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Relationship between Serum IgA concentration and epileptic seizures in children: A prospective study

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ABSTRACT

Purpose. This study investigated the relationship between serum immunoglobulin A (IgA) concentration and epileptic seizures in children.

Methods. Pediatric patients with epilepsy were included in this cross-sectional investigation. Serum IgA levels were analyzed using a biochemical analyzer during admission for initial diagnosis before any medical treatment was administered.

Results. Among the 94 patients, 19.1% had decreased serum IgA levels, with a median value of 0.57 g/L. No significant relationship existed between serum IgA concentration and gender, age, epilepsy type, seizure duration or epilepsy waves. Children with low IgA levels experienced more spastic episodes and had a higher seizure frequency compared to those without decreased IgA levels. Changes in serum IgA levels were significantly associated with seizure frequency after three months of treatment. Initially, the occurrence of seizures in the low IgA group was 10.5 times lower than in the non-low IgA group, but, after three months, the low IgA group had a significantly higher seizure rate (72.2%) compared to the non-low IgA group (19.7%). After six months, the low IgA group had a higher proportion of children without seizures (100% versus 84.8%), although the difference was not statistically significant.

Conclusion. Serum IgA concentration plays a crucial role in diagnosing and predicting outcomes for pediatric epilepsy.

Keywords: IgA level, pediatric, epilepsy, seizure

INTRODUCTION

The connection between epilepsy and the immune system has been researched extensively. The onset of seizures may occur before or after immune activation. The degree of involvement by innate and acquired immunity varies depending on the situation. Through persistent research, promising management and therapeutic options have emerged for many seizure patients. These alternatives involve utilizing drugs and non-traditional methods with anti-inflammatory or immunomodulatory characteristics. Although recent findings have shed light on the relationship between immunity and seizures, there is a lack of data regarding children and their practical implications [1].

Since the 1970s, there have been reports of alterations in serum immunoglobulin levels among individuals diagnosed with epilepsy. Among these changes, a deficiency in serum IgA has been frequently documented. The alteration of IgA levels has been observed primarily during the administration of phenytoin and carbamazepine as part of treatment for epilepsy [2,3].

The occurrence of epilepsy in some individuals may be linked to primary IgA deficiency, which is the most prevalent immune defect in humans. Most individuals with this deficiency do not experience

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any major health problems, but those with selective IgA deficiency may have a higher risk of upper respiratory tract infections. In addition, seizures could happen to patients who have ataxia telangiectasia, and they may also have a deficiency in IgA (and sometimes IgG). Primary IgA deficiency is related to the haplotype HLA-A1-B8 and DR3, while drug-induced defects are associated with the haplotype HLA-A2 [4].

Subjects diagnosed with IgA deficiency have a more frequent occurrence of autoimmune disorders, including Graves disease, rheumatoid arthritis, myasthenia gravis, systemic lupus erythematosus, type I diabetes, and celiac disease. This susceptibility is possibly due to the reduced mucosal immunity, primarily in the gastrointestinal tract, causing inflammation and breakdown of the protective barrier function of mucous membranes when exposed to microorganisms and food particles [5].

The identification of an immunological foundation may open up novel approaches for managing refractory epilepsy [4]. According to observation, conventional therapy for epilepsy has several shortcomings in treating epileptic conditions. Despite notable progress in managing epileptic patients through the use of recently developed antiepileptic medications and surgical methods, there are still instances where treatment is ineffective. The administration of immunoglobulin, steroids, and a ketogenic diet may be attempted to enhance therapeutic outcomes. Immunoglobulin therapy has been found to have beneficial effects in patients with autoimmune-related epilepsy; however, its long-term effectiveness is limited. Steroids have demonstrated significant improvement in various epileptic syndromes. The ketogenic diet has emerged as one of the most dependable treatments for pediatric epilepsy. It is conceivable that a genetic susceptibility to IgA deficiency could exist independently of the genetic determinants implicated in epilepsy pathogenesis. IgA deficiency may manifest across various epilepsy subtypes, regardless of familial history. Several studies indicate that IgA deficiency presents in patients diagnosed with generalized cerebral seizures and occasionally in those with partial epilepsies [6-8].

PATIENTS AND METHODS

Under the auspices of the Hue Center Hospital's Ethics Committee, a prospective study was conducted on pediatric patients with epilepsy who had been admitted to the Neurological Department between January 2020 and July 2022. The patient's parents provided informed consent for participation in the study. A complete medical history was obtained as per protocol and recorded in the clinical research database.

In accordance with the International League Against Epilepsy (ILAE) guidelines of 2010, all participants enrolled in this study underwent thorough examination and diagnosis for the epilepsy cohort. Alongside this, maternal history, clinical symptoms, and treatment outcomes were meticulously recorded, encompassing preterm birth, obstetric trauma, and mental retardation. Additionally, severe comorbidities such as traumatic head injury, cerebral and meningeal hemorrhage, and neonatal sepsis were identified through diagnostic evaluation.

The study conducted serum IgA testing upon admission, after three months of treatment, and after six months of treatment. A quantity of two to three milliliters of serum or plasma containing heparin or EDTA underwent hemolysis, and its turbidity was measured through an AU680 biochemical analyzer.

The application of statistical techniques to manipulate data was carried out by utilizing the SPSS 20 software. The qualitative aspects, such as gender, maternal history, and clinical symptoms, were reported in terms of frequency and percentage. On the other hand, quantitative variables, including IgA and seizure duration, were presented through measures such as median, 25th percentile, 75th percentile, mean index, and standard deviation.

The study utilized the t-Student test to compare the mean values of two independent samples that were normally distributed, while the non-parametric Mann-Whitney Wilcoxon test was employed to compare the mean values of two independent samples that were not normally distributed.

To compare the mean between three or more groups, the one-way ANOVA test was employed for normally distributed samples. In contrast, the Kruskal-Wallis test was utilized for non-normally distributed samples.

This scientific article compares the difference in proportions by using χ^2 test scores when the sample size is greater than or equal to five. However, if over 20% of the cells in the crossover table have an expected frequency of less than five, then either Yates-corrected χ^2 test or Fisher's Exact test is used instead of the χ^2 test.

RESULTS

From January 2020 to July 2022, a total of 94 patients the Neurological Department at Hue Center Hospital were recruited (51.1% male and 48.9% female). The general characteristics of the study group of pediatric patients with epilepsy are shown in Table 1.

Table 2 displays the correlation between IgA concentration and related factors. The percentage of young children aged below five years with low IgA levels was the lowest at 12.3%. However, the percentage was higher for children between the ages of 5 to

TABLE 1. General characteristics of the study group of epilepsy children

Variables	N	%
Age group		
< 5 years	(n = 57)	60.6
5 - 10 years	(n = 30)	31.9
11 - 15 years	(n = 7)	7.4
Epilepsy type		
The generalized epilepsy	(n = 84)	89.4
The partial epilepsy	(n = 5)	5.3
The unknown type	(n = 5)	5.3
Seizure duration		
< 5 minutes	(n = 59)	62.8
5 - < 15 minutes	(n = 26)	27.7
15 - < 30 minutes	(n = 7)	7.4
≥ 30 minutes	(n = 2)	2.1
Epilepsy wave		
Yes	(n = 50)	53.2
No	(n = 44)	46.8

TABLE 2. The relationship between serum IgA levels and associated factors

Variables	Low IgA levels		Normal and high IgA levels		P
Age group					
< 5 years	(n = 7)	12.3	(n = 50)	87.7	p > 0.05
5 - 10 years	(n = 8)	26.7	(n = 22)	73.3	
11 - 15 years	(n = 3)	42.9	(n = 4)	57.1	
Epilepsy type					
The generalized epilepsy	(n = 16)	19.0	(n = 68)	81.0	p > 0.05
The partial epilepsy + the unknown type	(n = 2)	20.0	(n = 8)	80	
Seizure duration					
< 5 minutes	(n = 8)	13.6	(n = 51)	86.4	p > 0.05
5 - < 15 minutes	(n = 6)	23.1	(n = 20)	76.9	
15 - < 30 minutes	(n = 3)	42.9	(n = 4)	57.1	
≥ 30 minutes	(n = 1)	50.0	(n = 1)	50.0	
Epilepsy wave					
Yes	(n = 9)	18.0	(n = 41)	82.0	p > 0.05
No	(n = 9)	20.5	(n = 35)	79.5	

10 years and 11 to 15 years, at 26.7% and 42.9%, respectively. Among pediatric patients suffering from local and unknown seizures, the proportion of those with low IgA levels was higher at 20.0% compared to the generalized group, which accounted for 19.0%.

The study found that a large number of individuals in the group who experienced seizures lasting at least 15 minutes had low levels of serum IgA. It was also observed that the proportion of children with low serum IgA levels in the group without epileptic waves (20.5%) was higher than in the group with epileptic waves (18%). However, no significant correlation was observed between gender, age, epilepsy type, seizure duration, and epileptic waves with IgA concentration ($p > 0.05$).

The study observed a statistically significant change in serum IgA levels based on the frequency of seizures ($p < 0.05$). It was found that there is a connection between the frequency of seizures after three months of treatment and IgA levels ($p < 0.01$) (Table 3).

TABLE 3. The factors related to serum IgA levels

Factors	P
Seizure frequency	$p < 0.05$
Treatments after 3 months	$p < 0.01$

DISCUSSION

The study focused on 94 newly diagnosed pediatric patients aged between 1 month to 15 years old who had epilepsy. Results showed that 19.1% of the patients had low IgA concentration, while 80.9% had normal and high levels. The median serum IgA test value was 0.57 (with a range of 0.32 – 1.21) g/L, with the highest value at 4.16 g/L and the lowest at 0.14 g/L. These findings were similar to another study conducted by Seager J. et al. in 1975, where they found that 16% of epileptic children starting antiepileptic drug treatment had low initial serum IgA levels [9].

Kumar S. (2013) conducted a study which revealed that IgA concentrations were lower in individuals with epilepsy compared to the reference population, with a mean value of 2 ± 1.1 g/L versus 2.8 ± 0.6 g/L. However, this difference was not statistically significant [10]. In a 2019 study by Elnady H. G. et al., 30 children with epilepsy and 20 children without epilepsy were examined. The study found that the average IgA level in the group of children with epilepsy was significantly lower than the reference group. Specifically, the mean IgA value for the epilepsy group was 0.798 ± 0.478 g/L, while the reference group had a mean IgA level of 1.22 ± 0.421 g/L, which was statistically significant ($p = 0.038$) [11]. In 1988, Eeg-Olofsson O. conducted a study on 24 patients with partial epilepsy and 30 of their first-generation relatives. The results showed that the average serum IgA levels in patients with epilepsy were lower than both their relatives and the general population. Specifically, the mean serum IgA concentration for epilepsy patients was 1.2 ± 0.7 g/L, compared to 1.8 ± 0.7 g/L and 1.8 ± 0.8 g/L for their relatives and the reference population, respectively. These differences were statistically significant, with p-value less than 0.01 [12].

Fontana A (1978) reported that some epileptic patients had low serum IgA levels without the use of hydantoins, while 20% to 25% of epileptic patients had low serum IgA levels associated with the use of hydantoins. In contrast, patients with epilepsy due to trauma, infection, or metabolic disturbances had

normal IgA levels irrespective of whether they received hydantoins treatment [3]. In a separate study by Ranua J. et al. in 2005, which involved 958 epilepsy patients, it was found that 8.2% of patients had low serum IgA levels compared to 1.9% in the control group. On the other hand, 89.2% of patients had normal serum IgA levels compared to 95.2% in the control group, and only 2.2% of patients had high serum IgA levels compared to 3.1% in the control group [13].

The findings showed a reduction in the levels of serum IgA in individuals with epilepsy, regardless of whether or not they were taking antiepileptic medication. However, the prevalence and average values of serum IgA differed among the studies due to varying testing methods, age groups studied, sample sizes, and differences in treatment approaches across the studies. Our study only included children who were recently diagnosed with epilepsy and had not received any antiepileptic medication. Additionally, the number of participants in our study was comparatively smaller than other studies, which could have resulted in variations in the study outcomes.

However, as per Callenbach et al.'s study conducted in 2003 on 282 pediatric patients, which involved measuring the levels of immunoglobulins (IgA, IgM, and IgG) before and after 9-12 months of treatment with antiepileptic medication, it was found that prior to beginning treatment, IgA levels in children were significantly higher (with a mean value of 1.08 [0.01 - 5.8] g/L) compared to healthy controls ($p < 0.001$) [14]. This variance could be attributed to differences in testing methods, sample sizes, and reference values used between the aforementioned study and ours.

Our study indicated that the percentage of children under five years old with decreased IgA levels was the least (12.3%). However, this rate increased in older age groups, with 26.7% in the group aged between 5 and 10 years and 42.9% in the age group of 11 to 15 years. Nonetheless, there were no statistically significant differences in serum IgA concentration changes across different age groups ($p > 0.05$).

Pediatric patients who experienced local and unknown seizures had a higher percentage of low IgA levels (20.0%) than those in the generalized seizure group (19.0%). However, there was no significant difference in IgA concentration based on seizure type ($p > 0.05$). A study by Ranua J. et al. conducted in 2005 on 958 epilepsy patients and 581 individuals in a control group reported that the proportion of patients with decreased IgA levels was higher in those with partial seizures (9.1%) compared to those with generalized seizures (3.3%) (RR = 4.7; CI = 2.6 – 8.9; $P < 0.0001$ and RR = 1.7; CI = 0.5 - 6.0; $P = 0.4$, respectively) [13]. As per our study, the percentage of patients with partial seizures who had decreased IgA levels was lower than that in the generalized seizure group. However, both rates were lower than those reported in the previous study since our research involved different study subjects and sample sizes compared to the author's study.

The prevalence of decreased serum IgA levels was higher in the group of patients who experienced seizures lasting 15 minutes or more (42.9% for the 15 - < 30 minutes group and 50.0% for the ≥30 minutes group) than in those with seizures that lasted less than 15 minutes (13.6% for the <5 minutes group and 23.1% for the 5 - <15 minutes group). Nonetheless, there was no significant difference in serum IgA concentration changes during the course of a seizure ($p > 0.05$).

Our study indicated that the percentage of children with reduced serum IgA levels was somewhat higher in the group without epileptic waves (20.5%) compared to those with epileptic waves (18.0%). However, the observed difference between these two groups was not statistically significant ($p > 0.05$).

Patients with epilepsy who had decreased serum IgA levels experienced spastic episodes more frequently than children with a high frequency of seizures (33.3% versus 11.5%). This difference was statistically significant ($p < 0.05$). Furthermore, the likelihood of having spastic episodes was 3.9 times higher in children with low serum IgA levels than those without low serum IgA levels.

The percentage of children experiencing seizures in the low serum IgA group was considerably higher than that in the non-low serum IgA group (72.2% versus 19.7%). This difference was statistically significant ($p < 0.01$). Additionally, children with decreased initial serum IgA levels had a seizure rate that was 10.5 times higher after three months of treatment compared to those without reduced serum IgA levels.

CONCLUSION

Serum IgA levels could be useful in diagnosing and predicting outcomes in children with epilepsy. Further studies are needed to outline the clinical relevance of altered immunity in children with epilepsy.

Competing interests:
The author declares that there is no conflict of interest.

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