Review Article

Acquired demyelinating disorders of central nervous system

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Abstract

Acquired demyelinating disorders of central nervous system (CNS) are rare disorders in the pediatric age group and are characterized by demyelination occurring at various sites in the nervous system. Demyelination can involve an isolated CNS site such as brain, spinal cord (transverse myelitis) and optic nerves (optic neuritis) or can involve multiple areas of the nervous system. This group of disorders includes transient single-time events like acute demyelinating encephalomyelitis (ADEM) to life-long conditions like multiple sclerosis (MS). Repeated acute episodes of demyelination may be a harbinger to the development of chronic demyelinating disorders. Early and accurate distinction between transient acute single-time demyelinating events and chronic relapsing conditions like MS is of paramount importance as treatment protocols and prognosis are widely different. Early disease modifying therapy may be beneficial in MS to suppress the ongoing and future relapses, whereas in ADEM, only short-term steroid therapy is all that is needed with an overall good prognosis.

Key words: *Acute demyelinating encephalomyelitis, Clinically isolated syndrome, Multiple sclerosis, Neuromyelitis optica, Optic neuritis, Transverse myelitis*

Acquired demyelinating disorders are characterized by demyelination occurring at various sites in the nervous system varying from an isolated central nervous system (CNS) site such as brain, spinal cord and optic nerves to multiple areas of the nervous system. Repeated acute episodes of demyelination may lead to chronic demyelinating disorders [1-5]. Early and accurate distinction between transient acute single-time demyelinating events like acute demyelinating encephalomyelitis (ADEM) and chronic relapsing conditions like multiple sclerosis (MS) is paramount importance as treatment protocols and prognosis are widely different [6-10]. Till a few years back, the term ADEM was being used to encompass all the clinical events involving acute focal neurologic deficits along with the features of demyelination on neuroimaging [11-14]. On the contrary, the diagnosis of MS was made if there were recurrent focal neurodeficits along with accrual of demyelinating lesions on neuroimaging that were separated in time and space [1,2,15-18].

This classification was marred by description of various new entities and varying natural histories of the demyelinating disorders [1-3,7]. Hence, it was thought that clinical, biologic, and radiographic delineation of the various monophasic and chronic childhood demyelinating disorders requires an operational classification system to facilitate the prospective research studies. Extensive literature review led International Pediatric MS Study Group (IPMSG) to formulate an operational classification of acquired demyelinating disorders so as to be able to interpret the future studies better [1-3]. This classification system has taken into account clinical presentation, recurrence, and neuroimaging features.

PATHOLOGY OF DEMYELINATING DISORDER

The pathological hallmark of ADEM is perivenular inflammation with limited sleeves of demyelination [19]. In some cases, large areas of demyelination occurs secondary to coalescence of many perivenous demyelinating lesions. Acute hemorrhagic leucoencephalitis is pathologically similar to ADEM, but additionally exhibits the petechial hemorrhages and venular necrosis. In MS also, though perivascular inflammation occurs, more prominent are confluent sheets of macrophage infiltration admixed with reactive astrocytes in completely demyelinated regions. These pathological differences suggest that brain histopathology could be a possible diagnostic gold standard and may be clinically useful to differentiate between ADEM and MS. However, the true utility of brain biopsy in distinguishing ADEM, MS and other idiopathic demyelinating disorder has not been examined so far [19].

EPIDEMIOLOGY

There are no clear studies of worldwide distribution of acquired demyelinating disorders of childhood. Incidence of these disorders

remains unidentified in our country due to lack of specific diagnosis, inadequate data and follow-up. Mean incidence of ADEM was estimated to be 0.4/1,00,000/year among persons <20 years of age [14]. Whereas ADEM is a disease of children and young adults with mean age at presentation ranging between 5 and 8 years in different studies [12,20], MS is considered to be a disease of young adults with mean age of onset 30 years and it is becoming increasingly recognized that MS affects children and adolescents prior to 18 years [7]. MS is twice more common in females as described in different studies [1,4,7]; whereas, ADEM has been described more frequently in boys with a female to male ratio of 0.6-0.8 [21]. There is little data in literature regarding the incidence of other demyelinating disorders like transverse myelitis (TM), optic neuritis (ON), neuromyelitis optica (NMO) and polyfocal demyelination. Recently in a prospective study from UK, incidence of acute transverse myelopathy in children under 16 years is at least 1.72 per million children per year [22].

There were multiple predisposing factors identified due to temporal and occasionally causal relationship in some reported case series, none of them is causative. Some of them are preceding viral infections, vaccination mainly influenza, varicella and measles. There are some case reports that have demyelination features with rabies and some viral diarrhea [2,3,23].

IPMSG CLASSIFICATION AND DEFINITION [2,3]

Clinically Isolated Syndrome (CIS)

- A monofocal or polyfocal, clinical CNS event with presumed inflammatory demyelinating cause
- Absence of a prior clinical history of demyelinating disease (e.g., ON, TM and hemispheric or brain-stem related syndromes)
- No encephalopathy that cannot be explained by fever
- The diagnosis of MS based on baseline magnetic resonance imaging (MRI) features is not met.

ADEM (Monophasic)

- First clinical event with presumed inflammatory or demyelinating cause, with acute or subacute onset that affects multifocal areas of the CNS. The clinical presentation must be polysymptomatic and must include encephalopathy (i.e., behavioral changes e.g., confusion, excessive irritability and/or alternation in consciousness e.g. lethargy, coma)
- Event should be followed by improvement either clinically on MRI or both, but there may be residual deficits
- No history of a clinical episode with features of a prior demyelinating event
- No other etiologies can explain the event
- New or fluctuating symptoms, signs, or MRI findings occurring within 3 months of the inciting ADEM event are considered part of the acute event
- Neuroimaging shows focal or multifocal lesion(s), predominantly involving white matter, without radiologic evidence of previous destructive white matter changes
  - Brain MRI, with fluid-attenuated inversion recovery (FLAIR) or T2-weighted images, reveals large (1-2 cm in size) lesions that are multifocal, hyperintense, and located in the supratentorial or infratentorial white matter regions; grey matter, especially basal ganglia and thalamus, is frequently involved
  - In rare cases, brain MRI shows a large (1-2 cm) single white matter lesion
  - Spinal cord MRI may show confluent intramedullary lesion(s) with variable enhancement, in addition to abnormal brain MRI findings above specified.

Recurrent ADEM (Obsolete Terminology as per IPMSG 2012)

- New event of ADEM with a recurrence of the initial symptoms and signs, 3 or more months after the first ADEM event, without involvement of new clinical areas by history, examination, or neuroimaging. Event does not occur while on steroids, and occurs at least 1 month after completing therapy
- MRI shows no new lesions; original lesions might have enlarged
- No better explanation exists
- Due to very low frequency of its occurrence (1.7-3.8%) in subsequent episodes after ADEM, the category of recurrent ADEM has been eliminated form 2012 IPMSG consensus definition [2].

Multiphasic ADEM

- ADEM followed by a new clinical event also meeting criteria for ADEM, but involving new anatomic areas of the CNS as confirmed by history, neurologic examination, and neuroimaging
- The subsequent event must occur at least 3 months after the onset of the initial event
- Presentation at subsequent event must be polysymptomatic including encephalopathy, with neurologic symptoms or signs that may differ or remained same as the initial event
- The second ADEM event can involve either new or a re-emergence of prior neurologic symptoms, signs and MRI findings.

NMO or ADEM as First Manifestation of NMO [2]

- Must have ON and acute myelitis as major criteria
- Must have either a spinal MRI lesion extending over three or more segments or be NMO positive on antibody testing
- Brain MRI not meeting criteria for pediatric MS
- Pediatric ADEM can also lead to a subsequent diagnosis of NMO. A positive anti-aquaporin-4 IgG titre during ADEM greatly facilitates this diagnosis [2].

Pediatric MS (Any of the Following) [2]

- Two or more nonencephalopathic (e.g., not ADEM like) clinical CNS events with presumed inflammatory cause, separated by more than 30 days and involving more than one area of the CNS
- One nonencephalopathic episode typical of MS associated with MRI findings consistent with 2010 Revised McDonald criteria for dissemination in space (DIS) and in which a follow-up MRI shows at least one new enhancing or nonenhancing lesion consistent with dissemination in time (DIT) MS criteria [18]
- One ADEM attack followed by a nonencephalopathic clinical event, 3 or more months after symptom onset, that is associated with new MRI lesions that fulfil 2010 Revised McDonald DIS criteria [18]
- First, single, acute event that does not meet ADEM criteria and whose MRI findings are consistent with the 2010 Revised McDonald criteria for DIS and DIT (applies only to children ≥12 years old) [24].

Diagnosis

Diagnosis of these disorders is primarily clinico-radiological. There are no biological or pathological markers available for the diagnosis of different demyelinating disorders [2,3,17]. Clinical features depend on the site of demyelination and can present with visual loss, pyramidal signs, cerebellar signs, encephalopathy, and bladder-bowel dysfunction. Radiological diagnosis is based on demonstration of demyelinating lesions on MRI.

Clinical Evaluation

Fever has been a frequently and commonly associated finding with ADEM [20,25]. Most of these episodes were preceded by viral prodromal illnesses. Motor weakness as unilateral or bilateral pyramidal signs was seen in two third of patients at first demyelinating episode [26]. Involvement of all four limbs is seen more frequently with TM. Multifocal involvement is the hallmark of ADEM. Sensory symptoms are less pronounced and parasthesias, numbness and pain are mainly associated with TM. Complete loss of sensory function below the level of cord involvement is common with TM. Sensory involvement is infrequent in ADEM and MS [4].

Seizures can be presenting symptoms if cortical grey matter is involved. Most of them had generalized tonic clonic seizures with occurrence of status epilepticus in some patients [21,25]. Encephalopathy presenting as altered consciousness ranging from irritability to unconsciousness. Cranial nerve involvement is also not uncommon specifically with ADEM and MS. Diminution or complete loss of vision can be the presenting complaints with ON, ADEM, MS and NMO. It is seen more frequently in MS patients than ADEM patients. In patient with TM always search for the involvement of vision and *vice versa*.

Bowel and bladder involvement is seen in TM and NMO while it is less common in ADEM and MS. Other clinical symptoms and signs as aphasia and extra-pyramidal signs (involvement of deep grey matter nuclei) are less common in ADEM patients [21,25,27]. Spinal cord involvement can be seen as an isolated illness TM or it can be seen in association with MS and ADEM; although, it is uncommon. When compared with patients who are eventually diagnosed to have MS, certain clinical characteristics are more frequent in patients with ADEM e.g., encephalopathy, seizures, fever, headache and meningeal signs [11,27]. Polysymptomatic presentation is more common in ADEM than MS where monosymtomatic presentation such as CIS, ON, TM or NMO is more common [2-4,19].

Detailed neurological examination is important for making a diagnosis. Glass glow Coma Score is important as encephalopathy is the diagnostic criteria for ADEM. Presence of any abnormal posturing or movements and cranial nerve involvement mainly 2^{nd}, 6^{th}, 7^{th}, 9^{th} and 10^{th} should be looked for. Detailed motor examination (including bulk of muscles, tone, power, co-ordination and reflexes), sensory examination (peripheral and central sensory examination) as well as examination for the cerebellar function are also important. Meningeal signs have been described more frequently in ADEM than in MS patients [21,25]. Other things to be seen are hypertension, aphasia and features of raised ICP etc.

Investigations

MRI brain and spine

MRI plays a pivotal role in confirming the presence of CNS lesions consistent with inflammatory demyelination and to exclude other CNS disorders [1-3,17,28,29]. MRI abnormalities in ADEM include as patchy poorly marginated areas of increased signal intensity on T2 and FLAIR sequences. These lesions are usually large, multiple and asymmetric. They typically involve subcortical and central white matter and cortical grey-white matter junction of cerebral hemispheres, cerebellum, brainstem, and spinal cord. Periventricular and corpus callosal lesions are rare but their presence favors the diagnosis of MS over ADEM [18,30,32] (Figs. 1 and 2).

Deep grey matter nuclei involvement, commonly as thalamus and basal ganglia involvement, is more frequent in ADEM than MS [26] and it could be unilateral or bilateral. MRI criteria of MS have not been standardized in children yet [17,18,24,31]. McDonald's criteria were approved to be used in children more than 10 years [2,3,31]. Main diagnostic criteria are dissemination of lesions in both space and over time [17,31]. Gadolinium contrast enhancement is more prominently seen in acute phase. It could be transient or of different forms like complete or incomplete ring, disc etc. [4,20,21]. Spinal cord involvement in TM may show T2 signal abnormalities. Both cervical and thoracic region involved; however, number of

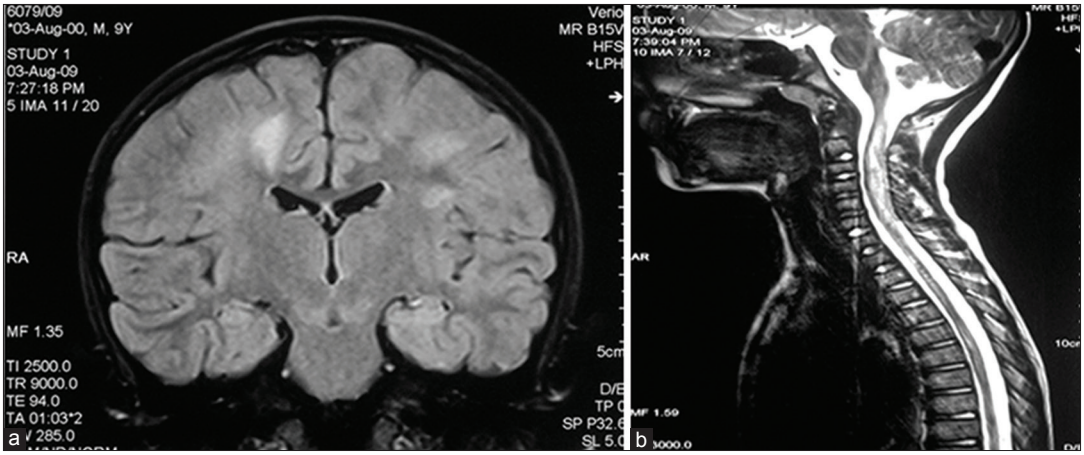

Figure 1: Magnetic resonance imaging (MRI) brain and spine of patient with multiple sclerosis (MS). (a) Fluid-attenuated inversion recovery sequence showing periventricular asymmetrical diffuse hyperintensities. (b) MRI spine T2-weighted sequence showing extensive cervical and thoracic hyperintensities (This patient was diagnosed MS)

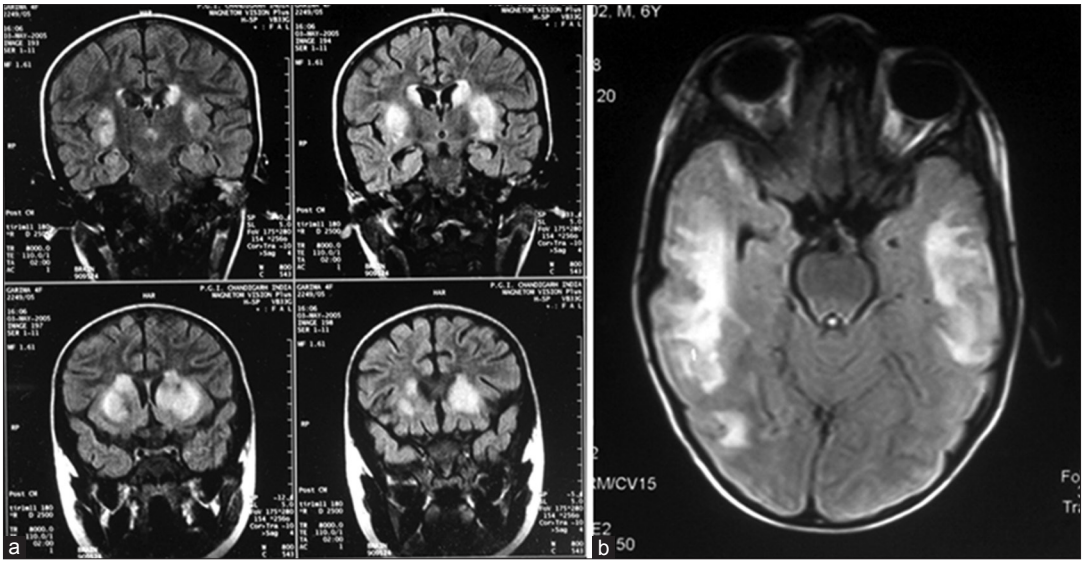

Figure 2: Magnetic resonance imaging brain of patient with acute demyelinating encephalomyelitis (ADEM) showing extensive hyperintensities in fluid-attenuated inversion recovery sequence. (a) Extensive hyperintensities involving periventricular white and deep grey matter involvement including thalamus and basal ganglia. (b) Diffuse white and grey matter involvement which is asymmetrical (these patients diagnosed as ADEM)

vertebral segments involved and gadolinium enhancement of the lesion varies [33]. Optic cuts of MRI are very important to rule out ON [34,35].

Identification of first episode of demyelination as MS or ADEM is difficult radiologically. One study by KIDMUS group [36] had suggested that periventricular lesions are more frequent in MS and number of total lesions did not differentiate ADEM from MS. These criteria had sensitivity of 81% and specificity of 95% to distinguish MS from monophonic ADEM at the time of first episode of demyelination [36].

There is no role of other modality of imaging such as MR spectroscopy. A recent study showed that the presence of some halo lesions (hypointense lesions in MRI) as more predictor of MS than ADEM on follow-up, but this requires long term follow-up.

Presence of at least 2 of following 4 criteria for DIS [18] on MRI (T2 and FLAIR) increases the likelihood of diagnosis of pediatric MS. Among children 12 years and older they have a positive predictive value of 76% and a negative predictive value of 100% [24,29,31].

(1) ≥1 periventricular lesions (2) ≥1 juxtacortical lesions (3) ≥1 Infratentorial lesions (4) ≥1 spinal cord lesions.

Cerebrospinal fluid (CSF) examination

Before making a diagnosis of demyelinating episode, infection must be excluded by CSF analysis and culture. In ADEM, CSF may be normal or show a lymphocytic pleocytosis in contrast to patients with MS, who rarely have CSF pleocytosis [19]. Detection of CSF oligoclonal bands may be useful in diagnosis

of MS [4,26]. Oligoclonal bands have been shown to develop over the course of the disease and may be absent in early stages or in younger patients [4,19]. CSF should be screened for NMO antibodies if suspicion of NMO is high [37,38].

Other investigations

Other investigations which have been found to support the diagnosis are visual evoked potentials (VEP), brainstem auditory evoked potentials (BERA), electroencephalogram (EEG) and somatosensory evoked potentials. Evoked potential testing can confirm the involvement or detect clinically silent deficits in visual, auditory or somato-sensory pathways. Anti-thyroid peroxidase antibodies, anti-N-methyl D-aspartate (NMDA) antibodies etc. [39] are helpful to exclude some rare causes of demyelinating disorders. There are some multisystem disorders which involves CNS causing demyelination such hemophagocytic lymphohistiocytosis (HLH), systemic lupus erythematosus (SLE), malignancy, viral infections and they require specific diagnostic test for particular disease like bone marrow aspiration, polymerase chain reaction, biopsy etc. [39].

Differential Diagnosis [30,39]

Demyelination is a physiological diagnosis and identifying etiological cause is useful in some disorder for which definitive treatment is available like viral infection, SLE etc. However, the diagnosis of demyelination can be made purely on clinic-radiological basis (Fig. 3), e.g., a patient with unilateral eye symptoms had bilateral demyelination of optic nerve on MRI will be unilateral ON and not bilateral ON. There are multiple differential diagnoses which include:

- CNS infections: Neurobrucelosis, herpes simplex encephalitis, HIV, neurocysticercosis, Post streptococcal infection, abscess.
- Vascular disorders: CADASIL, Moyamoya disease, carotid dissection
- Mitochondrial: MERRF, MELAS, LHON
- Inflammatory: SLE, neurosarcoidosis, antiphospholipid antibody Syndrome, CNS vasculitis
- Leukodystrophy: Metachromatic leukodystrophy, adrenoleukodystrophy
- Genetic/metabolic: Inborn errors of metabolism, amino acidurias
- Immunogenetic and antibody mediated disease: these are relatively rare includes Hashimotos encephalopathy, Familial HLH, anti-NMDA receptor antibody encephalitis
- Nutritional: B12 or folate deficiency
- Neoplastic: Lymphoma, astrocytoma.

Treatment

Treatment includes initial stabilization of airway, breathing, and circulation. If raised intracranial pressure is suspected, it should be managed by keeping head in midline and head end elevation position, sedation, osmotic therapy and maintenance of cerebral perfusion pressure >60 mm-Hg. Abortion of seizures should be achieved by antiepileptic drugs. Other supportive management includes physiotherapy for prevention of contracture, occupational therapy and good nursing support along with psychological or psychiatric management (Fig. 4).

SPECIFIC MANAGEMENT

The corticosteroids form the mainstay of treatment in almost all demyelinating disorders as basic pathology is inflammation and autoimmunity. There are no controlled studies to document the efficacy of corticosteroids in ADEM [27]. However, corticosteroids have become the mainstay of therapy in acute episode of demyelination because of significant improvement seen in majority of cases [9,10]. Intravenous steroids, preferably methylprednisolone or dexamethasone, can be used in acute episode. IV methylprednisolone at the dose of 10-30 mg/kg/day for 3-5 days has been recommended followed by 4-6 weeks of oral corticosteroids. Though, there were no RCT between dexamethasone and methylprednisolone, methylprednisolone was found to be better as compared to dexamethasone. There is no consensus about the dose of dexamethasone and different studies tried dose from 1-2 mg/kg (maximum of 16 mg/day). Similarly, there is no consensus about the follow-up treatment with steroids, but some institutional follow-up suggest better results with 4-6 weeks steroid therapy [25].

There is no role of immuno-modulatory therapy in demyelinating disorders in pediatric population. Some experimental treatments available are plasmapheresis and intravenous immunoglobulins, whereas intravenous and intraventricular interferon has been tried in MS. These modes of therapy are still experimental and need further research. For adult patients with MS, there are 10 approved MS DMTs with varying degrees of efficacy for reducing relapse risk and preserving neurological function, but their long-term benefits remain unclear. Some of them are interferon-beta, glatiramer acetate, mitoxantrone, natalizumab, fingolimod, teriflunomide, dimethyl fumarate, BG-12, alemtuzumab, rituximab, ocrelizumab, daclizumab [39].

Outcome

In treated patients, rapid clinical improvement has been seen within hours; although, complete recovery may evolve over days. More often, severely affected children require weeks or months to improve [27]. The most common sequelae seen following ADEM are focal motor deficits ranging from mild clumsiness and ataxia to hemiparesis or blindness. Behavioral and cognitive problems in patients are not uncommon. Less frequent late effects include development of seizures. Though death is possible in acute course of the illness, most of the studies do not mention death as a consequence of acute demyelinating

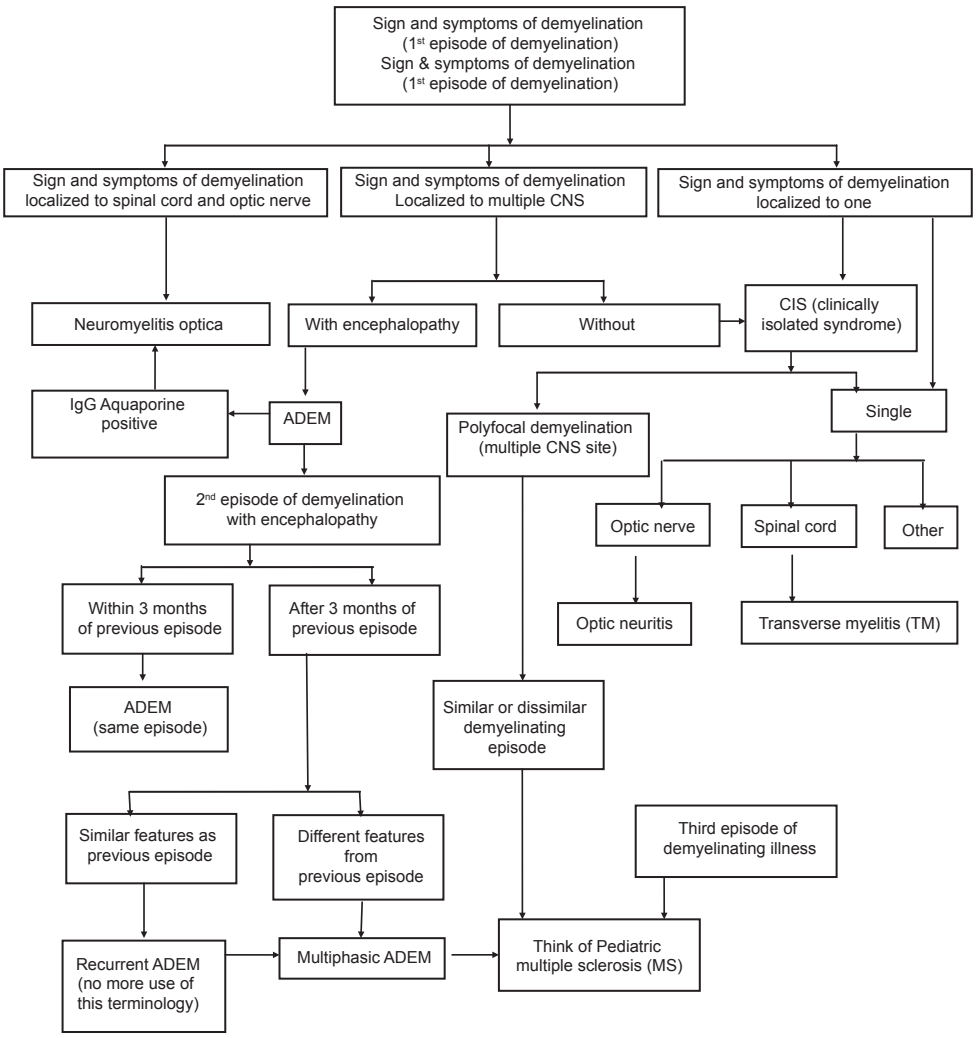

Figure 3: Classification of acquired demyelinating disorders of central nervous system

illness [27]. Physical sequelae and seizures have been found more frequently in patients of MS.

10% of children with an initial diagnosis of ADEM experience another ADEM attack (with encephalopathy), typically occurring in the first 2-8 years after the initial illness [21]. The MRI lesions seen in acute phase of ADEM often resolve slowly over a period of few months without appearance of new lesions [1-3] and new lesions generally do not appear unles s a clinical relapse has occurred [5,21,40-42]. The finding of new lesions on follow-up MRI is highly suggestive of MS. Mikaeloff in his study found that 14-20% of ADEM may evolve as MS but, the natural history of these disorders is so varied that it is very difficult to state the evolution of ADEM to MS. Therefore, prolonged follow-up clinically as well as radiologically is required.

In TM, patients usually have motor, sensory and sphincter disturbances [33]. Factors associated with a better functional outcome include older age at the time of diagnosis, shorter time to diagnosis, lower sensory and anatomic levels of spinal injury, absence of T1 hypointensity on spinal MRI during acute period, lack of leukocytes in CSF, and fewer number of affected spinal cord segments [43]. In ON, visual prognosis is perceived as satisfactory in children, especially young patients with bilateral disease; although, unilateral ON has also been reported to have better or similar visual prognosis [34,44-46]. The role of treatment in prognosis of ON is controversial [47].

Follow-up

Follow-up involve as clinical, radiological and electrophysiological consideration. Clinical follow-up involve detailed neurological examination, presence of neurodeficits and functional status. All patients with demyelinating lesions in the brain or spinal cord should undergo repeat MRI brain and spine at the end of 3 months to see for the residual lesions and appearance of any new lesion. This duration is suggested by the recent IPMSG consensus definition which states the evolution and characterization of these diseases with time duration of 3 months. The appearances of new lesions within 3 months are considered part of same episode while appearances after that time duration prompt for second episode or recurrence. Usual follow-up with occupational therapist and physiotherapist is very important. VEP, BERA and EEG during the follow-up should be done if indicated if new symptoms arises or for follow-up of previous insult.

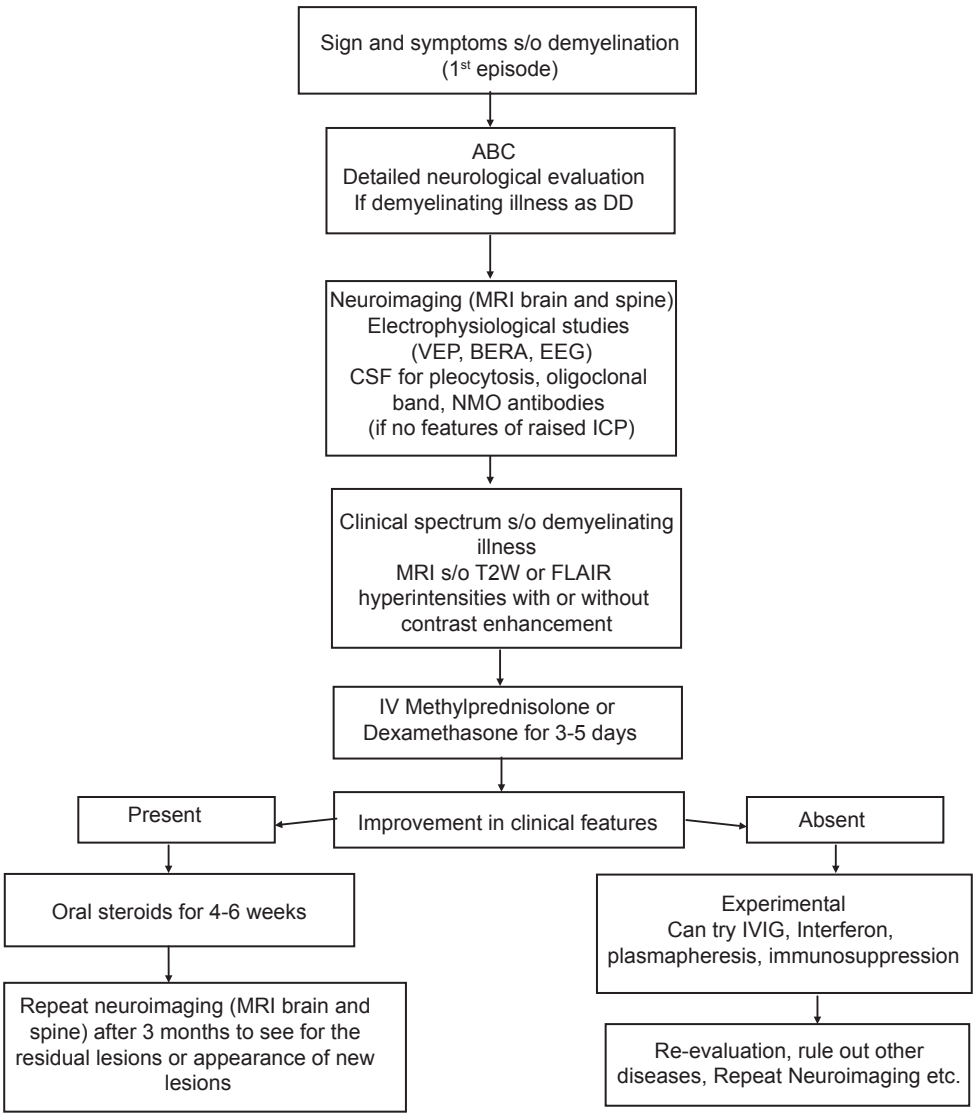

Figure 4: Algorithm for the treatment of demyelinating episode

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