Clinical approach in children with an acute demyelinating episode, differential diagnosis and role of MOG antibodies

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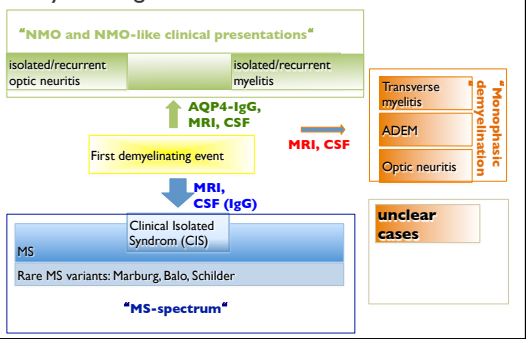
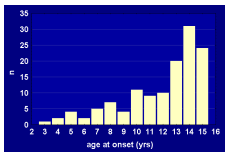
Differentialdiagnosis of inflammatory-demyelinating diseases of the CNS:



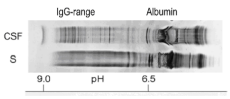
Important characteristics of children with MS

(1) Nearly exclusively relapasing-remitting (> 97%)

(2) Disease onset in the majority of children during or after puberty

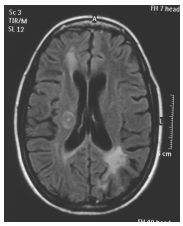


(3) CSF: Oligoclonal IgG present in the majority of children after the 2nd episode



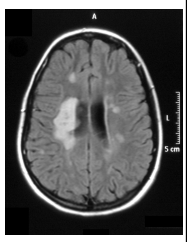
In children with severe episodes and persisting symptoms consider rare forms of MS or an alternative diagnosis!

video



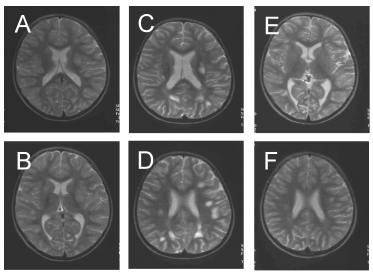
Acute dissiminating encephalomyelitis (ADEM)

- children < 8 years
- often preceeded by a viral infection
- encephalopathy and polyfocal neurological symptoms
- CSF: rarely OCB
- monophasic
- good recovery

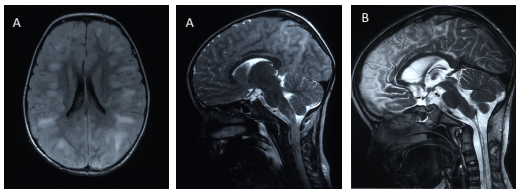


ADEM- MRI-changes are often reversible

1. MRI (Day 1) 2. MRI (Day 4) 3. MRI (after 8. weeks)



Note: children with ADEM AND infratentorial MRI changes often have neurological sequelae! (Nagl et al., 2010)



(A) 8 yo boy with encephalopathy, flaccid paresis of arms and legs after a viral infection and bilateral, hazy MRI- changes.
(B) Atrophy of the lower brain stem and myelon with severe tetraparesis after 12 month.

Neuromyelitis optica (NMO)

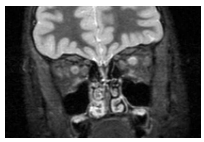
- Episodes with opticus neuritis and transverse myelitis
- MRI with lesions extending > 3 segments
- no MS typical cerebral lesions
- serum AQP4-IgG Ab present

Problem:
- often children with NMO do have no serum AQP-IgG Abs!
- limited forms with AQP4-Abs (recurrent ON brainstem syndroms).

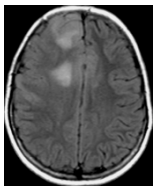
Optic neuritis

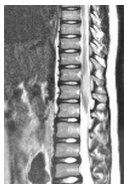
- bilateral or unilateral
- isolated or recurrent
- associated with MS, NMO, ADEM!!!!

- Risk factors for MS:
  1. presence of OCBs
  2. white matter lesions



Video and MRI





14 yo girl with fever, tiredness, hemiparesis, CSF: 44 cells/µl, complete recovery after steroids.

8 yo boy with altered conciousness, hemiparesis left after an URI, CSF: 120 cells/µl

12 yo girl with weakness left leg and back pain CSF: 88 cells/µl, Good response to steroids

Diagnosis: Ependymoblastoma

Neuromyelitis optica (NMO)- Definition

- Episodes with optikusneuritis and transverse myelitis
- spinale MRI with lesions extending more than 3 segments
- no MS typical cerebral lesions
- serum AQP4-IgG Ab present

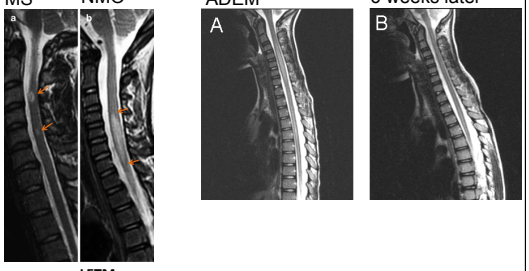
Problem:
- Often children with NMO do have no serum AQP-IgG Abs
- limited forms:
  recurrent ON with AQP4-Abs
  brainstem syndroms with AQP4-Abs

Transverse Myelitis- Definition

1. Symptoms indicative of a process located in the myelon: weakness of both legs, sensory symptoms associated with a sensory level, bladder dysfunction etc..
2. Laboratory signs of inflammation in the CSF: Pleocytosis, intrathecal IgG production (e.g. OCBs) or presence of lesions with contrast-medium enhancement in spinal imaging.
3. Absence of other diseases (e.g. tumour).

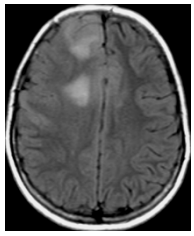
Transverse Myelitis- Imaging

MS NMO ADEM 6 weeks later



LETM-
Longitudinal Extensive Transverse Myelitis

Video and MRI



14 yo girl with fever, tiredness, hemiparesis right, CSF: 44 cells/µl, complete recovery after IVMP.

8 yo boy with altered Conciousness, hemiparesis left after an URI, CSF: 120 cells/µl

Diagnosis: ???

MR- imaging in Macrophage Activation Syndromes is very variable !!

Image to follow

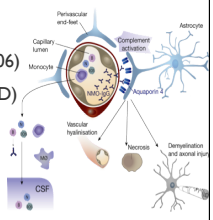
Antibodies and B-cells in CNS- demyelination

- B-cells, IgG, complement and B-cell chemokines in MS lesions.
- CSF IgG production in >95% of MS patients!
- CSF chemokine levels of CXCL13 correlate with disease progression in MS.
- AQP4 – Abs are instrumental in the pathogenesis of NMO!

ANTIBODIES AND NMO

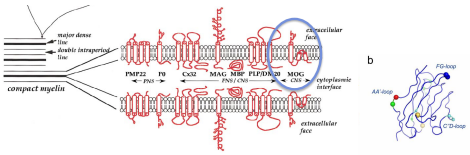
AQP4-IgG antibodies are important for:

- Diagnosis (Wingerchuk criteria 2006)
- Broader disease spectrum (NMOSD)
- Predictive for NMO after single manifestation of myelitis or ON
- Therapy monitoring
- Pathogenesis of NMO



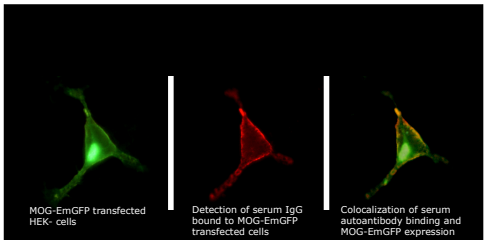
➡ **NMO is an autoantibody-mediated demyelinating disease!**

Myelin-oligodendrocyte- glycoprotein (MOG)

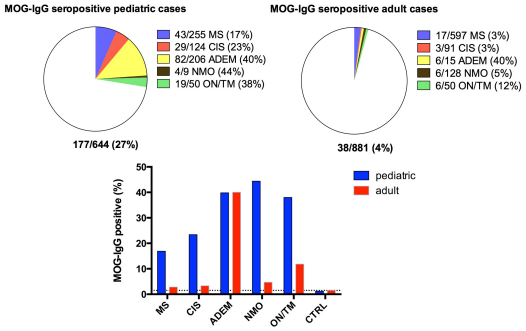


- is expressed on the outermost surface of the myelin sheath,
- human MOG-antibodies are from the IgG1-subtype and induce complement mediated cytotoxicity in-vitro,
- convincing evidence for the pathogenicity of MOG-antibodies from patients is missing.

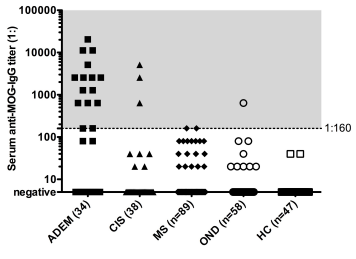
Cell-based assays, which express native, unfolded MOG protein are used for the detection of MOG antibodies:



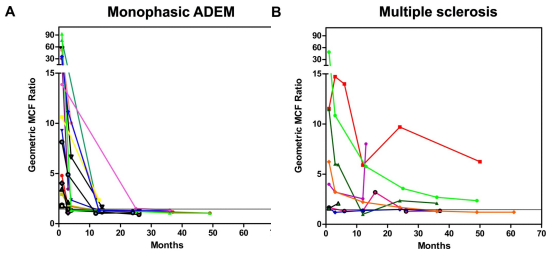
Frequency of MOG-antibodies in inflammatory-demyelinating diseases:



High MOG-antibody titers are present in 40% of children with ADEM! (di Pauli et al., JCI 2010)



MOG- antibodies decline over time in children with monophasic ADEM! (Proebstel et al., Neurology 2011)



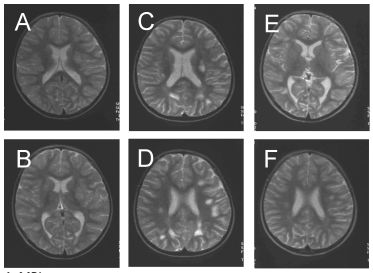
Clinical and neuroradiological differences of pediatric ADEM with and without antibodies to MOG (M. Baumann, JNNP, 2014)

Main findings:

1. Patients with MOG antibodies had a uniform MRI characterized by large, bilateral and widespread lesions,
2. an increased frequency of LETM,
3. a more favorable clinical outcome in contrast to children lacking MOG antibodies.

ADEM with MOG antibodies

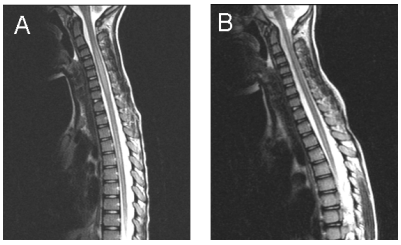
- 6 yo girl with weakness of both legs, bladder dysfunction, headache and irritability, OCB neg, CSF cells: 60/µl



1. MRI
2. MRI after 3 days
3. MRI after 8 weeks

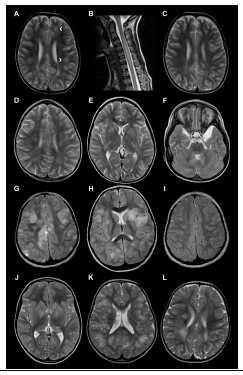
ADEM with MOG antibodies

- 6 yo girl with weakness of both legs, bladder dysfunction, headache and irritability, OCB neg, CSF cells: 60/µl



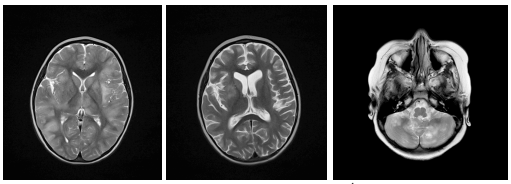
1. MRI 2. MRI after 8 weeks

MRI of children with ADEM and MOG antibodies.



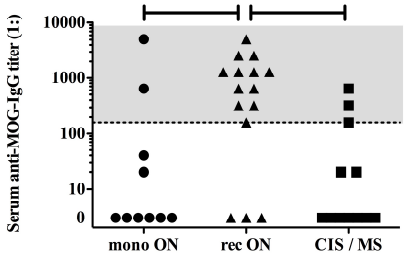
Spectrum of MOG-positive diseases: Multiphasic ADEM

- 6 yo girl with 5 episodes of encephalopathy and focal neurological signs in 3 years, OCB neg, CSF: 26/µl and high MOG-antibody titers.



07/2011 01/2012 05/2013

MOG- antibodies are often present in children with recurrent optic neuritis!



(Rostásy et al., Arch Neurol 2012)

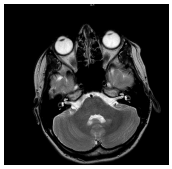
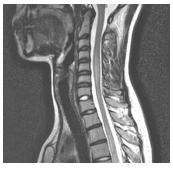
MOG-antibodies in children with optic neuritis

(Rostásy et al., Arch Neurol 2012).

	Monophasic ON (n=10)	Recurrent ON (n=15)	CIS/MS ON (n=12)	P-value
Female : male	8:2	9:6	10:2	ns
Age at sampling (y)	13 (5-18)	12 (2-18)	16 (9-18)	ns
Follow-up (y)	2.2 (1.7-4.8)	2.5 (0.9-6.2)	1.9 (1.7-4.7)	ns
AQP4-IgG	0 (0%)	0 (0%)	0 (0%)	ns
MOG-IgG	2 (20%)	12 (80%)	3 (25%)	0.003
Titer	0 (0-1:5,120)	1:640 (0-1:5,120)	0 (0-1:640)	0.007
OCB	2 (22%)	0 (0%)	11 (92%)	<0.001
cMRI normal:ON swelling:ADEM:MS	9:1:0:0	7:2:6:0	1:0:0:11	<0.001
sMRI normal:MS:NMO	6:0:0	12:1:2	6:5:0	0.04

MOGpos/AQP4neg pediatric NMO

- 12/2009: Weakness in both legs, bladder dysfunction
- 06/2010: Visual loss right eye
- MRT-c: cerebellar and myelon lesions spanning > 3 segments
- AQP4-antibodies absent

✓ Diagnosis: Neuromyelitis optica

✓ High MOG-antibody titer present!!!!

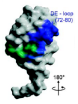
Persisting MOG-antibodies in AQP4-IgG negative pediatric NMO
(Rostasy et al., MSJ 2013).

No. Gender Age (y)	MOG-IgG titer	AQP4-IgG titer	Follow up (m)	rela-pses	ON	TM	LETM	no MS-like cMRI lesions	Tx
1/M/12	negative	1:320	27	3	yes	yes	yes	yes	RTX
2/F/15	negative	1:1,280	36	4	yes	yes	yes	yes	RTX
3/F/8	negative	negative	21	2	yes	yes	yes	yes	Aza
4/M/14	negative	negative	54	3	yes	yes	yes	no	Aza, Pred
5/F/15	negative	negative	12	1	yes	yes	yes	yes	none
6/F/14	1:2,560	negative	18	2	yes	yes	yes	yes	Aza, Pred
7/F/3	1:2,560	negative	48	3	yes	yes	yes	yes	IVIG
8/F/3	1:1,280	negative	28	2	yes	yes	yes	yes	IVIG

MOG-antibodies in children with MS

- 14 yo boy with headache, double vision and gait instability, CSF: OCB pos, 10 cells/ul.
- Remission after IVMP (20mg/kg 3/d).

✓ In children with MS
- MOG- antibodies are infrequently present ,
- but if present titers are low and do persist.



Summary:

- Spectrum of MOG-positive diseases includes children with ADEM, recurrent ON und aquaporin-negative NMO.
- Levels of MOG-antibodies in ADEM decline after the initial episode, which is then associated with a good prognosis.
- Persisting MOG-antibodies are found in children with recurrent ON and AQP4- negative NMO .

Open Questions:

- What is the role of MOG- antibodies play in the pathogenesis of ADEM, ON or NMO?
- Why do children with MOG-antibodies present with different and distinct clinical entities?
- Are other autoantibodies in MOG-negative demyelinating diseases instrumental in the disease process?

Thank you very much for your attention!!

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