Seroprevalence of Anti- N-methyl-D-aspartate receptor antibodies in children with seizures of unknown cause

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Introduction

- Epilepsy type of unknown cause is presumed to be due to an underlying cause not diagnosed yet.[1,2]
- Specific antibodies associated with seizures might be a cause and can be presented with signs and symptoms of encephalitis or presented primarily as recurrent seizures without features of encephalitis.[3,4]
- N-methyl-D-aspartate receptor (NMDAR) is a neuronal surface antibody and one common type implicated in disorders like epilepsy.[5] It is a primary excitatory neurotransmitter.
- Testing anti-NMDAR antibodies in children with seizure of unexplained cause might be a significant approach to identify the spectrum of this antibody-associated clinical disorders and to treat the disease early and extensively because of the intimidating course of the disorder and the recurrent relapses.
- In the human brain, NMDAR is a ligand of glutamate, the primary excitatory neurotransmitter. Its major function is in synaptic plasticity, substantial for memory function and excitotoxicity that is implicated in a number of diseases like epilepsy and Alzheimer's. It is detected all around the central nervous system (CNS), in approximately 80% of cortical neurons

Objective

The aim of this study was to determine the prevalence of anti-NMDAR antibodies in a group of patients presenting with seizures of unknown cause in comparison to corresponding healthy volunteers.

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Patients and methods

- A case – control study was conducted in two hospitals of Medical City Complex, Baghdad, in the period from February to October, 2019.
- Eighty children were enrolled in the study and divided into two groups: study group and control group with forty children in each.
- The inclusion criteria were: 1) Age ranged 2 - 18 years; 2) History of seizures, first or recurrent attacks with or without anti-seizure drugs and within the preceding 6 months.
- The exclusion criteria were: 1) children who had additional features like psychiatric or encephalopathic signs and symptoms like behavioral changes, disturbed level of consciousness, or movement disorders; 2) evidence of provoked seizures (structural, tumor, infection, metabolic or electrolyte disturbance, or fever (≥ 38 °C)); 3) well established electro-clinical epileptic syndrome; 4) personal or family history of autoimmune disorders or epilepsy; and 5) patients with pre-existing developmental, motor or psychiatric problems.
- The following were performed in the study group: a full history, complete physical and neurological examination; brain MRI (those with normal or non-specified signal changes were included); EEG (those with epileptic or normal findings, were included); and testing antibodies directed against NMDAR with enzyme linked immunoassay (ELISA) (a value equal or more than 2.1 were considered positive).
- Seizure type at presentation was classified into focal, generalized and unknown onset according to the latest ILAE report.
- The control group is consisted of hospitalized age- and sex-matched patients who had serum collected as part of their routine investigations for non-neurological disorders.

Reference

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Results

Table I. Variable characteristics of the study group stratified by anti-NMDAR antibody status.

Variable		Anti-NMDA +ve No. (%)	Anti-NMDA –ve No. (%)	p value
Age (years) Range Mean ± SD		3-12 7.1 ± 3.7	2-14 6.6 ± 3.3	0.76
Duration since seizure onset (months) Range Mean ± SD		0.25-2 0.95 ± 0.7	0.25-10 2.2 ± 2.5	0.3
Type of seizure	Focal	4 (80)	10 (29)	0.024
	Generalized	1 (20)	25 (71)	
Treatment with anti-seizure drugs	Treated	4 (80)	20 (57)	0.6
	Not treated	1 (20)	15 (43)	

Table II. Demographic and clinical characteristics of patients with positive anti-NMDAR antibodies.

Patient	Age (years)	Gender	Time of sampling since onset of seizure	Type of seizure	Type of epilepsy	MRI* & EEG^	ASD@	Follow up
1	5.5	Female	2 months	Focal to bilateral tonic-clonic	Focal	Normal	Levetiracetam 20mg/kg/day	Seizure free / On treatment
2	12	Female	1 month	Focal	Focal	Normal	Oxcarbazepine 15mg/kg/day	Lost contact
3	10	Female	2 weeks	Focal tonic	Focal	Normal	Carbamazepine 10mg/kg/day	Lost contact #
4	3	Male	2 days	Attack of Generalized tonic seizure	Non applicable	Normal	None	Seizure free / No treatment
5	5	Female	1 month	Focal	Focal	Normal	Levetiracetam 20mg/kg/day	Seizure free / No treatment

* Magnetic resonance imaging
^ Electroencephalography
@ Anti-seizure drugs
# Last contact was before 4 months during that time she was free of seizure and discontinued her treatment

Discussion, Conclusions and recommendations

❖ In the current study, the prevalence of anti-NMDA antibodies in patients with seizures of unknown causes was found to be 12.5%, which showed significant statistical feature (OR=12.5), yet it cannot be applied to the general population as the CI was 0.6 – 216.7, which may be related to the small size of the sample and we might have obtained different percentage if both CSF and serum were tested for anti-NMDAR antibodies.

❖ The demographic characteristics of children with positive anti-NMDAR antibodies was reported as the following (table II):

1. Female gender predominated (with a female:male ration = 4:1), which may be related to the fact that the risk of autoimmune diseases increases in female.
2. A significant statistical differences was reported between positive and negative patients in regard of the mean duration since the first seizure onset and timing of the samples.
3. A relative difference was found in regard of the mean age at first seizure presentation in the positive patients, between the current study and two other studies. [5,6]
4. The predominance of the focal seizures, which might be related to the inflammatory nature of this disorder affecting certain areas in the brain more than others.

❖ We were unable to reach a strong conclusion, in regard of measuring a cause– effect relationship. That necessitates a cohort study that includes longer follow up.

❖ There is a need for larger prospective analysis of paired serum and CSF anti-NMDAR antibody titer in children with isolated seizures of unknown cause to optimize the laboratory diagnostic sensitivity and characterize the true prevalence of these antibodies among those patients.

❖ It is recommended to consider and screen for autoimmune etiologies of epilepsy, particularly in epidemiologically typical circumstances.