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Utility of cerebrospinal fluid protein biomarkers in predicting the outcome of Guillain-Barre syndrome

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ABSTRACT

Objectives: The study aimed to investigate the potential of peripheral myelin protein 2 (P2) and Alpha B-crystallin (αBC) as predictive biomarkers in Guillain-Barré syndrome (GBS). Given the unpredictability of GBS prognosis, the need for specific and reliable biomarkers for disease development and intensity assessment is crucial.

Material and Methods: A prospective observational study was conducted on a cohort of 220 individuals diagnosed with GBS at a tertiary general hospital in South India. P2 and αBC levels in cerebrospinal fluid (CSF) were quantified using ELISA assay kits. The study spanned from March 2021 to April 2023, with participants aged 18–60 years. The study protocol adhered to ethical standards, and the Brighton criteria were employed for GBS diagnosis. CSF samples were collected at admission and two weeks post-onset. Data analysis utilised SPSS, and statistical significance was set at $p < 0.05$.

Results: Upon admission, mean P2 levels were 2.2 ± 0.5 ng/mL, and αBC levels were 9.8 ± 2.3 ng/mL. After two weeks, P2 increased to 4.8 ± 0.8 ng/mL, and αBC increased to 15.1 ± 2.3 ng/mL. A positive correlation was observed between the rise in P2 and αBC levels and enhanced muscle strength at 4 weeks and 6 months.

Conclusion: The study suggests a significant increase in P2 and αBC levels in GBS patients, correlating with improved muscle strength. P2 and αBC ratios in CSF between the second and first weeks may serve as prognostic markers for GBS. Limitations include a small sample size and the absence of a control group, necessitating caution in generalizability.

Keywords: Guillain Barre Syndrome, Biomarkers, Cerebrospinal fluid, Peripheral myelin protein, Alpha B crystalline, αBC, Prospective studies

INTRODUCTION

Guillain-Barré syndrome (GBS) is an acute inflammation of the nerve roots and peripheral nerves. Globally, it is the predominant cause of acute muscle weakness affecting the entire body. In general, most patients experience peak symptoms at about two weeks of disease onset. Most characteristically, the disease's pathogenesis involves demyelination of the nerve. The prognosis of the disease is unpredictable, and thus, a need for biomarkers presents itself.

Some studies have examined the significance of biomarkers in GBS. A study discovered that the peripheral neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR) and platelet to lymphocyte ratio (PLR) could serve as markers for disease activity in individuals with GBS.[1] Another study revealed that brain-derived neurotrophic factor (BDNF) could potentially serve as a biomarker for the initial phase of GBS.[2] But these biomarkers are nonspecific and

are affected by confounding factors. Hence, a neuro-specific protein could be an ideal biomarker that might offer useful information about the development and intensity of GBS, assisting in the process of diagnosing and making decisions about treatment.

Peripheral myelin protein 2 (P2) and Alpha B-crystallin (αBC) play essential roles in the peripheral nervous system. P2 is responsible for regulating lipid equilibrium and has a role in the formation of myelin in Schwann cells.[3] αBC regulates the interaction between Schwann cells and axons,[4] impacting the amounts of neuregulin and the expression of the ErbB2 receptor. Both proteins are vital to the remyelination of neurons.[5]

We hypothesised that GBS patients will experience an increase in levels of P2 and αBC from admission to 2 weeks after the commencement of the disease and that elevated levels of P2 and αBC will be positively associated with enhanced muscular strength. We studied the levels of P2 and αBC in the cerebrospinal fluid of individuals with GBS, to assess the potential of P2 and αBC as predictive biomarkers in GBS.

MATERIAL AND METHODS

This prospective observational study was performed at a tertiary general hospital located in South India, spanning from March 2021 to April 2023. The study included a cohort of 220 individuals who were diagnosed with GBS according to the Brighton criteria.[6] The study participants ranged in age from 18 to 60 years. Individuals with a medical history of autoimmune illnesses and demyelinating disorders were not included in the study.

All subjects provided written informed permission, and the study received approval from the Institutional Medical Ethics Committee. The sample size of 199 subjects was determined by taking into account previous studies, with a power of 80% and a 95% confidence interval. The objective was to detect a minimum difference of 1 ng/mL of P2 and αBC in CSF between samples collected from patients with GBS at admission and two weeks after the onset of symptoms. To accommodate for probable dropouts, an extra 10% of subjects were incorporated, leading to a total of 220 patients being included in the study.

CSF samples were taken from GBS patients using a sterile lumbar puncture procedure, yielding 2 mL of CSF at the time of admission and two weeks after the onset of symptoms. The selection of this time point was based on literature that suggests the sickness reaches its lowest point at around two weeks, followed by a reported recovery.[7] The second specimen was obtained promptly following the conclusion of the second week. The sufferers' recuperation was evaluated utilising the Medical Research Council (MRC) cumulative score at 4 weeks and 6 months after the commencement of the illness.

The P2 and αBC assays were quantified using commercially available ELISA assay kits provided by LSBio LTD, USA, Catalog No. LS-F5216-1 and Eagle Biosciences, Inc. USA, Catalog No. SKT -123, respectively.

Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS, version 22.0, Chicago, IL). The quantitative data were represented as the mean and standard deviation and evaluated using the Student's t-test. Statistical significance was established with a p-value below 0.05. In addition, the Pearson correlation coefficient was computed to evaluate the link between variables.

RESULTS

The objective of our study was to examine the involvement of P2 and αBC protein levels in GBS. The study involved participants with an average age of 34 (9.1) years, and the male-to-female gender ratio was 121:99. Upon admission, the mean P2 levels were 2.2 (0.5) ng/mL, while the mean αBC levels were 9.8 (2.3) ng/mL. Following a duration of 2 weeks, the mean P2 levels exhibited an increase to 4.8 (0.8) ng/mL, whereas the mean αBC levels saw an increase to 15.1 (2.3) ng/mL.

The mean MRC total score, which measures both muscle strength and function, was 26(3.4) upon admission, 39.9(4.8) after four weeks, and 54.4(3.7) after six months.

We found a positive correlation between the rise in P2 levels (quantified by the ratio of post-2nd week P2 to pre-2nd week P2) and the enhancement in muscle strength at both the 4-week and 6-month time points as depicted in Figure 1. Furthermore, there was a positive correlation between the rise in αBC levels and the amelioration of muscle weakness, as depicted in Figure 1.

DISCUSSION

The levels of P2 and αBC in GBS patients showed a considerable increase from admission to 2 weeks after the onset of the disease, fulfilling the purpose of measuring these biomarker levels. The rise in P2 and αBC levels exhibited a positive correlation with enhanced muscle strength, so substantiating the concept that these biomarkers are associated with the process of recuperation. Remyelination is typically the fundamental process that leads to recovery in most cases.

Oligodendrocytes in the central nervous system (CNS) and Schwann cells in the peripheral nervous system (PNS) are responsible for the formation of the myelin sheath.[5] In the PNS, Schwann cells elongate mobile projections that undergo a transformation into flat structures. These

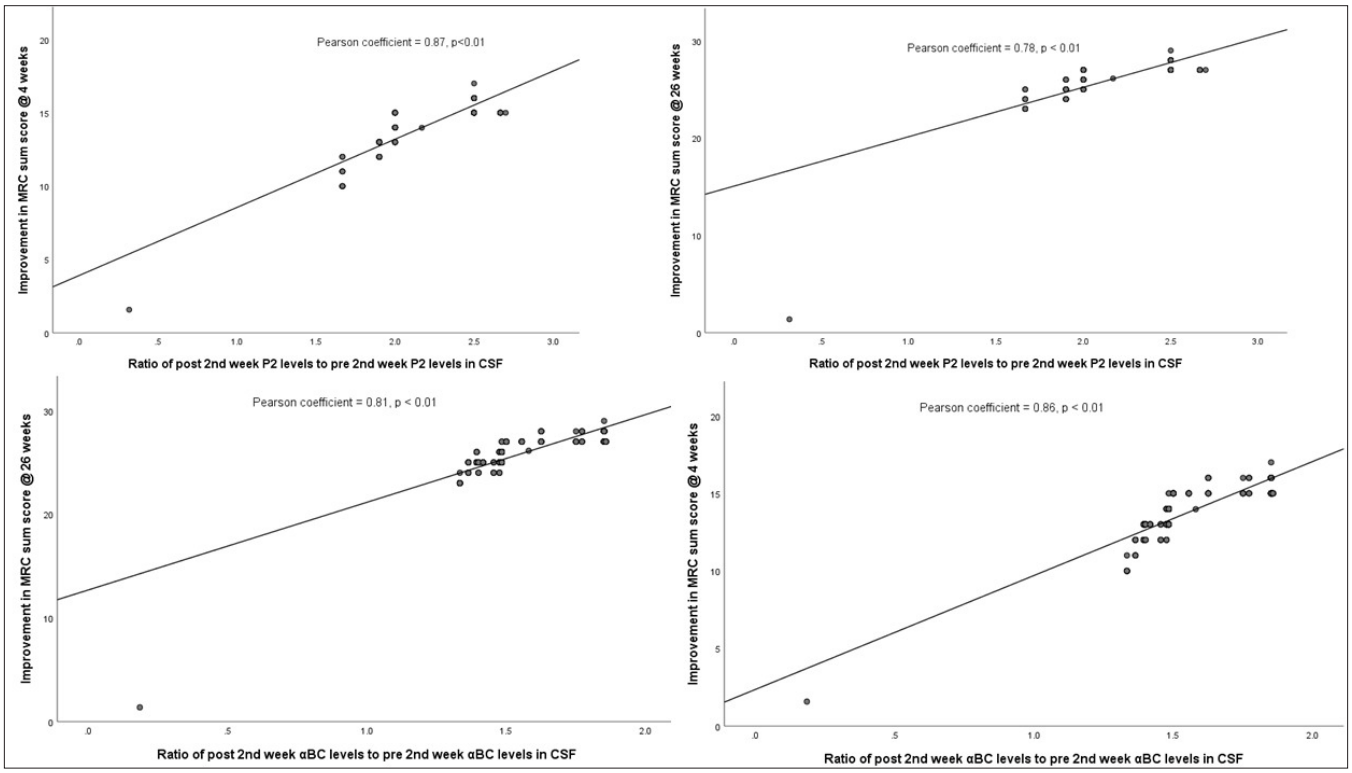

Figure 1: Post 2nd week P2 to the pre 2nd week P2 ratio had positive correlation with improvement at 4 weeks and 6 months. Post 2nd week αBC to the pre 2nd week αBC ratio had positive correlation with improvement at 4 weeks and 6 months.

structures then envelop axons, forming a stack of many layers of membranes.[6] The myelin sheath is a complex structure composed of multiple layers that wrap around the axon in a spiral manner, with an inner tongue that moves forward and extends sideways towards the node of Ranvier.[7] The myelin sheath serves as an insulator to facilitate the efficient transmission of nerve impulses. Any damage to the myelin might lead to a failure in nerve conduction. The primary pathogenic characteristic of GBS is demyelination.

The process of recovering the myelin sheath around axons is crucial for remyelination in GBS. Remyelination is a process that consists of a series of events that can be observed by alterations in the expression of various proteins. Identifying the proteins that are associated with recovery will assist in predicting the course of the disease. Our investigation indicates that P2 and αBC are promising contenders.

P2, is sometimes referred to as PMP2, FABP8 or M-FABP. It is a protein constituent of the myelin sheath in the peripheral nervous system. P2 is predominantly observed in Schwann cells, which are the glial cells responsible for myelination in the peripheral nervous system. It plays a role in maintaining the balance of lipids in the peripheral nervous system and contributes to the process of myelination in Schwann cells. P2 protein binds and transports fatty acids to membranes, hence controlling the composition of peripheral myelin. Studies have demonstrated that a lack of P2 has a negative impact on the process of remyelination in the peripheral nervous system. Furthermore, P2 has been found to have a functional role in facilitating remyelination.[3]

Our study revealed that an increase in P2 levels, as measured by the ratio of post-2nd week to pre-2nd week levels, correlates with better recovery in GBS patients. Thus, it could be a prognostic marker for patients afflicted with GBS.

αBC is a tiny heat shock protein that is consistently produced by axons in the PNS and Schwann cells. It has a crucial function in controlling Wallerian degeneration and remyelination following peripheral nervous system injury. The absence of αBC hinders the process of remyelination and is linked to a decrease in the population of myelinating Schwann cells and an increase in the number of non myelinating Schwann cells. αBC plays a role in controlling the communication between Schwann cells and axons, which in turn affects the levels of neuregulin and the expression of the ErbB2 receptor following injury to the peripheral nervous system. Recent research indicates that the absence of αBC hinders the process of remyelination following peripheral nerve damage and that αBC modulates communication between Schwann cells and axons.[4]

Our findings suggest that the observed correlation between higher post-2nd week to pre-2nd week αBC ratios and good

recovery in GBS may be attributed to the increased αBC associated with recovery.

CONCLUSION

Overall, this work presents convincing evidence that the concentrations of Peripheral myelin protein 2 (P2) and αBC in the cerebrospinal fluid (CSF) serve as excellent prognostic biomarkers for the prognosis of Guillain-Barré Syndrome (GBS). The results of our study show a notable rise in both P2 and αBC levels from the time of admission to two weeks after the commencement of the disease. This increase is strongly associated with enhanced muscle strength in patients with Guillain-Barré syndrome (GBS). This correlation implies that elevated levels of these biomarkers are predictive of a more positive prognosis in GBS, representing a significant advancement in our comprehension of the disease.

Moreover, the observed rise in P2 and αBC levels is likely associated with the phenomenon of remyelination, which is a crucial element in the recuperation from GBS. This correlation not only emphasizes the significance of these biomarkers in relation to GBS but also illuminates their function in the wider comprehension of peripheral nerve disorders.

Nevertheless, it is imperative to recognize the constraints of this investigation, such as its limited sample size and absence of a control group, which could potentially impact the applicability of the results. There might also be a selection bias due to convenience sampling. Some information bias may have occurred as MRC assessments have a subjective component. But then, the results may be generalizable to adult GBS patients in India. Even as caution extrapolating to pediatric or elderly populations, or other geographic settings may be necessary.

Future research should focus on reproducing these findings in bigger and more diverse groups of participants. It should also involve control groups to strengthen the evidence supporting the significance of P2 and αBC as predictive biomarkers in GBS. However, our study presents a hopeful new approach for predicting GBS outcomes at an early stage, which could result in more customized and efficient treatment methods for this unpredictable and frequently incapacitating disorder.

Ethical approval

The study was approved by the Institutional Medical Ethics Committee at Great Eastern Medical School and Hospital [Reg No: 86/IEC/GEMS/2020]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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