

## **Toward a standardized analysis of CSF in inflammatory neuropathies.**

*Commentary on «Oligoclonal IgG bands in inflammatory and non-inflammatory polyneuropathies»*

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**No evidence of CSF-restricted humoral response in CIDP.** The diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) typically relies on clinic and electrodiagnostic findings. A spinal tap and cerebrospinal fluid (CSF) analysis are sometimes performed, and an increased protein level in the CSF can be used as supportive diagnostic criteria.

However, the identification of increased CSF proteins with normal cell count, also referred to as albuminocytologic dissociation, is not specific to CIDP and can be observed in other inflammatory and non-inflammatory conditions affecting the central and/or peripheral nervous system (CNS a/o PNS), as well during aging, so that its interpretation in a patient with peripheral neuropathy is cumbersome.

Moreover, unique-to-CSF oligoclonal bands (OCBs) of immunoglobulin G, which represent the hallmark of a CSF-restricted neuroinflammation with intrathecal antibody production as seen in multiple sclerosis, have been previously reported in inflammatory neuropathies.

In particular transient CSF-restricted OCB have been observed in Guillain-Barré syndrome (GBS) (1), while a single IgG band was reported in chronic relapsing polyneuropathies (2).

However, their frequency and relevance in CIDP is questionable because of suboptimal and heterogeneous techniques used for their detection in previous studies.

In the paper by Ruiz M et al *on p XXX* (3) the authors reassessed with up-to-date and standardized techniques the role of CSF analysis in the diagnostic work-up of CIDP compared to either inflammatory, including GBS, anti-MAG antibody and multifocal motor neuropathy or non-inflammatory peripheral neuropathies (NINPs)

In particular, OCBs were found in 1/32 (3%) cases with NINP and 1/48 (2%) CIDP patients, confirming that OCBs are absent or very rare in CIDP. A mirror pattern, with systemic OCBs production but absent intrathecal IgG synthesis and possibly reflecting an ongoing peripheral antibody production, either in the context of autoimmunity or infection, was identified in thirteen (40.6%) patients with GBS vs nine (19%) patients with CIDP, three (16.6%) with anti-MAG antibody neuropathy and four (12.5%) with NINP. While CSF-restricted humoral response does not appear to be a feature of CIDP, a possible role of systemic humoral immune response activation in CIDP, as also supported by the recent identification IgG4 antibodies against nodal and paranodal

antigens in subsets of CIDP patients (4), as well as the contribution of infectious triggers, remains to be confirmed by future studies.

As an added value of their report, the authors tested in CIDP the use of albumin quotient ( $Q_{\text{alb}}$ = CSF/serum albumin ratio) and age-corrected blood-spinal nerve root barrier (B-SNR-B) damage index as a more accurate marker of inflammation-dependent increased permeability of the blood-nerve barrier. Despite being recommended for the assessment of albumin-cytological dissociation in CIDP,  $Q_{\text{alb}}$  and B-SNR-B are rarely used in clinical practice and most laboratories still rely on total protein count (5). Although the study did not show a significant difference in the percentage of patients with raised protein level or B-SNR-B damage, the use of  $Q_{\text{alb}}$  and B-SNR-B seems a reasonable approach, limiting the occurrence of false positive (e.g., increased concentration of plasma proteins from previous therapy with intravenous immunoglobulin or in case of paraproteinemia) or false negative results (e.g., low concentrations of plasma proteins from kidney or liver diseases) (6).

Larger multicenter studies are thus warranted both to validate the use of  $Q_{\text{alb}}$  and B-SNR-B damage index and to achieve a shared consensus about technical and interpretative guidelines for the analysis of CSF in inflammatory disorders of the PNS, and assess their impact on the clinical management of CIDP patients

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