High association of MOG-IgG antibodies in children with bilateral optic neuritis

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Abbreviations

Abs	antibodies
ADEM	acute disseminated encephalomyelitis
ADEMON	ADEM followed by ON
ADS	acquired demyelinating syndrome
AQP4	aquaporin-4
bilON	bilateral optic neuritis
CBA	cell-based assay
CIS	clinically isolated syndrome
IVIG	intravenous immunoglobulins
IVMP	intravenous methylprednisolone
LEON	longitudinally extensive optic neuritis
LETM	longitudinally extensive transverse myelitis
MDEM	multiphasic disseminated encephalomyelitis
MMF	mycophenolat mofetil
MOG	myelin-oligodendrocyte-glycoprotein
NMOSD	neuromyelitis optica spectrum disorders
OCB	oligoclonal bands
OCT	optic coherence tomography
ON	optic neuritis
PLEX	plasma exchange
RAPD	relative afferent pupillary defect
recON	recurrent optic neuritis
RNFL	retinal nerve fiber layer
RTX	rituximab
SCIG	subcutaneous immunoglobulins
VEP	visual evoked potentials

1. Introduction

Acquired demyelinating syndromes (ADS) in children encompass a broad spectrum of disorders: monophasic diseases such as acute disseminated encephalomyelitis (ADEM) or different subtypes of clinically isolated syndrome (CIS), and relapsing forms such as neuromyelitis optica spectrum disorders (NMOSD), multiple sclerosis (MS) or recurrent optic neuritis (ON). Discrimination between MS and other forms of ADS plays an important role, particularly with regard to therapeutic implications and prognosis. ON can occur isolated or in combination with other neurological deficits and is often the first clinical manifestation of MS or NMOSD associated with AQP4-antibodies (abs) [1,2]. Bilateral ON (bilON) occurs less frequently and is often thought to be a manifestation of NMOSD associated with AQP4-abs or MS [3,4].

During the last decade autoantibodies against myelin-oligodendrocyte-glycoprotein (MOG) have been described in different subsets of nonMS acute inflammatory, demyelinating CNS diseases [5–7]. MOG-abs are most often found in young children with ADEM, AQP4-negative NMOSD or in particular in children with recurrent ON. Clinical courses of MOG-IgG seropositive (MOG-positive) patients tend to be favorable. However, ON as a frequent feature of MOG-positive NMOSD can potentially lead to severe visual morbidity in the context of frequent relapses [8].

In order to better define the clinical entity of children presenting with bilateral ON, we analyzed the clinical phenotype, radiological findings, outcome and MOG- and AQP4-antibody status of pediatric patients presenting with bilON as a first manifestation of an ADS.

2. Material and Methods

2.1. Patients

For our BIOMARKER-study pediatric patients with a first suspected ADS were recruited since 2009, with intention to test them for MOG- and AQP4-abs. From this BIOMARKER-cohort of 902 children all patients with bilON were selected for this multicenter, observational case series. Upon entry into the BIOMARKER-cohort serum samples and clinical data of children with a suspected ADS were sent to us between 2009 and 2019 from 60 different clinical centers in Germany, Austria, Switzerland, Italy, Turkey, Croatia and Canada for testing of MOG-IgG- and AQP4-IgG-antibodies and included in a prospective study. 37/902 children presented with bilON. 30 patients from five different countries finally met the inclusion criteria for the present study: (I) age <18 years, (II) first inflammatory CNS episode with bilON, presenting with characteristic bilateral symptoms such as visual impairment, impaired color vision, pain on eye movement, optic disc swelling and/or pathological relative afferent pupillary defect (RAPD), (III) clinical, cerebral MRI- and cerebrospinal fluid (CSF) studies (cell count, oligoclonal bands (OCBs)) and ophthalmologist's report of first episode, (IV) AQP4- and MOG-IgG results within two months of first presentation. If available, results of visual evoked potentials (VEP) and optical coherence tomography (OCT), and follow-up data including treatment history and clinical outcome with focus on assessment of visual function were obtained. All patients and parents gave informed consent. BilON was classified into three degrees of severity. (1) Mild bilON: symptoms of bilON with loss of vision/color vision impairment/eye motility pain/delayed latency for P100 in VEP/signs of optic disc swelling/pathologic RAPD, not fulfilling criteria for (2) or (3). (2) Moderate bilON: unilateral profoundly visually handicapped (vision < 1/20 or < 0.05) OR bilateral visually handicapped (vision <0.3). Severe bilON (3) fulfilling following criteria: bilateral blindness (optional perception of contour or light) OR unilateral blindness and profoundly visually handicapped (vision < 1/20 or < 0.05) on the other eye, VEP bilaterally not reproducible. Relapse of ON was defined as an ON attack occurring at least 90 days after the initial episode. Seven patients with bilON were excluded because of missing clinical data or delayed antibody testing. Cerebral MRI studies, and if available spinal MRI studies,

were assessed by three independent observers unaware of the clinical presentation and antibody status (M.B., T.v.K., A.W.-P.) including the following sequences: cranial MRI in T2-, T1-, FLAIR-, and fat-suppressed sequences, gadolinium-enhanced T1-sequences in 26 patients, and additional spinal MRI with gadolinium-enhanced sequences in 17 children. Each optic nerve was divided into four segments: intraorbital, canalicular/intracranial, chiasm and optic tract. Assessment criteria included MRI brain and spinal cord abnormalities (quality, quantity and localization of cerebral and spinal lesions), signs of optic neuritis (optic nerve T2 hyperintensity, optic nerve enhancement with gadolinium, optic nerve swelling), laterality and localization of optic pathway abnormalities and extension of optic nerve involvement; longitudinally extensive ON (LEON) was defined as more than half of the prechiasmatic optic nerve length. Disagreements were subsequently solved in a consensus conference. 9/30 patients with bilateral ON as their main ADS have been reported previously (Hennes et al., 2017; Baumann et al., 2018).

2.2. Standard protocol approvals, registrations, and patient consents

The study was approved by the Ethics Committee of the Medical University of Innsbruck, Austria (Study number AN4059). All caregivers gave informed consent.

2.3. Antibody assay

Serum samples were analyzed for the presence of MOG- and AQP4-abs by live cell-based immunofluorescence assays as previously described [9]. MOG-IgG antibodies were tested using full-length MOG (alpha-1 isoform) and IgG (heavy and light chain, Dianova) specific secondary antibodies. Screening was performed at dilutions of 1:20 and 1:40 by at least two independent clinically blinded investigators (K.S. and M.R.), and positive serum samples were further diluted in two-fold increments to determine the end-point titers. Titer levels of $\geq$1:160 were classified as MOG-positive as previously described [9]. Using heavy chain specific secondary antibodies for IgM, IgG (Dianova) and IgG1 (Invitrogen) we excluded an isolated IgM reactivity in borderline (1:160 and 1:320) seropositive samples.

2.4. Statistical analysis

Statistical analysis was performed using IBM SPSS, release V.24.0 (IBM Corporation). We compared clinical, demographic, neuroradiological and serological data using the Mann-Whitney U test, Kruskal-Wallis test, Fisher's exact test and Chi square test. Statistical significance was defined as a two-sided p value of <0.05.

3. Results

3.1. Patients

30 patients with bilON at first ADS presentation and a complete data set were included (Fig. 1). The cohort consisted of 15 female and 15 male patients with a median age at onset of 8.0 years (range: 2–17 years). 27/30 (90%) patients had a first diagnosis of bilON defined as part of a clinically isolated syndrome (CIS) (CIS/bilON), two patients (7%) had a first diagnosis of NMOSD with concomitant longitudinal extensive transverse myelitis (LETM) and corresponding clinical symptoms, and one patient (3%) had bilON in the context of an ADEM episode. Clinical presentation and ON features of MOG-positive and -negative patients are summarized in Table 1. Intravenous methylprednisolone (IVMP) was the initial therapeutic approach in all patients with different timing and dosing schedules usually with 20 mg/kg/day. Six patients received IVMP over three days, 20 patients over five days and in four patients five days IVMP was followed by prolonged oral tapering over three to 12 weeks.

Comparison of clinical and immunological features according to MOG-IgG status at baseline.

Antibody testing via live CBA of the first serum sample obtained in the initial phase showed seropositivity for MOG-IgG in 22 patients (73%) with a median titer of 1:1280 (range: 1:160–1:5120). MOG-positive patients were only slightly younger (median 7.5y, range: 2-15y) compared to seronegative patients (median 8.5y, range: 5-17y). There was no difference in gender. All patients were seronegative for AQP4-abs. Laboratory findings in cerebrospinal fluid (CSF) are summarized in Table 1.

All seronegative patients had a monosymptomatic disease onset, compared to 77% of seropositive patients (17/22) (Table 1). All five patients with polysymptomatic presentation had high MOG-IgG titers ($\geq$1:1280; p-value 0.032) (Table 2). Degree of ON severity in MOG-positive and -negative patients is listed in Table 1.

3.2. Radiological findings

From a total of 30 radiological criteria assessed in 30 patients only 67 disagreements had to be solved in consensus, indicating a high interobserver agreement. 20/22 (91%) patients with bilON and MOG-abs had variable radiological findings of involvement of the optic nerves. In the seronegative group, 6/8 (75%) patients had radiological signs of ON. Radiological findings are summarized in Tables 2 and 3, including cerebral and spinal involvement at initial presentation.

3.3. Correlation of MOG-IgG status with clinical disease course

Follow-up data were available from all patients with a mean follow-up period of 27 months (median: 14 months, range: 4–141 months). All MOG-negative patients had a monophasic clinical course at time of last follow-up (mean: 21 months, median: 9 months, range: 5–74 months). MOG-positive patients had a mean follow-up of 30 months (median: 17 months, range: 4–141 months). 18/22 (82%) seropositive patients had a monophasic clinical course. 4/22 patients (18%) had more than one demyelinating episode (range: 2–5 episodes) associated with high MOG-IgG titers ($\geq$1:1280) at onset: Two patients were diagnosed with recurrent ON (recON) with a second episode of unilateral ON after seven and eight months, respectively. Two patients were diagnosed with NMOSD. One of them with bilON and LETM at first presentation had four subsequent episodes of unilateral ON. The second NMOSD patient initially presented with bilON and hazy, bilateral lesions in cMRI and had two subsequent events after four and six months with an acute brainstem syndrome amongst other symptoms.

Improvement of visual deficits after first application of IVMP was documented in 20/22 (91%) seropositive patients, compared to 6/8 (75%) in seronegative patients. 12 patients (40%; 10 MOG-positive, two MOG-negative patients) due to incomplete improvement received additional treatment modalities such as a repeated course of IVMP (n = 5), IVMP plus tapering (n = 3), sole oral prednisolone tapering (n = 3) or plasma exchange (PLEX) (n = 5). 7/22 (32%) MOG-positive patients received disease modifying therapies (IVIG, subcutaneous immunoglobulins (SCIG), glatiramer acetate, rituximab) due to recurrent attacks (3/7), insufficient improvement (3/7) or raising MOG-abs titer (2/7).

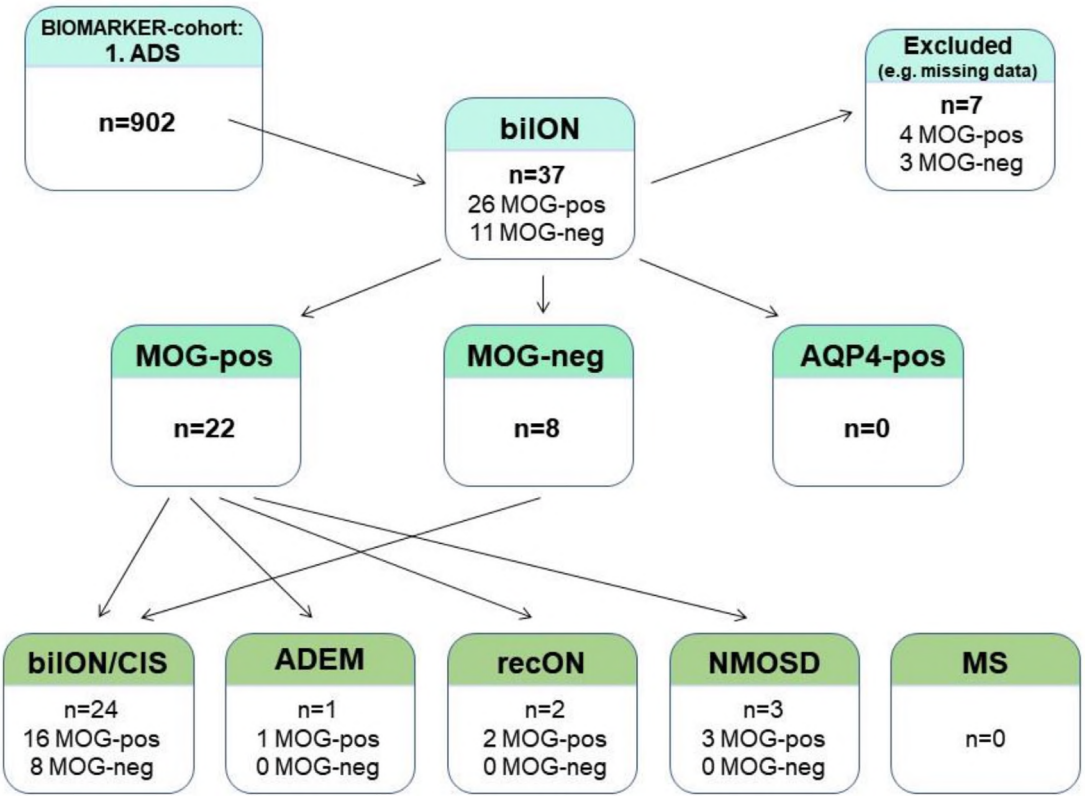

Fig. 1. MOG-antibody status and final diagnosis of pediatric patients presenting with bilateral ON as the first acquired demyelinating syndrome (ADS).
From our BIOMARKER-cohort of children with a first suspected ADS, 37 patients had a bilateral ON, of whom seven patients (MOG-pos: n = 4; MOG-neg: n = 3) were excluded because of missing clinical data or delayed antibody testing. 22/30 of the remaining patients were tested positive for MOG-ab, eight patients were tested negative for both MOG- and AQP4-abs. At time of last follow-up, patients had a final diagnosis of bilON/CIS (n = 24; 16 MOG-pos, 8 MOG-neg), ADEM (n = 1; 1 MOG-pos), recON (n = 2; 2 MOG-pos) and NMOSD (n = 3; 3 MOG-pos). No patient developed MS during the clinical course.
Abbreviations: ADEM = acquired disseminated encephalomyelitis; ADS = acute demyelinating syndrome; bilON = bilateral ON; CIS = clinically isolated syndrome; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorders; recON = recurrent ON.

3.4. Outcome

22/30 (73%) patients had no visual impairment or other neurological symptoms at last follow-up. Visual impairment was noted in eight patients (27%): 23% (5/22) of MOG-positive patients compared to 38% (3/8) of MOG-negative patients. No patient had further neurological sequelae.

One patient with MOG-positive ADEM and simultaneous bilON showed severe visual deficits after an episode of severe bilON and no improvement despite therapy (follow-up: 30 months). One seropositive patient developed severe visual deficits after frequent attacks of ON and TM and was diagnosed with NMOSD (follow-up: 141 months). One seropositive patient suffered from severe visual deficits initially followed by a unilateral ON with a chiasmatic hyperintense lesion after seven months on MMF and IVIG. She stabilized again under MMF, IVMP with oral prednisolone tapering in addition to RTX. After 12 months she still had left-sided mild visual residuals. Two further seropositive patients showed only mild visual deficits at follow-up (14 and 6 months, respectively) after a monophasic bilON episode.

3/8 (38%) MOG-negative patients with documented follow-up had visual impairment at last follow-up (mean: 21 months, range: 5–74 months). Two patients had monophasic bilON, one with mild visual residuals and one with severe visual residuals after progredient visual impairment despite three applications of IVMP and only mild improvement after PLEX. The latter receives SCIG monthly at time of last follow-up (12 months). The third seronegative patient with bilON showed no improvement with IVMP and oral taper and had severe visual residuals after 6 months.

In the clinical records optic nerve atrophy was documented by OCT, MRI or ophtamological examination in ten patients with concomitant visual impairment in four. 9/10 patients with documented optic atrophy were seropositive for MOG-IgG, of whom 6/9 had a monophasic disease course.

3.5. MOG-IgG titer at initial presentation and over time

In 15/22 seropositive patients serial testing of MOG-IgG was performed. In 14/15 (93%) patients titers decreased to a median of 1:160 (range: 0–1:640) over a mean period of 31 months (range: 2–141 months). A persisting MOG-IgG titer at 1:320 after eight months was observed in one patient. In nine patients decreasing titers were already seen within seven months after first presentation. In six patients (40%) titers dropped to negative levels over a mean period of 20 months (median: 7 months, range: 4–70 months). In one case with frequent ON attacks, severe visual sequelae and a final diagnosis of NMOSD first decline of MOG-IgG titers was documented after 39 months and was still at 1:320 after a follow-up period of 141 months.

4. Discussion

In our cohort of 902 children with ADS, 37 children presented with bilON. Our results further showed that the majority of these

Table 1
Demographic and clinical findings of MOG-antibody positive and negative patients with bilateral ON.

		MOG-neg		MOG-pos		p-value[a]
		n = 8		n = 22		
Age (years; mean)		9.3		7.9		
Sex	female	5	62.5%	10	45.5%	0.682
	male	3	37.5%	12	54.5%	
Presentation	neurologic polysymptomatic	0	0%	5	22.7%	0.287
	fever	0	0%	1	4.5%	1.000
	nausea	0	0%	5	22.7%	0.287
	headache	2	25.0%	6	27.3%	1.000
	fatigue	0	0	4	18.2%	0.550
Signs of ON	visual deficit	8	100%	22	100%	
	eye motility pain	2	25.0%	3	13.6%	0.589
	decrease of color vision	2	25.0%	5	22.7%	1.000
	path. RAPD	1	12.5%	6	27.3%	0.638
	papillary edema	3	37.5%	14	63.6%	0.242
ON severity	mild	5	62.5%	7	31.8%	0.245
	moderate	2	25.0%	6	27.3%	
	severe	1	12.5%	9	40.9%	
CSF findings	cell count (median)	1,5 (range: 0–54)		10 (range: 0–116)		
(n = 29)	OCB positive	2	25.0%	2	9.5%	
Follow-up	months (mean)	20.6		29.7		
	polyphasic	0	0%	4	18.2%	0.550
	visual residuals	3	37.5%	5	22.7%	0.643
	DMT at last fu	1	12.5%	5	22.7%	1.000

Abbreviations: CSF = cerebrospinal fluid; DMT = disease modifying therapy; fu = follow-up; OCB = oligoclonal bands; ON = optic neuritis; RAPD = relative afferent pupillary defect.
[a] All adjusted p-values for multiple comparisons using Bonferroni's correction for multiple comparisons were higher than 0.05.

Table 2
Clinical and radiological findings of patients with negative, low positive and high positive MOG-IgG titer.

		MOG-neg		MOG-pos low		MOG-pos high		p-value[a]
		(0:1–80)		(0:160–640)		(≥1:1280)		
		n = 8		n = 8		n = 14		
Presentation	neurologic polysymptomatic	0	0%	0	0%	5	35.7%	0.032
ON severity	mild	5	62.5%	4	50.0%	3	21.4%	0.305
	moderate	2	25.0%	2	25.0%	4	28.6%	
	severe	1	12.5%	2	25.0%	7	50.0%	
MRI ON lesion		6	75.0%	7	87.5%	13	92.9%	0.494
Intraorbital	no	4	50.0%	2	25.0%	3	21.4%	0.319
	unilateral	2	25.0%	1	12.5%	1	7.1%	
	bilateral	2	25.0%	5	62.5%	10	71.4%	
Canalicular/	no	2	25.0%	1	12.5%	1	7.1%	0.544
Intracranial	unilateral	1	12.5%	2	25.0%	6	42.9%	
	bilateral	5	62.5%	5	62.5%	7	50.0%	
Chiasma		3	37.5%	3	37.5%	1	7.1%	0.146
Optic tract	no	8	100%	5	62.5%	14	100%	0.057
	unilateral	0	0%	1	12.5%	0	0%	
	bilateral	0	0%	2	25.0%	0	0%	
LEON	no	5	62.5%	3	37.5%	3	21.4%	0.408
	unilateral	1	12.5%	2	25.0%	3	21.4%	
	bilateral	2	25.0%	3	37.5%	8	57.1%	
ON swelling	no	5	62.5%	1	12.5%	3	21.4%	0.115
	unilateral	2	25.0%	2	25.0%	6	42.9%	
	bilateral	1	12.5%	5	62.5%	5	35.7%	
MRI cerebral lesion		2	25.0%	3	37.5%	6	42.9%	0.551
MRI spinal lesion[b]	LETM	0	0%	0	0%	2	20.0%	0.453
	TM	2	40.0%	0	0%	3	30.0%	
Follow-up	polyphasic	0	0%	0	0%	4	28.6%	0.072
	MOG-ab at last fu	0	0%	1	12.5%	8	57.1%	0.044
	DMT at last fu	1	12.5%	0	0%	5	35.7%	0.109

Multiple neurological symptoms at disease onset were present in patients with high MOG-ab titers, but not in patients with low or negative titers (p = 0.032). Accordingly, recurrent disease course was observed in patients with high titers only (p = 0.072). Radiological findings at first presentation showed rare affection of the optic chiasma (p = 0.146) and optic tract (p = 0.057) in patients with high titers, compared to patients with low or negative titers. Serial MOG-ab testing showed persisting positive titers in more than half of patients with initial high titers (57%), compared to patients with initial low titers (12,5%) (p = 0.044).
Abbreviations: DMT = disease modifying therapy; fu = follow-up; LEON = longitudinally extensive optic neuritis; LETM = longitudinally extensive transverse myelitis; MS = multiple sclerosis; ON = optic neuritis; TM = transverse myelitis.
[a] All adjusted p-values for multiple comparisons using Bonferroni's correction for multiple comparisons were higher than 0.05.
[b] Number of patients with spinal MRI: 5/8 MOG-neg patients; 13/22 MOG-pos patients.

Table 3
MRI findings of MOG-antibody positive and negative patients with bilateral ON.

		MOG-neg		MOG-pos		p-value[a]
		n = 8		N = 22		
Cerebral lesion	no	6	75.0%	13	59.1%	0.749
	predominantly poorly marginated lesions	1	12.5%	6	27.3%	
	extensive confluent white matter changes	0	0%	1	4.5%	
	redominantly well-demarcated 'MS-like'	1	12.5%	2	9.1%	
ON lesion		6	75.0%	20	90.9%	0.284
Intraorbital lesion	no	4	50.0%	5	22.7%	0.105
	unilateral	2	25.0%	2	9.1%	
	bilateral	2	25.0%	15	68.2%	
Canalicular/	no	2	25.0%	2	9.1%	0.318
Intracranial lesion	unilateral	1	12.5%	8	36.4%	
	bilateral	5	62.5%	12	54.5%	
Chiasma lesion		3	37.5%	4	18.2%	0.345
Optic tract lesion	no	8	100%	19	86.4%	0.545
	unilateral	0	0%	1	4.5%	
	bilateral	0	0%	2	9.1%	
LEON	no	5	62.5%	6	27.3%	0.208
	unilateral	1	12.5%	5	22.7%	
	bilateral	2	25.0%	11	50.0%	
Gd Enhancement	no	0	0%	1	5.0%	0.601
Optic nerve[b]	unilateral	0	0%	2	10.0%	
	bilateral	6	100%	17	85.0%	
Gd Enhancement	no	3	50.0%	11	55.0%	0.977
Perineural[b]	unilateral	1	16.7%	3	15.0%	
	bilateral	2	33.3%	6	30.0%	
ON swelling	no	5	62.5%	4	18.2%	0.055
	unilateral	2	25.0%	8	36.4%	
	bilateral	1	12.5%	10	45.5%	
Spinal lesion[c]	no	3	60.0%	8	61.5%	0.565
	LETM	0	0%	2	15.4%	
	TM	2	40.0%	3	23.1%	

MR-imaging revealed lesions of the optic nerves in most patients (MOG-neg: 6/8; MOG-pos: 20/22). Bilateral intraorbital lesions were observed in 68,2% (15/22) of MOG-pos cases, whereas 50% (4/8) of MOG-neg patients had no intraorbital lesions. Swelling of the optic nerves was present in most MOG-pos patients (18/22), but rarely in MOG-neg patients (5/8). Results were not statistically significant due to a small MOG-negative patient group.
Abbreviations: Gd = Gadolinium; LEON = longitudinally extensive optic neuritis; LETM = longitudinally extensive transverse myelitis; ON = optic neuritis; TM = transverse myelitis.
[a] All adjusted p-values for multiple comparisons using Bonferroni's correction for multiple comparisons were higher than 0.05.
[b] Number of patients with Gd application: 6/8 MOG-neg patients; 20/22 MOG-pos patients.
[c] Number of patients with spinal MRI: 5/8 MOG-neg patients; 13/22 MOG-pos patients.

children were seropositive for MOG-abs and that not a single child with bilON was tested positive for AQP4-abs or was diagnosed with MS subsequently. Previously, a strong association of bilON with the presence of AQP4-abs has been postulated, but findings mainly relied on adult or Asian cohorts with NMOSD and incorporated not only symptoms at first presentation but also relapsing episodes [10–12]. Only recently MOG-positive NMOSD patients in pediatric and adult cohorts were identified [13–15].

In the present study, clinical presentation in MOG-positive bilON was mostly associated with profound visual impairment in both eyes, up to complete blindness and often with absent VEP. In contrast, visual function was largely preserved at least unilaterally in patients with MOG-negative bilON. Beside visual impairment, bilateral papillary edema and optic nerve swelling were prominent features in MOG-positive patients but not in seronegative patients. This is in line with our neuroradiological observations, showing a frequent involvement of the anterior part of the visual pathway in seropositive patients. In seronegative patients, the anterior part was less often affected. Further, our results show, that in particular the bilateral involvement of the intraorbital part discriminates MOG-positive from MOG-negative patients. Prominent optic disc swelling and frequent involvement of the intraorbital part of the optic nerve were recently reported in adult patients with MOG-positive ON [13,16–18], which is in stark contrast to patients with MS [19] and AQP4-positive NMOSD [20], who rarely present with papilledema. In the latter a more posterior inflammation with involvement of the intra-canalicular/intracranial optic nerve part and chiasma is usually observed [10,16,17,21], in contrast to more anterior inflammation with sparing of the chiasma in MOG-positive patients. Noticeably, especially patients with high MOG-ab titers had sparing of their chiasma.

Interestingly, in our cohort MOG-positive patients with bilON were younger at onset than seronegative patients. Usually, clinical presentation with isolated ON in MOG-positive children is described primarily in patients aged >10 years, compared to ADEM-like presentation with encephalopathy in young patients [22].

Longitudinally extensive optic neuritis (LEON) was more often observed in patients with MOG-abs compared to seronegative patients, which has been described already in adult patients with ON and MOG-abs [18,21] (Fig. 2). Akaishi et al. also found a high predictive value of lesion length for persisting visual impairment in AQP4-positive patients. In MOG-positive patients they described a favorable outcome, more pronounced LEON, more optic nerve swelling with inflammation of perineural tissue and more severe visual impairment in the acute phase [21,23]. Similarly, our results revealed that MOG-positive children are associated with mostly restitutio ad integrum despite LEON.

Characteristic laboratory findings in seropositive bilON showed high MOG-ab titers (median: 1:1280), slightly elevated cell count in CSF and absent OCBs. In a cohort of adult bilON patients, Ramanathan et al. also observed an association of bilON to MOG-abs,

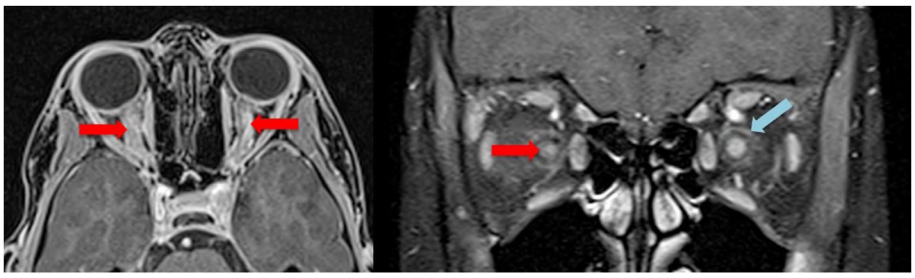

Fig. 2. Cerebral MRI of an eight-year-old girl with bilateral longitudinally extensive optic neuritis and MOG-antibodies.
Axial and coronal fat-suppressed, postcontrast T1-weighted images of an eight -year-old girl, who presented with moderate loss of vision in both eyes and bilateral papillary edema display marked bilateral contrast enhancement of the optic nerve (red arrow) as well as concurrent enhancement of the perioptic nerve sheath (blue arrow). MOG-abs testing was positive with a titer of 1:320. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

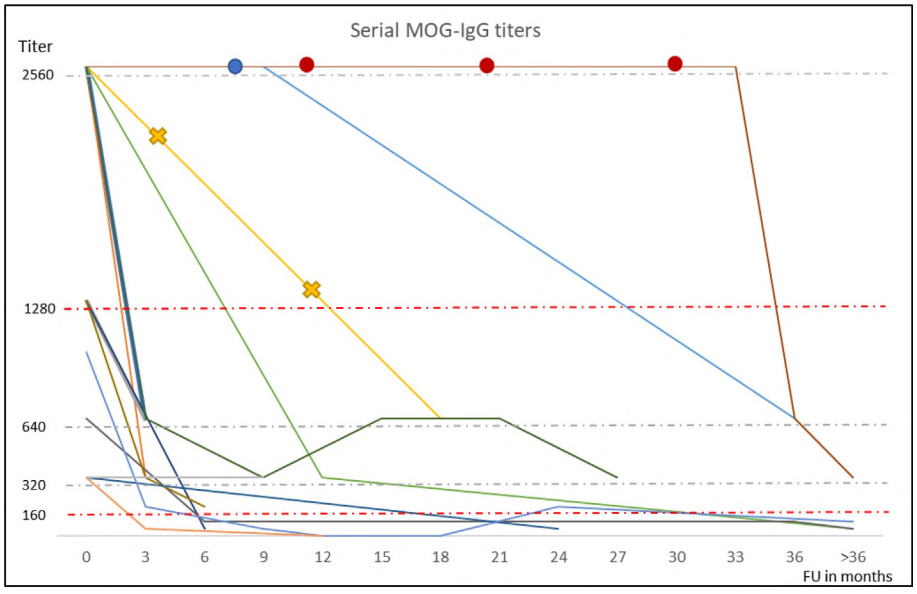

Fig. 3. Serial MOG-IgG titer and clinical course in MOG-IgG positive patients.
Every colour represents a patient with serial MOG-IgG testing.
Titer <1:160 - negative, titer >1:1280 – high positive
In 15/22 MOG-IgG positive patients serial MOG testing was performed. 3/15 patients had a relapsing clinical course. In all three patients MOG-IgG titers remained high or showed delayed descent respectively. Two patients had further ON attacks (**O**), one patient had two subsequent attacks with further neurological symptoms (**X**). In 12/15 patients with monophasic clinical course titers dropped to low or negative (<160) levels at first serial testing.
Abbreviations: FU = follow-up. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

but with significantly lower titers compared to our pediatric cohort: only 1/7 patient had a titer between 1:1000 and 1:2000 [13]. This is in line with previous findings, showing distinctly higher titers in children than in adults [24]. Absent intrathecal OCBs and papillary edema are further features that distinguish MOG-positive ON from ON in MS.

Nearly all MOG-positive patients showed a good response to therapy with IVMP, partly in combination with oral steroid tapering similarly to adult reports [13,23].

Two patients did not respond to IVMP treatment: in one patient complete resolution was observed after subsequent administration of IVIG and PLEX. The second patient presented with complete blindness and did not respond to repeated IVMP with oral tapering and PLEX. Treatment with RTX led to a stable disease course with no further episodes.

In our cohort most patients had a single episode and no further attacks during follow-up, contrary to previous studies, showing recurrent ON attacks in MOG-positive ON and bilON in the majority of patients mostly with time to first relapse in less than one year [13,16,25]. In our cohort the monophasic disease course was accompanied by declining or even undetectable levels MOG-ab titers (Fig. 3).

Notably, a small group of four MOG-positive patients with high MOG-ab titers had recurrent attacks. In all four patients further neurological symptoms or inflammatory lesions in MRI in addition to bilON were observed at first presentation, whereas a monophasic disease course was highly associated with isolated bilON. Polysymptomatic presentation and polyphasic disease course both showed an association to high MOG-ab titers. 2/5 patients with polysymptomatic disease onset and besides TM in MRI did not have a second demyelinating episode at last follow-up, however, in both patients follow-up was only four and six months, respectively. Hence, these two high-titer MOG-positive patients may have a high risk of relapse.

Despite an often severe clinical presentation, the majority of MOG-positive patients had a complete resolution of visual symptoms. As already mentioned, previous reports suggested that MOG-positive patients have a better visual acuity in follow-up studies

compared to AQP4-positive patients, in whom severe inquiry even after a single event is described [11,13,18,23,26,27]. In 10 children with MOG-abs, however, atrophy of the optic nerve on follow-up examination via fundoscopy or OCT was observed. Seven of these only had a single episode of bilON and only one child had mild permanent visual impairment. From the other MOG-positive patients no reports about the visual inspection of the optic disc was recorded. We therefore cannot exclude an even higher percentage of children with signs of optic atrophy. Hence, our results suggest a lasting physiological damage of the optic nerve already after a sole episode of MOG-positive ON, despite good visual acuity in follow-up studies, as it was recently reported by others [18].

The following limitations of this study have to be addressed. Most importantly, the number of included patients and in particular children with MOG-negative bilON was small, weakening the validity of comparing seropositive and seronegative groups. Secondly, although all patients fulfilled the inclusion criteria work-up, long term follow-up and serial MOG measurement varied between children. Especially, MR imaging for optic neuritis was not standardized, due to patient recruitment from different medical centers and countries. Unfortunately, OCT measurement at first presentation and during disease course in order to better quantify damage to the RNFL was only available from few selected patients and not part of this study. Thirdly, ethnicity was biased towards white population, because the cohort was recruited mainly in Europe. This is one probable explanation for the absence of AQP4- positive patients with bilON with a higher incidence in Asian populations [13].

5. Conclusion

BilON is a rare presentation in children with a first ADS and is strongly associated with serum MOG-abs, but not with AQP4-abs or MS. Children present with a severe vision loss and papilledema, resulting from LEON in the anterior part of the visual tract. They show distinct recovery with good response to IVMP. However, patients with initially high MOG-IgG titers and a polysymptomatic disease onset harbor a risk of a relapsing disease course.

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Declaration of competing interest

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