Pediatric Acquired Demyelinating Syndrome (ADS)—A Proposed Flowchart for Imaging Diagnosis

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Abstract

Pediatric acquired demyelinating syndromes (ADS) consists of a group of neuroinflammatory disorders, which include monophasic acute disseminated encephalomyelitis, multiple sclerosis, aquaporin-4 antibody-associated neuromyelitis optica spectrum disorder, myelin oligodendrocyte glycoprotein antibody-associated disease, and seronegative ADS. Various advances have been made in understanding their pathology, clinical, and imaging features for providing timely and precise diagnosis to ensure appropriate patient management. Imaging serves as an important tool in not only for diagnosis of demyelination but also helps in distinguishing them. In this case series, the authors have tried to assess distinctive imaging features of these disorders and arrive at an algorithmic approach for the diagnosis of various pediatric demyelinating disorders.

Keywords

- MOG antibody disease (MOGAD)
- demyelinating diseases
- acute disseminated encephalomyelitis (ADEM)
- magnetic resonance imaging (MRI)
- multiple sclerosis
- aquaporin-4 antibody associated neuromyelitis optica spectrum disorder (NMOSD)

Introduction

Pediatric acquired demyelinating syndromes (ADS), demyelination diseases occurring before 18 years of age, comprises monophasic ADS like acute disseminated encephalomyelitis (ADEM) or monophasic Optic Neuritis/Transverse Myelitis (ON/TM) and relapsing ADS. Relapsing demyelinating syndromes further include multiple sclerosis (MS), aquaporin-4 antibody-associated neuromyelitis optica spectrum disorder (AQP4-Ab-NMO-SD), myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), and seronegative ADS. Most common among the relapsing ADS is MS.[1]

In this article, we present a case series of 11 cases of pediatric ADS that have been evaluated with magnetic resonance imaging (MRI) and appropriate laboratory tests. Distinct imaging features were identified and described in an algorithmic approach that may help in arriving at a final diagnosis or narrowing the differential diagnosis.

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Materials and Methods

MRI scans of brain, orbits, and spine of eleven pediatric patients with demyelinating disease as one of the differentials were studied for identifying pattern of involvement. The group contained six males and five females with a range of age from 1 to 17 years and median age of 14 years. They presented with the complaints of headache (3/11), weakness (8/11), altered sensorium (1/11), excessive daytime sleepiness (1/11), tingling sensation in lower limbs (2/11), intractable hiccups or bulbar symptoms (2/11), blurring of vision (3/11), and retention of urine (1/11). Following sequences were performed: brain—axial T1, T2, fluid-attenuated inversion recovery (FLAIR), coronal T2, sagittal T1, diffusion-weighted imaging, susceptibility weighted imaging, contrast enhanced T1 fat-suppressed; spine—sagittal T1, T2, axial T1, T2 (for lesions), and orbit—sagittal T2, axial T2, and contrast-enhanced T1 fat suppressed using Siemens Magnetom Skyra 3T-MRI scanner, Germany.

Based on MRI patterns, appropriate antibody testing or cerebrospinal fluid (CSF) oligoclonal bands testing were suggested.

Results

After all workup, three children were provisionally diagnosed as ADEM, three children turned out positive for MOG-IgG antibodies, three were positive for AQP4 IgG antibodies, one classified under MS, and one though not tested for any antibody but treated as NMO-SD based on MRI findings.

Supratentorial Lesions

In 6 out of 11 patients, there were supratentorial lesions. All of them were hugely different from each other. The first girl, positive for MOGAD, had supratentorial T2/FLAIR periventricular, subcortical, and deep white matter hyperintensities, which were ill defined large and confluent involving bilateral frontoparietal lobes (►**Fig. 1**). This type of leukodystrophy pattern has been described as one of the supratentorial involvement pattern of MOGAD apart from the most common ADEM.[2–4]

Cortex and deep gray matter, corpus callosum involvement, and leptomeningeal enhancement have also been recognized in MOGAD.[2,3]

Another boy presented with ADEM like picture (►**Fig. 2**)—with multiple T2/FLAIR ill-defined periventricular and deep white matter lesions. He also had multiple noncontiguous lesions in spinal cord. Of those, one was long segment lesion involving both gray and white matter of cervical and upper thoracic cord with associated cord swelling. There was characteristic involvement of conus medullaris also. He also had T2/FLAIR hyperintensity with heterogeneous enhancement extending to perineural region in intraorbital part of left optic nerve. According to the findings, MOGAD-associated demyelination was strongly suspected,[2,5] but the patient was seronegative. He was treated as ADEM after ruling out other alternative diagnosis.

Third pattern recognized was multiple small ovoid T2/FLAIR hyperintense lesions in periventricular (arranged perpendicular to ventricular surface) and juxtacortical regions (►**Fig. 3**). These are described as characteristic for MS; however, they are reported in some MOGAD cases also.[6] A few of these showed diffusion restriction and ring like contrast enhancement, which signifies their active nature. However, the nonenhancing ones represent the old lesion. This satisfied the criteria of dissemination in time (DIT). Also, presence of CSF oligoclonal bands, as was seen in this patient, can be a representative of DIT. There were similar lesions in medulla as well as upper thoracic spinal cord, representing dissemination in space (DIS). It, thus, fit the 2017 McDonald's criteria for MS.[7]

A patient positive for AQP4-Ab showed T2/FLAIR hyperintensity around third ventricle in bilateral diencephalic region (diencephalic syndrome; ►**Fig. 4**). This area has been a characteristic area for AQP4-Ab-NMO-SD as plenty of AQP4 channels are present in the periaqueductal and periependymal surface of third and fourth ventricle.[2] However, there are also cases of MOGAD reported in diencephalic syndrome.[8]

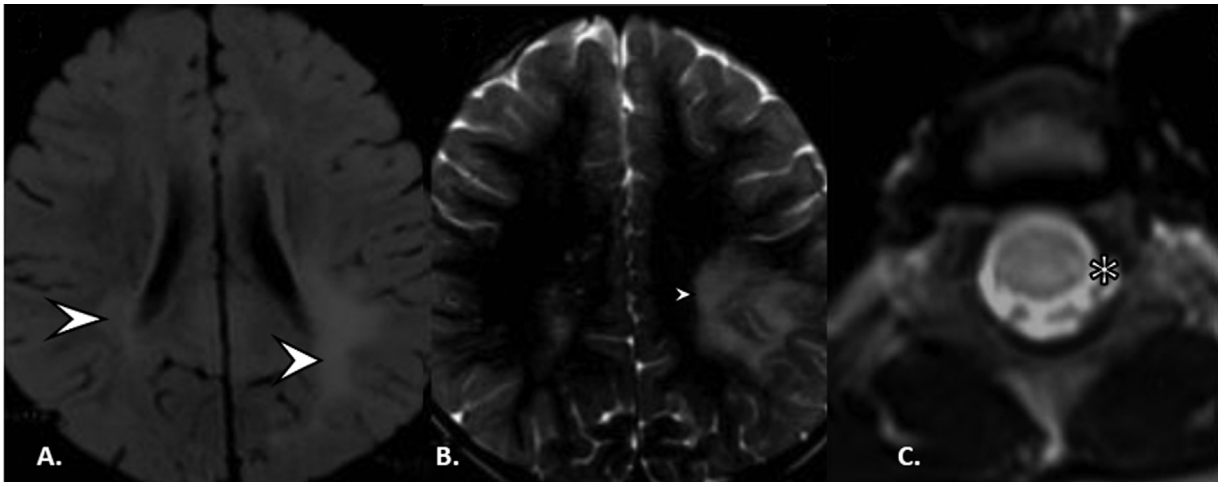

Fig. 1 Myelin oligodendrocyte glycoprotein antibody-associated disease (**A, B**) Axial fluid-attenuated inversion recovery and T2 image showing bilateral asymmetric ill-defined periventricular and subcortical white matter hyperintensities in frontoparietal lobes (arrowheads). (**C**) Axial T2-weighted imaging of spine showing hyperintensity involving both gray and white matter (asterisk).

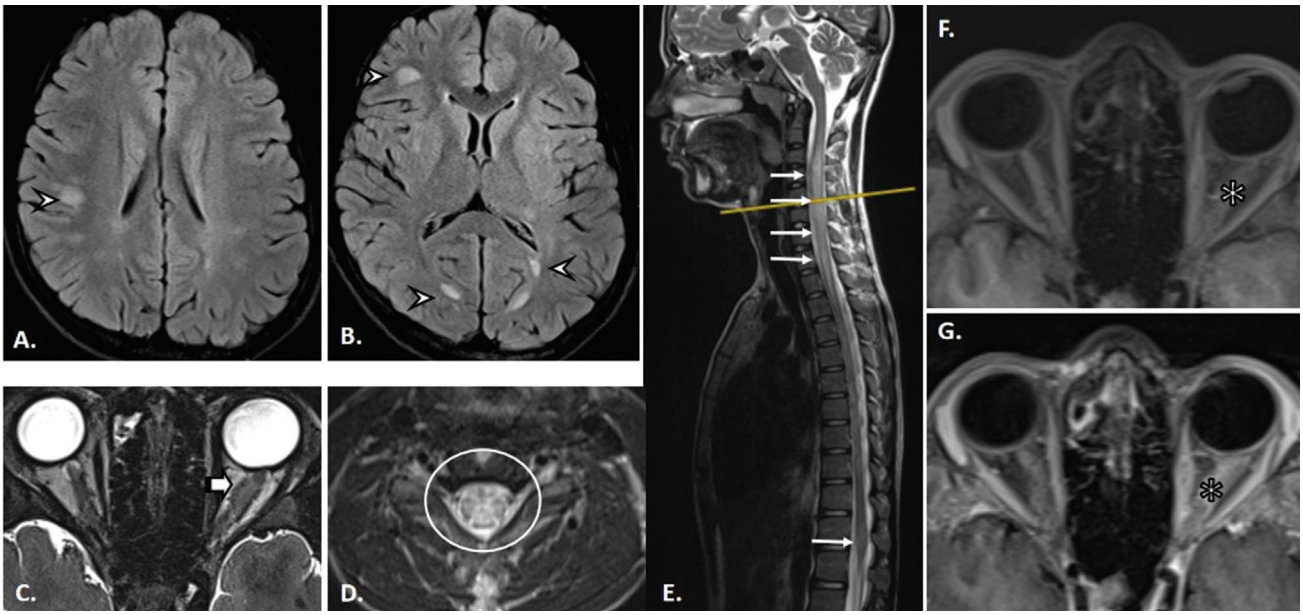

Fig. 2 Acute disseminated encephalomyelitis: (**A, B**) Axial fluid-attenuated inversion recovery images showing multiple small fluffy hyperintensities in subcortical and deep white matter (arrowheads). (**C**) Axial heavily weighted T2 image showing thickening and hyperintensity in intraorbital left optic nerve (short striped arrow). (**D, E**) Axial (circle) and sagittal images (arrows) of spine showing long segment involvement of gray and white matter of cervical and upper thoracic cord with cord swelling. Conus also involved (arrow). (**F, G**) Pre- and post-contrast T1 fat-suppressed images showing heterogenous enhancement of left optic nerve with perineural extension (asterisk).

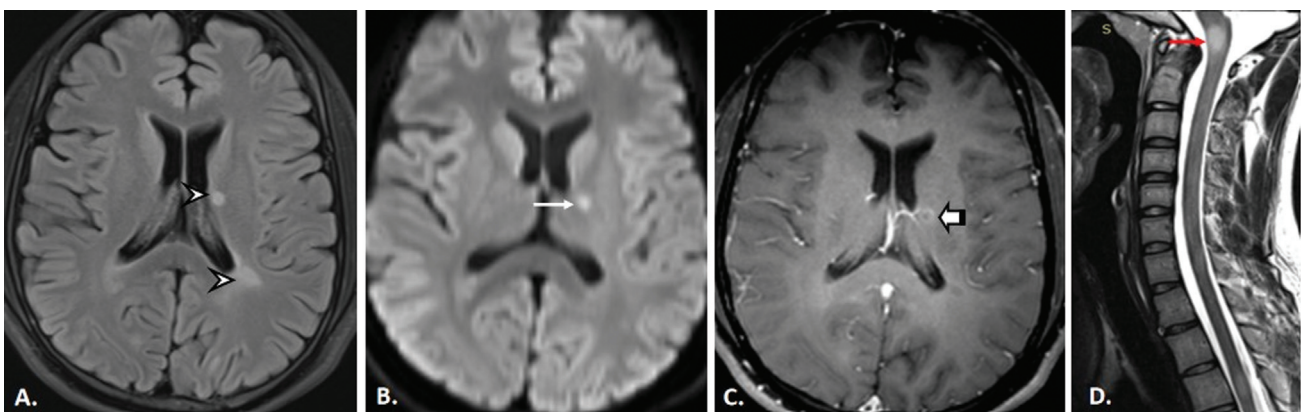

Fig. 3 Multiple sclerosis. (**A, B**) Axial fluid-attenuated inversion recovery image showing multiple small hyperintense lesions in periventricular and subcortical areas (arrowhead). (**C**) Axial diffusion-weighted imaging showing few of lesions showing diffusion restriction (arrow) suggesting active lesions. However, the lesions showing no diffusion restriction suggest old lesions. (**D**) Axial contrast-enhanced T1-weighting image showing ring like enhancement in the active lesions (short striped arrow). (**E**) T2-weighted sagittal image. There were lesions also in medulla and spinal cord, satisfying the criteria of dissemination in space (red arrow).

Two of our patients' MRI showed lesions suggestive of tumefactive demyelination. Such lesions, although most described for MS, are also reported in ADEM and other relapsing disorders discussed here.[9–12] First patient (►**Fig. 5**) had multiple large (>3cm), T2 hyperintensity in center with intermediate intensity rim. The center showed suppression on FLAIR sequence. There was e/o peripheral diffusion restriction and open ring enhancement with most of the rings opening toward ventricles. Second (►**Fig. 6**) one had two similar morphology lesions, except for the enhancement which was minimal in this case. And there were T2/FLAIR hyperintensity noted in pons. Both of our patients were seronegative and did not show any clinical signs of relapse for at least 3 months follow-up; hence, it can be considered under MS or ADEM, until any definitive e/o DIS and DIT.

Relapse, occurring in future, will lead to categorization into multiphasic ADEM/ADEM-ON or MS, based on the IPMSSG criteria.[13]

Infratentorial Lesions

Apart from two cases discussed above, there was one more patient with infratentorial brain stem lesion. Her MRI showed T2/FLAIR hyperintensity in dorsal medulla (area postrema syndrome) (►**Fig. 7**). There was thin rim like enhancement noted in the involved portion. This area has been considered

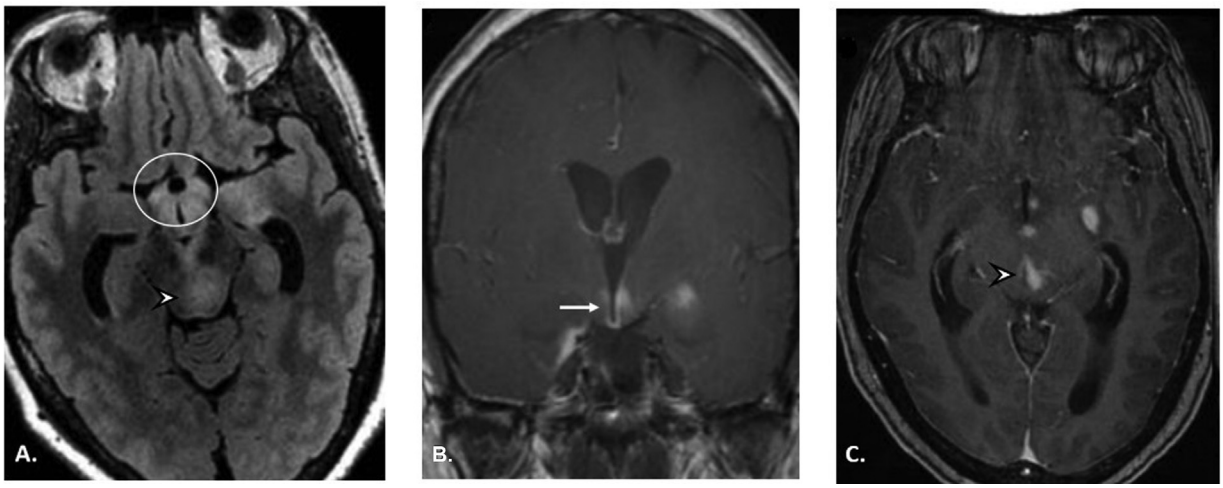

Fig. 4 Neuromyelitis optica spectrum disorder with anti- aquaporin-4 antibody positive. (**A**) Fluid-attenuated inversion recovery axial sections showing hyperintensity in left optic tract region and around aqueduct in mid brain (arrow). (**B**) Enhancing hyperintensities in periependymal location around third ventricle (arrowhead) with involvement of optic tracts (circle).

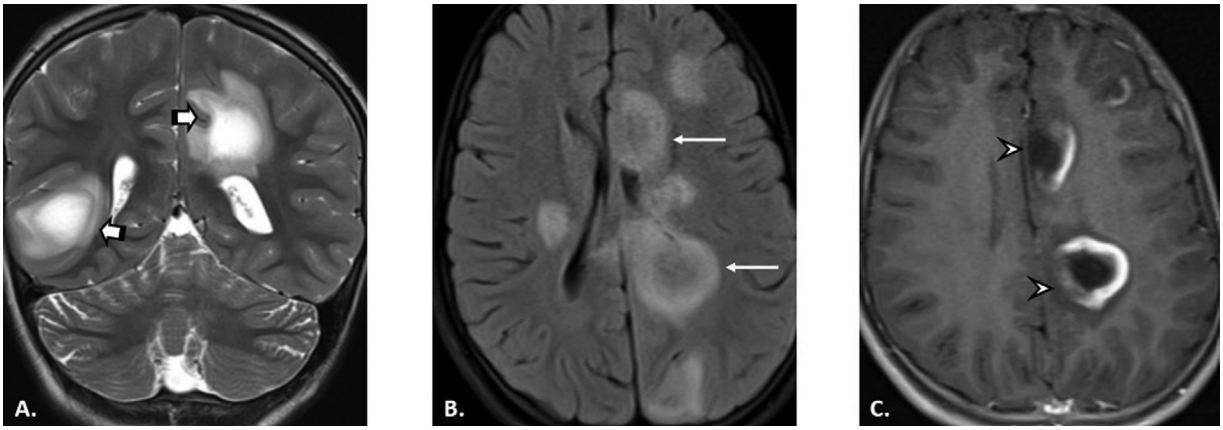

Fig. 5 Tumefactive demyelination. (**A**) Multiple large diffuse T2 hyperintensities (short striped arrow) showing peripheral restriction (arrow) and incomplete ring-like enhancement (arrowhead). These were considered as tumefactive demyelination which are more commonly seen in multiple sclerosis than neuromyelitis optica spectrum. Patient was seronegative.

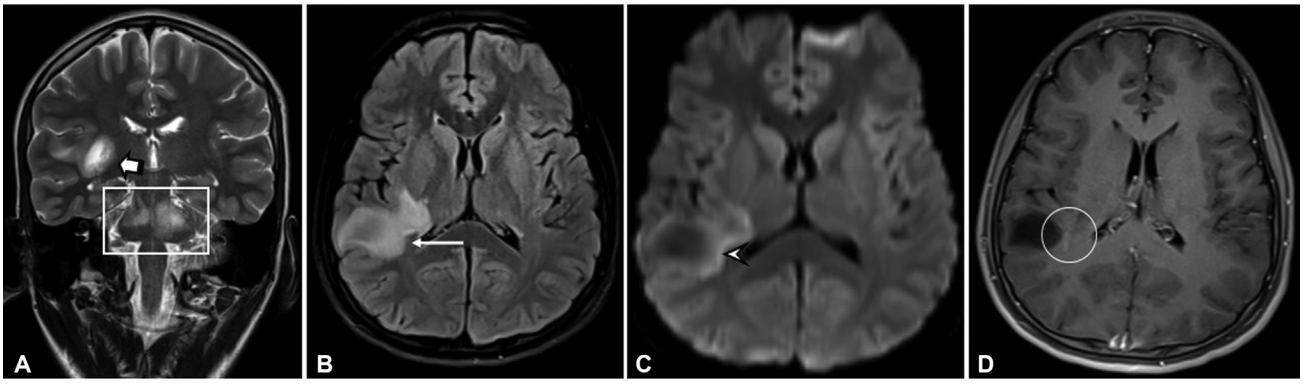

Fig. 6 Tumefactive demyelination. (**A**) T2 coronal images showing large diffuse T2 hyperintensity in right temporal lobe (short striped arrow) and in pons on both sides(rectangle). (**B**) Axial fluid-attenuated inversion recovery showing the lesion and surrounding extensive edema (arrow). (**C**) Axial diffusion-weighted imaging showing peripheral diffusion restriction (arrowhead). (**D**) Contrast-enhanced T1 axial images showing minimal peripheral enhancement (circle).

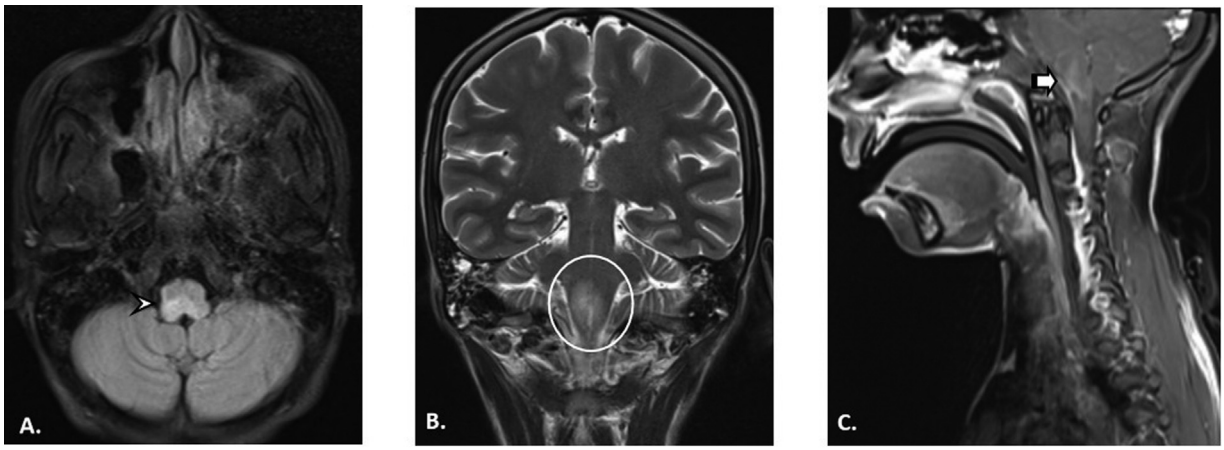

Fig. 7 Neuromyelitis optica spectrum disorder with anti- aquaporin-4 antibody positive. (**A**) Fluid-attenuated inversion recovery axial section showing hyperintensity in posterior medulla (arrowhead). (**B**) T2 coronal section showing hyperintensity in medulla (circle). (**C**). Contrast-enhanced sagittal section showing thin rim like enhancement in involved area (short striped arrow).

one of the most specific brain stems finding for AQP4 positivity and hence is included as one of the MRI requirements in International Panel for NMO Diagnosis (IPND) 2015 criteria.[14,15] The patient was tested positive for AQP4-Ab.

Spinal Cord Lesions

Out of eleven cases, six had spinal cord lesions. One patient of MS is already discussed with the supratentorial lesions. While among the rest, two were longitudinally extensive transverse myelitis. One in the thoracic cord, which turned out to be AQP4-ab positive, also showed with T2-weighted (T2w) bright spotty areas (hyperintensity as equal as surrounding CSF) in the involved segment, which is considered relatively specific and differentiating for NMO-SD from other differentials (►**Fig. 8**).[2,14] The T2w axial sections showed involvement restricted more in the gray matter, giving "H"-shaped pattern. This pattern is more commonly described for MOGAD, but can also be seen in other etiologies like AQP4-Ab-NMO-SD, viral myelitis, and spinal cord infarct.[2]

The second patient had a long segment involvement of upper cervical and thoracic cord but antibody testing could not be done (►**Fig. 9**). There was slight swelling of spinal cord in the involved segment. The patient was treated with steroids as MRI was suggestive of demyelination. The patient responded well to steroids. Considering the pattern of involvement in MRI, possibility of AQP4-Ab-NMO-SD could be considered.

Two of the patients had single short segment (<3 vertebral levels) transverse myelitis lesion in lower thoracic cord. Both were positive for MOGAD (►**Figs. 1** and **10**).

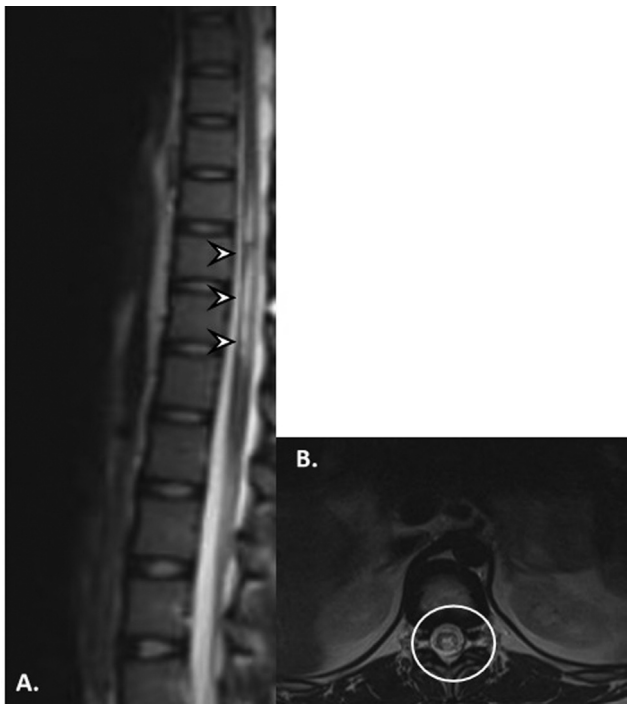

Fig. 8 Neuromyelitis optica spectrum disorder with anti-aquaporin-4 antibody positive. (**A**) T2 sagittal image showing long segment hyperintensity in thoracic cord causing (arrowheads). (**B**) T2 axial image showing hyperintensity involving gray and white matter of cord (circle).

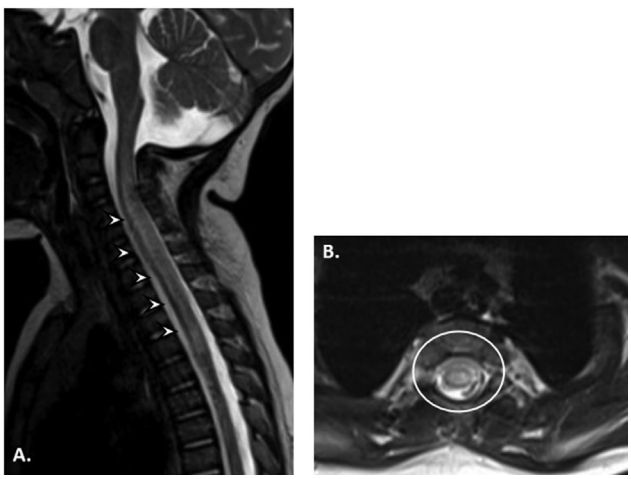

Fig. 9 Antibody status not available. (**A**) T2-weighted sagittal image showing long segment T2 hyperintensities in cervical and upper thoracic cord (arrowheads). (**B**) Axial T2-weighted showing involvement of gray and white matter (circle).

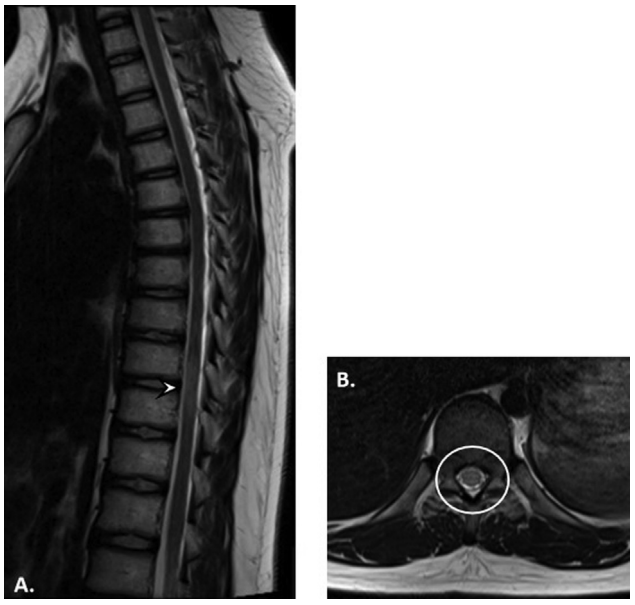

Fig. 10 Myelin oligodendrocyte glycoprotein antibody-associated disease. (**A**) T2 sagittal image showing short segment hyperintensity in thoracic cord (arrowhead). (**B**) T2 axial image showing hyperintensity involving gray and white matter of cord (circle).

Spinal cord swelling, as seen in two patients, is associated with acute phases of both AQP4-Ab-NMO-SD and MOGAD, but in chronic phase AQP4-Ab-NMO-SD is more associated with cord atrophy as compared with MOGAD.[2,14]

Optic Nerve Involvement

Finally optic pathway involvement was noted in three patients. Two (►**Fig. 2**, **11**) of them showed unilateral long segment (>50% of length) hyperintensity with heterogeneous neural as well as perineural enhancement of intraorbital part of optic nerve (anterior pathway). This pattern of enhancement is not seen in AQP4-Ab-NMO-SD and therefore can help differentiation between these two.[2] There was no abnormality found in optic chiasma that contrasts with AQP4-Ab-NMO-SD which involved the intracranial segments of optic nerve along with chiasma and optic tracts (posterior portions.[3,14] One of them turned out to be MOGAD positive (►**Fig. 11**), while second one was seronegative. The third one was involved of optic chiasma and optic tract (posterior optic pathway). She, as suspected, turned out AQP4 ab positive.

Algorithm

Based on certain distinct neuroimaging features of each disorder as noticed in this study as well as in previous studies, we arrived at an algorithm (►**Fig. 12**) that can help in narrowing the differential diagnosis or diagnose on MRI itself. This can be applied to any patient with suspicion of first attack of demyelination.

In a patient presenting with encephalopathic symptoms like altered sensorium, headache, recent onset seizures, lethargy; nonencephalopathic central nervous system symptoms like excessive sleepiness (diencephalic syndrome), intractable vomiting/hiccups (area postrema), limb weakness, paraesthesia (spinal cord symptoms); or decreased visual acuity (unilateral / bilateral), should undergo MRI scan of brain, orbits, and spine.

Based on the characteristic imaging features as demonstrated in multiple schematic diagrams (►**Figs. 13**–**15**), they can be categorized into the various pediatric ADS described (►**Fig. 12**).

Discussion

This series highlights the importance of having a meticulous approach in imaging evaluation of pediatric ADS.

Pediatric demyelinating diseases have been less studied due to their lower incidence; however, they have been reported in children as young as 2 years of age.[16] The previous studies on pediatric ADS show an incidence ranging from 0.6 to 1.66 per 100,000 children making it exceptionally rare.[17] The definite worldwide incidence for MS is still uncertain because of influence of genetic and environmental factors; previous studies predominantly done in Western population have reported a incidence of approximately 0.05 to 2.9 per 100,000 children.[16] MOGAD shows a higher incidence in pediatric population, compared with pediatric MS and NMO-SD.[4,18]

In the diagnosis of NMO-SD, serology is included as one of requirement in IPND criteria along with the six core clinical presentations and their corresponding radiological findings.[15]

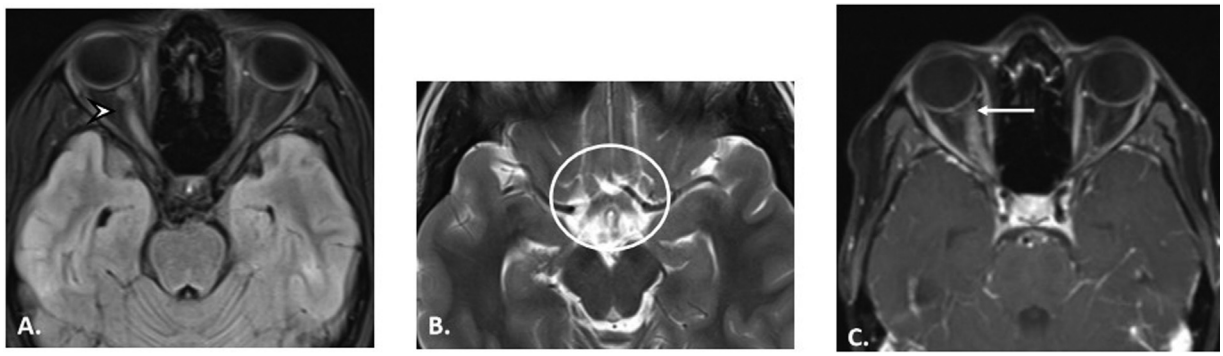

Fig. 11 Myelin oligodendrocyte glycoprotein antibody-associated disease. (**A**) Axial fluid-attenuated inversion recovery image showing diffuse hyperintensity in right intra-orbital optic nerve with its thickening (arrowhead). (**B**) Axial T2-weighted imaging showing normal signal intensity in optic chiasma (circle). (**C**) Post-contrast axial image showing heterogenous and perineural enhancement of involved segment of right optic nerve (arrow).

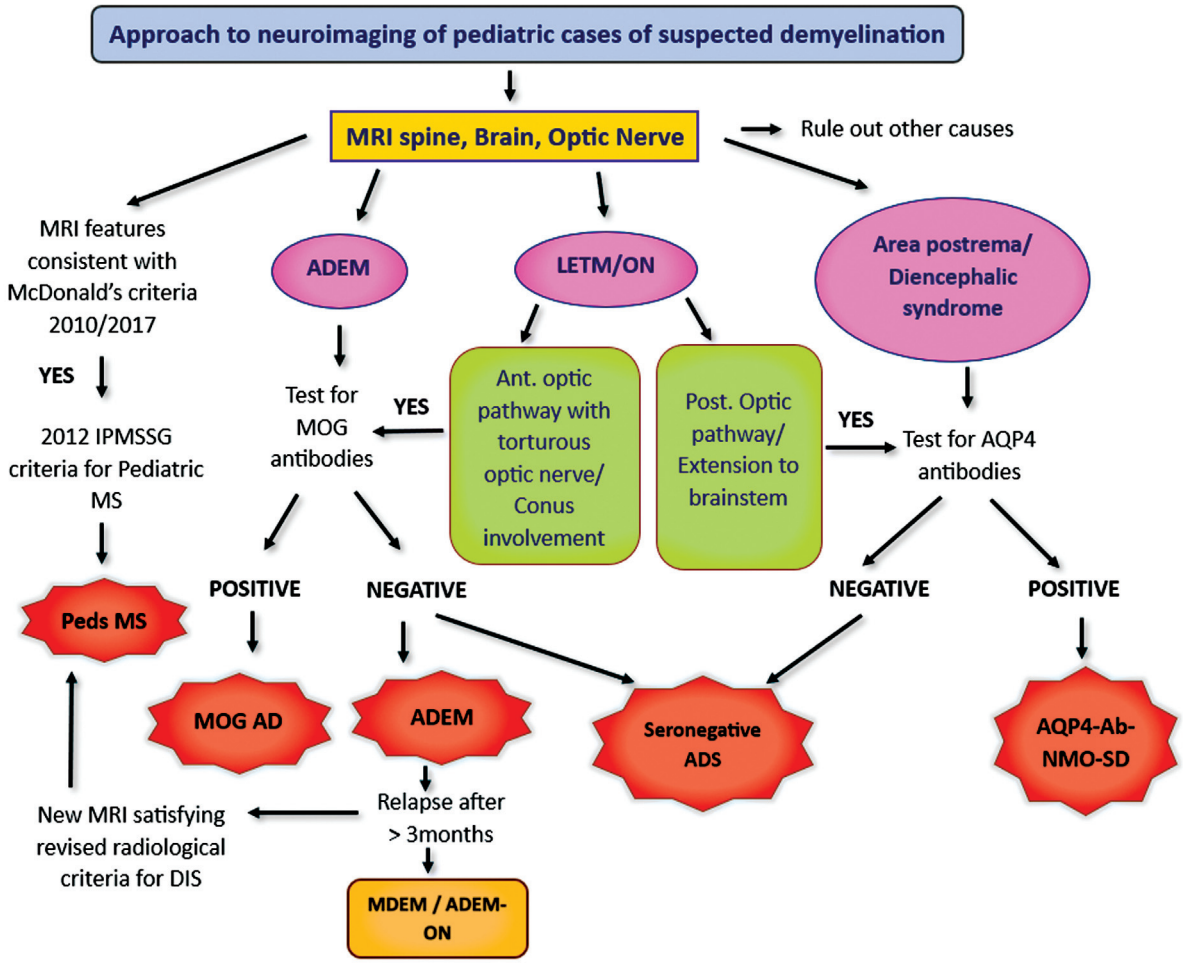

Fig. 12 Proposed diagnostic algorithm based on imaging features in pediatric ADS. MDEM, multiphasic acute disseminated encephalomyelitis. McDonald's criteria 2010 / 2017.[7,21] IPMSSG, International Pediatric Multiple Sclerosis Study Group criteria.[13] ADEM, acute disseminated encephalomyelitis; ADS, acquired demyelinating syndrome; AQP4, aquaporin-4; DIS, dissemination in space; LETM, longitudinally extensive transverse myelitis; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; MRI, magnetic resonance imaging; NMO-SD, neuromyelitis optica spectrum disorder.

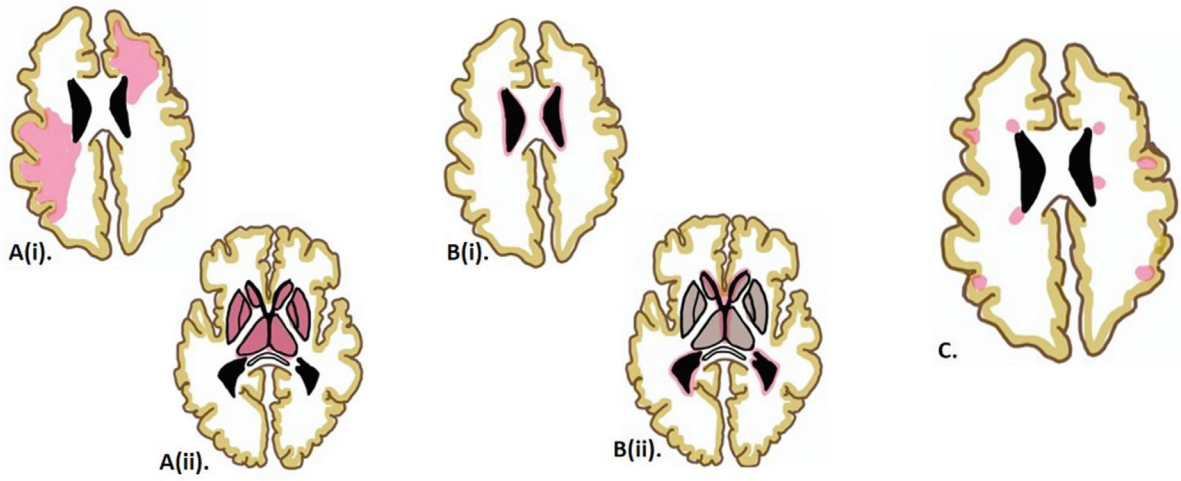

Fig. 13 Diagrams showing supratentorial involvement (**A**) myelin oligodendrocyte glycoprotein antibody-associated disease: (i) Confluent ill-defined large areas of subcortical and periventricular white matter. (ii) Involvement of deep gray matter. (**B**) Aquaporin-4-antibody-neuromyelitis optica spectrum disorder: (i, ii) periependymal involvement. (**C**) Multiple sclerosis: Multiple small ovoid plaque in periventricular (perpendicular to ventricular surface) and subcortical locations.

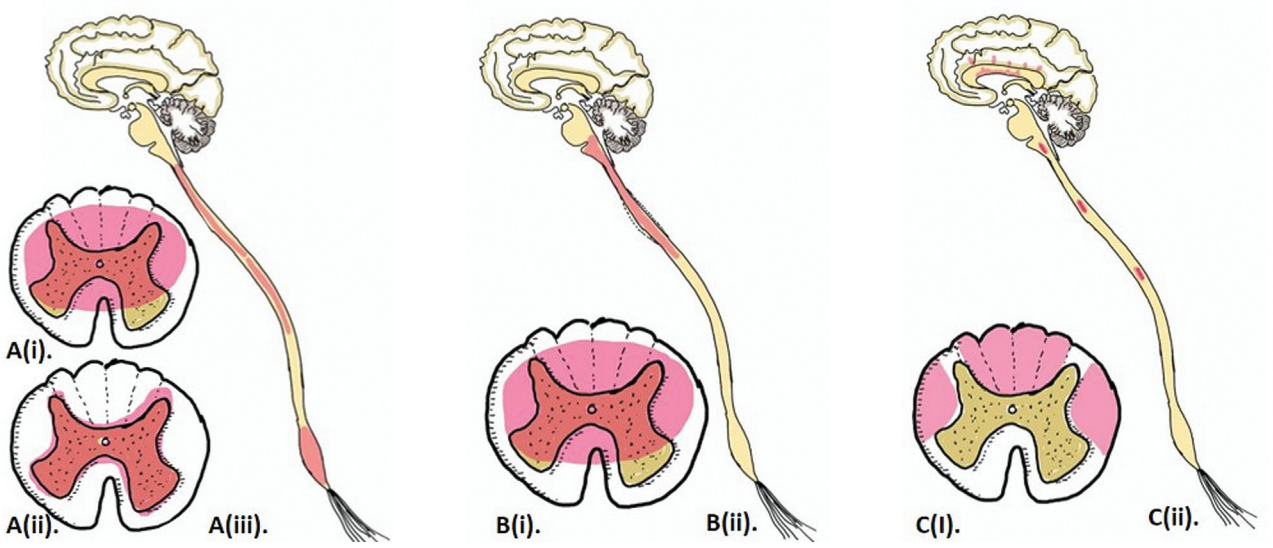

Fig. 14 Diagrams showing spinal cord involvement: (**A**) myelin oligodendrocyte glycoprotein antibody-associated disease (**i**) Involving both gray and white matter, (**ii**) Involvement of gray matter only giving "H"-shaped appearance axial sections and (**iii**) typically involving conus. (**B**) aquaporin-4-**antibody-n**euromyelitis optica spectrum disorder (**i**) involving both gray and white matter and (**ii**) upper segments of spinal cord with cervicomedullary extension. It can show cord swelling in acute swelling. (**C**) multiple sclerosis (**i**) involving dorsal and lateral white matter, (**ii**) small ovoid plaques arranged perpendicular to ventricle surface, involvement of corpus callosum, and small segmental involvement of spine.

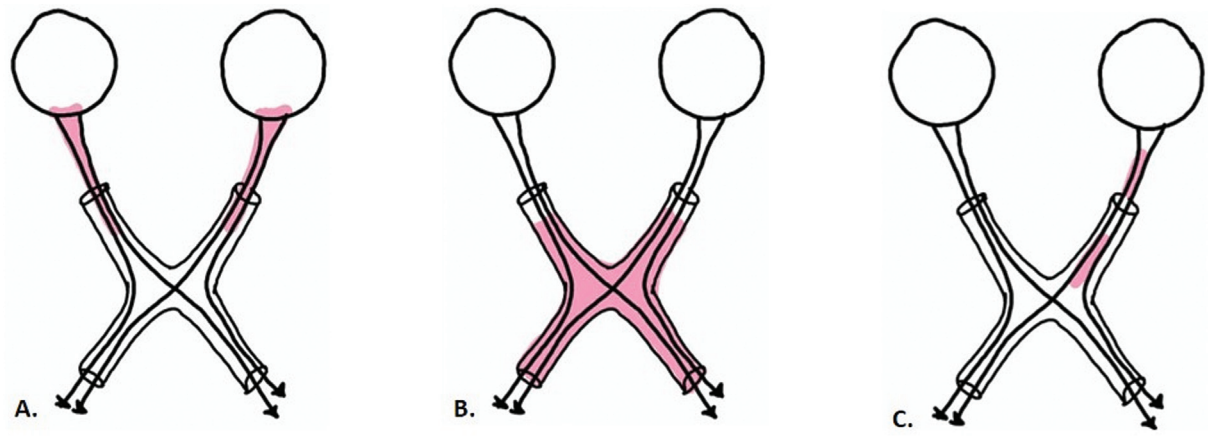

Fig. 15 Diagram showing optic nerve involvement. (**A**) Myelin oligodendrocyte glycoprotein antibody-associated disease: Bilateral anterior optic pathway involvement—optic disc and intraorbital optic nerve. (**B**) Aquaporin-4-**antibody-**Neuromyelitis optica spectrum disorder: Bilateral posterior optic pathway involvement—optic chiasma and optic tract. (**C**) multiple sclerosis: Unilateral multiple short segment lesions.

The cell-based serum assays is preferred over indirect immunofluorescence or enzyme-linked immunosorbent assay technique for the diagnosis due to its higher sensitivity.[15] Diagnosis of pediatric MS is made using IPMSSG 2012/McDonald's criteria 2017. MS, in children, usually presents with wide range of clinical presentation that is more often multifocal in younger children unlike adolescents.[19]

No prognostic factors for MOGAD have been described till now; however, recurrence can be predicted to some extent by the trend of MOGAD, as the recurrence is lower among the group showing declining antibody titer while higher in the case of persisting or high titer.[20] Though treatment of all these conditions in acute settings includes immunosuppression, it is of utmost importance to distinguish among them as disease-modifying therapies (e.g., interferon-β, fingolimod, and natalizumab) given for preventing relapses in MS can aggravate NMO-SDs.

Conclusion

Inflammatory demyelinating disease can be managed efficiently if diagnosed early, preventing its long-term sequelae. In a country like India where there are limited resources and many times not all investigations are available, it is challenging to diagnose rare diseases. Our series is an attempt to reach diagnosis with the help of imaging itself in the settings where other investigations, though not available, prompt treatment can be instituted. Though various radiological patterns have already been described, categorizing these patterns can help in early diagnosis of these disorders, which

will result in early diagnosis and proper treatment, thereby improving the prognosis.

Conflict of Interest
None declared.

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