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Neurofilament light chain level in cerebrospinal fluid can differentiate Parkinson's disease from atypical parkinsonism: Evidence from a meta-analysis

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ABSTRACT

A reliable test that facilitates the accurate diagnosis of Parkinson's and disorders will help with both, clinical management and therapeutic research. In this context, neurofilament light chain (NFL) is candidate for a biomarker in cerebrospinal fluid (CSF). A comprehensive literature search yielded 4 eligible studies. We expressed between-group difference of NFL concentration in CSF as the standardized mean difference. Four studies involved 166 Parkinson's disease (PD), 116 multiple system atrophy (MSA) and 73 progressive supranuclear palsy (PSP) patients. Patients with MSA showed higher concentration of NFL concentration in CSF than those with PD (standardized mean difference = 1.60, $P < 0.0001$). These studies were homogeneous ($P = 0.17$). NFL in CSF in PSP was significantly elevated relative to PD with homogeneous studies (standardized mean difference = 2.04, $P < 0.0001$; $P = 0.99$). The present meta-analysis suggested that NFL concentration in CSF in MSA and PSP was significantly increased relative to PD, and that this could help us to separate PD from atypical parkinsonian syndromes.

1. Introduction

Parkinson's disease (PD) is characterized by dopaminergic neuronal loss in substantia nigra pars compacta with cytoplasmic inclusion bodies, named as Lewy bodies, which causes resting tremor, rigidity, akinesia, bradykinesia and postural instability [1]. Based on pathological findings, PD is differentiated from multiple system atrophy (MSA) and progressive supranuclear palsy (PSP), but it is difficult to separate PD from MSA and PSP using only clinical features. Indeed, quite a few patients misdiagnosed as having idiopathic PD actually have MSA or PSP, and these are most common atypical parkinsonian syndromes [2–4]. This fact indicates that we cannot perform reliable clinical trial with disease modifying therapy. To address this issue, various methods have been used for differential diagnosis of parkinsonism. In this context, neurofilament light chain (NFL) concentration in cerebrospinal fluid (CSF) was reported to be helpful to differentiate PD from atypical parkinsonian syndromes [5–8]. A meta-analysis allows computing an estimate of the effect size for each study, which produces an overall effect. This method is useful to clarify the underlying overall effect of disease across published studies. Indeed, meta-analyses of magnetic resonance imaging (MRI) have revealed the lower fractional anisotropy and volume reduction in substantia nigra in PD relative to healthy controls, and putaminal volume loss in MSA compared to PD [9–11]. In this study, we performed a meta-analysis in order to provide more robust evidence of NFL as a diagnostic aid in parkinsonian disorders.

2. Materials and methods

2.1. Search strategies and study selection

Inclusion criteria in this study were: (1) measurement of NFL in CSF; (2) comparison between PD and atypical parkinsonism; (3) classified groups according to internationally agreed consensus criteria including the UK Parkinson's Disease Society Brain Bank criteria, the National Institute of Neurological Disorders and Stroke diagnostic criteria for PD [12], Quinn's criteria [13], Gilman's criteria [14] and the report of the National Institute of Neurological Disorders and Stroke-Society for Progressive Supranuclear Palsy International Workshop [15]; and (4) written in English. Studies which enrolled less than ten patients in each group were excluded. We performed a systematic search of PubMed using the following terms: “neurofilament light chain”, “NFL”, “Parkinson's disease”, “PD”, “cerebrospinal fluid”, and “CSF”. Abovementioned search was performed in November 2013, and yielded 8 papers. Of 8 studies, 5 were excluded because no patients with atypical parkinsonism were enrolled (1 paper), the number of enrolled subjects was less than 10 in PD group (1 paper), subjects were overlapped with other previous reports (1 paper), or two were review articles. Further information was sought through a manual search of references

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Table 1
Characteristics of studies included in this meta-analysis.

Study name	Group	Sample size	Age—year	Male (female)	Disease duration—years	HY	CSF erythrocytes—per μl	CSF Hb—ng/ml
Holmberg, 2001	PD	35	61.5 ± 10.5	20 (15)	10.6 ± 6.9	NA	NA	NA
	MSA	36	63.1 ± 9.4	23 (13)	4.7 ± 3.1	NA	NA	NA
	PSP	14	68.5 ± 4.6	9 (5)	4.5 ± 2.5	NA	NA	NA
Abdo, 2007	PD	31	52.5 ± 10.8	NA	3.6 ± 2.8	NA	NA	NA
	MSA-P	18	59.6 ± 6.6	NA	4.1 ± 2.1	NA	NA	NA
Constantinescu, 2010	PD	10	57.2	7 (3)	NA	2.9	<500	NA
	MSA-P	14	62.2	3 (11)	NA	3.0	<500	NA
	PSP	14	63.6	8 (6)	NA	2.8	<500	NA
Hall, 2012	PD	90	63 (56–71)	59 (31)	NA	2.5 (2–3)	NA	<1000
	MSA	48	64 (59–72)	22 (26)	NA	4.0 (3–5)	NA	<1000
	PSP	45	70 (64–74)	20 (25)	NA	4.0 (4–4)	NA	<1000

Abbreviations: CSF, cerebrospinal fluid; Hb, hemoglobin; HY, Hoehn–Yahr stage; MSA, multiple system atrophy; MSA-P, the parkinsonian variant of multiple system atrophy; NA, not available; PD, Parkinson's disease; PSP, progressive supranuclear palsy.

from recent reviews and relevant published original papers, and one study was added. Four studies were finally included in the present meta-analysis [5–8]. One study was performed in Netherlands [6], and the others were performed in Sweden [5,7,8]. In two of three studies [5,7], subjects were recruited during almost different periods (i.e. [5]: January 1993 to December 1998; [7]: January 1997 to January 2009). The subjects in the remainder might be considered to partially overlap across these two studies due to the lack of description of the recruitment period [8].

Two authors double-checked the inclusion criteria of the identified studies (WS and NM). The corresponding authors were contacted in order to obtain essential data if their results was not explicitly stated in papers or only represented graphically.

2.2. Data synthesis and statistics

A random-effects model was selected to calculate the summary effect. The corrected standardized mean difference (SMD) was employed to combine each effect (Hedge's g). The *P* value less than 0.05 was considered as significant. We assessed heterogeneity using *P* value of χ^2 statistics and I^2, which reflects the proportion of variability in the effect estimates due to heterogeneity. The amount of heterogeneity for each outcome was calculated based on DerSimonian–Laird model, with τ as an estimate for the standard deviation (SD) of the underlying true outcomes across studies. The *P* value less than 0.1 was considered as significant heterogeneity. Furthermore, we planned to perform a subgroup analysis to explore the cause of heterogeneity if significant heterogeneity was detected between studies. A sensitivity analysis was performed to test the robustness of our findings.

Publication bias was assessed by visual inspection of funnel plot asymmetry and applying the Egger's linear regression test, which examines whether the intercept deviates significantly from zero in a regression of the standardized effect against inverse of the standard error [16]. For publication bias, the *P* value less than 0.1 was considered as statistically significant. Analyses were performed using the library of "meta" and "metafor" in R software (http://www.r-project.org/) and Review Manager (RevMan 5.2) for Windows (http://ims.cochrane.org/revman).

3. Results

3.1. Study characteristics

Four studies of NFL concentration in CSF satisfied our inclusion criteria (166 PD patients, 116 MSA, 73 PSP). The pooled mean baseline characteristics were as follows: age (PD, range 52.5 to 63; MSA, 59.6 to 64; PSP, 63.6 to 70) year, male (PD, range 7 to 59; MSA, 3 to 23; PSP, 8 to 20), female (PD, range 3 to 31; MSA, 11 to 26; PSP, 5 to 25), disease duration (PD, range 3.6 to 10.6; MSA, 4.1 to 4.7; PSP, 4.5) years and Hoehn–Yahr stage (HY) (PD, range 2.5 to 2.9; MSA, 3.0 to 4.0; PSP, 2.8 to 4.0). Characteristics of included studies were summarized in Table 1.

3.2. NFL in CSF in patients with parkinsonism

Patients with MSA showed higher concentration of NFL in CSF than those with PD (SMD = 1.60, 95% confidence interval (CI) 1.22 to 1.98, $P < 0.0001$, 4 studies, n = 282; Fig. 1A). These studies were homogeneous ($P = 0.17$, $I^2 = 39\%$). NFL in CSF in PSP was significantly elevated relative to PD with homogeneous studies (SMD = 2.04, 95% CI 1.69 to 2.40, $P < 0.0001$, 3 studies, n = 208; $P = 0.99$, $I^2 = 0\%$; Fig. 1B). Sensitivity analyses demonstrated the robustness of our findings (Tables 2 and 3).

3.3. Publication bias

The funnel plot appeared slightly asymmetrical in each analysis (Fig. 2). However, there were no significant deviations of intercept

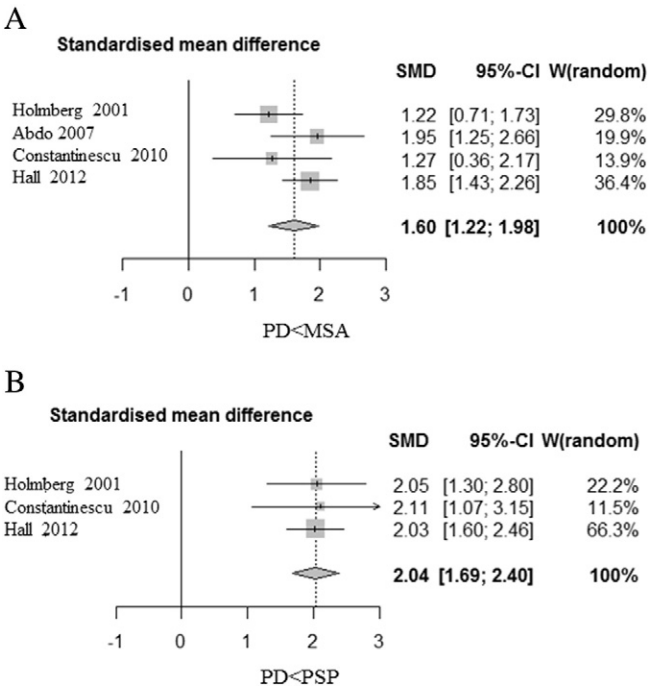

Fig. 1. Forest plot of standardized mean difference (SMD) of neurofilament light chain (NFL) concentration in cerebrospinal fluid (CSF) in Parkinson's disease (PD), multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). (A) NFL level in CSF was significantly increased in MSA relative to PD. The included studies were homogeneous. (B) PSP showed more elevated NFL concentration than PD with homogeneous studies.