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Apolipoprotein E serum levels in children with Guillain-Barre Syndrome in northwest of Iran

* Lida Saboktakin [1], Mohammad Barzegar [2], Ahad Ghazavi [3]

[1] M.D, Associate Professor of Pediatrics Endocrinology, Pediatrics Health Research Center, Department of Pediatrics, Tabriz University of Medical Sciences, Tabriz, Iran.

[2] M.D, Professor of Pediatrics Neurology, Pediatrics Health Research Center, Department of Pediatrics, Tabriz University of Medical Sciences, Tabriz, Iran.

[3] M.D, Associate Professor of Pediatrics Neurology, Neurophysiology Research Center, Urmia University of Medical Sciences, Urmia, Iran.

Abstract

Background: Guillain-Barre syndrome (GBS) is an acute immune-mediated disease that affects both adults and children. Many infectious and non-infectious conditions may trigger this disease. Apolipoprotein E (APOE) is a glycosylated protein that has a variety of lipid and non-lipid related functions. The present study aimed to evaluate the serum levels of APOE in children with GBS compared to healthy control subjects to evaluate the diagnostic and pathologic effects of APOE in GBS.

Methods: In a cross-sectional design, 124 participants were divided into the GBS group (n=61) and the control group (n=63). Blood sampling and measurement of APOE were done according to the manual of the Human APOE ELISA kit. Demographic variables and further data about GBS patients were collected from patients' medical records. Weight and height were measured using SECA scales. The analyses were performed using SPSS Statistics 21.0 software and appropriate analytical tests. P-values of <0.05 were considered statistically significant.

Results: Mean ±SD of APOE serum levels was 8.43±3.59 micrograms/ml in the GBS group and 35.28±11.18 micrograms/ml in the comparison group. The difference between the two groups was strongly significant (P<0.001). The mean level of protein in Cerebrospinal Fluid (CSF) in GBS patients was 184.36±19.09 mg/dl. There was not any significant difference in the demographic findings between the two groups.

Conclusion: Our study demonstrated that the serum levels of APOE in children with GBS are lower compared to healthy subjects.

Key Words: Acute flaccid paralysis, Apolipoprotein E (APOE), Auto-immunity, Guillain-Barre syndrome (GBS), Immune-mediated polyneuropathy, Neuropathy, pediatric, peripheral nervous system.

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Corresponding Author:

Lida Saboktakin, M.D, Associate Professor of Pediatrics Endocrinology, Pediatrics Health Research Center, Department of Pediatrics, Tabriz University of Medical Sciences, Tabriz, Iran. Email: lidasaboktakin343@gmail.com

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1- INTRODUCTION

Guillain-Barre syndrome (GBS) is an acute immune-mediated polyneuropathy of the human peripheral nervous system (PNS) occurring in both adults and children (1). It is considered as the leading cause of acute flaccid paralysis in children (2, 3). Its overall incidence is 1 to 2 per 100000 a year worldwide (4) and its prevalence among children is between 0.3 to 2 per 100,000 children a year (5).

This disease could be triggered by either infectious or non-infectious factors (6) and the body's immune response is the main cause of GBS (7). Many inflammatory and anti-inflammatory markers such as cytokines, C-reactive protein, albumin, and antioxidants are involved in the pathogenesis of GBS (8-12).

Apolipoprotein E (APOE) is a 34.2 KDa glycosylated protein, which has both lipid-related and non-lipid-related roles in human cellular homeostasis (13). It is also a useful component of the post-inflammatory process, as macrophages produce more APOE in peripheral nerve injuries (8, 13, 14).

Therefore, understanding the APOE's role in the progression and even prognosis of GBS may help to diagnose the disease at its earliest point and also achieve a more accurate prognosis. Many studies have assessed APOE's role in the progression and recovery of GBS (8, 10, 13, 15), but the difference in serum level of APOE between GBS patients and the normal population has not been widely studied.

The present study aimed to compare the serum level of APOE in GBS patients and their matched healthy population and to further assess the uses of APOE as a laboratory marker and predictor for diagnosis, progression, and prognosis of GBS.

2- MATERIALS AND METHODS

2-1. Design and sampling

In this cross-sectional study, 61 patients diagnosed with Guillain-Barre syndrome were compared to 64 healthy controls. Considering 80% power, 0.05 random error between groups, mean difference of 5 microgram/ml, and an allocation ratio of 1, the sample size was calculated as 60 participants in each group. Based on a 10% probability of participant dropout, 66 children were assigned to each group. Sampling was done in a census manner and 66 children with Guillain-Barre syndrome were enrolled in the study according to inclusion and exclusion criteria. Afterward, healthy comparisons were signed up from healthy children who had visited the children's development clinic of the hospital, matching the sex-age distribution of the GBS group.

2-2. Inclusion and Exclusion Criteria

Inclusion criteria for the GBS group encompassed children aged between 1 and 14 years with GBS diagnosis, clinically confirmed by electrophysiological measures. Subjects of the control group were normal healthy children with no prior or recent history of any metabolic, infectious, neurologic, or inflammatory diseases. Any patient with prior history of hospitalization, usage of corticosteroids or other immune-modulators and anti-inflammatory drugs, or failure to thrive and patients with kidney, endocrine, liver, metabolic or neurologic diseases, history of hypoxia/hypoxemia, and any disorders causing reduced production or increased clearance of acute-phase proteins such as C-reactive protein or APOE were excluded. Patients with the Miller Fisher variant of GBS and incomplete medical records were also excluded.

2-3. Procedure

Demographic information of the participants was collected using a

questionnaire. Height and weight were measured by a SECA measuring station and column scale (model: Seca 763), weight in kilograms including one decimal, and height in centimeters. BMI was then calculated by dividing weight in kilograms by square of height in meters. In the GBS group, as a patient was diagnosed with GBS after life-saving and emergency interventions at the hospital, a 5ml blood sample was taken after stabilization of the patient. The blood sample was drawn using a 5ml-Syringe and a 23-gauge needle (SUPA Company, Iran) from the venous structure of antecubital cavity or any other peripheral venous access as needed, after an 8-hour nocturnal oral fasting. In the comparison group, the sampling was done in the clinic by a well-trained nurse during the visit time using the same equipment and instructions. Then, following the instructions of the ELISA kit for measuring APOE level in serum, the venous blood samples were centrifuged and serum was separated from whole blood. Afterward, the serum was allowed to clot for 10-20 minutes at room temperature and then was centrifuged at 2000-3000 RPM for 20 minutes. The supernatants were collected carefully and according to the kit manual, then stored/measured as explained. Human Apolipoprotein E (APOE) ELISA kit [Bioassay Technology Laboratory] based on the Biotin double antibody sandwich technology was implemented for measuring APOE serum level [further technical instructions are available at Bioassay Technology Laboratory, Enzyme-linked Immunosorbent Assay Kit, and Human Apolipoprotein E (APOE) ELISA Kit]. For patients with GBS, further parameters such as hospitalization length, maximal disability period, Electrophysiological studies, history of recent infectious disease, and also CSF protein level were recorded using an additional checklist from the patients' medical records. GBS disability score was calculated for patients in the GBS group using a standard GBS disability score questionnaire.

2-4. Data Analysis

Statistical analyses were performed using SPSS 21.0 software for Windows (IBM, West Grove, PA, USA) on a personal computer. Qualitative variables were reported as frequency and percentage while quantitative variables were reported as Mean±SD or Median (range). The normal distribution of data was checked out based on the Kolmogorov-Smirnov test and P-P/Q-Q plots. The Chi-square test was used for comparing proportions and the Independent samples' T-test or Mann-Whitney U test was implemented to compare values between two groups. Pearson's or Spearman's correlation coefficients were used for correlation studies. P-values of ≤ 0.05 were considered statistically significant for all statistical tests.

3- RESULTS

132 children were, initially, enrolled in the study, 66 in the GBS group and the same in the comparison group. 5 patients in the GBS group (1: Type 1 Diabetes Mellitus, 1: prior history of Epilepsy, 1: Familial mixed Hyperlipidemia and 2: Technical issues in APOE serum level measurement) and 3 children in the comparison group (1: non-fasting Blood Sample, 1: high positive serum levels of CRP, 1: Technical issues in APOE serum level measurement) were excluded from the study. The data from the remaining 61 in the GBS group and 63 in the comparison group were analyzed. 26 GBS patients and 27 controls were male. The mean±SD of age was 5.67±3.2 years and 5.65±3.13 years; the median (Range) was 5(1.5-12.5) and 5(1.5-12) in GBS and Comparison groups, respectively. 15 children in the GBS group and 23 controls were the first child of the family, where 28 and 27 children were the second child of

the family in the GBS and comparison groups, respectively. Nine children were the third child of the family in GBS and 6 children were the third baby of the family in the Comparison group. Further, 3 children in the GBS group and 1 child in the comparison group were the 4th and 5th child of the family, respectively. The birth order was not statistically significant between the groups. Likewise, the birth body weight, admission body weight, height, and BMI were not statistically significant between the groups, as shown in **Table 1**.

Table-1: Demographic information of the patients with GBS and healthy controls

Variable		GBS group (n=61)	Comparison Group (n=63)	P-value
Name	Description			
Gender: Male	Number (%)	26 (42.65%)	27 (42.9%)	0.56*
Age (year)	Median (range)	5 (1.5-12.5)	5 (1.5-12.0)	0.98**
Birth Body weight (kg)	Mean±SD	3.29±0.41	3.18±0.37	0.86***
Admission Body weight (kg)	Median (range)	19.00 (12.00-54.00)	19.00 (12.00- 57.00)	0.72**
Height (cm)	Mean±SD	114.75±21.80	114.84±21.08	0.64***
BMI (kg/m^2)	Mean±SD	16.71±1.88	16.89±1.99	0.86***

* Chi-square Test. **Mann-Whitney U Test. *** Independent Samples' T-Test.
GBS= Guillain Barre Syndrome BMI= Body Mass Index

The mean±SD of APOE serum level was 8.43±3.59 micrograms/ml in the GBS group and 35.28±11.18 micrograms/ml in the comparison group; and the median (range) was 9(2.60-29.20) and 32.30(18-72.10) micrograms/ml in the GBS group and comparison group, respectively. The difference in the APOE serum level between the two groups was strongly significant (P <0.001).

Further variables were just observed in GBS patients and almost all of them were gathered from the patients' medical records. The serum level of APOE classified by gender is shown in the two groups (**Fig. 1)**. The mean level of protein in Cerebrospinal Fluid (CSF) was 184.36±19.09 mg/dl and ranged from 140.0 to 250.0; the median was 182.50 mg/dl, as seen in **Fig. 2**.

Just 1 patient had a positive history of GBS in his older sibling. The duration of hospitalization was 9.63±4.72 (median: 9.0) days and the average of days from disease onset to hospital admission was from less than a day to 45 days. From among the 61 GBS patients, 31 had a recent respiratory infection and 14 had a gastrointestinal infection. Results of electrophysiological studies were collected from medical records, where EMG/NCV reports were available just for 58 patients; 26 reports showed Acute Motor Axonal Neuropathy (AMAN), 29 showed Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP) and 3 showed Acute Motor and Sensory Axonal Neuropathy (AMSAN) patterns. From among the 61 patients, 13 had experienced complications during hospitalization; Cardiac arrest (6 patients), Hypotension (4 patients), Gastrointestinal Bleeding (3 patients), Respiratory infections (3 patients), and Pulmonary collapse (2 patients). 2 patients had experienced 3 types of complications, while others had 2 or fewer. GBS disability score was

calculated based on a standard disability score questionnaire, where 0 was "normal" and 7 was "dead".

One patient had scored 1, 8 patients scored 2, 14 patients scored 3, 31 patients scored 4 and 5 patients scored 5; while no patients had scored 0, 6, or 7. It means that no patients had a normal ability to move or walk and no patient died of GBS during hospitalization. Moreover, correlation analyses did not reveal any significant correlation neither between serum APOE levels and CSF protein (r=-0.146 p= 0.274) nor between serum APOE level and disease severity (r=-0.191 p=0.148).

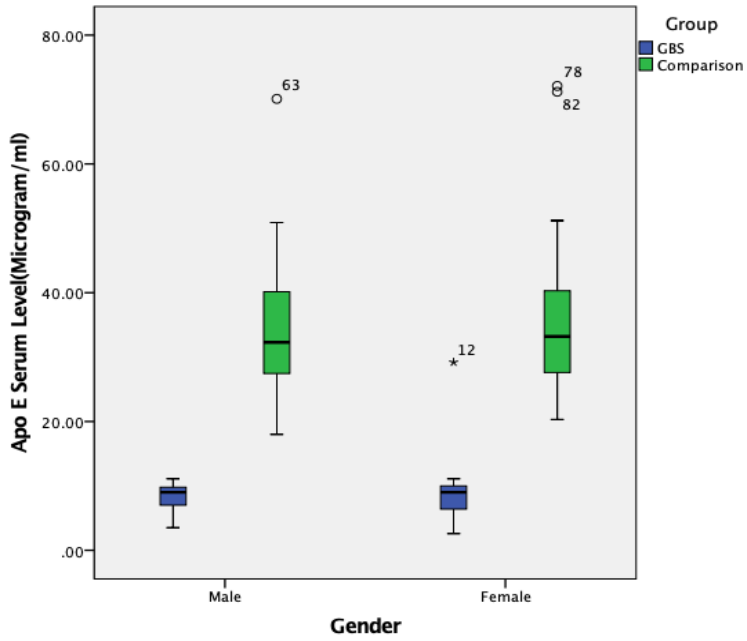

Fig. 1: Box plot on the serum levels of ApoE in two groups classified by gender

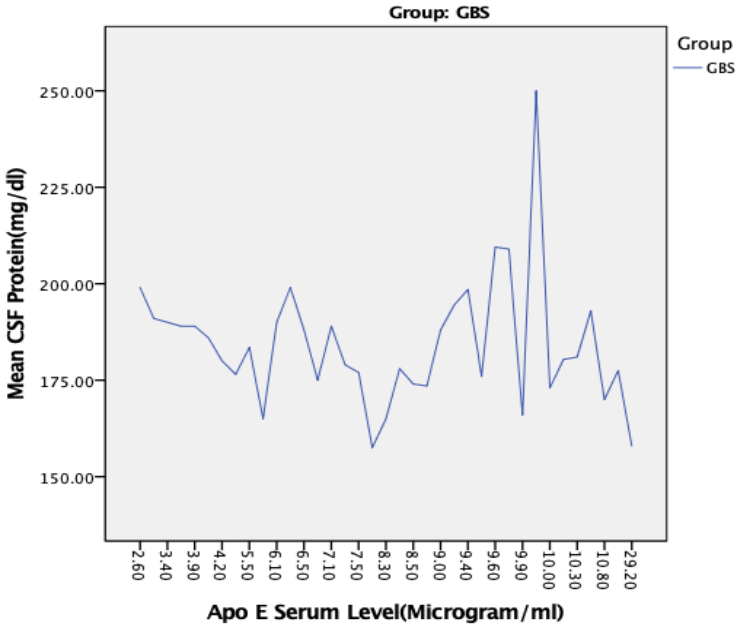

Fig. 2: Linear plot on the correlation of serum level of Apo E and CSF protein level in the GBS group

4- DISCUSSION

Guillain-Barre syndrome is an auto-immune disease of the peripheral nervous system, triggered by the improper and exaggerated response of the human immune system, both humoral and cellular immunity, to specific infectious or noninfectious conditions (6, 7, 17). This leads to monophasic immune-mediated destruction of myelin in PNS axons with subsequent complete or partial remyelination (14).

Accordingly, a diverse variety of inflammatory and immunologic factors may contribute to or have an impact on the course of the disease, both directly or indirectly (11, 12, 18), such as systemically and locally released cytokines, Toll-like receptors (TLRs) (19), complement components (20), and cellular chemotactic agents (21). Among these factors, the role of APOE and its polymorphism has been studied in many immune-mediated and neurologic conditions like multiple sclerosis (22), Alzheimer's disease (23), cerebrovascular disease (24), and neurodegenerative diseases including Parkinson's disease (25). Besides, there is a proven association between APOE e4 polymorphism and increased risk of peripheral neuropathy in HIV infection and diabetes mellitus (26).

APOE is a secreted 34 kDa protein of 299 amino acid residues derived from a 317 amino acid precursor protein that is cleaved to release an 18-amino-acid N-terminal signal peptide (27). APOE is mostly produced by the liver but CNS cells, macrophages, and cells in kidneys, adrenal glands, lung, and muscle tissues may take part in APOE synthesis (28). In addition to its physiological role in cholesterol transport, APOE has immunomodulatory properties (29)

Many research reports have presented APOE effects on GBS progression. For instance, Pritchard et al. hypothesized that outcome in Guillain-Barre´ syndrome is influenced by the APOE genotype (14). Laskowitz et al. concluded that APOE-deficient mice showed an abnormal humoral and cellular immune response (30) and Yu et al. explored the role of APOE in P0 peptide 180–199 induced experimental autoimmune neuritis (EAN) (31).

So, our results demonstrated a higher rate of GBS in female children (57.35% vs. 42.65%) as proved in previous studies (32, 33). The age range in our patients was from 1.5 to 12.5 years as it was in accordance with the results of previous epidemiologic studies in children (3, 33, 34), but against the results of Willison et al. (16) and Nasiri et al.(1), who stated that the cause might be the effect of age-distribution or regional disease epidemiology. Our results of height and weight and calculated BMI were all in normal ranges, according to the age- and sex-specific growth charts in Nelson's Textbook of Pediatrics, 20th edition.

Measured serum APOE level in our study was lower in GBS patients compared to normal comparisons, where based on ELISA kit for APOE that had been utilized for measurement, the normal range for APOE in Human serum was between 13.1 and 78.3 microgram/ml. We found that, unlike the comparisons having normal serum level of APOE, all patients with GBS had a reduced serum level of APOE, except one patient with a level of 29 microgram/ml, which was within the normal limits. Because no previous data on serum level of APOE in GBS patients is available, discussing our results is not possible.

There was no association between serum APOE level and CSF protein level in our GBS patients, but no sex- and age-adjusted data is available for CSF protein level in Childhood GBS to compare our results.

In several studies investigating the specific biomarkers of GBS either in CSF or serum, APOE was shown to decrease in CSF in GBS patients. Previous studies implemented comparative proteomic methods to show a decrease in CSF level of APOE and they have demonstrated the decline (35, 36). But obtaining CSF samples is an aggressive procedure and may be dangerous and have neurologic complications, as it has many contraindications. Considering these reasons, and though Guillain-Barre syndrome is a PNS disease, finding out an alternative factor for early diagnosis and also predicting the disease course is crucial. Our results showed a significant decline in serum APOE level in GBS patients, but because our measurement was done based on early samples driven as soon as the disease was diagnosed, interpreting the role of APOE in the disease course or its serum level fluctuations later in the disease course needs more studies. Further, performing another study based on the same design and larger sample size may lead to a better understanding of its diagnostic value even with setting a cut-off edge for early diagnosis. Beyond this, designing survival studies may reveal the prognostic value of APOE in Guillain-Barre Disease.

4-1. Limitations

Our study was a cross-sectional observational study with minor analytical aspects, so was unable to determine the exact role of APOE in the GBS pathophysiology and disease course. Further, our results demonstrated that APOE serum level is significantly lower in GBS patients; however, because GBS etiology could be multifactorial and on the other hand many medical conditions such as metabolic disorders could result in APOE serum level depletion, realizing the APOE as an indicator of GBS diagnosis, disease progression, and even the prognosis and complications needs further investigations based on larger sample sizes and measuring APOE level in serum, CSF, Urine in different types of designs, such as case-control studies, survival studies and even clinical trials for APOE therapeutic/ secondary and tertiary preventive effects in GBS. Utilizing advanced biostatistical methods including pathway analysis, Survival analysis, Multivariate regression and so on can be also helpful in controlling biases and acquiring more accurate results.

5- ACKNOWLEDGMENTS

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6- ETHICAL CONSIDERATIONS

The protocol of the study was first approved by the regional committee of ethics of Tabriz University of Medical Sciences (IR.TBZMED.REC 5.4.4880). In addition, a comprehensive description of the patients' situation and the diagnostic approach (blood sampling), the study protocol, aim, risks and benefits were explained to parents of children in each group. Then and there a written informed consent was signed by one of the parents of each child in each group.

7- CONFLICT OF INTERESTS

None.

8- FUNDING SOURCES

The study was funded by the Pediatrics Health research center and was conducted in Tabriz Children's Hospital, Tabriz University of Medical Sciences.

9- DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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