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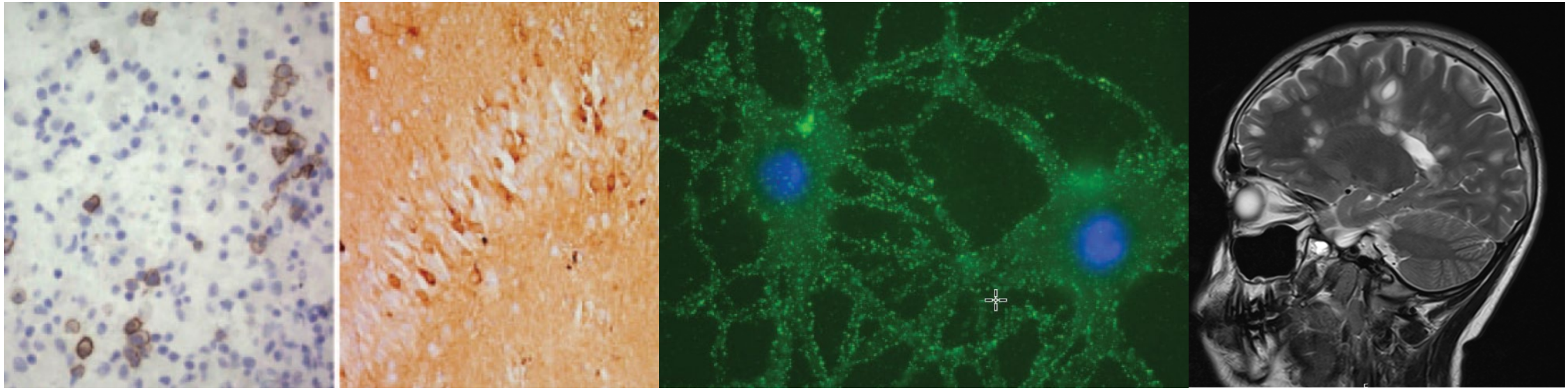
Neuropädiatrie Kinderspital Luzern

Institut für Sozial- und Präventivmedizin, Universität Bern

Pediatric Inflammatory Brain Diseases

Current Management



PD Dr. med. Sandra Bigi, MSc, Leitende Ärztin und Abteilungsleitung Neuropädiatrie

23.10.2023

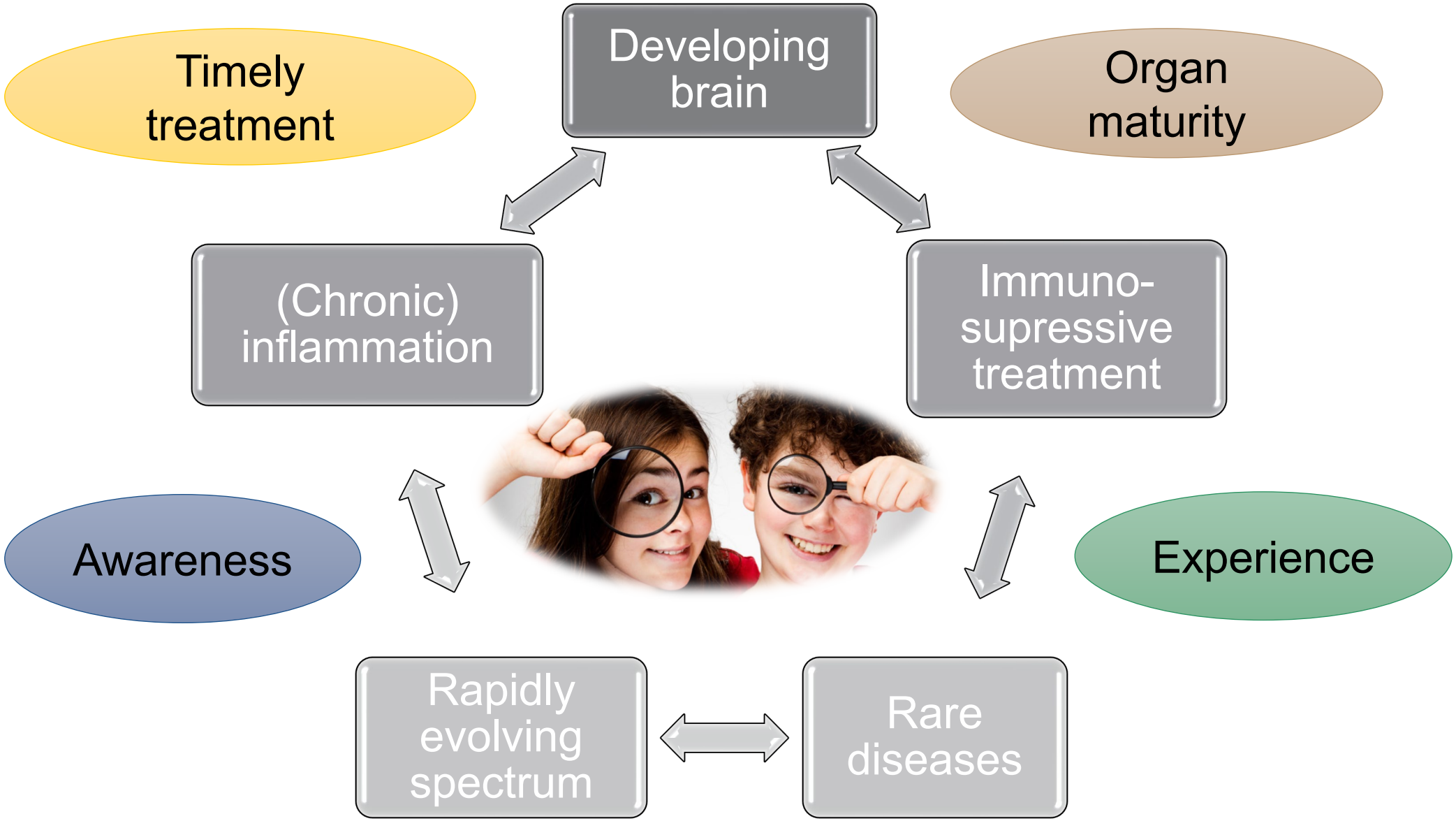
Disclosures

Research support from:
- Swiss MS Society
- Novartis
- Sanofi Genzyme
- Roche
- Biogen

Member of the SC of the Medico-scientific advisory Board of the Swiss MS Society
EPNS Board Member

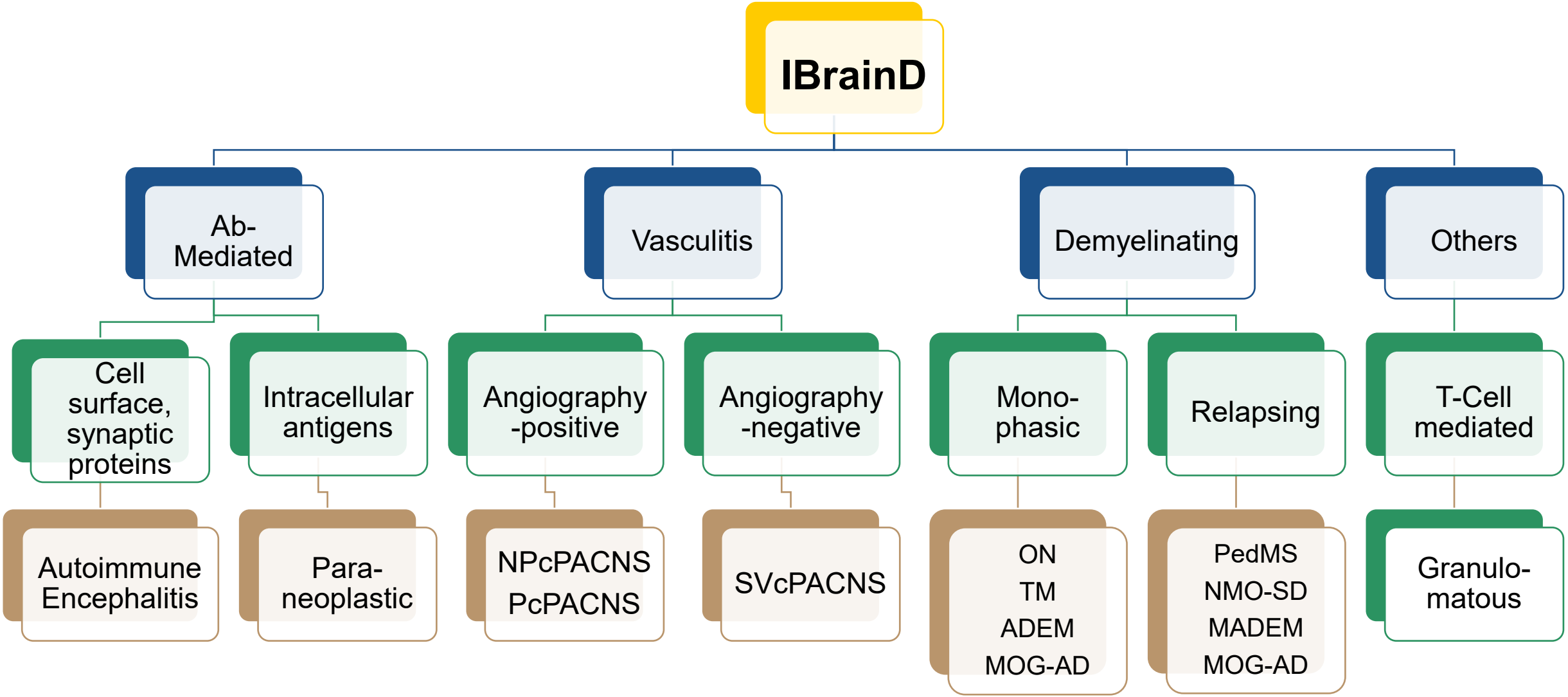
Outline

Setting the scene	Considerations in treating pediatric inflammatroy brain diseases
Managing selected entities	Autoimmune encephalitis Pediatric onset multiple sclerosis MOG-AD
Summary	Where to go from here


Timely treatment
Developing brain
Organ maturity
(Chronic) inflammation
Immuno-supressive treatment
Awareness
Experience
Rapidly evolving spectrum
Rare diseases

Goals in managing pediatric IBrainD

- Hetergeneous pot of phenotypically overlapping rare, sometimes very aggressive diseases
- Individually tailored treatment plan depending on underlying pathomechanisms
- Protect developing brain from ongoing chronic inflammation



SVcPACNS: Small vessel childhood primary angiitis of the CNS
NPcPACNS: Non-progressive childhood primary angiitis of the CNS
PcPACNS: Progressive childhood primary angiitis of the CNS.

Antibody-mediated IBrainD

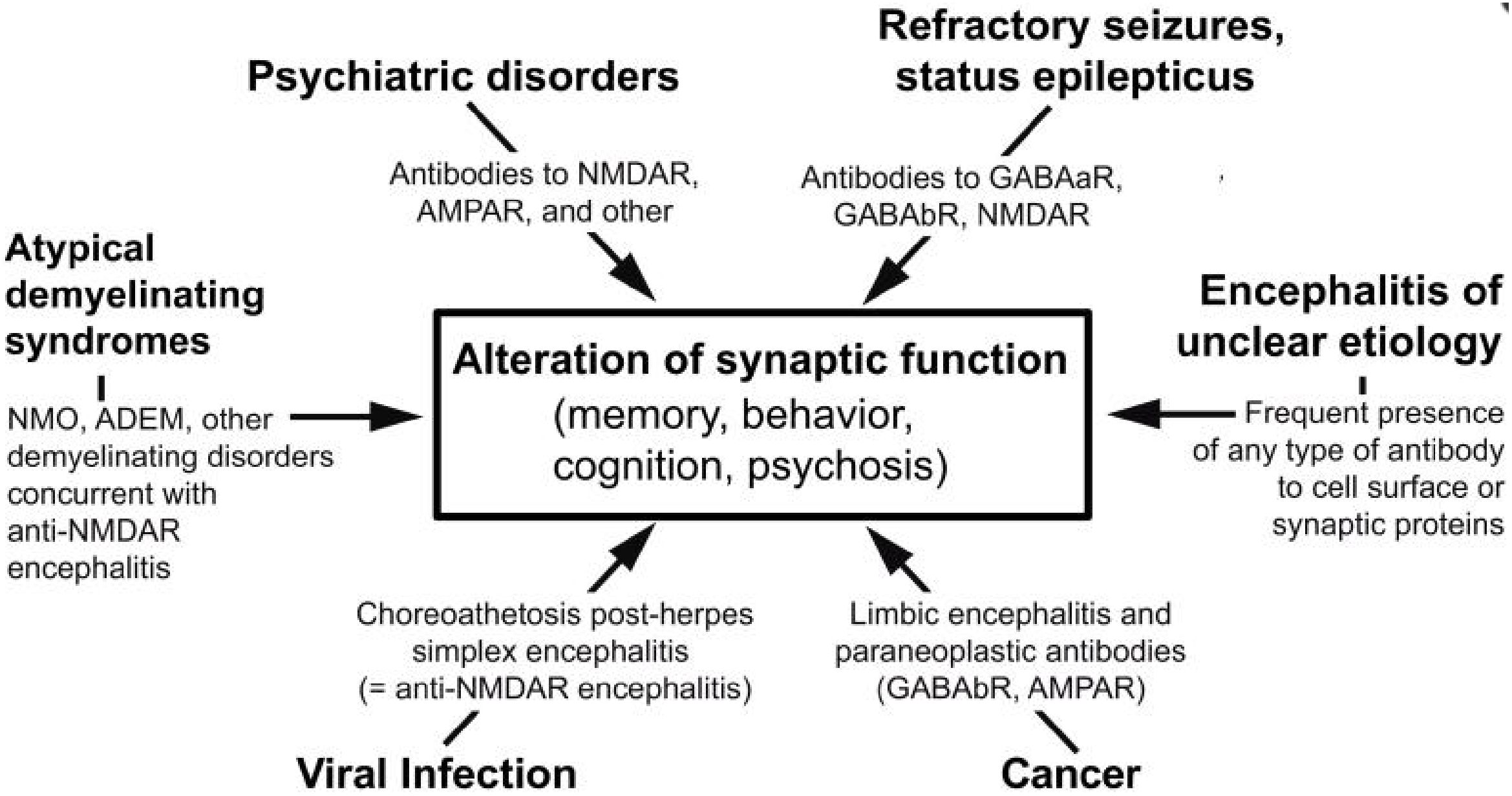
Classical paraneoplastic disorders with antibodies against intracellular antigens

Rare
Associated with malignancies
Older people
Antibody:
Cytotoxic T-cell-response
Monophasic
Treatment effect: limited

Autoimmune encephalitis with antibodies against cell-surface or synaptic proteins

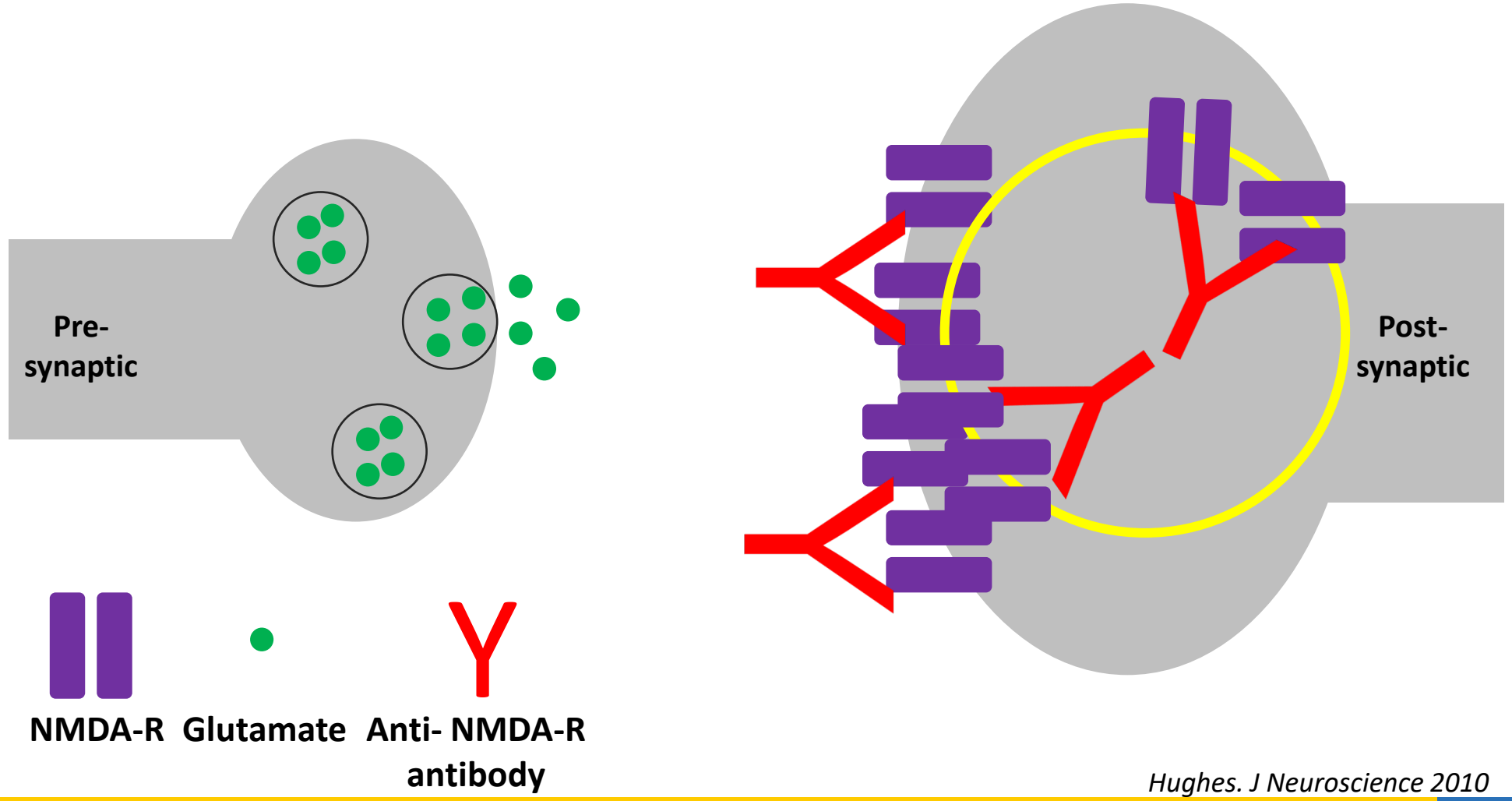
«more frequent»
Variable association with malingnancy
All age groups affected
Antibody:
Direct interaction with target antigen
Relapsing (20%)
Treatment effect: good

Adapted from Lancaster E. et al.; Neurology; 2011



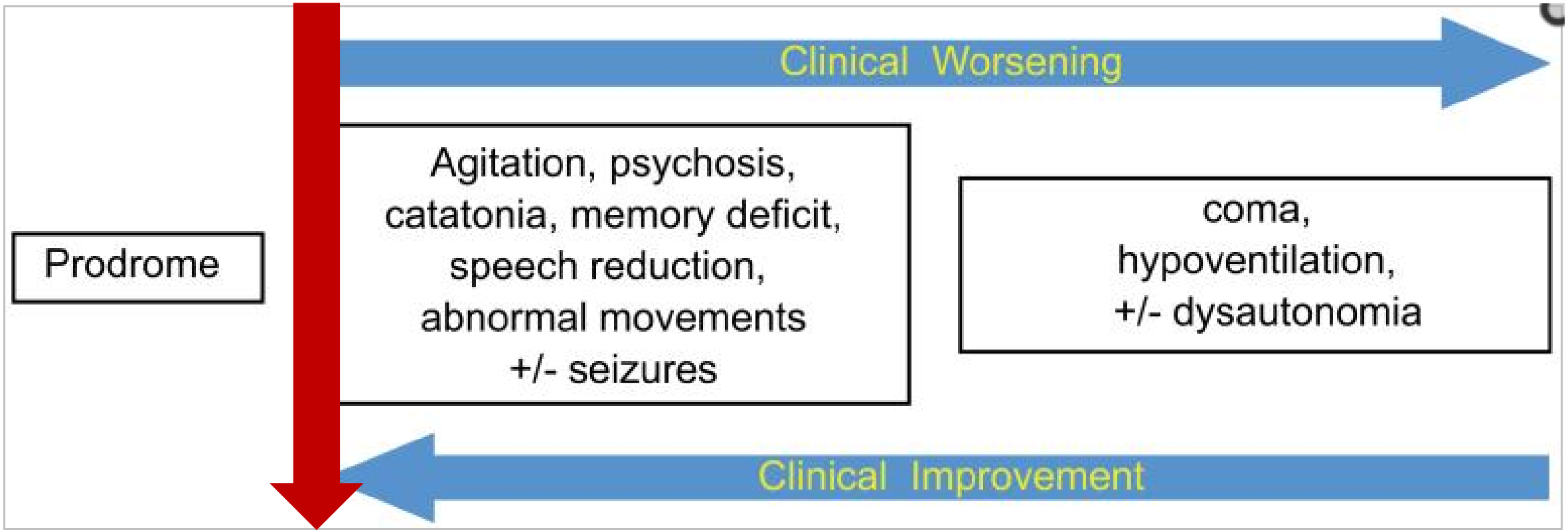
Leypoldt F et al; Ann NY Acad Sci; 2015

Antibody Cross-Link
→ NMDA-Receptor internalisation
↓ NMDA-Receptor-density between synapses



Hughes. J Neuroscience 2010

Awareness – Faster diagnosis



1. Leypoldt F et al; Ann NY Acad Sci; 2015

Awareness – Recognizing phenotypes

TABLE 1.
Proposed Classification of Phenotypes of Anti–*N*-Methyl-D-Aspartate Receptor Antibody Encephalitis According to Symptom Severity*

Classification	Seizures	Movement Disorder	Catatonia	Agitation/Aggression	Bizarre Behaviors
Type 1: "classic" (Patients 1 and 2)	Moderate	Moderate	Slight-moderate	Moderate	Slight-moderate
Type 2: "psychiatric" (Patients 3-5)	Slight	Slight-moderate	Slight or not present	"Severe"	"Severe"
Type 3: "catatonic" (Patients 6-8)	Slight-moderate	"Severe"	"Severe and/or prolonged"	Slight-moderate	Slight or not present

* Slight symptom severity defined as minimally present. Moderate symptom severity defined as present either some of the time and/or approximately 50% of the time. Severe symptom severity defined as present for most of the time. Prolonged symptom severity as referring to catatonia is defined as lasting >60 days.

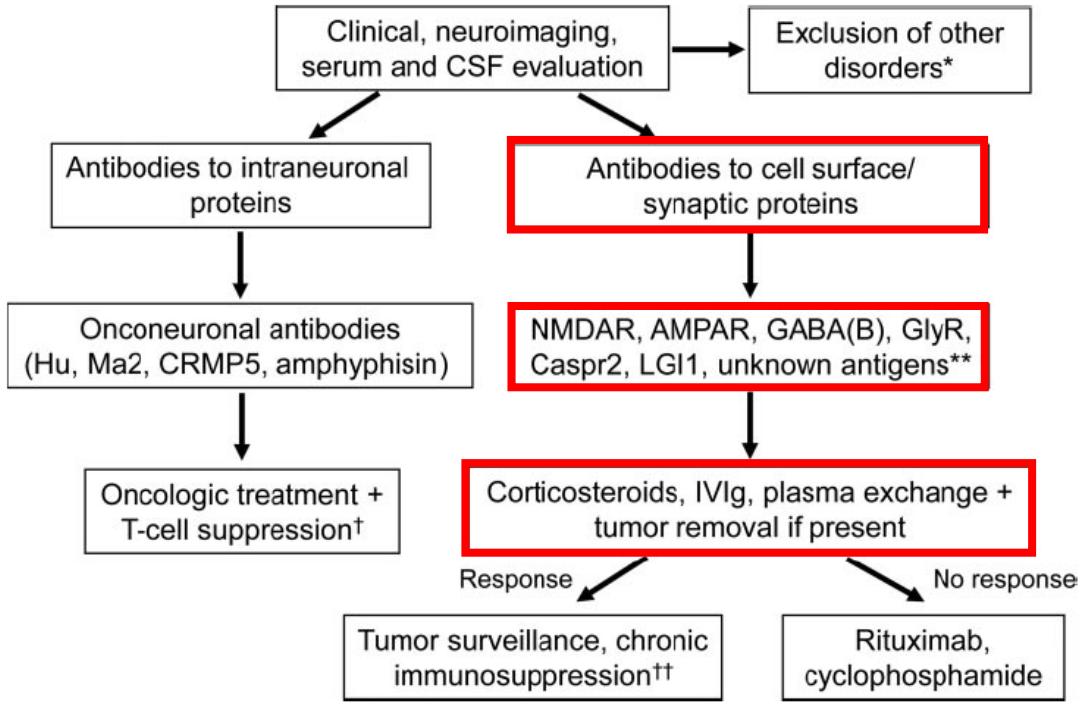
1. DeSena A et al; Ped Neurol; 2014

Time point of treatment initiation

- Definitive antibody testing **should not prevent** the initiation of immunotherapy:
  - **High index of suspicion** for AE
  - **Early treatment** leads to **better outcomes** and a reduction in relapse rate

Figure 5 Algorithmic approach to diagnosis and treatment of encephalitis with antibodies to intracellular and cell surface neuronal antigens

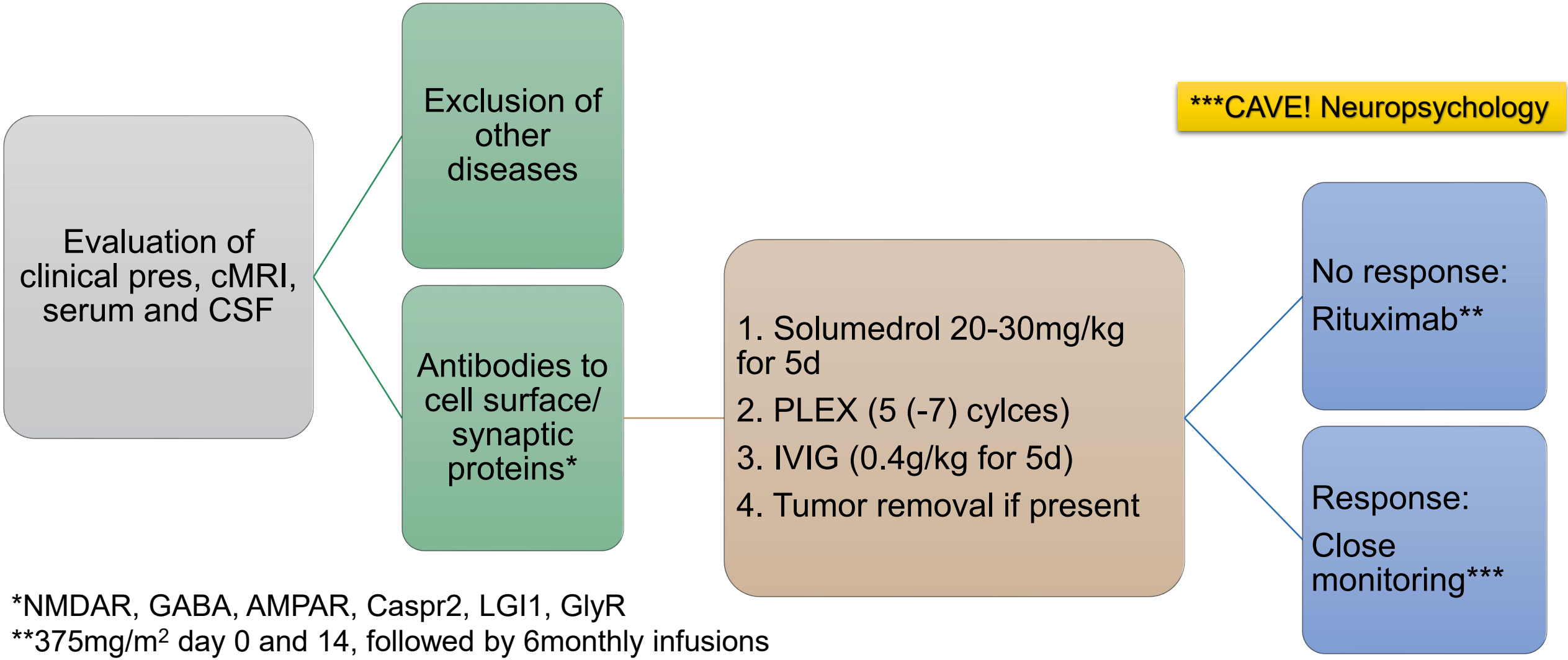
Lancaster E et al; ***Neurology*® 2011;77:179–189**



Hardy D; Ped Neurol 2022

Management of pediatric Ab-mediated IBrainD

Adapted from: Lancaster E; Neurology; 2011



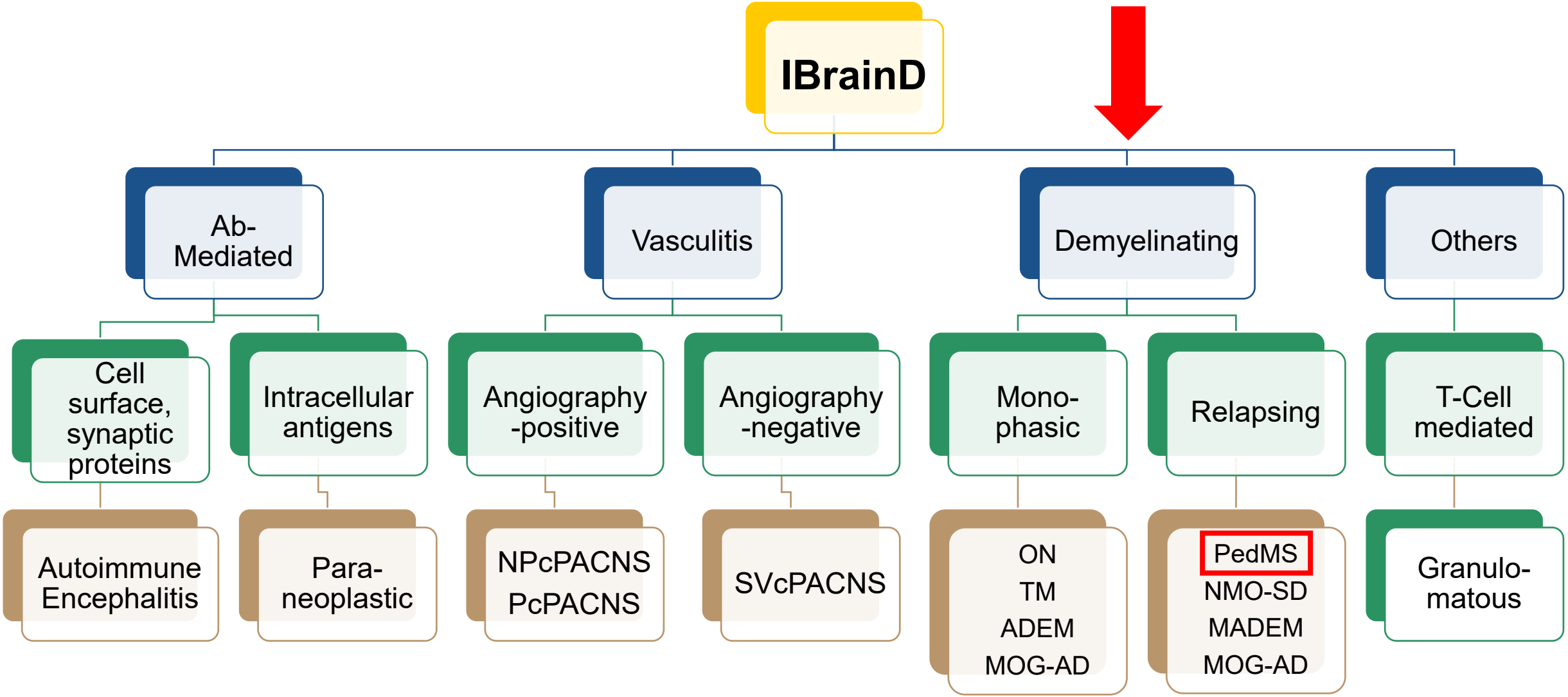
*NMDAR, GABA, AMPAR, Caspr2, LGI1, GlyR

**375mg/m^2 day 0 and 14, followed by 6monthly infusions

Cave Rituximab (CD20 depleting agent)

- Administration only in centers with experience and with standardized infusion plans
- Can lead to severe allergic reactions, particularly during the first application
- Requires regular laboratory follow-up every 3 months*
- Secondary immunoglobulin deficiency
- Increased risk of infections and poor response to vaccinations (no live vaccines)

*BB-Diff, mit Lymphozytensubpopulationen, Immunglobuline (IgA, IgG, IgM), freie Leichtketten i.S. (Kappa+Lambda, Ratio), ALAT, ASAT, GGT, Bilirubin, Crea/Hst GFR, Urinstatus



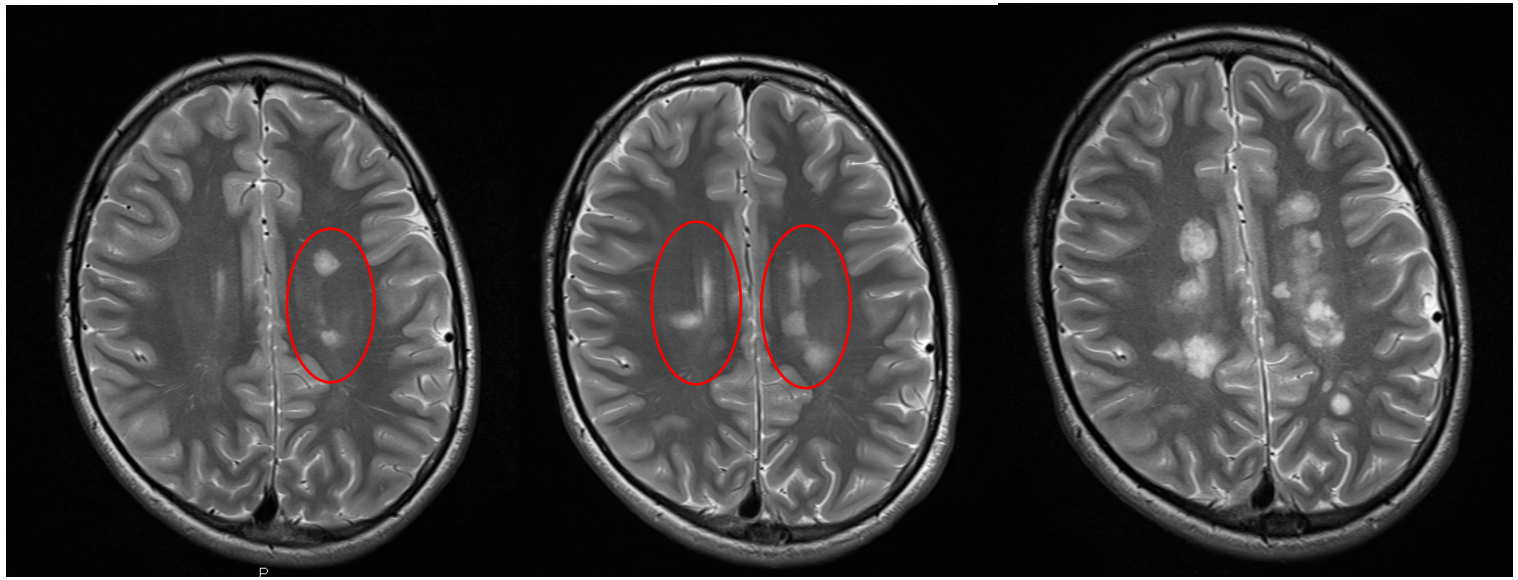
SVcPACNS: Small vessel childhood primary angiitis of the CNS
NPcPACNS: Non-progressive childhood primary angiitis of the CNS
PcPACNS: Progressive childhood primary angiitis of the CNS.

Management of acute demyelinating attacks in the pediatric population: A Swiss consensus statement

Hofer S et al.; CTN 2021, 5, 17

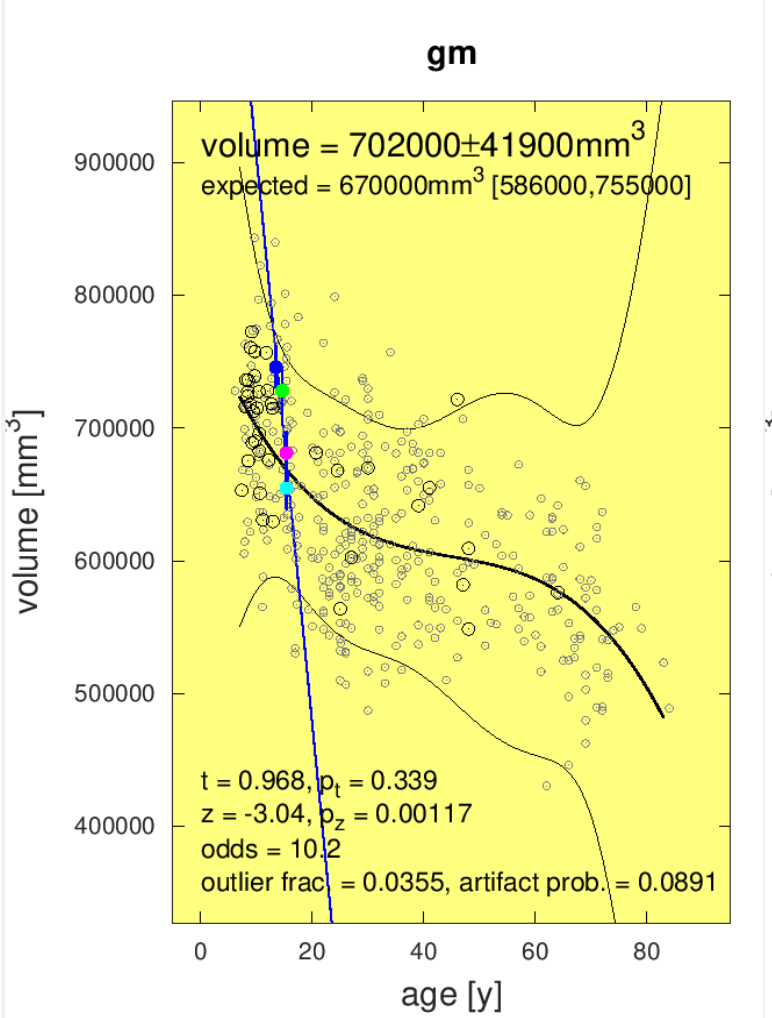
First-line treatment	**i.v. MP 20-30 mg/kg/die (max 1000mg/die) for 5 days***	**in selected cases: if restitutio ad integrum after 3 days, consider stopping early*
Use of oral prednisone taper	ON + TM + RRMS	No
	ADEM	Yes, 4-6 weeks
	NMO-SD	Maintanace therapy until longterm immunosuppression established (Prednisone 1 mg/kg/die for 2-6 months)
Second-line therapy	ON + RRMS	Repeat first line treatment → Plasma exchange
	ADEM	Plasma exchange / (IVIG)
	TM + NMO-SD	Plasma exchange

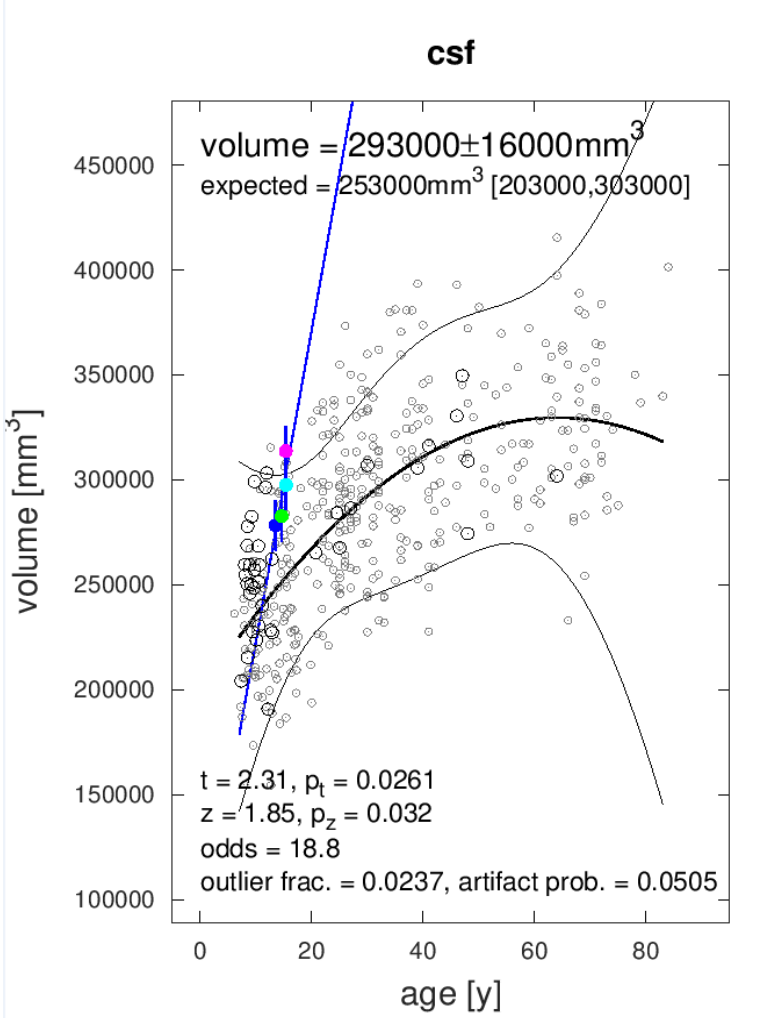
Clinical vignette – «natural history»



Axial T2	Axial T2	Axial T2
ttm start (IFN)	>6m after ttm start	1y after ttm stop
EDSS 1.0	EDSS 1.0	EDSS 4.5
	ttm escalation refused	«natural course»
Neuropsychology:	working memory ***IW 130***	***IW 106***

Natural course is not benign



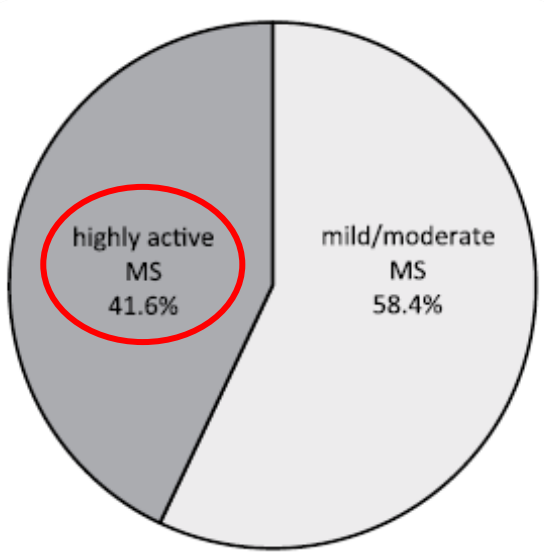


Rapid ↓ in brain volume, Rapid ↑ in csf volume/space

Courtesy of Dr. F. Wagner, Department Diagn. / Interv. Neuroradiologie, and Dr. Chr. Rummel, SCAN

Clinical characteristics – At the beginning

- Disease course and disease activity:
  - Relapsing remitting disease course in 95-100%
  - High relapse rate in early course (1.12-2.76 vs 0.3-1.78)
  - Shorter interval between first attacks
  - Rapid accrual of (infratentorial) brain lesions
  - Excellent recovery from first attacks
    - Plasticity and repair mechanisms of the developing brain



1. Renoux C et al, N Engl J Med 2007
2. O'Mahony J et al, Pediatrics 2015
3. Waldman A et al, Lancet Neurol 2014
4. Banwell B et al, Lancet Neurol 2007
5. Chitnis T et al, Mult Scler 2009
6. Yan K et al, Mult Scler Rel Dis 2020
7. Huppke P et al, Mult Scler 2017

Clinical characteristics – In the future

	EDSS 4
Time from onset to EDSS	20 y
Age at EDSS	34.6 y

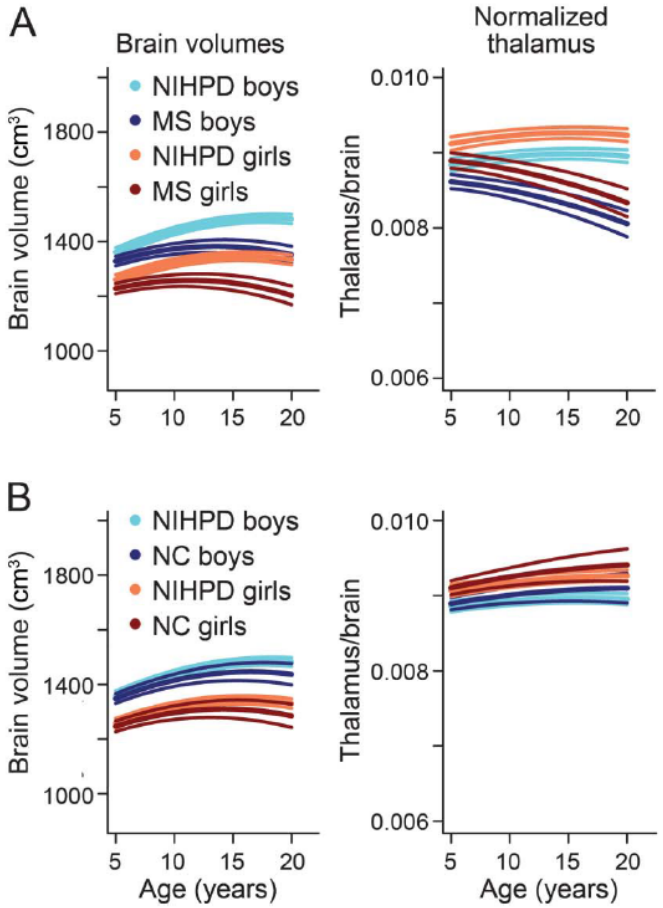
10 years younger compared to adult onset MS

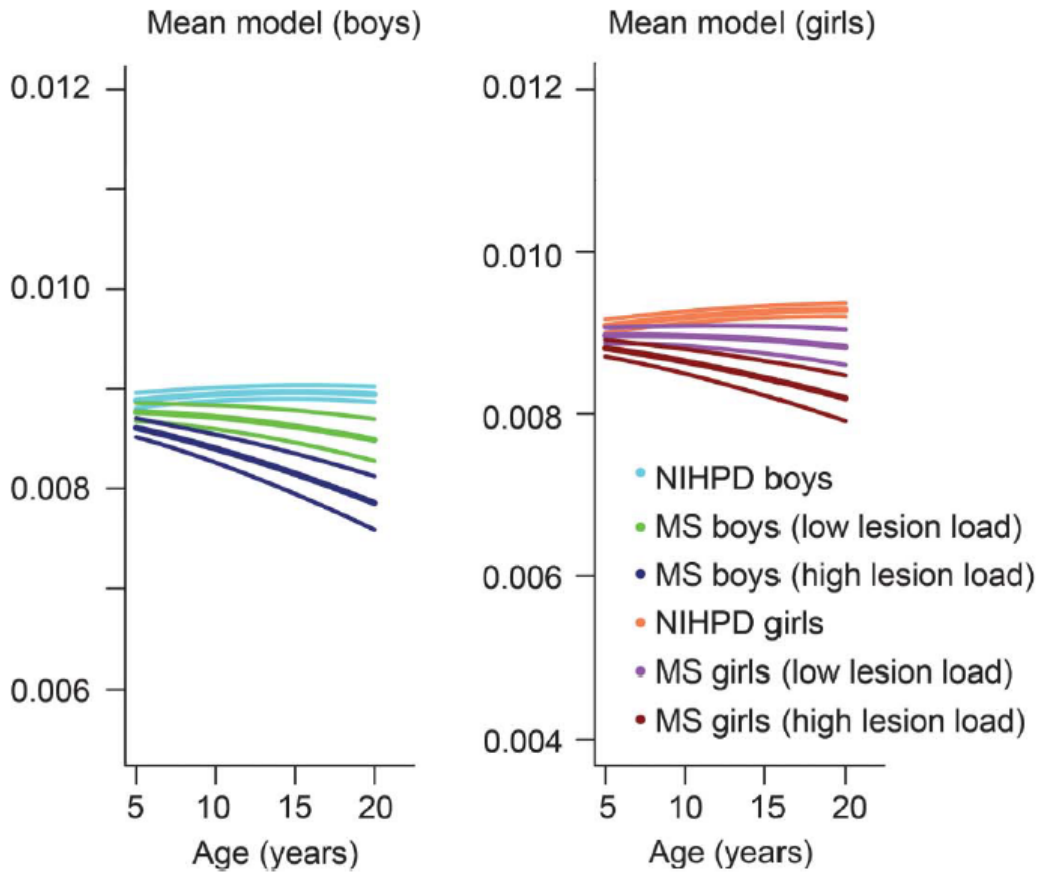
Brainstem attacks, poor recovery from a first attack and high frequency of relapses

→ increased risk of disability/secondary progressive disease course

1. Renoux C et al, N Engl J Med 2007;356:2603-13.
2. Simone et al, Neurology 59 (12), 1922-1928 (2002)
3. Waldman A et al; *Neurology, 2016*

Clinical characteristics – Impact on brain volume





1. Aubert-Broche et al. Neurology 2014

Clinical characteristics – Understand implications for therapy

- High relapse rate in early course
- Rapid accrual of inflammatory brain lesions
- Permanent disability (EDSS 4): 35 years

No reason to delay treatment in children with MS

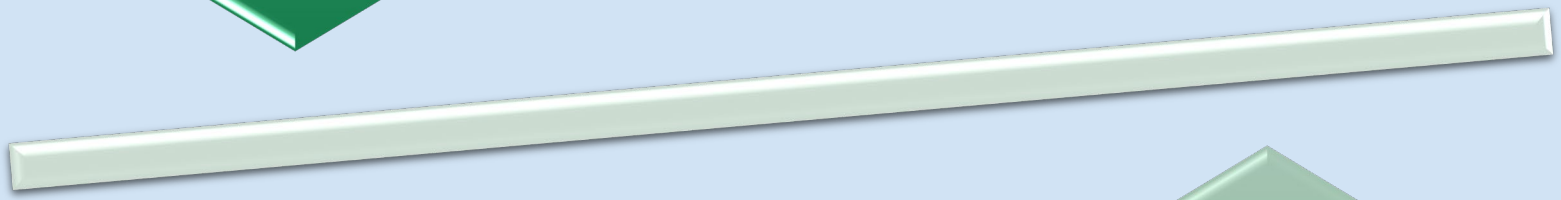
- Excellent recovery from first attack
  → no obvious disability, no disease activity/harm
  → delayed treatment start, treatment interruption

1. Venkateswaran S et al. Neurologist 2010
2. Gorman M et al. Arch Neurol 2009
3. Renoux C et al. Clin Neurol Neurosurg 2008
4. O'Mahony J et al. Pediatrics *2015*

Treatment – Strategies and paradigm shift

Induction

- Greater early disease suppression
- Limiting inflammation-mediated brain injury
- Safety?



Escalation

- Reduced potency
- Valuable in a lifelong disease
- Still valid?

1. Giovannoni G et al, Curr Opin Neurol 2018
2. Thompson AJ et al, Lancet 2018

Treatment – The role of high-efficacy treatment

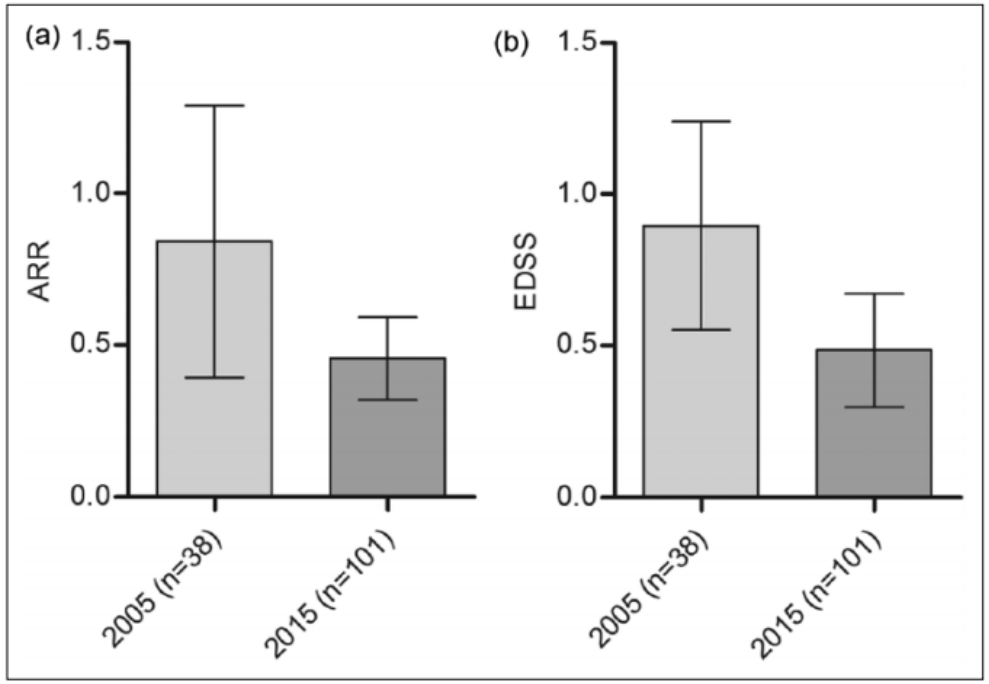
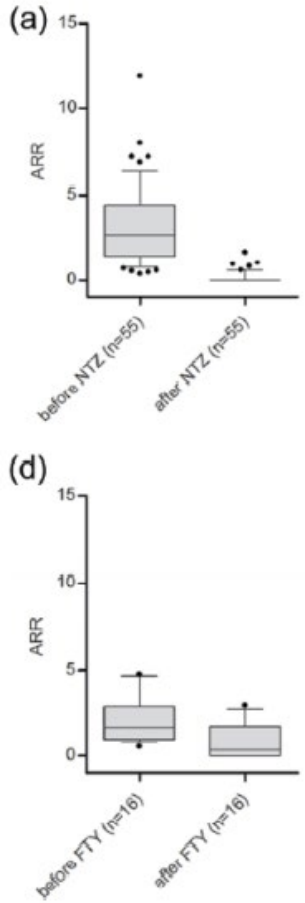
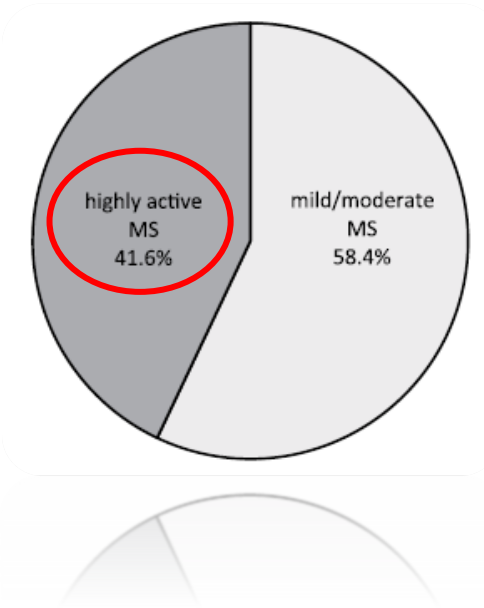


Figure 3. Effect of current treatment modalities on the clinical course of pediatric MS. (a) Relapse rate and (b) EDSS in the cohorts from 2005, all treated with first-line therapy and 2015 with 43% of patients on therapy with either NTZ or FTY. Mean with 95% CI.





1. Huppke P et al, Mult Scler 2017

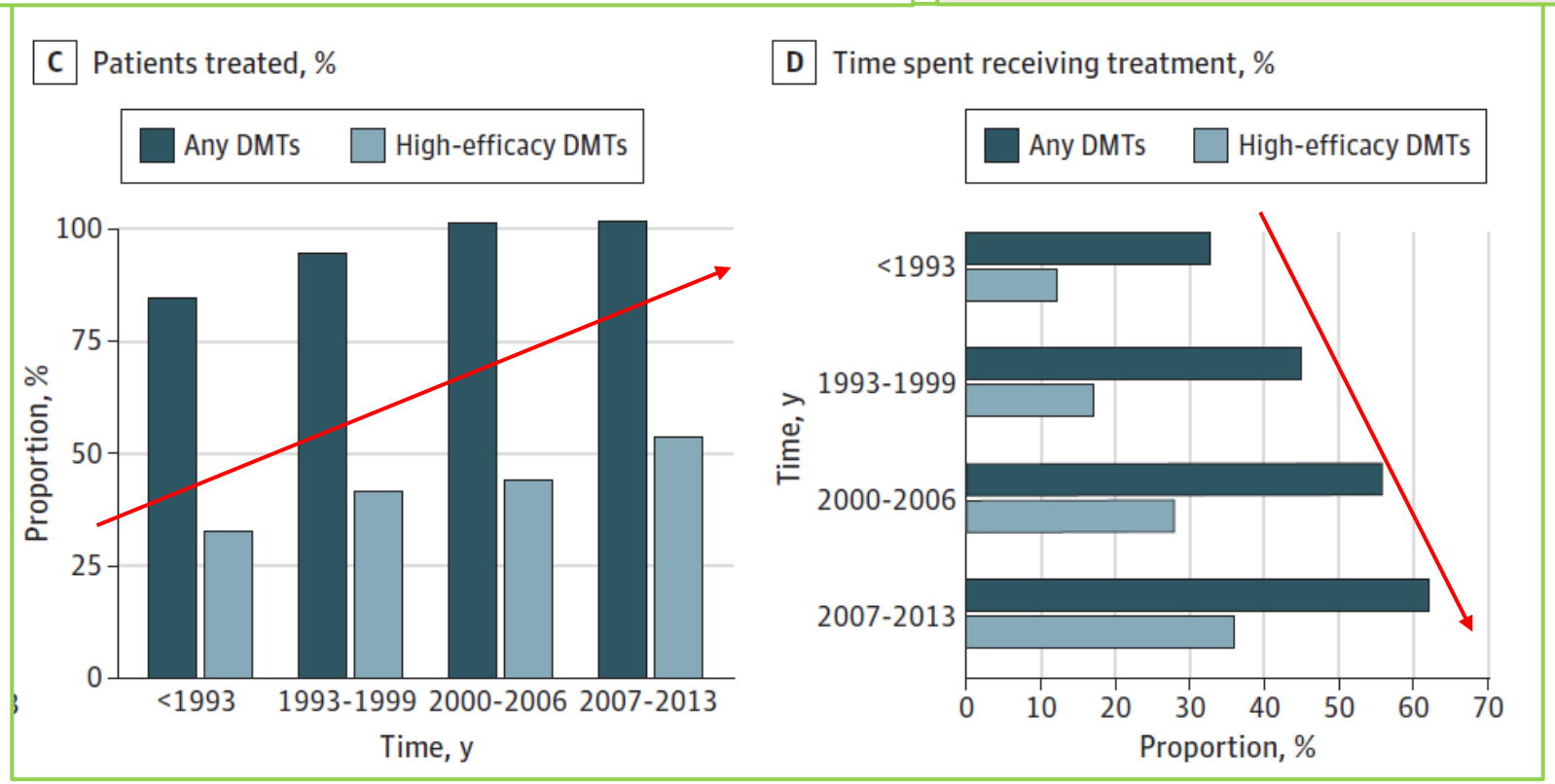
JAMA Neurology | Original Investigation

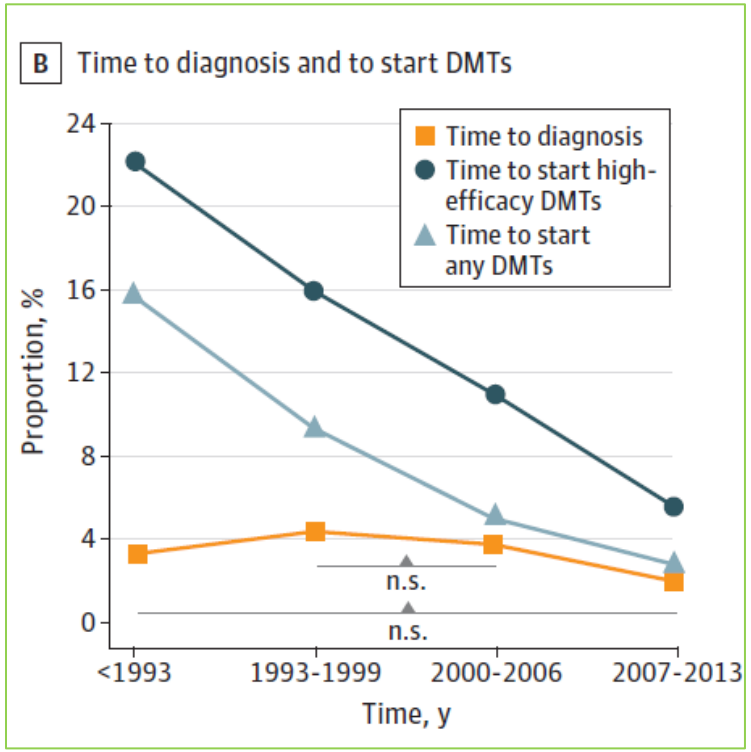
Risk of Persistent Disability in Patients With Pediatric-Onset Multiple Sclerosis

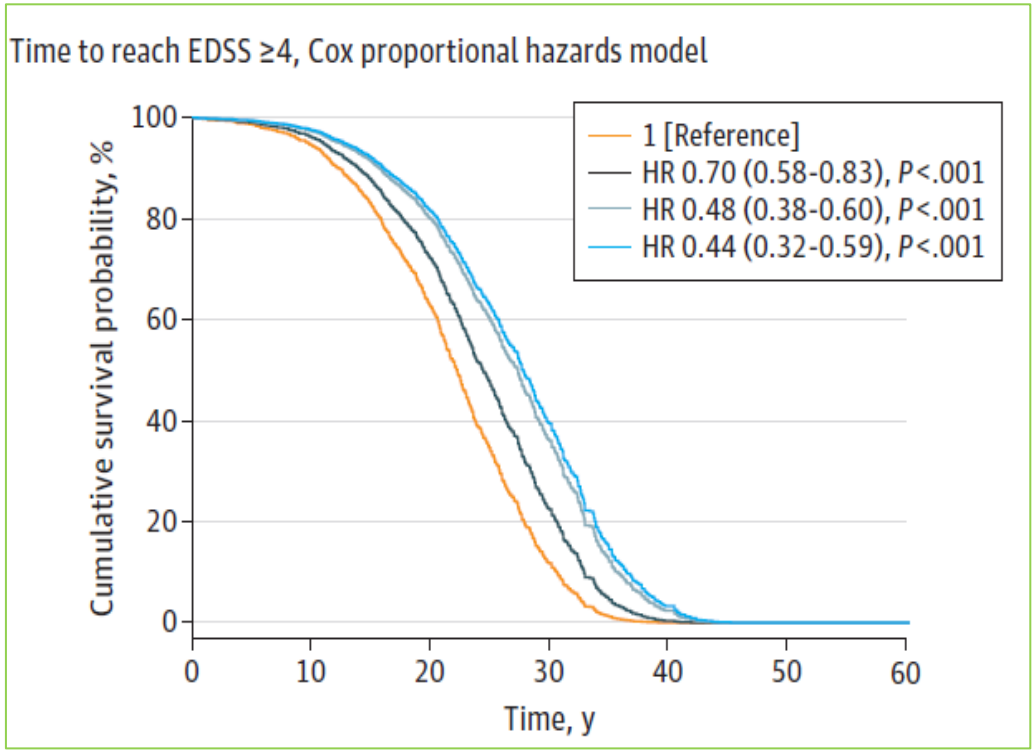
JAMA Neurol. 2021;78(6):726-735. doi:10.1001/jamaneurol.2021.1008
Published online May 3, 2021.

Damiano Baroncini, MD; Marta Simone, MD; Pietro Iaffaldano, MD; Vincenzo Brescia Morra, MD; Roberta Lanzillo, MD, PhD; Massimo Filippi, MD; Marzia Romeo, MD; Francesco Patti, MD; Clara Grazia Chisari, MD; Eleonora Cocco, MD; Giuseppe Fenu, MD; Giuseppe Salemi, MD; Paolo Ragonese, MD; Matilde Inglese, MD, PhD; Maria Cellerino, MD; Lucia Margari, MD; Giancarlo Comi, MD; Mauro Zaffaroni, MD; Angelo Ghezzi, MD; for the Italian MS registry

- Retrospective, multicenter
- More than 3000 ped onset MS patients
- Time to EDSS 4 and 6 by epoch of MS diagnosis







Findings:

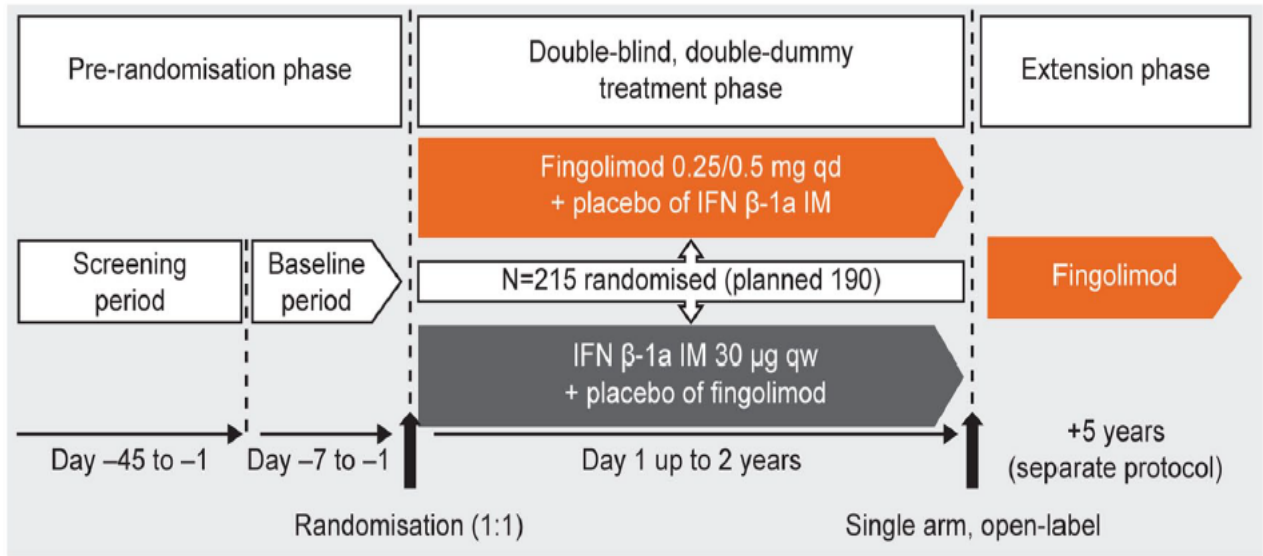
1. Use of DMT – particularly high-efficacy drugs - earlier and longer
2. Risk of persistent disability reduced by 50-70% in recent diagnosis epochs
3. Demographics & clinical disease activity at onset did not change significantly over time

JAMA Neurol. 2021;78(6):726-735. doi:10.1001/jamaneurol.2021.1008
Published online May 3, 2021.

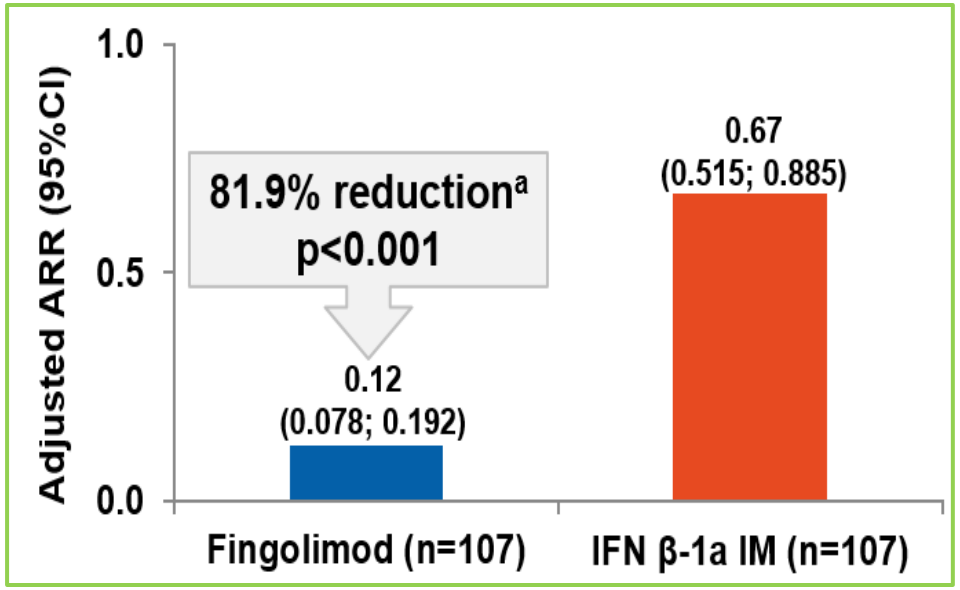
ORIGINAL ARTICLE

Trial of Fingolimod versus Interferon Beta-1a in Pediatric Multiple Sclerosis

Chitnis T et al, N Engl J Med 2018



T Chitnis, B Banwell *et al. MSJ 2021*



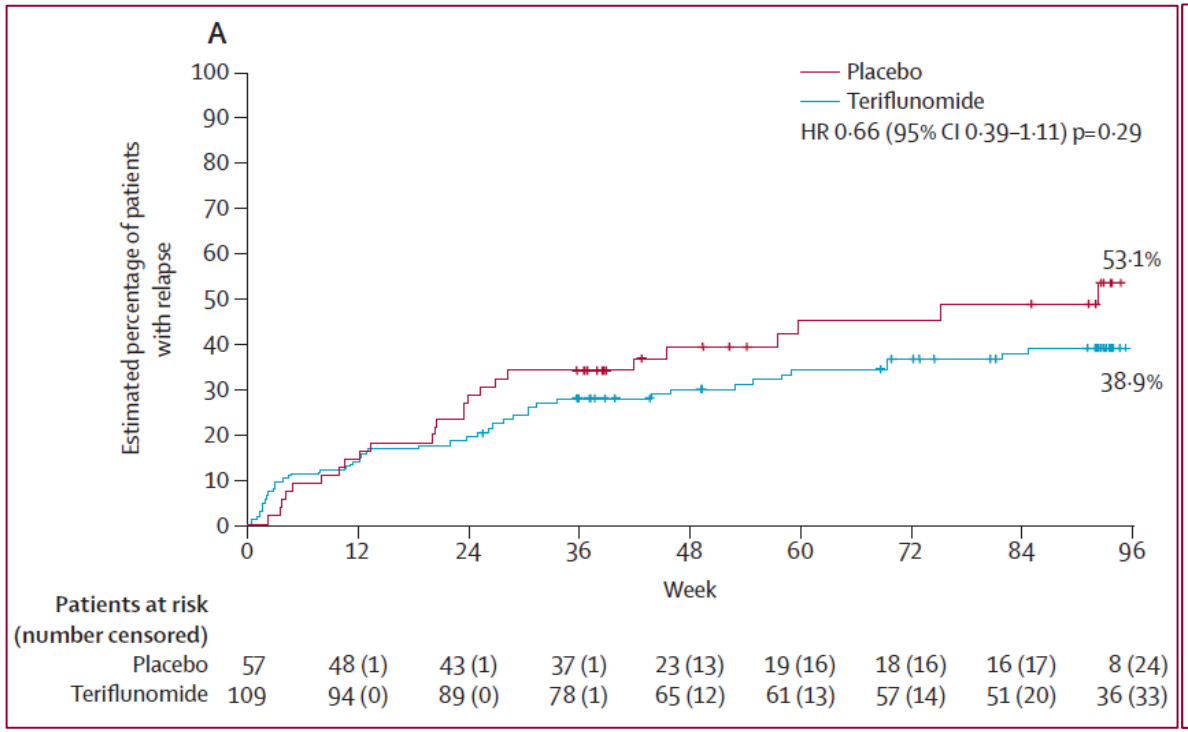
Relapse

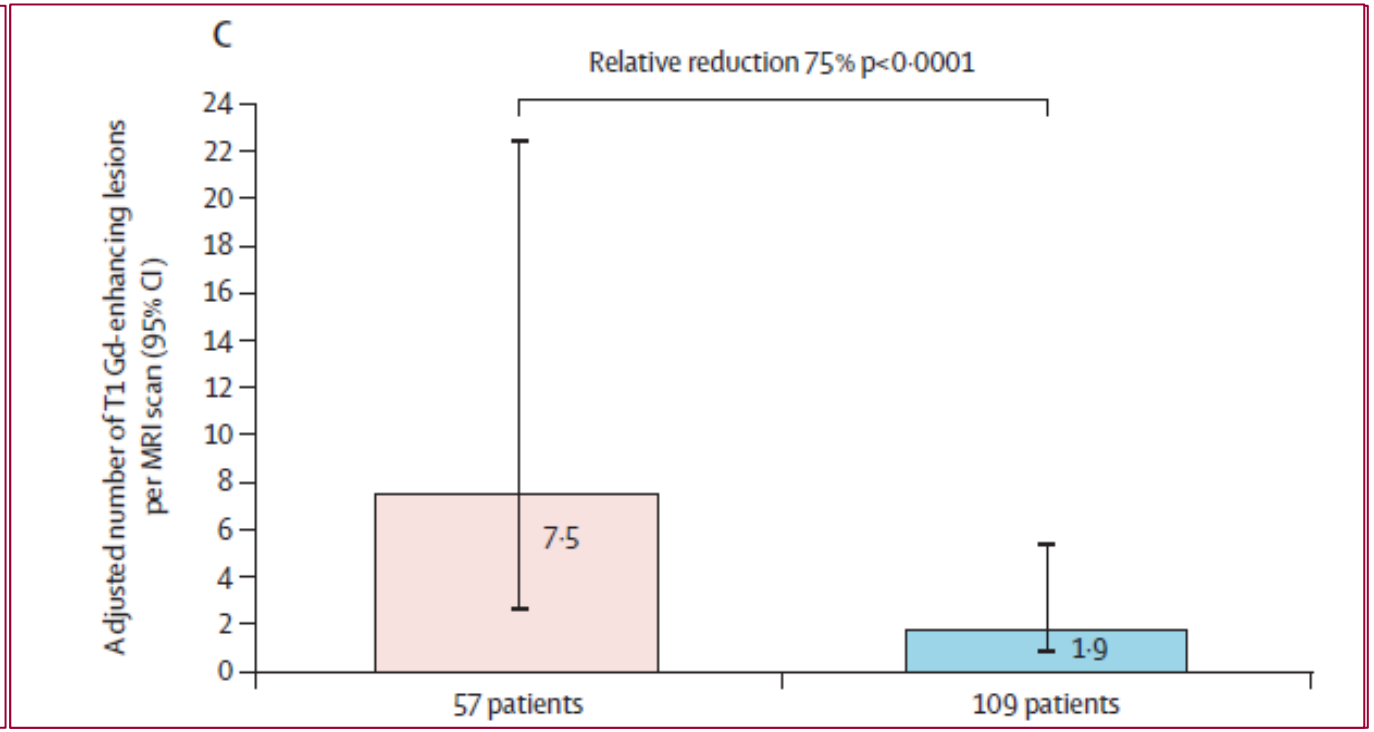
Safety and efficacy of teriflunomide in paediatric multiple sclerosis (TERIKIDS): a multicentre, double-blind, phase 3, randomised, placebo-controlled trial

Tanuja Chitnis, Brenda Banwell, Ludwig Kappos, Douglas L Arnold, Kivilcim Gücüyener, Kumaran Deiva, Natalia Skripchenko, Li-Ying Cui, Stephane Saubadu, Wenruo Hu, Myriam Benamor, Annaig Le-Halpere, Philippe Truffinet, Marc Tardieu, on behalf of the TERIKIDS Investigators

Lancet Neurol 2021; 20: 1001–11

MRI





Paediatric multiple sclerosis: a lesson from TERIKIDS

*Maria Pia Sormani, Emmanuelle Waubant

Adult results (1 phase 2, 2 phase 3 studies):

- In summary, 50% reduction of new MRI lesions and 30% reduction of ARR

TERIKIDS observed the same effect:

- Reduction of adjusted number of new/enlarged T2 lesions by 55% (p=0.00061)
- Reduction of adjusted number of new T1 Gd+ lesions by 75% (p<0.0001)
- Reduction of hazard of relapse by 34% (p=0.29)
- Approximately 600 needed for the observed effect to be significant

Substanzklasse	Medikament	Anwendung	Frequenz
Dimenthylfumarat*	Tecfidera™	Kapsel	2x Täglich
Fingolimod*	Gilenya®	Tablette	Täglich
Glatirameracetat*	Copaxone®	Spritze	Täglich
Interferone*	Avonex® Betaferon® Rebif®	Spritze	1-3x pro Woche
Teriflunamid*	Aubagio®	Tablette	Täglich
Ocrelizumab**	Ocrevus®	Infusion	Halbjährlich
Natalizumab**	Tysabri™	Infusion	Monatlich
Rituximab**	Mabthera®	Infusion	Halbjährlich

* zugelassene MS-Therapien

** Off-label MS-Therapien, die bei Kindern und Jugendlichen am häufigsten verwendet werden

Treatment – Towards an individually tailored treatment plan

- Factors influencing treatment decisions:
  - Age of the patient → patients <10y can be challenging
  - Factors affecting compliance
    - Route and mechanism of action
  - Activity of disease
  - Lesion load:
    - CAVE! infratentorial/spinal lesions
  - Recovery from first relapse

- Daily practice – “family package”:
  - Back to normality as soon as possible (patient)
  - Risk for side effects (parents)
  - Mood, fatigue and cognition require specific evaluation
  - Depressive episode in adolescents delayed
  - Loss in “body-trust” after first episode
  - Autonomy in disclosure of diagnosis

1. McGinley M et al, Neurotherapeutics 2017

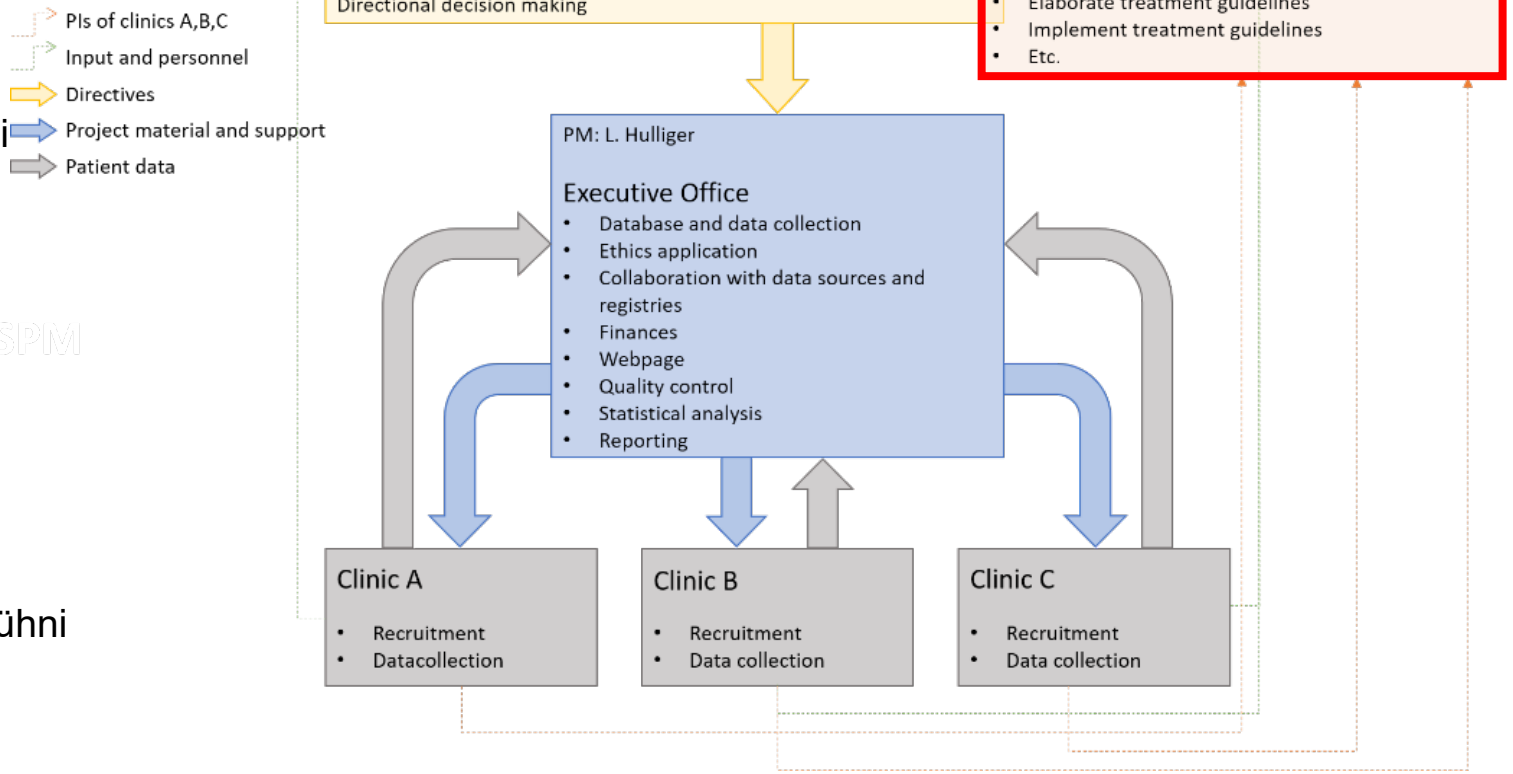
Swiss-Ped-IBrainD

Schweizer Register für entzündliche Gehirnerkrankungen im Kindesalter

SWISS PED IBRAIND
SWISS PEDIATRIC INFLAMMATORY BRAIN DISEASE REGISTRY

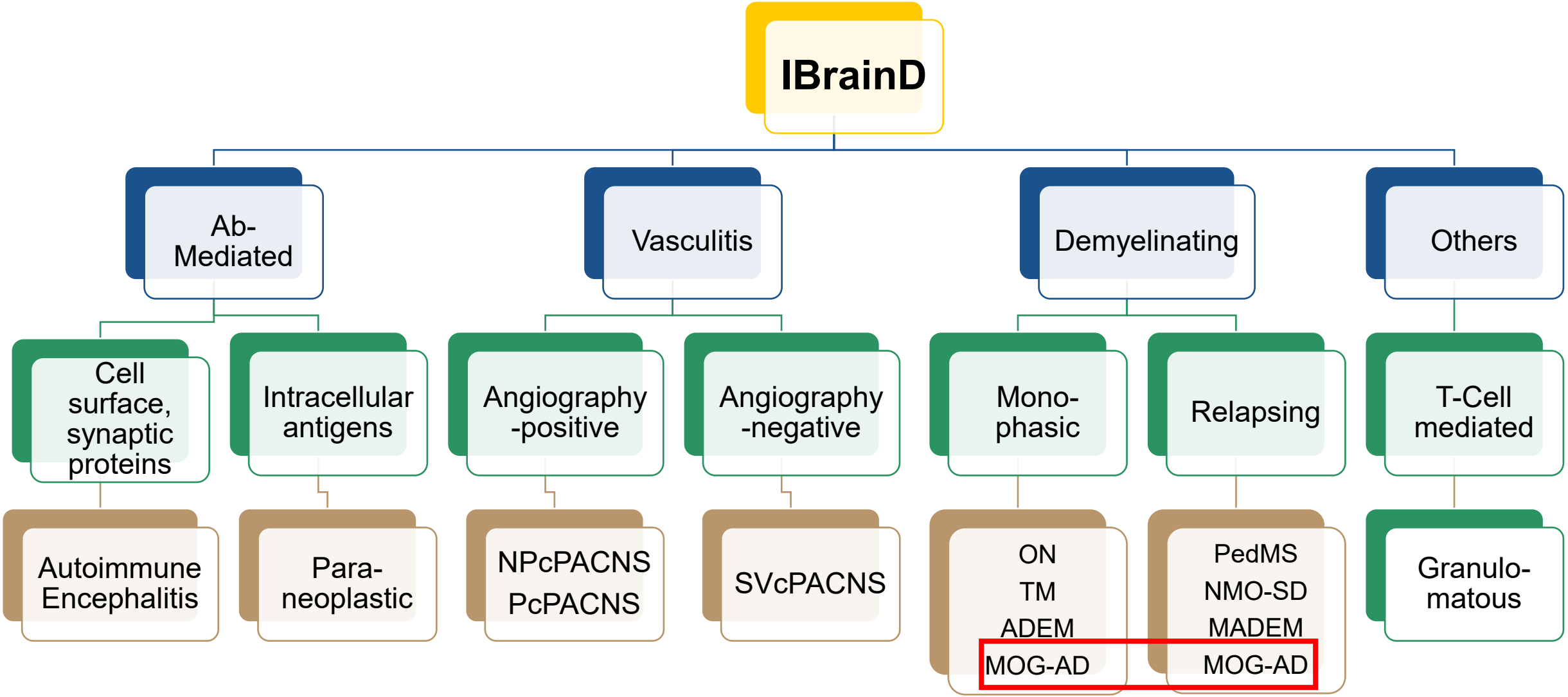
PD Dr. med. Sandra Bigi
Medical head

Prof Dr. med. Claudia Kühni
Head of CAH group



MSc Lorena Hulliger
Project manager

MSc Susanne Hofer
Data manager



SVcPACNS: Small vessel childhood primary angiitis of the CNS
NPcPACNS: Non-progressive childhood primary angiitis of the CNS
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MOG-AD – age dependent phenotypes

- Brain involvement in the young child
- ON/NMOSD-like in the older child (>9y)

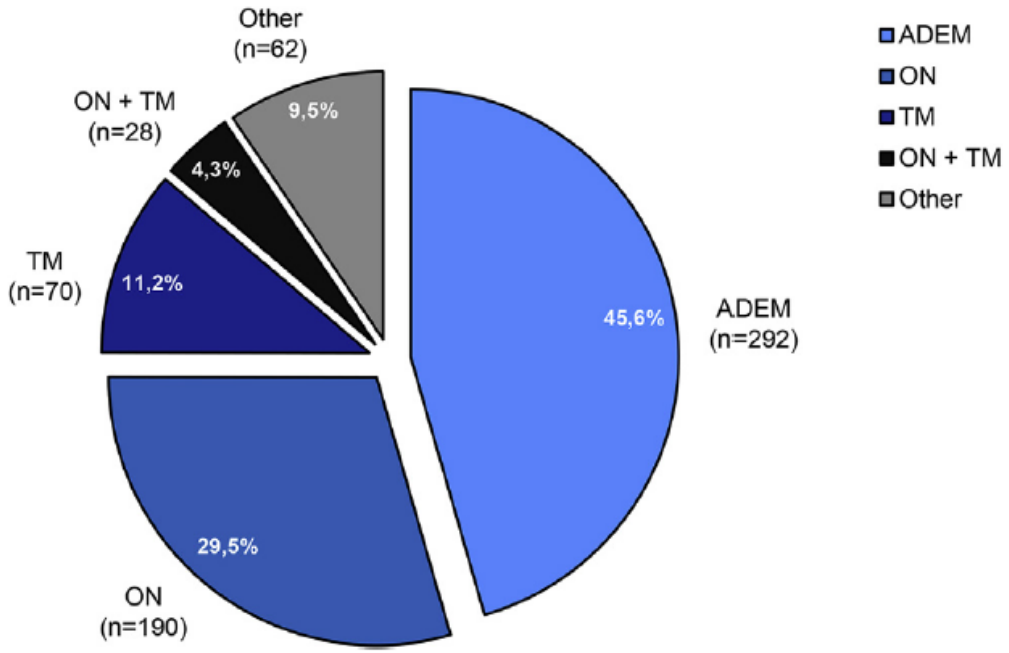


Fig. 2. Presenting clinical phenotypes within the paediatric MOGAD [11–13,17,20–27]. ADEM = acute disseminated encephalomyelitis, MOGAD = MOG-antibody-associated disorders, ON = optic neuritis, TM = transverse myelitis.

A.L. Bruijstens, C. Lechner, L. Flet-Berliac et al. EJPN 29 (2020), 2-13

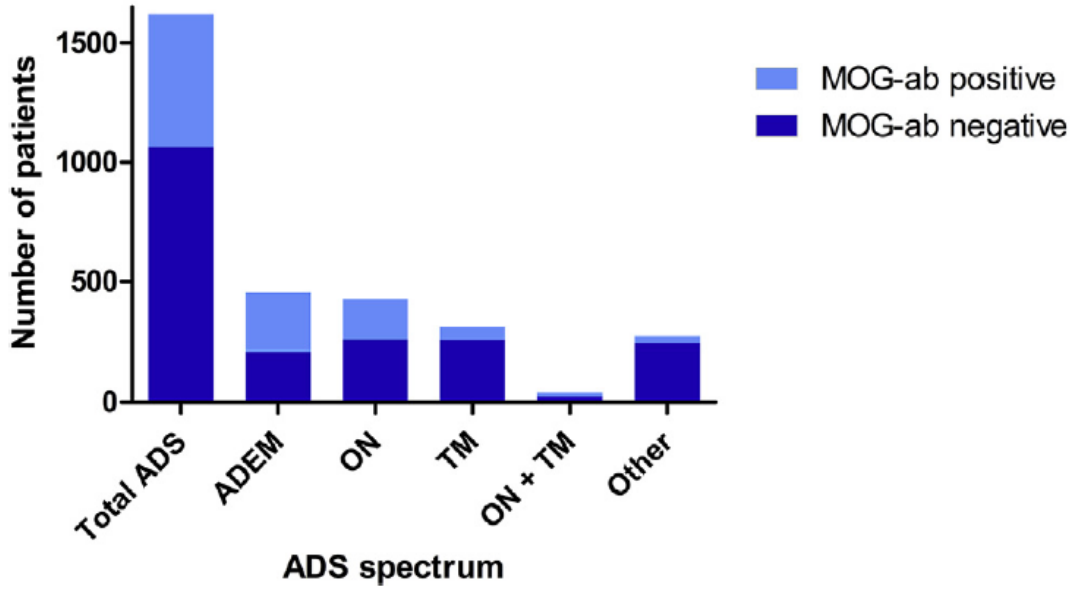


Fig. 1. ADS presenting phenotype, divided for MOG-ab-positive and negative patients [11–14,17–23].
ADEM = acute disseminated encephalomyelitis, ADS = acquired demyelinating syndrome, MOG-ab = myelin oligodendrocyte glycoprotein antibody, ON = optic neuritis, TM = transverse myelitis.

MOG-AD – Management of acute episode

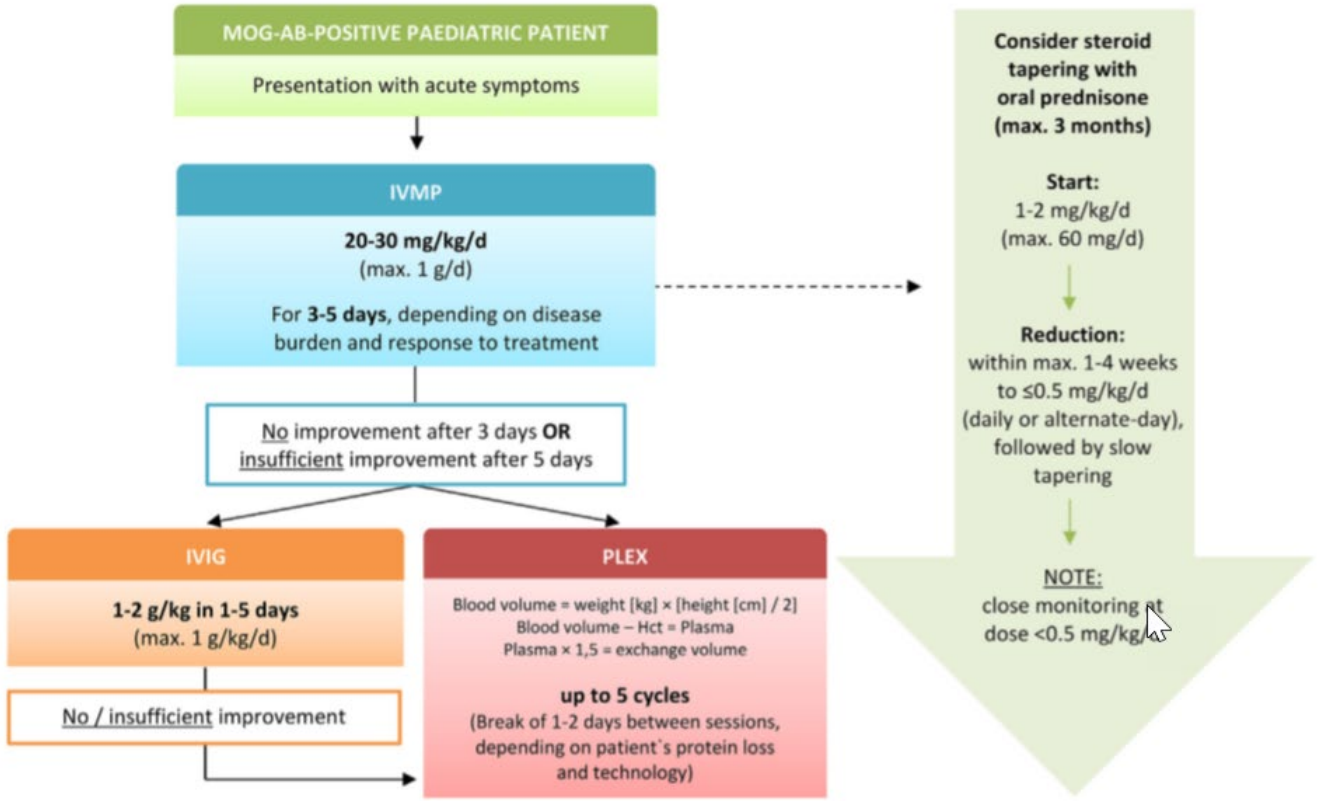


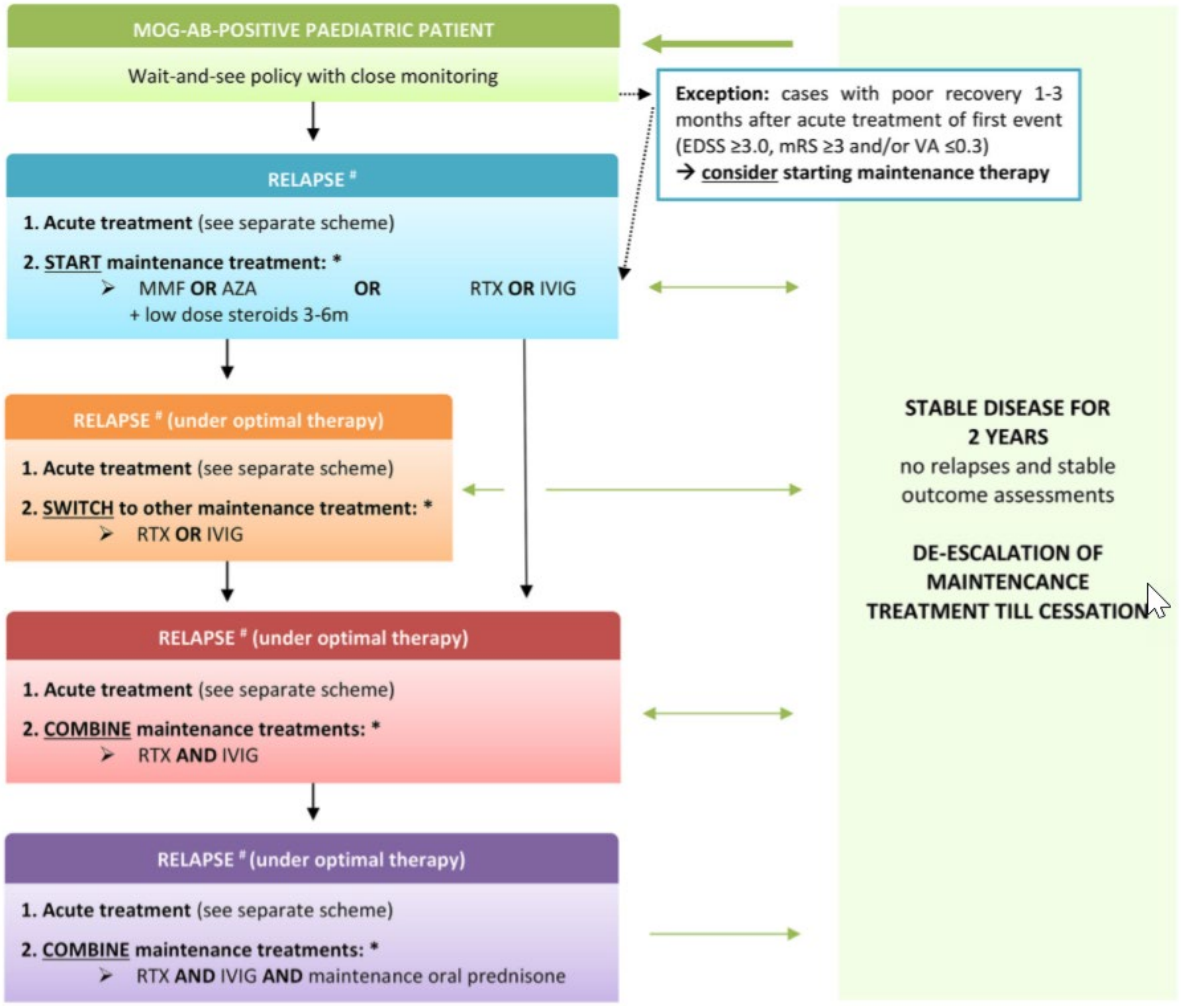
Fig. 1. Paediatric European Collaborative Expert Consensus recommendation for acute treatment in paediatric MOGAD. d = day, g = gram, IVIG = intravenous immunoglobulins, IVMP = intravenous methylprednisolone, kg = kilogram, mg = milligram, MOG-ab = myelin oligodendrocyte glycoprotein antibody, PLEX = plasma exchange, TM = transverse myelitis.

High dose i.v. Steroids
- 3-5 days

Consider IVIG/PLEX
- Depending on ttm response

1. Bruijstens et al; EJPN 29 (2020), 41-53

MOG-AD – Maintenance therapy



Maintenance only after relapse
- Escalation of maintenance if needed

Continue for 2 years (stable)
- De-escalation until cessation

1. Bruijstens et al; EJPN 29 (2020), 41-53

Summary I

- Autoimmune encephalitis in children:
  - Rare, potentially life-threatenting
  - Anti-NMDA-receptor encephalitis most frequent

- «Antibody-receptor-language»:
  - Clinical clues in particular types of autoimmune encephalitis

- Good outcome in classical autoimmunce encephalitis:
  - Early treatment initiation and rapid escalation important
  - Time is brain, also in autoimmune encephalitis

Summary II

- Pediatric MS:
  - Disease occurring in the developing brain:

    → Early cognitive impairment and brain atrophy
  - **Offer disease modifying therapy to all pediatric MS patients**

    → Specialised centres with high level expertise

    → Identify patients who benefit from early aggressive treatment
  - Design pediatric trials according to the needs of ped MS patients

Summary III

- MOG-AD:
  - Age-dependent phenotypes
  - Mostly monophasic
  - Maintenance therapy only for selected cases

- Standardized and structured approach in diagnosis and treatment:
  - Pediatric neuroinflammatory task force
  - Swiss Pediatric Inflammatory Brain Disease Registry

SWISS PED IBRAIND
Swiss-Ped-IBrainD
Swiss Pediatric Inflammatory Brain Disease Registry

Vielen Dank für die Aufmerksamkeit



Sandra.Bigi@luks.ch

SWISS PED IBRAIND Swiss-Ped-IBrainD Swiss Pediatric Inflammatory Brain Disease Registry

MOG-AD – titer and clinical severity

- Initial titer does not influence outcome or clincial severity

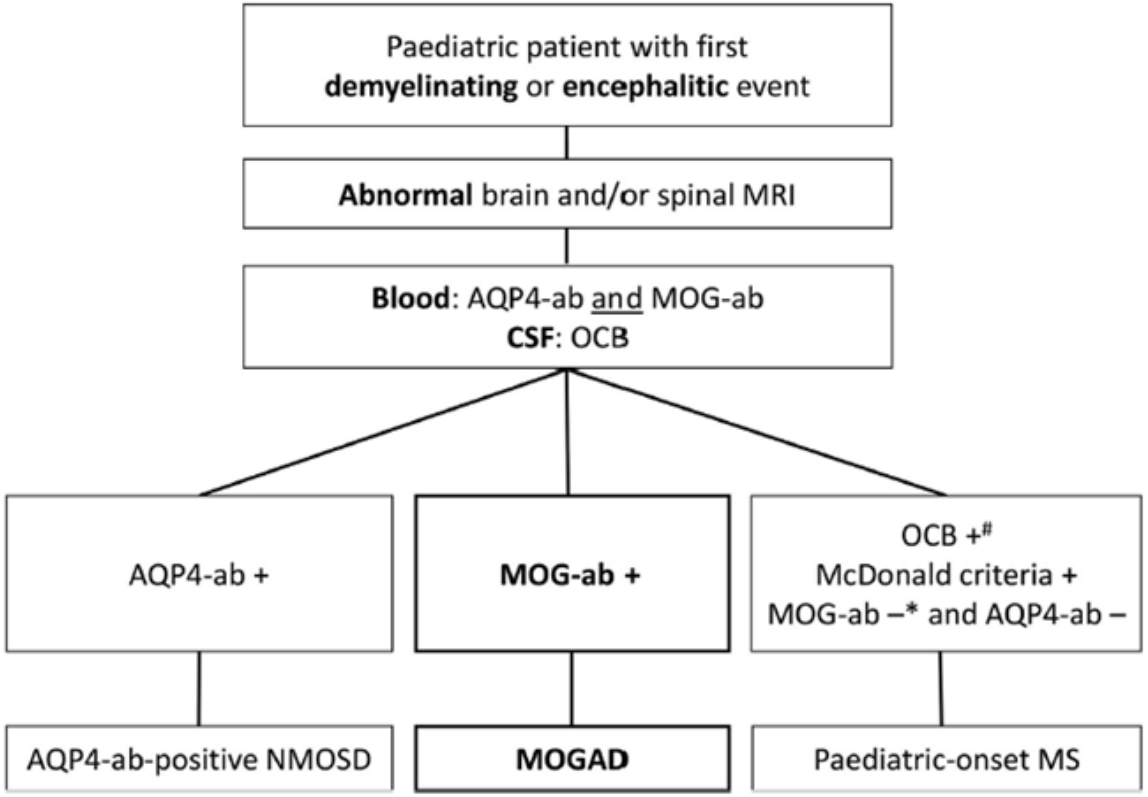
- Test within 3 months of acute episode:
  - Mostly monophasic (70-80%), become negative over time

- Conversion into seronegativity (median 12 months):
  ↓ risk for relapse
  → important time window for treatment decisions!

- Persistance of MOG-Ab:
  ↑ risk for relapsing disease (multiphasic ADEM, NMOSD-like, recurrent autoimmune encephalitis)

1. Armangue T et al.; EJPN 20 (2020) 22-31

MOG-AD – Influence on work-up and outcome



ıropean Collaborative Consensus recommendation on MOG-ab testing (in an accredited laboratory) in paediatric patients.
iatric-onset MS patients have OCB specific to the CSF [122].
n of paediatric-onset MS patients have MOG-abs (mostly low titre/weak positive CBA test result which rapidly declines durin[follow-up). H
ult in patient referral to a centre of expertise for further management.
in-4 antibody, CBA = cell-based assay, CSF = cerebrospinal fluid, NMOSD = neuromyelitis optica spectrum disorders, MOG-ab = my
ly, MOGAD = MOG-ab-associated disorders, MRI = magnetic resonance imaging, MS = multiple sclerosis, OCB = oligoclonal bands, + = pc

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- Overall good outcomes:
  - Full recovery 68-96%
  - Presenting phenotype might influence outcome, particularly TM

- Adverse outcomes:
  ↑susceptibility of the myelinating brain to MOG-Ab disease
  → damage to the not fully matured myelin
  → irreversible axonal loss

1. Bruijstens AL et al; EJPN 29 (2020), 2-13
2. Bruijstens AL et al.; EJPN 20 (2020) 32-40

MOG-AD – CAVE NMOSD-like phenotypes

Table 1
Differences between paediatric AQP4-ab-positive NMOSD and MOG-ab-associated NMOSD-like phenotypes.

	NMOSD-like phenotypes	
	MOG-ab+	AQP4-ab+
Demographics	More often in paediatric patients Equal distribution boys/girls No association with other AID	Rare in paediatric patients Predominance in girls Association with other AID
Clinical phenotypes		
***ON**	* Bilateral, longitudinally extensive with anterior involvement (disc oedema[a])	* Longitudinally extensive with chiasma/optic tract involvement
***TM**	* LETM with conus involvement	* LETM with cervico-thoracic spinal cord involvement
***NMOSD(-like)**	* Often simultaneous ON and TM, area postrema syndrome is rare	* Area postrema syndrome, isolated brainstem syndrome
Severity at onset	Severe	Severe
Recovery	Promptly after steroids and often completely, except for axonal damage on OCT (ON) and bowel/bladder problems (TM)	High risk for poor recovery
Disease course	More often monophasic, but relapses are possible	Relapsing

AID = autoimmune disease, AQP4-ab = aquaporin-4 antibody, LETM = longitudinally extensive transverse myelitis, MOG-ab = myelin oligodendrocyte glycoprotein antibody, NMOSD = neuromyelitis optica spectrum disorders, OCT = optical coherence tomography, ON = optic neuritis, TM = transverse myelitis, + = positive, − = negative.
[a] Discriminative feature for MOG-abs and AQP4-abs in mixed paediatric and adult studies, but not in paediatric studies exclusively.

6

1. Bruijstens et al; EJPN 29 (2020), 2-13

Clinical characteristics – Early signs of impairment

- Marked cognitive impairment in 1/3 at diagnosis & rapid worsening:
  - CAVE! Reassessment with newer therapeutic approaches required

- Lower brain volume at time point of diagnosis:
  - Neurodegenerative component preceding 1st attack
  - Active myelination & maturation of neural networks
    → reduced integrity in hemispheric NAWM*

- Explanation for increased susceptibility:
  - Vulnerability of developing brain
  - Impairment of subsequent maturation of white matter pathways
  - Neurodegenerative component preceding first attack
    → Loss of neuronal networks

*Normal appearing white matter

1. MacAllister et al, Neurology 2005
2. Amato MP et al, Neurology 2010
3. Amato MP et al, Neuology 2016
4. Julian L et al, J Child Neurol 2013
5. Reich DS et al, N Eng J Ned 2018
6. Till C et al, Neuropsychology 2013;
7. Aubert-Broche et al. Neurology 2014

No evidence of disease activity including cognition (NEDA-3 plus) in naïve pediatric multiple sclerosis patients treated with natalizumab

Monica Margoni[1,2] · Francesca Rinaldi[1] · Alice Riccardi[1] · Silvia Franciotta[1] · Paola Perini[1] · Paolo Gallo[1,3]

Journal of Neurology (2020) 267:100–105
https://doi.org/10.1007/s00415-019-09554-z

Table 1 Baseline demographic and clinical features of the 20 pediatric-onset multiple sclerosis patients included in the study

	Mean (SD)
Age at MS onset (years)	13.8 (2.7)
Pre-NTZ disease duration (months)	6.0 (4.0)
Age ad NTZ initiation (years)	14.2 (2.5)
Number of relapses prior NTZ initiation	2.1 (0.3)
Number of Gd+ MRI lesions prior NTZ initiation	1.2 (0.4)
EDSS at NTZ initiation	2.6 (0.7)

NTZ natalizumab, *EDSS* Expanded Disability Status Scale, *Gd* gadolinium, *MRI* magnetic resonance imaging

NEDA-3 plus:
- no clinical relapses
- no increase in disability
- no MRI activity and
- no cognitivedecline

Giovannoni G et al; Mult Scler Relat Disord; 2015, 4(4):329–333

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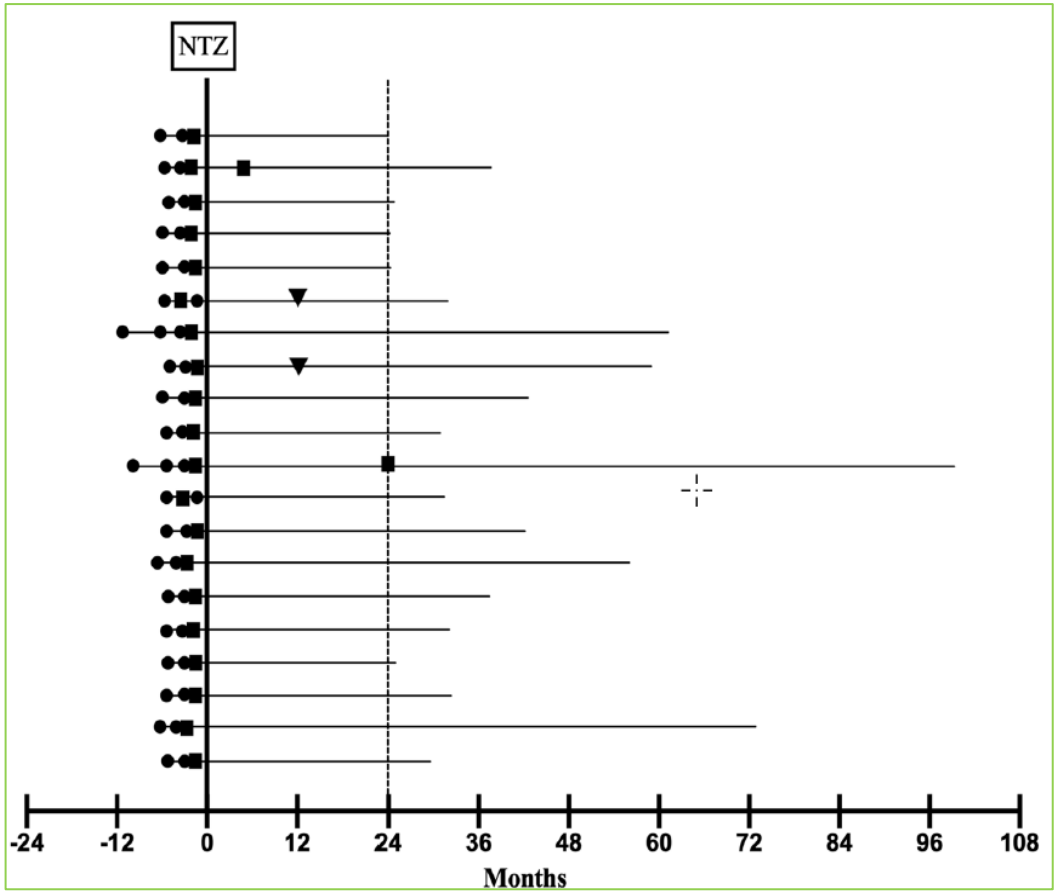
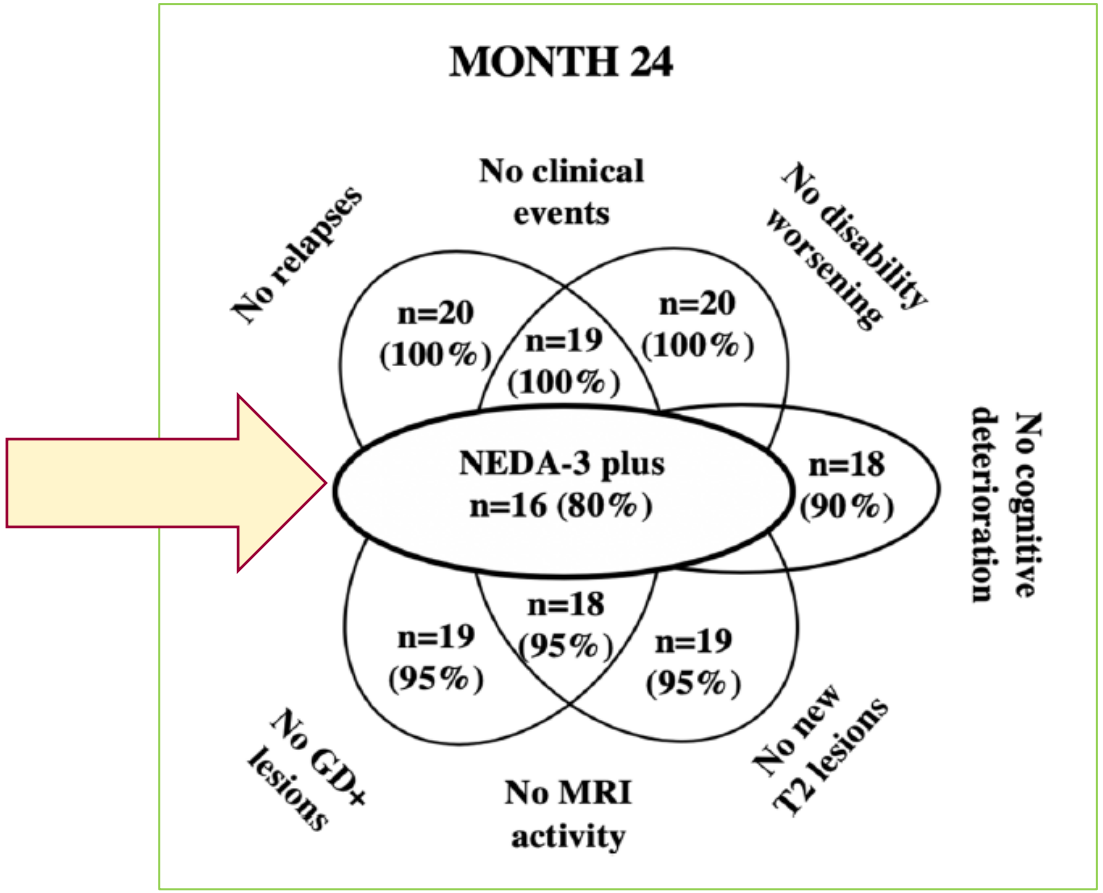




Original article EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY 23 (2019) 783–791

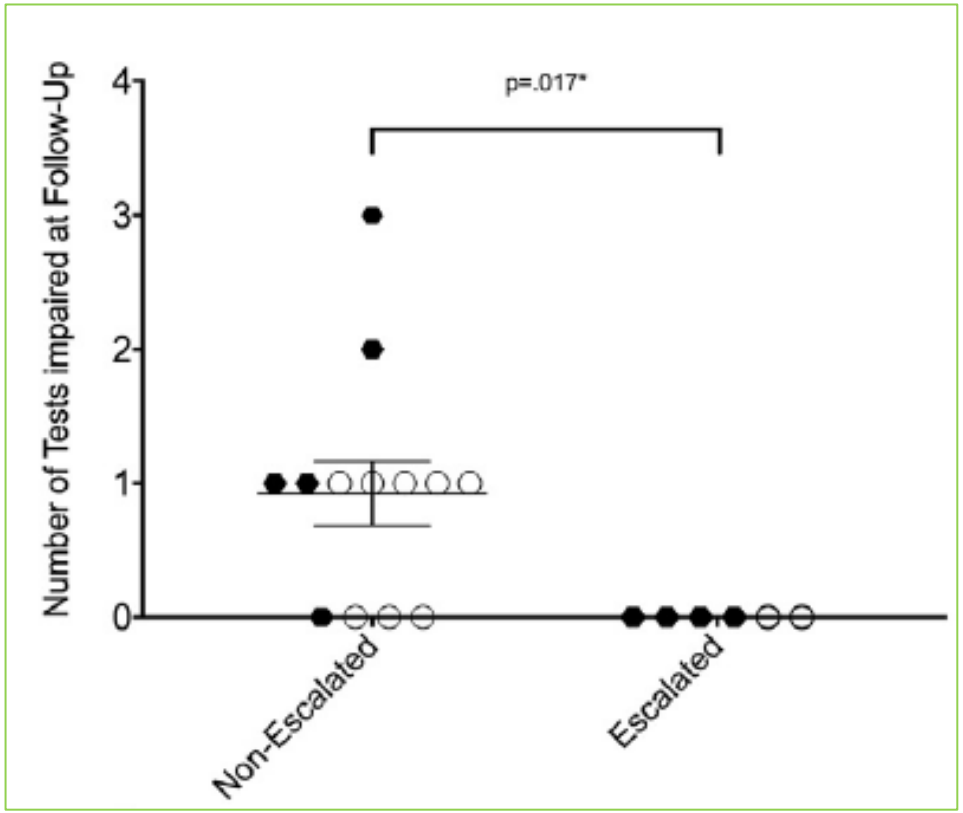
Early effective treatment may protect from cognitive decline in paediatric multiple sclerosis

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]

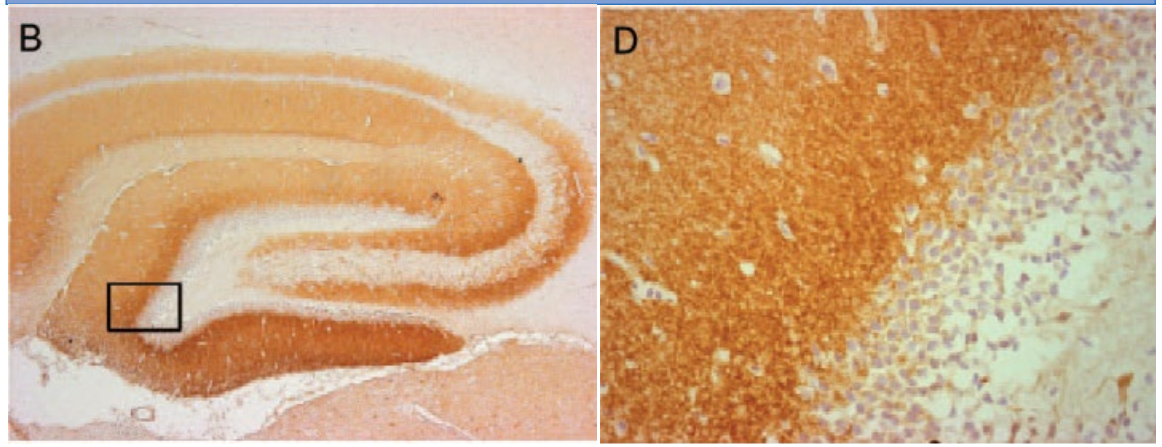
Table 1 – Baseline sample characteristics of the n = 19 paediatric MS patients.

Demographics	Mean (SD)	
Age (years)	15.05 (2.01)	
Sex (f/m)	14/5	
Education (years)	9.73 (1.52)	
Clinical and Paraclinical Measures	**Mean (SD)**	**Median (IQR)**
Disease Duration (months)	12.95 (23.52)	4.00 (9.00)
EDSS	0.50 (0.61)	0.00 (1.00)
Total Number of Relapses	2.68 (1.88)	2.00 (1.00)
Number of Lesions on MRI	21.44 (17.52)	15.50 (27.75)
Treatment		
Naïve, n	3	
Interferon beta-1a, n	16	

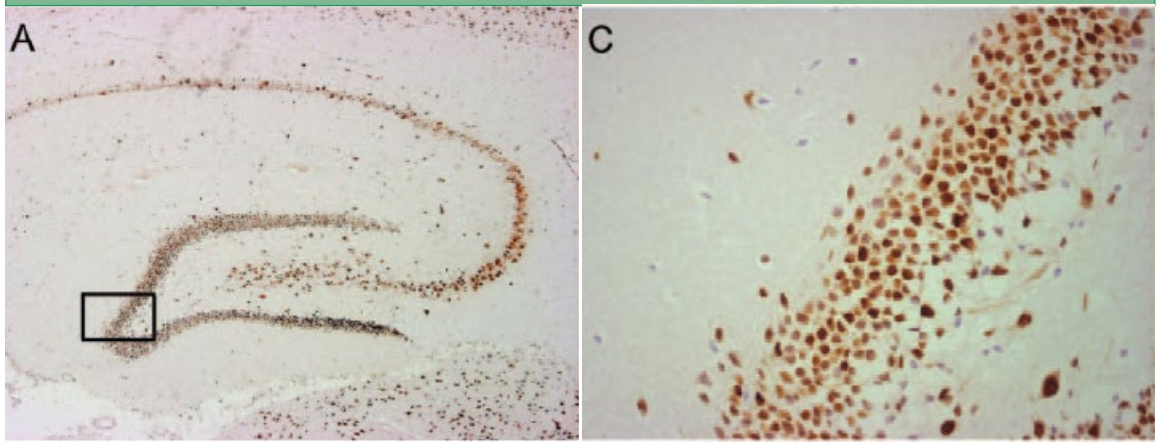
Note. EDSS = Expanded Disability Status Scale; Disease Duration = time since first symptoms; IQR=Interquartile range.



- **Cell-surface protein**
  - NMDA-Receptor-Antibody



- **Intracellular antigen**
  - Hu-Antibody



Lancaster E. et al.; Neurology; 2011

Clinical characteristics – Impact on brain volume

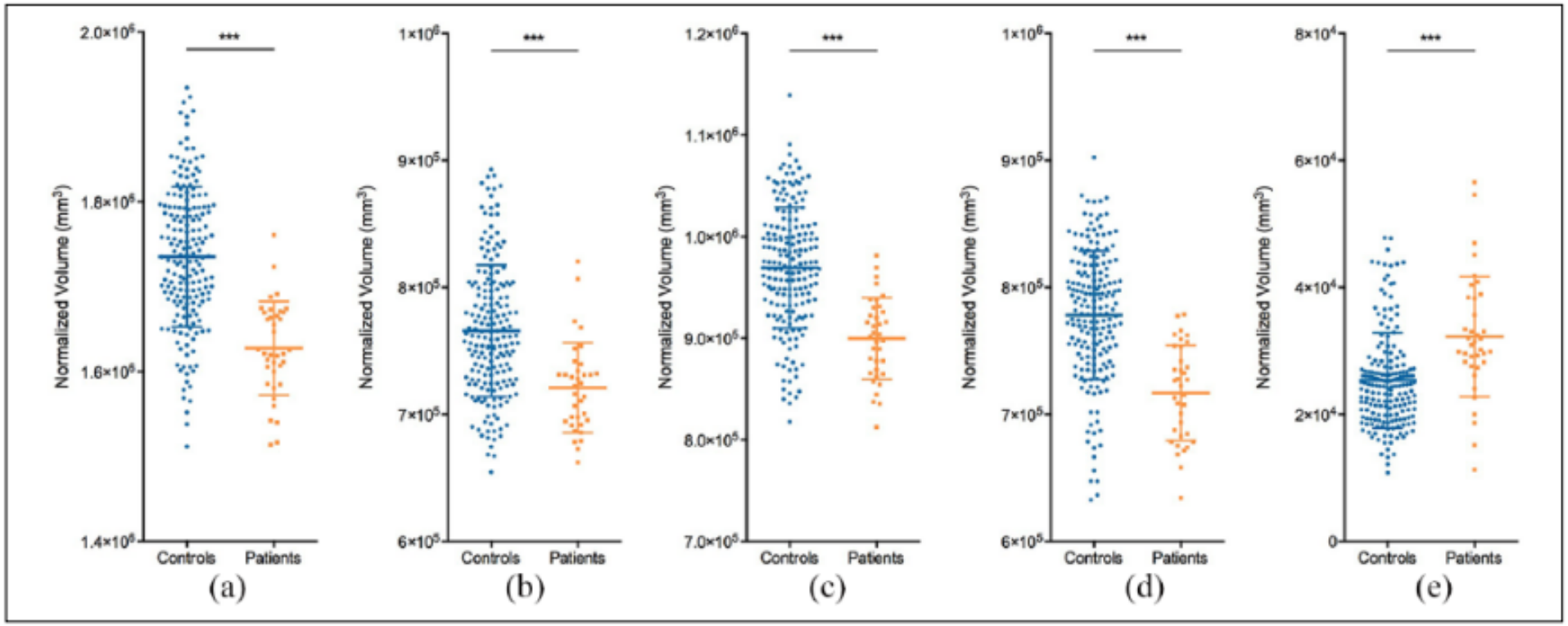


Figure 1. Brain atrophy at first clinical presentation. Normalized brain volumes (mm^3) at first clinical presentation. All brain volumes are significantly smaller in MS patients ($n=37$) at disease onset compared to matched (1:5) healthy controls ($n=185$): (a) whole brain volume, (b) white matter volume, (c) grey matter volume, (d) peripheral grey matter volume, and (e) ventricular CSF volume.

1. Bartels F et al; MSJ 2019

Table 1. Clinical clues in the recognition of particular types of autoimmune encephalitis

Clinical finding	Associated autoantibody disorders
Psychosis	NMDAR, AMPAR, GABA-B-R
Dystonia, chorea	NMDAR, Sydenham chorea, D2R
Hyperekplexia	GlyR
Status epilepticus	Most characteristic of GABA-B-R and GABA-A-R but NMDAR is much more common; may occur in other types as well
New onset type 1 diabetes	GAD65
Fasciobrachial dystonic seizures	LGI1
Neuromyotonia, muscle spasms, fasciculations	Caspr2
Stiff-person syndrome and/or exaggerated startle	GAD65, GlyR, Amphiphysin (with GAD65 being most common in stiff person/stiff limb and GlyR in PERM, and Amphiphysin in women with breast cancer)
CNS (myoclonus, startle, delirium) and gastrointestinal hyper-excitability	DPPX
Cranial neuropathies	Ma2, Hu, Miller-Fisher, Bickerstaff (but also infections like Sarcoidosis, Lyme, TB)
Cerebellitis	GAD65, PCA-1 (Yo), ANNA-1 (Hu), DNER (Tr), mGluR1, VGCC

CNS: central nervous system, TB: tuberculosis.

Lancaster E; JCN; 2016