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ORIGINAL ARTICLE

Early Diagnosis and Treatment of N-Methyl D-Aspartate Receptor Autoimmune Encephalitis in Children

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ABSTRACT

Background: Acute pediatric encephalitis is a debilitating neurological disorder that develops as a rapidly progressive encephalopathy (usually in less than 6 weeks) due to brain inflammation, autoimmune encephalitis (AE) is a heterogeneous group of recently identified disorders. Despite severe and even prolonged neurologic deficits, dramatic improvements may occur with proper immunotherapy in some patients with AE. Anti-neuronal antibodies have been discovered in cerebrospinal fluid (CSF) of patients,

Aim and Objectives: The current study aimed to test the relation of early diagnosis with the treatment of N-methyl D- Aspartate Receptor autoimmune encephalitis.

Methods: This is a Prospective observational cohort study that was carried out at the pediatric department, Faculty of Medicine, Zagazig University, the study was conducted on 36 cases.

Results*:* There was no statistically significant difference between the studied groups with and without autoimmune encephalitis regarding results of CSF analysis (a larger percentage without autoimmune encephalitis had abnormal CSF analysis). There is a statistically significant difference between the studied groups with and without autoimmune encephalitis regarding prognosis.

Conclusion: CSF NMDAR antibodies are highly sensitive biomarkers in the prediction of mortality and poor prognosis of encephalitis in children.

Keywords: CSF, Encephalitis, NMDAR, Autoimmune.

Conflict of Interest No financial disclosure

INTRODUCTION

Acute pediatric encephalitis is a debilitating neurological disorder that develops as a rapidly progressive encephalopathy (usually in less than 6 weeks) due to brain inflammation [**1].**It has a mortality rate of 3.5%, and about half of the surviving children do not recover fully**.** Over the last few years, an increasing number of non-infectious, mostly autoimmune, encephalitis cases have been identified, associated with antibodies targeting neuronal cell-surface antigens **[2].**Autoimmune encephalitis (AE) can affect patients at any age. In children, 46% of all cases with a probable diagnosis of AE were found to be mediated by autoantibodies, against NMDAR in 27% and VGKC-complex proteins in 17%. **[1].**The onset of autoimmune encephalitis is acute or subacute and most cases progress into a severe encephalopathy syndrome including altered mental status and a range of neurological and psychiatric symptoms **[3].** Some evidence described the pediatric presentation to be more 'neurological' than the more psychiatric presentation in adults, whereas other suggested neuropsychiatric presentation in 90% of children. However, in the acute phase, most patients progress towards a similar syndrome regardless of their age, including abnormal (psychiatric) behavioral and cognitive functions, seizures, movement disorder, reduced consciousness, speech disorder, autonomic dysfunction, hypoventilation, and memory deficit [**4].** Anti-NMDAR encephalitis is the most frequent type of AE. Anti-NMDAR encephalitis predominantly affects children under 18 years (around 40% of all cases). There is a female gender predominance of 4:1 which is less evident in children under 12 years **[1].**The diagnosis can be confirmed by the detection of IgG antibodies against the GluN1 (NR1) subunit of the NMDAR in the cerebrospinal fluid[**5].**Brain MRI is normal

in 66% of NMDAR encephalitis patients; the other 34% have nonspecific cortical or subcortical FLAIR/T2 abnormalities, sometimes involving posterior fossa or medial temporal regions, often with small areas of demyelination, and in a few cases with extensive demyelinating abnormalities**[6].**

METHODS

This Prospective observational cohort study was carried out at the pediatric department, Faculty of Medicine, Zagazig University during the period from January 2019 to June 2019. the study included 36 cases with encephalitis Patients admitted to the pediatric department, Faculty of Medicine, Zagazig University, but 2 cases were excluded from the study because they had contraindications to corticosteroids. Written informed consent was obtained from all childers' parents and the study was approved by the research ethics committee of the Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria: Patients under 18 years, male or female with a probable immune-mediated encephalopathy presented to PICU with encephalitis (depressed or altered level of consciousness lasting more than 24 hours, lethargy, or change in personality or behavior) with at least one of the following features: neuropsychiatric symptoms, seizures, movement disorder, or cognitive dysfunction,

Exclusion criteria: Patients with demyelinating disease, Presence of any other comorbidity except prematurity, - Patients with other neurological symptoms. The studied patients had treated by triple therapy and received corticosteroids. Then the all cases had been given corticosteroids (Methyl-prednisolone "Solu-Medrol" IV 30 mg/kg/day, Single dose for 5 days) and followed up for four months. **All patients were subjected to Personal history**: name, age, and gender. **Family history (**history of similar conditions).

History of the present illness Analysis of the complaint: Patient complaining of Fever (onset, duration, and grade), associated with seizures, cognitive symptoms (confusion or behavioral changes), or other abnormal movements.

Full Clinical examination: General examination of systems to discover predisposing factors and associated medical conditions, Complete clinical assessment of cases.

Laboratory investigation: CBC with differential count, CSF analysis.

-Brain MRI, Autoantibody testing of CSF for NMDAR antibodies.

Treatment: The patient was empirically treated for acute viral encephalitis with triple therapy for 3 weeks. The clonic movement was controlled by Diazepam. The corticosteroids were introduced from the 2nd day of admission (30mg/kg/ day) once daily IV for 5 days.

Between the 21st and 25th hospital day there was a significant improvement in the patient's condition and discharge on the 25th hospital day.Clinical follow-up after 4 months from discharge, the patient showed complete resolution of clinical symptoms.

Statistical Analysis: Data entry, processing, and statistical analysis were carried out using MedCalc ver. 18.2.1 (MedCalc, Ostend, Belgium). Tests of significance (Kruskal-Wallis, Wilcoxon's, Chi-square, logistic regression analysis, and Spearman's correlation) were used. Data were presented and suitable analysis was done according to the type of data (parametric and non-parametric) obtained for each variable. P-values less than 0.05 (5%) were considered to be statistically significant.

RESULTS

Table (1), showed that 67.6 % of patients were females. Their ages ranged from 4 to 16 years old with a mean age of 5.35 years. **Table (2),** showed that there was a statistically significant difference between the studied groups with and without autoimmune encephalitis regarding NMDAR antibodies in CSF. **Table (3),** showed that there was no significant relationship between the presence of autoimmune encephalitis and age or gender**,** no significant relationship between the presence of autoimmune encephalitis and any of the presenting symptoms, no statistically significant difference between the studied groups with and without autoimmune encephalitis regarding Glasgow coma scale (GCS)**. Table (4),** showed that there was no statistically significant difference between the studied groups with and without autoimmune encephalitis regarding results of MRI, there was no statistically significant difference between the studied groups with and without autoimmune encephalitis regarding White blood cells (WBCs), and results of White cell count (WCCs) in CSF, there was a statistically significant difference between the studied groups with and without autoimmune encephalitis regarding prognosis. **Table (5)** showed that there was no statistically significant difference between the studied groups with and without autoimmune encephalitis regarding clinical response to immunotherapy. **Table (6)** showed that the best cutoff of CSF NMDAR antibodies in the prediction of poor prognosis is ≥ 316.5 with the area under ROC curve 0.981, the sensitivity of 100%, specificity 88.9%, positive predictive value 66.7%,

negative predictive value 100%, positive likelihood ratio 9, negative predictive value 0 and accuracy of 90.9%. **Table (7)** showed that the best cutoff of CSF NMDAR antibodies in the prediction of mortality is ≥ 342.5 with the area under ROC curve 0.944, the sensitivity of 100%, specificity 83.3%, positive predictive value 37.5%, negative predictive value 100%, positive likelihood ratio 6, negative predictive value 0 and accuracy of 84.5%.

Figure (1) showed that about 76.4% of the studied patients had complete resolution of their symptoms after 4 months. Only four patients had permanent lesions, one had sensorineural hearing loss, two of them had a motor impairment and one had unsteady gaits. Also, one patient had died and by the end, three patients had been missed in follow-up.

Table (1): Distribution of the studied patients according to demographic characteristics and anthropometric measures:

	N=34		%
Gender**:** **Female** **Male**	 23 11		 67.6 32.3
	Mean ± SD	**Median**	**Range**
Age (years)	5.35 ± 4.92	3.5	4 – 16

Table (2): Comparison between the studied groups regarding NMDAR Antibody in CSF at time of admission

NMDAR antibody	N = 34		Z	P
	Negative N (19) 55.8 %	**Positive N (15) 44.1%**		
Mean ± SD **Median** **Range**	69.76 ± 20.27 62 50 - 133	634.1 ± 104.96 412 179 – 1240	-5.057	< 0.001**

Z Mann Whitney test

Table (3): Comparison between the studied groups (with and without autoimmune encephalitis) regarding demographic characteristics, presenting symptoms, and Glasgow coma scale (GCS)

Presenting symptoms	Negative NMDAR **N (19)**	Positive NMDAR **N (15)**	X^2/Z	P
Gender: **Male** **Female**	 6 (31.5%) 13 (68.5%)	 5 (33.3%) 10 (66.6)	0.007	0.936
Age (years)**:** **Mean ± SD** **Range**	 4.2 ± 3.25 4 – 12	 6.78 ± 5.45 5 - 16	-1.719	0.086
Fever at onset: **No** **Yes**	 13 (68.4%) 6 (31.5%)	 7 (46.6%) 8 (53.3%)	Fisher	0.307
Grades of Fever**:** **No Fever** **Low grade** **High grade**	 2 (10.5%) 12 (63.1%) 5 (26.3%)	 0 (0%) 13 (86.6%) 2 (13.3%)	2.081	0.353
Neurological symptoms: **Seizures** **Confusion** **Abnormal movement** **Behavioral changes**	 14 (73.6%) 19 (100%) 8 (42.1%) 14 (73.6%)	 11 (73.3%) 13 (86.6%) 5 (33.3%) 15 (100%)	 Fisher Fisher 0.02 Fisher	 1 0.190 0.878 0.053

Presenting symptoms	Negative NMDAR	Positive NMDAR	X^2/Z	P
	N (19)	**N (15)**		
GCS **Mean ± SD** **Median**	 11 ± 2.65 10	 9.53 ± 3 9.5	-1.44	0.15

Table (4): Comparison between the studied groups with and without autoimmune encephalitis regarding results of MRI, laboratory parameters, and the fate of the studied patients

Variables	**Negative NMDAR**	**Positive NMDAR**	X^2	**P**
	N=19 (%)	**N=15 (%)**		
MRI: **Normal (21)** **Abnormal (13)**	 13 (68.4%) 6 (31.5%)	 8 (53.3%) 7 (46.6%)	1.496	0.221
	Mean ± SD (Median)	**Mean ± SD (Median)**	**T/Z**	P
WBCs **Lymphocytes** **Neutrophils**	15.14 ± 7 (16) 7.76 ± 2.73 (8) 6.39 ± 3.15 (5)	15.59 ± 3.17 (15) 9.09 ± 1.76 (9) 5.03 ± 1.74 (8)	-0.226 -1.766 -1.145	0.821 0.077 0.252
WCCs in CSF **Lymphocytes** **Neutrophils**	19.68 ± 19.73 (17) 12.13 ± 14.56 (5) 7.94 ± 9.57 (4)	33.53±35.84 (13) 23.21±25.95 (8) 10.92±13.63 (4)	-0.313 -0.977 -0.42	0.754 0.329 0.675
	N=18	**N=13**	X^2	**P**
Mortality: **No** **Yes**	 18 (100%) 0 (0)	 12 (92.3%) 1 (7.69%)	Fisher	0.067
Prognosis: **Poor** **Good**	 0 (0) 18 (100%)	 5 (38.4%) 8 (61.6%)	Fisher	0.003*

Z: Mann Whitney test T: independent sample t-test

Table (5): Comparison between the studied groups with and without autoimmune encephalitis regarding clinical response to immunotherapy.

Variables	Negative	Positive	X^2	P
	N = 19 (%)	**N = 15 (%)**		
Response: **Bad** **Good**	 7 (36.8%) 12 (63.1%)	 3 (20%) 12 (80%)	Fisher	0.195

Table (6): Performance of NMDAR antibodies in CSF in the prediction of poor prognosis (death and residual impairment) among the studied patients

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	+LR	-LR	Accuracy	P
≥ 316.5	**0.981**	**100**	**88.9**	**66.7**	**100**	**9**	**0**	**90.9**	**<0.001****

Table (7): Performance of NMDAR antibodies in CSF in the prediction of mortality among the studied patients

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	+LR	-LR	Accuracy	P
≥342.5	**0.944**	**100**	**83.3**	**37.5**	**95.5**	**6**	**0**	**84.5**	**0.012***

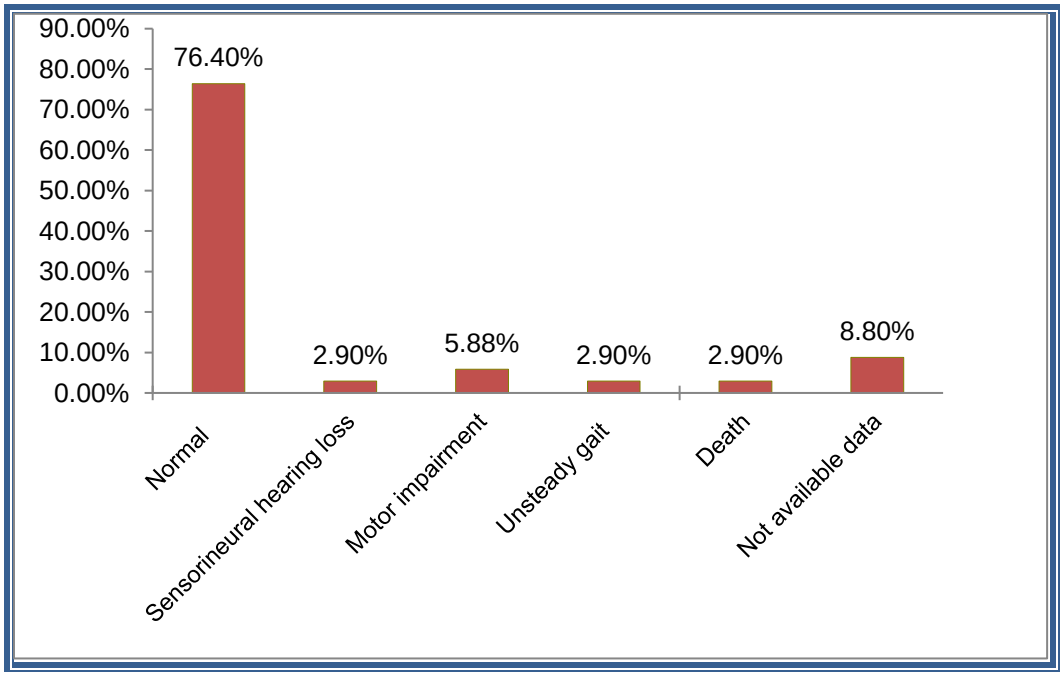

Figure (1): Simple bar chart showing the distribution of the studied patients according to the fate of the patient after 4 months.

DISCUSSION

Encephalitis is an inflammation of the brain. There are many causes of encephalitis, of which autoimmune encephalitis is one. Autoimmune encephalitis may be best conceptualized as an umbrella term that includes several disease types. These subgroups are based on whether the presenting autoantibody is targeting the cell surface proteins, intra- cellular synaptic proteins, intracellular antigens, or is linked to a known paraneoplastic process **[7].**

Autoimmune encephalitis is a broad diagnostic category that describes the subacute onset of neuropsychiatric symptoms whose etiology is linked with the clinical sequelae of the inflammatory response. The production of antibodies within the central nervous system or the periphery may be the result of molecular mimicry after an infectious process, systemic autoimmune disease(s), neoplasms, and/or paraneoplastic processes. Although the categorization of these antibodies is an ongoing effort, so too is the work of providing a meaningful nomenclature across the fields of psychiatry, neurology, rheumatology, and immunology **[8].**

Anti-NMDA Receptor Encephalitis has become a leading cause of autoimmune encephalitis in children, with 40% of patients being younger than age 18 years**. [9].**

The diagnosis can be confirmed by the detection of IgG antibodies against the GluN1 (NR1) subunit of the NMDAR in the cerebrospinal fluid**[5].**

Regarding the age of our studied patients presenting clinically with anti-NMDAR autoimmune encephalitis, the mean was 6.78 ± 5.45 and ranged from 5 to 16 years, which is in agreement with the study of **Hacohen et al. [10]** who found that the mean age at onset was 9.6 years (range 1.83–17).

Regarding the gender of our studied patients presenting clinically with encephalitis; 66.6 % of them were females and 33.3% were males. This agrees with the study of **Huang et al. [11]** who found that as for the anti-NMDA receptor antibody encephalitis specifically, it is documented to be more prevalent in females, and also the study of **Kim et al. [12]** who found that 75% were female and 80% of autoimmune disease occurs in females, females have stronger innate and adaptive immune responses than males. This results in faster clearance of pathogens and greater vaccine efficacy in females than in males but also contributes to their increased susceptibility to inflammatory and autoimmune diseases**.**

In the present study, 100 % of studied patients had a negative family history of autoimmune encephalitis. In disagreement with our study **Sartori et al., [13]** showed that only 19% of children with anti-*N*-methyl-d-aspartate receptor (NMDAR) encephalitis had a positive family history of autoimmune encephalitis or immune-mediated disease. The mechanism of autoimmune encephalitis associated with autoimmune disease is not yet fully understood. It may be due to a common immunological mechanism with genetic or environmental factors affecting the susceptibility of individuals.

In the present study, about 44.1 % of the studied

patients had NMDAR autoimmune encephalitis (had CSF NDMAR antibodies ≥ 160 picogram/ml). This came in agreement with a study done by **Gable et al., [14]** in The California Encephalitis project in which 20 patients were tested; they identified 10 as anti-NMDAR positive. i.e., 50%. Another 10 patients had viral encephalitis.

Moving to the clinical findings of our studied patients; 33.3 % of our positive anti-NMDA receptor antibody patients presented with abnormal movements either on presentation or during admission. This came in agreement with **Kaneko et al., [15]** who found that abnormal movements are one of the main presenting symptoms of anti-NMDA receptor antibody encephalitis.

In our study of patients with positive anti-NMDA receptor antibodies, 73.3% of patients had seizures, 86.6 % had confusion, 100% had behavioral changes and 53.3% had fever at presentation. They required mechanical ventilation for longer periods. The main cause for ICU admission was due to uncontrolled convulsions or disturbed consciousness levels. Also, 38.4 % of positive anti-NMDA receptor antibodies had poor prognosis and while in negative cases, none had poor prognosis and no mortality was detected, which is in agreement with the study of **Gressa-Arribas et al., [16]** who documented that the presence of anti-NMDA receptor antibody in the sera of patients with encephalitis carries a worse prognosis**.** Also, the study of **Hacohen et al. [10]** found that 77% of patients with positive anti-NMDA receptor antibody had seizures, 54% had movement disorders, 30% had fever at presentation.

In the present study, there was a statistically significant difference between the studied groups with and without autoimmune encephalitis regarding NMDAR antibodies in CSF. The mean NMDAR antibodies in CSF in the positive group was 634.1 ± 104.96 and in the negative group was 69.76 ± 20.27.

Greta-Arribas et al. [16] found that antibody testing is more sensitive in the CSF than in the serum, with up to 7% of patients demonstrating positive CSF titers with concurrent negative serum titers. The CSF antibody titers correlate strongly with the clinical disease course and remain elevated in those who experience a relapse or do not show primary clinical improvement.

In disagreement with our study, **Kaneko et al. (2016) [15]** in their work discussing the 5 cases with anti-NMDA receptor antibody encephalitis; found that all their patients recovered with no long-term sequel. This might return to the fact that all their patients were given immune-modulating treatment as steroids or immunoglobulins.

This difference in several deaths can be explained by the study of **Wandinger et al., 2011) [17]** who found that the prognosis of patients depends on early diagnosis, implementation of appropriate immunomodulatory therapy, and, in paraneoplastic cases, complete tumor removal (**.**

In the present study, 80% of positive anti-NMDA receptor antibody encephalitis had a good response to immunotherapy. This came in agreement with **Wandinger et al. [17]** who found that immune-mediated pathogenesis of anti-NMDA-receptor encephalitis is likely because patients frequently improve with immunotherapeutic treatment. Also, in agreement with the study of **Hacohen et al. [10]** who found that 90%, 73% respectively of positive anti-NMDA receptor antibody encephalitis had a good response to immunotherapy.

In the present study, Brain MRI was done on all our patients and it came back normal except for only 13 (38.2%) patients who had MRI abnormalities. This agrees with the study done by **Florance et al. [18]** which showed that 31% have abnormal MRI while 69% have normal MRI brain.

Conclusion: CSF NMDAR antibodies are a highly sensitive biomarker in the prediction of mortality and poor prognosis of encephalitis in children.

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