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Case Report

A Case of Post Viral Acute Longitudinal Extensive Transverse Myelitis (LETM): MOGAD- A New Horizon

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Abstract:

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a recently identified autoimmune disorder that presents in both adults and children. It is a group of central nervous system demyelinating diseases caused by auto antibodies against myelin oligosaccharide protein, a myelin sheath component protein, and present with a variety of symptoms, including optic neuritis, longitudinal extensive transverse myelitis (LETM), acute disseminated encephalomyelitis (ADEM), brainstem encephalitis, and corticobasal encephalitis. Although there are clinical phenotypic overlaps between MOGAD, multiple sclerosis, and aquaporin-4 antibody-associated neuromyelitis optica spectrum disorder (NMOSD) cumulative biological, clinical, and pathological evidence discriminates between these conditions. Here, we present a case of a young male with acute onset of spastic paraplegia with sphincters involvement and patchy loss of pinprick sensation with positive Anti-MOG Antibody shortly after viral febrile illness.

Key Words: *MOGAD, ADEM, LETM, NMOSD, demyelinating disease, spastic paraplegia*

Introduction:

Myelin-oligodendrocyte glycoprotein (MOG) constitutes a quantitatively minor component (0·05%) of CNS myelin[1] and is expressed on the outer lamella of the myelin sheath.[1,2] which makes it particularly susceptible to immune-mediated demyelination. In humans MOG is thought to be involved in completion and maintenance of the myelin sheath and in cell–cell communication. Myelin Oligodendrocyte Glycoprotein Antibody-associated Disease (MOGAD) is an inflammatory disease of the Central Nervous System (CNS) characterized by attacks of immune-mediated demyelination. Its clinical course can be monophasic or relapsing, with clinical presentation resembling Acute Disseminated Encephalomyelitis (ADEM), Optic Neuritis (ON), transverse myelitis, and brainstem demyelinating syndrome. The spinal cord presentation of MOGAD may be in the form of: a) longitudinally extensive transverse myelitis (involving three or more vertebral segments) or b) short lesions involving less than two vertebral segments[3,4]. The involvement of conus medullaris is observed more in MOGAD spectrum than any other reported demyelinating disorders[4-6].

Although there are clinical phenotypic overlaps between MOGAD, multiple sclerosis, and neuromyelitis optica spectrum disorder (NMOSD) associated with anti-aquaporin-4 (AQP4) antibodies (AQP4-NMOSD), cumulative biological, clinical, and neuropathological evidence clearly discriminates between these conditions. While patients with MS, MOGAD and NMOSD may present with similar clinical manifestations, such as optic neuritis and myelitis, those with MOGAD lack a clear sex predilection, and more commonly experience a monophasic course[7,8]. MOGAD also has the greatest predilection in children, representing 20–30% of inflammatory CNS syndromes in this population as compared to approximately 5% in adults. The current estimated range of incidence in the pediatric population is 3.1 per 1 million, as compared to 1.6 and 2.39 per 1 million among adults[8]. Diagnostic criteria of MOGAD required presence of core clinical demyelinating event which includes optic neuritis, transverse myelitis, Acute Disseminated Encephalomyelitis, cerebral monofocal or polyfocal deficits, brainstem or cerebellar deficits, cerebral cortical encephalitis, often with seizures[9], positive MOG antibody and exclusion of other diagnosis.

Case report:

A 22 years old man presented to the emergency department with high grade, intermittent fever (highest being recorded as 104° F) for 3 days along with runny nose, dry cough, headache and generalized bodyache. He had no other focal systemic complaints. Both general and systemic examination revealed no significant abnormalities apart from raised temperature. Initial investigations revealed normal complete blood count with normal differentials. CRP, liver function tests, renal function tests, chest x-ray were normal. Dengue NS1 antigen and COVID antigen were negative. He became afebrile in the next 2 days. He was diagnosed as viral fever and planned to be discharged. The night before discharge, he developed severe bilateral, symmetrical thigh and calf muscle pain along with weakness. There was also nocturnal urinary incontinence. He had no history of numbness, paresthesia and backache. There

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was no history of visual impairment, dysarthria, dysphagia, no history of nasal regurgitation, no breathing difficulty. He had no medical history, in particular, no history of TB contact. Family history was not significant. He was unmarried, student and belonged to a middle income family. He was a non-smoker, not taking any medications regularly. On examination, his upper limbs had normal tone with MRC grade 5 power, and his deep tendon reflexes were intact. In lower limbs, he had 3/5 power in proximal and distal muscles bilaterally according to MRC grading, with increased tone and grade 3 deep tendon reflexes with sustained ankle clonus. His plantar reflexes were bilaterally extensor. There was no muscle tenderness. Cerebellar functions were intact in both upper limbs. In lower limbs, cerebellar functions could not be assessed due to reduced muscle power. His gait could not be assessed. On sensory system examination, there was patchy impairment of sensations in thighs and some parts of calves but no definite sensory level. Joint position & vibration sensation was intact. No gross spinal deformity and no spinal tenderness was present.

On eye examination, his pupils were bilaterally equal and reactive to light, with intact extraocular movements. His visual acuity was normal and there is no relative afferent pupillary defect, colour vision impairment or disc pallor. The rest of the cranial nerves examination was unremarkable. There were no signs for meningeal irritation. His cardiovascular, respiratory and gastrointestinal examination was unremarkable. On the very next day his lower limb weakness progressed to such degree that he became bed bound with muscle power 0/5.

Repeat laboratory analysis demonstrates normal complete blood count, renal and liver function tests, serum electrolytes, coagulation profile, and urine routine examination. His hepatitis B and C screening was negative. Cerebrospinal fluid analysis was done which revealed mildly increased protein with 77 mg/dl, normal glucose, mild lymphocytic pleocytosis (total cell 80/cmm, Lymphocyte 98%).

MRI was performed within 48 h of the onset of paraparesis, which revealed a long-segment, intramedullary, expansile, heterogeneously enhancing spinal cord lesion extending from T4 vertebral level till conus medullaris with no post-contrast enhancement, likely due to inflammatory demyelinating aetiology. Few foci of blooming were also noted in the spinal cordon gradient sequences (Fig 1). MRI of Brain with contrast done which was reported as an essentially unremarkable study with no evidence of demyelinating plaques or any other significant abnormality. His HIV serology and VDRL were negative. NMO (aquaporin-4 IgG) was not available. The anti-MOG antibody test is strongly positive (> 1:100) in this patient. A diagnosis of MOGAD-associated longitudinally extensive transverse myelitis was made.

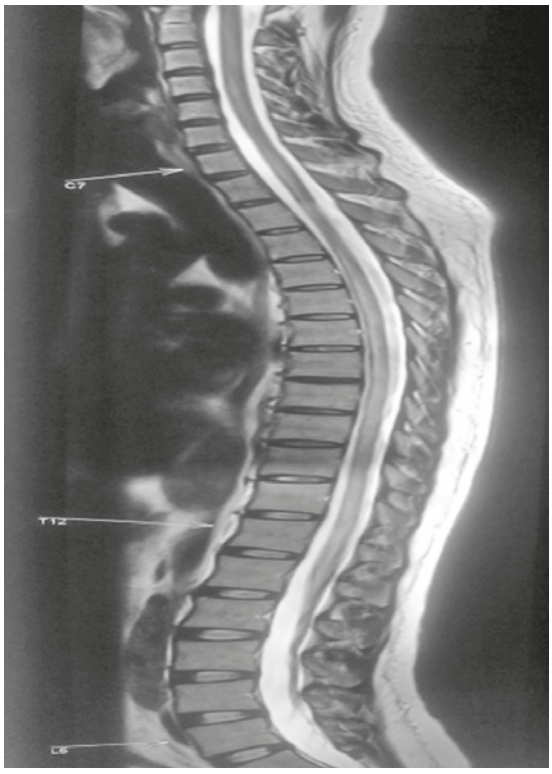

Figure 1: T2W sagittal image showing a long-segment T2 hyperintense signal extending from T4 upto conus medullaris, with few hypointense area in between.

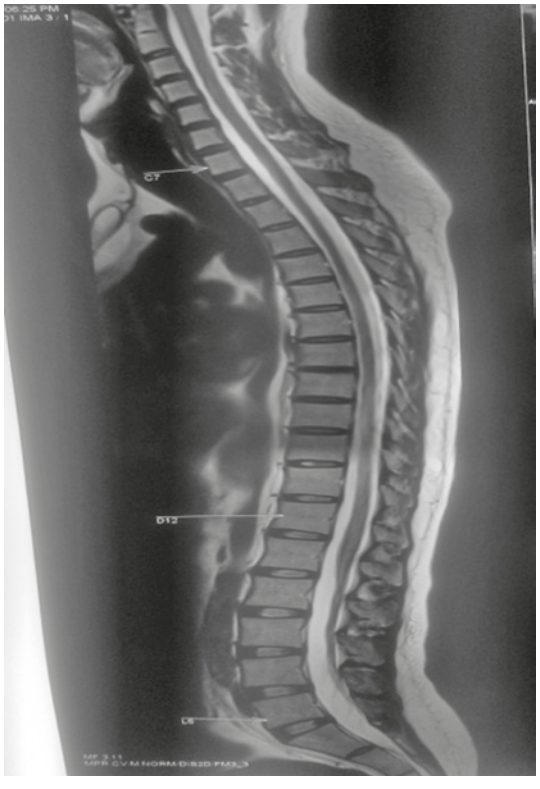

Figure 2: Follow-up MRI images after 14 days. T2 sagittal image showing significant reduction in the T2 hyperintensities within the spinal cord.

The patient was started on IV methylprednisolone 1 g/day for 5 days oral prednisolone 1mg/kg/day for next 10 days. Physiotherapy was ensured. Two weeks following treatment, the patient gradually improved and regained his ability to walk with muscle power 4/5 in both lower limbs. Follow up MRI of spine at two weeks revealed significant decrease in the spinal cord lesion (Fig. 2) suggesting good response to the treatment and establishing the diagnosis of MOGAD-positive longitudinally extensive transverse myelitis.

Discussion:

Myelin oligodendrocyte glycoprotein (MOG) is a protein on the surface of oligodendrocytes, is highly immunogenic and its exact function is unknown; it may act as a cell adhesion molecule, and its location on the outermost part of myelin sheath makes it more susceptible to immune-mediated CNS demyelination. It is a minor component of myelin sheath comprising 0.5%[10]. It was previously considered a potential antibody target for Multiple sclerosis patients, but since 2007 MOG-associated Immunoglobulin G (IgG) is considered a separate demyelinating disease. It is a rare autoimmune disorder[11]. MOG-IgG-associated disorders present mostly as Acute Disseminated Encephalomyelitis (ADEM) in children, optic neuritis, and severe myelitis in adults. Currently, few studies showed that it can present as brainstem and autoimmune encephalitis[12]. MOG-associated antibody disease showed a female predominance as compared to males[13]. MOGAD accounts for approximately 1·2–6·5% of all demyelinating syndromes in adults.[14,15] Proposed MOGAD diagnostic criteria is summarized in Table I.

Table I : Proposed MOGAD diagnostic criteria by an international panel of experts. This table is adapted from Banwell et al., 2023[9]

MOGAD diagnosis necessitates the fulfillment of 1, 2 and 3			
1.	Clinical demyelinating event	Optic neuritis	
		Myelitis	
		ADEM	
		Cerebral, brainstem or cerebellar deicits	
		Cerebral cortical encephalitis	
2.	Positive MOG-IgG test	Clear positive [titer ≥ 1:100]	No additional supporting features required
		Low positive [titer ≥ 1:10	A & B must be true
		and < 1:100]	A) AQP4-IgG seronegative
		Positive without reported titer	B) One or more supportin clinical
		Serum negative but CSF positive	or MRI features ψ
3.	Exclusion of better diagnoses, including MS		
	ψ Supporting clinical and MRI features		
	Optic neuritis	Simultaneous bilateral optic nerve involvement	
		Longitudinal optic nerve involvement [> 50% of the optic nerve length]	
		Optic disk edema/swelling	
		Perineural optic sheath enhancement	
	Myelitis	Longitudinally extensive myelitis (LETM)	
		Conus lesion	
		H-sign or central cord lesion	
	Brain, brain stem, or cerebral	Deep gray matter involvement	
	Syndrome	Multiple ill-deined T2 hyper-intense lesions in the supra-tentorial and	
		Infra tentorial white matter	
		Cortical lesion with or without lesional and overlying meningeal	
		enhancement	
		Ill-deined T2-hyperintensity involving medulla, pons, or middle	
		cerebellar peduncle	

MOGAD MOG antibody-associated disease, ADEM acute disseminated encephalomyelitis, MRI magnetic resonance imaging, AQP4 aquaporin 4, CSF cerebral spinal fluid, MS multiple sclerosis

Transverse myelitis is an initial presentation mainly in adults who are seropositive for MOGAD. It is a severe, disabling condition, and with the help of antibody assessment for NMOSD and MOG, we are able to identify the causes of transverse myelitis. MOG-IgG-associated myelitis presents as acute spastic myelitis. MOG-AD transverse myelitis is mostly longitudinally extensive (LETM). As in our case, MRI dorsolumbar spine showed a longitudinally extensive lesion extending from mid-thoracic region to conus. It showed no post-contrast enhancement as compared to AQP4-IgG seropositive myelitis. Deep grey matter lesions are more common in MOG-IgG myelitis[15.] It can also be associated with optic neuritis and brainstem encephalitis. We can differentiate MOG-AD from NMOSD and MS, although there are few clinical and radiological similarities between MOG-AD and NMOSD but can easily differentiate from MS. Silent lesions which are commonly found in MS are absent in MOGAD[16]. MOGAD has the greatest predilection for conus medullaris resulting in sphincter involvement and bladder dysfunction [17].

Biomarkers:

Assays for anti-MOG antibody detection: Over the last 10 years, great efforts have been made to improve anti-MOG antibody detection techniques. More consistent results were obtained when the substrate for the tests were recombinant antigens expressed on live cells. Their titres are higher during the acute attack in young children than in adolescents or adults[18] but more likely to become negative after the attack.[20]Timing of testing is important as antibody titres fluctuate and can decrease over months from presentation, and some patients can subsequently be tested negative.[19] Anti-MOG antibodies are now rarely found in patients with typical multiple sclerosis using cell-based assays. It is exceptionally rare for any patient to have serum antibodies to both MOG and AQP4.[14,20,] Finally, the usefulness of anti-MOG antibody detection in the CSF is not yet fully evaluated. When paired samples are analysed, there is a good concordance between serostatus and CSF status (ie, most CSF-positive patients are seropositive), but not all seropositive patients are CSF-positive, and only a small proportion are seronegative and CSF-positive.[21]

Imaging biomarkers:

Brain and spinal cord MRI: Brain MRI in MOGAD can be abnormal in more than 50% of patients, regardless of the clinical presentation.[14] In general, brain lesions are more wide spread in children than in adults, reflecting a higher disease burden. In addition to the deep white and grey matter lesions found in acute disseminated encephalomyelitis-like presentations, brainstem lesions are found in up to 40% of patients with MOGAD, frequently involving the pons and middle cerebellar peduncles.[22-25]. Although initially thought to be associated predominantly with white matter disease, both adults and children with MOGAD can experience cortical encephalitis and seizures. Brain MRI in these patients can be normal or have reversible cortical changes occasionally with leptomeningeal enhancement.

Spinal cord MRI findings in MOGAD such as the presence of longitudinally extensive T2 lesions, spanning at least three vertebral segments on sagittal sequences, or the hyperintensity of grey matter on axial sequences (longitudinally extensive transverse myelitis), can resemble those commonly seen in AQP4-NMOSD.[5] MRI features suggesting a diagnosis of MOGAD rather than AQP4-NMOSD or multiple sclerosis are involvement of the conus medullaris, abnormality confined to grey matter (sagittal line and axial H sign) and nerve roots, and scarcity of or minimal gadolinium enhancement.[5]

Treatment:

Attack treatment: There are currently no randomised control trials or evidence-based guidelines for the acute treatment of MOGAD. First line immunotherapy therefore consists of intravenous methylprednisolone (30 mg/kg per day or 1 g per day, for 3–5 days). Treatment escalation is warranted for patients who do not improve after intravenous methylprednisolone or individuals with a severe attack such as complete loss of vision, paralysis, or severe encephalopathy requiring admission to intensive care. Escalation therapies include plasma exchange (five exchanges on alternative days), immunoadsorption, intravenous immunoglobulins (total of 2 g/kg over 2 or 5 days), or plasma exchange followed by intravenous immunoglobulins.[26]

Chronic treatment for relapse prevention: The accumulation of disability in patients with antibody mediated diseases, such as MOGAD, is thought to be primarily relapse related. Because of the risk of disability due to incomplete relapse recovery, identifying patients at risk for relapse, and treating those with relapses, is the focus of current management. Currently there are no predictors of relapse risk and long-term outcome. No clinical trials have been done for patients with MOGAD and the current literature reports real-world clinical data, which are not optimal for evaluation of treatment efficacy. Data from the six largest retrospective studies on treatment of relapsing MOGAD [3,27,28] revealed that, at a median of 9–16 months after the start of treatment, the number of relapse free patients was 20 (69%) of 29 patients on intravenous immunoglobulin monotherapy, 30 (47%) of 63 on mycophenolate mofetil, 21 (39%) of 55 on azathioprine, and 47 (50%) of 94 on rituximab. Of note, although anti-CD20 therapy seems to show some effect, it appears to be less efficacious than in AQP4-NMOSD [29]. There are only anecdotal reports for use of alemtuzumab, dimethyl fumarate, and fingolimod, precluding judgment of treatment efficacy.

Prognosis:

The duration of immunosuppressive treatment for MOGAD remains uncertain, as the field currently lacks robust biomarkers to inform therapy. Specifically, it is challenging to identify patients who will remain monophasic after their first attack. Several indicators of disease activity have been proposed, including attack severity and frequency, MOG-IgG sero-status and titers, patient age, relapse-free interval, spinal cord involvement, and resultant neurological disability[30,31]. The identification of prognostic factors indicating the

likelihood of relapse and disability in a patient would catalyze a personalized treatment approach for MOGAD patients.

Adult MOGAD patients tend to have more recurrent episodes and poorer functional recovery compared to pediatric patients. Nevertheless, recurrent disease has been associated with elevated initial MOG-IgG titers, while transiently low titers have been shown to be associated with a monophasic course[32,33]. Long-term outcomes and disability are quite challenging to predict as studies with long follow-up are sparse for patients with MOGAD. While it is believed that, on average, even frequently relapsing MOGAD results in less disability than NMOSD, inter-patient variability has been documented[34]. Sufficiently powered prospective studies with extended follow-up would enable a more comprehensive understanding of the natural history of MOGAD, identify predictors of its course and establish guidelines for its treatment.

Conclusion:

Post infectious longitudinally extensive transverse myelitis (LETM) as a standalone finding without any involvement of optic nerves and brain may show MOGAD seropositivity and should be considered as one of the differential diagnosis in cases of acute myelopathy.

Conflict of interest: None declared

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