Postprint: Phenotypic Characteristics and Relapse Factors in Pediatric Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease

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Abstract

Background Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD) accounts for a significantly higher proportion in children than in adults. Although some studies have been conducted, the characteristics and associations of disease-related phenotypes and relapse risk in children remain unclear.

Objective To observe the phenotypic characteristics and relapse factors of serum MOG antibody-positive central nervous system (CNS) demyelinating diseases.

Methods A follow-up study was conducted on 54 children diagnosed with MOGAD at our hospital from December 2017 to December 2021, with retrospective analysis of clinical phenotypes, laboratory examinations, imaging characteristics, changes in MOG antibody titers in blood/cerebrospinal fluid, therapeutic efficacy, and high-risk factors for relapse during each attack. MOG antibodies were detected using cell-based assay (CBA).

Results The median age of onset for the 54 pediatric patients was 6.2 years (range: 0.5–15.0 years), with a male-to-female ratio of 1:1.07. Serum MOG antibody titers ranged from 1:10 to 1:320. Acute disseminated encephalomyelitis (ADEM) was the most common phenotype (24/54, 44.4%), followed by optic neuritis (ON) (14/54, 25.9%) and meningitis/encephalitis (10/54, 18.5%). Ten patients (10/54, 18.5%) were positive for MOG antibodies in both blood and cerebrospinal fluid, and two patients (2/54, 3.7%) were double-positive for N-methyl-D-aspartate receptor (NMDAR) antibodies in cerebrospinal fluid and MOG antibodies in blood. Among 78 demyelinating events, brain MRI showed acute lesions in 60/78 (76.9%) cases, with the most common locations being juxtacortical white matter (40/60, 66.7%), optic nerve (21/60, 35.0%), basal ganglia (19/60, 31.7%), cerebellum (17/60, 28.3%), brainstem (11/60, 18.3%),

and corpus callosum (11/60, 18.3%). Forty patients had a monophasic course (40/54, 74.1%), with the main clinical phenotypes being ADEM (23/40, 57.5%) and non-ADEM-like meningitis/encephalitis (10/40, 25.0%); 14 patients experienced a relapsing course with two or more episodes (14/54, 25.9%), with the main clinical phenotypes being ADEM with ON (8/14, 57.1%) and recurrent ON (3/14, 21.4%). During follow-up, 8 patients relapsed, but MOG antibody titers did not increase during the acute phase; in one case, the titer decreased from 1:100 to 1:32, while the remaining 7 patients showed no change in antibody titers. Twenty-eight children (28/54, 51.9%) achieved complete clinical recovery, while 11 children (11/54, 20.4%) had various sequelae, with visual impairment (6/11, 54.5%) being the most common sequela; some patients also had epilepsy (5/11, 45.5%), cognitive impairment (4/11, 36.4%), and motor impairment (2/11, 18.2%).

Conclusion MOGAD exhibits diverse clinical phenotypes, with ADEM, ON, and meningitis/encephalitis being common in children. MRI lesions are widespread, and leukodystrophy-like phenotypes can occur in infancy. First-onset ADEM combined with ON and recurrent ON are high-risk phenotypes for relapse; most children have a favorable prognosis, though some may have neurological sequelae.

Full Text

Phenotypic Characteristics and Recurrence Factors of Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease in Children

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Abstract

Background: The proportion of myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD) is significantly higher in children than in adults. Although some studies have been conducted, the characteristics and associations of disease-related phenotypes and recurrence risk in children remain unclear.

Objective: To observe the phenotypic features and recurrence factors of MOG antibody-positive central nervous system (CNS) demyelinating diseases in children.

Methods: We conducted a follow-up study of 54 children with MOGAD diagnosed in our hospital from December 2017 to December 2021. We retrospectively analyzed the clinical phenotype, laboratory tests, imaging characteristics, changes in MOG antibody titers in blood/cerebrospinal fluid (CSF), treatment efficacy, and high-risk factors for recurrence during each attack. MOG antibodies were detected using cell-based assay (CBA) with cell-transfection immunofluorescence.

Results: The median age at onset of the 54 children was 6.2 years (range: 0.5–15.0 years), with a male-to-female ratio of 1:1.07. Serum MOG antibody titers ranged from 1:10 to 1:320. Acute disseminated encephalomyelitis (ADEM) was the most common phenotype (24/54, 44.4%), followed by optic neuritis (ON) (14/54, 25.9%) and meningitis/encephalitis (10/54, 18.5%). Ten cases (10/54, 18.5%) were positive for MOG antibodies in both blood and CSF, while 2 cases (2/54, 3.7%) were double-positive for N-methyl-D-aspartate receptor (NMDAR) antibodies in CSF and MOG antibodies in serum. Among 78 demyelinating events, brain MRI showed acute lesions in 60/78 (76.9%) cases. The most common lesion locations were juxtacortical white matter (40/60, 66.7%), optic nerve (21/60, 35.0%), basal ganglia (19/60, 31.7%), cerebellum (17/60, 28.3%), brainstem (11/60, 18.3%), and corpus callosum (11/60, 18.3%). Forty patients (40/54, 74.1%) had a monophasic course, with main phenotypes of ADEM (23/40, 57.5%) and non-ADEM-like meningitis/encephalitis (10/40, 25.0%). Fourteen patients (14/54, 25.9%) experienced two or more relapses, with main phenotypes of ADEM with ON (8/14, 57.1%) and recurrent ON (3/14, 21.4%). During follow-up, 8 children relapsed, but their MOG antibody titers did not increase during the acute phase; one case decreased from 1:100 to 1:32, while the other 7 cases showed no change. Twenty-eight children (28/54, 51.9%) achieved complete clinical recovery, while 11 (11/54, 20.4%) had various sequelae. Visual impairment (6/11, 54.5%) was the most common sequela, with some patients also experiencing epilepsy (5/11, 45.5%), cognitive impairment (4/11, 36.4%), and motor impairment (2/11, 18.2%).

Conclusion: MOGAD exhibits diverse clinical phenotypes in children, with ADEM, ON, and meningitis/encephalitis being the most common. MRI lesions are extensive, and leukodystrophy-like phenotypes can occur in infancy. Initial presentation with ADEM combined with ON and recurrent ON are high-risk phenotypes for relapse. Most children have a favorable prognosis, though some may have neurological sequelae.

Keywords: Myelin oligodendrocyte glycoprotein; Child; Demyelinating disease; Clinical phenotype; Recurrence

Introduction

Inflammatory demyelinating diseases of the central nervous system (CNS) constitute a heterogeneous group of autoimmune inflammatory diseases, including multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), myelitis, and some complex cases with undetermined etiology. Different types of acquired demyelinating diseases often have overlapping clinical phenotypes, making definitive diagnosis difficult at initial onset, yet each disease requires different treatment strategies. Myelin oligodendrocyte glycoprotein (MOG) is a myelin protein expressed on the outermost layer of CNS myelin and is considered an important target in inflammatory demyelinating diseases [**?**]. MOG is expressed in mature oligodendrocytes and plays an important role in maintaining myelin integrity and cell adhesion, though its specific mechanisms remain unclear.

MOG antibody-mediated inflammatory demyelinating disease has emerged as a distinct disease spectrum, termed MOG-IgG associated disorders (MOGAD) [**?**]. Multiple studies have shown that the proportion of MOGAD patients who are children is significantly higher than that of adults [**?**, **?**]. MOGAD has a broad clinical spectrum, manifesting as ADEM, ON, brainstem encephalitis, myelitis, and meningitis/encephalitis, among others. These conditions are not easily recognized early, and some patients may experience recurrent attacks. Further research is needed to clarify the characteristics and associations of these related phenotypes and recurrence factors in children. The primary objective of this study was to evaluate the clinical phenotypes, treatment efficacy, and prognosis of pediatric MOGAD and to assess the relationship between phenotype and recurrence.

Methods

1.1 Study Subjects

We retrospectively analyzed the clinical data of 54 children with a definitive diagnosis of MOGAD who were hospitalized in the Department of Neurology of our hospital from December 2017 to December 2021. The data included age, sex, clinical phenotype, laboratory and imaging examinations, changes in MOG antibody titers, treatment efficacy, and recurrence status. This study was approved by the Ethics Committee of Children' s Hospital of Hebei Province (Medical Research Ethics Review 202103) and obtained informed consent from parents.

1.2 Diagnostic Criteria and Antibody Assay

MOGAD diagnostic criteria followed the 2020 Chinese Expert Consensus on Diagnosis and Treatment of MOGAD [**?**]. All 54 included children tested positive for serum MOG-IgG using cell-based assay (CBA) with full-length human MOG

as the target antigen. ADEM-ON was defined as ADEM accompanied by ON. Relapse was defined as new clinical manifestations and MRI lesions occurring more than 30 days after the initial attack, or more than 30 days after ADEM diagnosis.

Blood and/or CSF samples from the children were sent to Peking Union Medical College Hospital for detection of MOG-IgG, AQP4-IgG, and other autoimmune antibodies using CBA.

1.3 Statistical Analysis

Data analysis was performed using SPSS 22.0 statistical software. Normally distributed measurement data were expressed as mean ± standard deviation, while skewed distribution data were expressed as median. Comparisons between two groups were performed using independent samples t-test; non-normally distributed measurement data were expressed as median. Count data were expressed as number (percentage), and comparisons between groups were performed using chi-square test or Fisher' s exact test; comparisons among multiple groups were performed using chi-square test for multiple sample rates. $P<0.05$ was considered statistically significant.

Results

2.1 Clinical Characteristics

Among the 54 children with MOGAD, there were 26 males and 28 females, with a male-to-female ratio of 1:1.07. The median age at onset was 6.2 years (range: 0.5–15.0 years). Initial clinical symptoms were diverse, including encephalopathic manifestations such as decreased consciousness, delirium, apathy, somnolence, vomiting, and headache (31/54, 57.4%), fever (19/54, 35.2%), vision loss (14/54, 25.9%), seizures (8/54, 14.8%), and limb weakness (6/54, 11.1%). Forty-three children (43/54, 79.6%) presented with two or more clinical symptoms simultaneously at first attack. Serum MOG antibody titers ranged from 1:10 to 1:320. ADEM was the most common phenotype (24/54, 44.4%), followed by ON (14/54, 25.9%) and meningitis/encephalitis (10/54, 18.5%).

2.2 Imaging Findings

Among 78 acute demyelinating events, brain MRI showed new lesions in 60/78 (76.9%) cases. Brain lesions were extensive and varied [Figure 1: see original paper], often appearing as hyperintense signals on FLAIR imaging, with some showing confluent white matter lesions that were fluffy, diffusely distributed, and poorly demarcated, resembling leukodystrophy. Orbital MRI could show bilateral or unilateral optic nerve thickening or signal changes, sometimes involving the optic chiasm. Common intracranial lesion sites included juxtacortical white matter (40/60, 66.7%), optic nerve (21/60, 35.0%), basal ganglia (19/60,

31.7%), cerebellum (17/60, 28.3%), brainstem (11/60, 18.3%), and corpus callosum (11/60, 18.3%). Brain MRI lesions completely disappeared in 10 cases (10/60, 16.7%) and improved in 26 cases (26/60, 43.3%). Two cases (2/60, 3.3%) showed a leukodystrophy-like pattern on brain MRI at initial presentation and relapse. Nine children (9/54, 16.7%) showed only linear meningeal enhancement on cranial MRI with mildly elevated CSF white blood cells. Spinal MRI could show mild swelling of lesions with small patchy or strip-shaped hyperintense signals [Figure 1: see original paper]. Among 78 disease courses, spinal MRI showed lesions in 15 events (15/78, 19.2%), involving thoracic cord (6/15, 40.0%), conus medullaris (6/15, 40.0%), cervical cord (4/15, 26.7%), and lumbar cord (2/15, 13.3%).

2.3 Laboratory Examinations

All children underwent CSF examination after admission. CSF white blood cell count was elevated in 35 cases (35/54, 64.8%) (range: 13–106 $\times$ 10^6/L), with a median of 24.0 $\times$ 10^6/L. CSF protein median was 0.36 g/L (range: 0.20–0.89 g/L), with 12/35 (34.3%) $ 0.6g/L.CSFpressurewasmeasuredin28children(28/54, 51.9_{2}$O) that normalized after treatment. Ten children (10/54, 18.5%) were positive for MOG-IgG in both blood and CSF, with no cases showing simultaneous positivity for AQP4-IgG and MOG-IgG in CSF or serum. Two children (2/54, 3.7%) were double-positive for NMDA-IgG in CSF and MOG-IgG in serum.

2.4 Treatment and Recurrence

All children received first-line immunomodulatory therapy, with most acute clinical symptoms achieving remission. Forty children (40/54, 74.1%) had a monophasic course, with main phenotypes of ADEM (23/40, 57.5%) and non-ADEM-like meningitis/encephalitis (10/40, 25.0%). Fourteen children (14/54, 25.9%) experienced two or more relapses, with main phenotypes of ADEM with ON (8/14, 57.1%) and recurrent ON (3/14, 21.4%) ($P<0.05$). Other phenotypes and initial clinical manifestations showed no statistical significance between monophasic and relapsing courses ($P>0.05$) . During follow-up, 8 children (8/54, 14.8%) had two or more clinical attacks, with 2 cases (2/8, 25.0%) achieving symptom relief after mycophenolate mofetil treatment and 6 cases (6/8, 75.0%) showing improvement in symptoms and imaging after retreatment with methylprednisolone pulse therapy combined with immunoglobulin. MOG antibody titers did not increase in these 8 children at relapse; one case decreased from 1:100 to 1:32, while the other 7 cases showed no change. Twenty-three children (23/54, 42.6%) underwent sequential blood sampling (every 4–6 months) for evaluation: MOG antibody titers turned negative in 1 case (1/23, 4.3%), decreased in 1 case (1/23, 4.3%), and remained unchanged in 21 cases (21/23, 91.3%). At the most recent follow-up, 28 children (28/54, 51.9%) had complete resolution of clinical symptoms, while 11 (11/54, 20.4%) had various sequelae. Visual impairment (6/11, 54.5%) was the most common neurological sequela, with some patients also experiencing epilepsy (5/11, 45.5%), cognitive impair-

ment (4/11, 36.4%), and motor impairment (2/11, 18.2%).

Discussion

MOG-IgG–associated disorder (MOGAD) is an acquired inflammatory demyelinating disease that is easily misdiagnosed in its early stages. With increasing understanding of MOGAD, different clinical phenotypes can be identified based on clinical manifestations, laboratory tests, and imaging results, such as non-classical MS, ADEM, ON, AQP4-negative NMOSD, myelitis, or meningitis/encephalitis. Early identification and treatment of these combined factors have important implications for disease prognosis. This study found that initial clinical symptoms of MOGAD are diverse, manifesting as fever, headache, decreased consciousness, vision loss, motor impairment, and other symptoms, with corresponding clinical presentations depending on the affected sites. Some studies have shown that the ADEM phenotype is more common in pediatric MOGAD patients than in adults, exhibiting age dependence [**?**] and mostly monophasic courses. In our pediatric cohort, ADEM was the most common phenotype, followed by ON and non-ADEM-like meningitis/encephalitis, consistent with previous research. This age-dependent presentation of clinical phenotypes may reflect changes in MOG expression at different stages of brain development and CNS maturation during childhood [**?**].

Currently, the imaging characteristics of MOGAD patients remain unclear. On brain MRI, MOGAD patients show a significantly higher proportion of large intracranial lesions compared with AQP4-IgG-positive patients [**?**]. Imaging lesion distribution in children appears to be age-related, with lesions in younger children being more poorly demarcated and more extensive compared with older children [**?**]. Domestic reports indicate that 81.43% of MOGAD patients have abnormal intracranial lesions on cranial MRI, with 65.22% of supratentorial white matter lesions showing ADEM-like or leukodystrophy-like patterns, and leukodystrophy-like lesions occurring only in MOG antibody-positive patients [**?**]. In our study of 78 acute demyelinating events, 76.9% showed acute lesions on cranial MRI, involving supratentorial and infratentorial white matter, periventricular regions, brainstem, cerebellum, thalamus, temporal lobe, and retrobulbar optic nerve segments to varying degrees, which is basically consistent with domestic research data [**?**]. The leukodystrophy-like phenotype is common in young children, generally aged 2–4 years [**?**], but the youngest child with this phenotype in our case series was only 6 months old, which is rarely reported previously. Some reports suggest that MOG antibody-positive inflammatory demyelinating diseases tend to involve the lower spinal cord, such as thoracolumbar spinal cord and conus [**?**]. However, spinal MRI lesions in our study mainly involved the cervical and thoracic regions, which is inconsistent with previous research and may be related to sample size and enrollment bias during the specific time period, requiring further large-sample studies.

Seizures and encephalopathy may represent a new clinical phenotype of MOGAD, with or without demyelination [**?**]. Although the time interval between isolated seizures and new demyelinating events ranges from months to years, subsequent demyelinating events suggest that a potential immunopathogenic mechanism may already exist at the time of isolated seizures. A retrospective study found that 12.2% of children with MOGAD experienced seizures, including 2 with status epilepticus [**?**]. In our study, 14.8% of children had seizures, and 76.9% had abnormal cranial MRI findings, but no status epilepticus was found, nor were any cases positive for both AQP4 and MOG antibodies in CSF or serum. Although clinical presentations of MOGAD and AQP4-IgG-related NMOSD may overlap, the pathological hallmark of the latter is astrocytic injury with or without oligodendrocyte loss, and there is no evidence of astrocytic injury in MOGAD. This may be related to the fact that inflammation and myelin destruction primarily affect oligodendrocytes rather than astrocytes [**?**], and seizures and encephalitis-like manifestations are more common in MOGAD than in AQP4-IgG-positive NMOSD [**?**]. Our study showed that 9 children had non-ADEM-like encephalitis phenotype, with cranial MRI showing only meningeal enhancement, with or without varying degrees of elevation in CSF white blood cells and protein. Therefore, when seizures and encephalitis manifestations appear clinically with demyelinating lesions on brain MRI, the possibility of MOGAD should be considered.

In recent years, some scholars have identified concurrent CSF NMDAR antibodies with serum MOG-Ab positivity, which has the clinical and imaging features of both MOGAD and anti-NMDAR encephalitis. This is called the overlapping syndrome of MOG-antibody disease and NMDAR encephalitis (MNOS). Studies have shown that 4% of patients with NMDAR encephalitis have other concurrent antibodies, with approximately 50% being MOG-IgG [**?**]. Our study included 2 cases with concurrent CSF NMDA-IgG and serum MOG-IgG positivity, possibly related to the fact that NMDA receptors can also exist on the surface of oligodendrocyte membranes. Fan et al. [**?**] reported that 11.9% of 42 MOGAD patients had concurrent anti-NMDAR encephalitis; moreover, MNOS patients had milder or less obvious symptoms of psychiatric behavioral abnormalities and cognitive dysfunction compared with pure anti-NMDAR encephalitis patients, with recurrence rates similar to MOGAD, suggesting that MOG antibodies may play a major role in the pathogenesis of MNOS children. The 2 patients in our study had no common manifestations of anti-NMDAR encephalitis such as psychiatric behavioral abnormalities at onset, but presented with fever and encephalopathy, and developed psychiatric behavioral abnormalities during treatment. Therefore, clinical vigilance is required, and we recommend early combined detection of multiple immune antibodies to provide a basis for determining clinical phenotype and guiding treatment and course. For MOGAD combined with anti-NMDAR encephalitis, first-line treatment in the acute phase is steroid therapy, but there is no consensus on the duration of steroid treatment and the timing of second-line therapy. The 2 children in our group have not relapsed after first-line treatment, but due to the short follow-up period,

the recurrence rate cannot be evaluated. Recurrence factors for MNOS and the timing for initiating second-line therapy are directions for future research.

Recurrence factors for MOGAD have been a hot topic of discussion. Previous studies suggest that patients with a history of immune disease, ON at onset, severe condition at admission, high antibody titers, and CSF white blood cell count >50$×10^{6}$/L may have increased recurrence rates. Therefore, in clinical practice, we must inquire about patients' past medical history in greater detail, especially immune-related backgrounds, and carefully evaluate patients' conditions and laboratory tests to more comprehensively assess recurrence risk. Foreign studies also suggest that concomitant ON and persistent antibody positivity are associated with recurrence [**?**]. Our study shows that children with ADEM combined with ON at first onset and those with recurrent ON have a tendency to relapse, consistent with previous research and supporting ON as a high-risk factor for recurrence. The relationship between MOG antibody titer and clinical disease activity has been controversial. Some reports indicate that MOG antibody seropositivity is transient in children with monophasic ADEM, while 70%–80% of persistently seropositive children and adults relapse during follow-up [**?**]. This seems to suggest that persistent MOG antibody positivity can predict clinical progression or recurrence. However, other studies have shown that 81% of persistently MOG antibody-positive children cannot distinguish between monophasic and relapsing patients [**?**]. Our study found that among 8 children who relapsed during recent follow-up, MOG antibody titers did not show an increasing trend during acute attacks. Twenty-one of 23 children who underwent regular follow-up blood tests remained persistently positive for MOG antibodies but did not experience further attacks. Dynamic changes in antibody titers should continue to be emphasized in future follow-up to further clarify their correlation with recurrence and disease severity.

In summary, MOGAD forms a unique clinical spectrum with multiple phenotypes that can overlap. Pediatric MOGAD can onset in infancy, with clinical phenotypes dominated by ADEM, followed by ON and non-ADEM-like meningitis/encephalitis. Long-term prognosis depends on different clinical phenotypes, early correct treatment, improvement during acute attacks, and imaging changes. Most children have a good prognosis after immunotherapy, but those with initial phenotype of ADEM combined with ON and those with recurrent ON are prone to relapse and require clinical vigilance. The validity of MOG as a biomarker requires long-term follow-up and research.

Author Contributions: WANG Xin was responsible for research conception, data collection, manuscript drafting, statistical analysis, and figure preparation, and took overall responsibility for the final version. ZHAO Ruibin provided imaging guidance for enrolled cases. LIU Chong and LIU Tian selected enrolled cases, processed data, and performed statistical analysis. LU Cui and CHEN Didi collected data. YANG Huafang provided core supervision and technical support.

Conflict of Interest: The authors declare no conflict of interest.

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Note: Figure translations are in progress. See original paper for figures.