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Blood Neurofilament Light Chain and Glial Fibrillary Acidic Protein as Candidate Biomarkers in *CSF1R*-Related Disorder

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Abstract

Background and Objectives

Colony-stimulating factor receptor 1-related disorder (*CSF1R*-RD) is an underrecognized, adult-onset genetic leukodystrophy with a devastating clinical course. Disease monitoring is critical as patients with *CSF1R*-RD can benefit from hematopoietic stem cell transplantation. Here, we aimed to compare blood neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) levels between patients with *CSF1R*-RD and those with alternative diagnoses and to correlate blood biomarkers values with clinical severity.

Methods

We analyzed 22 patients with *CSF1R*-RD and patients with fronto-temporal lobar degeneration due to *GRN* pathogenic variants (*GRN*-FTLD, n = 22), CADASIL (N = 9), cerebral adrenoleukodystrophy (13), and primary progressive multiple sclerosis (n = 14).

Results

NfL and GFAP were elevated in *CSF1R*-RD and *GRN*-FTLD as compared with the other groups. After adjusting for age, GFAP was higher in patients with *CSF1R*-RD compared with those with *GRN*-FTLD ($p = 0.035$). Among *CSF1R*-RD patients, both NfL ($p = 0.0054$) and GFAP ($p = 0.0065$) correlated with Expanded Disability Status Scale scores. For a subset of patients with cognitive testing, GFAP correlated with the processing speed index of the Wechsler adult intelligence scale ($p = 0.025$) and state anxiety ($p = 0.0088$).

Discussion

Our results show that blood NfL and GFAP are promising biomarkers of disease progression in patients with *CSF1R*-RD.

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Introduction

Colony-stimulating factor receptor 1-related disorder (*CSF1R*-RD), an autosomal dominant disease caused by pathogenic variants in *CSF1R*, is one of the main causes of adult-onset leukodystrophy.[1] Even if some individuals may remain asymptomatic throughout their life, *CSF1R*-RD is usually characterized by a rapidly evolving disease encompassing cognitive, psychiatric, and motor dysfunction with onset usually within the 4th or 5th decade and a mean survival of 6 years.[2]

Allogenic hematopoietic stem cells transplantation (aHSCT) can halt disease progression in *CSF1R*-RD.[3] Unfortunately, characteristic MRI features are frequently overlooked, thus

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Glossary

ANCOVA = analysis of covariance; **ANOVA** = analysis of variance; **CALD** = cerebral forms of adrenoleukodystrophy; **EDSS** = Expanded Disability Status Scale; **FDR** = false discovery rate; **FTLD** = frontotemporal lobar degeneration; **GFAP** = glial fibrillary acidic protein; **MS** = multiple sclerosis; **NfL** = neurofilament light chain; **PPMS** = primary progressive multiple sclerosis; **STAI** = State-Trait Anxiety Inventory; **WAIS-IV** = Wechsler adult intelligence scale.

precluding a rapid orientation toward a reference center for timely diagnosis.[4] Common misdiagnoses include primary progressive multiple sclerosis (PPMS) and frontotemporal lobar degeneration (FTLD), particularly FTLD due to *GRN* pathogenic variants (*GRN*-FTLD).[5-7]

Along with diagnostic issues, prognostication is important, especially in subjects converting from an asymptomatic carrier status to a symptomatic disease and to assess treatment response. Thus, biomarkers of disease evolution are warranted. Neurofilament light chain (NfL) levels have been shown to be higher in *CSF1R*-RD compared with patients with relapsing remitting multiple sclerosis (MS)[8] but were not compared with patients with PPMS. In addition, little is known about the correlations between NfL and markers of disease severity in *CSF1R*-RD. Glial fibrillary acidic protein (GFAP) has been studied in cerebral forms of adrenoleukodystrophy (CALD)[9] as well as in *GRN*-FTLD,[10] but not yet in *CSF1R*-RD.

The objective of our study was to analyze blood NfL and GFAP in *CSF1R*-RD compared with common differential diagnoses and to study the association between these candidate biomarkers and disease severity.

Methods

Study Participants

Montpellier University Hospital provided anonymized samples from patients with *CSF1R*-RD (n = 7), PPMS (n = 14), and CADASIL (n = 9), while Pitié-Salpêtrière University Hospital provided samples from patients with *CSF1R*-RD (n = 15), *GRN*-FTLD (n = 22), and CALD (n = 14).

Clinical Assessment

Clinical data included age at onset, age at blood sampling, gender, and main clinical symptoms—including the Expanded Disability Status Scale (EDSS). Neuropsychological assessments, including The Wechsler adult intelligence scale (WAIS-IV), the State-Trait Anxiety Inventory (STAI), and the Beck Depression Inventory, were available for 7 patients with *CSF1R*-RD.

Biological Measurements

GFAP and NfL were measured using the Elecsys assay (Roche Diagnostics, Swiss). The results showed low interassay variation. In a few cases where plasma was not available (n = 11), serum was used instead as we found high correlations between NfL measures in serum and plasma (R^2 = 0.99, unpublished data).

Statistical Analysis

Disease groups were compared using Fisher test or Student *t* test or analysis of variance (ANOVA) or Kruskal-Wallis adjusted for multiple comparisons with false discovery (FDR) post hoc. Correlations were assessed with nonparametric Spearman rank correlation coefficient (rho). The coefficients from the linear relation ($R^2 > 0.99$) linking serum to plasma NfL/GFAP concentrations were used to compute plasma values. Log-transformed NfL and GFAP concentrations were compared using analysis of covariance (ANCOVA) adjusted for age and sex.

Standard Protocol Approvals, Registrations, and Patient Consents

Written informed consent was obtained from patients. Montpellier University Centre (2019_IRB-MTP_06-10) and Paris Necker (RBM 02-59) ethics committee approved the study.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

The main characteristics of the cohort are presented in Table 1. *CSF1R*-RD patients (female to male ratio = 1) had a median age at onset of 47.5 (IQR: 37.4–53.8) years and a median disease duration of 2.9 (2–6.2) years. The main differences between the groups included age at onset (higher in *GRN*-FTLD, lower in CALD) and age at blood sampling (higher in PPMS, CADASIL, and *GRN*-FTLD). EDSS was higher in patients with PPMS (6.5) than in *CSF1R*-RD,[5] but disease duration was longer (1.8 vs 2.9 years, respectively).

NfL levels were higher in *CSF1R*-RD and in *GRN*-FTLD than in CADASIL, CALD, and PPMS patients (Table 1; Figure 1A). Similarly, GFAP levels were higher in *CSF1R*-RD and *GRN*-FTLD than in other groups (Table 1; Figure 1B). Given that patients with *GRN*-FTLD were older than patients with *CSF1R*-RD, we analyzed biomarkers adjusting for age and sex and found higher GFAP values in *CSF1R*-RD as compared with *GRN*-FTLD ($p = 0.035$, eFigure 1A), while no difference was observed for NfL (eFigure 1B).

In a subset of 12 *CSF1R*-RD patients with available EDSS at the time of blood sampling, we identified a strong association between clinical disability and both NfL (rho = 0.75; $p = 0.0054$,

Table 1 Main Characteristics of the Patients According to Each Group

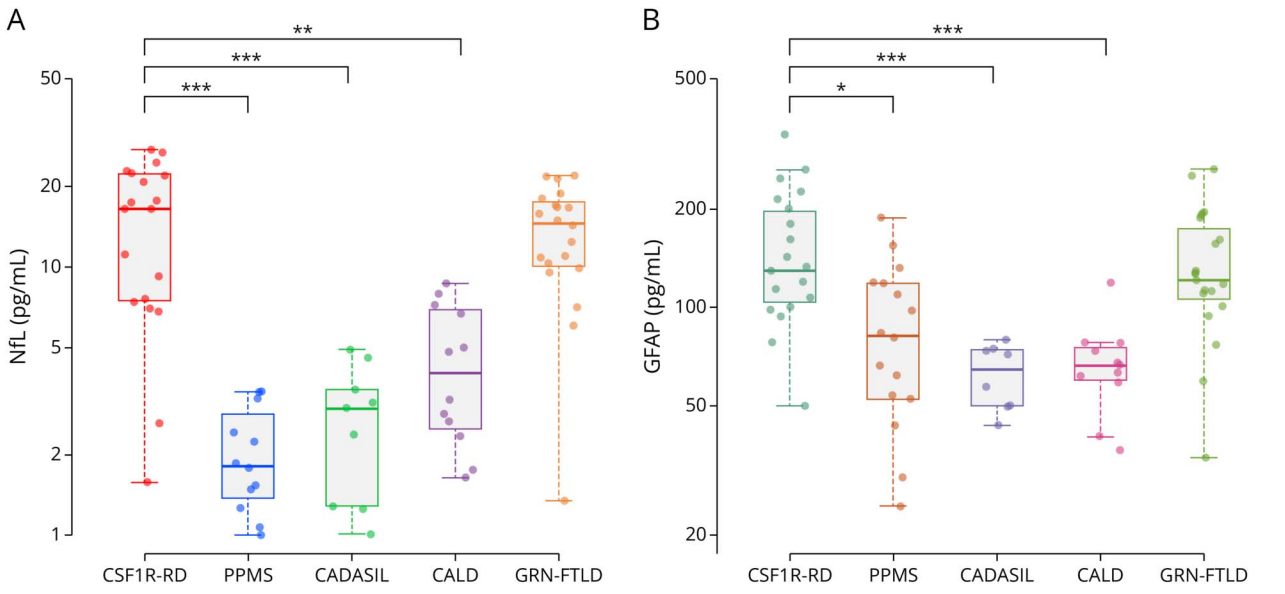
N = 80	*CSF1R*-RD	PPMS	CADASIL	CALD	*GRN*-FTLD	*p* Value
n	22	14	9	13	22	—
Age, y	47.5 (37.4–53.8)	63.5 (59–68.5)	60 (58–62)	37 (31–51)	62.4 (58.8–65.8)	<0.001[a]
Sex, f (%)	11 (50)	7 (50)	7 (77.8)	0 (0)	9 (40.9)	0.0017[b]
Disease onset	44.5 (36–51)	40 (33.2–50.8)	52.5 (44.5–58.2)	—	57.5 (55.2–63)	<0.001[a]
Disease duration	2.9 (2–6.2)	18 (14.2–28.8)	7 (3–10.5)	—	2.9 (2.4–3.5)	<0.001[c]
EDSS,/10	5 (3.8–5.4)	6.5 (5.6–7.9)	—	—	—	0.0056[d]
WM abnormalities[e]	—	—	—	—	10 (45.5)	—
NfL, pg/mL	16.9 (7.6–22.5)	2 (1.5–3.4)	3 (1.3–3.5)	4.8 (2.7–7.2)	15.4 (10.4–18.6)	<0.001[c]
GFAP, pg/mL	131.5 (105.3–218)	81.9 (52.6–119.1)	71.7 (50–74.5)	66.2 (58.9–77.5)	121 (106–174.5)	<0.001[c]

Abbreviations: CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CALD = Cerebral AdrenoLeuko-Dystrophy; *CSF1R*-RD = *CSF1R*-related disorder; EDSS = Expanded Disability Status Score; GFAP = glial fibrillary acidic protein; NfL = neurofilament light chain; PPMS = primary progressive multiple sclerosis; WM = white matter.
[a] ANOVA.
[b] Fisher exact test.
[c] Kruskal-Wallis test.
[d] Student *t* test.
[e] Except for the *GRN*-FTLD ones, all patients (100%) exhibited WM abnormalities.

Figure 2A) and GFAP (rho = 0.73; *p = 0.0065*, Figure 2B). Despite a small sample size of patients with *CSF1R*-RD (n = 7), GFAP, but not NfL, was also correlated with the processing speed index of the WAIS-IV (rho = −0.67; *p = 0.025*, eFigure 2A) and state anxiety of the STAI (rho = 0.88; *p = 0.0088*, eFigure 2B).

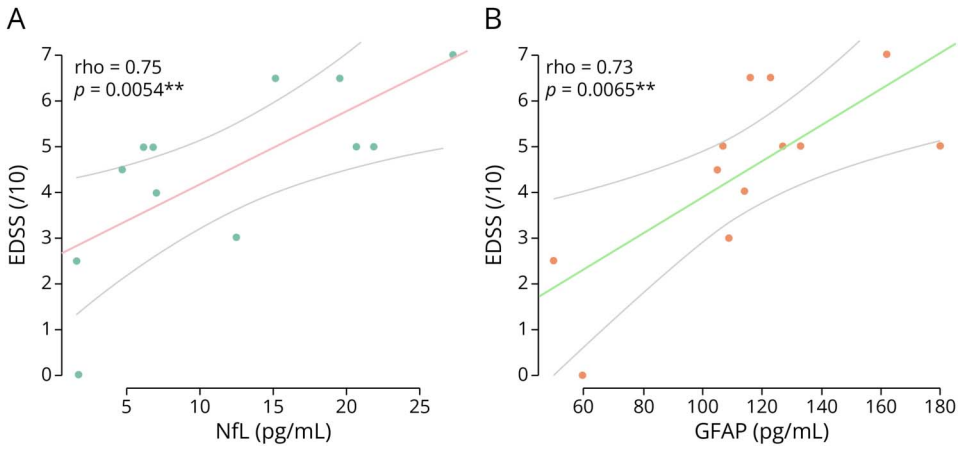
NfL and GFAP concentrations are displayed longitudinally for 1 *CSF1R*-RD patient partially presented previously and showed a sharp increase at the time of aHSCT followed by a prompt decline 6 months post-transplant to levels close to normal values for both NfL and GFAP (eFigures 3, A and B).[3]

Figure 1 NfL and GFAP Levels



Absolute levels of blood NfL (A) and GFAP (B) according to disease group. Concentrations are presented individually and with boxplots representing median values, first and third quartiles, and minimal and maximal values. Group effect was assessed using Kruskal–Wallis test by ranks adjusted for multiple comparisons with FDR post hoc; ***: $p < 0.001$, **: $p < 0.01$ and *: $p < 0.05$. GFAP = Glial Fibrillary Acidic Protein; NfL = Neurofilament Light chain.

Figure 2 Correlation Between NfL and GFAP Levels and EDSS Score



Trend lines based on linear regression coefficients, along with their 95% CIs, were added to facilitate visualization of the relationships between variables. Spearman rank correlation coefficients and corresponding *p* values are also reported. EDSS = Expanded Disability Status Score; GFAP = Glial Fibrillary Acidic Protein; NfL = Neurofilament Light chain.

Discussion

Our results confirm that not only blood NfL but also GFAP are markedly increased in patients with *CSF1R*-RD compared with disease mimics such as *GRN*-FTLD (after adjusting for age), PPMS, or leukodystrophies such as CADASIL and CALD. Furthermore, NfL and GFAP levels are well correlated with disability and disease severity in patients with *CSF1R*-RD. Both circulating biomarkers seem also sensitive to treatment intervention such as aHSCT. The totality of these data suggests that blood NfL and GFAP are promising biomarkers for disease monitoring in *CSF1R*-RD to evaluate disease progression as well as response to treatments in clinical trials.

NfL levels have been shown to be markedly increased in the blood and CSF of patients with *CSF1R*-RD, highlighting neuronal injury, compared with other neurodegenerative diseases.[8] In MS, NfL levels were only reported in patients with relapsing remitting forms while the most common differential diagnosis to *CSF1R*-RD is PPMS.[11] Our study addresses this gap and shows a clear difference of NfL levels between patients with *CSF1R*-RD and PPMS. Our data for patients with CALD are consistent with previous studies showing that (1) NfL levels were only slightly elevated in adults compared with children with CALD and (2) GFAP levels were not different from controls.[12] Similarly, NfL and GFAP levels were higher than controls in patients with CADASIL and PPMS but only moderately.[13,14] In addition, marked increase of blood NfL has already been reported in patients with *GRN*-FTLD[10] and may reflect the rapid disease progression and pronounced brain atrophy also observed in *CSF1R*-RD. Similarly, increased GFAP levels in *CSF1R*-RD and *GRN*-FTLD may also reflect prominent astrocytic dysfunction in these diseases.

Our study has limitations inherent to research concerning rare diseases, especially the relatively low number of patients in each group and the retrospective nature of the data.

Nevertheless, we confirm the potential interest of blood NfL and GFAP in CSF1R-RD. Its usefulness to monitor disease progression and response to treatments should be studied in larger cohorts, including presymptomatic individuals to assess how these biomarkers can help identifying disease onset. Other biomarkers may also be relevant to monitor disease progression in *CSF1R*-RD such as serum CSF1R[15] as well as emerging biomarkers evaluating astrocytic (e.g., CHI3L1) and microglial (e.g., sTREM2) dysfunctions.

Author Contributions

X. Ayrignac: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. C. Marelli: major role in the acquisition of data; analysis or interpretation of data. S. Lehmann: major role in the acquisition of data; study concept or design; analysis or interpretation of data. C. Huiban: major role in the acquisition of data; analysis or interpretation of data. H.A.F. Yska: major role in the acquisition of data; analysis or interpretation of data. P. Labauge: major role in the acquisition of data; analysis or interpretation of data. I. Le Ber: major role in the acquisition of data; analysis or interpretation of data. F. Mochel: major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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