Clinical Profile and Neuropsychiatric Outcome in Children with Anti-NMDAR Encephalitis

Six children with anti-NMDAR encephalitis were followed-up for 6 to 24 months. They presented with seizures, neuropsychiatric symptoms and movement disorder, particularly orofacial dyskinesia and choreoathetosis. Immunosuppressive therapy resulted in varying degrees of improvement; none relapsed. Expressive aphasia was the last symptom to regress.

Keywords: *Aphasia, Autoimmune encephalitis, Corticosteroids, Treatment*.

Anti-N-methyl, D-aspartate receptor (Anti-NMDAR) encephalitis is increasingly being reported among children. It is diagnosed by the presence of antibodies in cerebrospinal fluid (CSF) [1]. Clinical criteria for early recognition include subacute onset of memory deficits, altered mental status and psychiatric symptoms, besides seizures and focal neurological deficits [2]. Appropriate treatment results in a favourable long-term outcome. We describe the presentation, response to treatment and outcome of six children with anti-NMDAR encephalitis.

These patients reported to us over a period of 3 years (2014-17). Clinical features at presentation and follow-up were recorded. Diagnosis was based on positive CSF anti-NMDAR antibody (indirect immunofluorescence on transfected cells). Treatment of all 6 patients was initiated with methylprednisolone (30 mg/kg, 5 pulses), followed by intravenous Immunoglobulin (2 g/kg). Rituximab (375 mg/m^2, 4 weekly doses) was administered to three children, and plasmapheresis was performed for one patient. Long-term immunosuppression was initiated with Prednisolone and continued with Azathioprine. Screening for teratoma was done by ultrasonography. Neuropsychiatric outcome was monitored with the Liverpool outcome score [3]. Follow-up period ranged from 6 to 24 months.

The age of patients ranged from 2- to 11-years; five out of six patients were girls. Three children had prodromal symptoms (fever, headache and vomiting). All patients presented with seizures and abnormal behaviour. CSF had lymphocytic pleocytosis with normal protein and sugar, and was positive for anti-NMDAR antibody in all patients. EEG and MRI brain did not reveal any specific diagnostic changes. No patient required mechanical ventilation or inotropes. The mean time to improvement was 5 weeks. No patient relapsed during the follow-up period. Expressive aphasia was the last symptom to regress. Two children managed to return to school. There was no mortality. Clinical features and outcome are detailed in the ***Table* I**.

Anti-NMDAR encephalitis was first described in 2007 [1]. A position paper on Autoimmune encephalitis outlines criteria that permit early diagnosis on clinical grounds, given that accurate pathological diagnosis may not be possible in resource-constrained settings [2]. Behavioral abnormality, movement disorders, focal neurological deficits and autonomic disturbances have been described [1,4-8]. In this case series, orofacial dyskinesia and choreoathetosis were diagnostic pointers; life-threatening autonomic disturbances, commonly seen in adults, did not occur. Several options of immunotherapy for this condition have been recommended with varying results [4,5]. This case series is too small to provide a recommendation for optimum treatment.

Armangue, *et al*. [8], in a series of 20 children, reported a long-term outcome of substantial recovery in 17%, moderate to severe disability in two children, and one death. The median time to improvement was 11.5 days. The last symptoms to improve were related to executive functions. A recent study of Indian children suggests that prepubertal disease is more severe with poor cognitive outcome and persistent psychiatric symptoms [9]. We observed residual behavioral abnormalities, including temper tantrums, emotional lability and insomnia. Reading, writing, memory and speech were affected, which improved over time.

Improved awareness among pediatricians will prompt early recognition and treatment of this devastating disease. Prolonged follow-up for cognitive and psychiatric sequelae is warranted.

Contributors: VMA: clinical management and data collection, study concept and design, and drafted the manuscript; JM: clinical management and follow-up, data collection, concept and design of the study, and drafting and revising the manuscript; PK: clinical management of the cases, concept and design of the study, and critical revision of the manuscript. All authors approved the final version.
Funding: None; *Competing interest*: None stated.

TABLE I CLINICAL FEATURES, TREATMENT AND OUTCOME OF SIX CHILDREN WITH ANTI-NMDAR ENCEPHALITIS

Case No.	*Age*	*Clinical features**			*Treatment in the acute phase*	*Follow-up (months)*	*Sequelae*	*Liverpool outcome score#*
		Neuropsychiatric symptoms	*Movement disorder*	*Autonomic dysfunction*				
1	7 y	Hallucinations, abnormal behaviour, emotional lability, mutism	Choreoathetosis, dystonia, orofacial dyskinesias, ophisthotonus	Sleep disturbance, enuresis	MPS+IVIg+RTX	24	Mutism, Memory deficits	3
2	3 y	Abnormal behaviour, mutism	Orofacial movements	Sleep disturbance	MPS+IVIg	18	Regression of speech	3
3	11 y	Emotional lability, screaming spells, mutism, abnormal sensorium	Choreoathetosis, dystonia, catatonia, opisthotonus, orofacial dyskinesias	Insomnia, enuresis, tachycardia	MPS+IVIg+RTX+PLS	8	Mutism, aggressiveness, incontinence	2
4	23 m	Irritability, altered behaviour, mutism	Choreoathetosis, orofacial dyskinesias, dystonia, ophisthotonus	Sleep disturbances, enuresis	MPS+IVIg+RTX	6	Speech delay	2
5	6 y	Abnormal behaviour, mutism, weakness	Choreoathetosis, dystonia, orofacial dyskinesias	Sleep disturbances, enuresis	IVIg	6	Hemiparesis, mutism	3
6	7 y	Hallucinations, abnormal content of speech	Clonic twitching of extremity, orofacial dyskinesias	Insomnia	IVIg	6	Dysgraphia	4

*#Total score range 33-75, Final score range 1-5; 1 = Death, 2 = Severe sequelae, impairing function sufficient to make patient dependent, 3 = Moderate sequelae mildly affecting function, probably compatible with independent living, 4 = Minor sequelae with no effect, or only minor effects on physicial function, 5 = Full recovery; *Seizures were present in all patients; MPS: Methyl Prednisolone; IVIg: IV Immunoglobulin: RTX: Rituximab; PLS: Plasmapheresis.*

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Fecal Calprotectin as a Screening Marker for Inflammatory Bowel Disease

We compared fecal calprotectin and endoscopic findings of 53 children with possible inflammatory bowel disease and found an optimal cut-off of 68 µg/g in Receiver operative curve [AUC 0.88 (95% CI 0.79, 0.97)] to discriminate inflammatory bowel disease with other inflammatory gastrointestinal conditions.

Keywords: *Crohn's disease, Diagnosis, Ulcerative colitis*.

Diagnosis of Inflammatory bowel disease (IBD) is confirmed by clinical evaluation and a combination of endoscopic, radiological, histological investigations. Non-invasive biomarker such as fecal calprotectin, which is released during times of cell stress/damage, it is a highly sensitive marker of intestinal inflammation, and represents a novel and under-utilized modality to aid in diagnosis of IBD. Growing body of literature has identified fecal calprotectin (FCP) as a non-invasive predictive test with high sensitivity for inflammatory bowel disease.

This cross-sectional study was done over a period of one year in Apollo Children's Hospital, Chennai, a tertiary referral center in Southern India. Ethics approval was obtained from Institute Ethics Committee, and informed consent of participants was obtained. We tested 53 consecutive patients (mean (SD) age 9.7(4) years), who presented with inflammatory bowel disease symptoms as per European Crohn's and Colitis Organization guidelines [1,2]. The presenting complaints necessitating FCP testing and colonoscopy/endoscopy were: chronic abdominal pain (52, 98.1%), chronic diarrhea (51, 96.2%), mucoid stools (38, 71.7%), blood in stools (28, 52.8%), prolonged fever (6, 11.3%), pallor (9,17%), oral ulcers (4, 7.5%), glossitis (2, 3.8%) and angular cheilitis (2, 3.8%). Many patients presented with combination of symptoms mentioned above.

FCP using enzyme-linked immunosorbent assay by LIAISON Calprotectin Assay (negative <6.2 mg/kg) was performed at baseline for all enrolled patients along with radiological investigations as deemed appropriate. Colonoscopy along with endoscopy was performed on all patients the subsequent day before the results of the FCP were available and a final confirmation with tissue biopsy reports was done for diagnosis of inflammatory bowel disease.

Of the 53 children, 17% had biopsy-confirmed diagnosis of inflammatory bowel disease; eight (15.1%) had Crohn's disease and one (1.9%) had Ulcerative colitis. Receiver Operating Characteristics (ROC) curve revealed an optimal cut-off for FCP level of 68 mg/kg to discriminate between IBD and non-IBD causes of inflammation and this value had sensitivity of 100%, specificity of 70%, positive predictive value of 40%, negative predictive value of 100%, and likelihood ratio for a positive test of 3.4. The area under the curve of the ROC