ADYNOVI®▼

(rurioctocog alfa pegol)

Takeda

Personalised prophylaxis to meet a wide range of activity demands according to patients' PK profile[1–5]

ADYNOVI is indicated for the treatment and prophylaxis of bleeding in patients ≥12 years with haemophilia A (congenital factor VIII deficiency).[1]

For long-term prophylaxis, the recommended dose is 40 to 50 IU/kg twice weekly at intervals of 3 to 4 days. Adjustments of doses and administration intervals may be considered based on achieved FVIII levels and individual bleeding tendency.[1]

LOW ABR[1,2,4,6]

- **90% ABR reduction with twice-weekly prophylaxis (n=120)**
  vs on-demand (n=17) treatment in patients with severe haemophilia A (absolute mean reduction 39.1: from 43.4 to 4.3) (primary endpoint met, p<0.0001)[*1,2,6]
- **Mean ABR 1.6 in real-world study**
  vs 6.2 with previous SHL FVIII (p=0.001) (n=30)[4]

WHAT TREAMENT GOALS DO YOU HAVE FOR YOUR PATIENTS?

- **How attainable are zero bleeds with a FVIII trough level of 8–12% vs 1–3%?**
  Clinically meaningful trend for improved bleed protection in some patients with a target FVIII trough level of 8–12% (62% [95% CI, 49–75%]; n=58) vs 1–3% (42% [95% CI, 29–55%]; n=57). (PROPEL proof-of-concept study: primary endpoint compared patients achieving zero bleeds at two FVIII levels [6-month dose adjustment period]; not significant; p=0.0545)[5]
- **Can dosing intervals potentially be extended in some patients?**
  Potential for reduced dosing frequency in some patients with zero spontaneous bleeds for 6 months on ADYNOVI prophylaxis (CONTINUATION study [n=151]: co-primary endpoints were incidence of confirmed FVIII inhibitory antibody development and ABR for all spontaneous bleeds)[†3]

ADYNOVI SAFETY PROFILE[1]

- Very common adverse reactions (≥1/10): headache. Common adverse reactions (≥1/100 to <1/10): diarrhoea, nausea, rash, dizziness
- Hypersensitivity or allergic reactions have been observed rarely and may, in some cases, progress to severe anaphylaxis (including shock)
- Development of neutralising antibodies to factor VIII (inhibitors) may occur

See the Summary of Product Characteristics for a full list of adverse reactions.

Suitable for use with myPKFiT™

SCAN QR CODE TO FIND MORE INFORMATION AND RESOURCES ON ADYNOVI VIA THE NEWLY LAUNCHED RARE DISEASE HUB.

Or speak to your Takeda representative to find out more.

VIEW PRESCRIBING INFORMATION & ADVERSE EVENT INFORMATION BY CLICKING ANYWHERE ON THIS PAGE.

ABR: annualised bleeding rate; CI: confidence interval; FVIII: factor VIII; PK: pharmacokinetic; SHL: standard half-life.

*Full-analysis set.[2,6]

†Study limitations: lack of randomisation, patient option to switch dosing regimen based on response, small patient numbers preventing robust data comparisons between subgroups, and point estimates of mean ABRs reported rather than median values to account for differences in follow-up periods between groups.

1. ADYNOVI UK Summaries of Product Characteristics (GB & NI). **2.** Konkle BA, *et al. Blood* 2015;126(9):1078–85. **3.** Chowdary P, *et al. Haemophilia* 2020;26(4):e168–78. **4.** Aledort L, *et al. J Manag Care Spec Pharm* 2020;26(4):492–503. **5.** Klamroth R, *et al. Blood* 2021;137(13):1818–27. **6.** Takeda data on file EXA/UK/ADYN/0001, November 2020.

Treatment should be under the supervision of a physician experienced in the treatment of haemophilia A.[1]
Intended for UK healthcare professionals who manage patients with haemophilia A.

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ADYNOVI▼
Rurioctocog alfa pegol
(Recombinant Coagulation Factor VIII)

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SHORT REPORT

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Screening for neurodegeneration in Langerhans cell histiocytosis with neurofilament light in plasma

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Summary

Patients with Langerhans cell histiocytosis (LCH) may develop progressive neurodegeneration in the central nervous system (ND-CNS-LCH). Neurofilament light protein (NFL) in cerebrospinal fluid (CSF) is a promising biomarker to detect and monitor ND-CNS-LCH. We compared paired samples of NFL in plasma (p-NFL) and CSF in 10 patients (19 samples). Nine samples had abnormal CSF-NFL (defined as ≥380 ng/l) with corresponding p-NFL ≥ 2 ng/l. Ten samples had CSF-NFL < 380 ng/l; eight (80%) with p-NFL < 2 ng/l ($p < 0.001$; Fisher's exact test). Thus, our results suggest that p-NFL may be used to screen for ND-CNS-LCH. Further studies are encouraged, including the role of p-NFL for monitoring of ND-CNS-LCH.

KEYWORDS
central nervous system (CNS), Langerhans cell histiocytosis, neurodegeneration, neurofilament light chain protein (NFL)

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INTRODUCTION

Langerhans cell histiocytosis (LCH) is an inflammatory myeloid neoplastic disorder with a wide range of clinical manifestations.[1,2] While survival recently has improved markedly,[1–3] long-term consequences are still frequent including various forms of central nervous system (CNS) involvement, here referred to as CNS-LCH.[1,2,4] A severe long-term complication is LCH-associated neurodegenerative CNS-LCH (ND-CNS-LCH), that may develop years after assumed remission.[1,2,4] It may present as cognitive and/or motor dysfunction that is often slowly progressive and diagnosed by characteristic magnetic resonance imaging (MRI) findings.[4] Patients with CNS-risk lesions, defined in Table 1, are particularly prone to develop diabetes insipidus (DI), and those with DI and/or *BRAF* V600E mutations to develop ND-CNS-LCH.[4,5] In a Swedish population-based study, at least 24% of all children diagnosed with LCH developed radiologic signs of ND-CNS-LCH which corresponds well with the reported 5.9% 15-year cumulative incidence of clinical ND-CNS-LCH in France, since 25% of patients with radiological ND-CNS-LCH have been reported to develop clinical ND-CNS-LCH.[5–7] There is, thus, an urgent need to prevent the development of neurodegeneration, such as by earlier detection and improved methods to monitor and evaluate treatment attempts.

Neurofilament light protein (NFL) in cerebrospinal fluid (CSF), a well-established biomarker of neuroaxonal damage, is a promising biomarker for ND-CNS-LCH.[8–11] However, lumbar puncture (LP) for CSF sampling requires sedation in small children and may, albeit rarely, be associated with complications.[12] We therefore initiated this pilot study with the aim of comparing NFL in plasma (p-NFL) and CSF (CSF-NFL) sampled simultaneously to see if they correlate, and if p-NFL can be used to screen for neurodegeneration and in therapeutic monitoring.

PATIENTS AND METHODS

Patients

We retrospectively studied all paediatric and adult LCH patients at Karolinska University Hospital, Stockholm, Sweden, with paired p-NFL and CSF-NFL samples from 1 December 2019 to 31 October 2021, to a total of seven children and three adults (n = 10). Consecutive samples were obtained from two children (five occasions each) and one adult (two occasions). In total, 19 paired blood and CSF samples were collected simultaneously.

All patients had biopsy-verified LCH at diagnosis, where nine were CD1a-positive and one diagnosed on morphology alone. *BRAF* V600E mutations were detected in five of six sequenced patients.

Clinical, laboratory and radiology data were extracted from the patients' medical files. The patient characteristics are presented in Table 1. The seven children's age at sampling ranged from 2.5 to 8.3 years (median 6.4 years). The three adults were diagnosed with LCH in adulthood and were 25–45 years old at sampling. Brain MRI was performed prior to 16 of the 19 samplings. Additional information on patients and sampling time points in relation to disease activity is presented in Text S1.

The study was approved by the Ethics Review Board of Sweden (2019-03956). Written informed consent was obtained from all patients.

Laboratory analyses

Cerebrospinal fluid-NFL concentration (normal reference value < 380 ng/l) was measured as a clinical laboratory routine assay at Karolinska University Laboratory, Stockholm, Sweden, using a commercial enzyme-linked immunosorbent assay NF-light kit (Uman Diagnostics, Umeå, Sweden).

Plasma was collected after ficoll separation of blood, aliquoted and frozen. Plasma-NFL concentrations were measured in samples collected at similar time points as the CSF using NF-Light Advantage Single molecule array (Simoa) assay on an HD-X Analyser, as described by the kit manufacturer (Quanterix, Billerica, MA, USA), at the Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden. The clinically validated lower limit of quantification of the assay was 2 ng/l.

Statistics

To evaluate the value of p-NFL for screening for abnormal CSF-NFL, Fisher's exact test was used. We also studied the strength and direction of the association between p-NFL and CSF-NFL using Kendall's tau-b (τb) correlation coefficient (two-sided test). In Figure S1, the correlation between p-NFL and CSF-NFL was calculated using Pearson correlation.

TABLE 1 Clinical, neuroradiological and neurochemical characteristics of the patients

Pat no[a]	Gender	Age at sampling (age at diagnosis)[b]	Maximal extent of disease[c]	Organs involved[d]	CNS-risk lesions[e]	Therapy prior to sampling[f]	Time from last therapy to sampling[b]	Extent of disease at sampling/*Organs involved at sampling*[g]	MRI findings at sampling/*Cognitive/neurological symptoms at sampling*	CSF-NFL (ng/l)/*p*-NFL (ng/l)[h]
1	Male	8 y 4 m (10 m)	MS RO−	Skin*, bone*, mucosa*, external otitis*	No	PRED, VBL, 6MP, MTX	5 y 4 m	NAD	Normal/*No*	260/<2
2	Female	2 y 8 m (8 m)	MS RO−	Skin*, bone*, lung*	Yes	PRED, VBL	Ongoing	NAD	Normal/*Stumbling (parent report)*	130/15
3	Male	6 y 10 m (2 y 9 m)	SS mf RO−	Bone*	Yes	Local (steroids), PRED, VBL, MTX, 6MP	2 y 3 m	NAD	Normal/*No*	140/<2
4	Female	7 y 0 m (1 m)	MS RO+	Skin*, spleen*	No	PRED, VBL, 6MP, MTX	3y 9 m	NAD	Normal/*No*	150/<2
5	Male	2 y 6 m (7 m)	SS mf RO−	Bone*	Yes	PRED, VBL, VCR, ARA-C, clofarabine	7 m	SS mf RO−/*Bones: occipital, ilium*	Normal/*No*	130/<2
6.1	Male	6 y 5 m (5 m)	MS RO−	Bone*, CNS (DI, ND)	Yes	PRED, VBL, VCR, ARA-C, MTX, 6MP, DEXA	1 y 10 m	NAD/*DI, ND*	Not done (earlier MRI: Signs of ND with increased signal in dentate nucleus since 2 years of age)/*Balance problems, reduced executive function, language disorder*	600/4.4
6.2	Male	6 y 11 m (5 m)				BRAFi	Ongoing	Uncertain (mastoiditis with negative microbiology and without LCH findings in biopsy)/*DI, ND*	Unchanged/*Unchanged*	270/2.4
6.3	Male	7 y 3 m (5 m)					4 m	Uncertain/*DI, ND*	Not done/*Unchanged*	540/5.6
6.4	Male	7 y 9 m (5 m)					10 m	MS RO−/*bones: temporal, DI, ND*	Unchanged/*Unchanged*	580/2.8
6.5	Male	8 y 1 m (5 m)				BRAFi (50% reduction)	Ongoing	NAD/*DI, ND*	Not done/*Unchanged*	380/2.4
7.1	Male	3 y 2 m (2 y 8 m)	MS RO−	Skin*, bone*, CNS (DI)	Yes	PRED, VBL, 6MP	Ongoing	MS RO−/*bones, DI, CNS*	Missing "bright spot", pituitary stalk enlarged/*No*	420/8.1
7.2	Male	3 y 6 m (2 y 8 m)				BRAFi	Ongoing	NAD/*DI*	Missing "bright spot", pituitary stalk normalized, pineal cyst smaller/*No*	240/<2

(Continues)

TABLE 1 (Continued)

Pat no[a]	Gender	Age at sampling (age at diagnosis)[b]	Maximal extent of disease[c]	Organs involved[d]	CNS-risk lesions[e]	Therapy prior to sampling[f]	Time from last therapy to sampling[b]	Extent of disease at sampling/*Organs involved at sampling*[g]	MRI findings at sampling/*Cognitive/ neurological symptoms at sampling*	CSF-NFL (ng/l)/*p*-NFL (ng/l)[h]
7.3	Male	3 y 9 m (2 y 8 m)				BRAFi	Ongoing	NAD/*DI*	Pituitary stalk normalized/*No*	200/<2
7.4	Male	4 y 3 m (2 y 8 m)				BRAFi	Ongoing	NAD/*DI*	Unchanged/*No*	170/<2
7.5	Male	4 y 7 m (2 y 8 m)				MTX, 6MP	Ongoing	NAD/*DI*	Unchanged/*No*	260/<2
8	Female	25 y (23 y)	MS RO−	Skin*, CNS* (DI*, ND*)	No	ARA-C, DEXA, BRAFi, MEKi, Cladribine, Clofarabine	3 m	Uncertain (suspected GI findings)/*DI, ND*	Unchanged signs of ND/*Ataxia, needs support for walking, nystagmus*	720/2.3
9.1	Male	39 y 0 m (25 y)	MS RO−	Skin*, CNS (DI, brain stem, suspected ND)	No	Radical surgery, PRED, Ara-C	2 y 11 m	MS RO−/*CNS, DI*	Missing "bright spot" and slightly thickened pituitary stalk unchanged. Possible ND lesions in cerebellum/*Memory*	970/2.0
9.2	Male	39 y 4 m (25 y)				Cladribine, DEXA	Ongoing	MS RO−/*CNS, DI*	Progress of possible ND lesions in cerebellum. Focal signal enhancement in brain stem/*Balance and memory problems*	1000/2.8
10	Female	45 y (40 y)	MS RO−	Skin*, adrenal gland, CNS (DI, suspected ND)	No	MTX	Ongoing	MS RO−/*DI, CNS, adrenal gland*	Thickened pituitary stalk. Pituitary adenoma. Unchanged susp signs of ND since last MRI 2 years ago/*No*	820/9

[a] *x*.1–*x*.5 are different samples from the same patient.
[b] m, months; y, years.
[c] SS, single system; uf, unifocal; mf, multifocal; MS, multisystem; RO+, risk organs involved; RO−, risk organs not involved.
[d] Organs involved at diagnosis (*); CNS, central nervous system [tumorous or focal Langerhans cell histiocytosis (LCH) lesions, including thickened pituitary stalk or neurodegenerative lesions in the CNS]; DI, diabetes insipidus; ND, neurodegeneration.
[e] Central nervous system (CNS)-risk lesions: craniofacial bones (orbit, temporal bone, mastoid, sphenoid, zygomatic, ethmoid, maxilla, paranasal sinuses, cranial fossa).
[f] PRED, prednisolone; VBL, vinblastine; 6MP, 6-mercaptopurine; MTX, methotrexate; VCR, vincristine; ARA-C, cytarabine; DEXA, dexamethasone; BRAFi, BRAF inhibitor; MEKi, MEK inhibitor.
[g] NAD, non-active disease.
[h] CSF-NFL, neurofilament light in cerebrospinal fluid; p-NFL, neurofilament light in plasma.

RESULTS

Correlation between plasma-NFL and CSF-NFL

Plasma-NFL levels ranged from <2–15 ng/l and CSF-NFL from 130–1000 ng/l. Using Kendall's tau-b, we found an association between p-NFL values and CSF-NFL values ($r = 0.39$; $p = 0.028$). Using Pearson correlation, we found no correlation between p-NFL and CSF-NFL (Figure S1).

Plasma-NFL as screening for abnormal CSF-NFL

Nine samples had abnormal CSF-NFL (≥380 ng/l), all of which had corresponding p-NFL levels ≥2 ng/l. Ten CSF-NFL values were <380 ng/l; eight (80%) of the paired p-NFL values were <2 ng/l ($p < 0.001$; Fisher's exact test). Thus, the sensitivity of p-NFL ≥ 2 ng/l to identify abnormal CSF-NFL (≥380 ng/l) was 100% and the specificity 80%.

Plasma-NFL in relation to clinical and neuroradiological findings

All nine samples from the four patients with cognitive/neurological symptoms (samples 2, 6.1–6.5, 8, 9.1–9.2) had p-NFL ≥ 2 ng/l while only two of 10 samples from patients without cognitive/neurological symptoms had p-NFL ≥ 2 ng/l (patients 7 and 10, both with new-onset DI). All samples from the two patients with neuroradiologically verified neurodegeneration (6.2, 6.4, 8) and all four samples from three patients with active non-neurodegenerative CNS lesions [enlarged pituitary stalk (7.1, 9.1–9.2, 10); focal signal enhancement in brain stem (9.2)] at sampling had p-NFL ≥ 2 ng/l (Table S1).

Monitoring with p-NFL over time

Sequential samples of paired blood and CSF were available in three patients; three baseline and nine follow-up samplings. Changes in p-NFL and CSF-NFL followed a similar trend, except for sample 4 in patient 6. In samples 3–5 in patient 7, p-NFL was below the detection limit (Figure 1). Brief information on these three patients is provided in Text S1.

Plasma-NFL levels in relation to treatment with mitogen-activated protein kinase pathway inhibitors

All three first samples taken after initiating mitogen-activated protein kinase pathway inhibitors (MAPKi) (while on or 2 weeks after such therapy) showed reduced p-NFL levels (samples 6.2, 6.5 and 7.2) while the p-NFL level had increased in one of the first samples taken after discontinuation of MAPKi (sample 6.3) and remained undetectable in the other (sample 7.3) (Figure 1).

DISCUSSION

Neurodegeneration in LCH may, markedly, reduce the quality of life, and there is an urgent need of novel strategies to identify, prevent, treat and monitor ND-CNS-LCH. Brain MRI is the golden standard for diagnosis and monitoring of ND-CNS-LCH, but it takes time for MRI findings of neurodegeneration to develop and to regress. CSF-NFL has been reported as a promising marker to monitor ND-CNS-LCH,[8,11] but LP requires sedation in small children and may be associated with complications.[8,12] Our findings are encouraging since they suggest that p-NFL may be used as a screening tool for ND-CNS-LCH, and thereby avoid the use of LP for routine monitoring. Instead, LP could then potentially be reserved for patients with elevated p-NFL, or clinical or neuroradiological findings of CNS involvement, as well as for monitoring of therapeutic interventions.

One obvious question is how NFL, a marker of neuroaxonal damage, gets into the blood. Based on the trafficking of other proteins degraded in the CNS, it has been suggested that partially degraded fragments of neurofilaments drain directly into CSF and blood via multiple routes. These include direct drainage into CSF and blood via arachnoid granulations as well as lymphatic drainage into the subarachnoid and perivascular spaces.[13]

In our cohort, p-NFL and CSF-NFL did not correlate well, but 100% of the samples with CSF-NFL ≥ 380 ng/l ($n = 9$) had a corresponding p-NFL above the detection level (≥2 ng/l), suggesting that p-NFL ≥ 2 ng/l clinically would indicate further analysis of CSF-NFL. Moreover, all samples with p-NFL < 2 ng/l had a corresponding CSF-NFL below the lower reference value (<380 ng/l), suggesting that patients with p-NFL < 2 ng/l may not need prompt CSF-NFL analysis, but could instead be followed with continued p-NFL screening. The sensitivity of this screening method in our cohort was 100% and the specificity 80%.

Since NFL analysis now is commercially available, p-NFL may be of value as a screening test for ND-CNS-LCH. Even though there may be a risk of missing patients with elevated CSF-NFL, blood samples are easy to repeat and since neurodegeneration is a slow process, a moderate delay in the diagnosis of ND-CNS-LCH may be acceptable if numerous LPs can be avoided. Furthermore, assessment for ND-CNS-LCH should be completed with MRI, neurological and neuropsychological evaluations.[1,2]

In line with our previous report on the value of monitoring the effect of MAPKi in ND-CNS-LCH by CSF-NFL,[11] we here observed a similar trend in that p-NFL levels also had a tendency to decrease during treatment with MAPKi.

This study has limitations, in particular the small number of patients and the limited number of sequential samples. Nevertheless, the results of the 19 paired samples evaluated in this study are encouraging, and further studies on p-NFL

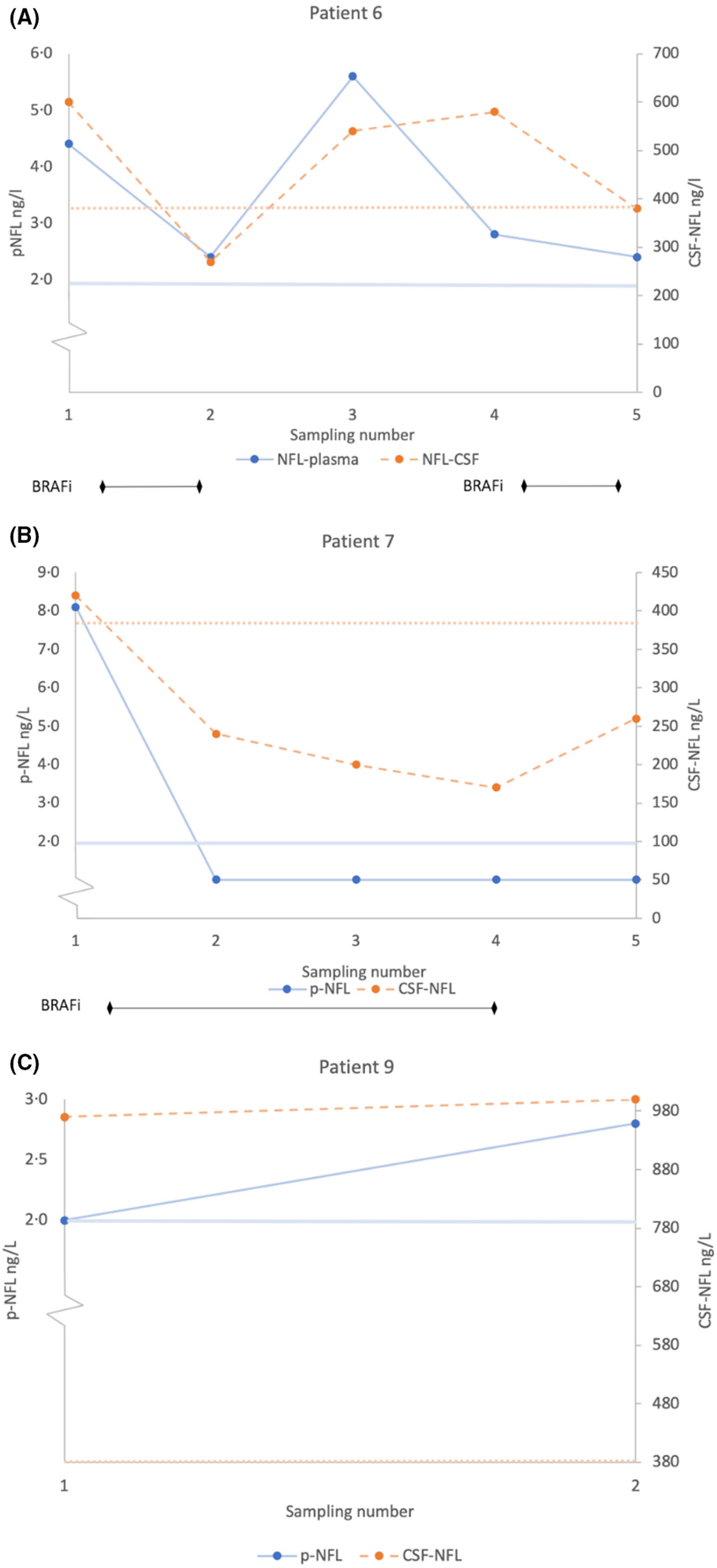
(A)
Patient 6
pNFL ng/l
CSF-NFL ng/l
6·0
5·0
4·0
3·0
2·0
700
600
500
400
300
200
100
0
1
2
3
4
5
Sampling number
NFL-plasma
NFL-CSF
BRAFi
BRAFi
(B)
Patient 7
p-NFL ng/L
CSF-NFL ng/L
9·0
8·0
7·0
6·0
5·0
4·0
3·0
2·0
450
400
350
300
250
200
150
100
50
0
1
2
3
4
5
Sampling number
p-NFL
CSF-NFL
BRAFi
(C)
Patient 9
p-NFL ng/L
CSF-NFL ng/L
3·0
2·5
2·0
980
880
780
680
580
480
380
1
2
Sampling number
p-NFL
CSF-NFL

FIGURE 1 Plasma (p)-NFL (neurofilament light protein) over time of three patients. The normal reference value for cerebrospinal fluid (CSF)-NFL is <380 ng/l (depicted as a dotted line). The lower limit of detection for p-NFL is 2 ng/l (depicted as a continuous line). The period marked BRAFi represents the time on BRAF-inhibitor therapy. In addition, patient 7 received vinblastine, prednisolone and 6-mercaptopurine at sampling 1, and 6-mercaptopurine and methotrexate at sampling 5 while patient 9 was administered dexamethasone and cladribine between sampling 1 and sampling 2, and MEK-inhibitor after sampling 2. Brief information on the three patients is provided in Text S1

in LCH are warranted to validate our results. Moreover, blood–brain barrier permeability itself may be a confounder, since the NFL quotient in blood compared to CSF could be selectively increased following periods of inflammation, such as that seen in relapse of multiple sclerosis, positively skewing blood NFL levels. Recent studies on this topic present conflicting results.[14,15]

In conclusion, our study suggests that p-NFL may be a useful screening test for neurodegeneration in LCH. With the NFL assay method used in our study, p-NFL ≥ 2 ng/l would indicate the need of further evaluation by CSF-NFL. Our data cannot confirm whether p-NFL can be used to monitor CNS-LCH development and treatment effects in individual patients. More studies with larger cohorts are needed before our results can be incorporated into clinical diagnostics. Nevertheless, the results are encouraging since it would be a major improvement if LCH-associated neurodegeneration could be monitored more frequently and thereby detected earlier.

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CONFLICTS OF INTEREST

HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Alector, Annexon, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Pinteon Therapeutics, Red Abbey Labs, Passage Bio, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). KB has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, BioArctic, Biogen, Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, all outside the submitted work. JIH has served as a consultant for Sobi, outside the submitted work. The other authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Malin Sveijer interpreted data, drafted the manuscript, made tables and figures. Tatiana von Bahr Greenwood helped to conceive the study, treated patients, provided samples and data, interpreted data, and assisted in drafting the manuscript and Table 1. Martin Jädersten treated patients, and provided samples and data. Egle Kvedaraite helped to conceive the study. Henrik Zetterberg and Kaj Blennow were responsible for the measurements of neurofilament in plasma and interpreted data. Magda Lourda handled the plasma samples. Désirée Gavhed helped to conceive the study, interpreted data, and assisted in drafting the manuscript and Table S1. Jan-Inge Henter conceived the study, consulted on patients, interpreted data, and assisted in drafting the manuscript, the tables and the figures. Malin Sveijer, Tatiana von Bahr Greenwood, Désirée Gavhed, and Jan-Inge Henter verified the underlying data. All authors revised the manuscript critically for important intellectual content, had access to all the data in the study, and accept responsibility to submit for publication.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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