Peer Review File

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Reviewer Comments

Reviewer comment 1:
-- I think some mention should be given in Introduction or Discussion that apart from neurodegenerative disease, the field of CNS infections also heavily depends on CSF analyses for diagnostic purposes and, thus, high quality material for biomarker studies. The paper on kynurenine by Sühs KW et al. J Inf Dis 2019; 220:127-138 might serve as a good example, and might be of particular relevance to the present paper because in that study the authors decided to use a mix of various noninflammatory CNS disorders as "normal" controls (none of which could be considered really normal).

Author response:
Thank you for pointing this out. We use the term “Neuropsychiatric disorders” because our study applies to a broad spectrum of CNS disorders, including CNS infections. We do sometimes highlight neurodegenerative disorders, because most initiatives of CSF biobanking focus on these diseases. However, we agree that some mention should be given to CNS infections, as the immune response is not only involved in fighting the infection, it can also be responsible for some of the consequences of CNS infections.
We have added the following sentences about CNS infections (highlighted in red) to the introduction (Page 4, Line 92-99):
“For a long time, the main source of information about the CSF was from analysis of CSF from patients with suspected bacterial meningitis. More recent work has progressed beyond the traditional biochemical and microbiological analyses in these patients. A recent example is a study that investigated the role of the tryptophan – kynurenine – nicotinamide adenine dinucleotide pathway in patients with acute CNS infections (bacterial and viral), but then compared the findings with those from patients with auto-immune encephalitis, multiple sclerosis, and patients with non-inflammatory CNS conditions who cannot be considered to be neurologically normal [Sühs et al. 2019].

To do this, however, it was necessary to shuffle other sentences around, to maintain a consistent flow of ideas and topics, and to improve readability. Sentences that have been moved are highlighted green. We also made minor deletions of repetitive text to try to keep the overall length of the introduction the same as it was before.

Reviewer comment 2:
-- Please discuss why several other standard CSF parameters are not being measured upon sample collection, e.g. lactate, immunoglobulins.

Author response:
In our hospital, albumin, total protein, glucose and cell count are routinely analyzed, but not lactate or immunoglobulins.
Spinal anesthesia is contraindicated in patients with clinical signs of infection and in patients with significant cardiovascular disease. Neurological diseases with a significant inflammatory component are usually also regarded as a contraindication for spinal anaesthesia. In particular, spinal anaesthesia is usually avoided in MS, and in patients with dementia sufficient to impair their ability to co-operate. For this reason, we did not consider it a priority to routinely measure immunoglobulins or lactate.
We do measure CSF leukocyte count, which is also a good indication for inflammatory processes (as the paper by Sühs KW et al. states; CSF leukocyte count is a good marker to distinguish between bacterial or viral CNS infections and autoimmune inflammation, and noninflamed controls)
Having said that, as we keep up to 8ml of CSF from each patient, it might be possible to perform these assays at a later stage.
For now, we have not amended the text, but should you wish us to, then we would be happy to do so.