



# Elevated cerebrospinal fluid levels of beta-2-microglobulin in patients with Guillain-Barré syndrome and their correlations with clinical features

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## Abstract

**Backgrounds** Beta-2-microglobulin ( $\beta$ 2-MG) levels vary in many infectious and autoimmune diseases. We investigated plasma and cerebrospinal fluid (CSF)  $\beta$ 2-MG levels in patients with Guillain-Barré syndrome (GBS) and their correlations with clinical parameters.

**Methods** CSF samples from 50 patients with GBS including 19 acute inflammatory demyelinating polyneuropathy (AIDP), 6 acute motor axonal neuropathy (AMAN), 10 acute motor-sensory axonal neuropathy (AMSAN), 7 Miller-Fisher syndrome (MFS), and 8 unclassified patients were collected. Moreover, 23 CSF samples from patients with non-inflammatory neurological disorders (NIND) as controls were collected. Plasma samples from 42 enrolled patients and 29 healthy individuals were also collected. The  $\beta$ 2-MG levels were measured by immunoturbidimetry on automatic biochemical analyser. Besides, clinical data were extracted from electronic patient documentation system.

**Results** CSF levels of  $\beta$ 2-MG, lactate dehydrogenase (LDH), and lactate were significantly increased in patients with GBS ( $p = 0.004$ ,  $p = 0.041$ ,  $p = 0.040$ , respectively), particularly in patients with AIDP ( $p < 0.001$ ,  $p = 0.001$ ,  $p = 0.015$ , respectively), whereas no statistically significant difference was found in plasma levels of  $\beta$ 2-MG. Furthermore, CSF levels of  $\beta$ 2-MG were positively correlated with Hughes functional score ( $r = 0.493$ ,  $p = 0.032$ ), LDH ( $r = 0.796$ ,  $p < 0.001$ ), and lactate ( $r = 0.481$ ,  $p = 0.037$ ) but not with protein ( $r = -0.090$ ,  $p = 0.713$ ) in AIDP patients.

**Conclusions** CSF  $\beta$ 2-MG levels may help identify AIDP and indicate clinical severity. CSF LDH and lactate levels correlate with CSF  $\beta$ 2-MG levels; interaction among these biomarkers would need further investigation.

**Keywords** Guillain-Barré syndrome · Acute inflammatory demyelinating polyneuropathy · Beta-2-microglobulin · Lactate dehydrogenase · Lactate

## Introduction

Guillain-Barre syndrome (GBS) is an immune-mediated disorder on peripheral nerves and their spinal roots [1], which is characterised by rapidly progressive symmetrical weakness of the limbs or cranial nerve-innervated muscles, usually accompanied by hyporeflexia or areflexia [2]. Currently, GBS is considered to cover a spectrum of clinicopathological subtypes. According to different pathological phenotypes, GBS is divided into two major subtypes: acute inflammatory demyelinating polyneuropathy (AIDP), in which immune attack mainly targets at the myelin sheath and related Schwann-cell components; axonal subtypes, including acute motor axonal neuropathy (AMAN) and acute motor-sensory axonal neuropathy (AMSAN), in which immune injury mainly takes place

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on the nerve axon membranes [1, 3]. Besides, Miller-Fisher syndrome (MFS), which is characterised by a triad of ataxia, ophthalmoplegia, and areflexia, is recognised as one of the GBS clinical variants [4].

Beta-2-microglobulin ( $\beta$ 2-MG), a protein of low molecular weight (11,800), is non-covalently binding to the heavy chain of the major histocompatibility complex (MHC) class I, presenting on the membranes of all nucleated cells, prevailing on lymphocytes and macrophages, and widely existing in various body fluids such as serum, urine, cerebrospinal fluid (CSF), saliva, and colostrum [5–7]. Because of the association with immunocytes and MHC class I,  $\beta$ 2-MG is essential for the stable expression of antigen-presenting molecules [8]. The change of  $\beta$ 2-MG levels may indicate immune cell turnover and immune activation [9, 10].  $\beta$ 2-MG in both CSF and plasma (or serum) have been studied in many neurological disorders, such as meningitis, encephalitis, brain tumours, neurosyphilis, cerebral infarction, Alzheimer's disease, multiple sclerosis, and central nervous system (CNS) leukaemia [7, 11]. However, there are few studies on CSF and plasma levels of  $\beta$ 2-MG in GBS patients. In a small sample study, researchers observed increased CSF  $\beta$ 2-MG levels in five patients with GBS [12]. However, Adachi et al. found no elevation of CSF  $\beta$ 2-MG levels in GBS patients, whereas the serum  $\beta$ 2-MG levels were slightly increased [13].

On the whole, CSF and plasma  $\beta$ 2-MG levels and their associations with clinical parameters in GBS patients remain unclear. In this study, we investigated plasma and CSF  $\beta$ 2-MG levels in patients with GBS and their correlations with disease severity. In addition, we preliminarily explored the levels of CSF LDH and lactate and their associations with CSF  $\beta$ 2-MG in patients with GBS.

## Methods

### Study population

In this study, a total of 50 patients with GBS admitted to Tianjin Medical University General Hospital, Tianjin, China, from March 2018 to December 2019 were included. Inclusion criteria were meeting levels 1 or 2 of the *Seivar's* criteria; detailed documentation of clinical disease course; samples and assay results obtained within 28 days from onset; no previous identified damage of peripheral nerve or preceding immunotherapy in another facility; and no documented comorbidities that would be indicative of altered  $\beta$ 2-MG levels (such as CNS leukaemia, any CNS infections, acute or chronic kidney disease). According to the Hadden electrophysiology classification criteria (for AIDP and AMAN) [14] and Sejvar criteria (for AMSAN) [4], GBS patients in this cohort were subclassified into 5 subtypes, including AIDP ( $n = 19$ ), AMAN ( $n = 6$ ), AMSAN ( $n = 10$ ), MFS ( $n = 7$ ), and unclassified patients ( $n = 8$ ). Twenty-three patients with non-

inflammatory neurological disorders (NIND) were enrolled as controls, whose conventional CSF parameters were within the range of normal reference values. According to the discharge diagnoses, NIND controls included 4 cases with subacute combined degeneration of the spinal cord, 9 cases with chief complaint of dizziness or headache on admission but no detected organic lesions, 6 cases with mental illness, 2 cases with folic acid deficiency neuropathy, 1 case with spinal vascular malformation, and 1 case with cerebral venous sinus thrombosis. Twenty-nine healthy individuals who admitted in the Health Care Center of the hospital were enrolled as healthy controls (HC).

### Extraction of clinical data

By reviewing the electronic patient documentation system, we extracted the following parameters: (1) the Hughes functional score (HFS), a neurological evaluation score on general functioning in patients with GBS, ranging from 0 (normal health), 1 (mild neurological symptoms or signs, capable of running), 2 (capable of walking at least 5 m, but incapable of running), 3 (capable of walking 5 m with support or walker), 4 (bed-ridden), 5 (mechanical ventilated), to 6 (dead). HFS was calculated at nadir; (2) detailed electrophysiology reports from two experienced technicians. Nerve conduction studies including motor nerve, sensory nerve, and F-wave analyses were performed in the median, ulnar, tibial, and peroneal nerves ( $n = 43$ ); (3) conventional CSF parameters. CSF lactate and LDH levels had been measured using commercial diagnostic reagent kit on automatic biochemical analyser; (4) evidence whether the onset of GBS was associated with a preceding infection (diarrhoea or upper respiratory tract infection); (5) evidence whether autonomic nerve was involved; (6) results from tests of anti-ganglioside antibodies (anti-GS-ab, including anti-GM1-ab, anti-GD1b-ab, anti-GQ1b-ab).

### Blood and CSF sampling

CSF samples from 50 patients with GBS and 23 patients with NIND were obtained by lumbar puncture before treatment. Blood samples from 42 enrolled patients (16 AIDP, 5 AMAN, 8 AMSAN, 6 MFS, and 7 unclassified patients) and 29 HC were collected in EDTA-coated tubes, and centrifuged at 3000 rpm for 10 min at 4 °C. CSF samples and supernatant were collected, divided into aliquots, and stored at  $-80$  °C pending analyses. All samples were not thawed or refrozen before analysis.

### Measurement of $\beta$ 2-MG concentrations

Plasma and CSF concentrations of  $\beta$ 2-MG were measured by immunoturbidimetry, using commercial diagnostic reagent (Medicalsystem Biotechnology Co., Ltd.) on automatic

biochemical analyser (Hitachi 008AS). The detection range is 0.8–2.9 mg/L.

## Statistical analyses

Continuous data were described by mean  $\pm$  standard deviation (SD), and discrete variables were described by median value (interquartile, IQR). Mann-Whitney *U* test was used for continuous data analyses. Kruskal-Wallis test and Bonferroni correction were applied for multiple comparisons. Categorical variables were compared by Fisher's exact test or chi-square test. Correlation analyses were performed using Spearman correlation test. All statistical analyses were computed with SPSS Statistics version 23.0 (IBM Corporation), and graphs were performed using GraphPad Prism 6.07. Two-tailed *p*-values  $< 0.05$  were considered statistically significant.

## Results

### Demographic and clinical characteristics of the study population

Demographic and clinical characteristics of the study population are described in Table 1. Since both AMAN and AMSAN were axonal neuropathies, the two subtypes were combined into one group. There were no statistically significant differences in age, gender, preceding infection rate, autonomic nerve involved rate, anti-GS-ab positive rate, CSF dissociation rate, and time interval between lumbar puncture and onset among different groups. Besides, no correlation was found between CSF  $\beta$ 2-MG levels and the time of CSF analysis in GBS patients or in the subtypes ( $p < 0.05$ ).

### CSF $\beta$ 2-MG levels were increased in patients with GBS, especially in patients with AIDP

CSF  $\beta$ 2-MG levels were significantly higher in patients with GBS than those in patients with NIND (Fig. 1,  $p = 0.004$ ). Similar results were also observed in patients with AIDP but not in other subgroups when compared with NIND (Fig. 1,  $p < 0.001$ ). In the intergroup comparison, CSF  $\beta$ 2-MG levels in patients with AIDP patients were significantly higher than those in the axonal subgroup (Fig. 1,  $p = 0.015$ ). Besides, there was no significant difference of plasma  $\beta$ 2-MG levels in patients with GBS compared to HC ( $1.66 \pm 0.55$ ,  $1.40 \pm 0.32$ ,  $p = 0.085$ ).

### CSF levels of LDH and lactate were increased in patients with GBS, especially in patients with AIDP

We also compared CSF concentrations of LDH and lactate in patients with GBS. CSF LDH and lactate concentrations were significantly increased in patients with GBS than those in patients with NIND ( $p = 0.041$ ,  $p = 0.040$ , respectively). Across the four different GBS subtypes, CSF levels of LDH and lactate were significantly higher only in patients with AIDP than those in NIND ( $p = 0.001$ ,  $p = 0.015$ , respectively). However, no significant differences of CSF LDH and lactate levels were found among other subgroups.

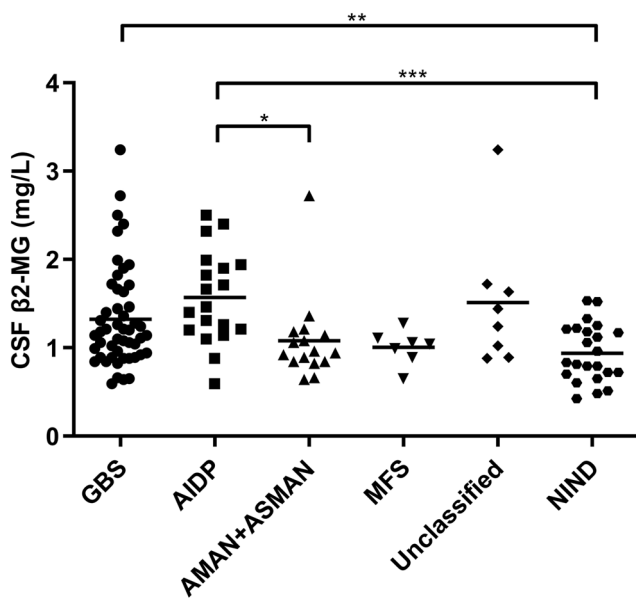
### Correlation between CSF $\beta$ 2-MG levels and plasma $\beta$ 2-MG, CSF LDH, and CSF lactate levels in patients with GBS

We explored further relationships between CSF  $\beta$ 2-MG levels and plasma  $\beta$ 2-MG, CSF LDH and CSF lactate levels in

**Table 1** Demographic and clinical characteristics of the study population

|   | GBS<br>( <i>n</i> = 50) | AIDP<br>( <i>n</i> = 19) | AMAN+AMSAN<br>( <i>n</i> = 16) | MFS ( <i>n</i> = 7) | Unclassified<br>( <i>n</i> = 8) | NIND<br>( <i>n</i> = 23) | HC<br>( <i>n</i> = 29) |
|---|-------------------------|--------------------------|--------------------------------|---------------------|---------------------------------|--------------------------|------------------------|
| Age, years (mean $\pm$ SD)                                      | 50.1 $\pm$ 16.73        | 53.58 $\pm$ 19.35        | 44.56 $\pm$ 14.30              | 46.71 $\pm$ 14.02   | 55.88 $\pm$ 15.40               | 47.26 $\pm$ 17.97        | 50.52 $\pm$ 14.72      |
| Gender (f/m)  | 21/29                   | 6/13                     | 11/5                           | 1/6                 | 3/5                             | 14/9                     | 13/16                  |
| Preceding infection, <i>n</i> (%)                               | 24 (48%)                | 7 (36.8%)                | 11 (68.8%)                     | 4 (57.1%)           | 2 (25.0%)                       | -                        | -                      |
| Autonomic nerve involved, <i>n</i> (%)                          | 7 (14%)                 | 2 (10.5%)                | 4 (25.0%)                      | 1 (14.3%)           | 0 (0.0%)                        | -                        | -                      |
| Anti-GS-ab positive, <i>n</i> (%)                               | 29 (58%)                | 8 (42.1%)                | 11 (68.8%)                     | 5 (71.4%)           | 5 (62.5%)                       | -                        | -                      |
| Time interval between lumbar puncture and onset (mean $\pm$ SD) | 12.46 $\pm$ 7.00        | 12.58 $\pm$ 6.50         | 12.81 $\pm$ 7.21               | 7.29 $\pm$ 1.11     | 15.40 $\pm$ 8.48                | -                        | -                      |
| CSF dissociation, <i>n</i> (%)                                  | 44 (88%)                | 16 (84.2%)               | 14 (87.5%)                     | 6 (85.7%)           | 8 (100.0%)                      | -                        | -                      |
| HFS at nadir (median, IQR)                                      | 2.00, 2.00–3.00         | 3.00, 2.00–4.00          | 3.00, 2.00–3.75                | 1.00, 1.00–2.00     | 2.00, 2.00–3.00                 | -                        | -                      |
| CSF protein (mean $\pm$ SD, g/L)                                | 0.95 $\pm$ 0.70***      | 1.13 $\pm$ 0.84***       | 0.72 $\pm$ 0.28***             | 0.87 $\pm$ 0.90***  | 1.03 $\pm$ 0.74***              | 0.31 $\pm$ 0.08          | -                      |
| CSF $\beta$ 2-MG (mean $\pm$ SD, mg/L)                          | 1.32 $\pm$ 0.57**       | 1.57 $\pm$ 0.52***       | 1.08 $\pm$ 0.48                | 1.00 $\pm$ 0.20     | 1.51 $\pm$ 0.77                 | 0.94 $\pm$ 0.33          | -                      |
| CSF LDH (mean $\pm$ SD, U/L)                                    | 18.84 $\pm$ 6.14*       | 21.38 $\pm$ 6.39**       | 17.99 $\pm$ 6.01               | 15.59 $\pm$ 2.27    | 17.39 $\pm$ 6.74                | 15.86 $\pm$ 4.04         | -                      |
| CSF lactate (mean $\pm$ SD, mmol/L)                             | 1.58 $\pm$ 0.34*        | 1.66 $\pm$ 0.34**        | 1.54 $\pm$ 0.20                | 1.42 $\pm$ 0.42     | 1.62 $\pm$ 0.45                 | 1.40 $\pm$ 0.34          | -                      |

GBS, Guillain-Barré syndrome; AIDP, acute inflammatory demyelinating polyradiculoneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor-sensory axonal neuropathy; MFS, Miller-Fisher syndrome; NIND, non-inflammatory neurological disorders; HC, healthy controls; Anti-GS-ab, anti-ganglioside-antibody; CSF, cerebrospinal fluid; HFS, Hughes functional score; SD, standard deviation; IQR, interquartile range;  $\beta$ 2-MG, beta-2-microglobulin; LDH, lactate dehydrogenase. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  in comparison with NIND



**Fig. 1** CSF concentrations of  $\beta$ 2-MG in patients with GBS, subtypes of GBS and NIND. CSF, cerebrospinal fluid;  $\beta$ 2-MG, beta-2-microglobulin; LDH, lactate dehydrogenase; GBS, Guillain-Barré syndrome; AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor-sensory axonal neuropathy; MFS, Miller-Fisher syndrome; Unclassified, unclassified patients; NIND, non-inflammatory neurological disorders. \* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$

patients with GBS. The significant correlation between CSF  $\beta$ 2-MG and LDH levels was observed in patients with GBS ( $r = 0.568$ ,  $p < 0.001$ ). However, there were no significant correlations between CSF  $\beta$ 2-MG levels and plasma  $\beta$ 2-MG ( $r = 0.252$ ,  $p = 0.107$ ) or CSF lactate levels in patients with GBS ( $r = 0.233$ ,  $p = 0.103$ ). Moreover, CSF  $\beta$ 2-MG levels were significantly positively correlated with plasma  $\beta$ 2-MG, CSF LDH, and CSF lactate levels in AIDP patients (Fig. 2a,  $r = 0.793$ ,  $p < 0.001$ ; Fig. 2b,  $r = 0.796$ ,  $p < 0.001$ ; Fig. 2c,  $r = 0.481$ ,  $p = 0.037$ ). However, there were no significant correlations between CSF  $\beta$ 2-MG levels and CSF levels of LDH and lactate in other subgroups.

### Correlation between $\beta$ 2-MG levels and other clinical characteristics in patients with GBS

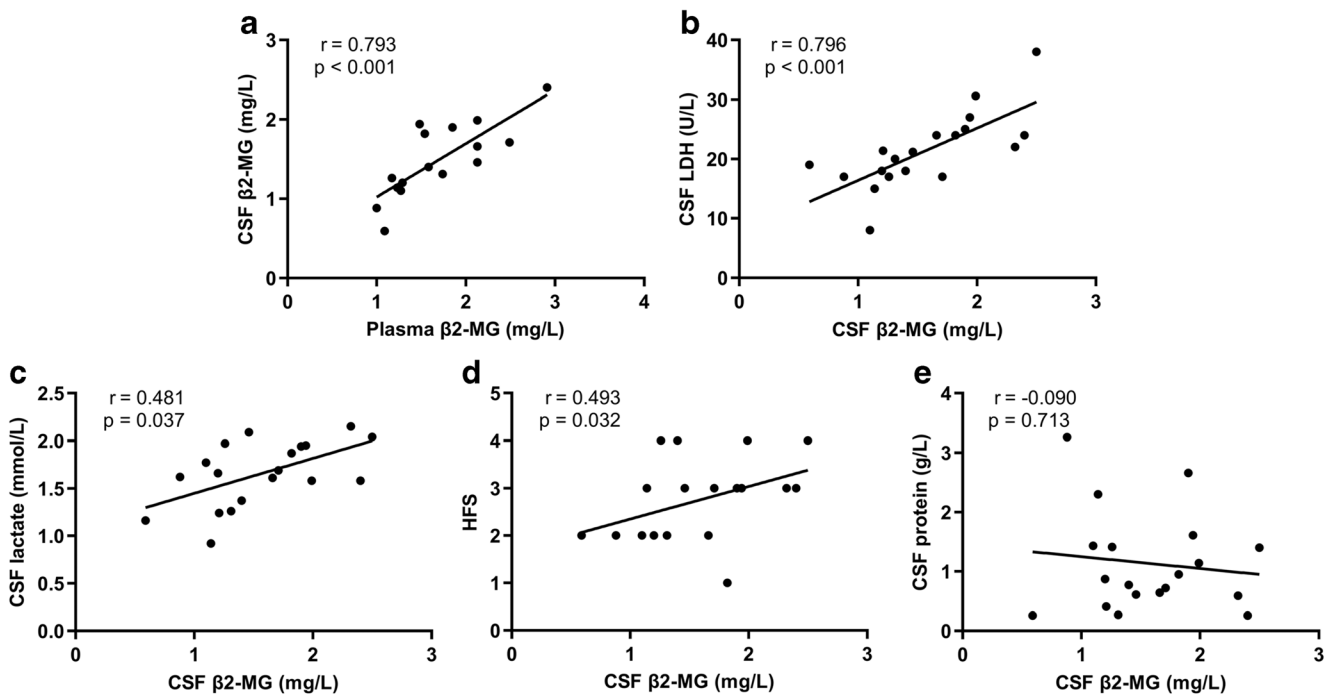
Several studies have confirmed the concentration of  $\beta$ 2-MG in CSF was related to the age [15–17]. We also confirmed that CSF  $\beta$ 2-MG levels were correlated with age in patients with GBS ( $r = 0.524$ ,  $p < 0.001$ ), AIDP ( $r = 0.631$ ,  $p = 0.004$ ), and NIND ( $r = 0.644$ ,  $p = 0.001$ ). In addition, positive correlation between CSF  $\beta$ 2-MG levels but not CSF LDH or lactate levels and HFS was observed in patients with AIDP (Fig. 2d,  $r = 0.493$ ,  $p = 0.032$ ). However, no correlation was found between CSF  $\beta$ 2-MG levels and HFS in patients with GBS ( $r = 0.169$ ,  $p = 0.241$ ). Moreover, though in our study CSF protein levels were higher in patients with AIDP (Table 1),

no correlation was found between CSF  $\beta$ 2-MG and protein (Fig. 2e,  $r = -0.090$ ,  $p = 0.713$ ).

## Discussion

$\beta$ 2-MG is a component of MHC class I molecule which plays an important role in T cell-mediated immune activation by participating in antigen presentation. There is evidence that cells lack of  $\beta$ 2-MG significantly reduced the immunogenicity to CD8<sup>+</sup> T cells [18]. Therefore, we consider that  $\beta$ 2-MG may be a protein related to T lymphocyte activation. Besides, CSF  $\beta$ 2-MG levels were increased in autoimmune diseases, such as multiple sclerosis, neuro-Behcet's disease, and neurosarcoidosis, in which T cells play a role [12, 19–21]. Thus, we investigated the CSF and plasma levels of  $\beta$ 2-MG in patients with GBS, and found that CSF  $\beta$ 2-MG levels in GBS patients were significantly increased in our study. We suspect this finding may result from the immune activation which occurred on proximal nerve roots. It has been demonstrated that dorsal root ganglia and dorsal roots are in direct contact with the CSF in the subarachnoid space [22], and this physiological structure creates a pathway for inflammatory signaling molecules affected by local nerve injury entering into CSF. Besides, in the pathogenesis of GBS, the breakdown of blood-nerve-barrier (BNB) and blood-CSF-barrier (BCB) may be a key event [23, 24]. Previous study supported the theory that protein can leak from blood through the blood-nerve barrier [25]. In our study, the strong correlation of  $\beta$ 2-MG between CSF and plasma in AIDP patients may be also attributed to the dysfunction of BNB and BCB. However, although we found plasma  $\beta$ 2-MG levels were increased in patients with GBS, the trend was not statistically significant. This may be due to the limited sample size of our study.

Our study showed CSF  $\beta$ 2-MG levels were significantly increased, especially in patients with AIDP but not in other subgroups. It has been demonstrated that antibodies and complement are involved in the pathogenesis of GBS [26–28]. However, unlike in other subtypes, specific antibody biomarkers in AIDP have not been identified [1]. Previous study has showed that T cells are abundant in early lesions of AIDP, and circulating activated T cells and serum soluble IL-2 receptor concentrations are increased in the acute stage [29], indicating that T cell-mediated immunity directed against unknown antigens on the surface of Schwann cells or the myelin sheath may play a great part in the pathogenesis of AIDP [30]. One hypothesis suggests that activated T cells penetrate the endothelium and release cytokines that activated endoneurial macrophages which ultimately invade myelin by the subsequent release of toxic mediators [30, 31]. Though another hypothesis suggests that an antibody-mediated attack fixes complement to the outer layer of the Schwann cell membrane and causes vesicular dissolution [27], the two mechanisms are



**Fig. 2** Correlations between plasma levels of  $\beta 2$ -MG, CSF levels of LDH and lactate as well as HFS and CSF  $\beta 2$ -MG levels in patients with AIDP. **a** Correlation between CSF  $\beta 2$ -MG and plasma  $\beta 2$ -MG levels in patients with AIDP. **b** Correlation between CSF levels of  $\beta 2$ -MG and LDH in patients with AIDP. **c** Correlation between CSF levels of  $\beta 2$ -MG and lactate in patients with AIDP. **d** Correlation between CSF  $\beta 2$ -MG

levels and HFS in patients with AIDP. **e** Correlation between CSF levels of  $\beta 2$ -MG and protein in patients with AIDP. CSF, cerebrospinal fluid;  $\beta 2$ -MG, beta-2-microglobulin; LDH, lactate dehydrogenase; HFS, Hughes functional score; AIDP, acute inflammatory demyelinating polyneuropathy

not mutually exclusive. Therefore, we suppose the T cell-mediated immune response may be related to the increase of CSF  $\beta 2$ -MG levels in patients with AIDP. Moreover, in our study, we found CSF  $\beta 2$ -MG levels were positively related to the HFS at nadir in patients with AIDP. This suggests that  $\beta 2$ -MG may have potential value to be a marker of disease severity of AIDP.

LDH is a tetrameric enzyme that increases the rate of interconversion of pyruvate to lactate. It is an accepted marker for cellular damage, released by all types of cells after loss of membrane integrity [32]. It is generally considered that poor CNS oxygenation or high metabolic activity may increase lactate concentration in the CSF [33, 34]. However, recent studies reported that during the rapid proliferation of antigenic stimulated T cells, glucose was utilised for aerobic glycolysis, which resulted in the generation of extracellular lactate [35]. This phenomenon has been demonstrated in some autoimmune diseases such as rheumatoid arthritis [36]. In our study, CSF LDH levels were also increased in patients with GBS and AIDP, which was consistent with previous study [37]. Besides, we also found that CSF lactate levels were significantly increased in patients with GBS, especially in AIDP. There were significant correlations between CSF LDH, lactate levels, and  $\beta 2$ -MG levels in patients with AIDP, which may be the secondary effects of immune attack and immune stimulation. The poor correlation between CSF  $\beta 2$ -MG and

protein also supports the increase of CSF  $\beta 2$ -MG which may not be simply due to a leakage of the proteins through BCB and BNB, but the presence of some degree of intrathecal immune activation. However, we did not find a correlation between CSF LDH or lactate levels and the HFS at nadir in patients with AIDP, suggesting that these two indicators lack specificity in patients with AIDP.

There are some limitations in our study. First, the sample size of this study is small and we did not obtain samples from patients with GBS after treatment. Second, we did not explore the exact mechanisms underlying the interaction of  $\beta 2$ -MG and T cell activation. Further studies are needed to explore the CSF and plasma levels of  $\beta 2$ -MG and their underlying mechanisms in patients with GBS.

## Conclusions

The main findings of this retrospective study were that CSF  $\beta 2$ -MG levels were significantly increased in patients with AIDP and positively correlated with HFS, suggesting that CSF  $\beta 2$ -MG may be a potential biomarker for AIDP and may have potential value to predict the disease severity. Moreover, CSF LDH and lactate levels were elevated and correlated with CSF  $\beta 2$ -MG levels in patients with AIDP.

The mechanisms underlying these interactions need further exploration.

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**Author contributions** Ming-Qi Liu: experimental design, manuscript writing, data analysis. Jing Wang: data collection and collation. Chen-Na Huang: data collection. Yuan Qi: experimental design, manuscript revising. Lin-Jie Zhang: manuscript revising, acquisition of funding. Ming Yi: manuscript revising. Sheng-Hui Chang: data analysis. Li-Sha Sun: technical help, experiment implementation. Li Yang: experimental design, acquisition of funding.

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**Availability of data and material** The data that support the findings of this study are available on reasonable request from the corresponding author.

**Code availability** Not applicable for this study.

## Declarations

**Conflict of interest** The authors declare no competing interests.

**Ethics approval** The study was approved by the ethics committee of Tianjin Medical University General Hospital and followed the principles outlined in the Declaration of Helsinki for all human experimental investigations.

**Informed consent** Informed consent was obtained from all participants included in the study.

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