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Neurofilament light chain as a blood biomarker to differentiate psychiatric disorders from behavioural variant frontotemporal dementia

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ABSTRACT

The overlapping symptoms of behavioural variant frontotemporal dementia (bvFTD) and primary psychiatric disorders (such as depressive disorder, schizophrenia spectrum, and bipolar disorder) present a challenge for the differential diagnosis of bvFTD in middle and older-aged people. Neurofilaments are cytoskeletal proteins in the neurons, and several studies have reported elevated levels of neurofilament light chain (NfL) in cerebrospinal fluid of neurodegenerative as well as psychiatric disorders. The study aims to determine the utility of serum NfL levels as a biomarker to differentiate between bvFTD and psychiatric disorder. In our study, we investigated the levels of NfL in the serum of schizophrenia (n = 11), depression (n = 28), bipolar (n = 11), bvFTD (n = 20) patients and controls (n = 27) by single molecule array (Simoa) technology. The schizophrenia, depression and bipolar patients did not show significant changes in serum NfL levels in comparison to the control group ($p > 0.99$). The serum NfL levels were significantly elevated in bvFTD patients in comparison to the control cohort ($p < 0.0001$), depression ($p < 0.0001$), schizophrenia ($p < 0.0002$) and bipolar patients ($p < 0.0083$). We propose serum NfL as a biomarker to differentiate bvFTD from psychiatric disorders and to rule out neurodegeneration in the course of psychiatric disorders.

1. Introduction

Frontotemporal dementia (FTD) refers to a group of heterogeneous disorders that are characterized by neurodegeneration of frontal and temporal lobes of the brain. The most common form of FTD is behavioural variant frontotemporal dementia (bvFTD). The symptoms of bvFTD primarily include progressive changes in personality and behavior that often manifest as disinhibition, loss of insight, and loss of empathy. The early behavioural symptoms are usually not accompanied by cognitive or memory impairment(Lanata and Miller, 2016). Due to the overlap of its psychological symptoms with those of primary psychiatric disorders such as mood disturbances, euphoria, and apathy; bvFTD at an early stage may be misdiagnosed as a psychiatric condition (severe depression, bipolar disorder, and schizophrenia)(Pose et al., 2013). In a large study, up to 50% of bvFTD patients had a previous diagnosis of bipolar disorder or schizophrenia(Woolley et al., 2011).

Neurofilaments are intermediate filaments of neurons. They consist of neurofilament light (NfL), neurofilament medium (NfM), neurofilament heavy (NfH) chains, and alpha-internexin subunits. Neurofilaments provide structural support for axon caliber. They are also present in the synapses and may play a role in neurotransmission and though in the modulation of behaviour(Yuan et al., 2015).

NfL is released into CSF and blood in several neurodegenerative disorders, elevated serum/plasma NfL levels were found in Alzheimer's disease, bvFTD and amyotrophic lateral sclerosis(Khalil et al., 2018; Lu et al., 2015; Mattsson et al., 2017; Steinacker et al., 2018; Verde et al., 2018). Interestingly, the NfL levels correlated with brain atrophy in bvFTD and increased over the course of the disease (Steinacker et al.,

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2018).

Changes in NfL levels were reported in psychiatric disorders. CSF analysis demonstrated slightly elevated NfL levels in elderly women with depression and patients with bipolar disorder(Gudmundsson et al., 2010; Jakobsson et al., 2014). Proteomic analysis revealed significantly reduced NfL levels in the dorsolateral prefrontal cortex in schizophrenia and bipolar disorder (Pennington et al., 2008) while the levels of NfL were slightly increased in the prefrontal cortex of patients with depression(Wesseling et al., 2014).

Although alterations of NfL were described in both bvFTD and psychiatric disorders, there is no study with a direct comparison of serum NfL concentrations in these diseases to estimate the degree of NfL changes and the differential diagnostic potential. In this study, we investigated the serum NfL levels in patients with primary psychiatric disorders (schizophrenia, bipolar disorder and depression) and bvFTD to determine their utility as a biomarker to differentiate between bvFTD and the mentioned psychiatric disorders.

2. Methods

2.1. Participants and clinical characterization

The study was approved by the local ethics committee. All participants provided written consents for the study according to institutional guidelines. The study cohort consisted of 97 age-matched patients ($p = 0.0743$) as follows: 11 bipolar patients (4 manic, 3 depressive and 4 mixed episode), 11 schizophrenia patients (6 paranoid and 5 undifferentiated), 28 patients with depression (7 organic mood disorder, 9 severe depressive episode with psychosis and 12 severe episode without psychotic symptoms), 20 bvFTD (9 possible, 5 probable and 6 genetic bvFTD (4 due to *C9orf72* mutations,2 *MAPT* mutations) and 27 controls without any sign of neurodegeneration, neuro-inflammation or psychiatric conditions. Patients of the control group had a semi-structured interview to rule out a psychiatric disorder and did not show any inflammatory or neurodegenerative process in CSF analysis. The clinical characterization of the psychiatric patients was according to DSM-5, the bvFTD patients were characterized in line with the current criteria (Rascovsky et al., 2011).

2.2. Sample collection and serum NfL analysis

Blood samples were centrifuged (800 g, 5 min) to obtain the serum and aliquots were stored at −80 °C until analysis. Serum NfL analysis was conducted on a single molecule array HD-1 Analyzer using single molecule array (Simoa) NF-light reagent kit (Quanterix®, Lexington, MA) according to the manufacturer's instructions.

2.3. Statistical analysis

Two-tailed unpaired Kruskal-Wallis test and Dunn's post-hoc-test were used to determine statistical differences at a significance level of 5% between the studied groups. Varying sensitivity and specificity according to different cut-offs were plotted on the receiver operating characteristic (ROC) curve. The optimal cut-off level for dichotomizing values was selected as the situation maximizing the Youden index. Spearman correlation was applied for in the correlation analysis. GraphPad Prism 7 was used for the statistical analysis (GraphPad, La Jolla, CA, USA).

3. Results

Demographic characteristics of the studied groups in Table 1.

The study cohort consisted of 97 age-matched patients, the comparison of the ages in the study groups using two-tailed unpaired Kruskal-Wallis test and Dunn's post-hoc-test did not show a significant difference $p = 0.0743$. The diagnoses of the control group are provided in Supplementary Table 1. Schizophrenia, depression and bipolar patients did not show significant differences in the levels of serum NfL in comparison to the controls (Fig. 1 A), and no significant differences were detected between the psychiatric subtypes. The serum NfL levels were significantly elevated in bvFTD patients in comparison to the controls ($p < 0.0001$), depression ($p < 0.0001$), schizophrenia ($p < 0.0002$) and bipolar patients ($p < 0.0083$) (Fig. 1 A).

The serum NfL levels correlated directly with age in both the psychiatric disorders and controls ($r = 0.588$ and $p < 0.0001$), yet no correlation with age was detected in bvFTD patients ($r = -0.323$, $p = 0.164$).

Serum NfL levels above 35.7 pg/ml distinguished bvFTD from depression with 70% sensitivity (95% confidence Interval (CI) 45.72%–88.11%), 92.8% specificity (95% CI 76.5%–99.12%) and 0.89 area under the ROC curve (95% CI 0.8 to 0.98, $p < 0.0001$). Levels > 26.55 pg/ml differentiated bvFTD from bipolar disorder with 80% sensitivity (95% CI 56.34%–94.27%), 90.91% specificity (95% CI 58.72%–99.77%) and 0.94 area under the ROC curve (95% CI 0.81 to 1.01 $p = 0.0002$). Interestingly, a cut-off of > 17.7 differentiated bvFTD from schizophrenia with 100% sensitivity (95% CI 83.16%–100%) and 72.73% specificity (95% CI 39.03%–93.98%) and 0.9 area under the ROC curve (95% CI 0.77 to 1.03, $p = 0.0003$) (Fig. 1 B).

4. Discussion

Our analyses showed that serum NfL is increased in bvFTD but not in psychiatric disorders, thereby providing a good discriminatory power to assist in the differential diagnosis.

In accordance with previous reports, we confirmed that serum NfL levels are elevated in bvFTD patients (Rohrer et al., 2016; Steinacker et al., 2018). The current study is the first to investigate the levels of serum NfL in psychiatric disorders. In our cohorts, no significant changes were observed when comparing psychiatric patients with the control group. Elevated serum NfL levels (> 23.7 pg/ml) in bvFTD had 85% sensitivity and 78% specificity in distinguishing of bvFTD from all psychiatric disorders as a combined group. This result highlights the potential use of serum NfL as a biomarker in the differentiation between bvFTD and psychiatric disorders. In recent years, several proteomic studies identified potential biomarker candidates for psychiatric conditions, yet no biomarker has been validated(Al Shweiki et al., 2017; Comes et al., 2018). An initial step might be the identification of biomarkers that at least allow a distinction between different diagnostic entities. In this respect, NfL presents a supplementary parameter to neuroimaging in the distinction of bvFTD from primary psychiatric disorders.

The serum levels of NfL did not differ between psychiatric and the control patients. Serum NfL has been reported to be elevated in several disorders with ongoing neurodegenerative processes (Khalil et al., 2018; Mattsson et al., 2017; Steinacker et al., 2015) and may help in ruling out neurodegeneration in psychiatric patients. However, a study with a larger cohort may be essential to generalize the finding.

In conclusion, serum NfL is a promising and easily accessible biomarker candidate for the differential diagnosis of bvFTD from psychiatric disorders as well as to rule out an ongoing neurodegeneration process in psychiatric disorders.

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Table 1
Demographic characteristics and serum NFL levels of the study groups.

Diagnostic Category	Sub-groups	Group size	Gender	Age	Serum NFL (pg/mL)
Depression	Organic mood disorder (7) Major depressive disorder (21)	28	13M/15F	52.1 (46.2–58.4)	15.7 (12.4–25)
Bipolar disorder	Depressive (3) Mixed (4) Manic (4)	11	7M/4F	51.4 (33.5–58.1)	17.8 (12.6–23.1)
Schizophrenia	Paranoid (6) Undifferentiated (5)	11	5M/6F	41.1 (31.4–48.5)	11.6 (9.8–23.5)
bvFTD	Possible (9) Probable (5) Genetic (6)	20	10M/10F	50.6 (44.9–52.5)	72.7 (28.3–90)
Controls		27	10M/17F	46.8 (39.1–54.1)	15.1 (11.3-19-1)

Given values are the median and interquartile range.

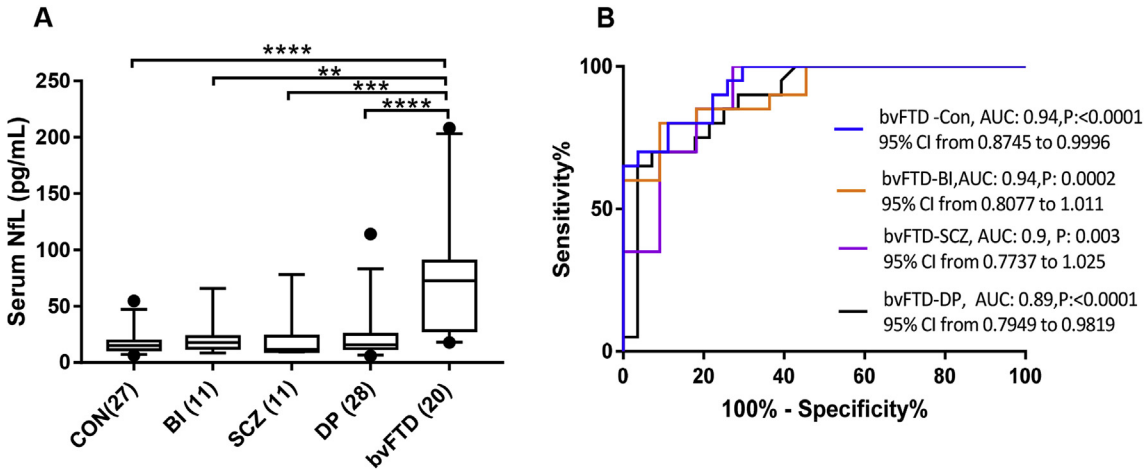

Fig. 1. Serum neurofilament light chain (NfL) differentiates bvFTD from primary psychiatric disorders. (A) Serum NfL levels in the different patient cohorts (number of patients in brackets). Boxes are the median concentrations and interquartile range; whiskers are 5% and 95% percentiles. Points represent values below 5% percentile and above 95% percentile. Asterisks refer to statistically significant differences with unpaired Kruskal-Wallis test and Dunn's post hoc test, ****p < 0.0001, ***p < 0.001, **p < 0.01. (B) Receiver operating characteristic (ROC) curves of serum NfL for differentiation between bvFTD and controls, bvFTD and bipolar disorder, bvFTD and schizophrenia and bvFTD and depression. CON = controls; BI = bipolar disorder; SCZ = schizophrenia; DP = depression, and bvFTD = behavioural variant frontotemporal dementia, CI = confidence interval, AUC = area under the curve.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.03.019.

Disclosure

The authors report no conflict of interests.

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