Cerebrospinal fluid biomarkers in Guillain-Barré syndrome – Where do we stand?

Abstract Guillain-Barré syndrome (GBS) is an acute inflammatory polyneuropathy affecting the myelin-protein sheathing and the axons themselves to various degrees. Damage to these structures causes biomarkers to be released into the adjacent body fluid compartment. In case of the proximal nerve roots these biomarkers diffuse into the cerebrospinal fluid (CSF). Here we review the literature on CSF biomarkers in GBS, including a discussion of CSF basic findings, myelin sheath-associated markers (myelin basic protein), axonal damage markers (neurofilaments, tau, anti-ganglioside antibodies), glial and neuronal markers (neuron specific enolase, 14-3-3 proteins, S100B, hypocretin-1), immunological markers (different chemokines and complement factors, cystatin C, tumor necrosis factor-α) as well as recent advances in the field of CSF proteome analysis in GBS. Second, the different pathophysiological mechanisms reflected by these biomarkers are discussed. Finally, candidate biomarkers are reviewed with regard to their clinical relevance to act as a surrogate for the disease process, their value for improving prognostic accuracy and their potential to be used as predictors of treatment response.

Key words Guillain-Barré syndrome · cerebrospinal fluid · biomarkers

Introduction

Guillain-Barré syndrome

Guillain-Barré syndrome (GBS) is an acute inflammatory polyneuropathy that consists of several pathophysiologically distinct subtypes [25]. In western countries, the most common subtype is acute inflammatory demyelinating polyradiculoneuropathy (AIDP), while rarer forms including acute motor axonal neuropathy (AMAN) or acute motor and sensory axonal neuropathy (AMSAN) are characterized by primary axonal degeneration [15, 24, 25].

GBS is a frequently postinfectious immune-mediated disease with both cellular and humoral immune mechanisms contributing to the pathology. A number of infectious agents are thought to induce antibody production against specific gangliosides and glycolipids, such as GM1 and GD1b, distributed throughout the myelin in the peripheral nervous system [76]. The best established link for an antecedent illness triggering the development of GBS exists for Campylobacter jejuni infections [15, 56]. Griffin et al. and Yuki et al. discussed the evidence for a glycolipid expressed on axons, the ganglioside GM1 and GD1a, which could cross-react with lipooligosaccharides expressed on C. jejuni [15, 64, 80]. This process known as carbohydrate mimicry triggers an immunological cascade, which strips the axon of its myelin sheet with resulting conduction block and demyelination of the peripheral and autonomous nervous system, thus causing the typical symptoms in GBS [16, 21].
plements as discussed below further contributes to nerve damage. This mechanism is corroborated by the immuno-histochemistry in nerve biopsies and post-mortem material from patients with GBS [55]. There is clear evidence for lymphocytic infiltration of the spinal roots and peripheral nerves, followed by macrophage-mediated multifocal stripping of myelin [55]. This phenomenon results in disruption of nodal sodium channel clusters, detachment of paranodal myelin terminal loops and thus defects in the propagation of electrical nerve impulses with eventual conduction block and flaccid paralysis. In some patients with severe disease, a secondary consequence of the severe inflammation is axonal disintegration and loss, whereas a subgroup of patients may have a primary immune attack directly against axons [15].

So far, the pathogenesis of GBS as well as the relation between the different pathophysiological subtypes remains controversial. While the pathomechanisms underlying AIDP have been associated with T cell immunity directed against myelin proteins [31, 56], antibodies against gangliosides on the axolemma have been suggested to be responsible for the primary axonal subtypes [16, 21].

**Anatomy and pathology of the blood-CSF barrier in the spinal nerve roots**

The proximal parts of the dorsal and ventral nerve roots are located in the subarachnoid space floating freely in the cerebrospinal fluid (CSF). The subarachnoid space also contains numerous small arterioles and capillaries (Fig.1). The nerve roots as well as the vessels in the subarachnoid space are partially covered by pia mater, which is composed of several layers of meningeal cells. The capillary walls consist of endothelial cells, separated by an interval of 300 Å from a basement membrane of approximately the same width [12]. Where endothelial cells overlap, there are tight junctions between their cell membranes. The basement membrane separates the endothelial cells from the extracellular space of the nervous system. It consists of filaments and granules around the limit of resolution of the electron microscope [12].

In GBS, light microscopy of nerve roots revealed swelling and fragmentation of myelin. There was an infiltration of mononuclear cells into the nerves, with some macrophages being filled with large amounts of myelin [21]. The most common pattern of myelin disruption was found to be an unraveling of individual myelin lamellae simultaneously externally and adjacent to the axoplasm [21].

In GBS, a leak of plasma proteins from the nerve root blood vessels into the CSF could be caused by a disturbance of microcirculation as a result of the swelling of the nerve root, which may lead to retrograde stasis of capillaries due to venular congestion. Another factor may be a release of vasoactive substances like calcitonin gene-related peptide (CGRP) and substance P [67]. Neuropeptides such as substance P and CGRP are produced in the dorsal root ganglion [14]. Substance P and CGRP cause plasma extravasation on the blood vessels and substance P leads to vascular dilatation by releasing histamine [14].