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A Rare Case of Paediatric Myelin Oligodendrocyte Glycoprotein Antibody-Associated Demyelinating Disease Mimicking Typical Multiple Sclerosis

Case Report

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Abstract

Acquired demyelinating disorders of CNS are rare among the pediatric age group, the common ones among them being ADEM, MOGAD, MS and NMOSD. Clinical history and MRI of the CNS may reveal some soft indicators that help differentiate the demyelinating disorders, which are extremely important from the perspective of treatment and prognosis. However, a few overlapping clinical and imaging features may be seen among these disorders. We present a case of pediatric MOGAD, which had initially mimicked pediatric MS clinically and imaging-wise. We also present his clinico-radiological follow-up over a period of 6 years.

Keywords: Pediatric; Demyelinating disorder; Acute disseminated encephalomyelitis; Myelin oligodendrocyte glycoprotein antibody-associated demyelinating disease; Multiple sclerosis; Neuromyelitis optica spectrum disorder

Introduction

Acquired demyelinating disorders of the central nervous system (CNS) among the pediatric age group have a rare occurrence, with an annual incidence of approximately 0.5-1.66 per 100,000 children. The two most important immunoglobulin G (IgG) antibodies playing a role in the pathogenesis of these disorders are aquaporin-4 antibody (AQP-4 Ab) and myelin oligodendrocyte glycoprotein antibody (MOG- Ab). An MRI of the brain and spinal cord is important in characterizing the demyelinating lesions, both symptomatic and subclinical, and in predicting the probability of further recurrences. Serial MRI may also help in establishing the diagnosis, and monitoring treatment response [1]. This report describes a rare case of pediatric myelin oligodendrocyte glycoprotein antibody-associated demyelinating disease (MOGAD), its clinico-radiological correlation, and its follow-up over 6 years.

Case Report

March 2015

An 8-year old male child presented with acute, painless, diminished vision and was unable to read the question sheet. There was no history of (h/o) redness in the eye, increased lacrimation, or watering. No h/o headache, vomiting, seizures, or altered sensorium. There was no h/o preceding fever, cough, cold, loose stools, or recent vaccination before the onset of illness. There was no h/o weakness. There was a past h/o on and off headache since 6 years of age. The patient was also a known case of (k/c/o) bilateral (B/L) myopia, which was corrected with refractive lenses. There is a family h/o stroke in paternal grandmother in 2012. Neurological and fundoscopic examinations showed normal findings. The child was admitted to our hospital for 15 days and evaluated. Cerebrospinal fluid (CSF)

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analysis during hospital stay revealed no cells, protein of 7 mg/dl, and glucose of 103 mg/dl. Oligoclonal bands (OCB) were detected. CSF anti-aquaporin 4- immunoglobulin G antibodies (APQ4-IgG) were negative. Testing for MOG-Ab was not done.

MRI brain (plain + contrast) study revealed multiple demyelinating T2 FLAIR hyperintense foci in the deep white matter of B/L cerebral parenchyma including the corpus callosum (Figure 1), typical Dawson fingers, and the 'dot-dash' signs of early MS, thus demonstrating dissemination in space. However, none of them showed post-contrast enhancement or restriction on DWI. Thus dissemination in time could not be demonstrated. MRI revealed no abnormalities in B/L optic nerves. Even though findings that are typical of Multiple Sclerosis (MS) were seen in this MRI, it did not fulfil the 2017 revised McDonald criteria [3]. Despite this, in view of the CSF OCB being positive, a diagnosis of clinically isolated syndrome/Paediatric MS was made [1].

A diagnosis of ADEM was ruled out as the patient did not have any recent h/o infection or vaccination. Neuromyelitis Optica Spectrum Disorder (NMOSD) was unlikely since the patient was APQ4-IgG negative. The child was treated with pulse methylprednisolone for 5 days followed by oral steroid for 10 days. The child had complete recovery of vision within 6 days following the onset of illness.

May 2019

Following the first episode, the child was asymptomatic for four years till May 2019, when he gradually developed weakness in his upper and lower limbs, with difficulty in walking and in raising his left arm. There was slurring of speech and change in handwriting over the next 4 days. There was no h/o headache, blurring of vision, vomiting, seizures or altered sensorium during this event. On examination, his vitals were found stable and his higher mental functions were found normal. On cranial nerve examination, difficulty in blowing mouth and whistling was found. On sensory examination, there was a loss of pain sensation in both upper limbs. Power was found to be 4/5 in all limbs.

MRI Brain (Plain + Contrast) study revealed multiple foci of T2 FLAIR hyperintensity in the deep white matter of the cerebrum, confluent hyperintensity in B/L periventricular white matter, B/L middle cerebellar peduncles, B/L dentate nuclei and extending into the white matter of B/L cerebellar hemispheres (Figure 2). No focus of contrast enhancement was seen in the present scan. As compared to the previous MRI scan done in March 2015, new lesions were seen. Also, there was more extensive white matter involvement in the present scan as compared to the previous scan. Thus, dissemination of demyelinating lesions in both space and time could be substantiated, which led to the fulfillment of Modified McDonald criteria 2017 [3]. In view of a relapsing attack and a positive OCB in CSF, a diagnosis of MS was made. However, pediatric MS has a rare incidence. Moreover, B/L symmetrical cerebellar peduncle involvement along with B/L confluent periventricular white matter involvement in the pediatric population is an atypical finding in multiple sclerosis, and more in favor of MOGAD [4]. Phenotypical similarity in MRI findings may also be seen in pediatric leucodystrophies [5]. Spinal cord MRI screening revealed no lesions.

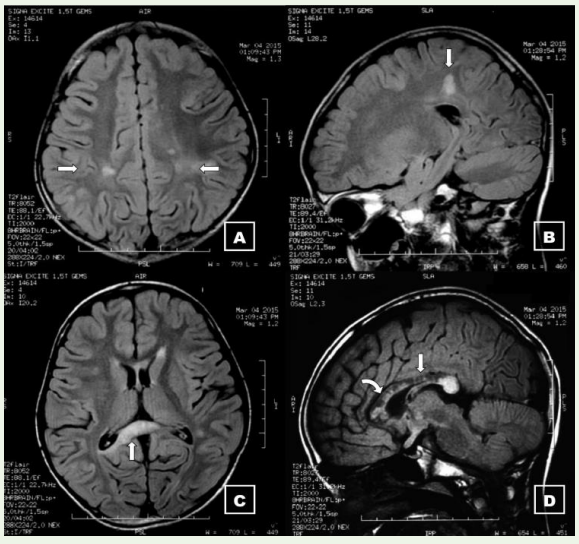

Figure 1: T2 FLAIR weighted images of MRI brain done in March 2015. A) Axial image at the level of centrum semiovale showing few hyperintense lesions (arrows) in B/L cerebral deep white matter. B) Parasagittal image showing deep periventricular white matter triangular hyperintense lesion seen with the apex pointing away from the lateral ventricle and orientation of the lesion is perpendicular to the lateral ventricle (arrow). These findings are typical of "Dawson's finger" usually seen in Multiple Sclerosis (MS) [2]. C) Axial image at the level of the 3rd ventricle showing hyper-intensity with the thickening of the splenium of the corpus callosum. D) Sagittal image shows alternating areas of hyper and iso-intensity along the undersurface of the posterior aspect of the body of the corpus callosum. The findings are typical of the dot-dash signs of early MS (arrow0). The anterior aspect of the body of the corpus callosum shows hyperintense lesions perpendicular to the ependymal surface (curved arrow) [2].

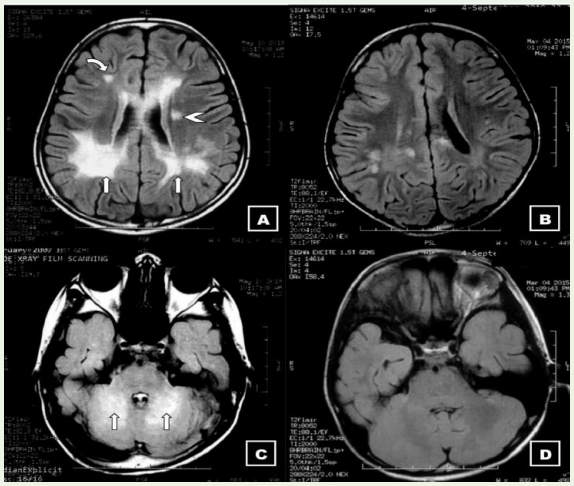

Figure 2: T2 FLAIR axial images of the brain. A) Image at the level of the body of the lateral ventricle shows B/L symmetrical confluent periventricular deep white matter hyperintensities (arrows). A triangular Dawson finger-like lesion was seen in periventricular white matter on the left side (arrowhead). The right frontal lobe shows a small hyperintense focus in subcortical white matter (curved arrow). As compared to the previous scan at the same level (B), the white matter lesions are more extensive. C) Image at the level of the fourth ventricle shows symmetrical hyperintensities in B/L middle cerebellar peduncle, B/L dentate nuclei, and extending into the deep white matter of B/L cerebellum. The previous MRI (D) on comparison showed only mild hyperintensity in the right middle cerebellar peduncle.

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The child was admitted for one week and treated with pulse methylprednisolone for 5 days followed by oral prednisolone for 8-10 days. There was complete recovery of limb weakness by the third day following the initiation of treatment.

July 2019

The child presented with similar complaints and clinical findings as of those in May 2019. The neuromotor symptoms were predominantly on the left side of the body. MRI Brain (Plain + Contrast) study revealed bilateral white matter T2 FLAIR hyperintense demyelinating lesions, a few of them showing contrast enhancements suggestive of acute lesions (Figure 3). These acute lesions were more concentrated on the right brain, thus correlating with the left-sided neuromotor symptoms. An open ring pattern of enhancement was seen in the right middle cerebellar peduncle lesion with corresponding hyperintensity on T2 FLAIR images. Spinal cord MRI screening, once again, revealed no demyelinating lesion. The child was again treated with pulse methylprednisolone and oral steroids which showed complete recovery within a few days. The child was evaluated for the above symptoms in September 2019 at a referral hospital when he was found to be positive for MOG antibody. A diagnosis of MOGAD was made and was treated with a schedule of tapering oral steroids for 3 months and an escalating schedule of mycophenolate.

January 2020

The child again developed gradual onset of weakness in his left-sided upper and lower limbs, with occasional falls while walking. There is history of difficulty in grasping objects with the left hand, and slippage of chappals from the left foot. There is also a history of slurring of speech and change in handwriting, which worsened over the next 3 days. There is also h/o mild blurring of vision in his left eye during this event. There is no h/o fever headache, altered sensorium or seizure. The child was evaluated at the referral hospital for the above symptoms. On examination, cerebellar signs such as dysmetria were present (left more than right) and incoordination in the heel-shin test. Pyramidal signs on the left were seen. Visual Evoked Potential (VEP) test showed left anterior optic pathway dysfunction. Somatosensory Evoked Potential (SSEP) test done by stimulating the left tibia did not evoke right sensory cortical potentials.

MRI Brain (Plain+Contrast) study revealed confluent areas of T2 hyperintensities in the periventricular white matter and the deep white matter of frontal and parietal lobes (Figure 4). Left cerebellar white matter and left middle cerebellar peduncle showed mild expansion and T2 hyperintensity, which correlated clinically with cerebellar signs. There was no contrast enhancement or diffusion restriction. Classical "T1 black hole sign" was seen in right temporal lobe white matter, which is typical for MS. Since the patient was having recurrent sensorimotor deficits predominantly on the left side, 3D TOF (Time of Flight) MR Angiography was performed, which ruled out any vascular abnormality. Spinal cord screening once again revealed no lesion. The child was given pulse methylprednisolone for 5 days, followed by rituximab. The patient was discharged on a schedule of tapering dose of oral prednisolone, followed by prolonged maintenance on low-dose prednisolone.

February 2021

A follow-up MRI Brain (Plain + Contrast) was done for the child

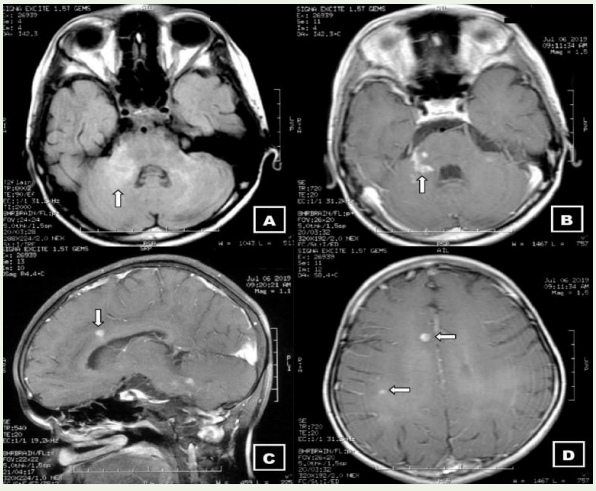

Figure 3: MRI Brain images of the child after the 3rd clinical relapse.
A) Axial T2 FLAIR image at the level of the 4th ventricle shows a hyperintense lesion with thickening of the right middle cerebellar peduncle (arrow). Note the reduction in hyperintensity in the left middle cerebellar peduncle as was seen in the previous scan (Figure 2C)
B) Axial T1 T1 FS+C image showing the same lesion as in (A) with open ring pattern of enhancement, typical of demyelinating lesions (arrow). C) Sagittal T1 FS+C image showing enhancing small focus in the pericallosal white matter (arrow).
D) Few enhancing small foci in the right centrum semiovale suggestive of acute demyelinating lesions (arrows).

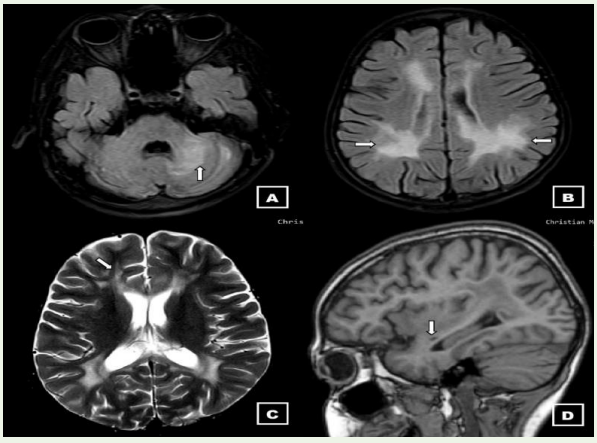

Figure 4: MRI Brain of the patient in January 2020 has done at a referral hospital.
A) Axial T2 FLAIR image at the level of the 4th ventricle shows hyperintensity in left cerebellar white matter and left cerebellar peduncle (arrow). Note – there is a resolution of right middle cerebellar peduncle hyperintensity as compared to the previous scan (Figure 3A)
B) Axial T2 FLAIR image at the level of the body of lateral ventricles show confluent symmetrical hyperintensities in B/L corona radiata (arrows).
C) Axial T2W image at the level of the internal capsule shows hyperintensity along the subcortical U-fibre of the right frontal lobe (arrow). Subcortical U-fibre involvement is classically described in cases of MS [2].
D) Sagittal T1W image shows hypointense small focus in the periventricular white matter of right temporal lobe, thus giving a classical appearance of "T1 black hole sign" (arrow). This finding is seen in demyelinating diseases with relapsing and remitting courses and is classically described for MS [6].

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who had been asymptomatic for the past one year. The findings were similar to the previous scan, with no significant radiological disease progression. Few hyper-enhancing foci were seen in the right peri-trigonal white matter suggestive of an acute demyelinating lesion. The MRI findings are shown in Figure 5. Spinal cord MRI screening showed no demyelinating lesion.

Discussion

Myelin oligodendrocyte glycoprotein (MOG) is a specific protein found in the outer layers of myelin sheath in the CNS. Earlier, MOG was associated with MS as per animal model studies [7]. Recent advances have shown MOG antibodies to be more closely associated with ADEM and AQP4-Ab negative NMOSD [8,9], rather than MS. Also, CNS imaging has shown many differences in the phenotype of MOG antibody-positive patients from AQP4-Ab positive NMOSD and MS [6,10]. These have lead to a conclusion in recent times that MOGAD is a separate clinical entity.

In the case of this child, with MRI showing multiple demyelinating lesions, MOGAD and MS were considered as differentials based on clinical and radiological findings. ADEM was not considered since the patient had no h/o recent vaccination or infection. The discussion on differentials is summarized in Table 1.

Table 1 show that our case had multiple findings in favor of MS as well as MOGAD. Our case did not fulfil the international criteria for MOG-IgG testing [11]. Yet, the positivity of the antibody test clinched the diagnosis of MOGAD. Ramnathan et al. concluded that there is a significant overlap of radiological findings in MS and MOGAD [12]. They recommended testing of all pediatric-onset demyelinating disorders for MOG-IgG due to the high pretest probability of MOGAD in this population.

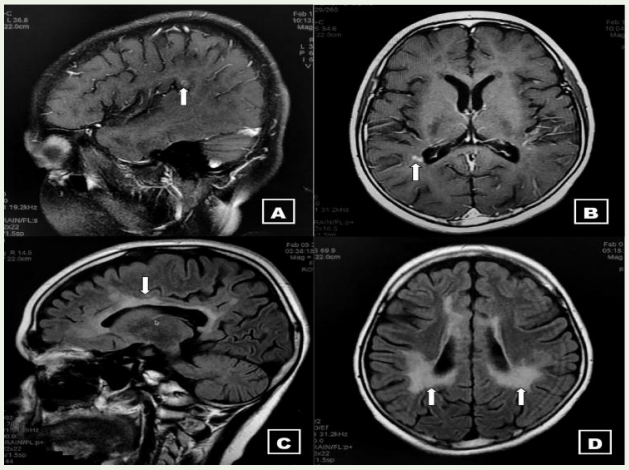

Figure 5: MRI Brain dated February 2021.
A) Sagittal T1 FS+C show a single acute demyelinating lesion showing open ring enhancement (arrow).
B) Axial T1 FS+C image at the level of 3rd ventricle shows right peritrigonal hyper-enhancing white matter lesion which has a perpendicular orientation to right lateral ventricle (arrow).
C) Sagittal T2 FLAIR image shows hyperintensity involving almost the entire corpus callosum. Compare with the 1st MRI scan in March 2015 (Figure 1D) which showed partial callosal involvement.
D) Axial T2 FLAIR image at the level body of lateral ventricle shows symmetrical hyperintensity of B/L periventricular white matter. There is no significant progression of white matter involvement as compared to theprevious scan (Figure 4B).

Table 1: Differentials for our case of pediatric-onset demyelinating disease.

	MS	MOGAD	NMOSD
Points in our case typical of diagnosis	• Dawson's fingers • T1 black hole sign • Dot-dash sign • Subcortical U-fibre involvement • Periventricular hyperintensities which are perpendicular to the orientation of lateral ventricles • Relapsing and remitting course • CSF oligoclonal bands • Fulfillment of modified McDonald criteria 2017	• B/L cerebellar peduncle lesions • B/L large confluent cerebral white matter symmetrical lesions mimicking leucodystrophies phenotypically • VEP showing Left anterior segment optic neuritis • MOG-IgG positive	Optic neuritis
Points in our case atypical of diagnosis	None	Discrete (non-fluffy) lesions	• No lesions in peri-aqueductal area, area postrema, thalamus, or hypothalamus • Corpus callosum lesions perpendicular to its long axis • No involvement of spinal cord

Few salient features that were noted in our case and worth mentioning were as follows:

- Between the 1st and 2nd episodes of the disease, there was an asymptomatic period of 4 years. However, a comparison of both the MRIs showed significant progression in the involvement of B/L cerebral white matter. We may conclude that there was an ongoing process of subclinical demyelination during these years.
- Initial disease morphology was classically that of MS, but later follow up MRI started showing features of MOGAD
- The periventricular white matter had more extensive involvement in parietal lobes compared to frontal or temporal lobes.
- Most relapses had predominant ipsilateral and unilateral (left-sided) neuromotor deficits.
- Our case mostly did not show a strong correlation between clinical deficits and imaging findings.
- Imaging findings did not show changes in the optic nerve when clinically optic neuritis was present.

It is extremely important to identify MOGAD apart from MS as there is a difference in the management of the two disease entities. Chronic immune suppression may be recommended for patients with a relapsing disease or who develop steroid dependence,

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especially if there is incomplete recovery. Commonly used chronic immunosuppressive agents include mycophenolate mofetil, azathioprine, rituximab, and monthly IVIG. Most multiple sclerosis disease-modifying agents are not effective in preventing attacks of MOGAD [13].

Conclusion

Based on our experience with this case and its continuous follow-up, we would like to recommend pediatric-onset demyelinating disorder for MOG-IgG testing as imaging findings alone can mimic MS.

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