

Single Case – Headache

# A Case of HaNDL with Low Cerebrospinal Fluid Level of Neurofilament Light Chain

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## Keywords

HaNDL · Headache · Neurofilament light · Cerebrospinal fluid · Diagnosis

## Abstract

Diagnosis of the syndrome of headache and neurological deficits with cerebrospinal fluid (CSF) lymphocytosis (HaNDL) is based on clinical features, and no diagnostic biomarkers are available. We present a case presenting with characteristic features of HaNDL and an MRI lesion in the splenium of corpus callosum. CSF neurofilament light chain (NFL) levels were assessed in this patient together with 7 additional HaNDL patients, 18 multiple sclerosis (MS) patients, and 15 primary headache patients. Both HaNDL and primary headache patients showed significantly lower NFL levels than MS patients. Our results suggest that increased CSF levels of NFL and neuroaxonal loss are not characteristic features of HaNDL. Neurological disorders mimicking HaNDL often present with increased levels of NFL, and thus CSF measurement of NFL might be useful in differential diagnosis of HaNDL.

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## Introduction

The syndrome of transient headache and neurological deficits with cerebrospinal fluid (CSF) lymphocytosis (HaNDL) is characterized by episodes of temporary neurological symptoms accompanied or followed by headache [1]. The diagnosis is established by clinical features, CSF findings, and exclusion of other etiologies. Several neurological disorders such as meningoencephalitis, stroke, and epilepsy may mimic HaNDL, and there are currently no diagnostic and prognostic biomarkers of disease.

An important question regarding pathophysiology of HaNDL is whether neurological symptoms are induced by neuro-destructive disease processes (e.g., viral infections or anti-neuronal autoimmunity) or merely by functional alterations (e.g., cortical spreading depression) in the cerebral cortex. CSF levels of neurofilament light chain (NFL), a protein of the neuronal cytoskeleton and a biomarker of axonal damage, have been found to be increased in several neurological disorders [2]. To find out whether neuroaxonal damage is an inherent feature of HaNDL, we measured CSF NFL levels in a cohort of HaNDL patients including an index patient with abnormal neuroimaging findings.

## Case Report

A 33-year-old man with no history of primary headache presented with a 4-day history of episodes of migraine-like headache and alternating hemiparesis lasting between 15 min to a few hours. He denied any symptoms between the episodes, and his neurological examination was normal on admission. Neuroimaging studies showed a non-contrast-enhancing T2 hyperintense lesion with restricted diffusion in the splenium of the corpus callosum. Blood biochemistry, complete blood count, antibodies for rheumatologic/vasculitic disorders and EEG were normal. His episodes subsided in 2 days under paracetamol treatment.

Two days later, he developed a 20-min episode of left hemiparesis and dysarthria followed by severe headache. CSF analysis showed increased white blood cells ( $16/\text{mm}^3$ ), elevated protein (146 mg/dL) and normal glucose concentration. Anti-neuronal antibodies associated with autoimmune encephalitis and paraneoplastic disorders were negative in serum and CSF, and no evidence of bacterial or viral pathogens were found. CSF level of NFL was 425 pg/mL (age-adjusted reference  $<500$ ). Next day, he had a 20-min episode of headache, dysarthria, and left hemiparesis. The patient remained symptom-free under flunarizine treatment in a 6-month follow-up. His repeat cranial MRIs (performed 2 and 6 months after discharge from the hospital) were normal, but a repeat CSF analysis was not available. The patient was diagnosed as having HaNDL despite having displayed an MRI lesion, since nonspecific transient brain lesions in corpus callosum and other regions have been previously described in HaNDL [3, 4].

## NFL Measurement in Patient Cohorts

To better characterize NFL levels in HaNDL, CSF levels of NFL were measured by ELISA (IBL International, Hamburg, Germany) in 18 relapsing remitting multiple sclerosis (RRMS) patients (11 women/7 men;  $32.9 \pm 4.6$  years old) fulfilling revised McDonald criteria [5], 15 patients with primary headache (9 women/6 men;  $33.4 \pm 4.8$  year-old), and 8 HaNDL patients including the above-described case (5 women/3 men;  $33.2 \pm 3.8$  years old) diagnosed as per

relevant criteria [1]. All CSF samples were obtained during the clinically active stage of the respective disorders and kept at  $-80^{\circ}\text{C}$  until use. CSF samples were obtained in primary headache patients to differentiate putative meningitis and/or brain hemorrhage and were found to have normal cell count and protein concentration. The number of episodes of HaNDL patients ranged between 3 and 8, and all HaNDL cases presented with a combination of two or more of hemiparesis, dysarthria, aphasia, and loss of consciousness. All HaNDL CSF showed increased white blood cell count (16–507/ $\text{mm}^3$ ) and protein level (56–146 mg/dL). Cranial MRI of the additional 7 HaNDL patients were normal. Patients with HaNDL and primary headache showed significantly lower CSF NFL levels than RRMS patients, samples of whom were used as positive control. There were no significant differences among headache and HaNDL patients (Fig. 1).

## Discussion

In contrast with MS, which is characterized with neuroaxonal degeneration and elevated CSF NFL levels [6], HaNDL patients showed lower NFL levels similar to headache patients. Thus, in line with the transient nature of the disease, permanent neuron death is not a prominent feature of the disease, and HaNDL symptoms are putatively caused by electrophysiological dysfunction of the neurons.

However, elevated CSF NFL levels were recently reported in 2 HaNDL patients [7]. These patients appear to have slightly more severe clinical features and enhanced findings of CSF inflammation than the herein presented index case. Nevertheless, other HaNDL patients in our cohort also showed lower NFL levels despite displaying loss of consciousness and higher cell counts in CSF. CSF NFL levels are often correlated with the MRI lesion load [2]. However, two previously reported HaNDL patients with elevated CSF NFL levels had normal neuroimaging results [7]. On the other hand, our index HaNDL case with an MRI lesion could have been expected to display increased NFL levels on the basis of neuroaxonal damage but by contrast showed normal CSF NFL levels suggesting that transient brain lesions in HaNDL do not necessarily indicate neuronal loss. A putative explanation of the discrepancy between our and previously reported HaNDL cases [7] might be the heterogeneous etiology of HaNDL. Higher NFL levels may have been caused by currently uncharacterized viral agents or anti-neuronal antibodies inducing central nervous system inflammation masquerading as HaNDL [8]. The least that can be asserted based on our results is that increased CSF levels of NFL are not a characteristic feature of HaNDL.

Notably, neurological disorders mimicking HaNDL (e.g., encephalitis and acute ischemic stroke) often present with remarkably increased CSF levels of NFL [9–11]. Therefore, CSF measurement of NFL might assist the differential diagnosis of HaNDL. Low CSF NFL levels may serve as an auxiliary finding that supports the diagnosis of HaNDL.

## Statement of Ethics

Study was approved by the institutional review board. Subjects have given their written informed consent to publish their case.

## Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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## Author Contributions

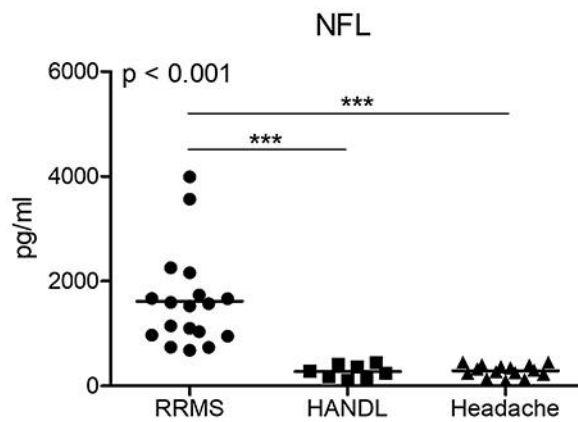
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**Fig. 1.** Cerebrospinal fluid neurofilament light chain (NFL) levels of patients with relapsing remitting multiple sclerosis (RRMS), HaNDL, and primary headache disorders. Horizontal bars indicate mean values. Statistical analysis by ANOVA yielded a  $p$  value of  $<0.001$  (upper left corner). \*\*\*  $p < 0.001$  by Tukey's post hoc test.