thomas Rossor
Michael Eyre
Vanessa Lee
Claire Thompson
Sarah Crichton
Sirrane VishnuVardhan
Naomi De Souza
Christina Benetou

Children's Neurosciences

Sarosh Irani; J Palace;
Patrick Waters; M Leite

Evelina Paediatric Research

Tom Arichi, David Edwards, Jo Hajnal, **David Carmichael**, Enrico De Vita

European Network on Rare Primary Immunodeficiency, AuToinflammatory and Autoimmune diseases

Service de neurologie pédiatrique, Hôpitaux Universitaires Paris Sud, Le Kremlin Bicêtre

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Abdel-Mannan O, Absoud M, Ambergaonkar G, Anand I, Byrne S, Chitre M, Chong WK, Crichton S, De Goede C, Eyre M, Forsyth R, Gadian J, Garrood I, Gilmour S, Gray V, Hacohen Y, Hansen K, **Hemingway C**, Hussain N, Israni A, Jones G, Kneen R, Lim MJ, Livingston J, Mankad K, Mordekar S, Nischal K, Ram D, Rossor T, Vassallo G, West S, Whitehouse W, Williams H, Wassmer E

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