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Acquired Demyelinating Disorders of the CNS in Children

R. Govender[1], Jo M. Wilmshurst[2] and Nicky Wieselthaler[2]
[1]University of Kwa-Zulu Natal, Durban
[2]University of Cape Town, Cape Town
South Africa

1. Introduction

Acquired Demyelinating disorders of the central nervous system in children span a wide spectrum. These conditions may be mono-phasic and self limiting or multi-phasic. Children may present with mono-focal (optic neuritis) or multi-focal (Acquired demyelinating encephalomyelitis) clinical findings.

These demyelinating disorders also share many common clinical, radiological and laboratory features. Early classification of whether the disease is either mono- or multi-phasic has diagnostic and therapeutic implications. Identification of patients who present with a first demyelinating event and are at risk for evolution to multiple sclerosis, allows disease modifying therapeutic agents to be initiated early and thus preserve brain function.

The aetiology of acquired demyelinating conditions is multi-factorial namely – genetic, post-infectious, post-immunization and possibly due to a T-cell mediated auto-immune response to myelin basic protein triggered by an infection or immunization.

This chapter will cover the aetiologies, consensus definitions, clinical presentation, neuro-imaging, evolution and therapeutic advances in acquired demyelinating disorders in children. The pivotal role of neuro-imaging in unraveling the pathology, aetiology and diagnosis of these disorders is also highlighted.

Clinical and neuro-imaging features of other acquired white matter lesions (via infections, toxins, nutritional deficiencies, and osmotic myelinolysis) disease are also discussed.

2. Definitions

The International Paediatric Multiple Sclerosis Study group in 2007 proposed consensus definitions for the demyelinating disorders in children (Krupp *et al.,* 2007). This group was convened to define an operational classification system for the demyelinating disorders. Consensus definitions aid in standardization of diagnosis, investigation, management and further research of these conditions.

3. Imaging techniques for white matter disorders

Magnetic Resonance Imaging (MRI) is the diagnostic modality of choice for evaluating white matter disorders. Sophisticated applications of magnetic resonance technology, such

	Definition
Acquired Demyelinating Encephalomyelitis (ADEM)	A first clinical event with a presumed inflammatory or demyelinating cause, with acute or sub-acute onset that affects multifocal areas of the CNS and must include encephalopathy
Recurrent ADEM	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 neuro-imaging
Multi-phasic Demyelinating Encephalomyelitis (MDEM)	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 neuro-imaging. The event must develop within 3 months of the initial event.
Neuromyelitis Optica (NMO)	Must have optic neuritis and acute myelitis as major criteria and a spinal MRI lesion extending over three or more segments or be NMO positive on antibody testing
Acute Transverse Myelitis (ATM)	A focal inflammatory disorder of the spinal cord resulting in motor, sensory and autonomic dysfunction
Schilder's Disease	A sub-acute demyelinating disorder characterized by bilateral large and vaguely symmetrical lesions
Paediatric Multiple Sclerosis (MS)	A clinical syndrome of multiple clinical demyelinating events involving more than one area of the central nervous system with dissemination in time and space on imaging*
Clinically Isolated Syndromes (CIS)	A first acute clinical episode of CNS symptoms (without encephalopathy) with a presumed inflammatory demyelinating cause; for which there is no prior history of a demyelinating event

*Important caveats in the definition of Paediatric MS put forward by the study group include:

1. The combination of an abnormal CSF (presence of Oligoclonal bands or an elevated IgG index) and two lesions on the MRI, of which one must be in the brain, can also meet dissemination in space criteria.
2. The MRI can meet the dissemination in space criteria if it shows 3 of the following 4 criteria (1) nine or more white matter lesions or one gadolinium enhancing lesion, 2) three or more periventricular lesions, 3) one juxta-cortical lesion, 4) an infra-tentorial lesion.
3. MRI can be used to satisfy criteria for dissemination in time following the initial clinical event, even in the absence of a new clinical event if new T2 or gadolinium enhancing lesions develop within 3 months of the initial clinical event.
4. A second non-ADEM event in a patient is insufficient to make the diagnosis of paediatric MS if the first event meets the criteria for ADEM. MS can only be diagnosed if there is further evidence of dissemination in time on the MRI (new T2 lesions > 3months since the second event) or a new clinical event (> 3months since the second event).

Table 1. Definitions of Acquired Demyelinating Disorders (Adapted from Krupp *et al* 2007)

as magnetization transfer imaging, magnetic resonance spectroscopy, and diffusion tensor imaging, provide quantitative information about the extent of damage that occurs in the white matter.

1H magnetic resonance spectroscopy (MRS) is a valuable technique to non-invasively acquire in-vivo information about biochemical processes in patients with neurologic disorders. MRS measures N-acetyl-aspartate (NAA), total creatine, choline-containing compounds, and lactate. NAA has been considered a marker of neuronal integrity, whereas the levels of choline and lactate are indicative of cell membrane turnover and anaerobic glycolysis (Bizzi *et al.*, 2001). NAA is located almost exclusively in neurons and neuronal processes and thus provides information about neuronal integrity (De Stefano *et al.*, 1995).

MRS studies on patients with white matter disorders have shown reduction in NAA in areas that appear normal on conventional MRI studies suggesting that a significant amount of axonal damage is present in these patients (Arnold *et al.*, 1990; van Der Knaap *et al.*, 1992). Abnormalities in NAA on MRS have also shown a correlation with long term functional outcomes. The author suggests that the extent of axonal damage rather than demyelination may be more reliable in monitoring disease evolution in primary white matter disorders (De Stefano *et al.*, 2000).

Diffusion-weighted MR imaging (DWI) provides further information that may not be apparent on conventional MR images. Engelbrecht et al showed that diffusion restriction precedes brain myelination and is further increased during myelination (Engelbrecht *et al.*, 2002).

4. Acquired Demyelinating Encephalomyelitis (ADEM)

ADEM initially described by Lucas (1790) is characterized by acute onset of diffuse neurological signs with multi-focal white matter involvement. In 1931 a series of case studies was reported in The Lancet. McAlpine described 3 sets of patients with ADEM: -post-vaccination, post-infectious, and those with spontaneous occurring disease. The International Paediatric MS study group further defined ADEM (see Table 1).

4.1 Pathogenesis

The aetiology of ADEM is not completely understood. The pathogenesis is thought to be auto-immune mediated. The seasonal distribution and high rate of antecedent infections (Dale *et a*l., 2000; Murthy *et al.*, 2002; Govender *et al.*, 2010) reported in ADEM suggest a link to an infectious aetiology. Infectious diseases are common in childhood however the rate of preceding infection reported in these series exceed the rate of childhood infectious diseases described (30-50%). The auto-immune reaction is thought to be on the basis of molecular mimicry. The offending infection serves as an antigenic trigger and shares epitopes with various autoantigens of myelin such as myelin basic protein, proteolipid protein, and myelin oligodendrocyte protein (Alvord et al., 1987). This theory shares many similarities with experimental allergic encephalitis. A second theory is that the antigenic trigger activates T cells which cross the blood-brain barrier and react against similar myelin epitopes. ADEM was associated with the class II alleles HLA-DRB1*01 and HLA-DRB*03 in a Russian study (Idrissova *et al.*, 2003). Pathological studies of children

with ADEM showed that peripheral and cerebrospinal lymphocytes have increased reactivity to myelin basic protein (Lisak and Zweiman, 1977). Viral infections described in the context of ADEM include Herpes Simplex Virus-1, Cytomegalovirus (CMV), HIV (Human Immunodeficiency virus), Measles, Mumps, Rubella, Ebsteinne Barre Virus (EBV) and Varicella Zoster Virus (VZV). ADEM occurs after one of every 1000 cases of measles, with a fatality rate of 20% (Tselis and Lisak, 1998). Bacterial antigens implicated include Mycoplasma, Campylobacter, Streptococci and Borrelia Burgdofferi. Dale *et al*. described a subgroup of ADEM associated with Group A β hemolytic streptococcus, abnormal basal ganglia imaging and elevated antibasal ganglia antibodies (Dale *et al*., 2001). Some studies fail to identify the agent responsible for the pre-demyelinating infection (Murthy *et al*., 2002). The authors postulate that the inciting agents are uncommon or unusual organisms that can not be identified by routine laboratory testing. Vaccines, specifically the influenza, rabies and smallpox vaccines have also been reported to precipitate ADEM (Saito *et al*., 1998). Post-vaccination ADEM is thought to be the result of immune mediated mechanisms rather than the cyto-pathic effects of the virus. ADEM is reported after the administration of drugs such as sulfonamides and streptomycin, further supporting an immunological basis of the pathogenesis.

4.2 Epidemiology

There are few epidemiological studies of ADEM in children. Prevalence studies are also complicated by the use of inconsistent case-definitions of ADEM. The estimated incidence in California is 0.4/100,000 population per year (Leake *et al*., 2004) and in Canada is 0.2/100,000 per year (Banwell *et al*., 2009). The mean age of presentation of ADEM in children ranges from 5-8 years (Hynson *et al*., 2001; Tenembaum *et al*., 2007). There is no specific ethnic distribution (Leake *et al*., 2004). Some studies indicate a slight male predominance (Murthy *et al*., 2002; Tenembaum *et al*., 2007). Prevalence in resource poor countries would be expected to be higher because of the significant frequency of childhood infections. However it is probably under-estimated because of limited access to health care facilities and MRI facilities.

4.3 Clinical presentation

ADEM has a wide clinical spectrum of presentation. The hallmark of the disease is an acute presentation of multifocal neurological signs with encephalopathy consistent with diffuse brain involvement usually following a viral infection or immunization. However, events may range from sub-clinical episodes diagnosed by MRI showing mult-ifocal white matter lesions, to a more fulminant presentation with seizures and encephalopathy. Seizures are reported to be more common in children compared to adults with ADEM (Tenembaum *et al*., 2007). Fever and meningism are also common in ADEM prompting treatment for meningo-encephalitis in the initial management (Dale *et al*., 2000). Multi-focal neurological signs are pathognomic for ADEM and include hemiparesis, paraparesis, cranial nerve involvement and ataxia. Atypical presentations include concomitant peripheral nervous system involvement (Kinoshita *et al*., 1996), presentation as an isolated acute psychotic episode (Moscovich *et al*., 1995) or with an extra-pyramidal syndrome (dystonia and behaviour disturbances) (Dale *et al*., 2001).

4.4 Laboratory investigations

In the absence of specific biological markers diagnosis is based on a combination of historical features, clinical and MRI characteristics. Other investigations are usually done to exclude other differential diagnosis (e.g. meningitis, metabolic encephalopathies). In resource poor settings where the burden of disease is predominantly infectious illnesses and because of the overlap of symptoms, infectious aetiologies must be excluded first. Peripheral blood leucocytosis is documented in ADEM (Jacobs *et al*., 1994). CSF studies in ADEM are usually abnormal (in > 67% of cases), typically showing a moderate pleocytosis with an elevated protein content (Miller *et al*., 1956; Govender *et al*., 2010). CSF Oligoclonal bands synthesis may occur in ADEM; however this tends to disappear when the patient recovers.

Electrophysiological studies have limited value in ADEM. Slow-wave abnormalities on electro-encephalogram are compatible with an encephalopathic state (Dale *et al*., 2000). The spindle coma pattern has been described in a child with post measles ADEM (Bortone *et al*., 1996). Visual evoked potentials though are useful in detecting asymptomatic optic tract lesions (Dale *et al*., 2000).

4.5 Neuro-imaging

MRI is the investigation of choice. Since CT is often non-diagnostic for white matter lesions in patients with ADEM, this study is often normal or shows non-specific hypo-densities in the white matter.

Lesions are most easily recognized on T2 weighted (T2WI) and FLAIR MRI sequences. T2WI are more sensitive than T1 weighted images (T1WI) in detecting lesions (Sheldon *et al*., 1985). T1WI shows hypo-intense lesions. The lesions of ADEM are multi-focal and often do not correlate with clinical signs. Lesions tend to involve the cerebellum, the cerebral cortex and brainstem **(Figure 1 a-g).** They usually involve the sub-cortical, central and periventricular white matter. Lesions are typically hyper-intense, patchy, asymmetric and ill-defined. Diffusion-weighted imaging (DWI) and apparent diffusion co-efficient (ADC) maps may be helpful to prognosticate outcome. Low ADC values and restricted diffusion on DWI may suggest a worse outcome as this may indicate permanent tissue damage (Barkovich., 2007). A case study of ADEM with MRS reported reduced NAA and an elevation of choline and lactate (Gabis *et al*., 2004). These authors suggest a place for H MRS studies in longitudinal follow-up studies of ADEM to assess the response to immunomodulating therapies. Deep grey matter lesions in the thalami and basal ganglia have also been described (Baum *et al*., 1994; Govender *et al*., 2010) **(Figure 2a-e).** Lesions in the corpus callosum are uncommon and considered atypical for ADEM **(Figure 3).** Contrast enhancement of lesions post gadolinium administration indicates activity of the lesions **(Figure 4).** This correlates with the pathological finding of inflammation and demyelination in experimental allergic encephalitis. Non-enhancing and partially enhancing lesions in the presence of enhancing lesions have been described in ADEM and are thought to be because of lesions of differing ages and the evolution of the disease over several weeks (Schwaz *et al*., 2001;, Govender *et al*., 2010).

Concomitant spinal cord lesions have been described in ADEM (Hynson *et al*., 2001;, Murthy *et al*., 2002;, Govender *et al*., 2010) **(Figure 5a,b)**. Spinal cord lesions in ADEM typically have ill-defined margins, extend over multiple vertebral segments, are thoracic in location and result in mild cord expansion (Singh *et al*., 2002).
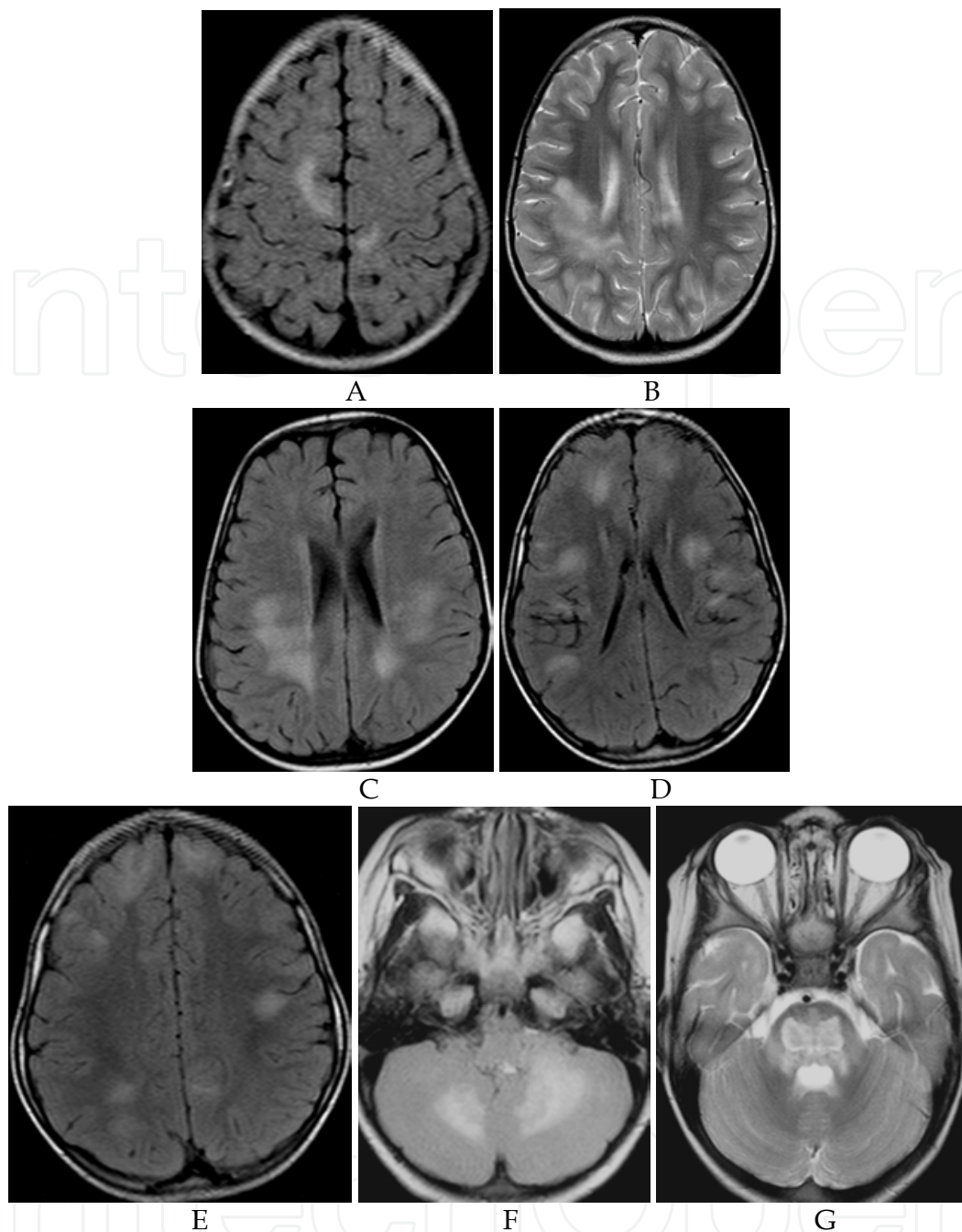
Fig. 1. A - Flair axial MRI demonstrating bilateral asymmetrical cortex and sub-cortical white matter high signal intensities consistent with ADEM. B- T2 axial MRI demonstrating right ill-defined peritrigonal white matter high signal intensity lesion consistent with ADEM. C- Flair axial MRI demonstrating bilateral, fairly symmetrical high signal intensities in the posterior white matter consistent with ADEM. D - Flair axial MRI demonstrating bilateral asymmetrical high signal intensity lesions in the sub-cortical and deep white matter consistent with ADEM. E- Flair axial MRI demonstrating bilateral asymmetrical high signal intensity lesions in the cortex and sub-cortical and deep white matter consistent with ADEM. F - Flair axial MRI demonstrating hyper-intense lesions in the brachium ponti consistent with ADEM. G - T2 axial MRI of the brain demonstrating large hyper-intense pontine lesion with surrounding oedema
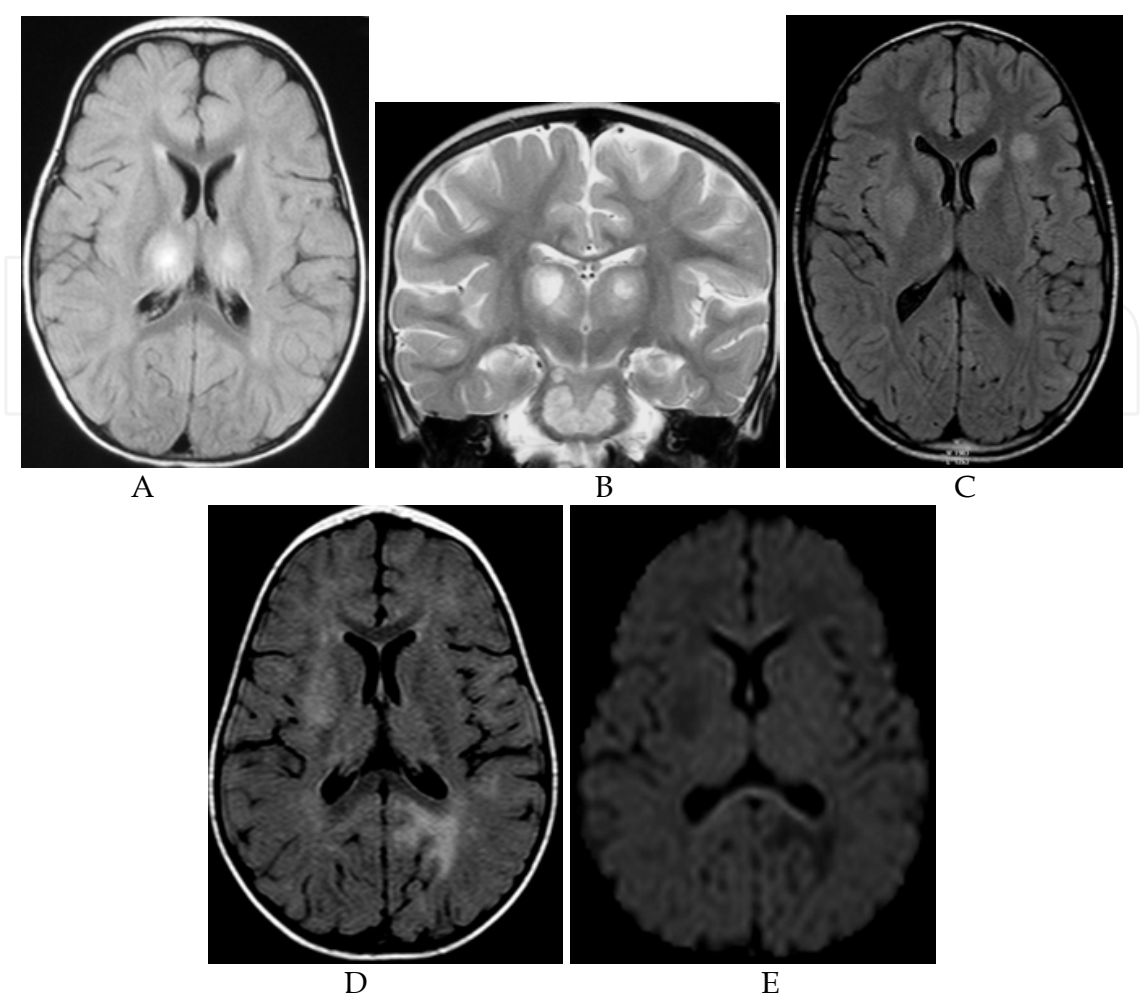
Fig. 2. A- Flair axial MRI of the brain demonstrating bilateral symmetrical hyper-intense thalamic lesions. B- T2 coronal MRI of the brain demonstrating bilateral symmetrical rounded hyper-intense thalamic lesions as well as a large hyper-intense pontine lesion. C- Flair axial MRI demonstrating bilateral high signal intensity lesions in the basal ganglia and deep white matter on the left consistent with ADEM. D- Flair axial MRI demonstrating asymmetrical basal ganglia and white matter high signal intensities consistent with ADEM. E- DWI of 2D shows no evidence of restricted diffusion.
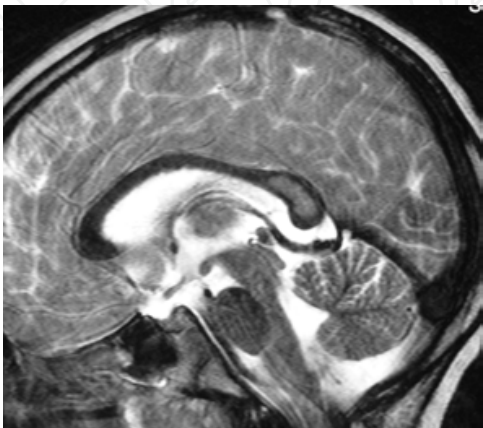

Fig. 3. T2 sagittal midline brain MRI demonstrating a well-defined rounded lesion in the splenium of the corpus callosum, which is unusual for ADEM.
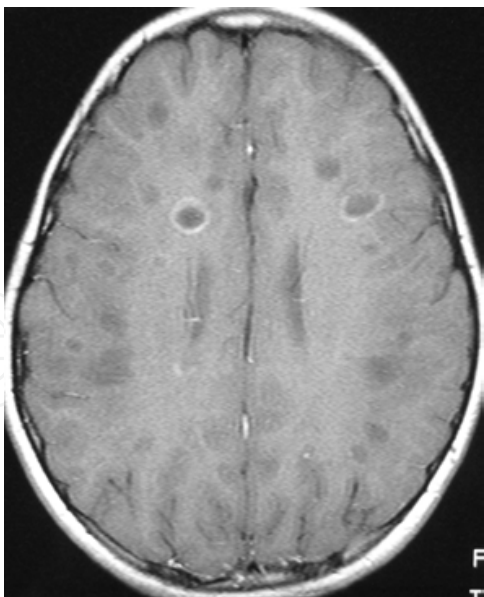
Fig. 4. T1 with contrast axial MRI demonstrating multiple hypo-intense white matter lesions of varying sizes, some with ring enhancement. This patient was diagnosed with ADEM.

A   B

Fig. 5. A- T2 sagittal MRI of the cord showing diffuse abnormal high signal intensity throughout the cord with cord expansion in the cervical region. There was no associated enhancement. This together with the brain lesions seen in 5B is consistent with ADEM. B-Flair axial MRI demonstrating bilateral high signal intensity lesions in the basal ganglia and deep white matter on the left consistent with ADEM.

4.6 Treatment

There are no standard treatment protocols as there are insufficient large scale studies to form consensus for optimal management. Supportive care (e.g. respiratory support for patients with brainstem involvement, anti-epileptics for seizure control) in the acute phase is vital.

Therapies recommended are mainly immunomodulating agents targeting the immune-based mechanism of the disease. Corticosteroids are considered the mainstay of treatment based on the rapid improvement in symptoms following therapy (Straub *et al.*, 1997;, Tenembaum *et al.*, 2007). However widely varying doses, formulations, duration of therapy and tapering have been reported with corticosteroid use (Hynson *et al.*, 2001; Murthy *et al.*, 2002; Tenembaum *et al.*, 2007; Govender *et al.*, 2010). A single study reported worse outcomes in patients who received corticosteroids (Boe *et al.*, 1965). Methylprednisone, dexamethasone and ACTH are used. Most reports in paediatric patients have used IV methylprednisolone (10 to 30 mg/kg/day) or dexamethasone (1 mg/kg) for 3 to 5 days (Dale *et al.*, 2000; Hyson *et al* 2001; Tenembaum *et al* 2002; Govender *et al.*, 2010) followed by a taper for 4 to 6 weeks with full recovery reported in 50 to 80% of patients. In resource poor countries high dose corticosteroids must be used with caution and only commenced once commonly occurring infections like tuberculosis and cytomegalovirus (CMV) are excluded. Outcomes on efficacy of corticosteroid treatment are mainly compared to historical controls. Worse outcomes are linked to shorter duration of treatment (Tenembaum *et al.*, 2007). Other treatment modalities suggested include intravenous immunoglobulin, plasmapheresis and glatiramer acetate (Abramsky *et al.*, 1977; Stricker *et al.*, 1992; Finsterer *et al.*, 1998). There is some evidence to suggest that patients may respond to a combination of methylprednisolone and immunoglobulin if they fail to respond to either separately (Straussberg *et al.*, 2001).

4.7 Prognosis

ADEM is by definition a monophasic illness (variants are discussed in Section 4.8). Mortality during the post-measles ADEM period in the 1950's was reported as 10-30% (Johnson *et al.*, 1985). At follow-up, approximately 60-80% of children have no neurologic deficits (Menge *et al.*, 2007). This study also reports a mortality rate of 5%. The extent and site of lesions on the initial MRI do not predict the clinical outcome. Motor deficits persist in 8-30% (Dale *et al.*, 2000; Tenembaum *et al.*, 2007) of patients and include paraparesis, hemiparesis and ataxia. Neuro-cognitive deficits are also documented post ADEM (Hahn *et al.*, 2003; Jacobs *et* al., 2004). These include deficits in short term memory, verbal processing skills and complex attention. Patient with early onset ADEM (<5year of age) were also more likely to have cognitive deficits and behaviour problems (Kumar *et al.*, 1998). Follow-up MRI's showed complete or partial resolution of abnormalities in the majority of cases (Kesslering *et a*l., 1990; Dale *et al.*, 2000; Tenembaum *et al* 2007; Govender *et al.*, 2010). However, residual gliosis and demyelination persist in some patients (Kesselring *et al.*, 1990). Clinical as well as imaging follow-up (at least 3 months later) **(Figure 6)** is important to monitor for evolution to MS. Risk factors for relapse are discussed in greater detail in Section 10.

4.8 Variants of ADEM

Definitions for Recurrent and Multi-phasic ADEM are described in Table 1.

Acute Hemorrhagic Leukoencephalitis is a rare, hyper-acute form of ADEM with a mortality rate of about 70% (Davies *et al.*, 2006). Pathological studies show a necrotizing vasculitis

with haemorrhage, oedema and a neutrophilic infiltration (Stone and Hawkins, 2007). Seventy percent of survivors have neurological deficits (Stone and Hawkins, 2007).
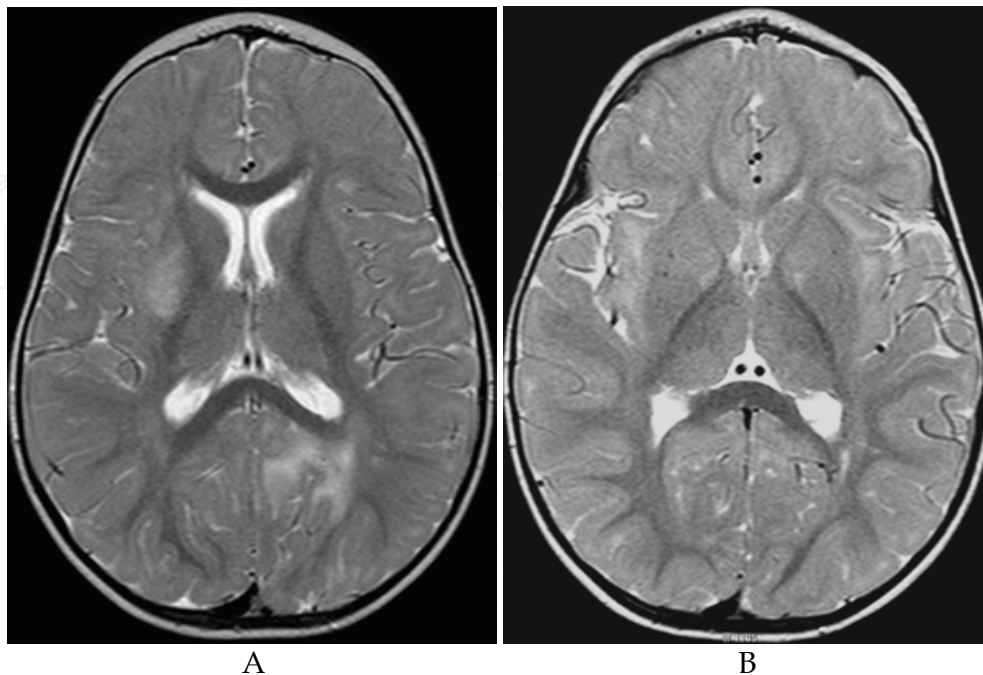

Fig. 6. A- T2 axial MRI demonstrating asymmetrical basal ganglia and white matter high signal intensities consistent with ADEM. B- T2 axial MRI in same patient at 3 months follow-up showing resolution of lesions.

5. Transverse myelitis

5.1 Epidemiology

Acute Transverse myelitis (ATM) is a focal inflammatory disorder of the spinal cord resulting in motor, sensory and autonomic dysfunction with evidence of inflammation on CSF or MRI studies. The initial definition was proposed by the Transverse Myelitis Consortium Working Group in 2002 and refined by the more recent consensus definitions for paediatric demyelinating disease (Krupp *et al.*, 2007). The incidence is reported as 1- 8 per million people per year (Berman *et al.*, 1981). There are no gender or ethnic differences in the prevalence of ATM (Berman *et al.*, 1981). ATM is often difficult to distinguish clinically from ischaemic cord lesions, fibro-cartilagenous emboli or traumatic spinal cord lesions. ATM is also an important differential diagnosis for acute flaccid paralysis in childhood.

5.2 Pathogenesis

The aetiology of ATM is thought to be immune-mediated. In 30-60% of patients ATM is para-infectious (Jeffrey *et al.*, 1993; Kalra *et al.*, 2009). Molecular mimicry and super-antigen mediated mechanisms have been postulated (Kaplin *et al.*, 2005). Positive anti-GM1 antibodies following Campylobacter and CMV infections have been implicated in the aetio-pathogenesis. Neuromyelitis optica—immunoglobulin G is an aquaporin-4–specific water channel antibody, which has been associated with neuromyelitis optica and longitudinally extensive transverse myelitis in adults (Lennon *et al.*, 2004). This is discussed further in Section 6.

5.3 Clinical presentation

Clinical presentation is that of acute or sub-acute onset of bilateral spinal cord dysfunction (that may be asymmetrical) with associated sphincter dysfunction and pain. A sensory level may not be easily elicitable in the paediatric population. The clinical features depend on the location of the lesion. High cervical cord lesions can present with respiratory failure. The thoracic segment is the commonest site of cord involvement in ATM (Kneubusch *et al.*, 1998).

5.4 Investigations

Initial evaluation of a patient with an evolving myelopathy must include a gadolinium enhanced MRI of the spine to exclude a compressive myelopathy. If there is no evidence of a compressive lesion a lumbar puncture should be performed. CSF pleocytosis and an elevated protein (IgG index) on the CSF support a diagnosis of ATM. Brain MRI and eye examination with visual evoked potentials are recommended to exclude demyelination in other parts of the neuro-axis.

Other investigations recommended include para-infectious markers- EBV, VZV, CMV, Herpes Simplex virus serology and stool for campylobacter cultures. If there are signs of a systemic inflammatory disorder, auto-immune screens and serum angiotensin converting enzyme levels should be performed to exclude other causes of an acute myelopathy (e.g. vasculitides).
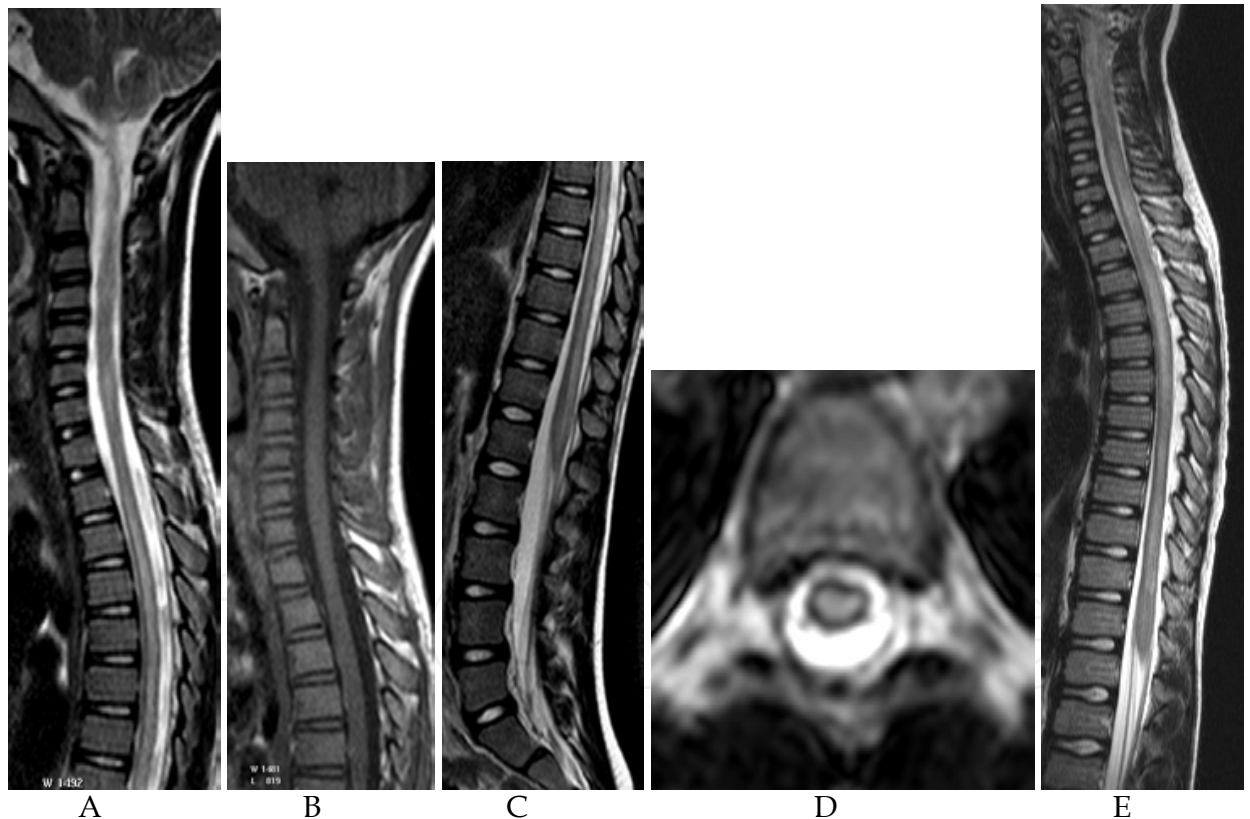

| A | B | C | D | E |

Fig. 7. A- T2 sagittal MRI of the cord showing diffuse abnormal increased signal intensity consistent with transverse myelitis. B- T1 sagittal MRI of the cord showing no abnormal signal intensity. There was no contrast enhancement. C- T2 sagittal MRI of the distal cord showing diffuse abnormal increased signal intensity consistent with transverse myelitis. D- T2 axial MRI of the cord showing abnormal increased signal intensity consistent with transverse myelitis. E- T2 sagittal MRI of the cord showing diffuse abnormal increased signal intensity and cord swelling consistent with transverse myelitis.

5.5 Neuro-imaging

MRI of the spinal cord usually shows nonspecific localized hyper-intense signal on T2WI sequences with, in some cases, segmental cord enlargement and/or focal enhancement **(Figure 7 a-e).** Acute partial transverse myelitis described in adults is characterized by MRI lesions that are asymmetrically placed and spanning fewer than 2 vertebral segments in length; these patients have been found to have a greater risk of progression to multiple sclerosis (Ford *et al.*, 1992). Longitudinally extensive myelitis (spanning > 3 vertebral segments) is shown to have a lower risk of progression to MS in adults (Pittock *et al*, 2006). Lesions of ATM in children are typically longitudinal, demonstrate rim enhancement and are centrally located.

5.6 Treatment

Previous case series did not demonstrate any benefit from the use of low dose corticosteroids (Dunn *et a*l., 1986; Adams *et al.*, 1990). Recent reports demonstrate the benefit of high dose corticosteroids (10-30mg/kg per day for 3-5 days) on recovery (Defrense *et al.*, 2001; Sebire *et al.*, 1997). Compared to historical controls patients treated with steroids walked independently sooner. If there is no clinical response to steroids within 5-7 days plasma exchange was used as adjunctive therapy in isolated case reports. Supportive measures include respiratory support and early management of a neuropathic bladder.

5.7 Prognosis

Various studies have looked at prognostic indicators for ATM. Jain *et al.* (1983) described backache at onset, acute course (within hours), spinal shock and a cervical sensory level as poor prognostic features. Other studies did not demonstrate this (Govender *et al.*, 2010). Early recovery (within one week of presentation), age less than 10 years at presentation and lumbosacral spinal level on clinical assessment were significant predictors of a good outcome (De Goede *et al.*, 2010). The extent of lesions on MRI has not shown consistent correlation with outcome (Pradhan *et al.*, 1997; Adronikou *et al.*, 2003). Berman *et al's* series (1987) described more than one-third of the patients with ATM making a good recovery; in one-third of patients recovery was only fair; 14 patients failed to improve and 3 demised.

In the series by Dunne *et al* (1986) that assessed the risk of progression to multiple sclerosis in children with ATM, definite evidence of multiple sclerosis did not develop in any of the patients. In the series by Pidcock *et al* of the 47 children with acute transverse myelitis, 2 experienced recurrent transverse myelitis, 1 was diagnosed with neuromyelitis optica, and 1 developed multiple sclerosis on follow-up (Pidcock *et al.*, 2007).

6. Neuromyelitis Optica (NMO)

The association between myelitis and optic problems was first described in 1870 by Thomas Clifford Allbutt (Murray, 2005). In 1894 Eugene Devic described 16 patients with visual impairment who developed paraparesis, sensory deficits and sphincter dysfunction within weeks. They recognized that these symptoms were the result of inflammation of the optic nerve and spinal cord. NMO is a recurrent demyelinating disorder affecting the optic nerves and the spinal cord. Modifications to the definition of NMO in 2005 incorporated the inclusion of patients with brain lesions, and included the NMO-IgG antibody as a confirmatory test.

The Mayo Clinic proposed a revised set of criteria in 2006. The new guidelines for diagnosis requires both absolute criteria and two of the three supportive criteria to be present to make a diagnosis of NMO (Wingerchuck *et al.*, 2006).

Absolute criteria:
1. Optic neuritis
2. Acute myelitis

Supportive criteria:
1. Brain MRI not meeting criteria for MS at disease onset
2. Spinal cord MRI showing contiguous T2-weighted signal abnormality extending over 3 or more vertebral segments, indicating a relatively large lesion in the spinal cord
3. NMO-IgG seropositive status.

The association of NMO with the serum autoantibody marker NMO-IgG was reported in 2004 (Lennon *et al.*, 2004). NMO-IgG is 73% sensitive and 91% specific for distinguishing NMO from classical MS. The new diagnostic criteria allows for the diagnosis of NMO in patients who are NMO-IgG antibody negative. NMO antibodies play a key role in the pathogenesis. These antibodies are directed against the aquaporin-4- receptors located in the cell membrane of astrocytes (Pearce, 2005). Aquaporin-4 is the most abundant channel facilitating water transport across membranes in the brain. NMO-IgG is also detected more commonly in patients with NMO symptoms who have clinical or serological evidence for SLE than in those who do not (McAdam *et al.*, 2002).

6.1 Clinical characteristics

Clinical characteristics include painful visual loss, weakness, sphincter dysfunction and sensory deficits. Loss of red color vision, a relative afferent pupillary defect and visual field defects are other features of optic neuritis in children. Other complications such as ataxia and respiratory failure result from extension of cervical cord lesions into the brainstem.

6.2 Investigations

Diagnostic evaluation includes an MRI of the brain. During acute optic neuritis attacks, an orbital MRI may identify optic nerve gadolinium-enhancement. MRI of the brain is usually normal. However, brain lesions located in the hypothalamus, brainstem, and periventricular areas have been described in children who have typical features of NMO (Pittock *et al.*, 2005). These are considered to be the aquaporin-4 rich areas of the brain.

Patients with signs of myelitis should have a spinal MRI with contrast. The lesions are typically longitudinally extensive, centrally based in the cord and extend over three or more vertebral segments. All patients should have a serological test for the NMO-IgG antibody. A negative test however does not exclude the diagnosis. CSF pleocytosis also supports the diagnosis. In patients with longitudinal myelitis and no visual symptoms, visual evoked potentials can sometimes detect asymptomatic visual pathway dysfunction.

6.3 Treatment

The recommended treatment for acute attacks of myelitis or optic neuritis is high dose methylprednisone. Prophylactic long-term immunosuppression is recommended for established NMO and patients who have a single attack of myelitis and are NMO-IgG positive (Wingerchuck *et al.*, 2005). There are no efficacious preventative therapies demonstrated by controlled trials in NMO. Intravenous immunoglobulin is an alternative for patients who do not respond to corticosteroids.

Characteristics of NMO that help to distinguish it from classical MS include:
- Prominent CSF pleocytosis (more than 50 WBC) with a polymorphonuclear cell predominance (Mandler *et al*., 1993; O Riordan *et al*., 1996)
- Lower frequency of CSF oligoclonal banding (15-30% in NMO compared to 85% in MS)
- Bilateral symmetrical optic neuritis
- At disease onset, the brain MRI scan is normal or reveals nonspecific white matter lesions
- MRI of the spinal cord showing longitudinally extensive, central lesions (MS lesions are more peripherally located in the cord and extend over one to two segments in length)

7. Schilder's disease/myelinoclastic diffuse sclerosis

This disorder was initially described by Schilder in 1912 and later clarified by Poser (1992). There are further reported cases of solitary, large plaque like lesions, which were histologically confirmed to be foci of demyelination (Kumar *et al*., 1998; Gutling and Landis, 1998). The aetiology is unclear; however an association with tuberculosis was described in 3 South African children (Pretorius *et al.,* 1998). Schilder's Disease occurs predominantly in children (peak age 5-14 years) (Afifi *et al*., 1994).

The Poser criteria (1992) for diagnosis are:
- one or two roughly symmetrical large plaques (greater than 2 cm diameter)
- pathological analysis is consistent with sub-acute or chronic myelinoclastic diffuse sclerosis
- adrenoleukodystrophy and peripheral nervous system involvement must be excluded.

7.1 Clinical presentation
The clinical presentation is non-specific and includes neuroregression, seizures, ataxia or signs of raised intra-cranial pressure.

7.2 Neuro-imaging
The lesions of Schilder's Disease are typically large and plaque-like and have also been termed tumefactive demyelination. MRI is the most accurate modality of delineating the lesions that are often confused with brain neoplasms or abscesses. Making the distinction between demyelination and infection/malignancies early is important to prevent unnecessary surgical procedures and toxic therapies like radiation and chemotherapy (McAdam *et al.,* 2002). MRI studies demonstrate 1 or 2 large confluent lesions in the deep white matter, usually the centrum semiovale **(Figure 8 a-f).** Lesions are at least 2 cm in size in 2 of 3 dimensions. No additional lesions should be observed on imaging of the brain or spinal cord- this would suggest MS or ADEM. On T1WI, tumefactive demyelination lesions reveal a hypo-intense central area with a thick surrounding band of moderately increased intensity. Lesions are centrally hyper-intense on T2WI. Enhancement, when present, is incomplete. The lesions are characterized by enhancement limited to one side of the lesion; usually the rim facing the lateral ventricles (McAdam *et al*., 2007). Demyelination can be distinguished from other ring enhancing lesions (brain abscesses, tumors, parasitic infections) by the presence of other demyelinating plaques elsewhere in the central nervous system.
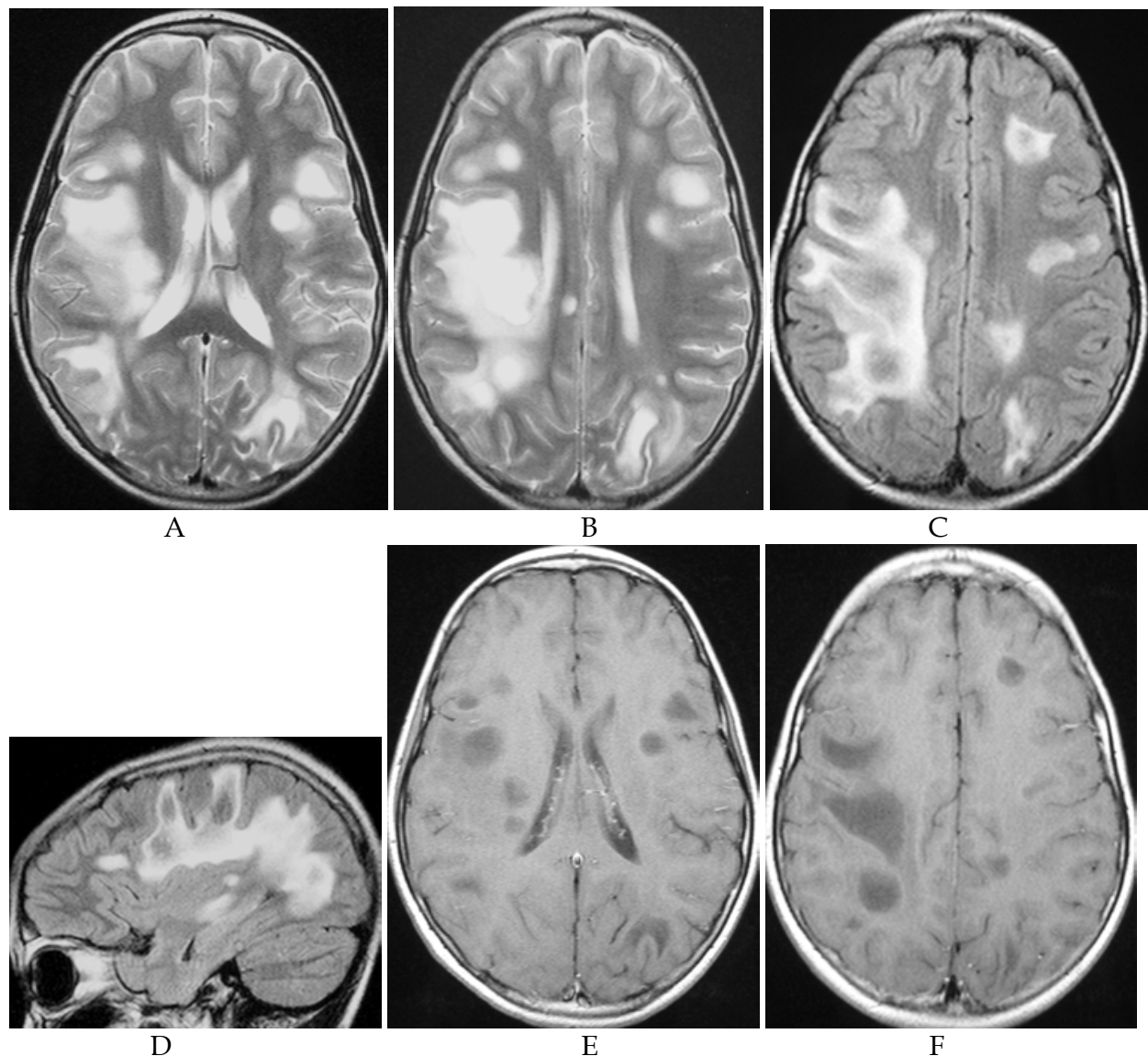
Fig. 8. A & B – T2 axial MRI demonstrating multiple well-defined hyper-intense white matter foci surrounded by more ill-defined areas of increased white matter signal intensity consistent with Schilder's Disease. C- Flair axial MRI demonstrating multiple hyper-intense lesions of varying sizes within the white matter with some areas of suppression within the plaques consistent with Schilder's Disease. D- Flair parasagittal MRI demonstrating large flame- shaped white matter plaque with some areas of suppression within the lesions consistent with Schilder's Disease. E & F- T1 with contrast axial MRI demonstrating multiple non- enhancing hypo-intense lesions of varying shapes and sizes within the white matter.

Other supportive diagnostic tests include an elevated CSF protein and an elevation of CSF IgG in 50-60% of patients with Schilder's Disease. Many patients with a large ring enhancing lesion will have a brain biopsy mainly to exclude other disorders.

7.3 Treatment
The treatment of choice is high dose intravenous corticosteroids. A rapid clinical and radiological response to high dose corticosteroids favors the diagnosis of demyelination.

8. Multiple Sclerosis (MS)

MS is defined in Table 1 (Krupp *et al.*, 2007). MS in children is likely an under-recognized phenomenon that poses a unique set of challenges in terms of diagnosis and management. Early accurate diagnosis of MS is vital to facilitate early institution of disease modifying agents.

8.1 Epidemiology

Childhood onset MS is an uncommon entity however, an estimated 2- 5% of patients with MS have onset of symptoms of MS before 16 years of age (Duquette *et al.*, 1987; Boiko *et al.*, 2002). The youngest reported patient with MS presented at 10 months of age. This was an indigenous African child who died at 6 years of age after 11 episodes of relapsing neurological symptoms (Shaw and Alvord, 1987). Similar to adult studies, a female preponderance is reported for MS in adolescence (Duquette *et al.*, 1987; Govender *et al.*, 2010). However there is no gender predilection in children presenting with MS under 6 years of age (Banwell *et al.*, 2007).

A crude period prevalence for patients of European ancestry was 25.63 per 100 000 and for patients of indigenous African descent was 0.22 per 100 000 (Bhigjee *et a*l., 2007). Adult studies have described a more severe clinical and radiological phenotype in patients of African indigenous ancestry compared to patients of European ancestry (Kaufmann *et al.*, 2003; Bhigjee *et al.*, 2007). A retrospective single centre analysis showed a significantly higher relapse-rate in African-American children, compared with whites, suggesting a more aggressive disease course in the former group (Boster *et al.*, 2009).

8.2 Pathogenesis

Genetic and environmental factors are implicated in the aetiology of MS. Twin studies show a 20-30% higher risk of disease in monozygotic twins compared to dizygotic twins. Allelic variation in the MHC class II region exerts the single strongest effect on genetic risk (Ramgopalan SV *et al.*, 2009). The HLA DR1B is the gene marker associated with higher risk of MS (Ness *et al.*, 2007). Alleles of IL2RA, IL7RA (Hafler et al., 2007), the ecotropic viral integration site 5 (*EVI5*) (Hoppenbrouwers *et al.*, 2008) and kinesin family member 1B (*KIF1B*) genes (Aulchenko *et al.,* 2008) have recently been shown to increase susceptibility to MS.

Epidemiological studies implicate environmental factors such as geographical variations (Kurtzke and Hyllested, 1979), season of birth (Sadovnick *et al.,* 2007) and migration patterns (Pugliatti *et al.*, 2006) in the aetiology of MS. Emerging evidence supports sunlight or vitamin D as an important environmental factor in aetiology (Ramgopalan SV *et al.*, 2009). Children exposed to parental smoking also have a higher risk of MS (Mikaeloff *et al.*, 2007).

8.3 Sub-types of MS

The National MS Society in the US in 1996 categorized MS into four internationally recognized forms (Lublin and Reingold, 1996).

Relapsing-remitting: refers to MS that has exacerbations/relapses followed by symptom-free periods of remission. This is the commonest form of MS in children (Ruggierri *et al.*, 2004).

Primary Progressive: It is characterized by gradual clinical decline from the time of disease onset with no distinct periods of remission or relapses. There maybe plateau periods during the disease but no periods of being symptom free. This entity, though rare in children, is reported (Duquette *et al.*, 1987; Govender *et al.*, 2010).

Secondary Progressive: This type begins with a relapsing remitting course which may last several years before the onset of the secondary progressive stage. Secondary progressive

multiple sclerosis is a second-stage, chronic, progressive form of the disease where there are no periods of remission, only breaks in attack duration with no recovery from symptoms. Relapsing progressive: have a steady neurologic decline but also suffer clear superimposed attacks. This is the least common of all subtypes.

An acute/ Malignant MS (Marburg variant) form presenting with a fulminant, rapidly fatal disease has also been described.

8.4 Clinical presentation

Children present with a wide variety of clinical symptomatology including motor, sensory, visual, cerebellar and brainstem dysfunction (Shaw and Alvord., 1987; Sindern *et al*., 1992; Ghezzi *et al*., 1997; Dale *et al*., 2000; Boiko *et al*., 2002; Pohl *et al*., 2006; Govender *et al*., 2010). Motor manifestations are described as the most common clinical presentation (Duquette *et al*., 1987; Sindern *et al*., 1992; Pohl *et al*., 2006). Polysymptomatic presentation is reported to be more frequent in childhood onset MS compared to adults (Ghezzi *et al*., 1997; Dale *et al*., 2000; Boiko *et al*., 2002). However monosymptomatic presentation is also reported in children (Duquette *et al*., 1987). Encephalopathy and seizures also occur in MS (Gusev *et al*., 2002). Eye involvement is described in up to 50 % of children with MS (Pohl *et al.,* 2006). Optic neuritis in MS is more likely to be unilateral (Dale *et al*., 2000). Optic tract involvement may be asymptomatic and diagnosed only by abnormal visual evoked potentials (Pohl *et al*., 2006). Fatigue in children is more frequent compared to adults with MS (Gusev *et al.,* 2002). Cognitive decline is reported in 30-66% of children with MS (Banwell and Anderson 2005; Banwell *et al*., 2007a).

8.5 Laboratory evaluation

Diagnostic evaluation is to exclude other conditions affecting predominantly the white matter and to look for supportive evidence for MS. The workup should also include CSF studies (including cell count, total protein, IgG index, evidence of oligoclonal bands, and cytology) (Hahn *et al*., 2007). CSF Oligoclonal bands are reported in 72-84% of children with MS (Sindern *et al*., 1992; Dale *et al*., 2000). Oligoclonal bands may be absent initially and only develop during the course of the illness. Leucocytosis in the peripheral blood, though described in MS (Dale *et al*., 2000; Govender *et al*., 2010), is uncommon and non-specific. Neuro-physiological testing such as visual and auditory evoked potentials are also of diagnostic importance in detecting sub-clinical evidence of demyelination.

8.6 Imaging

Lesions of MS are typically multiple, discrete, plaque-like and involve predominantly the white matter (Mikaeloff *et al*., 2004). Commonly involved areas in MS include the corpus callosum, periventricular and sub-cortical white matter **(Fig 9a-g)**. Lesions of MS are typically iso- or hypo-intense on T1WI, and hyper-intense on T2W1 and FLAIR sequences. Enhancement of active lesions post-gadolinium may be solid, ring-like or arc-like **(Fig 10a-c).** Children tend to have fewer lesions and less enhancement (Banwell et al., 2007b). However, some children lack typical MRI findings of MS and have either large tumefactive lesions with peri-lesional oedema (Hahn et al., 2004) or deep grey matter involvement. Basal ganglia affectation in MS, though described, is uncommon **(Figure 11 a,b).** Younger children with MS may also have more diffuse, bilateral ill defined lesions (Mikaeloff *et al*., 2004). The International Pediatric MS Study Group strongly recommended additional imaging of the entire spinal cord to identify other sites of demyelination **(Figure 12 a,b).** The cervical spinal cord is the commonest region involved in MS.
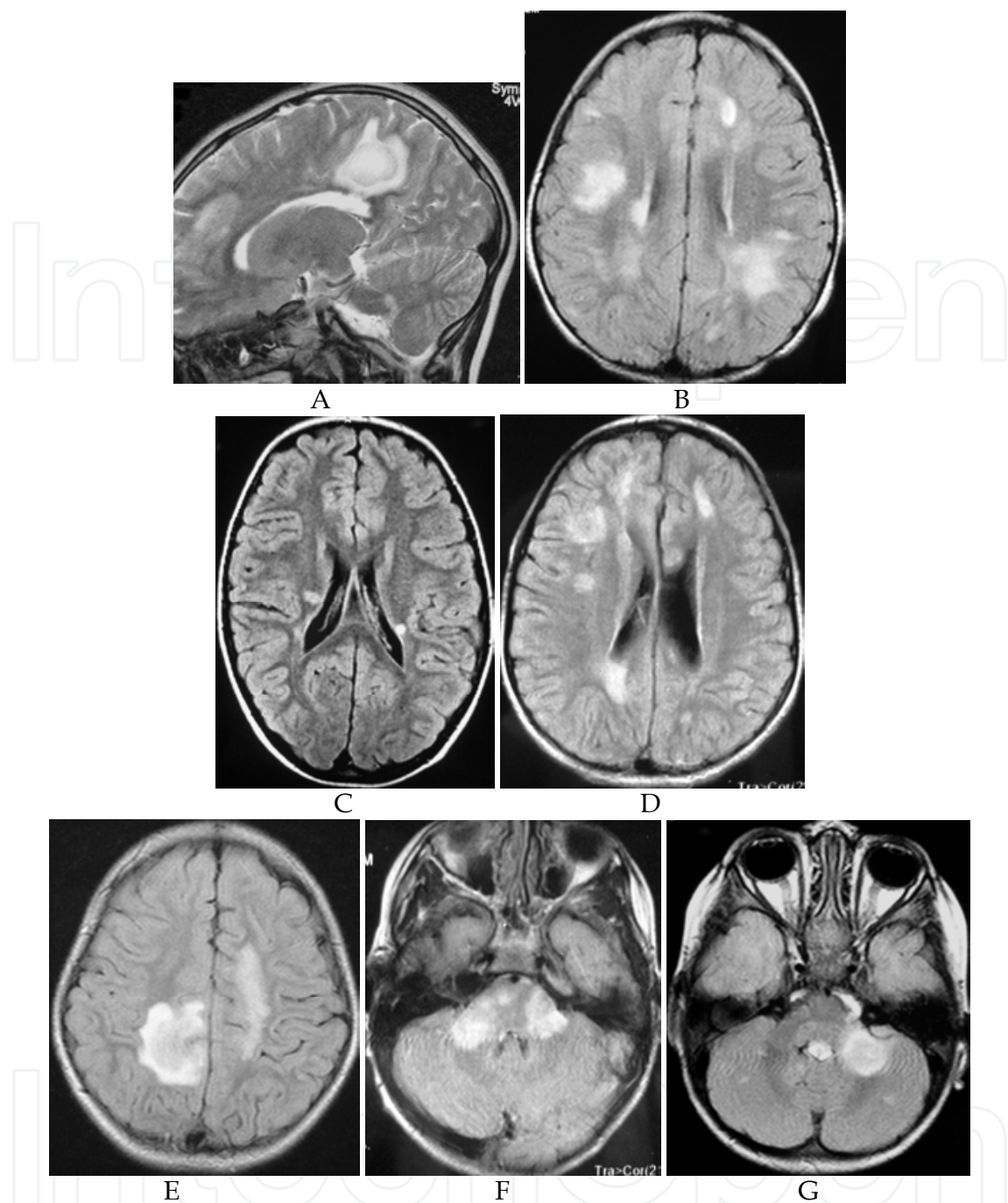
Fig. 9. A- T2 parasagittal MRI of the brain demonstrating flame-shaped hyper-intense lesion perpendicular to lateral ventricle consistent with MS. B- Flair axial MRI demonstrating multiple asymmetrical hyper-intense plaque-like lesions in the centrum-semiovale. Features are consistent with MS. C -Flair axial MRI of brain demonstrating 2 periventricular hyper-intense white matter lesions consistent with MS. D- Flair axial at level of lateral ventricles demonstrating asymmetrical hyper-intense white matter lesions consistent with demyelination and MS. E- Flair axial of brain demonstrating hyper-intense right parietal white matter plaque-like lesion and left subtle white matter hyperintensity consistent with MS. F- Flair axial of brainstem demonstrating pontine and brachium pontis high signal intensity lesions consistent with demyelination. G-Flair axial MRI demonstrating rounded hyper-intense lesion in left brachium pontis consistent with demyelination.

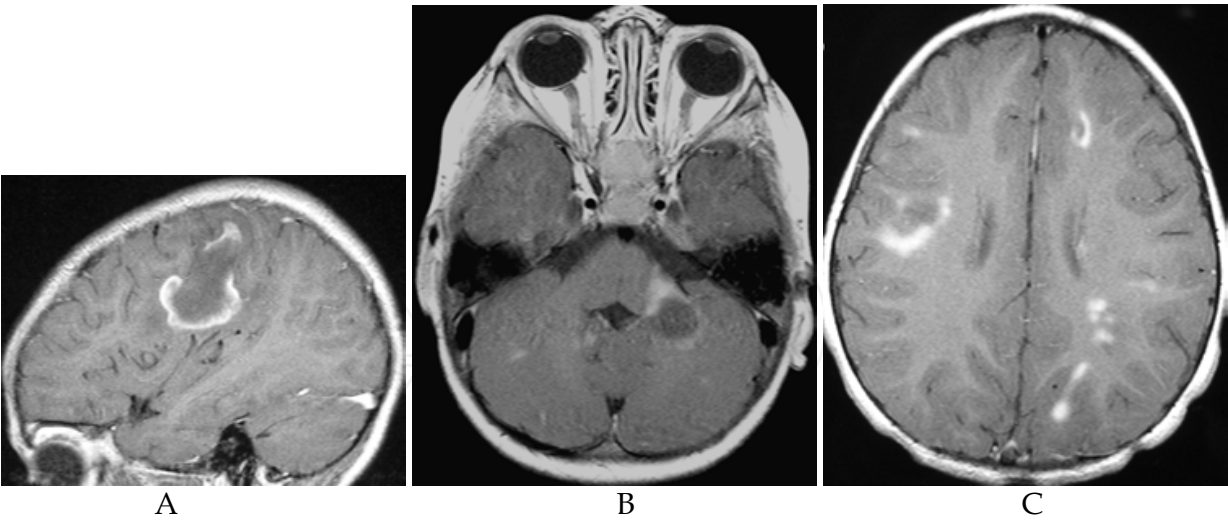| A | B | C |

Fig. 10. A- T1 with contrast parasagittal MRI of brain demonstrating rim-enhancing plaque-like lesion typical of active demyelination in a patient with MS. B- T1 with contrast axial MRI demonstrating ring enhancement of left brachium pontis lesion consistent with active demyelination in a patient with MS. C- T1 with contrast axial MRI demonstrating ill-defined irregular marginal enhancement of the plaque-like lesions consistent with active demyelination in a patient with MS.
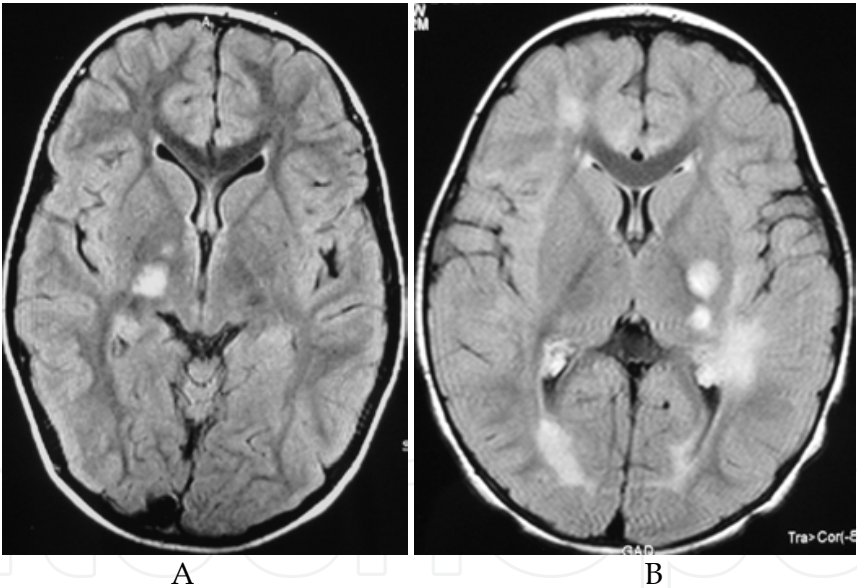

| A | B |

Fig. 11. A- Flair axial MRI of brain demonstrating 2 lesions in the right basal ganglia. This is unusual for MS. B- Flair axial MRI demonstrating multiple hyper-intense lesions in the periventricular white matter as well as left basal ganglia(atypical) consistent with MS.

MRS reveals a reduction in NAA and an elevation in choline, lipids and lactate in active lesions (Smith AB, 2009). Volumetric MRI studies reveal progressive loss of tissue in white matter tracts early in the course of the disease (Miller *et al.*, 2002). A single study of Magnetization transfer imaging and Diffusion tensor imaging in children with MS suggested that there was no evidence of white matter degeneration in normal appearing white matter areas (Tintore *et al.*, 2000).
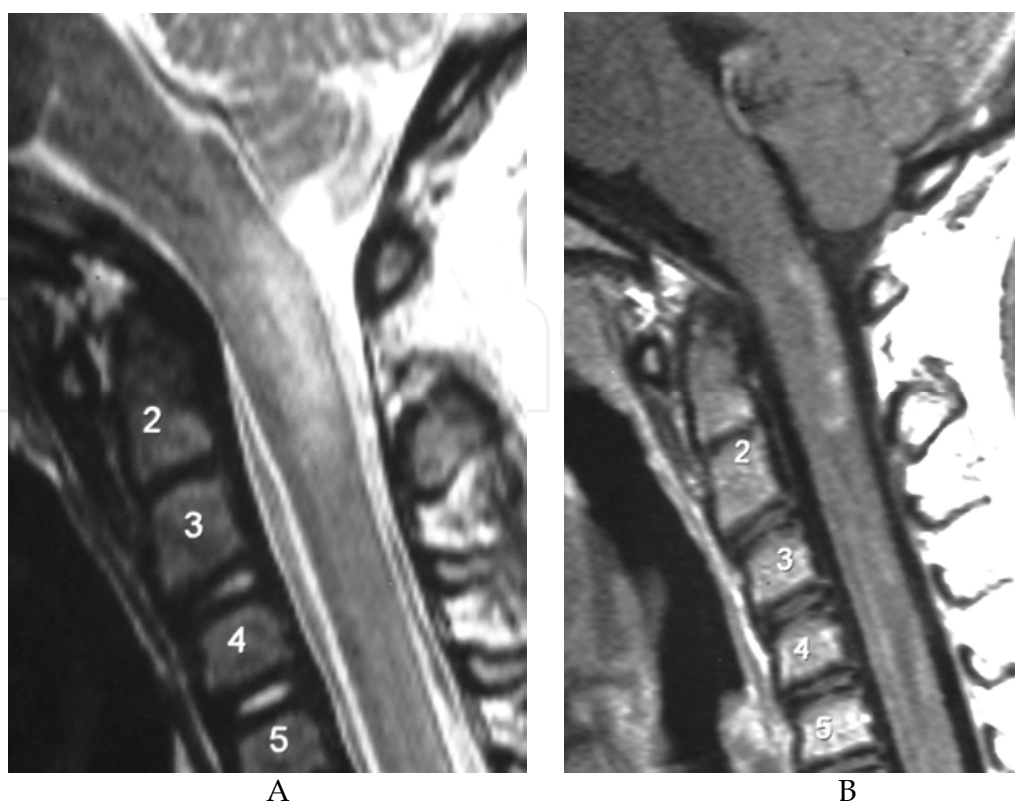
Fig. 12. A- T2 sagittal MRI of cervical spine in a patient with MS demonstrating an ill-defined expansile hyper-intense lesion in the proximal cord consistent with demyelination. B- T1 with contrast sagittal MRI of cervical spine in a patient with MS demonstrating ill-defined contrast enhancement of the lesion in 12A consistent with active demyelination.

8.7 Treatment

MS is a chronic condition with significant impact on all aspects of the family's life. Management should be trans-disciplinary involving psychologists, physiotherapists, occupational therapists and school teachers.

8.7.1 Management of relapses

The mainstay of managing relapses is high dose corticosteroids. High dose IV corticosteroids (10-30mg/kg/day) for 3-5 days, is usually used with an optional oral tapering dose. High dose oral steroids were found to be efficacious in adults (Morrow *et al.*, 2004). Plasmapharesis and IVIG are alternatives to be considered if steroids are not effective (Hahn *et al.*, 1996; Duzova and Bakkaloglu, 2008).

8.7.2 Disease modifying therapy

These therapies are known to alter the disease course and outcomes. They reduce the frequency and severity of relapses (Mikaeloff *et al.*, 2001; Kornek *et al.*, 2003; Tenembaum and Segura, 2006;). Patients on therapy are shown to have better outcomes compared to untreated patients (Mikaeloff *et al.*, 2008). First line agents include Interferon beta 1a, 1b and Glatimer acetate. Case reports of second line therapies used include Natalizumab, Cyclophosphamide and Mitoxantrone.

Study	No. of patients	Treatment	Outcomes
Ghezzi *et al*, 2007	52	Interferon beta 1a	Reduction in relapse rate Reduction in *EDSS score
Tenembaum and Segura, 2006	24	Interferon beta 1a	Reduction in relapse rate
Kornek *et al,* 2003	7	Glatimer Acetate	Reduction in relapse-2/7 Stable EDSS- 3/7
Huppke *et al*, 2008	3	Natalizumab	Induction of remission in all
Makhani *et al,* 2009	17	Cyclophosphamide	Reduction in relapse rate Stabilization of EDSS

* EDSS: Extended Disability Status Scale

Table 2. Studies of specific treatment interventions in MS

8.8 Prognosis

Most children with MS follow a relapsing, remitting course with increasing neuro-disability (Boiko *et al.,* 2002). A slower rate of progression of disease compared to adults suggests more plasticity and potential for recovery in the developing CNS (Simone *et al.,* 2002). Children tend to have more relapses in the first 2 years of the disease (Simone *et al.,* 2002; Mikaeloff *et al.,* 2006). Patients with childhood-onset MS also take longer to reach the stage of severe disability but reach irreversible neurological disability at a younger age compared to patients with adult onset disease (Renoux *et al.,* 2007). More severe disease was noted in girls; when the time between the first and second attacks was <1 year; for childhood-onset multiple sclerosis fulfilling MRI diagnostic criteria at onset; for an absence of severe mental state changes at onset; and for a progressive course (Mikaeloff *et al.,* 2006).

9. Clinically isolated syndromes

These episodes may be mono-focal (the clinical features can be attributed to a single CNS site) or multi-focal if the clinical features can not be explained by a single lesion. These include isolated optic neuritis, transverse myelitis, brainstem **(Fig 13 a-d)** or cortical lesions. Typically in contrast to ADEM there is no associated fever or encephalopathy. A CIS often poses a diagnostic and therapeutic challenge. Multiple lesions (> 4 lesions) (Morissey *et al.,* 1993) on the MRI increase the risk of evolution to MS. In adult studies up to 80% of patients with a CIS evolve MS (Brex *et al.,* 2002). Brainstem lesions in CIS are associated with a worse prognosis (Tintore *et al.,* 2010). Children with CIS tend to have more infra-tentorial lesions
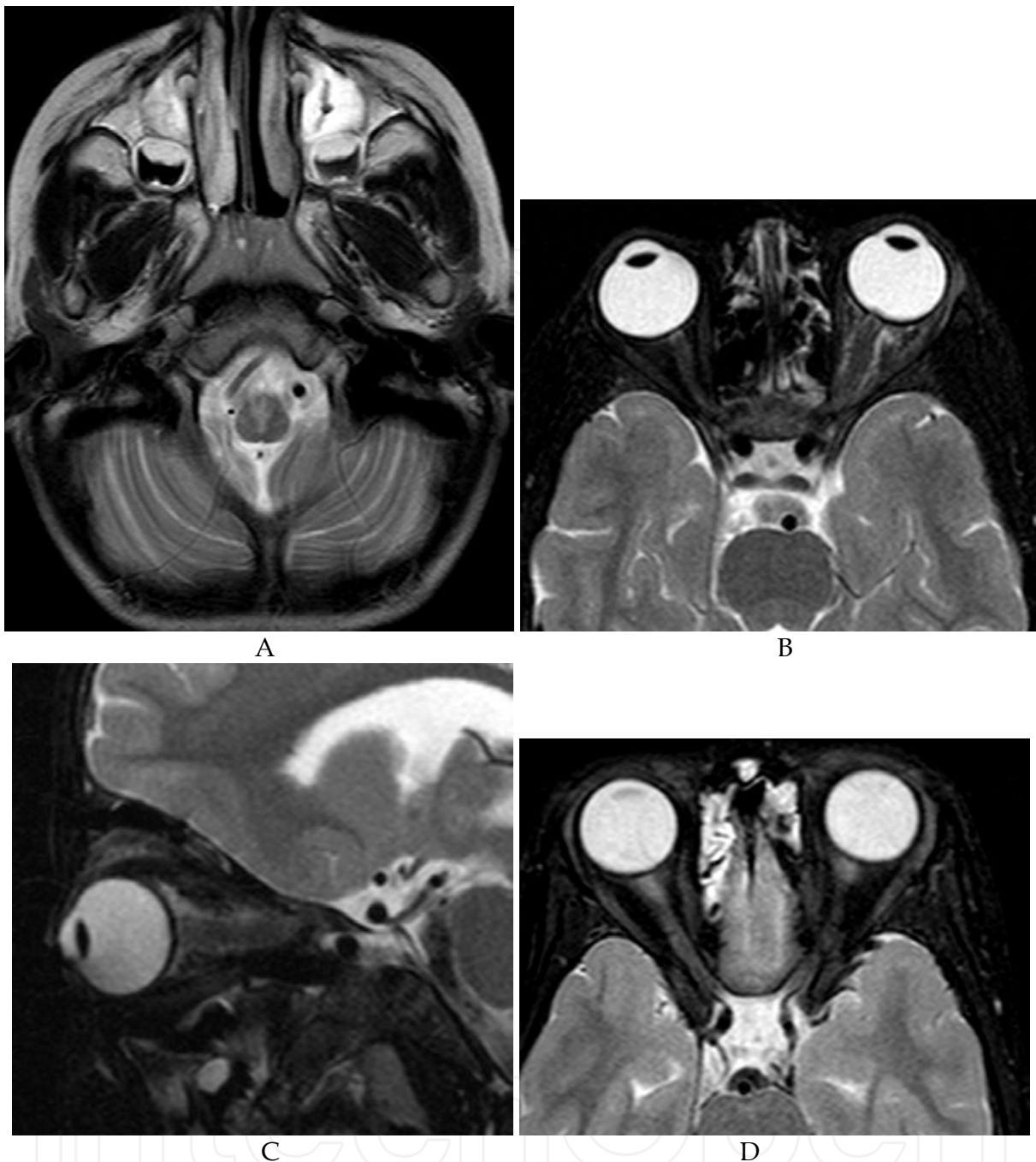
Fig. 13. (B&C same patient) Clinically Isolated Syndrome. A- T2 axial MRI demonstrating abnormal increased signal in the brainstem which was the only abnormal lesion. Clinically this patient had a CIS. B- T2 fat saturation axial MRI demonstrating a left swollen hyper-intense optic nerve with resultant proptosis. Features consistent with a unilateral Optic Neuritis. Remainder of brain and spine were normal. C- T2 fat saturation sagittal oblique MRI demonstrating a left swollen hyper-intense optic nerve. Features consistent with a unilateral Optic Neuritis. Remainder of brain and spine were normal. D- T2 fat saturation axial MRI of the optic nerves demonstrating abnormal high signal intensity within the proximal portions of the nerves and swelling of the nerves. Features consistent with Optic Neuritis (worse on the right). Remainder of brain and spine were normal.

Characteristic		ADEM	1st MS event
Demographics	Age of presentation	Younger	Onset >10yrs
	Sex	Slight male predominance	Female predominance
	History of Pre-demyelinating event	More frequent	Less frequent
	Seasonal distribution	More frequent	Less frequent
	Family history of demyelinating disease	Not present	More frequent
Clinical Presentation	Seizures	More frequent	Less frequent
	Encephalopathy	More frequent	Less frequent
	Headache, fever	More frequent	Less frequent
	Optic Neuritis	Bilateral	More frequent Unilateral
	Mono-focal vs. Poly-focal signs	Polysymptomatic	Mono-focal
Laboratory features	Elevated CSF protein	Less frequent	More frequent
	Leucocytosis in CSF	More frequent	Less frequent
	Oligoclonal bands in CSF	Less/ Usually transient	More frequent Persistent
	Serum Leucocytosis	More frequent	Less frequent
MRI Characteristics	Lesion definition	Ill Defined	Well-defined
	Lesion load	Greater	Lower
	Periventricular Lesions	Less frequent	More frequent
	Juxta-cortical Lesions	More frequent	Less frequent
	Cortical Lesions	More frequent	Less frequent
	Corpus Callosum Involvement	Less frequent	More frequent
	Brainstem/ Cerebellum	More frequent	Less frequent
	Spinal Cord Involvement	More frequent	Less frequent
	Deep Grey matter involvement	More frequent	Less frequent
	Contrast enhancement	Less frequent	More frequent
Outcome	Cognitive deficits	Less frequent	More frequent
	No neuro deficit after 1st event	Less likely	More likely

Table 3. Markers comparing ADEM to a first episode of MS

Disorder	Example	Clinical/ Laboratory	Radiological
Infections	HIV Encephalopathy	Developmental delay, pyramidal tract signs, microcephaly	-Confluent bilateral symmetrical white matter changes -cerebral atrophy -basal ganglia calcification
	Progressive Multi-focal Leucoencephalopa thy (JC Virus)	Immunocompromised	-Multi-focal ↑T2 WI lesions -Propensity for frontal/ parieto-occipital areas -Subcortical U fibres involved
Other infections	Sub-acute Sclerosing Panencephalitis, Lymes Disease, Neurosyphillus, HTLV1, Borreliosis		
Auto-immune/Vasculitides	Systemic Lupus Erythematosus	Multi-system auto-immune disorder Anti-nuclear factor positive	-Multi-focal ↑T2WI/FLAIR -Infarcts -Contrast enhancement of active lesions
	Isolated CNS angiitis, CADASIL (adult disorder-rare in children)		
Tumor	CNS Lymphoma	Insiduous onset, CSF cytospin –malignant cells	-↓ T1WI -↑ T2WI -GM involved more frequently -MRS may help
	Medulloblastoma, Astrocytoma		
Leukodystrophies	Adrenoleukody-strophy	Boys with hyperpigmentation of skin, behaviour and learning problems, Abnormal very long chain fatty acids	-Symmetrical, confluent -predominantly posterior involvement -Splenium and cortico-spinal tracts involved -Leading edge enhancement in peri-trigonal area

	Metachromic Leukodystrophy, Krabbe's Disease, Alexander's disease		
Mitochondrial	Leigh's Disease	Neuro-regression with dystonia/opthalmoplegia Hyperlactataemia	-Bilateral symmetrical ↑T2WI/FLAIR of Putamen and caudate nuclei -Can have diffuse cortical WM hyperintensities
Nutritional Deficiencies	Vitamin B12 deficiency	Anaemia, peripheral neuropathy, Myelopathy	-Periventricular ↑T2WI
	Vitamin E, Folate deficiency		
Toxins/ Drugs	Radiation	History of exposure	-Diffuse, bilateral periventricular and central WM involved -T1WI ↓, T2WI↑ -Sparing of sub-cortical U Fibres
	Lead, Isoniazid		
Infiltrative	Sarcoidosis	Cranial neuropathies, aseptic meningitis, visual disturbances	-Discrete periventricular lesions -May have hypothalamic and meningeal enhancement
	Histiocytosis	Visual disturbances, hypothalamic dysfunction	-Hypothalamic/ cerebellar T1WI ↓, T2WI↑ -Skull/ mastoid lesions
Osmotic Demyelination Syndrome		Rapid correction of Hypo-or hypernatraemia	-Symmetric changes in BG/ Cerebral cortical WM -T1WI↓ - ↑ FLAIR/T2WI ↑ -Pontine : Usual central with sparing of cortico-spinal tracts

Table 4. Main differential diagnosis of acquired white matter diseases on MRI

(Ghassemi *et al.*, 2008). This may be related to the differences in myelination patterns and maturation in children compared to adults. A radiologically isolated syndrome (RIS) is defined by incidental MRI findings suggestive of MS in an asymptomatic patient lacking any history, symptoms, or signs of MS (Okuda *et al.*, 2009).

10. Risk of recurrence after a first demyelinating event

Predicting the risk of a first episode of demyelination evolving on to MS is important as new immunomodulating therapies become available. Early initiation of disease modifying therapy reduces the risk of relapse and long-term disability (Jacobs *et al.*, 2000). Patients with "ADEM" progressing to MS vary from 0-29% (Belman *et al.*, 2007). Multiple historical, clinical, laboratory and radiological criteria are used to predict the risk of recurrence/ progression to MS (Table 3).
A seasonal pattern, a history of a precipitant, seizures, bilateral optic neuritis and encephalopathy are considered more likely in ADEM compared to MS (Dale *et al.*, 2005). Inflammatory markers, a high cerebrospinal fluid protein and leucocytosis are also more common in ADEM (Kesselring *et al.*, 1990). MRI characteristics that are predictive of evolution to MS include well defined lesions that are peri-aqueductal or perpendicular to the corpus callosum (Dale *et al.*, 2000), deep grey matter involvement and lesions that enhance post contrast (Govender *et al.*, 2010).

11. Differential diagnosis of white matter disease in children

The differential diagnosis for a child who presents with a neurological symptom and white matter lesions on neuro-imaging is vast and includes infectious diseases, leukodystrophies, tumors, vasculitides, toxins and vitamin deficiencies. In resource poor countries, CNS infections must be excluded first as they are common and have acute therapeutic implications.
CNS infections must be excluded in children presenting acutely especially with fever and encephalopathy. CNS infections that may present with multifocal white matter lesions include HTLV-1, Borreliosis and Subacute Sclerosing Panencephalitis. In resource poor settings HIV Encephalopathy **(Figure 14 a,b)** is common and is also characterized by confluent white matter lesions. Progressive Multi-focal Leukoencephalopathy **(Figure 14 c),** is also common in immuno-compromised patients.
Neurometabolic disorders, such as Adrenoleukodystrophy **(Figure 14 d,e),** presents with primary white matter disease.
Osmotic Myelinolysis (Figure 14 f,g) is thought to be related to osmotic shifts associated with rapid correction of fluid and electrolyte abnormalities (especially sodium abnormalities). Malnourished children are at greater risk for developing myelinolysis. Lesions typically occur in the pons but have also been reported in extra-pontine sites such as the basal ganglia, cerebral cortex and cerebellar peduncles.
Nutritional deficiencies such as vitamins B12, E and folate deficiencies may also cause white matter lesions.
Drugs and toxins implicated in demyelination include tin, lead, isoniazid and radiation.
Collagen Vascular Diseases refer to a group of auto-immune mediated disorders. The neurological manifestations are diverse. Neuro-imaging may show multi-focal white matter lesions- involving the cortex, cerebellum or spinal cord.
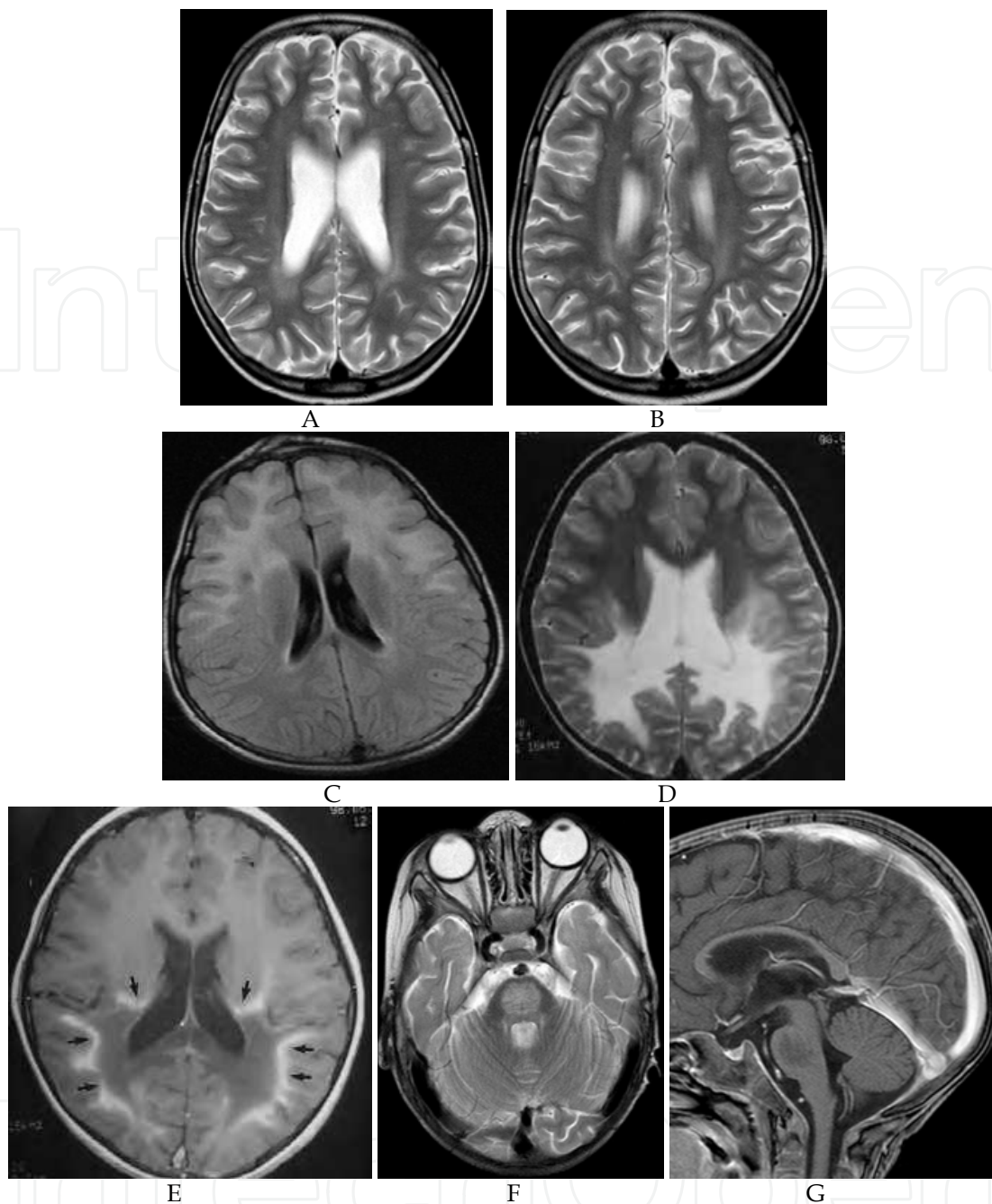
Fig. 14. A & B- T2 axial MRI demonstrating diffuse brain shrinkage/atrophy with ex-vacuo dilatation of the ventricles and abnormal increased signal intensity in the deep white matter bilaterally. This patient has features of HIV encephalopathy. C- Flair axial MRI demonstrating bilateral symmetrical increased signal intensity in the frontal white matter. This patient was diagnosed with PML. D- T2 axial MRI demonstrating bilateral symmetrical confluent abnormal increased white matter signal intensity in the posterior white matter consistent with Adrenoleukodystrophy. E- T1 with contrast axial MRI of same patient as 14D demonstrating peripheral enhancement of the white matter lesions. F- T2 axial MRI demonstrating well-defined rounded hyper-intense lesion in the pons. Note peripheral sparing of the pons. (Compared to figure 14G). Features consistent with Osmotic/ Pontine Myelinolysis. G- T1 with contrast sagittal MRI of the same pontine lesion as 14F showing no contrast enhancement. Features consistent with Pontine Myelinolysis.

12. Conclusion

Acquired demyelinating disorders in children are a diverse, challenging group of conditions that are probably under-diagnosed. Early recognition is essential for optimal patient management as some of these disorders cause significant long-term sequelae. Advances in the last decade include establishing consensus definitions and improvement in neuro-imaging techniques. These advances set the stage for international collaborative studies to better define other areas such as understanding the aetio-pathogenesis, identifying biomarkers and standardizing treatment protocols of this diverse group of conditions.

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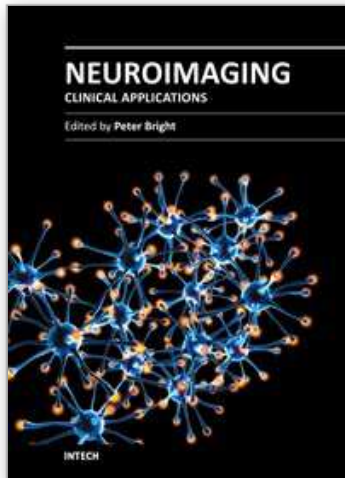
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