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ORIGINAL RESEARCH

Paediatric autoimmune encephalitis: experience of a tertiary care hospital in Bangladesh.

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Abstract

Background: Autoimmune encephalitis (AIE) is a distinct type of encephalitis where production of autoimmune antibodies causes neuroinflammation. The core clinical features are encephalopathy, psychiatric disorder, movement disorder and seizure. The investigation and treatment modalities are different from that of infectious encephalitis. There are limited studies in the paediatric population, particularly in developing countries such as Bangladesh. This study describes patients with AIE from a tertiary care hospital. **Method:** This is a retrospective study done with children aged one to 16 from January 2018 to December 2019. AIE was diagnosed based on clinical, electrographic and neuroimaging features and was confirmed with detection of autoantibodies in CSF. Treatment was given according to the published literature. **Results:** A total of 15 children were studied, of which 14 suffered from anti-NMDAR encephalitis and one from anti-MOG antibody syndrome. The mean age was 5.98 and 4.5 years, respectively. Seizures were the most common clinical feature, mostly focal in nature. Other manifestations were movement disorder, psychiatric disorder, loss of consciousness, etc. Most of the patients recorded an abnormal EEG, of which a focal epileptic discharge was the commonest. Eight out of 15 showed an abnormal MRI of the brain. Cortical hyperintensity was an important feature located mostly in the temporal region. In the case of an anti-MOG antibody syndrome there was a demyelinating lesion in multiple areas. The cornerstone of the treatment was mostly combination immunotherapy with IV methylprednisolone and IV immunoglobulin followed by oral steroids. The majority of the patients showed improvement and three patients had a complete recovery. Complications observed were epilepsy, speech disorder, cognitive disorder, behavioural disorder, ataxia and visual impairment.**Conclusion:** Timely diagnosis and prompt treatment of AIE is very important as proper treatment can show significant improvement.

Keywords: Autoimmune encephalitis; anti-NMDAR encephalitis; anti-MOG antibody syndrome.

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Introduction

Autoimmune encephalitis (AIE) is a type of antibody-mediated inflammatory disorder of the central nervous system. AIE is manifested by various neurological and psychiatric symptoms. Until now, many of the AIE disorders have been described with the advent of molecular diagnostics. The patients usually present with a subacute onset of behavioural disorder, psychiatric manifestation, encephalopathy or movement disorder (MD). There is involvement of the limbic system, characterised by amnesia, confusion, epileptic seizures, as well as extra-limbic brain structures [1]. AIE is caused by development of autoantibodies triggered by viruses and tumours. More than 10 synaptic antineuronal and glial antibodies associated with AIE have been identified, and new antibodies are being described at an astonishing pace [2, 3, 4].

The incidence of AIE has been rising globally and presents an emerging form of encephalitis. The incidence rates of autoimmune encephalitis are 0.8/100,000 and is rising [2]. Research has therefore evidenced an interest in AIE, as the modality of diagnosis and management is different from that of infectious encephalitis, in that detection of autoantibodies is important and immunotherapy is the cornerstone of treatment [5, 6].

In a resource-limited country such as Bangladesh, AIE diagnosis is difficult and expensive. This study has been done to describe a series of cases diagnosed and managed as AIE in a tertiary care hospital in Bangladesh.

Methods

Subjects: This study was done in the Department of Pediatric Neurology, Institute of Pediatric Neurodisorder and Autism (IPNA), Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. Children from 1–16 years of age who were hospitalised and diagnosed as having AIE were

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retrospectively studied from January 2018 to December 2019 (a total of 24 months). Detail data of the patients were collected and analysed.

Method: The patients clinically presented with the following features and were thought to have AIE: i) Abnormal behaviour (mental symptoms) or cognitive dysfunction; ii) language dysfunction (continuous mandatory language that cannot be interrupted, language reduction and silence); iii) seizures; iv) movement dysfunc¬tion, dyskinesia or muscle rigidity, and/or abnormal posture; v) decreased consciousness; and vi) autonomic dysfunction or central hypoventilation, vi) status epilepticus [7]. Diagnosis was confirmed with detection of autoantibodies in serum or CSF.

We gathered the clinical data of 15 patients retrospectively, including age, sex, prodromal symptoms and major clinical mani¬festations. All patients underwent magnetic resonance imaging (MRI) of the brain and electroencephalograms (EEGs). Tumour screening was done. Exclusion of other possible causes were done by a vasculitis panel (antinuclear antibody [ANA], anti-double-stranded [anti-DS] DNA, anticardiolipin antibodies, antiphospholipid antibodies, urine R/E [urinalysis]), cerebrospinal fluid (CSF) for a viral panel, urinary vanillylmandelic acid (VMA), a computerised tomography (CT) scan of the abdomen, chest, an MRI of the spine, etc.

Treatment: In all patients, the first line of treatment was given with either intravenous methylprednisolone (IVMP) (30 mg/kg/day, for five consecutive days) or high dose intravenous immunoglobulin (IVIG) (400 mg/kg/day, for five days) or both in combination, given together or sequentially. In some cases, a maintenance steroid was given orally at a dose of 0.5-2 mg/kg/day for a period of four weeks up to six months. No continuous improvement at four weeks following immunotherapy indicated treatment failure. Treatment failure cases and relapse cases were subjected to second line treatment, i.e., CD20 monoclonal antibodies (rituximab), 375 mg/m^2, once a week for four weeks. In some cases, pulse therapy with IVMP and IVIG was repeated monthly. Treatment is described in the result section. Symptomatic management was given with antiseizure drugs, antidystonic drugs and antipsychotic drugs.

***Follow-up*:** Patients were followed up for a period of 4–36 months.

Results

Clinical demography of studied children: In this study, a total of 15 children diagnosed with AIE were analysed. Fourteen cases (93.33%) were that of anti-N-methyl-d-aspartate receptor encephalitis (anti-NMDAR encephalitis) and one case (6.66%) was that of anti-myelin oligodendrocyte glycoprotein syndrome (anti-MOG antibody) syndrome. The mean age was 5.98 years in the case of anti-NMDAR encephalitis and 4.5 years in anti-MOG antibody syndrome. In the case of NMDAR encephalitis, more than half were female, while one case of anti-MOG antibody syndrome was male (Table 1).

Clinical features of the studied subject: About 42.8% patients of anti-NMDAR encephalitis presented with a prodrome of fever and one patient of anti-MOG had fever. Four cases had a cough and other gastrointestinal features. One patient had a history of varicella infection.

More than half of the patients with anti-NMDAR encephalitis (57.14%) had seizures, mostly focal in nature. Patients with anti-MOG antibody syndrome had generalised seizures. Three patients with anti-NMDAR encephalitis had status epilepticus (SE). Other features observed were MDs (35.71%), sleep disorder (7.14%) and behavioural disorder/psychiatric disorders, etc. Four patients with anti-NMDAR encephalitis had cognitive decline. Other features observed in the AIE were speech disorder, focal deficit, loss of consciousness, ataxia and autonomic features (Table 1).

Movement disorder in studied subject: Patterns of MDs present in anti-NMDAR encephalitis were ataxia (21.42%), choreoathetosis (21.42%), dystonia (2), oromandibular dyskinesia (1), bruxism (1) and myoclonus (1). One patient with anti-MOG antibody syndrome had ataxia (Table 1).

Psychiatric manifestations in the studied subject: Four patients showed personality changes in the form of altered behaviour, excessive talkativeness, and mood swing. Three patients showed aggression, three patients had psychosis, two patients had irritability, two patients had a sleep disorder and one had hallucinations (Table 1).

EEG finding of the studied subject: An EEG was performed in all patients. In 14 (93.33%) patients, the EEG was abnormal. Nine out of 15 patients showed focal discharges, most patients had discharges from temporal areas alone or along with other areas, namely occipital, frontal and parietal. A generalised slowing was present in four (28.57/patients with anti-NMDAR encephalitis and one patient with anti-MOG antibody encephalitis. Other features were periodic lateralised epileptic discharges (PLEDs) in one patient, a delta brush in one patient, nonconvulsive status epilepticus in one patient, new onset refractory status epilepticus (NORSE) in one patient and epileptic encephalopathy in one patient (Table 2).

CSF features of studied subjects: A CSF study was done in all patients. In 9 (64.28%) patients with anti-NMDAR encephalitis, pleocytosis was found, but in none of the patients was the CSF cell count more than 100 cell/HPF. A mild increase of CSF protein was found in five patients with anti-NMDAR encephalitis. In all patients with anti-NMDAR encephalitis, CSF was positive for anti-NMDAR antibodies. CSF was positive for anti-MOG antibody in one case of anti-MOG antibody syndrome. A herpes simplex PCR test was positive in two cases of anti-NMDAR encephalitis (Table 2).

Neuroimaging (MRI of the brain) of studied subjects: An MRI of the brain with contrast was done in all patients. Out of 15 patients, eight showed an abnormal finding in MRI. In the case of patients with anti-NMDAR encephalitis, 50% showed a nonspecific/normal finding. Cortical hyperintensity was found in eight (57.14%) patients (temporal five, parietal two and occipital one). Other findings were subcortical white matter hyperintensity (1) and basal ganglia hyperintensity (1). In the patient

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Figure 1. An MRI of the brain showing temporal lobe hyperintensity in a case of anti-NMDAR encephalitis (**A**).

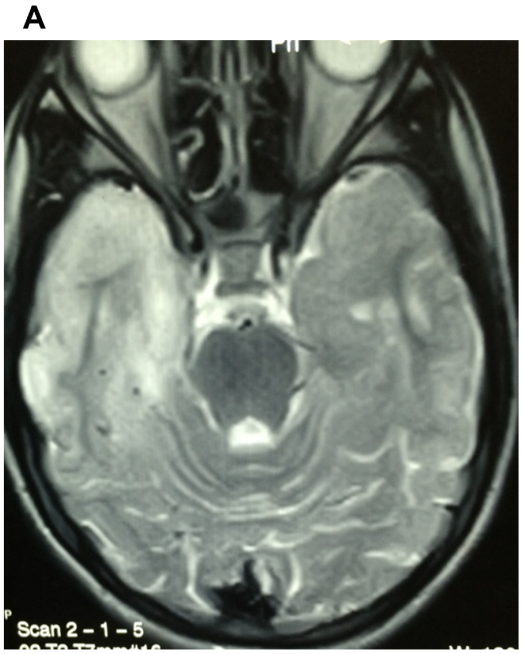
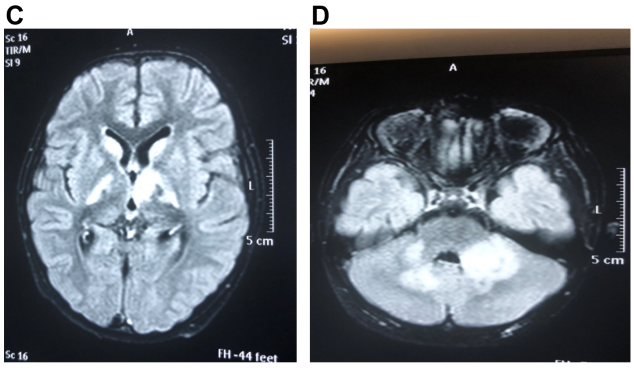


Figure 2. An MRI of the brain showing bilateral basal ganglia hyperintensity in a case of anti-MOG antibody syndrome (**C**). An MRI of the brain showing a cerebellar demyelinating lesion in a case of anti-MOG antibody syndrome (**D**).



with anti-MOG antibody syndrome, features found were subcortical white matter hyperintensity, deep white matter hyperintensity, and cerebellar and brainstem involvement. Infratentorial involvement of the brain was present only in the anti-MOG antibody syndrome. An MRI of the spine was normal in this case (Table 2) (Figure 1, 2).

Treatment profile and follow-up of studied subjects: Immunotherapy was the first-line therapy in all the patients. In most of the patients, a combination of IVMP and IVIG had been given. In other patients, this combination was offered but only IVMP was given due to financial constraints. In the patients with **anti-NMDAR encephalitis**, eight patients received both IVMP and IVIG, followed by oral steroids for a duration of eight weeks to six months. Here one patient had a relapse and in one patient there was no improvement with first-line immunotherapy. In both the cases, rituximab was given. Both the patients tolerated the drug and there was significant improvement. Only three patients showed complete recovery and the others had some complications. During the follow-up period, we observed the following sequelae: epilepsy in six patients, speech disorder (three), cognitive disorder (two), ataxia (two) and behavioural disorder (two).

In the case of the patient with **anti-MOG antibody** syndrome, treatment was given with IVMP and IVIG as initial immunotherapy, followed by oral steroids. The child went to near-complete recovery. Then in three months' time, he again developed headache, visual impairment and ataxia. Rituximab was offered but denied. Then four more pulses of IVIG and IVMP were given. A low-dose steroid was continued for a period of six months. Here, significant improvement was noted. At his one-year follow-up, the patient had occasional diplopia and cognitive problems. (Table 3)

Discussion

AIE is a major cause of encephalitis. It is now as common as infectious etiology of encephalitis [8]. Up till now, there has been scant research in countries such as Bangladesh. Moreover, most of the published research in AIE focus upon adult patients. Therefore, we analysed cases of AIE presenting from a tertiary care centre. In this study we saw two different types of AIE – anti-NMDAR encephalitis and anti-MOG antibody syndrome. We found a few other types of AIE in our study, such as limbic encephalitis, Hashimoto's encephalopathy, anti-AMPAR encephalitis, anti-GABA-AR encephalitis, anti-LGI1 and anti-CASPR2 encephalitis, anti-GAD encephalitis, anti-DPPX encephalitis [9]. This may be due to constraints of investigation facilities and a limited number of cases.

The most common clinical feature of anti-NMDAR encephalitis in this study was new onset seizures observed in 57.14% patients. Seizures were also the persistent feature of other studies in paediatric AIE. In a study in paediatric anti-NMDAR encephalitis, 73% of patients had seizures, while in the case of adults, only 14% had seizures [10, 11, 12]. Meanwhile, in another case series by Galbe *et al.*, about 80% had seizures with an age range of 11–31 years [13]. In our study, status epilepticus was present in 21.42% of patient, which was lower than in a study done by Zhang J. *et al.* where they found SE in 34.8% of the patients. They also showed that patients with SE had a poor outcome [10]. Although in previous literature it was shown that generalised tonic-clonic seizures were the predominant type of seizure, focal seizures were found to be the most common in this study, possibly due to the small sample size [14].

Other initial features in patients with anti-NMDAR encephalitis were abnormal behaviour/psychotic disorder (50%), altered consciousness (42.85%), MDs (35.71%), speech disorder (35.71%), cognitive decline or memory loss (28.57%), ataxia, visual disorder, headache, sleep disorder and autonomic features. None of the patients had any tumours or other autoimmune disorders. Regarding prodromal features, six patients had fever, a

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Table 1. Demographic characteristics and clinical features of the studied subjects (N15).

	Anti-NMDAR encephalitis N=14 (%)	Anti-MOG antibody syndrome N=1(%)
Age	5.98 years (range 1.9–14 years)	4.5 years
Sex		
Male	6 (42.85)	1 (100)
Female	8 (57.14)	
Clinical features		
Fever	6 (42.8)	1 (100)
Prodromal symptoms		
Cough/runny nose	4 (28.57)	
Diarrhoea	1 (7.14)	
Vomiting	1 (7.14)	
Varicella infection	1 (7.14)	
Seizure	8 (57.14)	1 (100)
Status epilepticus	3 (21.42)	
Headache	2 (14.28)	1 (100)
Cognitive decline/memory loss	4 (28.57)	
Speech disorder	5 (35.71)	
Focal deficit	1 (7.14)	
Movement disorder	5 (35.71)	1 (100)
Abnormal behaviour/psychiatric symptoms	7 (50)	
Loss of consciousness/altered level of consciousness	6 (42.85)	1 (100)
Visual disturbances	2 (14.28)	
Sleep disorder	1 (7.14)	1 (100)
Ataxia	3 (21.42)	1 (100)
Autonomic features	1 (7.14)	
Movement disorder*		
Ataxia	3 (21.42)	1 (100)
Choreoathetosis	3 (21.42)	
Dystonia	2 (14.28)	
Oromandibular dyskinesia	1 (7.14)	
Bruxism	1 (7.14)	
Myoclonus	1 (7.14)	
Psychiatric manifestations#		
Personality change	4 (28.57)	
Aggression	3 (21.42)	
Psychosis	3 (21.42)	
Irritability	2 (14.28)	
Sleep disturbances	2 (14.28)	
Hallucinations	1 (7.14)	

**In cases with anti-NMDAR encephalitis, five patients had movement disorder (some patients had more than one type of MD)*
#In cases with anti-NMDAR encephalitis, seven patients showed abnormal behaviour/psychiatric disorder (some patients had more than one type of psychiatric disorder)

cough/runny nose, gastrointestinal symptoms and varicella infection. In a study done by Dalmau J. *et al.* they found prodromal symptoms in about 70% of the patients. The symptoms were fever, headache, nausea, vomiting, diarrhoea and flu-like symptoms, most presenting two weeks before the onset of neurological manifestations [14].

Some clinical features which are less likely to be seen in infectious encephalitis, are commonly seen in anti-NMDAR encephalitis. Firstly, manifesting early in the course of the illness, patients may display psychiatric symptoms, such as schizophrenia-like behaviour (psychosis and hallucinations). In some reported cases, the authors also mentioned aggression, behaviour change and personality disorder [13, 14]. Secondly,

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Table 2. Investigation profile of the studied subjects (N15).

	Anti-NMDAR encephalitis N=14 (%)	Anti-MOG antibody syndrome N=1 (%)
EEG*		
Delta brush	2 (14.28)	
Focal slowing	1 (7.14)	
Generalised slowing	3 (21.42)	1 (100)
PLEDs	1 (7.14)	
New onset status epilepticus (NORSE)		
Nonconvulsive status epilepticus	1 (7.14)	
Focal epileptic discharges		
Temporal	4 (28.57)	
Temporal+Occipital	1 (7.14)	
Temporal+Frontal	2 (14.28)	1 (100)
Frontal+Parietal	1 (7.14)	
Occipital+Parietal+Frontal		
Epileptic encephalopathy	1 (7.14)	
Normal/nonspecific	1 (7.14)	
CSF study		
CSF cell count		
Normal (<5/HPF)	5 (35.71)	
Pleocytosis (>5/HPF)	9 (64.28)	1 (100)
CSF protein		
<40 mg/dl	8 (57.14)	
40–80 mg/dl	5 (35.71)	1 (100)
>80 mg/dl	1 (7.14)	
Anti-NMDAR antibodies	14 (100)	-
Anti-MOG antibodies	-	1 (100)
HSV PCR	2 (14.28)	-
Neuroimaging (MRI of brain)		
Cortical hyperintensity		
Temporal lobe		
Parietal	5 (35.71)	
Frontal	2 (14.28)	
Occipital	1 (7.14)	
Subcortical white matter involvement	1 (7.14)	1 (100)
Deep white matter involvement	1 (7.14)	1 (100)
Basal ganglia hyperintensity		1 (100)
Cerebellar involvement		1 (100)
Brainstem involvement		1 (100)
Nonspecific/normal	7 (50)	

**More than one type of abnormality was present in the EEG of some patients.*

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MDs are more common in AIE, such as dystonia, orofacial dyskinesias, choreoathetosis, myoclonus and neuromyotonia, etc. [13]. Interestingly, in this study MDs were only present in cases of anti-NMDAR encephalitis (5) and was absent in RE and anti-MOG antibody syndrome.

Studying the CSF plays an important role in the diagnosis of anti-NMDAR encephalitis. Testing of the autoantibodies plays a pivotal role. Commercial tests for antibodies to NMDAR are widely available but expensive for developing countries such as Bangladesh. Although autoantibodies can be detected in serum, CSF is the most sensitive and specific [15, 16]. All cases of anti-NMDAR encephalitis in this study were diagnosed based on CSF autoantibodies.

In literature, a normal MRI of the brain was observed in most of the cases of anti-NMDAR encephalitis. Only about 33–55% of patients showed an abnormal MRI. The brain lesions often occurred in the medial temporal lobe, frontal cortex, and parietal cortex. Atrophy of the brain and infratentorial lesions are other

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Table 3. Treatment profile of studied subject and follow-up (N15).

	Anti-NMDAR encephalitis N=14 N (%)	Anti-MOG antibody syndrome N=1 N (%)
First line immunotherapy		
IVMP only	4 (28.57)	
IVMP and IVIG	8 (57.14)	1 (100)
Second line therapy		
Rituximab	2 (14.28)	-
Maintenance therapy: oral steroid	8 (57.14)	1 (100)
Relapse	1 (7.14)	1 (100)
Prognosis		
Complete recovery	3 (21.42)	
Epilepsy	6 (42.84)	
Speech disorder	3 (21.42)	
Cognitive dysfunction	2 (14.28)	1 (100)
Ataxia	2 (14.28)	
Behavioural disorder	2 (14.28)	
Visual impairment		1 (100)

IVMP-Intravenous methylprednisolne, IVIG-Intravenous immunoglobulin

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less common features. Rare cases have been reported with demyelinating lesions such as that of *neuromyelitis optica* spectrum disorders (NMOSD), associated with anti-aquaporin-4 antibodies, or demyelinating diseases associated with myelin oligodendrocyte glycoprotein antibodies (MOG-ab) [17, 18]. The finding of this study coincides with that of the published paper. None of the cases of anti-NMDAR encephalitis had infratentorial or demyelinating lesions. Temporal lobe involvement was present in almost 35% of patients. In half of the patients, the MRI was normal. In other patients there was involvement of the parietal and occipital lobe and the basal ganglia.

Treatment options for AIE are broadly immune-suppressing agents and therapeutics targeted to antibody-mediated disease pathogenesis [19, 20]. Thus, corticosteroids are used in the treatment which broadly acts by inhibiting the inflammatory process. But corticosteroids are less specific for the antibody-mediated immune process, and their efficacy is limited in cases of AIE. Moreover, they are associated with several systemic side effects [21]. Other modalities using targeting of the immune mediated process are IVIG, plasma exchange, rituximab, cyclophosphamide, myocophenolate mofetil, etc. For preventing a relapse, low-dose steroids or steroid-sparing agents are given [22, 23]. There is no randomised controlled trial for the treatment of AIE, and immunotherapeutic agents currently used in AIE do not have a definite indication due to the low level of supporting evidence. Given the rarity of AIE, international collaboration for prospective clinical trials is imperative to establish treatment guidelines. Thus, for treating our study patients we followed the published paper [20, 23]. We started with either a combination of IVMP plus IVIG, or IVMP on its own, only in those patients with anti-NMDAR encephalitis. Then an oral steroid was given in some patients. In case of a relapse, we used either rituximab or pulses of IVMP and IVIG. Response to treatment was dramatic in most of the cases with first-line immunotherapy.

Anti-MOG antibody syndromes are immune-mediated inflammatory conditions of the central nervous system that frequently involve the optic nerves and the spinal cord [24]. This syndrome results from damage to myelin oligodendrocyte glycoprotein (MOG), a membrane protein expressed on oligodendrocyte cell surfaces and on the outermost surface of myelin sheaths. Due to the particular location, MOG acts as a good antigen candidate for autoimmune demyelination. One patient initially presented with anti-MOG antibody syndrome with a prodrome of fever followed by a progressive headache. Gradually he started having visual problems manifesting as diplopia and blurring of vision. Opthalmological evaluation showed optic neuritis. Meanwhile he developed generalised seizures, hemiparesis, ataxia and extreme lethargy. An MRI of the brain was suggestive of a demyelinating disorder. We initially diagnosed the case as acute disseminated encephalomyelitis (ADEM). A CSF study was nonspecific. We also sent the autoimmune panel which was aquaporin 4 negative and anti-MOG antibody positive. Treatment was given with IVMP and IVIG as initial immunotherapy followed by oral steroids. The child relapsed. Our case has similarity with reported cases. The clinical features found in anti-MOG antibody syndrome are myelitis (48%), optic neuritis (42%), area postrema syndrome (10%), brainstem/diencephalic/cerebral symptoms (14%), and simultaneous optic neuritis and myelitis (4%) [25, 26, 27, 28]. In our case CSF was nonspecific, although some studies reported pleocytosis [29]. Furthermore, it has been mentioned in the literature that infratentorial lesions in the brainstem and cerebellum are quite common in anti-MOG antibody syndrome. We also found infratentorial lesions but only in this case. Although this case did not have any spinal lesions, reported cases mentioned that two-thirds of the patients had spinal cord involvement, of which the majority were longitudinally extensive lesions [30]. There is no current consensus regarding the treatment. We treated the patient in view of the published

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cases. Most of the authorities suggested acute immunotherapy with IVMP and IVIG followed by oral steroids for prevention of relapse. In the case of relapse, repeated treatment with acute immunotherapy is suggested [31].

Recovery from AIE encephalitis usually occurs as a multistage process that happens in the reverse order of symptom presentation [22]. About 75% of patients with anti-NMDAR encephalitis recover or have mild sequelae; all other patients remain severely disabled or die [14]. Spontaneous neurological improvement has been reported, but usually occurs at the expense of a longer hospital stay and slower recoveries [32]. During the follow-up, only 21.42% of patients with anti-NMDAR encephalitis showed complete recovery. The rest all had certain complications, but none died or deteriorated after treatment initiation. The most common sequelae we observed was epilepsy (42.84%). Other complications in this group were speech disorder, cognitive dysfunction, ataxia and behavioural disorder. The patient with anti-MOG antibody syndrome showed a marked recovery with minimal residual symptoms.

Conclusion

In this study, we described the clinical features of anti-NMDAR encephalitis and anti-MOG antibody syndrome with treatment protocol. Although it is a retrospective study, it may highlight the pattern of AIE in Bangladesh. However, further prospective studies with larger case numbers are suggested.

Abbreviations

anti-GAD:	anti Glutamic Acid Decarboxylase
AIE:	Autoimmune encephalitis
AMPAR:	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
CASPR2:	Contactin-associated protein-like 2
DPPX:	dipeptidyl-peptidase-like protein 6
GABAAR:	γ-aminobutyric acid A receptor
LGI1:	Leucine-rich glioma-inactivated 1
anti-MOG antibody:	anti-myelin oligodendrocyte glycoprotein antibody
NMDAR:	N-methyl-D-aspartate receptors

Competing interests

None.

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