American Journal of Medicine and Medical Sciences 2025, 15(4): 1002-1005
DOI: 10.5923/j.ajmms.20251504.32

Clinical, Biochemical, and Immunological Markers of Hyene Barete Syndrome

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Abstract The article presents the clinical, biochemical, and immunological markers of giyen-pare syndrome and correction methods. As a result of the planned study, a comprehensive clinical, electro-physiological, and biochemical study will be conducted, resulting in data on the features of the clinical manifestations of Guillain-Barré syndrome, and the existence of clinical and electro-physiological variants of the disease will be confirmed. In each variant, the clinical and electrophysiological characteristics have been clarified, which must be taken into account for the timely diagnosis of the disease.

Keywords Guillain-Barre syndrome, Immunological markers, Correlation analysis

1. Introduction

Guillain Barré syndrome (GBS) is one of the most severe diseases of the peripheral nervous system and the most common cause of acute peripheral paralysis. The disease was first described in 1859 by the French neurologist Landry, and later studied in detail in 1916 by his compatriots Guillain, Barre, and Strolem. The incidence of GBS ranges from 1 to 4 per 100,000 population per year (on average 6.1). Men are usually more likely to get sick than women at a ratio of 1.1-1.7: 1. HBS is possible at any age, but overall, the incidence increases with age. In people under 18 years of age, this is 0.8 per 100,000 population, and in people over 60 years of age - 3.2 per 100,000 population [10,11,13]. Two peaks of morbidity are frequently recorded: from 15 to 35 years and from 50 to 75 years. GBS remains unknown. It is assumed that the disease is based on autoimmune mechanisms, where the role of the triggering factor is assigned to viruses and bacteria. More than two-thirds of patients with GBS have a history of infectious diseases, usually caused by Campylobacter jejuni (35% of cases), less often by Cytomegalovirus (15%), Epstein-Barr virus (10%), Micoplasma pneumoniae (5%). In addition, the causative agents can be herpes simplex and herpes zoster, influenza, Coxsackie, hepatitis B viruses, as well as vaccinations (against influenza, sometimes measles, mumps, measles), surgical interventions, and peripheral nerve damage. The medical literature describes cases of lymphoproliferative diseases, GBS in systemic lupus erythematosus [1,5,8].

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Received: Mar. 11, 2025; Accepted: Mar. 26, 2025; Published: Apr. 10, 2025
Published online at http://journal.sapub.org/ajmms

Guillain-Barré syndrome (GBS) is an acute inflammatory polyneuropathy manifested by progressive weakness and numbness in the extremities, involvement of cranial nerves, and in 1/3 of cases, damage to the respiratory muscles. Currently, this disease is the primary cause of severe acute progressive peripheral paresis.

SGB is characterized by a single-phase course and is associated, as a rule, with a positive prognosis for recovery. With timely diagnosis and adequate pathogenetic therapy, paresis in most patients regresses completely or almost completely, regardless of the severity of the disease in the acute phase. According to foreign researchers, the incidence of SGB averages 1-2 cases per 100,000 population per year. There is no official data on the incidence of SGB in Uzbekistan [1].

Considering the observed trend towards an increase in the number of patients with severe forms of SGB, as well as those with persistent residual deficit, the work devoted to the search for prognostically unfavorable factors of the course and consequences of this disease deserves special attention. The clinical, biochemical, immunological, and neurophysiological prognostic criteria discussed to date have demonstrated their high significance in a number of studies, however, all of them still remain the subject of active discussions, and some are used only within the framework of scientific works and are inaccessible to wide practice. In this regard, there is a need to clarify the significance of the known and search for new prognostic factors, which are distinguished by their accessibility and ease of practical application [2,6,14,16].

2. Purpose of the Study

To substantiate a pathogenetically justified concept for the

development of Guillain-Barré syndrome to assess the severity of the course and predict outcomes, to develop pathogenetic correction.

3. Research Methods

Research methods included anamnesis collection, clinical and neurological examination, brain electroencephalography (EEG), and magnetic resonance imaging (brain MRI).

Clinical and neuro-physiological examination. Upon admission, all patients underwent a comprehensive neurological examination, evaluated according to international scales: the North American Motor Deficiency Scale (SASH), the Neuropathy Impairment Score (NIS), and a study of six muscle groups recommended for functional assessment in SGB (Kleyweg R.P. et al., 1991) using the Medical Research Council sumscore (MRC) scale. The stage of the disease according to CASH characterized the mobility of patients with SGB from 0 (normal) to the 5th stage (the need for mechanical ventilation). The NIS scale result was a point assessment of the degree of paresis, suppression of tendon reflexes, and sensory disturbances ranging from 0 (normal) to 244 (maximum severity of polyneuropathy symptoms). The result on the MRC scale ranged from 0 (tetraplegy) to 60 (normal) and was used to assess the risk of incomplete recovery according to the modified outcome scale for SGB in all patients included in the study.

Biochemical research. Blood serum and cerebrospinal fluid samples were taken from 35 patients with SGB before the start of pathogenetic therapy. Blood collection was carried out on an empty stomach from the ulnar or subclavian vein into vacuum tubes of the Vacuette type with a coagulation activator. The serum was obtained by centrifugation on a laboratory centrifuge OPn-8UXL4.2 for 15 minutes at 3000 rpm. Cerebrospinal fluid (CSF) collection was performed on the same day during lumbar puncture in accordance with the standardized protocol for cerebrospinal fluid collection and storage (Teunissen C.E., 2009). Serum and CSF samples were frozen in the freezing chamber of the SANYO MDF-U32V low-temperature refrigerator at -58°C. The study of NfH, tau, GFAP for all patients was conducted simultaneously in the laboratory of hemorheology and homeostasis of the FSBU "NSN" of the RSA using R&D Systems (USA, Canada) and Biovendor (Greece) reagents. The "Sandwich" principle of the solid-phase enzyme-linked immunosorbent assay (ELISA) method was used. Measurements were carried out on the PerkinElmer (USA) Victor 2 immunoenzymatic microplate reader at a wavelength of 450 nm.

All patients participating in biochemical studies were randomized into groups according to the presence or absence of 12.

(IVL, including prolonged, requiring tracheostomy; bulbar disorders, pronounced motor deficiency according to SASH after 6 months). A comparison of the concentrations of the indicated biomarkers at the onset of the disease was conducted between these groups.

4. Research Results

Among the patients we examined, 14 (27%) patients had diarrhea, 34 (65%) had acute respiratory diseases, and 4 (8%) had CKD developed against a background of complete well-being. When conducting a comprehensive neurological examination with an assessment according to international scales, the NIS score in patients upon admission ranged from 28 to 199.5 points (Me=103 [LQ=63, UQ=130.5]). The score on the MRC scale on the first day of hospitalization ranged from 0 to 60 points (Me=33 [LQ=24, UQ=46]). Based on a point assessment of age, the preceding infection, and the MRC result for all patients, a rehabilitation prognosis was determined using the mEGOS system, the numerical expression of which ranged from 0 to 9 points (Me=5 [LQ=3, UQ=7]). This result was unsatisfactory (mEGOS > 7 points) in 14 patients (27%). The severity of neurological deficit in SAC varied from 2 to 5 stages with a predominance of severe motor disorders (Me=4 [LQ=4, UQ=5]). In 11 (21%) patients, neurological symptoms continued to progress after admission to the hospital. Electroneuromyography of the nerves of the hands and feet revealed primary demyelinating nerve damage in 38 (73%) patients, and primary axonal damage in 14 (27%) patients.

Results of biochemical research. Determination of the concentration of markers of proximal axonal damage (NfH, tau, GFAP) in blood serum and cerebrospinal fluid was carried out in 35 patients with CKD. In all cases, the level of each biomarker in the cerebrospinal fluid was higher than its serum content. In the sample being studied, vital functional disorders were analyzed. A decrease in lung vital capacity was observed in 29 patients (83%), but only 10 patients required mechanical ventilation, which continued in our observations from 7 to 286 days. When analyzing the level of biomarkers in two groups - patients who needed mechanical ventilation and patients who were on self-respiration - significant differences were obtained in the level of NfH in both cerebrospinal fluid and blood serum, taken upon admission, when more than half of the patients in the group with mechanical ventilation did not have time to develop a respiratory failure clinic. For the first time, we have shown that in patients requiring mechanical ventilation, the concentration of heavy neurofilament chains in the cerebrospinal fluid and blood serum is significantly higher than in patients without such a need. Using ROC analysis, the optimal level of blood serum neurofilament in terms of sensitivity and specificity, equal to 0.144 ng/ml, was selected, exceeding which would allow predicting the development of respiratory failure with the need for mechanical ventilation. We also analyzed the level of biomarkers in subgroups of patients with varying durations of mechanical ventilation and revealed significant differences in the concentration of tau protein and gliofibrillar acid protein, both in the cerebrospinal fluid (p=0.016) and in blood serum (p=0.010). When analyzing the correlation between the level of GFAP and the duration of mechanical ventilation, we revealed a direct correlation between the concentration of this biomarker in

cerebrospinal fluid and blood serum and the duration of respiratory support (R=0.820 (p=0.007) and R=0.825 (p=0.003), respectively). Using ROC analysis, we established limiting concentrations of GFAP, as well as tau protein, both in blood serum and cerebrospinal fluid, allowing us to assume with high sensitivity and specificity the patient's need for prolonged mechanical ventilation and tracheostomy. Thus, for the first time in the world, we have shown that the analysis of the content of markers of proximal axonal damage in cerebrospinal fluid and blood serum allows us to predict the involvement of respiratory muscles in the pathological process and to judge the probable duration of mechanical ventilation in patients with various forms of CKD. Another, equally important clinical sign of severe SGB is bulbar syndrome, which, if not diagnosed in a timely manner, leads to aspiration complications. In the sample we studied, bulbar disorders were noted in 20 patients (57%), among whom 14 patients had indications for nasogastric tube placement. When analyzing the level of biomarkers in the groups with tube and natural feeding, we established a significantly higher concentration of NfH in the blood serum of patients receiving tube feeding, and using ROC analysis, a prognostic neurofilament level of 0.094 ng/ml was determined, exceeding which allowed us to predict the development of pronounced bulbar disorders in patients with SGB. After 6 months from the onset of the disease, an assessment of motor disorders according to the North American scale was conducted among patients with a known level of biomarkers. 1 patient was excluded from the study due to severe somatic pathology, 26 patients (76%) regained the ability to move independently (group A), 8 patients (24%) could not walk 5m without support and support, which was equated to an unfavorable result (group B). When assessing the level of biomarkers in blood serum and cerebrospinal fluid taken upon admission to the hospital at the onset of the disease, significant differences were found between these two groups of patients in several indicators. A direct correlation was found between the level of GFAP in the CSF (R=0.384, p=0.029), serum GFAP (R=0.360, p=0.039), serum NfH (R= 0.503, p=0.003) and the degree of motor disorders 6 months after the onset of SGB, as well as a reverse correlation between the SASH result and the NfHlique/NfHlique ratio (R= -0.444, p=0.011). As can be seen, the neurofilament in blood serum as a marker of the rehabilitation prognosis has the most optimal combination of sensitivity and specificity.

Thus, our study demonstrated the possibility of using markers of proximal axonal damage to predict the course of Guillain-Barré syndrome in the phase of neurological symptoms progression, as well as the rate of restoration of lost functions, such as independent breathing and walking. According to the data we obtained, determining these biomarkers specifically in blood serum is a more sensitive method, which, in combination with the ease of obtaining the material, compared to CSF, will allow for the widespread use of this type of research in practice.

5. Conclusions

In severe forms of Guillain-Barré syndrome, the prognostic significance of biomarker axonal damage (neurofilament heavy chains - NfH, tau protein - tau) and astrocyte protein (gliofibrillar acid protein - GFAP) has been established. These biomarkers allow, with high sensitivity and specificity, to predict the development of a severe course of Guillain-Barré syndrome, requiring mechanical ventilation and tube feeding, even at the onset of the disease.

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