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Decreased intrathecal synthesis of prostaglandin D_2 synthase in the cerebrospinal fluid of patients with acute inflammatory demyelinating polyneuropathy

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ABSTRACT

Prostaglandin D_2 synthase (PGDS) is the most abundant brain protein in cerebrospinal fluid (CSF) and is tied closely with inflammatory processes. This study investigated whether CSF PGDS levels in patients with acute inflammatory demyelinating polyneuropathy (AIDP) are altered. The results suggest that PGDS concentration is significantly increased in the CSF of AIDP patients compared with the control patients ($p<0.05$) due to a blood-CSF barrier dysfunction, whereas the intrathecal synthesis of PGDS, reflected by the CSF PGDS/albumin ratio, is significantly decreased in AIDP compared with the control group ($p<0.05$). The changes of CSF PGDS/albumin ratio are only observed in AIDP patients, but not in Miller Fisher Syndrome (MFS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), or multiple sclerosis (MS) patients.

1. Introduction

Guillain-Barre´ syndrome (GBS) is an acute inflammatory disease involving the peripheral nervous system (PNS), and characterized by acute limb weakness over days to 4 weeks. GBS is the major cause of acute neuromuscular paralysis around the world, with annual incidence of 0.6 to 4 cases per population of 100,000 (Hughes and Rees, 1997). GBS consists mainly of four subtypes, including acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN), and Miller Fisher syndrome (MFS) (Fisher, 1956; Feasby et al., 1986; McKhann et al., 1993; Hughes and Cornblath, 2005). These subtypes are considered as autoimmune disorders and antecedent infection has been identified in some cases. AIDP is the most common subtype of GBS in the North America and Europe, whereas AMAM and AMSAM, involving predominantly axons, are more frequently diagnosed in Japan and China (Ho et al., 1995; Griffin et al., 1995; Ogawara et al., 2000). The MFS subtype, which has the triad of ophthalmoplegia, ataxia, and areflexia, is less associated with limbs weakness or respiratory failure (Hughes and Cornblath, 2005).

Diagnosis of GBS depends on the clinical presentation, laboratory data, and electrophysiological test (Asbury and Cornblath, 1990). An elevated CSF protein concentration with albuminocytologic dissociation is present in about 85% of patients 2–3 week after the onset of disease (Paradiso et al., 1999), but the nature of the altered CSF proteins has only recently been explored in a few studies of differentially-expressed proteins in the CSF of GBS using proteomics (Chang et al., 2007; Jin et al., 2007; Lehmensiek et al., 2007). In one of our previous studies, two-dimensional electrophoresis (2-DE) and mass spectrometry were applied to analyze the protein profiles in the CSF of GBS patients, which revealed three up-regulated proteins (orosomucoid, haptoglobin, and apolipoprotein A-IV) and two down-regulated proteins (prostaglandin D_2 synthase [PGDS], and transthyretin) (Chang et al., 2007). Increased intrathecal synthesis of haptoglobin was specifically demonstrated for GBS patients (Chang et al., 2007), probably resulting from astrocyte secretion activated by pro-inflammatory cytokines. While GBS is an inflammatory disease involving predominantly the peripheral nerves, central nervous system (CNS) lesions secondary to the pathological progress in the PNS were found with microglial activation and inflammatory infiltration in the spinal ganglia, spinal posterior tracts, and brain stem (Maier et al., 1997). For this reason, we investigated whether other CNS proteins are involved in the inflammatory process and whether they are specific to GBS, which may shed light on the pathophysiology of GBS. PGDS is the most abundant brain-synthesized protein in the CSF and has the ability to catalyze prostaglandin H_2 (PGH_2) to prostaglandin D_2 (PGD_2) that is one of the inflammatory cytokines. Although the phenomenon of down-regulated CSF level of PGDS has been observed in GBS patients in our previous study (Chang et al., 2007), the case number was too small to make a difference statistically and whether such alteration is also

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present in other neurological diseases is unknown. Therefore, in the present study, we used western blot analysis to validate changes in the CSF PGDS in a large series of AIDP patients and investigated if it is also altered in other neuroinflammatory diseases.

2. Materials and methods

2.1. Patients and sample preparation

CSF samples from 18 AIDP (6 females, 12 males, mean age 42.28±3.80 years), 9 MFS (5 females, 4 males, mean age 51.67±8.13 years), 10 chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) (5 females, 5 males, mean age 43.40±3.12 years), and 14 multiple sclerosis (MS) (9 females, 5 males, mean age 33.86±2.92 years) patients were collected. Patients with AIDP fulfilled the standard diagnostic criteria (Asbury and Cornblath, 1990). The patients with other neurological diseases, including MS (McDonald et al., 2001) and CIDP (Van den Bergh and Pieret, 2004), all fulfilled the respective diagnostic criteria. The severity of AIDP was graded using a functional scale modified from Hughes et al. (1978) at the time of their maximum neurological deficit during admission to the hospital as well as three months after recovery during outpatient clinical follow-up. Eighteen CSF and serum samples were obtained from the control patients (11 females, 7 males, mean age 45.17±4.17 years) who were admitted due to migraine, tension headache, spontaneous intracranial hypotension, and degenerative spine diseases. These control patients were confirmed to have no systemic infection; chronic renal, cardiac or liver dysfunction; autoimmune diseases; or malignancies. Examination of the control CSF samples also showed an absence of inflammation (no pleocytosis). Eighteen, 11, 10, and 15 CSF samples from the 18 controls were used for comparison with the AIDP, MFS, CIDP, and MS groups, respectively. A standard case collection form was used to record age of onset, gender, clinical manifestations, and results of CSF and serum biochemistry surveys. Venous blood was sampled simultaneously with the CSF sampling for each subject. CSF and serum examinations were performed after obtaining informed consent from the patients and control individuals. This study was performed under a protocol approved by the institutional review boards of Chang Gung Memorial Hospital (ethical license No: 96-0285B).

CSF samples were centrifuged immediately after collection, aliquoted, frozen at −80 °C, and stored until analysis. Serum samples were maintained at 4 °C for 1 h and then centrifuged, aliquoted, frozen at −80 °C, and stored until analysis. White blood cell counts, total protein concentration, and albumin concentration of the CSF and

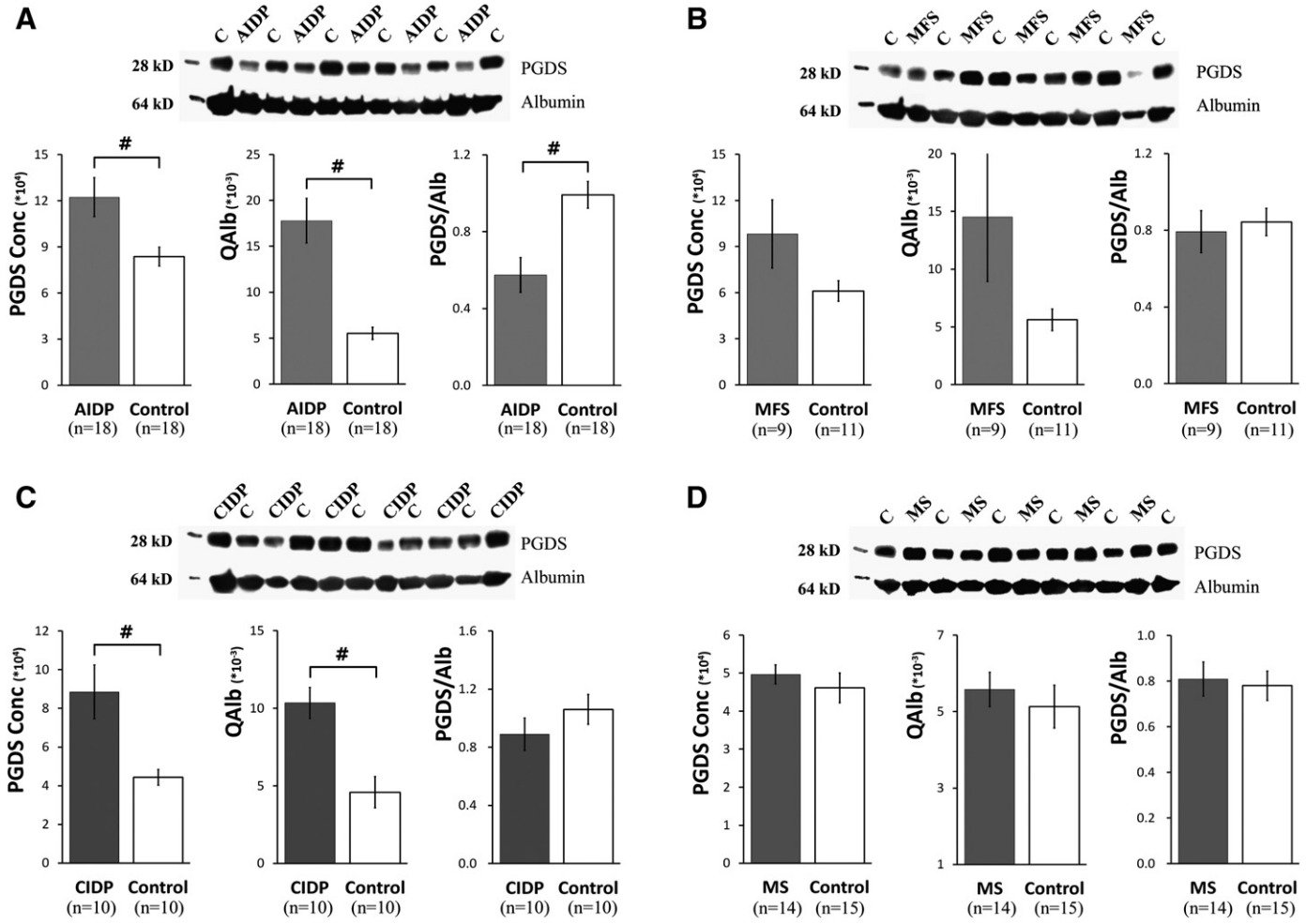

Fig. 1. Representative Western blots of CSF PGDS (28 kD) and CSF albumin (64 kD) in acute inflammatory demyelinating polyneuropathy (AIDP), Miller–Fisher syndrome (MFS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and multiple sclerosis (MS) patients and their corresponding controls (C) (upper panel in A, B, C and D). The results for CSF PGDS concentration (Conc), Q_{Alb} and CSF PGDS/Alb ratio for each disease group in comparison with their corresponding control groups are illustrated with bars (mean±SE) (lower panel in A, B, C and D). In AIDP patients, the CSF PGDS concentration and Q_{Alb} are significantly increased and the PGDS/Alb ratio is significantly decreased versus the controls (A). The CSF PGDS concentration and Q_{Alb} are significantly increased in the CIDP patients, but the CSF PGDS/Alb ratio in the CIDP patients is not significantly changed compared with the controls (C). The CSF PGDS/Alb ratio, CSF PGDS concentration, and Q_{Alb} of MFS (B) and MS patients (D) are not significantly different from that of their corresponding controls. # indicates a significant difference compared to the controls, $p<0.05$, two-tailed Student's t test.