Original Article

Clinical Profile and Outcome of Pediatric Demyelinating Disorders in Calabar, Nigeria: A Case Series

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Abstract

Background: Demyelinating disorders of the central nervous system (CNS) are rare disorders characterized by inflammation and the selective destruction of CNS myelin. The incidence of this disorder is increasing in developed countries. Nigerian studies on the pediatric population on the subject are very scarce. **Aims:** The aim of the study was to document the epidemiology, clinical profile, and impact of late presentation on the treatment outcome of demyelinating diseases of the CNS in pediatric patients. **Methods:** The retrospective review of patients aged 1–15 years admitted in a tertiary hospital from January 2018 to December 2022 with various symptoms suggestive of demyelinating CNS disorders. The diagnosis was clinically and radiologically confirmed. Information retrieved from the case notes included patients' demographics, clinical symptoms and signs, number of days with symptoms to presentation in the hospital, results of the magnetic resonance imaging (MRI), treatment, and treatment outcomes. Data were entered in Excel sheet and results were presented in tables and percentages. **Results:** The incidence of demyelinating disorders over the period was 0.013% (10 out of 769 patients admitted over the period). Acute demyelinating encephalomyelitis (ADEM) was the most common disorder seen in the study population (60%, n = 6), followed by transverse myelitis and two (20%) had optic neuritis (ON). Most of the patients with ADEM were in the 1–5-year age group. The female-to-male ratio was 2.3:1. Paraplegia, visual impairment, and ataxia were the most common clinical presentations in the study population. One of the patients met the criteria for the diagnosis of multiple sclerosis during follow-up. Human immunodeficiency virus (HIV) was identified as the cause of demyelination in one case. Most of the patients improved with steroids. **Conclusion:** ADEM was the most common clinical phenotype seen in this study. Patients with ADEM and ON had a better prognosis than transverse myelitis. Late presentation was also identified as a poor prognostic factor. Follow-up of cases is very important to monitor disease progression to multiple sclerosis.

Keywords: *ADEM, demyelinating disease, neuritis, transverse myelitis*

Introduction

Acquired demyelinating syndromes (ADS) are rare immune-mediated demyelinating disorders of the central nervous system (CNS) characterized by inflammation and selective destruction of the CNS myelin sheath.[1] Multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), transverse myelitis (TM), clinically isolated syndrome (CIS), and Devic disease (neuromyelitis optica [NMO]) are collectively known as ADS.[2]

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ADEM is characterized by acute or sub-acute onset of multifocal neurologic deficits with encephalopathy, often following a viral illness.[3] ADEM typically presents as a monophasic disorder associated with multifocal neurologic symptoms and disability. ON is an inflammation of the optic nerve that can be caused by any inflammatory condition or may be idiopathic.[3] TM is defined as a focal inflammatory disorder of the spinal cord resulting in motor, sensory, and autonomic dysfunction that develops over hours or days in patients in whom there is no evidence of a compressive lesion.[3.4] NMO is characterized by acute TM and ON with a relapsing course over months to years resulting in severe disability or death.[5]

In children, ADS is rare with unknown prevalence; a study from Canada showed an incidence of 0.9 per 100,000.[6] In the Canadian study, TM accounted for approximately 20% of all pediatric ADS cases, while ADEM and ON accounted for 20–30% and 23%, respectively. The estimated incidence in California is 0.4/100,000 population per year,[7] while a Dutch study reported an incidence of 0.80/100,000 per year.[8] ADEM is an uncommon disorder with an unknown incidence in sub-Saharan Africa (SSA),[5] while neuromyelitis optica spectrum disorders (NMOS) seem to be the most frequent inflammatory demyelinating disease of the CNS in SSAs. The incidence of NMO in SSA may be similar to worldwide rates, though studies in the SSA population are scarce.[5] In Nigeria in 1971, Osuntokun[9] reported 95 cases of NMO, compared to just two cases of MS observed over the same time period. Most cases of demyelinating disorders reported in SSA are in the adult population.[10]

Etiology of ADS is unknown, but genetic and environmental factors have been implicated in the pathogenesis of the disease.[11] The environmental factors identified occur post-infectious and post-immunization possibly due to a T-cell mediated auto-immune response to myelin basic protein triggered by an infection or immunization.[4] A few documented cases of ADEM in children in Nigeria interestingly reported typhoid fever and malaria as possible post-infectious causes of ADEM.[12,13]

This condition often poses a diagnostic and therapeutic challenge. With the exception of the NMO-IgG autoantibody found in NMO, there are no disease-specific biomarkers for these conditions, making it difficult to distinguish among them at the time of the initial presentation.[3] However, certain clinical features, laboratory results, and imaging findings can usually lead to the correct diagnosis. Early diagnosis and appropriate treatment determine prognosis and outcome. Most studies in the literature on ADS were done in Europe and the Asian continent, with reports that the incidence of this disease is rising in developed countries[14] and a paucity of data on the disease in Nigeria, there is a need to report epidemiological findings in children of SSA ancestry. The study aimed to document the epidemiology, clinical profile, and treatment outcome of demyelinating disorders of the CNS in Nigerian children managed at the University of Calabar Teaching Hospital over a five-year period.

Subjects and Methods

The retrospective review of 10 patients admitted to a tertiary care hospital from January 2018 to December 2022 with various symptoms suggestive of demyelinating CNS disorders. Clinical history, patterns of disease evolution, neurologic examination, laboratory, and imaging with brain and/or spinal magnetic resonance imaging (MRI) were used for diagnosis. Neurophysiological studies were not done. All the patients were reviewed by a pediatric neurologist and an ophthalmologist and received supportive treatment and high dose IV methyl prednisolone for five days, then put on an oral prednisolone tapering dose for four weeks. Physiotherapy for rehabilitation was done where applicable. The outcome of follow-up surveillance for MS was noted. Other information retrieved from the case note included sex, age, number of days with symptoms to presentation in the hospital, and treatment outcome. Their neuroimaging records were also reviewed. The information from the cards was then entered into a spreadsheet specifically designed for the study. Data were expressed in percentages and proportions and presented in tables.

Results

The incidence of demyelinating disorders over the period was 0.013% (10 out of 769 patients admitted

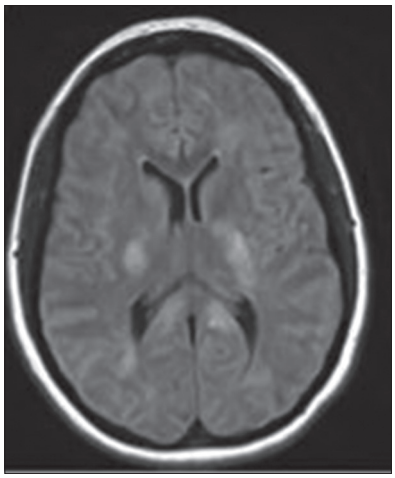

Figure 1: FLAIR axial MRI of a patient with ADEM showing biateral high signal intensities in the posterior white matter

Table 1: Demographic characteristics of the patients

Frequency	Clinical Phenotypes			Total
	Adem	Tranverse Myelitis	On	
	6	2	2	10
Age				
1–5	4	0	1	5
6–10	0	0	1	1
11-15	2	2	0	4
Gender				
Male	2	1	0	3
Female	4	1	2	7
History of recent infection	4 (67%)	1 (50%)	1 (50%)	6 (60%)

ADEM=acute disseminated encephalomyelitis

Table 2: Frequency of first clinical symptoms

Symptoms	Adem	Transverse Myelitis	On	Total
Ataxia	3	1	1	5
Speech disorder	3	0	0	3
Decreased LOC	5	0	0	5
Visual disturbances	2	0	2	4
Sensory symptoms	2	2	0	4
Seizures	2	0	0	2
Paraplegia/paraparesis	5	2	0	7
Quadriplegia	0	1	0	1
Sphincter dysfunction	2	2	0	2

over the period). The highest proportion of subjects was in the 1–5-year age group. The proportion of females (n = 7, 70%) was higher than that of males (n = 3, 30%) with a F: M of 2.3:1 [Table 1]. Presenting phenotypes consisted of ADEM (*n* = 6, 60%), ON (*n* = 2, 20%) and TM (*n* = 2, 20%). Paraplegia, visual impairment, and ataxia were the common clinical presentation in the study population [Table 2]. Most of the patients with ADEM had multiple hyper-intense supratentorial brain lesions on T2/fluid-attenuated inversion recovery (FLAIR) images [Figure 1], and a few of the patients had cortical and/or subcortical white matter lesions that were bilateral and asymmetric in size and location [Table 3]. The Cerebrospinal Fluid Analysis (CSF) analysis for patients with suspected ADEM showed normal findings in half of the cases, others showed mildly elevated protein and lymphocytosis. In TM, the lesions involved the white matter of the spinal cord in multiple segments of the cord [Figure 2]. The CSF results of the patients with TM had mildly elevated protein and lymphocytosis. Two of the patients with ON had no light perception vision at presentation with severe disc swelling. Most of the patients improved with steroids. In cases with ADEM, five had monophasic ADEM while one (25%), a 14-year-old male, developed a recurrent disease that met the criteria for MS over the next 18 months of follow-up, three patients had full recovery while two patients had

Table 3: Neuroimaging findings

Site of lesion	No. of cases
White matter	6
Spinal cord	7
Brain stem	4
Basal ganglia/thalamus	2
Optic nerve	3
Cerebellum	3
Normal findings	1

Table 4: Definitions of different CNS demyelinating disorders as applicable in the study

Demyelinating disorder	Definition
ADEM	(1) A polysymptomatic clinical event with acute/sub-acute onset that must include encephalopathy (behavioral change or altered consciousness). (2) MRI brain shows multifocal lesions
TM	Weakness and/or numbness of both legs±arms, usually with maximal deficits one week after symptom onset supported by demyelination on MRI spine in the absence of encephalopathy.
ON	Acute or subacute loss of vision and≥1 of: relative afferent pupillary defect (unilateral cases), visual field deficit or scotoma, impaired color vision, optic disc edema, or abnormal visual evoked potentials.
MS	One ADEM attack followed by a non-encephalopathic clinical event, three or more months after symptom onset, that is associated with new MRI lesions that fulfil 2010 Revised McDonald DIS criteria[31]

Adapted from Krupp LB *et al*.[32]

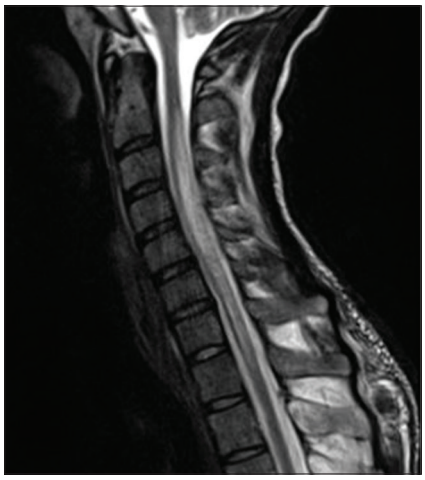

Figure 2: T2 saggital MRI of the cord showing diffuse abnormal increased signal intensities in a patient with Transverse myelitis

a mild disability. The two patients with ON recovered their visual acuity fully. One patient with TM and high cervical cord involvement developed cardiopulmonary failure and died and another had a severe motor

disability. Late presentation was associated with poorer outcomes. Human immunodeficiency virus (HIV) was identified as the possible cause of demyelination in one case of TM.

Discussion

In our study, ADEM was the most common clinical phenotype. However, in many other studies, MS was identified as the most common clinical phenotype.[2,14,15] Only one case developed MS over the following period in this study. ON was however reported to be more common than ADEM in a Canadian study.[6] It is probable that some of the children with ADS (especially ON) in our study were not managed in the pediatric neurology unit, as some of them had been followed by ophthalmologists.

Gender distribution showed a female preponderance with a female to male ratio of 2.3:1; this was similar to the study in the Netherlands[8] but lower than the study by Etamadifar (4.5:1) in Iran.[16] Generally, this is consistent with other studies that found that ADS was more common in females.[2] The age distribution pattern showed that the 0–5-year age group has the highest contribution; this was also comparable to other studies.[14] In addition, this is further explained by the predominance of ADEM in the sample. ADEM is generally more common in younger children.

A history of recent infection was positive in 67% of our patients, mostly in patients with ADEM. Inaloo *et al*.[14] reported a recent infection in 46.5%. The infection triggers in our cases were mainly non-specific upper respiratory tract infections and gastroenteritis. Other Nigerian case reports have implicated typhoid fever and malaria.[12,13] No case of post-immunization cause was noted. However, one of the patients with TM was found to be HIV positive at presentation. In this study, the most common presenting feature was paraplegia followed by visual impairment and ataxia. Decreased levels of consciousness, seizure, and paraplegia, were the most frequent features in ADEM cases [Table 4], consistent with other studies.[17,18]

MRI is the imaging modality of choice to demonstrate white matter lesions in ADEM, ON, and TM [Table 4]. Lesions are most easily recognized on T2 weighted (T2WI) and FLAIR MRI sequences.[4] The lesions of ADEM are multi-focal and involve the cerebral, brainstem, and cerebellum. They usually involve the sub-cortical, central, and periventricular white matter. Lesions are typically hyper-intense in T2 weighted sequence, patchy, asymmetric, and ill-defined.[4] Deep gray matter lesions in the thalami and basal ganglia were found in our patients, as previously reported by other studies.[4] The MRI of the spinal cord in TM usually shows a nonspecific localized hyper-intense signal on T2WI sequences with, in some cases, segmental cord enlargement and/or focal enhancement. CSF studies in ADEM are usually abnormal (in >67% of cases, typically showing a moderate pleocytosis with an elevated protein content.[4] This was seen in half of the cases with ADEM in our series. Similar findings are also seen in the CSF of patients with TM.

Immunomodulation is the mainstay of treatment. Three modalities are recognized; these include the use of glucocorticoids, intravenous immune globulin, and plasma exchange.[19] However, the effectiveness of these treatments for ADEM has not been definitively confirmed, as there are no prospective clinical trial data to determine optimal treatment, including dose or duration.[20] A widely accepted first-line treatment for demyelinating disorders is high-dose intravenous glucocorticoids.[21,22] The use of IV methylprednisolone (20–30 mg/kg per day, maximum 1 gm daily) or dexamethasone (1 mg/kg per day) for three to five days, followed by oral glucocorticoid taper over four to six weeks is beneficial. This was associated with full recovery in approximately 60–90% of patients.[19] Methylprednisolone-treated patients had significantly better outcomes with respect to disability status when compared with those treated with dexamethasone. In our series, patients received high-dose IV methylprednisolone at 30 mg/kg for five days. We began the taper with oral prednisone 1–2 mg/kg per day up to a maximum of 60 mg per day and then reduced the dose by 10 mg every five days to allow for a total tapering duration of four to six weeks. Nearly 30% of patients do not respond to IV methylprednisolone.[23] In cases of unsatisfactory improvement after a 5-day corticosteroid course, the generally accepted second-line treatment is intravenous immunoglobulin (IVIG).[20] Data from small case series and case reports suggest that IVIG is beneficial as rescue therapy in patients with ADEM who fail to respond to Methylprednisolone[24,25] or as initial therapy.[26] The usual total dose is 2 g/kg administered over two to five days. Plasma exchange is an efficient but invasive method of removing circulating autoantibodies and immune complexes.[20] Limited data suggest that plasma exchange is beneficial in children with ADEM who fail treatment with IVIG and/or methylprednisolone.[27,28] However, the largest series of retrospective studies reported improvement following plasma exchange in six children with ADEM who did not respond to initial treatment with glucocorticoids followed by IVIG.[28] Generally, 5–7 single-volume exchanges consisting of 1–1.5 plasma volumes are applied every other day.[3] Because of potential adverse effects like hypotension,

and hypocalcaemia, plasma exchange constitutes the first choice only in cases of fulminant or severe symptoms or extensive inflammation on imaging.[20]

In patients with ON, there has been no randomized controlled trial in children, but an adult study demonstrated that IV methyl prednisolone followed by oral prednisone accelerates visual recovery and provides a better visual outcome at six months.[29] Patients with insufficient responses may have IVIG or plasma exchange, as described above. Supportive care in ADEM including airway management, seizure control, and correction of fluid and electrolyte disturbances is also essential.[20] Physical therapy also plays a role in rehabilitation in ADEM and TM.

Prognosis of ON as seen in our patients was good, as both of them fully recovered, this was comparable to other studies.[14,15,18] Residual disability was more common with TM and ADEM, as reported by other studies.[8,14,30] Motor deficits persist in 8–30%[19] of patients and include paraparesis, hemiparesis, and ataxia. Acute course (within hours), spinal shock, and a cervical sensory level have been reported as poor prognostic features in TM.[19,30] In our study, late presentation also contributed to the outcome as the only mortality was a patient with TM and cervical cord involvement who presented three weeks after the onset of symptoms. The presentation was delayed as the patient initially sought traditional medication before presentation in our facility. In our series, only one patient with ADEM developed MS in follow-up. Follow-up is very essential to monitor the progression of all clinical phenotypes for progression to MS.

Conclusion

Demyelinating disorders of the CNS are not common in children in Nigeria and their prevalence and incidence in Nigeria remain unknown. ADEM was the most common clinical phenotype seen in Calabar. Patients with ADEM and ON had a better prognosis than TM. Late presentation was also identified as a poor prognostic factor. Follow-up of cases is very important to monitor disease progression, which may ultimately culminate to MS with attendant physical and cognitive disabilities. In addition, there is a need to develop a register for patients in our environment and raise more awareness to improve management and prognosis.

Limitations of study

Viral studies and para-infectious markers, nerve conduction tests, and CSF IgG were not utilized in these diagnoses because of the unavailability of these facilities.

Notable in this study was that all the patients received a uniform treatment regimen of IV methylprednisolone followed by oral steroids.

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Conflicts of interest

There are no conflicts of interest.

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