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Cerebrospinal fluid myelin basic protein is elevated in multiple system atrophy

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ABSTRACT

Introduction: Parkinson's disease (PD) and multiple system atrophy (MSA) have overlapping symptoms, challenging an early diagnosis. Diagnostic accuracy is important because PD and MSA have a different prognosis and response to treatment. Here, we aimed to evaluate the diagnostic value of brain-specific structural proteins in cerebrospinal fluid (CSF) of PD and MSA patients, as well as their association with cognitive decline.

Methods: CSF samples were collected from patients with clear signs of parkinsonism, but with uncertain diagnosis at the time of inclusion. Clinical diagnoses of PD (n = 55) and MSA (n = 22) were established after 3 and 10 years of follow-up and re-evaluated after 12 years, according to the most updated clinical criteria. CSF from controls (n = 118) was studied for comparison. Neuron-specific enolase (NSE), glial fibrillary acidic protein (GFAP), S100 calcium-binding protein B (S100B) and myelin basic protein (MBP) levels in CSF were measured using ELISA. Protein levels were also correlated with cognitive decline, i.e. worsening of the mini mental state examination (MMSE) over a period of three years.

Results: MBP concentrations were increased in MSA compared to PD and controls ($p < 0.005$) and could differentiate MSA and PD with high accuracy (AUC = 0.781; $p < 0.001$). Concentrations of MPB, GFAP and S100B, but not NSE, were significantly elevated in PD patients compared to controls ($p = 0.05$). None of the brain-specific structural proteins correlated with MMSE progression.

Conclusions: Our results demonstrate that MBP differentiates PD from MSA at early stages of the disease, indicating that demyelination and axonal damage may already occur in early stages of MSA.

1. Introduction

Parkinson's disease (PD) is the most common neurodegenerative disorder of movement affecting 1% of the population worldwide older than 65 years [1]. The motor symptoms of PD are bradykinesia with rigidity and/or rest tremor. The prodromal phase of PD features non-motor symptoms, such as olfactory dysfunction, psychiatric symptoms, REM-sleep behavior disorder, autonomic dysfunction, pain and fatigue [1]. At later stages, dementia might also occur. Diagnosis of PD is based on the typical motor symptoms that, however, only appear after 50–80% of dopaminergic neurons have died [2]. Establishing a correct diagnosis of PD can be challenging, especially at early stages, as its phenotype shares many clinical features with other types of parkinsonism, such as multiple system atrophy (MSA). Like PD, MSA is a progressive alpha-synucleinopathy, but it is a more rapidly progressive neurodegenerative disease with a mean survival of 9 years after symptom onset and poor response to dopaminergic therapy [3].

Because of the different prognosis and treatment needs, an early stage biomarker to differentiate PD from MSA is needed. Levels of the brain-specific structural proteins neuron-specific enolase (NSE), S100 calcium-binding protein B (S100B), glial fibrillary acidic protein (GFAP) and myelin basic protein (MBP) in cerebrospinal fluid (CSF) may comprise such biomarkers. NSE is a glycolytic enzyme predominantly present in neurons and endocrine cells and elevated concentrations in CSF may occur as a consequence of neuronal damage [4]. S100B is a calcium-binding protein highly expressed by astrocytes and oligodendrocytes. Elevated S100B concentrations in CSF have been found in Alzheimer's diseases (AD), frontotemporal dementia (FTD) and vascular dementia in comparison to controls [5–7]. GFAP is the major protein constituent of glial intermediate filaments in differentiated

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astrocytes [8] and its levels in CSF are higher in dementia [9,10]. MBP is the second most abundant protein in the myelin sheets of axons in the central nervous system [11] and elevated levels may be observed in CSF due to demyelination.

In a previous study, using CSF collected from established cases of PD and MSA, we observed increased concentrations of MBP and NSE in MSA versus PD patients [12]. In the present study, we aimed to analyze whether these biomarkers of structural brain damage are similarly associated with PD and MSA at a stage of disease when clinical diagnosis is still uncertain and whether these proteins may function as early biomarkers for diagnosis. We also aimed to determine the correlation of these biomarkers with cognitive function.

2. Methods

2.1. Patients

A total of 55 PD and 22 MSA cases were selected based on CSF availability from a prospective cohort study performed at the Radboud university medical center (Nijmegen, the Netherlands) [13]. In this study, 156 patients, referred to our center between January 2003 to December 2006 because of parkinsonism and diagnostic uncertainty, were included. Exclusion criteria were age younger than 18 years, history of brain surgery or neurodegenerative diseases other than parkinsonism or unstable comorbidity. All patients underwent a structured interview, detailed and standardized neurologic examination, blood collection, lumbar puncture and other ancillary investigations within 6 weeks after inclusion. The study design, methods and patient population have been extensively described elsewhere [13]. These patients were followed up for three and ten years and a clinical diagnosis was established by two expert neurologists in movement disorders based on a repeated structured interview and extensive neurological examination. In 2018, twelve years after inclusion, all diagnoses were re-evaluated and updated according to the most recent clinical criteria [13–15], disease course based on the patients' medical files, follow-up visits and neuropathological examination whenever available. Disease severity and cognitive function were evaluated using the Hoehn and Yahr (HY) scores, the Unified Parkinson's Disease Rating Scale (UPDRS) part III (motor score), the International Cooperative Ataxia Rating Scale (ICARS) and the Mini-Mental State Examination (MMSE).

The control group consisted of 118 patients aged above 40 years with no neurological disease and who underwent a lumbar puncture because of a suspected neurological disorder that was ruled out after extensive investigation. For each biomarker data was available for a subset of the entire control group (Table 1).

All participants provided written informed consent and the study was approved by the local Medical Ethics Committee. Usage of CSF leftovers from patients as controls in research projects was approved by the local Medical Ethics Committee.

2.2. Cerebrospinal fluid samples

Lumbar puncture was performed as described previously [13]. CSF samples had no blood contamination (leukocyte number count fewer than 5 cells/μL and erythrocyte number fewer than 200 cells/μL) [16,17].

2.3. ELISA

NSE and S100B concentrations in CSF were analyzed with an immunoluminometric assay (*Byk Sangtec, Dietzenbach, Germany*) using the Liaison automated analyzer (*Byk Sangtec*). The assays were linear up to 100 μg/L for NSE and 30 μg/L for S100B. The inter-assay variation coefficients were < 5.3% (NSE) and < 11% (S100B). MBP concentrations in CSF were analyzed using a commercial ELISA (*DSL, Webster, Texas*). The assay was linear up to 10 μg/L and the inter-assay variation coefficient was < 10%. Concentrations in CSF of GFAP were measured using a homemade sandwich ELISA [18,19]. The assay was linear up to 250 μg/L and the inter-assay variation coefficient was < 14%.

2.4. Data analysis

Statistical analyzes were performed using IBM SPSS Statistics (v.25.0.0.1). Kruskal-Wallis test with Bonferroni correction was performed to assess differences between groups for age, baseline and follow-up parameters. Chi-square test was used to assess sex differences. A p value < 0.05 was defined as significant.

Group comparison for CSF biomarker was performed by rank analysis of covariance to correct for age and sex. Briefly, the dependent variables and the covariates were ranked. Then, a linear regression of the ranks of the dependent variable on the ranks of the covariates was performed and the unstandardized residuals were saved. Finally, an ANOVA with Games Howell correction was performed using the unstandardized residuals. The Games Howell post hoc test is used to compare groups with unequal variances. Spearman's correlation was used to assess relationship between levels of brain-specific structural proteins in CSF and MMSE, HY or ICARS progression. Disease progression was calculated by subtracting scores at 3-year follow-up from scores at baseline of either MMSE, HY or ICARS and divided by time (3 years). The MSA group was further stratified into fast and slow disease progression. For that we calculated the median of HY and ICARS progression. Values equal or below the median were considered as slow progression and values above the median as fast progression. We also took the use of a wheelchair within 5 years of symptom onset as a parameter of disease progression, considering usage of wheelchair as rapid progression.

GraphPad Prism (v.5.00) was used to perform receiver operating characteristic (ROC) curve analysis of biomarkers for PD versus MSA. Biomarker models were created using binary logistic regression and probability values of the logistic regression were used to run the ROC curve analysis.

3. Results

Group comparison revealed significantly increased levels of GFAP in CSF of PD patients compared to controls (1.9 ± 1.1 μg/L vs. 1.4 ± 1.3 μg/L, $p = 0.014$) (Fig. 1A). S100B concentrations were increased in PD patients compared to controls (3.2 ± 1.3 μg/L vs. 2.5 ± 0.6 μg/L, $p = 0.044$) (Fig. 1B). The concentrations of NSE were comparable in PD, MSA and controls (11.6 ± 4.2 μg/mL vs. 12.4 ± 4.1 μg/mL vs. 9.4 ± 4.8; $p = 0.096$ and $p = 0.147$) (Fig. 1C). MBP concentrations were higher in MSA compared to both PD patients (1.7 ± 1.1 μg/L vs. 1.2 ± 1.1 μg/L, $p = 0.005$) and controls (0.6 ± 0.4 μg/L, $p < 0.0001$) and were also elevated in PD compared to controls ($p < 0.0001$) (Fig. 1D).

The area under the curve (AUC) for MBP analysis in the differentiation of MSA from PD, considering sex and age as covariates, was 0.781 ($p < 0.001$). We aimed to determine whether the combination of MBP, GFAP, NSE and S100B added value to MBP alone for the differential diagnosis. The AUC for the combined brain-specific structural proteins was 0.744 ($p < 0.001$), indicating that only MBP contributes to the differential diagnosis of PD and MSA (Fig. 2).We did not find a correlation between any of the brain-specific structural proteins and the change in MMSE score over a period of three years, neither in the PD nor in the MSA group ($p > 0.05$).

MSA patients showed different progression speed, thus, we divided the patients into fast and slow disease progression using the medians of both HY and ICARS scales as cut-offs, as well as the use of wheelchair after 5 years of symptoms onset. We did not observe differences in CSF MBP levels in fast versus slow progressors, based on either HY, ICARS or use of wheelchair (HY: $p = 0.806$, ICARS: $p = 0.073$, use of wheelchair: $p = 0.271$).

Table 1
Characteristics of the patients included in the analysis.

N	Controls				MSA (-P, –C, -P/C)	PD	p value‡
	118				22 (15, 6, 1)	55	
	NSE	**S100B**	**GFAP**	**MBP**	**pos/prob/def/clin**	**pos/prob/def/clin**	
	48	48	47	38	4/15/3/0	1/38/1/15	
Age (at inclusion)	55.9 ± 8.8				60.7 ± 7.1	57.1 ± 10.0	0.035
Sex (men/women)	66/52				15/7	38/17	0.002
Disease duration since first symptoms (months)	N.A.				33.9 ± 26.4 (22)	34.2 ± 26.3 (55)	0.906
Disease severity (baseline)							
HY score	N.A.				2.4 ± 1.0 (22)	2.0 ± 0.6 (55)	0.002
UPDRS-III score	N.A.				29.0 ± 13.9 (21)	26.5 ± 11.9 (52)	0.338
ICARS score	N.A.				11.7 ± 11.7 (18)	2.8 ± 3.0 (50)	< 0.001
MMSE score	N.A.				28.0 ± 2.2 (21)	28.4 ± 2.1 (55)	0.512
Disease severity (3 years follow-up)							
HY score	N.A.				3.8 ± 1.4 (17)	2.3 ± 0.7 (52)	< 0.001
UPDRS-III score	N.A.				32.5 ± 9.3 (11)	28.8 ± 13.6 (47)	0.131
ICARS score	N.A.				23.5 ± 19.0 (10)	2.5 ± 2.2 (43)	< 0.001
MMSE score	N.A.				25.8 ± 2.8 (11)	28.2 ± 2.2 (44)	0.005
Use of wheelchair at 5 years follow-up (yes/no)	N.A.				12/10	3/52	< 0.001
Survival after 12 years (dead/alive)	N.A.				21/1	11/44	< 0.001

Data are represented as mean ± SD (number of patients included). p value was considered significant when < 0.05. MSA: multiple system atrophy; MSA-P: MSA parkinsonian type; MSA-C: MSA cerebellar type: MSA-P/C: MSA mixed parkinsonian and cerebellar types; PD: Parkinson's disease; NSE: neuron-specific enolase; S100B: S100 calcium-binding protein B; GFAP: glial fibrillary acidic protein; MBP: myelin basic protein; pos: possible; prob: probable; def: definite; clin: clinically established; N.A.: not applicable; HY: Hoehn and Yahr; UPDRS-III: Unified Parkinson's Disease Rating Scale part III (motor score); ICARS: International Cooperative Ataxia Rating Scale; MMSE: Mini-Mental State Examination. ‡Kruskal-Wallis or Mann-Whitney *U* test with Bonferroni correction and Chi-square for sex differences.

We also calculated whether the CSF MBP levels differed between MSA subtypes. We did not observe differences in MBP levels (p = 0.384) between MSA-P and MSA-C. However, the number of patients per group is relatively small. Finally, we calculated whether disease progression was different between the different MSA subtypes according to HY, ICARS progression and use of wheelchair. Although ICARS progression was higher in the MSA-C group, the difference was statistically not significant (p = 0.087). HY progression (p = 0.385) and use of wheelchair (p = 0.588) were also not different between MSA subtypes.

4. Discussion

The main finding of our study is that CSF MBP levels are increased in CSF of MSA patients in comparison to PD. Previously, we reported on the same CSF biomarkers in other cohorts of PD and MSA patients [20].

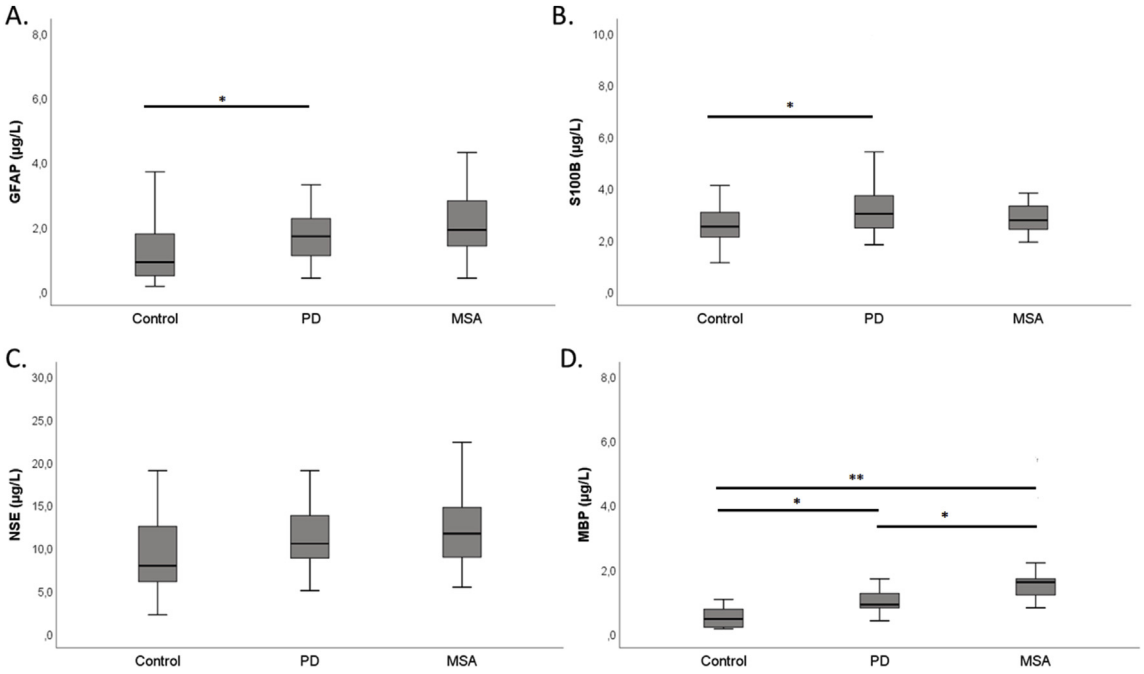

Fig. 1. Glial fibrillary acidic protein (GFAP), S100 calcium-binding protein B (S100B), neuron-specific enolase (NSE) and myelin basic protein (MBP) levels in CSF. GFAP **(A)** and S100B **(B)** were significantly increased in CSF of PD patients compared to controls (p < 0.05). NSE **(C)** showed no significant differences between groups. MPB **(D)** levels in CSF were higher in MSA than PD and controls, as well as in PD in comparison to controls (p < 0.001). Data were analyzed using rank analysis with age as covariant followed by ANOVA with Hochberg as a post hoc test. A p value < 0.05 was considered as significant. * indicates p value < 0.05 and ** < 0.001. Boxplot plots represent median and interquartile range. PD: Parkinson's disease; MSA: Multiple system atrophy.

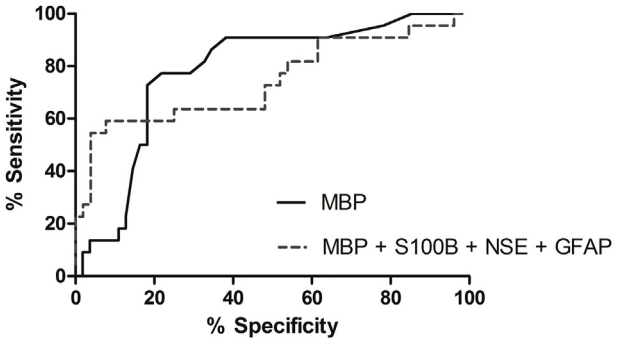

Fig. 2. Receiver operating characteristic (ROC) curve analysis of PD versus MSA. The combination of all brain-specific structural proteins (black dotted) did not have an added value to MBP alone (solid black) (AUC = 0.744 and 0.781 respectively, p value < 0.001). In all cases, the covariates sex and age were included in the models.

This previous cohort not only had a longer disease duration (PD: 39 months vs. 34 months; MSA; 45 months vs. 34 months), but the clinical diagnosis was also defined after non-standardized follow-up, whereas in the present study it was defined after extensive and structured 3 and 10 years follow-up. The increased MBP levels in CSF of MSA patients is consistent with our previous study [20], but the present study indicates that demyelination already occurs at early stages of the disease and is more severe in MSA than PD. In line with our previous study, we observed comparable levels of the glial proteins GFAP and S100B levels in CSF from PD and MSA patients. In contrast, in the previous study we found increased NSE levels in MSA in comparison to PD patients [20], which we did not observe now. Because this study focused on patients at early stage of the disease, the results might suggest that more advanced neuronal degeneration occurs at later stages of disease in MSA, but not at earlier stages of MSA.

We observed increased levels of GFAP, S100B and MBP, but not of NSE, in CSF of PD in comparison to controls. These results are partly in agreement with previous studies, showing no differences in S100B and NSE levels in serum [21] and in CSF [22] between PD and controls. Yet, other studies reported no significant differences in CSF GFAP levels between PD and controls [9,23]. To our knowledge, no data on differential levels of MBP between PD and controls have been reported yet. The present study also showed significantly increased levels of MBP, but not GFAP, S100B and NSE in CSF of MSA patients in comparison to controls. These results are in line with previous studies [23,24].

Several studies have reported increased levels of the glial proteins S100B and GFAP in CSF and in serum of patients with dementia, i.e. AD, FTD and dementia with Lewy bodies (DLB) [9,10,22,25–27]. The higher levels in CSF and serum of GFAP and S100B in dementia might indicate an association between glial proteins and cognitive functioning, since S100B levels in CSF [26,28] and in serum [29], and of GFAP in serum [9] and CSF [27] correlated with the severity of cognitive dysfunction in AD patients. To our knowledge, no studies have been performed on the association of GFAP and S100B in CSF and cognitive decline in PD and MSA patients. We did not find a correlation between GFAP or S100B levels in CSF and cognitive decline in PD and MSA patients, indicating that correlation of these markers with cognitive decline may be specific for dementias, in which cognitive decline is the major symptom, in contrast to parkinsonian disorders.

In contrast to other studies [30,31], we did not find differences in disease progression between MSA-P and MSA-C. CSF MBP levels were also not different between MSA subtypes. However, our MSA cohort is relatively small and prohibits us to draw definite conclusions.

The strength of our study is that, in contrast to most other biomarker studies, our cohort is especially useful for evaluation of early biomarkers. Our patients presented diagnostic uncertainty at inclusion and their clinical diagnosis was re-evaluated twelve years after inclusion. This experimental design reflects the daily clinical situation when biomarkers are most needed. However, our study also presents some drawbacks. First, our group of MSA patients was relatively small, especially for the correlations between biomarkers and cognitive decline, which may have led to underpowered results in the MSA group. The small number of MSA patients also limited the comparison of MSA subtypes, which would be interesting to further explore in a bigger cohort. Second, the final diagnosis was based on clinical evaluation according to international diagnostic criteria, but has not been confirmed by post-mortem neuropathologic examination. On the other hand, we have reduced the risk of misdiagnoses by the very long follow-up of the patients.

Our results demonstrate that MBP can differentiate PD from MSA at early stages of disease, indicating that demyelination may occur relatively early in MSA. The brain-specific structural proteins did not correlate with MMSE in either MSA or PD, suggesting that, unlike in dementia syndromes, these proteins are not suitable biomarkers for prediction of cognitive decline in parkinsonism syndromes.

Ethics approval

This study was approved by the Central Committee on Research Involving Human Subjects in the region Arnhem-Nijmegen (2002/188) and all participants provided written informed consent. Informed consent covered all the CSF biomarkers studies.

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request indefinitely after publication date.

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Authors' contributions

AS and AvR collected the data. AS performed the data analysis and wrote the manuscript. AS, HBK, MMV interpreted the data and revised the manuscript. MMV, BRB, RAJE and AS were responsible for the design and conceptualization of the study. AS, HBK, AvR, RAJE, BRB and MMV read the manuscript for intellectual content and commented on the final version of the manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

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