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Atypical Presentation of Anti-MOG Ab Disease

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INTRODUCTION

Myelin oligodendrocyte glycoprotein antibodies (MOG-IgG) associated diseases are a spectrum of central nervous system demyelinating disorders. Clinical differentiations from multiple sclerosis, neuromyelitis spectrum disorder (NMOSD) with or without Aquaporin antibody (AQP4-Ab), are very narrow.[1,2] Recurrence of illness, specific antibody positivity, and response to immunotherapy favors diagnosis. NMOSD and MOG associated diseases share common involvement pattern of optic nerve and cervico-dorsal myelitis.[2,3] MOG involves rhombencephalon especially pontine white matter tract, while NMOSD has predilection around the periventricular Aquaporin channels.[4] Involvement of conus and caudal nerve roots are rare involvement in MOG antibody associated diseases.[5]

We present three cases of MOG-IgG positive patients with bilateral optic neuritis, conus cauda syndrome, and pontine demyelination mimicking Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS).

CASE REPORT

Case 1. A 20-year-old male student presented with acute onset progressive painless asymmetric vision loss of five days. He had no prior comorbidities or addictions. He never experienced any focal neurological symptoms earlier. His general and neurological examinations were normal (Table 1). His intraocular pressure was normal. Maximal visual acuity in the right eye was finger counting at 1-meter; left eye was perception of light. Fundus examination revealed blurred disc margin bilaterally. Ophthalmological evaluation, including retina, anterior chamber, and posterior chamber, was unremarkable.

Routine blood parameters, including complete hemogram, liver function test, renal function test, and serum blood glucose level, were normal. Cerebrospinal fluid (CSF) examination revealed protein level (27 mg/dl) with mild lymphocytic pleocytosis (seven total cells, 86% mononuclear and 14% polymorphonuclear). HbsAg, Anti HCV Ab, and HIV Ab status were negative. Pattern visual evoked potential (VEP) was not recordable on the left eye; right eye P100 latency was prolonged 154.2 ms (amplitude 4.46 µV).

Table 1. Clinical and laboratory findings of MOG Ab positive patients.

Parameters	Case 1	Case 2	Case 3
Age (in years)	20	37	29
Gender	Male	Female	Female
Duration of illness	5 days	30 days	7 days
Symptoms	Bilateral vision loss	Bilateral lower limb weakness, bladder and bowel involvement	Gait ataxia, slurred speech, horizontal diplopia (bilateral)
Preceding illness	Nil	Undergone caesarian section at term for fetal distress under spinal anesthesia, postoperative day one noticed paraplegia	Fever for six days one week prior to neurological deficit
Onset and progression	Acute, right followed by left. Nadir at five days	Acute, maximal at onset	Acute, progression for one week
Past or chronic illness	No	No	No
Treatment received before admission to our Institute	Nil	IV Methyl prednisolone 500 mg x five days	Nil
General examinations and vitals	Normal	Normal	Normal
Neurological examination (abnormal findings)	VA: Right eye: finger counting from 1 meter Left eye: PL+/ PR+ Bilateral optic disc margin blurred	Bilateral lower limb motor power (MRC) 1/5 with weakness of lower truncal muscles. Sensation loss below umbilical level, bladder catheterized and stool incontinence	Higher mental function- normal Bilateral optic disc margin: blurred. Bilateral 6th cranial nerve palsy, left LMN facial palsy, hand incoordination +, gait: ataxic
Biochemical parameters	Urea: 25 mg/dl Creatinine: 0.8 mg/dl LFT: Normal Na+: 134 meq/l K+: 4.5 meq/l Hb%: 14.5 gm% TLC: 8500/cumm N: 52%,L 37% TPC: 232000/ cumm Urine R/E: normal. HIV: NR HbsAg: NR Anti HCV Ab: NR ANA: Neg ANCA: Neg TFT: N CRP: Neg	Urea: 18 mg/dl Creatinine: 0.7 mg/dl LFT: Normal Na+: 136 meq/l K+: 4.3 meq/l Hb%: - 12.5 gm% TLC: 7500/cumm N: 55%,L 45% TPC: 260000/ cumm Urine R/E: normal. HIV: NR HbsAg: NR Anti HCV Ab: NR ANA: Neg ANCA: Neg TFT: N CRP: Neg	Urea: 19 mg/dl Creatinine: 0.6 mg/dl LFT: Normal Na+: 139 meq/l K+: 4.2 meq/l Hb%: 12.9 gm% TLC: 11590/cumm N: 75%,L 18% TPC: 274000/ cumm Urine R/E: normal. HIV: NR HbsAg: NR Anti HCV Ab: NR ANA: Neg ANCA: Neg TFT: N CRP: Neg
CSF Examination	Total cells: 7 85% MNC, 15% PMNC Glucose: 93 mg/dl Protein: 27 mg/dl	Total cells: 8 68% MNC, 32% PMNC Glucose: 98 mg/dl Protein: 104 mg/dl	Total cells: 52 88% MNC, 12% PMNC Glucose: 144 mg/dl Protein: 45 mg/dl
Pattern VEP (P100)	Left: no wave Right: 154.2 ms Amp: 4.46 µV	Prolonged	Left: 129.9 ms Amp: 4.19 µV Right: 123.9 ms Amp: 3.29µV
SSEP (tibial)	Bilateral prolonged CSCT	Bilateral prolonged CSCT	Bilateral prolonged CSCT

Table 1. Clinical and laboratory findings of MOG Ab positive patients. *continued.*

Parameters	Case 1	Case 2	Case 3
BAER	Normal	Normal	Normal
MRI Brain/spine	Normal	Swelling of cord at conus, T2 hyperintense signal in most of cross section of cord up to 3 cm, patchy enhancement on post contrast. Cauda equina nerve roots are thickened and enhancement on post contrast. Brain normal	Multiple T2 & FLAIR hyperintense and contrast enhancing lesion in pons, medulla, cerebellum and left frontal white matter region. Spine normal
Serum IgG Anti-NMO Ab (cell-based assay)	Negative	Negative	Negative
Serum IgG Anti -MOG Ab (cell-based assay)	Positive	Positive	Positive
Treatment	IV methylprednisolone 1 gm daily for five days followed by oral prednisolone 40 mg daily	IV methylprednisolone 1 gm daily for five days followed by oral prednisolone 40 mg/day	IV methylprednisolone 1 gm daily for five days followed by oral prednisolone 30 mg daily
Response to treatment after two weeks	Vision improved in both eye- finger counting from 3 meters distance bilaterally	Both lower limbs having antigravity movement	Walking without support, hand incoordination improved, able to maintain daily life activities with minimal help, diplopia improved.
Last follow- up	1 month: VA 6/18	3 months: Walk with walker aid, urine incontinent	3 months: Improved, mild spasticity of limbs

VA: visual acuity, CSF: cerebrospinal fluid, VEP: visual evoked potential, SSEP: somato sensory evoked potential, BAER: brain stem auditory response, MOG: myelin oligodendrocyte glycoprotein, NMO: neuromyelitis optica, CSCT: central sensory conduction time; LFT: liver function tests

Contrast enhanced magnetic resonance imaging (MRI) of the brain and spine were done to look for any demyelinating lesions in central neuroaxis which was unremarkable (Figure 1). Evaluation for underlying autoimmune pathology included serum anti-nuclear antibody, anti-neutrophilic cytoplasmic antibody; C-reactive protein (CRP) level was negative. Serum IgG anti-MOG Ab was positive by cell-based assay and simultaneous anti-aquaporin-4 antibody status was negative. CSF oligo-clonal band was negative. Tibial somato-sensory evoked potential (SSEP) showed bilaterally prolonged central sensory conduction time (CSCT), which also favored the background demyelinating pathology. Brainstem auditory evoked potential was normal bilaterally.

The patient was managed with intravenous methyl prednisolone 1 gram daily for five days followed by oral prednisolone 40 mg daily which was tapered over the next six months. At one-month follow-up, his visual acuity improved to 6/18 bilaterally.

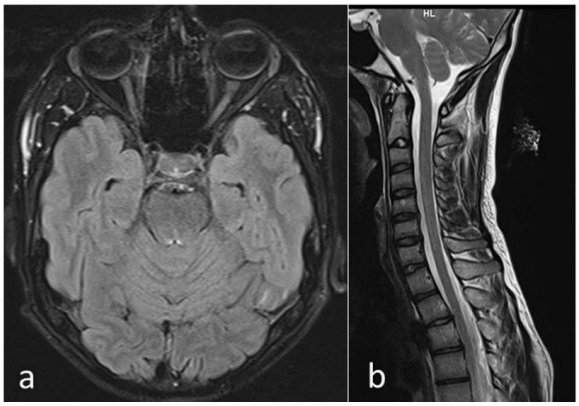

Figure 1. Axial FLAIR image (a) at the orbit level shows normal signal of both optic nerves. Sagittal T2WI (b) of cervical spine shows normal cord signal.

Case 2. A 30-year-old female presented with acute onset paraplegia with bladder and bowel involvement following caesarean section under spinal anesthesia. On post-operative day one, she developed weakness of lower limb, associated truncal weakness, and sensory level below umbilicus. This patient had no prior comorbidity and did not suffer from any focal neurological symptoms earlier. General examination was unremarkable. Neurological examination revealed power (Medical Research Council scale) 1/5 in bilateral lower limbs, diminished tendon reflexes in lower limbs, and sensory impairment below D10 level. She developed urinary retention on day two of her weakness and again re-catheterized after removal during recovery from post-spinal anaesthesia period. Before reaching our clinic, she received intravenous methyl prednisolone pulse therapy of 1 gm for five days, though no significant improvement was noted in form recovery of power in lower limbs and she was in bed bound state (Modified Rankin Scale - 5).

Routine blood parameters, including complete hemogram, liver function test, renal function test, thyroid function test, and serum blood glucose level, were normal (Table 1). Her HbsAg, Anti HCV Ab, and HIV Ab status were negative. Cerebrospinal fluid (CSF) examination revealed elevated protein level 104 mg/dl with mild lymphocytic pleocytosis (eight total cells, 62.8% mononuclear and 37.2% polymorphonuclear cells). MRI of the spine showed swelling of spinal cord at conus level with increased T2 signal and patchy contrast enhancement (Figure 2), the rest of spinal cord and brain was normal. Pattern VEP done was prolonged bilaterally, and tibial SSEP also was prolonged bilaterally. Serum IgG anti-MOG Ab done by cell-based assay was positive. Her brainstem auditory evoked response (BAER) was normal bilaterally. Serum anti-aquaporin-4 antibody status was negative and CSF oligo-clonal band was not detected. Routine urine examination revealed no proteinuria or hematuria. Evaluation of secondary central nervous system (CNS) demyelinating etiologies was non-contributory. Serum ANA antibody, anti-neutrophilic antibody, and CRP were negative. CT scan of thorax and abdomen to evaluate organ involvement in background of inflammatory diseases and rule out infective aetiology was non-contributory.

The patient was managed with IV methylprednisolone 1 gm daily for five days followed by oral prednisolone 40 mg daily which was tapered over the next year with overlapping therapy with azathioprine. At discharge after 15 days, her lower limb motor power improved to MRC grade 3 bilaterally. Follow-up at three months, she was ambulatory with minimal support, though urine and stool were incontinent.

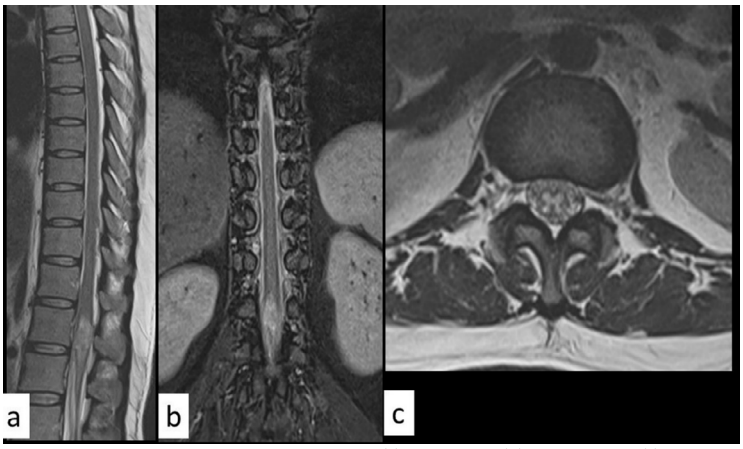

Figure 2. MRI of dorsal spine sagittal (a), coronal (b), and axial (c). T2WI shows focal cord expansion at the conus with increased cord signal intensity predominantly at the center.

Case 3. A 29-year-old female was admitted with acute onset gait ataxia, slurred speech, and bilateral horizontal diplopia that progressed over seven days. She had self-limiting fever one-week prior onset of neurological symptoms. General examination was normal. Neurological evaluation revealed bilateral optic disc edema, left 6th cranial nerve palsy, and left facial lower motor type palsy. Power of lower limb was grade 4/5 with brisk reflexes and positive cerebellar signs. She had no prior comorbidity and no history suggestive of any prior connective tissue disease.

Routine blood parameters, including complete hemogram, liver function test, renal function test, thyroid function test, and serum blood glucose level, were normal. Her HbsAg, anti HCV Ab, and HIV Ab status were negative. Erythrocyte sedimentation rate was 30 mm in the first hour. CSF examination revealed lymphocytic pleocytosis (52 total cells, 88% mononuclear cells and 12% polymorphonuclear cells) with normal protein 45 mg/dl and sugar level. Pattern VEP revealed prolonged P100 latency bilaterally (left: 129.9 ms; right: 123.9 ms) with preserved amplitude. Serum IgG anti-MOG Ab (done by cell-based assay) was positive and anti-NMO Ab was negative (Table 1). MRI of the brain revealed multiple discrete T2 and FLAIR hyperintense lesions in pons, medulla, middle cerebellar peduncles, and left frontal white matter showing patchy contrast enhancement. Her tibial SSEP was prolonged bilaterally though BAER was normal. CSF oligo-clonal band was not detected, and IgG Index was negative. Routine urine examination revealed no proteinuria or hematuria. Evaluation for secondary CNS demyelinating etiologies was non-contributory. Serum ANA antibody, anti-neutrophilic antibody, and CRP were negative. CT scan of the thorax and abdomen to evaluate organ involvement in background of inflammatory diseases and rule out infective etiology was normal.

The patient was managed with IV methylprednisolone 1 gram daily for five days followed by oral prednisolone 30 mg daily. At discharge after 28 days, she was able to walk independently. A repeat MRI of the brain showed significant decrease in lesion size and enhancement (Figure 3). At a three-month follow-up, mild residual spasticity in lower limbs were noted though cranial nerve features and cerebellar deficits were resolved.

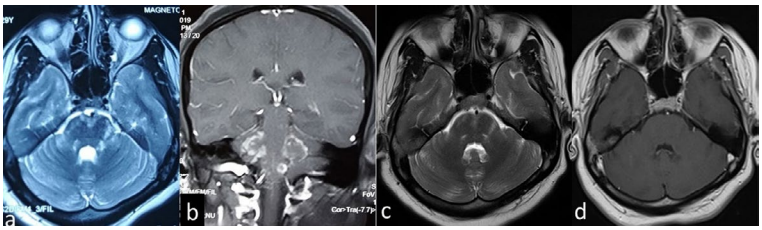

Figure 3. Axial T2WI brain MRI (a) shows multiple hyperintense lesions in pons and middle cerebellar peduncle. Post contrast coronal T1WI (b) shows patchy and curvilinear enhancement mimicking CLIPPERS. Follow up MRI: Axial T2WI (c) and post contrast T1WI (d) shows reduced size and number of the lesions and no enhancement.

DISCUSSION

The three cases highlighted the CNS spectrum of MOG Ab disease. Case 1 was a classic case of bilateral optic neuritis. However, cases 2 and 3 were atypical presentations of MOG disease spectrum. In adults, MOG disease usually is associated with optic neuritis and myelitis in more than 80% of cases.[1,2] In a study, 31 (18.7%) out of 166 episodes had bilateral optic neuritis, myelitis in 32 (19.3%), and brain and stem involvement in 44 (26.5%).[3] MOG Ab associated spinal cord lesions are longitudinally extensive transverse myelitis of cervico-dorsal spinal cord similar to NMOSD (AQP4-Ab+) lesions. Involvement of lower spinal cord and sacral roots are rare but pathognomonic of MOG disease.[4-6] The second case developed paraplegia following caesarean section under spinal anesthesia, which concerns clinicians about operative and other differentials. Recovery of motor power is brisk, however, bladder and bowel control showed poor recovery, as also seen in case 2.[7]

CLIPPERS are a radiological diagnosis of an inflammatory brain stem syndrome of uncertain etiology and T-cell-predominant CSF leukocytosis. CLIPPERS associated with MOG Ab are diagnosed increasingly.[8,9] Clinically, they present with subacute onset brain stem dysfunction. Imaging revealed T2 hyperintense lesions with ill-defined margins in posterior fossa predominantly involving pons and measuring more than 2 cm. Multiple punctate and curvilinear post contrast enhancement in the pons with or without extension to cerebellum and cerebellar peduncle is characteristic of the syndrome. The lesions may extend caudally to the medulla and cervical spinal cord, cranially to the midbrain and supratentorial parenchyma. Enhancement decreases after treatment as the patients respond to corticosteroids.

CLIPPERS responds to corticosteroids both clinically and radiologically and have fair chance to relapse on stopping steroids.[10] Our cases have subclinical involvement of the optic nerve and myelitis as evidenced by VEP latency prolongation and prolong central sensory conduction time in tibial SSEP. MOG Ab is expressed specifically in the central nervous system on the surface of myelin sheaths and oligodendrocyte processes.[11] In humans, presence of MOG Ab are debated

as pathogenic themselves or an epiphenomenon secondary to immune upregulation following prior demyelination or infection. In our series, cases 2 and 3 had preceding illness prior to neurological presentation.

Human MOG Ab might play a minor role in the pathophysiology of inflammatory demyelination, however, there are highly specific markers in specific clinical settings.[12] However, recent developments have established its plausible role in human MOG Ab associated CNS demyelination and its varying clinical spectrum. The exact pathophysiologic effect of human MOG Ab needs further critical evaluation in CNS and PNS demyelination.

CONCLUSIONS

The present case series highlighted the importance to test for anti-MOG antibodies in patients presenting with conus cauda syndrome and CLIPPERS, especially when MRI shows demyelinating features.

REFERENCES

[1] Cobo-Calvo A, Ruiz A, Maillart E, et al. OFSEP and NOMADMUS Study Group. Clinical spectrum and prognostic value of CNS MOG autoimmunity in adults: The MOGADOR study. Neurology 2018; 90(21):e1858-e1869. PMID: 29695592.

[2] Jurynczyk M, Messina S, Woodhall MR, et al. Clinical presentation and prognosis in MOG-antibody disease: A UK study. Brain 2017; 140(12):3128-3138. PMID:29136091.

[3] Akaishi T, Sato DK, Takahashi T, Nakashima I. Clinical spectrum of inflammatory central nervous system demyelinating disorders associated with antibodies against myelin oligodendrocyte glycoprotein. Neurochem Int 2019; 130:104319. PMID:30365980.

[4] Vazquez Do Campo R, Stephens A, Marin Collazo IV, Rubin DI. MOG antibodies in combined central and peripheral demyelination syndromes. Neurol Neuroimmunol Neuroinflamm 2018; 5(6):e503. PMID: 30246057.

[5] Sundaram S, Nair SS, Jaganmohan D, Unnikrishnan G, Nair M. Relapsing lumbosacral myeloradiculitis: An unusual presentation of MOG antibody disease. Mult Scler 2020; 26(4):509-511. PMID: 30931808.

[6] Sato DK, Callegaro D, Lana-Peixoto MA, et al. Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders. Neurology 2014; 82(6):474-481. PMID: 24415568.

[7] Juryńczyk M, Jacob A, Fujihara K, Palace J. Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease: Practical considerations. Pract Neurol 2019; 19(3):187-195. PMID: 30530724.

[8] Symmonds M, Waters PJ, Küker W, Leite MI, Schulz UG. Anti-MOG antibodies with longitudinally extensive transverse myelitis preceded by CLIPPERS. Neurology 2015; 84(11):1177-1179. PMID: 25681455.

[9] Berzero G, Taieb G, Marignier R, et al. CLIPPERS mimickers: Relapsing brainstem encephalitis associated with anti-MOG antibodies. Eur J Neurol 2018; 25(2):e16-e17. PMID: 29356261.

[10] Matesanz S, Kotch C, Perrone C, Waanders AJ, Hill B, Narula S. Expanding the MOG phenotype: Brainstem encephalitis with punctate and curvilinear enhancement. Neurol Neuroimmunol Neuroinflamm 2019; 6(6):e619. PMID: 31519713.

[11] Delarasse C, Della Gaspera B, Lu CW, et al. Complex alternative splicing of the myelin oligodendrocyte glycoprotein gene is unique to human and non-human primates. J Neurochem 2006; 98(6):1707-1717. PMID: 16903876.

[12] Peschl P, Bradl M, Höftberger R, Berger T, Reindl M. Myelin oligodendrocyte glycoprotein: Deciphering a target in inflammatory demyelinating diseases. Front Immunol 2017; 8:529. PMID: 28533781.

Keywords: myelin-oligodendrocyte glycoprotein, optic neuritis, myelitis, demyelinating diseases