Longitudinal Correlation between Neurofilament light Chain and UMSARS in Multiple System Atrophy

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Key words

MSA, NfL, UMSARS, neurodegeneration, biomarker

Abbreviations

APS: Atypical parkinsonian syndromes, MOCA: Montreal Cognitive Assessment, MSA: Multiple System Atrophy, MSA-C: Multiple System Atrophy of the cerebellar type, NfL: Neurofilament light chain, PD: Parkinson's disease, REM: Rapid Eye Movement, UMSARS: Unified Multiple System Atrophy Rating Scale, UMSARS-ME: Unified Multiple System Atrophy Rating Scale - Motor Examination

Introduction

Multiple System Atrophy (MSA) is defined by a hypokinetic or cerebellar movement disorder in combination with autonomic dysfunction [1]. Reliable biomarkers for diagnosis or disease progression are largely missing. Blood and cerebrospinal fluid (CSF) levels of neurofilament light chain (NfL) have been reported to be elevated in MSA [2,3] and seem to distinguish between MSA and Parkinson's disease (PD) [4]. We present a patient with MSA of the cerebellar type (MSA-C), whose disease progression was followed using the Unified Multiple System Atrophy Rating Scale (UMSARS) and plasma NfL levels over 254 days.

Case report

A patient with progressive gait ataxia, slurred speech, erectile dysfunction and polysomnographically proven REM sleep behavior disorder presented to our clinic at the age of 65. Symptom onset was approximately one year before. During follow-up the patient reported urinary stress incontinence. Medical and family history were negative for neurological and psychiatric diseases. Neurological examination showed moderate staggering of gait with postural instability, action tremor, hypermetric saccades, dysdiadochokinesia and hypokinesia of both hands. He did not show signs of hyposmia with a normal SniffinSticks test. The patient fulfilled the current criteria for a probable MSA-C [1]. Cell count, protein, glucose, tau and amyloid-β in CSF were normal. FDG-PET showed severe glucose hypometabolism in cerebellar hemispheres and vermis. Levodopa 600mg daily did not have any effect on motor symptoms and was therefore discontinued. Depression was treated with venlafaxin 75mg at baseline.

The patient was followed clinically using UMSARS and with longitudinal plasma biosampling 7 times over a time-course of 254 days. The patient was asked to document potential falls, headaches or head trauma of any kind. No further standardization of sample collection was implemented. Levels of plasma NfL were measured on the SIMOA platform (Quanterix, Billerica, USA) using a commercial assay [5]. All samples were analyzed in the same plate blinded to clinical information. Pearson coefficient and correlation were calculated using GraphPad Prism 7 for MAC. During the course, the patient showed progressive decline, in particular increasing unsteadiness and worsening of cerebellar dysarthria. No falls or head trauma were reported. Initial UMSARS-total was 21; UMSARS-ME (motor examination) was 10. After 10 months, UMSARS increased to 41; UMSARS-ME to 18. Baseline NfL at baseline was 146 pg/ml and increased to 187.2 pg/ml at day 254. A correlation between NfL and UMSARS-ME was observed ($p<0.0001$; figure).

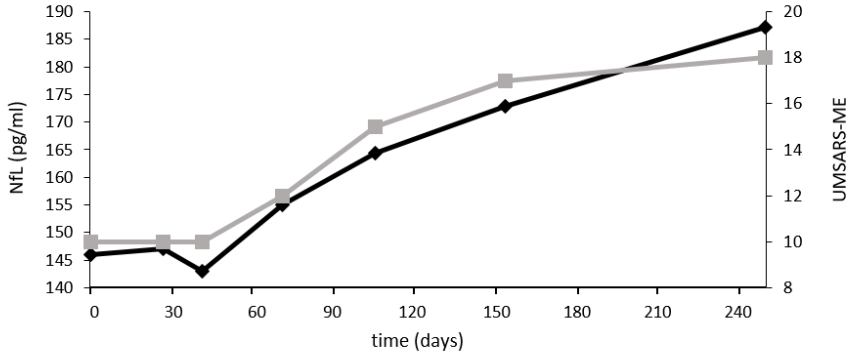
Discussion

This patient with MSA-C showed increasing plasma NfL levels, which is in line with previous studies [2,3]. During observation period, plasma NfL levels were rising and a significant positive association between NfL and UMSARS aswell as UMSARS-ME was observed (figure). The data points towards a potential use of NfL as a biomarker for disease progression in MSA-C, concerning motor (UMSARS-ME) and non-motor symptoms captured with total UMSARS, and highlight that the correlations between NfL and clinical phenotype suggest also a good correlation of phenotype and NfL with underlying neurodegenerative disease processes.

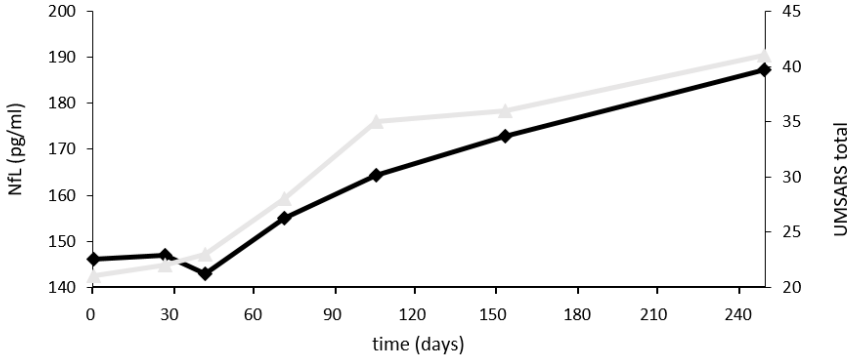
Conclusion

The case of our patient with MSA-C illustrates the potential use of plasma NfL levels correlating with clinical progression. Further research in this direction is warranted.

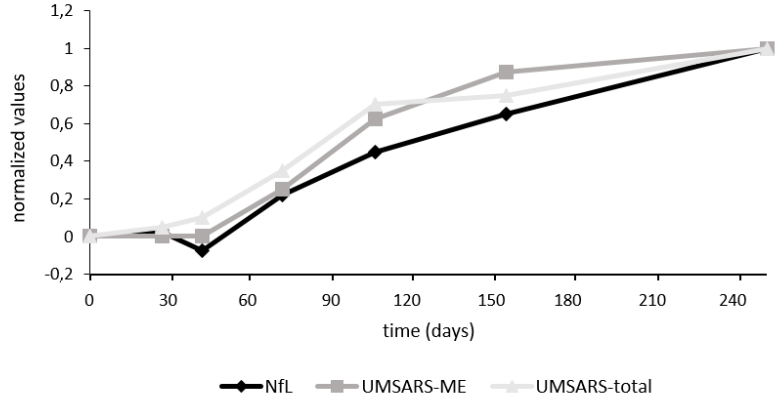
1A


NfL (pg/ml)
UMSARS-ME
time (days)

1B


NfL (pg/ml)
UMSARS total
time (days)

1C


normalized values
time (days)
NfL
UMSARS-ME
UMSARS-total

1D

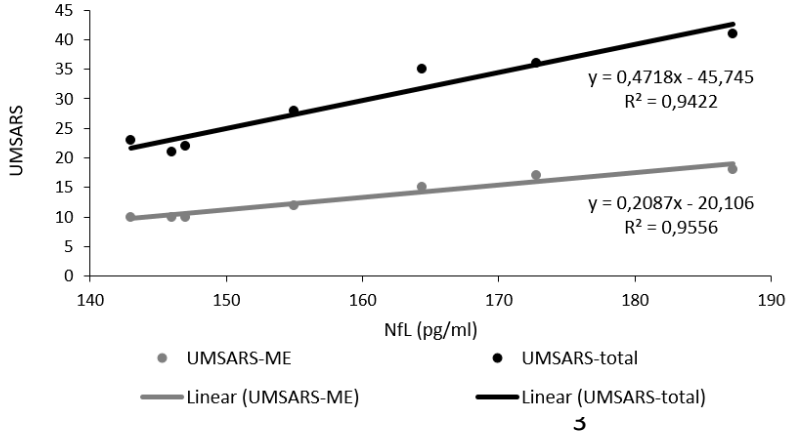

UMSARS
y = 0,4718x - 45,745
R² = 0,9422
y = 0,2087x - 20,106
R² = 0,9556
NfL (pg/ml)
UMSARS-ME
UMSARS-total
Linear (UMSARS-ME)
Linear (UMSARS-total)

Figure: Increase of Neurofilament light chain (NfL) and Unified MSA Rating Scale (UMSARS) over time. Figure 1A shows the increase of plasma NfL in pg/ml in correlation to UMSARS-motor examination (ME) over a period of 254 days with a Pearson coefficient of correlation of 0.9775; $p<0.0001$, figure 1B shows the increase of plasma NfL and total UMSARS with a Pearson coefficient of correlation of 0.942; $p<0.0001$. Figure 1C displays the normalized values of NfL, UMSARS-total and UMSARS-ME to baseline values. Figure 1D shows the correlation analysis with $R2=0.9422$ between UMSARS-total and NfL and $R2=0.9556$ between UMSARS-ME and NfL.

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Author's Roles

Carla Palleis: Conceptualization, data curation, formal analysis, investigation, methodology, writing-original draft. Estrella Morenas-Rodriguez: Methodology, investigation, formal analysis, resources, writing – review and editing, funding acquisition. Francisco Jesús Martínez Murcia: Conceptualization, Formal analysis, writing – review and editing. Armin Giese: Conceptualization, writing – review and editing. Brigitte Nuscher: Investigation, writing – review and editing. Günter Höglinger: Conceptualization, writing – review and editing. Christian Haas: Conceptualization, Writing – review and editing. Kai Bötzel: Conceptualization, Writing – review and editing, supervision. Johannes Levin: Conceptualization, investigation, methodology, supervision, writing – review and editing. All authors read and approved the final manuscript.

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