Rare Encephalitis-Like Presentation of a Pediatric Patient with Dual Positive Aquaporin-4 and Myelin Oligodendrocyte Antibodies: A Case Report with Review of Literature

Dear Sir,

Neuromyelitis optica spectrum disorder (NMOSD) and Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) are primary neuro-immunological syndromes affecting the optic nerves, brainstem, and spinal cord. Based on the basic pathophysiology, NMOSD belongs to the spectrum of astrocytopathy, while on the other hand MOGAD is an oligodendrocytopathy.[1] Dual seropositivity though extremely rare has been previously described in literature.[2-10] In this study we report a rare case of central nervous system (CNS) demyelination in a child who presented with clinical features of encephalitis and was later detected to have coexisting aquaporin4 (AQP4) and MOG autoantibodies.

A 5-year-old girl, developmentally age-appropriate, presented with acute onset episodes of unprovoked vomiting that persisted for 3 days, preceded by a three-day history of febrile illness. This was followed 2 days later by new onset left focal seizures that started to occur at a frequency of twice a day. Around a week later, she developed acute onset left hemiparesis. On examination at presentation, child was drowsy, with normal pupillary reactions and no evidence of relative apparent pupillary defect. She had paucity of left sided movements and spasticity. Clinically, possibility of viral meningoencephalitis was considered.

She was admitted in the emergency department and investigated. Among the relevant positive investigations, cerebrospinal fluid (CSF) evaluation revealed pleocytosis (34 cells/cu mm), with lymphocytic predominance (25 cells/cu mm), normal protein and sugar levels. Brain MRI showed irregular, cortical, and subcortical hyperintensities involving the right frontal, bilateral medial temporal, right parietooccipital, and right posterolateral thalamus, without contrast enhancement. A spinal MRI revealed cervical and upper dorsal spine patchy hyperintense lesions. Electroencephalography (EEG) showed diffuse high-amplitude delta waves with no evidence of any epileptiform discharges. Her visual evoked potentials (VEP) tested by flash VEP method showed normal latencies. Formal ophthalmology consultation was sought, where she was opined to have normal fundi. Work-ups for neuro-infections including Human Immunodeficiency virus (HIV), venereal disease research laboratory test (VDRL) for neurosyphilis, cartridge-based nucleic acid amplification testing (CBNAAT) for CNS tuberculosis, CSF Herpes simplex virus polymerase chain reaction (HSV PCR), enterovirus PCR, Dengue PCR, Chikungunya PCR and Weil Felix and antibodies against scrub typhus were negative. Serum AQP4 and MOG antibodies were measured using cell-based assay to rule out the encephalitic presentation of MOGAD. Initially, serum tested strongly positive for serum anti-MOG antibodies. She was subjected to treatment with 10 cycles of small volume plasma exchange (SVPP). Subsequently, she was initiated on pulse parenteral steroids on a monthly basis. She responded suboptimally to the standard available management pipelines. Hence, during follow-up course for second pulse of IVMP, a repeat antibody titer was done that revealed strong positivity for both AQP4 and MOG autoantibodies. Repeat testing, done around one month later, revealed the same results.

Child was aggressively managed with pulse intravenous methylprednisolone and monthly SVPP exchanges. IVMP pulses were continued for the next consecutive 6 months and maintenance immuno-modulation therapy with azathioprine was initiated. Serum AQP4 antibodies became negative in the third month of illness, while serum MOG antibodies were still weakly positive at 6 months into illness. In her last follow-up at 18 months from the symptom onset, the child was symptomatically better and had no further relapse [Figure 1].

Discussion

A large retrospective study by Kunchok *et al*.[4] from Mayo Clinic on 15,598 patients who were tested for both MOG and AQP4 antibodies, a total of 10 cases were detected to have coexistence of dual antibodies. Interestingly, while the IgG-AQP4 titers were within the high range (1:10000), the titers of IgG-MOG antibodies were low (1:40). The dual positive subgroup had an overwhelming female preponderance, and belonged to the age group ranging from 30 to 61 years (median 47 years). The phenotype was more dominant toward NMO rather than MOG.[4] Along similar lines, a study by Yan *et al*.[2] identified 10 cases out of 125, with dominant NMO phenotype and the presence of coexisting MOG autoantibody. The unique features reported in the study were unlike typical MOGAD phenotype, as these patients had a multiphasic course, higher predisposition to clinical relapses, greater preponderance of multifocality on neuroimaging, a more severe degree of residual disability and more severe attenuation of retinal nerve layer[2,5,11] [Table 1]. The proposed hypotheses leading to greater severity include synergism of MOG autoantibody with AQP4, driving a higher degree of tissue damage compared to single antibody alone.[2] Despite representing a small proportion (0.05%) of CNS myelin proteins, MOG antibodies have been isolated from patients with NMOSD and found to trigger cytotoxic effects.[2] In similar lines, *in vitro* mice models have shown that the incorporation of MOG-specific B and

Table 1: Literature review on patients presenting with dual seropositivity

Study	Total cases recruited in the study	Number of cases with dual seropositivity	Age (years)	Sex	Clinical presentation and site of involvement	Brain MRI	Spine MRI	Antibodies	Measurement technique of antibodies	Treatment
Hasse *et al.* 2001[10]	14	3	53, 37 and 55	2 F 1M	All had Myelitis with Bilateral ON: 2 cases Unilateral ON: 1 case	NA	Cervical lesion 3 cases	2 cases showing 2+ for anti-MOG, 1 case showing 1+ for anti-MOG	Immunoblot and ELISA	NA
Kezuka *et al.* 2012[5]	23	6	48, 35, 41, 50, 48, and 68	6 F	ON	Right optic nerve hyperintensities	NA	Dual positive	NMO: Immunofluorescence MOG: ELISA	IVMP 4 cases IVMP+PLEX: 2 cases Oral steroids
Höftberger *et al.*, 2014[8]	2	2	58 and 50	2 F	LETM, ON	Normal: 1 White matter lesions: 1	NA	Dual positive		1 RTX 1 AZA
Yan *et al.* 2016[2]	125	10	32 (15-60)@	10 F	Isolated LETM: 5 cases LETM and ON: 1 case LETM, ON, and cerebral: 2 cases Isolated ON: 1 case ON and cerebral: 1 case	ADEM-like lesions: 3 MS-like lesions: 4	LETM: 8	Dual positive	Fluorescence-activated cell sorting	IVMP Oral steroids Immunomodulation: RTX 3 cases, AZA 4 cases, Methotrexate 1 case, HCQ 1 case
Hyun *et al.* 2017[9]	1	1	32	M	LETM	LETM	LETM	Dual positive, AntiSSA (1+), Anti-nuclear (1+): speckled pattern		AZA
Kunchok *et al.* 2019[4]	15598	10	47 (30-61)@	9 F	Dominant NMO phenotype	NA	NA	Dual positive	Flow cytometry	NA
Ishikawa *et al.*, 2019[7]	1	1	24	F	ON	NA	NA	NA		Steroids, IVIg, AZA
Aggarwal *et al.* 2022[3]	1	1	NA	F	Left hemiparesis, incessant hiccups	Tumefactive lesion in right lentiform, cerebral peduncle, temporal lobe, and area prostrema	Normal	NMO and MOG strongly positive	Cell-based assay	IVMP, PLEX, and RTX
Spiezia *et al.* 2022[6]	1	1	62	F	Bilateral ON, quadriparesis	NA	C2-T1 central hyperintense lesion	Dual positive	Cell-based assay	

AZA: azathioprine, ELISA: enzyme-linked immunosorbent assay, HCQ: Hydroxychloroquine, IVMP: Intravenous methylprednisolone, PLEX: plasma exchange, Met: Methotrexate, MOG: Myelin oligodendrocyte, NMO: Neuromyelitis optica, ON: optic neuritis, NA: not available. @in median (range). RTX: Rituximab, ADEM: Acute disseminated encephalomyelitis, LETM: Longitudinally extensive transverse myelitis

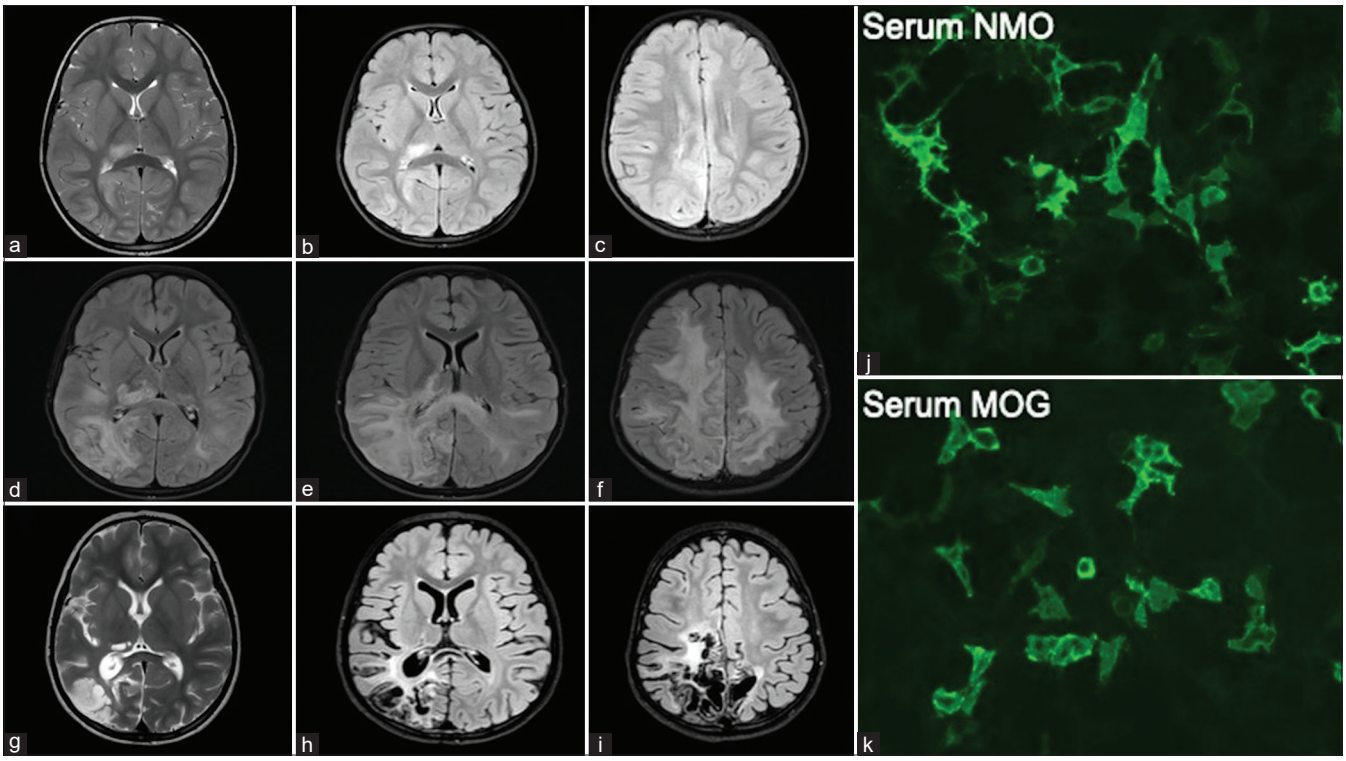

Figure 1: Sequential imaging of the child (a-c): at onset showing patchy subcortical areas of edema, T2/Flair hyperintensities with diffusion restriction in right posterolateral thalamus, parieto-occipital and medial temporal regions; (d-f): 2 weeks into illness showing increased edematous changes in the previously described region; (g-i): 3 months into the illness evolution to cystic encephalomalacia and gliosis in the previously affected areas; (j and k): Cell-Based Immunoassay showing dual seropositivity of both serum NMO and MOG antibodies at 2 months into illness

T-cells can lead to a clinical phenotype akin to NMOSD.[12] The possibility of MOG autoantibody positivity emerging as an epiphenomenon has been proposed in previous studies.[4] Cross-reactivity of microglial cells expressing AQP4 to MOG has also been implicated in the pathogenesis.[1]

Unlike previously reported cases, where the majority of dual seropositive patients had predominant LETM with or without ON as the chief clinical manifestations, our patient presented with a primarily acute onset encephalitis-like illness. Eventually, the patient was detected to have MOG autoantibody with strongly positive titers that later turned out to be dual AQP4-MOG positive. To our knowledge this case represents the youngest diagnosed case with dual positivity, expanding the range of age further. Moreover, this constitutes the first case who presented with an isolated encephalitis-like syndrome. The rarity of the existence of combined AQP4 and MOG antibodies is highlighted by the fact that this represents only the second case reported from India.[3] Unlike previously available literature, the presentation of our patient resembled a cerebral presentation of MOGAD syndrome, which probably explains the better therapeutic response at follow-up.[13]

The case adds to the growing body of evidence regarding the coexistence of dual MOG and AQP4 antibodies in neuroinflammatory disorders. Future studies are required to confirm the actual seroprevalence of dual antibodies in patients presenting with CNS demyelination.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Graber DJ, Levy M, Kerr D, Wade WF. Neuromyelitis optica pathogenesis and aquaporin 4. J Neuroinflammation 2008;5:22. doi:

10.1186/1742-2094-5-22.
2. Yan Y, Li Y, Fu Y, Yang L, Su L, Shi K, *et al*. Autoantibody to MOG suggests two distinct clinical subtypes of NMOSD. Sci China Life Sci 2016;59:1270-81.
3. Agarwal A, Aliyar A, Rao S, Mahadevan A, Garg A, Srivastava A. NMOSD and MOGAD dual positivity: An extremely rare phenomenon. Ann Indian Acad Neurol 2022;25:1174-6.
4. Kunchok A, Chen JJ, McKeon A, Mills JR, Flanagan EP, Pittock SJ. Coexistence of myelin oligodendrocyte glycoprotein and aquaporin-4 antibodies in adult and pediatric patients. JAMA Neurol 2020;77:257-9.
5. Kezuka T, Usui Y, Yamakawa N, Matsunaga Y, Matsuda R, Masuda M, *et al*. Relationship between NMO-Antibody and Anti–MOG antibody in optic neuritis. J Neuro-Ophthalmol 2012;32:107-10.
6. Spiezia AL, Carotenuto A, Iovino A, Moccia M, Gastaldi M, Iodice R, *et al*. AQP4-MOG double-positive neuromyelitis optica spectrum disorder: Case report with central and peripheral nervous system involvement and review of literature. Int J Mol Sci 2022;23:14559. doi: 10.3390/ijms232314559.
7. Ishikawa H, Kezuka T, Shikishima K, Yamagami A, Hiraoka M, Chuman H, *et al*. Epidemiologic and clinical characteristics of optic neuritis in Japan. Ophthalmology 2019;126:1385-98.
8. Höftberger R, Sepulveda M, Armangue T, Blanco Y, Rostásy K, Cobo Calvo A, *et al*. Antibodies to MOG and AQP4 in adults with neuromyelitis optica and suspected limited forms of the disease. Mult Scler J 2014;21:866-74.
9. Hyun J-W, Woodhall MR, Kim S-H, Jeong IH, Kong B, Kim G, *et al*. Longitudinal analysis of myelin oligodendrocyte glycoprotein antibodies in CNS inflammatory diseases. J Neurol Neurosurg Psychiatry 2017;88:811.
10. Haase CG, Schmidt S. Detection of brain-specific autoantibodies to myelin oligodendrocyte glycoprotein, S100β and myelin basic protein in patients with Devic's neuromyelitis optica. Neurosci Lett 2001;307:131-3.
11. Banwell B, Bennett JL, Marignier R, Kim HJ, Brilot F, Flanagan EP, *et al*. Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD Panel proposed criteria. Lancet Neurol 2023;22:268-82.
12. Bettelli E, Baeten D, Jäger A, Sobel RA, Kuchroo VK. Myelin oligodendrocyte glycoprotein-specific T and B cells cooperate to induce a Devic-like disease in mice. J Clin Invest 2006;116:2393-402.
13. Whittam DH, Karthikeayan V, Gibbons E, Kneen R, Chandratre S, Ciccarelli O, *et al*. Treatment of MOG antibody associated disorders: Results of an international survey. J Neurol 2020;267:3565-77.

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