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CSF neurofilament light concentration is increased in presymptomatic CHMP2B mutation carriers

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Abstract

Objective
A rare cause of familial frontotemporal dementia (FTD) is a mutation in the CHMP2B gene on chromosome 3 (FTD-3), described in a Danish family. Here we examine whether CSF biomarkers change in the preclinical phase of the disease.

Methods
In this cross-sectional explorative study, we analyzed CSF samples from 16 mutation carriers and 14 noncarriers from the Danish FTD-3 family. CSF biomarkers included total tau (t-tau) and neurofilament light chain (NfL) as a marker for neurodegeneration, phosphorylated tau (p-tau) as a marker for tau pathology, β-amyloid (Aβ) 38, 40, and 42 (Aβ38, Aβ40, and Aβ42) to monitor Aβ metabolism, and YKL-40 as a marker of neuroinflammation. Aβ isoform concentrations were measured using a multiplexed immunoassay; t-tau, p-tau, NfL, and YKL-40 concentrations were measured using sandwich ELISAs.

Results
CSF NfL concentration was significantly increased in mutation carriers vs noncarriers. Further, CSF NfL concentration was significantly higher in symptomatic mutation carriers compared to presymptomatic carriers, and also significantly higher in presymptomatic carriers compared to noncarriers. No differences in t-tau and p-tau and YKL-40 concentrations between controls and mutation carriers were observed. CSF concentrations of the Aβ peptides Aβ38 and Aβ40 but not Aβ42 were significantly lower in mutation carriers compared to noncarriers.

Conclusions
Increased NfL levels in presymptomatic individuals and in symptomatic patients with FTD-3 indicate a continuous process of neurodegeneration from the presymptomatic to symptomatic state. Although not specific for FTD-3 pathology, our data suggest that CSF NfL could serve as a valuable biomarker to detect onset of neurodegeneration in FTD-3 mutation carriers.
A truncating mutation in the CHMP2B gene (c.532-1G>C) on chromosome 3 results in early-onset frontotemporal dementia (FTD) (chromosome 3–linked FTD [FTD-3] or CHMP2B-FTD). This rare cause of FTD was first described in a large Danish family and later a different CHMP2B mutation was identified in an unrelated Belgian patient with familial FTD. The disease is mapped through 6 generations from the first known case in 1876 and the family now counts more than 500 individuals. FTD-3 is characterized by progressive cognitive deficits with behavioral changes. FTD-3 brains present primarily with frontal degeneration as well as temporal and dominant parietal lobe dysfunction.

The histopathologic hallmarks of CHMP2B-FTD include ubiquitin-positive inclusions, autofluorescent aggregates, and p62-positive inclusions, while there is no tau, TAR DNA-binding protein 43, or fused in sarcoma pathology.

The core CSF biomarkers used for dementia diagnosis are β-amyloid 42 (Aβ42), total tau (t-tau), and phosphorylated tau (p-tau). A large subset of FTD cases have pathologic tau changes with robust increases in CSF t-tau and p-tau levels but normal levels of Aβ42. CSF biomarkers in familial FTD have been investigated in individuals with mutations in MAPT, GRN, or the C9ORF79 repeat expansion but not in CHMP2B mutation carriers.

In this cross-sectional explorative study, we analyzed the CSF biomarkers Aβ42, t-tau, and p-tau in 30 individuals from the Danish FTD-3 family. We further included neurofilament light (NfL) as a marker of neuronal injury and YKL-40 as a marker of neuroinflammation in our analysis.

Methods

Study population

The FTD-3 family has been subject to extensive studies over more than 20 years within the Frontotemporal Dementia Research in Jutland Association (FReJA) collaboration, and biological material has been collected during the years for linkage analyses, gene identification, and functional studies.

The disease has been tracked through 6 generations, and clinical characteristics have been recorded in 45 cases of disease, providing information about natural history, clinical characteristics, and age at onset (AAO).

Samples from a total of 30 individuals were included: 10 affected CHMP2B mutation carriers, 6 presymptomatic CHMP2B mutation carriers, and 14 noncarrier family members (table). In the affected FTD-3 patients, the mean AAO was 60.5 years (SD 4.8 years).

Standard protocol approvals, registrations, and patient consents

The study was approved by the Ethics Committee of the Capital Region of Denmark (H-1-2012-041), and written informed consent was obtained from each participant before enrollment. Subject age was recorded as the age of the individual on the day of lumbar puncture.

Collection of CSF

In brief, CSF samples were obtained by lumbar puncture and collected in polypropylene tubes, centrifuged at 2,000 g for 10 minutes, aliquoted into cryo tubes, and stored at −80°C until further use.

Immunoassays

Aβ triplex

CSF concentrations of Aβ38, Aβ40, and Aβ42 were measured using V-plex Peptide Panel 1 Kits Aβ38, Aβ40, and Aβ42 (Meso Scale Discovery system, Rockville, MD) according to the manufacturer’s protocol: 60 μL of CSF was diluted 2-fold in diluent provided with the kit. Calibrator samples and controls were prepared according to manufacturer’s protocol. On 96-well MSD plates precoated with capture antibodies, 25 μL of sample, calibrator, or controls were added to each well followed by addition of 25 μL of detection antibody and incubation at room temperature for 2 hours. Finally, the plate was washed in kit washing buffer and read in a Meso Scale Discovery imager at appropriate wavelength.

Total tau

CSF t-tau concentration was measured by the hTau Ag ELISA assay (INNOTEST, Fujirebio, Japan) according to the manufacturer’s protocol: on a 96-well microtiter plate pre-coated with anti-human tau antibody, 25-μL samples, controls, and standards ranging from 50 to 2,500 pg/mL were added followed by incubation with a biotinylated detection antibody to tau and addition of peroxidase-conjugated streptavidin. The reaction was developed with tetramethyl benzidine (TMB) chromogen solution and subsequently stopped with 0.9 M sulfuric acid and quantified at 450 nm in a microplate reader.

Phosphorylated tau

The CSF concentration of tau phosphorylated at amino acid 181 (p-tau) was measured by the p-tau (181p) ELISA assay (INNOTEST, Fujirebio, Japan) according to the manufacturer’s protocol: on a 96-well microtiter plate precoated

AAO = age at onset; Aβ42 = β-amyloid 42; AD = Alzheimer disease; FTD = frontotemporal dementia; FTD-3 = chromosome 3–linked frontotemporal dementia; GLM = general linear modeling; NfL = neurofilament light; p-tau = phosphorylated tau; t-tau = total tau; TMB = tetramethyl benzidine.
with anti-human p-tau antibody, 75-μL samples, controls, and standards ranging from 15.6 to 1,000 pg/mL were added followed by incubation with a biotinylated detection antibody to p-tau and addition of peroxidase-conjugated streptavidin. The reaction was developed with TMB chromogen solution and subsequently stopped with 0.9 M sulfuric acid and quantified at 450 nm in a microplate reader.

**Neurofilament light chain**

CSF NfL concentration was measured by sandwich ELISA with the antibody NfL21 used for coating the plates (monoclonal mouse antibody against NfL [in-house]). The coating concentration was 0.5 μg/mL in carbonate buffer (pH 9.6).

Briefly, 50 μL CSF (1:2 dilution), 100 μL calibrator, and 50 μL PBST (0.05% tween) were added to the coated plates and incubated 1 hour while shaking at room temperature followed by overnight incubation at +4°C. For detection, a biotinylated NfL23 mouse monoclonal antibody against NfL (in-house) was used together with streptavidin–horseradish peroxidase diluted 1:20,000 (100 μL/well).

Following wash, 100 μL TMB substrate (TMB One ready-to-use substrate, Kem En Tec Diagnostic, Taastrup, Denmark) was added to each well and plates were incubated for 20 minutes in the dark at room temperature. The reaction was stopped with 100 μL/well of 0.2 M H2SO4 and absorbance was quantified at 450/650 nm in a microplate reader.

**YKL-40**

CSF YKL-40 concentration was measured using a solid-phase sandwich ELISA (Human Chitinase 3-like 1 Quantikine ELISA kit, R&D Systems, Oxon, UK) according to the manufacturer’s protocol: 50 μL of CSF was diluted 2-fold in diluent provided with the kit. Calibrators and controls were prepared according to protocol.

On a capture-antibody precoated 96-well microtiter plate, 50 μL of CSF sample, calibrator, or controls were added followed by addition of 200 μL of conjugate and incubation at room temperature for 2 hours. Finally, each well was washed in the provided washing buffer, followed by addition of 200 μL substrate solution, and subsequently stopped with 50 μL of the provided stop solution. Quantification was carried out at 540/570 nm in a microplate reader.

All biochemical measurements were performed by board-certified laboratory technicians who were blinded to clinical information. The measurements were performed in one round of experiments using one batch of reagents. Intra-assay coefficients of variation were below 10%.

### Statistical methods

Data were analyzed using SAS software (Enterprise Guide 7.1, 2014, SAS Institute Inc, Cary, NC). Concentrations of each biomarker were compared between controls and CHMP2B mutation carriers, and between affected individuals and pre-symptomatic mutation carriers. As some biomarkers were
found to be age-dependent, participant age was included in a subsequent analysis using general linear modeling (GLM). Where it was necessary, logarithmic transformation was performed to obtain normal distribution.

Results

CSF data for all measured markers are shown in the table.

Participant age and sex distribution did not differ significantly between mutation carriers and noncarriers (t\(29\) = -0.63, \(p = 0.53\) and \(\chi^2[1] = 0.28, p = 0.59\), respectively).

In our dataset, t-tau, p-tau, and YKL-40 levels were found to be age-dependent, participant age was included in the analysis (GLM, \(F_{1,28} = 6.68, p = 0.0153\); \(F_{1,28} = 5.14, p = 0.0314\); \(F_{1,28} = 6.37, p = 0.0176\), respectively) while A\(β38\), A\(β40\), A\(β42\), and NfL were not (GLM, \(F_{1,28} = 2.45, p = 0.1288\); \(F_{1,28} = 1.80, p = 0.1906\); \(F_{1,28} = 0.22, p = 0.6450\); \(F_{1,27} = 0.38, p = 0.4935\), respectively).

When adjusted for age-dependency, statistical analysis showed no difference in t-tau and p-tau levels between controls and mutation carriers (GLM, \(F_{3,26} = 3.29, p = 0.5173\), and \(F_{1,26} = 3.86, p = 0.69\), respectively). Levels of A\(β38\) and A\(β40\) but not A\(β42\) were significantly decreased in mutation carriers compared to noncarriers (GLM, \(F_{1,28} = 6.23, p = 0.02\); \(F_{1,28} = 4.75, p = 0.04\); and \(F_{1,28} = 1.87, p = 0.18\), respectively) (figure 1). A\(β42/Aβ38\), A\(β42/Aβ40\) t-tau/A\(β42\), and p-tau/A\(β42\) ratios were not found to be significantly different between the 2 groups (GLM, \(F_{1,28} = 0.23, p = 0.63\); \(F_{1,28} = 0.05, p = 0.83\); \(F_{3,25} = 2.37, p = 0.68\); and \(F_{3,25} = 1.96, p = 0.73\), respectively).

YKL-40 CSF levels did not differ significantly between mutation carriers and noncarriers after adjustment for age (GLM, \(F_{3,26} = 2.64, p = 0.57\) (figure 1).

CSF levels of NfL were significantly higher in mutation carriers compared to noncarriers (GLM, \(F_{1,28} = 53.92, p \leq 0.0001\)) (figure 2). When adjusting for participant age, this difference persisted (GLM, \(F_{3,26} = 29.44, p = 0.021\)). Symptomatic mutation carriers had significantly higher NfL levels than presymptomatic mutation carriers (GLM, \(F_{1,14} = 8.61, p = 0.0109\)), while presymptomatic carriers had significantly increased NfL levels compared to noncarriers (GLM, \(F_{1,17} = 10.97, p = 0.004\)).

In the age-corrected model, levels of NfL were found to be significantly increased in symptomatic mutation carriers when compared to presymptomatic carriers (GLM, \(F_{3,12} = 7.02, p = 0.0064\), while the significant difference between presymptomatic mutation carriers and noncarriers disappeared (GLM, \(F_{3,15} = 9.94, p = 26.22\)).

As illustrated (figure 2), NfL levels were high in mutation carriers years prior to the expected clinical onset of 58 years. Even when adjusting for participant age, this elevation was significant (GLM, \(F_{3,26} = 29.44, p = 0.021\)).

Discussion

In this explorative study, we analyzed CSF samples from 10 affected CHMP2B mutation carriers, 6 presymptomatic CHMP2B mutation carriers, and 14 noncarriers from the Danish FTD-3 family. Further investigations on the diagnostic performance of the markers are needed to clarify the influence of age on the levels of the investigated biomarkers.

In our FTD-3 cohort, mutation carriers had significantly increased levels of CSF NfL compared to controls. Interestingly, this increase could be detected in presymptomatic individuals several years prior to expected AAO. Even the youngest presymptomatic mutation carrier (participant age 32, which is 26 years prior to expected clinical onset) had higher CSF NfL levels than some of the oldest noncarriers (figure 2). This suggests that the neurodegenerative process is ongoing in mutation carriers several decades before onset of symptoms, as was also reported in individuals with autosomal inherited Alzheimer disease (AD) in the Dominantly Inherited Alzheimer Network (DIAN) cohort.10

In contrast to our findings, a recent publication from the GENFI consortium found that CSF NfL levels were significantly increased in symptomatic carriers of mutations in other FTD-causing risk genes, GRN, MAPT, or C9orf27, when compared to presymptomatic carriers and that presymptomatic carriers and control participants had similar NfL levels.11 In that study, the symptomatic mutation carriers’ NfL levels correlated with disease severity, brain atrophy, and survival.11 In recent years, neurofilaments have been investigated in several neurodegenerative diseases12 and a meta-analysis has concluded that both NfL and neurofilament heavy are increased overall in patients with sporadic AD, FTD, and vascular dementia.13 Other studies have shown that CSF NfL levels were increased in sporadic FTD when compared to other dementia groups or healthy controls.14-15 Our results and the results from the studies of sporadic FTD cases suggest that NfL may be applied as biomarker of neurodegenerative progression and disease severity.

We detected a significant decrease in CSF A\(β38\) and A\(β40\) levels, but not in A\(β42\) levels, in mutation carriers compared to noncarriers. The A\(β42/Aβ38\) and A\(β42/Aβ40\) ratios, however, did not differ between mutation carriers and controls. These results concur with the hypothesis that FTD-3 is not an amyloid disease, as no amyloid pathology has been identified.2,20 Substantiating this further, amyloid ligand PET scans in 4 affected patients with FTD-3 have shown no accumulation of amyloid (unpublished material). Lower A\(β38\) and A\(β40\) concentrations in CSF have been noted in PSEN1 mutation carriers and may indicate impaired \(γ\)-secretase processing of APP.21 Lower A\(β38\) and A\(β40\) have also been seen in
neuroinflammatory conditions. Finally, there are some indications that reduced neuronal/synaptic activity may lead to less $\beta$-amyloid production in general.

In MAPT, GRN, and C9ORF72 mutation carriers, levels of $\beta$-amyloid 42 are generally found to be within normal range while levels of t-tau and p-tau are not well-characterized due to lack of consistent CSF profile for these patients.

We did not observe a difference in CSF p-tau levels in mutation carriers compared to noncarriers in the current study. This finding is not surprising as patients with FTD-3 do not display the hyperphosphorylated tau pathology that is otherwise observed in other FTDs. Also, we found no significant increase in CSF t-tau levels. This was surprising as t-tau is known to be a general marker of neurodegeneration and it is well-described that patients with FTD-3 have brain atrophy even early in disease. The CSF level of the inflammation marker YKL-40 was found to increase with age in both mutation carriers and noncarriers in our FTD-3 cohort. This finding concurs with another study showing that CSF YKL-40 levels did not differ between patients with FTD and controls. YKL-40 is a secreted 40-kDa glycoprotein belonging to the member of the human chitinase activity family. YKL-40 is expressed in several tissues including astrocytes and microglia in the brain. It has been shown that YKL-40 plays an important role in astrocyte

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**Figure 1 CSF biomarkers in CHMP2B mutation carriers compared to noncarriers**

Box plots show CSF concentrations of $\beta$-amyloid 38, $\beta$-amyloid 40, $\beta$-amyloid 42, total tau (t-tau), phosphorylated tau (p-tau), and YKL-40 analyzed by immunoassays. Levels of the $\beta$-amyloid peptides $\beta$-amyloid 38 and $\beta$-amyloid 40 were significantly decreased in mutation carriers compared to noncarriers ($p = 0.02$ and $p = 0.04$, respectively). Levels of $\beta$-amyloid 42, t-tau, p-tau, and YKL-40 were not found to differ significantly between the 2 groups.
and microglial response to neuroinflammation. Our finding suggests that the observed increase is a consequence of age rather than mutation status and therefore YKL-40 may not be a valuable marker of disease in FTD-3. However, in some studies, CSF levels of YKL-40 have been shown to be increased in patients with AD and FTD when compared to cognitively healthy controls. Other studies have found that CSF YKL-40 levels in patients with FTD are increased compared to patients with AD. Since FTD is a clinically and pathologically heterogeneous disease, differences in the individual cohorts analyzed could explain why CSF YKL-40 concentrations vary among different studies (for review, see reference 35).

To our knowledge, all studies of YKL-40 as a CSF biomarker in patients with FTD have reported on sporadic cases and therefore might not reflect the pathology of genetic FTD. In spite of our finding that YKL-40 cannot be used as a marker to differentiate mutation carriers from controls, these results do not necessarily imply that neuroinflammation is not an important aspect of FTD-3 pathology. Recently, microglial activation was studied thoroughly in a FTD-3 mouse model. Early microglial proliferation and a clear proinflammatory phenotype was observed in the CHMP2B mutant mice compared to wild-types, which is similar to the inflammatory profile found in FTD-3 brains. These data suggest that neuroinflammation could be a pathologic driver of FTD-3 disease and that it might be valuable to measure CSF biomarkers of neuroinflammation in patients with FTD-3. However, in order to differentiate between disease development and normal aging, a more specific CSF marker than YLK-40 should be used.

Taken together, our results suggest that the unchanged levels of tau in CSF corroborate the absence of tau pathology in these patients. The decreased levels of Aβ38 and Aβ40 may be due to a general downregulation of APP processing; however, this needs to be further investigated. Our observations of increase in NfL levels in presymptomatic individuals and even further increase of NfL levels in affected patients with FTD-3 indicate a continuous process of neurodegeneration during the presymptomatic to symptomatic state. Furthermore, our study implies that NfL is a sensitive marker of the widespread neurodegeneration occurring in patients with FTD-3, even decades before symptom onset.

**Author contributions**

Nina Rostgaard: study concept and design, analysis and interpretation of data, drafting/revising the manuscript for content, and obtaining funding. Peter Roos: study concept and design, statistical analysis, analysis and interpretation of data, drafting/revising the manuscript for content, and obtaining funding. Erik Portelius: study concept and design, acquisition of data, interpretation of data, drafting/revising the manuscript for content, and obtaining funding. Kaj Blennow: study concept and design, acquisition of data, interpretation of data, drafting/revising the manuscript for content, and obtaining funding. Henrik Zetterberg: study concept and design, acquisition of data, interpretation of data, drafting/revising the manuscript for content, and obtaining funding. Anja H. Simonsen: study concept and design, analysis and interpretation of data, and drafting/revising the manuscript for content. Jørgen E. Nielsen: study concept and design, analysis and interpretation of data, drafting/revising the manuscript for content, and obtaining funding.

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Disclosure

N. Rostgaard, P. Roos, and E. Portelius report no disclosures relevant to the manuscript. K. Blennow has served as a consultant or on advisory boards for Alzheon, BioArctic, Biogen, Eli Lilly, Fujirebio Europe, IBL International, Pfizer, and Roche Diagnostics, and is co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Venture-based platform company at the University of Gothenburg. H. Zetterberg has served on advisory boards of Roche Diagnostics, Eli Lilly, and Pharmasum Therapeutics, and is co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Venture-based platform company at the University of Gothenburg. A. Simonsen and J. Nielsen report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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CSF neurofilament light concentration is increased in presymptomatic CHMP2B mutation carriers

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Study question
Can a biomarker predict the onset of neurodegeneration and clinical symptoms in patients with chromosome-3-linked frontotemporal dementia (FTD-3)?

Summary answer
CSF neurofilament light chain (NfL) was elevated in patients with FTD-3 (CHMP2B mutation carriers) before the age at clinical onset and further increased in symptomatic carriers.

What is known and what this article adds
Several studies of familial FTD have described predictive changes in core CSF biomarkers of dementia, including total and phosphorylated tau. This is the first study to examine CSF biomarkers in FTD-3, a rare form of early-onset FTD caused by a truncating mutation in the gene CHMP2B on chromosome 3.

Participants and setting
CSF samples were collected from FTD-3 family members including 10 symptomatic carriers, 6 presymptomatic carriers, and 14 noncarriers.

Design, size, and duration
The study used an exploratory cross-sectional design that evaluated CSF biomarkers of FTD pathology among individuals with CHMP2B mutation.

Primary outcomes
Primary outcomes were CSF markers including total tau and NfL (indicators of neurodegeneration), phosphorylated tau (indicator of tau pathology), β-amyloid 38, 40, and 42 (indicators of amyloid processing), and YKL-40 (a neuroinflammatory marker).

Main results and the role of chance
After adjustment of the generalized linear model for age-dependency, Aβ38 and Aβ40 but not Aβ42 were significantly decreased in mutation carriers compared to noncarriers. In both the unadjusted and adjusted models, NfL was higher in mutation carriers compared to noncarriers (F3,26 = 29.44, p = 0.021) and higher in symptomatic carriers compared to presymptomatic carriers (F3,12 = 7.02, p = 0.0064). NfL levels were elevated in carrier individuals prior to the age of expected clinical onset, 58 years (F3,26 = 29.44, p = 0.021), supporting the utility of NfL as a biomarker for neurodegeneration.

Bias, confounding, and other reasons for caution
The study was inherently limited by the characteristics and size of the target population and a small sample size.

Generalizability to other populations
The findings are generalizable to individuals with FTD-3.

Study funding/potential competing interests
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