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REVIEW ARTICLE

Anti-NMDA Receptor Encephalitis in Children: Report of Four Cases from Bahrain

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Abstract

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a newly described subtype of limbic encephalitis. This disease is probably the commonest autoimmune encephalitis predominantly affecting children and young adults. It has a higher incidence among young females. Patients manifest with a constellation of symptoms including psychosis, dyskinesia, and seizures. Antibodies against NR1/NR2 heteromers of the NMDAR glutamate receptor mediate this type of encephalitis. Patients with anti-NMDAR encephalitis might have underlying tumors, which are typically teratomas. Exploring for occult tumor and resection is crucial in management. First-tier immunotherapy include steroids, intravenous immunoglobulin and plasma exchange, while rituximab and cyclophosphamide are frequently used as second-tier immunotherapy. Around 80% of patients achieve almost complete recovery, however some patients suffer from cognitive deficits or death. Early diagnosis and prompt treatment can lead to better recovery and outcome. The unique feature of this disease reflects the intimate relationship between psychiatry and neurology. In this article, we describe the clinical phenotype and outcome of four affected children from Bahrain.

Keywords: Anti-NMDAR encephalitis, Limbic encephalitis, Epilepsy, Psychosis, Dyskinesia, Immunotherapy

Introduction

Anti- Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an immune mediated disease frequently overlooked owing to a lack of awareness. Dalmau was the first to describe twelve women with prominent psychotic symptoms, seizures, frequent dyskinesias, and decreased level of consciousness; with all harboring teratomas.[1] In 2007, the California encephalitis project study began identifying cases of anti-NMDAR encephalitis which were four folds more frequent than herpetic encephalitis.[2] The clinical manifestations of anti-NMDAR encephalitis are variable and profound. It can cause severe psychotic and neurologic deficits in a previously healthy child and should be included in the differential diagnosis of central nervous system vasculitis and other inflammatory brain diseases.[3] The hallmark of the disease is detection of anti-NMDAR antibodies in both serum and cerebrospinal fluid (CSF). The sensitivity of

anti-NMDAR antibody testing is higher in CSF compared to serum.[4] Most children respond to either first line immunotherapy (steroids, intravenous immunoglobulin, and plasmapheresis) or second line (rituximab).[5] The incidence of the disease is 1 patient per 1.5 million people per year; although a relatively rare disease,it is one of the commonest forms of autoimmune encephalitis.[2] Susceptiblity to the disease is irrespective of age however, young adult females between 25-35 years of age are most frequently affected.[2,6,7] Around 20% of the patients will develop focal neurological deficits or die; common reported sequelae involve defective attention, memory and executive functions.[5]

Case reports

The subjects of our study were four children diagnosed over five years in a single medical center. The demographics of our patents were as follows: three girls and one boy within the age range of five to thirteen years; the duration of admission lasting from one month up to six months. All subjects were followed up in the outpatient clinic until resolution of symptoms or as necessary. Cases showed features of encephalopathy and confusion. The three patients (cases 1,2 and 4) developed acute psychosis with severe agitation, irritability, bouts of rage, screaming, and shouting, associated with visual and auditory hallucinations. The visual hallucinations were described as well-formed objects such as: insects, monsters, fire flames etc. while the complex auditory hallucinations were described as hearing voices and scary sounds.

Interestingly case 1 presented with acute psychosis three weeks after her initial isolated cluster of generalized tonic clonic seizures which occurred over a day and was managed with phenytoin. She remained symptom free during this interval; until she presented with acute psychosis and irritability through the emergency department. Psychiatry consultation was sought initially, but with the background of recent seizures neurology consultation was therefore requested. At this time, she showed a clear encephalopathy picture with delirium and fluctuating bouts of aggression followed by periods of somnolence. Her electroencephalogram (EEG) was decisive in providing evidence of background slowing with more emphasis over left posterior temporal region. Eventually she drifted into status epilepticus both convulsive and non-convulsive seizures.

All patients developed a plethora of seizures. Two of them (case 1 and 3) were admitted to the pediatric intensive care unit to control their seizures and required intubation and anesthetic medications.

Seizures were polymorphic, mainly dozens of complex partial seizures in the form of unresponsiveness, starring and automatism; at times generalized tonic clonic seizures were noticed. In case 2, the parents did not notice clear epileptic events but during EEG, he developed dialeptic seizures with arrest of activity and hypermotor seizures, which was possibly overlooked by the guardian. This pattern of epileptiform activity was only noticed during that time when the EEG was taken.

Dyskinesia also was reported in all cases. Some of them subtle, orofacial dyskinesia or dystonic posturing of the extremities; except case 3 who developed severe hyperkinetic and ballistic movements associated with autonomic instability in the form of tachycardia, hyperthermia and perspiration requiring heavy sedation to control her dyskinesia.

Three cases described history of viral prodrome, with low-grade fever, coryza like symptoms at times, with vomiting few days prior to their presentation.

Investigations

Serial EEG studies were done and included long term monitoring. All showed slowing of background activity during the acute phase, with further focal slowing and epileptiform discharges over the temporal regions either unilateral or bilateral. Ictal events were recorded in three patients. Two of them were of temporal lobe onset alternating from right and left temporal regions except the boy, which lateralized to the right hemisphere.

Neuroimaging was done in all patients, in case 1 and 2 left mesial temporal signal intensity were seen (figure 1), extending to the left frontopolar region in case 4.

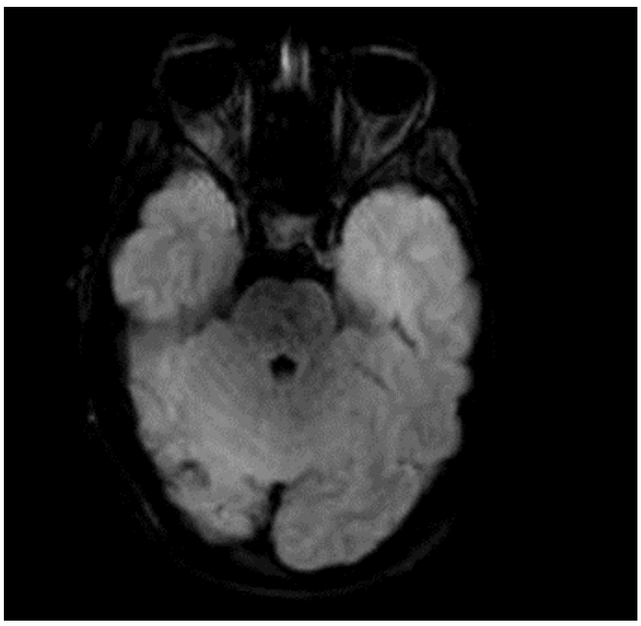

Figure 1: FLAIR MRI axial images depicting left anterior temporal high signal intensity from case 4.

Extensive laboratory tests were done, including blood and cerebrospinal fluid (CSF). CSF demonstrated lymphocytic pleocytosis in cases 3 and 4, with normal protein and sugar. Bacterial cultures and virology screens were all negative; anti- NMDA antibodies titer were elevated in all patients both in serum and CSF except case 2 which was negative in blood.

Treatment and outcome

The patients were managed initially with standard treatment of plausible viral encephalitis at the time of presentation. The treatment was adjusted according to CSF anti NMDA antibodies results; all received Methylprednisolone pulse therapy followed by tapering dose of oral Prednisolone followed by intravenous immunoglobulin (IVIg). Case 1 and 2 underwent plasma exchange for five session each. All eventually received Rituximab 375 mg/m^2 surface area in two doses, two weeks apart. Case 4 underwent resection of right ovarian cystic teratoma (dermoid cyst). Three patients did very well and fully recovered on follow up and anti-epileptic medications were discontinued. Case 1 who had protracted hospital course and very high titers of anti-NMDA antibodies also showed significant improvement. However, she had residual psychiatric and cognitive impairment although she has been integrated in regular school she has poor academic performance. She is currently receiving anxiolytic medication and oxcarbazepine. Her EEG still shows left temporal paroxysmal activity.

Clinical features and tests are summarized in table 1 and 2.

Table 1: Clinical manifestations

Patient number	Age at presentation (years)	Gender	Psychiatric symptoms	Seizures	Dyskinesia
1	10	Female	Severe psychosis, hallucinations	Convulsive, non-convulsive status epilepticus	Orofacial dyskinesia
2	5	Male	Confusion, fear	Hypermotor, dialeptic seizures	Limb dystonia
3	13	Female	Severe psychosis, hallucinations	Convulsive, non- convulsive status epilepticus	Severe dyskinesia, choreoathetosis
4	6	Female	Anxiety, fear	Complex partial seizures	Orofacial dyskinesia

Table 2: Diagnostic tests and outcome

Patient number	CSF (WBC/ protein)	MRI brain	EEG in acute phase	Treatment	Outcome	Teratoma
1	Nil Normal	Left temporal	Background slow activity, bilateral independent temporal sharp waves	corticosteroids, IVIg, plasma exchange, rituximab	Mild psychosis, cognitive impairment (7 years)	Nil
2	2 cells/µL Normal	Normal	Background slow activity, right hemispheric seizures	corticosteroids, IVIg, rituximab	Full recovery (2 years)	Nil
3	10 cells/µL Normal	Left temporal	Background slow activity, bilateral independent temporal sharp waves	corticosteroids, IVIg, rituximab	Full recovery (2 years)	Nil
4	212 cells/µL Normal	Left temporal	Background slow activity, left temporal sharp waves	Corticosteroids, IVIg, plasma exchange, rituximab	Full (2 recovery)	Right ovarian teratoma (10 cm size resected)

Discussion

Anti- NMDAR encephalitis is an autoimmune disease that was first described by Dalmau *et al* in 2007. It was regarded as the most common autoimmune encephalitis, ranking after pediatric acute demyelinating encephalomyelitis. The disease encompasses a wide range of clinical features, varying between neurological and psychiatric symptoms, all attaining variable degrees.[6]

Pathogenesis

Anti-NMDAR encephalitis is a neuroinflammatory disorder that is charactarized by the presence of IgG autoantibodies against the GluN1 subunit of the NMDAR. The disease is stratified into two stages, the first stage consists of psychiatric symptoms such as delusions, hallucinations, agitation, insomnia, accompanied by seizures and dysautonomia, this stage lasts up to 3 months. The following second stage which corresponds to around 6 months or longer is a stage of recovery. In both stages, the aforementioned antibodies can be detected in the CSF and tend to progressively decrease in titer.[7] According to a study done by Yang Sai *et al*, it was concluded that Herpes Simplex Virus (HSV) infection served as a potential trigger for children older than 6 years of age, findings of CSF autoantibodies against the NMDAR 4 weeks following HSV infection confirmed the association. Another confirmed trigger of the disease, observed in an older age group were tumors (mostly ovarian teratomas).[1] The role anti-NMDAR antibodies in the pathogenesis of the disease has been established in both vivo and vitro models, the crosslinking of the antibodies and the NMDARs results in an alteration of their surface dynamics, internalization ultimately instead of apoptosis leading to impairment of synaptic plasticity and NMDAR function and quantity.[8] It was hypothesized that the NMDAR expressed in the nervous tissue contained within the teratoma is transported to a regional lymph node where they are exposed and presented to the immune system.[8] Naïve B cells with the cooperation of CD4 T cells differentiate into antigen experienced cells that cross the blood brain barrier where they undergo restimulation, maturation into antibody producing plasma cells and eventually clonal expansion and NMDAR antibody generation. The other less frequent trigger of autoimmune encephalitis caused by HSV, share a similar pathological process of antibody production, whereby the triggering mechanism is initiated by the virus providing a milieu of neuronal degeneration and extensive inflammatory infiltrates that lead to antigen presentation in the deep cervical lymph nodes. The antibodies remain at detectable

quantities as long as the patient suffers active disease or substantial neurological deficits, in some patients, antibodies may remain detectable at lower titers months or years after recovery.[9]

Clinical manifestations

The disease has posed great challenge to both neurologists and psychiatrists due to the nonspecific symptoms the disease entitles. In pediatric patients' neurological symptoms are the first to arise, such as seizures, considered as a core manifestation of this autoimmune encephalitis, the types of seizures are variable and include generalized tonic clonic seizures, focal seizures, persistent state of epilepsy, persistent state of refractory. They have been shown to be more common in females than males, prior to the onset of puberty, after puberty the ratio is reversed. Reason is ascribed to the changes in sex hormone levels.[10] A study concluded that although patients may suffer epileptic symptoms, one can be patient with giving a final diagnosis of epilepsy.[9] Motor dysfunction such as athetosis, ballismus, orofacial dyskinesia, opisthotonos, with predominance of cerebellar ataxia and hemiparesis in children; the presence of movement disorders is an indication that the disease has progressed to a more advanced stage. Behavioral and psychiatric symptoms occurred in younger females such as irritability, agitation, aggression, hallucinations. These symptoms can be more pronounced in children and it is attributed to the stronger impact the disease has on the underdeveloped nervous system. Autonomic dysfunction, hyperthermia, hypertension, hypotension, cardiac conduction defects and urinary incontinence are common manifestations in the pediatric age group with unique to anti-NMDAR encephalitis, in contrary to viral encephalitis.[11] Collectively these manifestations can be preceded by nonspecific prodromal symptoms such as fever, cough and vomiting.[11]

Diagnosis and investigation

Graus *et al* proposed a diagnostic criterion for anti NMDAR encephalitis.[7] At least four of the following six groups of symptoms occurring within 3 months; cognitive dysfunction, speech dysfunction, behavioral abnormality, seizures, motor dysfunction, decreased level of consciousness, autonomic dysfunction, cases with 2 of the aforementioned plus teratoma and at least one of the following findings: CSF abnormality (oligoclonal bands, pleocytosis), EEG remarkable for diffuse slowing or disorganized activity, extreme delta brush activity, exclusion of other disorders.

The definitive diagnostic method of anti NMDAR encephalitis is the detection of antibodies against the NMDAR GluN1 subunit in the CSF. Other diagnostics such as EEG were remarkable for extreme delta brush border in a retrospective study done by Yang Sai *et al*.[6] Radiological investigations such as magnetic resonance imaging (MRI) can detect abnormal findings in the temporal lobe, cerebral cortex and subcortical white matter regions.[6]

Treatment

First line therapy consists of Methylprednisolone shock treatment and high dose intravenous immunoglobulin. Treatment failure warrants the advent of second line treatment.[6] Rituximab, the CD20 monoclonal antibody, causing effect by diminishing the B cells and preventing them from entering the CNS, in addition to plasma replacement or cyclophosphamide treatment which permeates the blood brain barrier and increases the production of anti-inflammatory markers;[6] tumor resection is carried out if indicated.[1] This approach is based on a study conducted by Maarten J et al, which included 472 patients, among the 221 (47%) patients who did not improve with first line treatment , second line treatment proved to be beneficial.[12] Till to date, there are no studies that compare first line therapies with upfront use of Rituximab.[7] Supportive treatment is also implicated when necessary such as antiepileptics and antipsychotics, also respiratory and cardiac support.

Outcome and prognosis

Referring to Dalmaus original case series, almost seventy five percent of patients with anti-NMDA R antibodies recover fully ore with mild sequelae.[7] In the retrospective study conducted by Yang Sai *et al* in twenty-one patients twelve cases achieved full recovery, five had mild disability and two with moderate or severe disability. The fully recovered patients had varying lengths of recovery time

ranging between 3-12 months. The rate of recovery also differed, it was observed that patients 6 years old and younger recovered at a much faster rate than patients 6 years old and higher.[6]

Conclusion

This is the first case series from Bahrain to focus on description of anti-NMDAR encephalitis in pediatric age group. The clinical presentations were profound but potentially reversible with prompt treatment. The outcome of our patients parallels the reports from literature.

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