



E.U. paediatric MOG consortium consensus: Part 4 – Outcome of paediatric myelin oligodendrocyte glycoprotein antibody-associated disorders



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ABSTRACT

There is increasing knowledge on the role of antibodies against myelin oligodendrocyte glycoprotein (MOG-abs) in acquired demyelinating syndromes and autoimmune encephalitis in children. Better understanding and prediction of outcome is essential to guide treatment protocol decisions. Therefore, this part of the Paediatric European Collaborative Consensus provides an oversight of existing knowledge of clinical outcome assessment in paediatric MOG-ab-associated disorders (MOGAD). The large heterogeneity in disease phenotype, disease course, treatment and follow-up protocols is a major obstacle for reliable prediction of outcome. However, the clinical phenotype of MOGAD appears to be the main determinant of outcome. Patients with a transverse myelitis phenotype in particular are at high risk of accruing neurological disability (motor and autonomic), which is frequently severe. In contrast, having a single episode of optic neuritis any time during disease course is broadly associated with a lower risk of persistent disability. Furthermore, MOG-ab-associated optic neuritis often results in good functional visual recovery, although retinal axonal loss may be severe. The field of cognitive and behavioural outcome and epilepsy following demyelinating episodes has not been extensively explored, but in recent studies acute disseminated encephalomyelitis (-like) phenotype in the young children was associated with cognitive problems and epilepsy in long-term follow-up. In conclusion, main domains of importance in determining clinical outcome in paediatric MOGAD are visual, motor, autonomic and cognitive function. A standardised evaluation of these outcome domains in all children is of importance to allow adequate rehabilitation and follow-up.

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Abbreviations	
ADS	acquired demyelinating syndrome
ADEM	acute disseminated encephalomyelitis
ADEM-ON	ADEM followed by monophasic or recurrent ON
AQP4-ab	aquaporin-4 antibody
AQP4-ON	AQP4-ab-associated ON
AQP4-TM	AQP4-ab-associated TM
CNS	central nervous system
EDSS	expanded disability status scale
FSS	functional status scale
MDEM	multiphasic disseminated encephalomyelitis
MOG-ab	myelin oligodendrocyte glycoprotein antibody
MOGAD	MOG-ab-associated disorders
MOG-ON	MOG-ab-associated ON
MOG-TM	MOG-ab-associated TM
mRS	modified rankin scale
NMOSD	neuromyelitis optica spectrum disorders
OCT	optical coherence tomography
ON	optic neuritis
PROMs	patient reported outcome measures
RNFL	retinal nerve fibre layer
RON	relapsing ON
TM	transverse myelitis
VA	visual acuity

1. Introduction

Myelin oligodendrocyte glycoprotein (MOG) is expressed on the outer surface of the myelin sheath and oligodendrocytes exclusively in the central nervous system (CNS) [1]. Over the last decade, our understanding of the role of antibodies against MOG (MOG-abs) in acquired demyelinating syndromes (ADS) and autoimmune encephalitis (AE) in children and adults has increased [2–4]. The clinical spectrum of MOG-ab-positive disorders is wide and the term MOG-ab-associated disorders (MOGAD) is recommended to describe this spectrum of phenotypes [5]. Only in recent years studies have been published on MOG-ab status in prospective cohorts of children with ADS and AE, thus limiting the length of follow-up of many patients in these cohorts [4,6,7]. Nevertheless, these studies have shown that there is a high heterogeneity not only in clinical phenotype, but also in disease severity and disease course. Better understanding and prediction of outcome is essential to guide treatment protocol decisions [8]. While outcome related to radiological imaging and biomarkers is described in this special issue Part 2 and Part 3, respectively [9,10], this part of the Paediatric European Collaborative Consensus provides an oversight of existing

knowledge of clinical outcome assessment in paediatric MOGAD. Furthermore, consensus recommendations on defining and assessment of outcome in paediatric MOGAD are included.

2. Key elements of outcome assessment in paediatric MOGAD

There are several obstacles in attaining a correct estimate of disease characteristics and subsequent outcome. It is crucial to take the following key elements into account when assessing outcome.

In general, definition of outcome and selection of outcome variables has implications for assessment. The used outcome measures vary widely between studies analysing MOGAD patients. Whereas in some studies outcome variables such as motor or cognitive function are clearly described, others have used composite scales merely indicating “abnormal outcome” without always defining what this refers to. In a number of studies, the number of relapses or a relapsing disease course alone is considered outcome, without regard to the prevalence of subsequent deficits. While relapses are an important determinant of outcome, they cannot be considered as an outcome parameter per se and the delineation between these entities needs to be clear in our effort to

understand outcome and prognostic markers.

More specific for paediatric MOGAD is the phenotypical diversity, and its correlation to outcome needs to be addressed. In addition to the frequent MOGAD clinical presentations of acute disseminated encephalomyelitis (ADEM), optic neuritis (ON) and transverse myelitis (TM), also other less typical and rare presentations such as MOG-ab-positive encephalitis-like and leukodystrophy-like phenotypes, and non-classifiable syndromes are seen [5]. Additionally, prevalence of these diverse phenotypes differs according to age: Clinical events in patients nine years or younger have been shown to be more likely to affect the brain, whereas in patients older than nine years clinical events are more likely to affect the optic nerve [11]. Comparing outcome without considering age and its relation to the clinical phenotype is thus likely to give misleading results. In contrast, age appears not to differ with MOG-ab status within a clinical presentation as demonstrated in ADEM, ON and neuromyelitis optica spectrum disorders (NMOSD)-like phenotypes [5,12–17]. Furthermore, co-existence of other antibodies may also affect disease course and outcome, as indicated in adult studies of recurrent isolated ON positive for MOG-abs and Glycine receptor antibodies [18], and in demyelinating syndromes positive for MOG-abs and N-methyl-D-aspartate receptor (NMDA-R) antibodies [19]. However, the importance of such antibody co-existence has not been sufficiently characterised yet to estimate its influence on outcome. Finally, as most studies are of a retrospective and observational character, it is difficult to correct for treatment effect, which may influence outcome.

In conclusion, outcome may generally be evaluated from an immunobiological (monophasic vs. relapsing disease) or neurobiological (recovery following clinical attack) basis or a combination of both (progressive, relapse dependent or independent disability accrual). Regarding functional outcome, the MOGAD phenotype will likely determine the most affected domains; cognition in patients with ADEM phenotype, bladder and motor problems with TM phenotype, visual problems with ON phenotype and epilepsy with encephalitis-like phenotype. As the functional outcome will be highly dependent on the clinical phenotype, in future studies a standardised classification, as suggested in this special issue Part I [5], will be of importance in order to correctly predict outcome.

3. Outcome in general

A large mixed adult and paediatric cohort with 252 MOG-ab-positive patients showed that 78% of these patients had a good (not further specified) or full recovery from the initial attack, with more often a full recovery in paediatric patients and patients presenting with ON and ADEM/ADEM-like phenotypes [20]. At last follow-up, 41% had a full recovery, but around 25% had moderate or severe disability (again not further specified), which was associated with poor recovery from initial attack and with number of relapses. Another mixed cohort with 59 MOG-ab-positive patients showed that 42% of patients had a full recovery at last follow-up, also more common in case of ON or ADEM phenotype [21]. Of the patients experiencing residual disability, 24% had visual acuity (VA) loss, 15% sensory deficits, 14% motor deficits, 12% cognitive deficits, 10% bladder dysfunction and 3% epilepsy, but numbers specifically for paediatric patients were not shown [21]. Several studies with exclusively paediatric MOG-ab-positive patients described recovery of included patients and reported a complete recovery in 75–96% of patients in general [22,23], in 79% of patients with ADEM phenotype [12], and in 68% of patients with NMOSD (-like) phenotypes [13]. Overall, in paediatric patients low expanded disability status scale (EDSS) scores are reported at last follow-up; median EDSS 0–1, range 0–6 [7,13,23–25]. Importantly, although

numbers are limited in paediatric studies, cases with severe permanent sequelae have been reported [11–13]. Additionally, poor physical functioning may not always be reflected in EDSS scores, as is shown for ADS patients (regardless of MOG-ab status) [26].

In conclusion, paediatric MOG-ab-positive patients generally have a good outcome at last follow-up (overall 68–96% full recovery), but this is dependent on the onset attack type and possibly the number and type of following attacks during the disease course. Outcome and disability due to paediatric MOGAD potentially involves multiple domains including visual, motor, autonomic and cognitive functions, which are discussed below in detail.

4. Visual outcome

The optic nerve is an important target in MOG-ab-associated inflammation in both adult and paediatric patients, and often results in papillitis with prominent disc oedema due to anterior optic nerve involvement as well as simultaneous bilateral ON [2,5,15,21]. Isolated ON is the most common presenting clinical MOGAD phenotype in adulthood and second most common in childhood, after ADEM [27,28]. Moreover, ON can occur in association with additional inflammatory demyelinating attacks; at onset during an ADEM episode or simultaneously with TM; and sequentially as relapse in NMOSD-like phenotypes or following initial ADEM episode (ADEM-ON) [11–13]. This results in high percentages of optic nerve involvement at least once during total disease course, as observed in 47% of paediatric and 63% of adult MOG-ab-positive patients in a recent nationwide study in the Netherlands, including in total 61 patients [28]. The numbers in paediatric patients may even be underestimated, as ON diagnosis can be missed in young patients who may not be able to recognise and report their symptoms adequately, especially those presenting with encephalopathy in case of ADEM. The frequent and often bilateral optic nerve involvement in MOGAD underlines the importance of knowledge about the visual prognosis in these patients.

4.1. Visual disability

During acute MOG-ab-associated ON (MOG-ON), patients often have very severe vision loss, with a reported VA of 0.1 or less in 44–80% of paediatric patients, comparable to paediatric aquaporin-4-ab-mediated ON (AQP4-ON) [15,17,29,30]. However, MOG-ON patients overall showed a prompt and good recovery after steroid treatment, resulting in a VA of ≥ 0.5 in 98% [17], ≥ 0.8 in 89% [27] and complete recovery in 56–73% [30,31] of paediatric patients. MOG-ab-positive children with bilateral ON showed a comparable recovery [31]. This functional visual recovery of paediatric patients with MOG-ON was significantly better than observed in AQP4-ON [15,29,30], but comparable to double seronegative (i.e. MOG-ab and AQP4-ab negative) [15,29] and multiple sclerosis (MS) patients with ON [30], all paediatric. While the visual impairment at onset of disease was comparable in paediatric and adult MOG-ON patients [17,32–34], paediatric patients showed a better recovery at follow-up [17].

Only a few studies have analysed the relation between (the number of) relapses and visual outcome in MOG-ab-positive patients and reported inconsistent results. In adult MOG-ON patients, more relapses were associated with accumulating damage and functional visual impairment [35]. In paediatric MOG-ab-positive ADEM-ON patients, a high proportion of visual residual deficits was reported (60–70%) [36,37], which as described above, is higher than observed in paediatric MOG-ON patients. However, these visual residual deficits were not related to the number of relapses [37], possibly due to the small sample size. Furthermore, a study with paediatric ON patients (including MOG-ab-positive, AQP4-ab-

positive and MS patients) showed no relation between number of ON episodes and visual impairments in the whole group [30]. Further studies with larger sample sizes are needed to analyse a possible association between relapses and visual impairment.

4.2. OCT outcome

Optical coherence tomography (OCT) has been demonstrated to be a reliable and reproducible non-invasive technique to quantitatively measure axonal loss following ON in adults [38]. OCT, either measuring the retinal nerve fibre layer (RNFL), or its sub-components, the peripapillary region (pRNFL) and the ganglion cell and inner plexiform (GCIPL) layer, appeared to have utility in evaluating patients with MOG-ON [35,39]. In a recent meta-analysis of ten studies (two with paediatric and four with mixed paediatric and adult cohorts), the RNFL was identified to be more severely affected in antibody-mediated ON, but did not appear to distinguish between AQP4-ON and MOG-ON [40].

Despite its limitations, in part due to the paucity of good control data and careful controlling of acute oedema that can confound measurements, data from paediatric cohorts are beginning to emerge. Outside the acute period, which best evaluates the neurodegenerative sequelae following ON, two studies inform on the potential role of OCT. In a cohort of 42 children with relapsing demyelinating syndromes (MS, AQP4-ab-positive NMOSD and MOGAD), RNFL correlated with visual outcomes regardless of aetiology or frequency of relapses [30]. Worryingly, in a group of paediatric patients with MOG-ON, progressive reduction in RNFL occurred in the absence of overt clinical relapses and even with preservation of VA [16].

5. Motor and autonomic outcome

5.1. Motor disability

Irreversible deficits in motor function are reported in 6–15% of all MOGAD patients [21,25,41], and in up to 25% of MOGAD patients with a non-ON phenotype [42]. One study analysed 54 MOG-ab-positive patients (including 16 children) who presented with isolated TM or TM as component of a multifocal disease presentation like ADEM or NMOSD-like phenotypes [43]. At onset of disease, motor function was severely affected in the majority of these patients; only 26% of patients were able to walk independently, while the remaining needed a cane or walker (41%) or were even wheelchair dependent (33%). Nonetheless, these patients showed overall a good recovery, with a median modified rankin scale (mRS) of 1, resembling no significant disability (patients are able to carry out usual activities, despite some symptoms). In total, 6% of patients needed gait aid at last follow-up. Also in a large mixed paediatric and adult cohort of 75 prospectively followed MOG-ab-positive patients, 7% of patients ($n = 5$) had a limited mobility at last follow-up, defined as EDSS ≥ 4.0 , resembling limited walking distance or requiring gait aid [20]. However, four of these patients (80%) suffered from severe permanent motor disability (EDSS ≥ 6.0). Importantly, all these patients with limited mobility had a TM attack (with or without ON); in three patients TM was the onset attack (60%), and the disability was related to this onset attack; in the remaining two the disability was related to a subsequent TM relapse following ON (20%) and ADEM (20%), respectively. This is similar to the findings of other mixed paediatric and adult cohorts, which showed that the risk of having any neurological deficit and disability was substantially higher in TM compared to other demyelinating phenotypes (74–90% in TM versus 40–56% in ON and 41–53% in ADEM) [20,21]. Additionally, although younger patients were more likely to have a full recovery

than adults [20,41], in an exclusively adult MOG-ab-positive cohort complete recovery was only observed in 35% of MOG-ab-positive TM (MOG-TM) patients as compared to in 53% of MOG-ON patients [44].

In adults, MOG-ab-positive patients with (limited forms of) NMOSD-like phenotypes are shown to generally have a more favourable outcome with lower median recovery EDSS scores [45–49], and lower risk of motor disability [42,48], compared to AQP4-ab-positive patients, although accompanying brainstem involvement in MOG-TM increased EDSS scores at follow-up [46]. Additionally, the previously described mixed paediatric and adult study analysing MOG-ab-positive patients with TM once during disease course, showed lower mRS scores at follow-up, compared to (mainly adult) AQP4-ab-positive TM (AQP4-TM) patients [43]. In contrast, a paediatric study comparing 45 patients with such NMOSD-like phenotypes showed no differences in general recovery and EDSS scores specifically between MOG-ab positive, AQP4-ab positive or double seronegative patients (median EDSS 0 (range 1–6), 1 (range 0–4) and 1 (range 0–7), respectively) [13]. However, due to the rarity of AQP4-ab-positive NMOSD in paediatric patients [49], this study only included five AQP4-ab-positive patients, which may have influenced the outcome results. Compared to adult MS patients, the children and adults with MOG-TM showed no differences in mRS scores or the use of gait aid at last follow-up, although follow-up duration varied considerably (median 7.5 vs. 2 years, respectively) [43].

In conclusion, although the majority of MOGAD patients show a good overall recovery, MOG-TM is associated with the highest risk of permanent motor disability. Moreover, if permanent motor disability is present, it is often severe.

5.2. Autonomic disability

Besides the risk of irreversible motor sequelae, there is risk of autonomic disability following MOGAD, including bowel, urinary or sexual problems. Bowel problems can include constipation or incontinence; urinary problems can include urgency, hesitancy, incontinence and/or (frequent) urinary tract infections; sexual problems, which only have been reported for men, are usually caused by erectile dysfunction [46].

In a mixed paediatric and adult MOGAD cohort with prospectively collected data of 75 patients, permanent bowel and bladder dysfunction was reported in 20% and 28% of patients, respectively [20]. All these patients had a TM (isolated or as part of a multifocal disease; combined with ON or with ADEM/ADEM-like phenotype), and persistent bowel dysfunction only occurred in patients with bladder dysfunction as well. In the majority of these patients the bladder dysfunction originated from the onset attack (71%), and more than half of these patients required long-term catheterization (62%). Interestingly, severity of bladder dysfunction was not related to the severity of motor disability, as only 15% of the patients requiring catheterization had accompanying permanent motor disability (EDSS ≥ 4.0). This is in line with findings of the other mixed paediatric and adult cohort analysing TM in MOGAD, in which only 6% required gait aid (EDSS ≥ 6.0), but 44% of patients had bowel and/or bladder dysfunction at last follow-up [43]. Permanent erectile dysfunction is reported in 21–33% of male patients [20,43], of which almost half presented with TM [20]. It is not clear how many of the permanently disabled patients were children in these two described mixed cohorts, but statistical analysis of one showed that outcome was not significantly influenced by age at onset [20]. In adult MOG-TM cohorts higher percentages of persistent bowel, bladder and erectile dysfunction were reported already after a single TM episode; 38%, 59% and 46%, respectively [46]. In exclusively paediatric MOGAD cohorts, these symptoms

have only rarely been reported, possibly because these symptoms may be more difficult to recognise in paediatric patients, especially in young children. Studies which did report on bowel and/or bladder dysfunction in childhood included patients with ADEM or encephalitis-like phenotype as onset attack [4,12,37].

A recent study compared a large number of adult patients with MOG-TM to adult patients with AQP4-TM [46]. After a single TM episode, MOG-TM patients had more often persistent bladder dysfunction and erectile dysfunction, while the need for long-term catheterization and presence of persistent bowel symptoms was equal compared to AQP4-TM. However, while in AQP4-TM long-term catheterization was associated with severity of disease at last follow-up, in MOG-TM it was not [46], in line with studies described above [20,43]. Importantly, MOG-TM patients were shown to have a higher prevalence of conus involvement [43,46], which was associated with the need of long-term catheterization [46].

In conclusion, there is a high frequency of permanent autonomic disability following MOGAD as a result of the predilection of the conus in MOGAD with spinal cord involvement, most often affecting bladder function. The occurrence of these symptoms is only reported in a few studies with paediatric patients and observed in lower percentages. However, whether this indeed represents a better recovery in paediatric patients with less risk of autonomic disability, or whether this is due to under-reporting of these symptoms in paediatric patients remains to be determined. Nonetheless, it is relevant to be aware of the risk of autonomic disability and to monitor these symptoms during follow-up.

6. Cognitive outcome

Memory impairment, attentional problems, poor concentration and/or learning or academic difficulties are reported cognitive residual deficits following MOGAD, ranging from 10 to 50% of paediatric MOG-ab-positive patients [4,11,22,25,37,50,51]. In none of these studies cognitive impairment was tested in a structured fashion. Presence of these cognitive residual deficits (in the majority of studies also not further specified) was associated with a young age (<10 years old) [51], ADEM/ADEM-like phenotype [11,20,51] and abnormal intracranial MRI findings [11,25], including deep grey matter (thalamic and putaminal) lesions [51]. There is little data regarding whether cognitive sequelae increase with a relapsing disease course. A study comparing MOG-ab-positive ($n = 19$) and negative ($n = 14$) ADEM patients reported no cognitive deficits in the MOG-ab-positive patients (of which 79% had a monophasic disease course) [12]. Some studies with relapsing MOG-ab-positive patients reported high percentages of cognitive impairment in multiphasic disseminated encephalomyelitis (MDEM; 50–67%) [11,22,52] and ADEM-ON (30–47%) [11,37]. These studies showed a strong association to clinical presentation, as cognitive problems were significantly less frequently observed in NMOSD-like phenotypes (9%) and relapsing ON (RON; 0%) [11].

Fatigue, mood disorders and anxiety are not generally reported as a subsequent problem in children following MOGAD. These symptoms can interact with cognitive impairment and reduce health-related quality of life. As these are prevalent in other ADS such as MS [26,52,53], this may be an under-reported parameter in MOGAD. Importantly, the consequences of MOGAD on the developing brain and subsequent early cognitive dysfunction must be evaluated in children and should not be extrapolated from adult studies.

7. Other disabilities

Refractory epilepsy has been reported as residual deficit in

MOG-ab-positive patients as well [12,21,22,24,25,50]. While it was only observed in 3% of patients in a mixed paediatric and adult cohort [21], an exclusively paediatric cohort from China reported epilepsy in 14% of patients [25]. This can be explained by the fact that all patients with permanent problems in cerebral function or with epilepsy had an ADEM-like or leukodystrophy-like presentation [25], which are phenotypes mainly occurring in paediatric patients [5]. Interestingly, MOG-ab-positive ADEM patients were shown to have a greater risk of post-ADEM epilepsy, compared to the MOG-ab-negative ADEM patients [54]. Other reported residual sequelae include sensory deficits [21], brainstem dysfunction [25] and behavioural problems [24].

8. Prognostic factors for outcome

8.1. Relapsing disease course as outcome assessment

Whereas initial studies of MOGAD mainly identified a monophasic and benign disease course, recent data with longer clinical follow-up have demonstrated that a subset of patients will have a relapsing disease course [5,24,55]. The clinical challenge is to distinguish a worsening of symptoms following an initial improvement after acute treatment (often referred to as “flare-up”) from a true relapse, as these can have different prognostic and therapeutic implications [5,8]. Therefore, the consensus group defined a relapse as a new clinical episode accompanied by radiological evidence depending on the subtype of MOGAD, appearing at least one month subsequently to the last acute attack. On the contrary, a “flare-up” needs to be considered in case of re-occurrence of symptoms within one month (and up to three months in ADEM patients) after start of acute treatment and not meeting definition of a relapse [5,8].

In many studies, multiphasic disease and a relapsing disease course are regarded as outcome parameters, based on the concept that relapsing disease will accrue disability. Although this may be true, there is little supporting evidence from the paediatric literature yet. As discussed above, the chance of full recovery following an initial episode of paediatric MOGAD appears to be high, overall ranging from 68 to 96% [12,13,22]. In contrast, a relapsing disease course appears to be associated with worse outcome with full recovery seen in only 31–50% of paediatric patients [11,25,50]. However, it has to be noted that the described studies were not designed for direct comparison. Additionally, two large mixed paediatric and adult cohorts with MOG-ab-positive patients showed that disability was worse with increasing number of relapses [20,21]. Furthermore, all the patients with a high number of relapses (≥ 7) had residual deficits (none returned to an EDSS of 0), which is suggestive of cumulative disability with relapses [21]. In the following, we will consider prognostic factors for a relapsing disease course and the development of functional disabilities separately.

8.2. Prognostic factors for relapsing disease course

During the past years, the prognostic value of the presence of MOG-abs has been analysed in several studies. MOG-abs were initially associated primarily with ADEM and with a monophasic disease course. In two cohort studies from 2011, each with 25 ADS patients and serial MOG-ab testing, it was observed that the ADEM patients with rapidly decreasing MOG-ab titres had no further relapses during two to five years follow-up [56,57], while the small subgroup of paediatric patients with high and persisting MOG-ab titres had a tendency to relapse [57]. Subsequently, several reports described an association between patients with a relapsing disease course and persisting high MOG-ab titre levels, both in

small cohorts [13,36,50,58] and a larger cohort of 210 paediatric patients with a first ADS [24]. This larger paediatric study described a relevant prognostic value of high persisting MOG-ab titres ($\geq 1:1280$) for a multiphasic disease course, whereas rapidly decreasing titre levels pleaded for a monophasic course, as supported by others [20,56–58]. However, two more recent large paediatric studies showed that a minor proportion of patients still have further relapses after converting from a seropositive to negative status (13%) [55], with some cases showing reconversion to seropositive status during the relapse(s) [49,55]. Nevertheless, this risk of relapse after conversion to seronegative status was clearly lower than observed with persistent seropositive status (13% vs. 38%, respectively) [55]. Therefore, a persistent positive MOG-ab titre during follow-up has prognostic value, but importantly, because median time to become seronegative is one year [55], the MOG-ab titre at onset of disease has not [7,24,49,55,58].

Relapse risk is dependent on the clinical onset attack of MOGAD, with a clear association between ON and frequent relapses in both paediatric and adult patients [21,59,60]. Interestingly, some studies even reported a higher frequency of relapses in MOG-ON compared to AQP4-ON patients [15,30,32,35], observed for adult [32,35] and paediatric [15,30] patients. Additionally, in ADEM-ON patients a shorter time to first relapse was associated with a higher frequency of relapses after the first ON [37]. Only a minor proportion of children presenting with MOG-TM had relapses, 0–14% with recurrent MOG-TM [13,21,49,55] and 14–21% with recurrent NMOSD-like phenotypes [13,21], which is lower compared to patients with MOG-ON (31–46%) [21,49,55]. Of the children presenting with an ADEM phenotype, about one third will subsequently have a recurrent disease course [24,49].

Older age at onset of disease has also been described as a strong predictor for a multiphasic disease course [24,55]. However, the age-related distribution of clinical phenotypes of MOGAD has to be considered [5]; patients with higher age at onset more often present with ON phenotype that has a higher tendency to relapse [36,44,59], compared to the ADEM phenotype which is a presentation seen mainly in younger patients. Nevertheless, when comparing MOG-ON patients in different age groups, children showed a lower annualized relapse rate compared to adults [17], supporting older age as prognostic factor for relapse.

8.3. Prognostic factors for poor outcome

Although MOGAD patients often have severe disease burden at onset, symptoms in children have a high potential of complete resolution following treatment with intravenous methylprednisolone. The severity of symptoms during onset attack is not predictive for the clinical outcome, but possibly the recovery from this initial event is, as reported in one large mixed study [20].

Importantly, the clinical phenotype of MOGAD appears to be the main determinant of outcome. Particularly patients with a TM phenotype are of high risk of neurological residuals, potentially severe, both described in paediatric and adult cohorts [20,21,44]. In contrast to the TM phenotype, the ON phenotype ever during disease course was shown to be associated with a lower risk of persistent disability [21].

In comparison to visual and motor deficits, the field of cognitive and behavioural residual deficits or epilepsy after demyelinating episodes has not been extensively explored. Recent studies have demonstrated that an ADEM(-like) phenotype [11,20,25,51,54] and extensive supratentorial white matter lesions during an acute attack [11,25] often lead to cognitive problems and epilepsy in long-term follow-up. Additionally, a recent study reported that presence of deep grey matter lesions and young age (<10 years) was associated with academic difficulties, a surrogate marker of cognition

[51].

Finally, laboratory findings in blood or cerebrospinal fluid (CSF) do not seem to have a predictive value for the disease course or outcome. However, one study hypothesised that elevated CSF protein might be a marker for a more necrotic or inflammatory process, as all paediatric patients with neurological sequelae (5/20) had elevated protein levels compared to 13% in the group of patients without sequelae (2/15) [22].

9. Consensus recommendations on outcome assessment in paediatric MOGAD

As described in previous sections, only few publications give detailed information on visual, motor, bowel/bladder, or cognitive sequelae in paediatric MOGAD. There is no standard reporting or scoring of sequelae in these patients, which impedes direct comparison. Functional visual recovery is often good, although OCT scans show severe damage, which may progress regardless of clinical relapses. Permanent motor and bowel/bladder disabilities are mainly associated with a TM phenotype. While permanent motor disability appears to be rare, bowel/bladder sequelae may be more prevalent, as in adult MOGAD patients. In contrast, cognitive dysfunction is mainly associated with an ADEM phenotype, but most studies do not mention this outcome parameter specifically and none have performed any structured testing. Comparing existing data in paediatric MOGAD to describe outcome and different outcome parameters is therefore complex. Table 1 gives an overview of the risk of disability severity per outcome domain in the typical phenotypes of paediatric MOGAD, based on personal experience. This includes the risk of sequelae, and if present, the severity of those sequelae.

One of the conclusions from this and the other reviews in this focus topic [5,10] is that the large heterogeneity in disease phenotype, disease course, treatment and follow-up protocols is a major obstacle for determining outcome. In order to resolve this, a standardised classification of a) clinical phenotypes as suggested in this special issue Part 1 [5], b) timing of follow-up assessment and c) determination of adequate outcome domains are essential steps. The main domains of importance in determining clinical outcome in paediatric MOGAD are visual function, motor function, autonomic function and cognition. As a considerable proportion of MOGAD will have a multiphasic disease course with combinations and overlap of different clinical phenotypes, e.g. ADEM-ON, TM followed by ON or reversed, we recommend assessing all of the main domains according to a standardised protocol in all children with MOGAD, rather than letting the initial presentation determine an outcome evaluation protocol. The different domains that should be assessed and possible testing tools are described below and summarised in Table 2. One obvious and common issue for all tests and domains is that age must be considered when choosing appropriate testing methods. Composite scales such as the mRS and the functional status scale (FSS) may be useful as research tools to allow comparison on a group level, but are not designed for all the needed domains and include others that are of less importance in MOGAD.

9.1. Recommendations visual domain

Assessment of visual outcome has become an important component of evaluating outcome in demyelinating disorders also beyond ON. Optimising the evaluation of vision in children, utilising low contrast as well of high contrast VA and OCT is important for correct evaluation of outcome. Timing of visual evaluation with OCT should be at least six months after ON due to possible confounding of acute oedema.

Table 1
Risk of disability severity per outcome domain in typical phenotypes of paediatric MOGAD*.

Domain	ADEM phenotype	ON phenotype	TM phenotype	NMOSD-like phenotype
Visual function	+	+/+ [#]	(+)	+/+ [#]
Motor function	+	(+)	+++	+++
Autonomic function	++	(+)	+++	+++
Cognition	+++	(+)	(+)	+
Health Related QoL	+++ [^]	+++ [†]	+++ [§]	+++ ^{†, §}

No to minimal risk (+), mild risk +, moderate risk ++, high risk +++.

*Including risk of sequelae, and if present, the severity of sequelae; based on personal experience.

[#]Mild risk of functional sequelae +, but moderate risk of axonal damage on OCT ++.

[^]e.g. cognitive problems, academic difficulties, bowel/bladder dysfunction.

[†]e.g. concerns about going blind.

[§]e.g. bowel/bladder dysfunction, motor disability.

ADEM = acute disseminated encephalomyelitis, NMOSD = neuromyelitis optica spectrum disorders, OCT = optical coherence tomography, ON = optic neuritis, QoL = quality of life, TM = transverse myelitis.

Table 2
Recommendations on outcome assessment following paediatric MOGAD.

Domain	Parameters	Possible testing tools
Visual function	Visual acuity Retinal fibres	High and low contrast VA OCT with (p)RNFL and MV
Motor function	Gross motor function Fine motor function Manual dexterity	EDSS MACBII ASIA
Autonomic function	Urological assessment	Six-minute walk test Voiding/defecation diary and questionnaires Physical examination Uroflowmetry with EMG Determination of PVR with ultrasound
Cognition	Global intelligence Attention Language Executive functioning Verbal learning and memory Visuospatial processing, learning and memory	WISC-IV, WASI-II SDMT, TMT WASI-II TMT, CNT SRT Beery VMI, BVMTR MUSICADO
Health Related QoL	Fatigue Quality of Life	PedsQL with fatigue module MUSICADO

Abbreviations: ASIA = American spinal injury association impairment scale, BVMTR = brief visuospatial memory test–revised, CNT = contingency naming test, EDSS = expanded disability status scale, EMG = electromyogram, MABC = movement assessment battery for children, MUSICADO = multiple sclerosis inventory of cognition for adolescents, MV = macular volume, OCT = optical coherence tomography, PedsQL = paediatric quality of life inventory, (p)RNFL = (peripapillary) retinal nerve fibre layer, PVR = post-voiding residue, QoL = quality of life, SDMT = symbol digit modalities test, SRT = selective reminding test, TMT = trail-making test, VA = visual acuity, VMI = visual-motor integration, WASI = Wechsler abbreviated scale of intelligence, WISC = Wechsler intelligence scale for children.

9.2. Recommendations motor domain

Motor outcome in demyelinating diseases is typically assessed by the EDSS. Although EDSS assessment remains difficult in children, especially in the lower range and in case of encephalopathy, it should be evaluated in conformity with other ADS. However, as EDSS does not reflect physical functioning well in the paediatric population [26], it is important to also include other validated scales. One such scale is the ‘movement assessment battery for children second edition’ (MABCII), which includes manual dexterity, ball and balance skills [26]. Alternative scales include the ‘American spinal injury association’ (ASIA) impairment scale. Functional measures such as the six-minute walk test used in neuromuscular disorders have not been validated for paediatric ADS, but may offer important information. Timing of motor evaluation should be at least six months after the clinical attack.

9.3. Recommendations autonomic domain

Bladder function should be assessed with standard urological testing for screening of neurogenic bladder problems, including voiding/defecation diary, questionnaires and a physical examination. In patients with signs of bladder problems, uroflowmetry with

electromyogram (EMG) and determination of post-voiding residue (PVR) with ultrasound should be performed in order to detect and treat urinary problems and prevent potential damage to the upper urinary tract [61]. Patients and/or parents should be asked for bowel dysfunction, and depending on the age of the patient, erectile dysfunction should be evaluated. All patients should be examined early in their disease with follow-up evaluation at six months after the clinical attack.

9.4. Recommendations cognitive domain

Cognitive outcome should assess global intelligence, attention, language, executive functioning, verbal learning and memory, visuospatial processing, learning and memory, as suggested for paediatric MS [62]. Adjustment for the age of the patient, but also the differences on developmental trajectories and pattern of cognitive dysfunction related to that age, need to be considered when selecting test batteries [62]. The recently described ‘multiple sclerosis inventory of cognition for adolescents’ (MUSICADO) is a brief screening instrument to assess cognitive dysfunction, fatigue and loss of health-related quality of life in paediatric-onset MS [63], and may also be useful in MOGAD. Timing of first cognitive evaluation should be at least six months after the clinical attack and after

cessation of steroid treatment. Follow-up evaluations should be performed every year or once in two years.

9.5. Recommendation additional tests

In addition to the above-mentioned domains, standardised and validated questionnaires of 'patient-reported outcome measures' (PROMs) completed by patients to measure their perception of their functional well-being health status and quality of life should be performed. Fatigue and signs of depression should also be evaluated. The MUSICADO test may fill this purpose.

In conclusion, a standardised evaluation of above-mentioned outcome domains in all children is of importance to allow adequate rehabilitation and follow-up for the individual child. Furthermore, careful longitudinal follow-up will unravel if timing (first event versus relapse) and the severity of relapses are additional confounders in addition to the inflammatory load as measured by clinically evident or silent relapses. Only then will we be able to extend the utility to inform on treatment decisions.

Author agreement and contribution

Arlette L. Bruijstens: Active participation in multiple consensus discussions, data extraction, interpretation of the data, draft and revision of the manuscript.

Markus Breu: Active participation in multiple consensus discussions, data extraction, interpretation of the data, draft and revision of the manuscript.

Eva-Maria Wendel: Active participation in multiple consensus discussions, data extraction, interpretation of the data, draft and revision of the manuscript.

Evangeline Wassmer: Active participation in multiple consensus discussions, revision of the manuscript for content.

Ming Lim: Active participation in multiple consensus discussions, data extraction, interpretation of the data, draft and revision of the manuscript.

Rinze F. Neuteboom: Active participation in multiple consensus discussions, data extraction, interpretation of the data, draft and revision of the manuscript.

Ronny Wickström: Active participation in multiple consensus discussions, data extraction, interpretation of the data, draft and revision of the manuscript.

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Declaration of competing interest

Arlette L. Bruijstens, Markus Breu and Eva-Maria Wendel have no conflict of interest to declare. Evangeline Wassmer has served as a consultant for Novartis and Biogen, PTC therapeutics, GMP-Orphan and Alexion. She is an investigator in trials with Alexion, Biogen Idec, Sanofi and Novartis. Her MS research projects have been funded by the UK MS Society, Action Medical Research and Birmingham Children's Hospital Research Foundation. Ming Lim has received consultation fees from CSL Behring, Novartis and Octapharma; received travel grants from Merck Serono; and was

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