Reviewer's report

Title: Elevated Nerve Growth Factor and Neurotrophin-3 Levels in Cerebrospinal Fluid of Children with Hydrocephalus

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Reviewer: Dr Marrianne Juhler

Level of interest: A paper whose findings are important to those with closely related research interests

Advice on publication: Other (see below)

The authors present the results of immunosorbent assay for NGF and Neurotrophin-3 in the cerebrospinal fluid of 42 hydrocephalic children at different ages (0.4 - 14.3 yrs). The results are compared to a control group of 22 children with a similar age distribution. The levels of NGF are significantly elevated in hydrocephalics compared to controls. Similar, but less significant results were obtained for Neurotrophin-3.

The concept in academically interesting in addressing question of predicting the long-term outcome in treated hydrocephalus, and it is a clinically relevant issue to define a measurable parameter to aid the often difficult question of shunt-malfunction.

The paper is written in quite good English and needs no language revision.

The following comments can be made on the datapresentation, data analysis and the conclusions:

. the main conclusion is that elevated levels of both proteins are created as an adaptive response of the brain to prolonged increase of ICP. There is, however the paper contains no documented data of ICP, which could have been fairly easily obtained. Thus the main conclusion is not sufficiently supported.
. A number of statements are made on their relation between NGF and various clinical parameters (age, presence or absence of headache, other typical symptoms of elevated ICP, different etiologies of hydrocephalus). These interpretations are simply stated without the aid of data (e.g. in tables), and the reader is left with no possibility to evaluate the validity of these conclusions. The lack of an age distribution table/figure and a table depicting the relation between etiologies and the protein levels is particularly felt.
. the possibility of hydrocephalus severity or duration to elevated protein levels is not presented at all
. the CSF samples are collected at different times during the course of diagnosis and treatment of hydrocephalus. This inconsistency in data sampling carries a risk for the validity and comparability of the raw data, as the protein levels could potentially vary in response to e.g. sequential taps or to a shunting procedure.

. A mean of 1.5 samples were obtained per patient - are some patients represented several times in the data and others only once? If so, this could influence both the mean and range/distribution of data.

. 9 samples of the total 65 samples (almost 15%) have a very low or unmeasurable level of NGF. Obviously, a biomodal distribution of NGF in hydrocephalics must be contemplated. How are the low-NGF-value patients different from patients with elevated levels of NGF.

. the authors correctly speculate that NGF and Neurotrophin-3 are probably both produced intrathecally. This question could be easily answered by measuring and calculating the indices to albumin similar to the way this is done to demonstrate intrathecal IgG synthesis in multiple sclerosis.

In conclusion, the paper is highly relevant to pediatricians and neurosurgeons, but unfortunately there are serious shortcomings in the analysis and presentation of the data. As a result of these shortcomings, the conclusions seem less solid than they probably are. The general impression is thus, that the paper seems "premature" and would improve significantly by a thorough revision.

In its present form, it cannot be recommended for publication.

**Competing interests:**

None declared.