INPLASY PROTOCOL

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The authors report no competing interests.

Blood neurofilament light chain in Parkinson's disease and atypical parkinsonisms: a protocol for systematic review and meta-analysis

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Review question / Objective: Neurofilament light chain (NfL), an index of neuroaxonal injury, is a promising diagnostic and prognostic fluid biomarker with high translational value in many neurodegenerative disorders. Blood NfL measurement has been an exciting and active field of research in idiopathic Parkinson's disease (PD) and atypical parkinsonisms. However, blood NfL levels in these parkinsonisms from existing literature were inconsistent. No comprehensive meta-analysis has ever been conducted.

INTRODUCTION

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in these parkinsonisms from existing literature were inconsistent. No comprehensive meta-analysis has ever been conducted.

Condition being studied: Idiopathic Parkinson's disease (PD) presents typical asymmetrical motor symptoms with slow progression and a marked and sustained response to dopaminergic treatment. Unlike idiopathic PD, atypical parkinsonisms, including multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), and dementia with Lewy bodies (DLB), show additional clinical signs like gaze palsy, apraxia, ataxia, early cognitive decline, and dysautonomia. Idiopathic PD and atypical parkinsonisms show considerable overlap in symptoms. Correct diagnoses of parkinsonian disorders are important for patient counselling, prognostic assessment, and therapeutic implications, but also for research purposes. However, their differential diagnoses on clinical grounds remain challenging, particularly in early disease stages. Sustained efforts have been made to develop reliable biomarkers to aid their accurate diagnoses. Neurofilament light chain (NfL) is among the most promising candidate biomarkers of neuroaxonal injury irrespective of the underlying cause and has been extensively investigated in neurodegenerative diseases. With the development of ultrasensitive assay technologies in recent years, a growing number of studies have investigated blood (serum/plasma) NfL levels in idiopathic PD and atypical parkinsonisms. Atypical parkinsonisms commonly showed increased blood NfL levels; However, the degree of elevation varied considerably between these disorders. In addition, blood NfL levels in idiopathic PD were inconsistent across studies.

METHODS

Search strategy: Three major biomedical electronic databases: PubMed, Embase, and Web of Science were comprehensively searched from inception to July10, 2020. The following search terms were used:

(neurofilament OR (neurofilament light chain) OR nfl) AND ((Parkinson disease) OR parkinsonism OR Parkinson* OR (atypical parkinsonian disorders) OR (multiple system atrophy) OR (progressive supranuclear palsy) OR (Steele-Richardson-Olszewski syndrome) OR (corticobasal syndrome) OR (corticobasal degeneration) OR (dementia with Lewy bodies) OR (Lewy body dementia)) AND (blood OR serum OR plasma). Additionally, references of eligible articles and relevant systematic reviews/meta-analyses will be hand-searched.

Participant or population: Parkinsonisms (multiple system atrophy [MSA], progressive supranuclear palsy [PSP], corticobasal syndrome [CBS], and dementia with Lewy bodies [DLB]) and healthy controls (HCs).

Intervention: Measurement of blood (serum/plasma) NfL concentrations in patients with parkinsonisms and HCs.

Comparator: Blood NfL levels in the following comparisons: PD vs HC, MSA vs HC, PSP vs HC, CBS vs HC, DLB vs HC, MSA vs PD, PSP vs PD, CBS vs PD, and DLB vs PD.

Study designs to be included: Original observational studies (including case-control, cohort, and cross-sectional studies).

Eligibility criteria: Inclusion criteria Studies will be included if they: (1) were original observational studies (including case-control, cohort, and cross-sectional studies) in English; (2) included patients with idiopathic PD and atypical parkinsonisms (MSA, PSP, DLB, and CBS) according to the established diagnostic criteria; (3) measured blood (serum/plasma) NfL concentrations in patients with parkinsonisms and HCs; (4) provided sufficient information for meta-analysis (number of participants and mean and standard deviation (SD) for blood NfL levels for each group). If some data were not eligible, they will be transformed from available data or will be obtained using

graph-based data mining methods. Exclusion criteria The following exclusion criteria will be applied: (1) studies were in the form of reviews, letters, editorials, conference abstracts, animal research, case reports, and protocols; (2) studies enrolled repetitive patient samples or were overlapped with another study with a larger sample size. In case of longitudinal studies, we will only extract baseline data for analysis.

Information sources: Three major biomedical electronic databases: PubMed, Embase, and Web of Science were comprehensively searched from inception to July10, 2020.

Main outcome(s): Blood NfL levels in the following comparisons: PD vs HC, MSA vs HC, PSP vs HC, CBS vs HC, DLB vs HC, MSA vs PD, PSP vs PD, CBS vs PD, and DLB vs PD.

Data management: Data from eligible studies will be extracted using a standardized spreadsheet, including the following information: the first author's surname, year of publication, type of parkinsonisms, the numbers of patients and healthy controls, age, gender distribution, the mean and SD values of the blood NfL levels of each group, NfL analysis methods, analysis kit brand, disease duration, Hoehn and Yahr (H-Y) scale, Unified Parkinson's Disease Rating Scale, part III (UPDRS-III) score, and Mini-Mental State Examination (MMSE) score.

Quality assessment / Risk of bias analysis: Quality assessment of the included studies will be performed using the Newcastle Ottawa Scale (NOS).

Strategy of data synthesis: Meta-analyses will be conducted using the STATA software version 13.0 (StataCorp, College Station, TX, USA). The standardized mean differences (SMD) as the measure of effect size and 95% confidence intervals (CI) were calculated of each comparison of blood NfL levels (PD vs HC, MSA vs HC, PSP vs HC, CBS vs HC, DLB vs HC, MSA vs PD, PSP vs PD, CBS vs PD, and DLB vs PD).

Subgroup analysis: Each comparison of blood NfL levels (PD vs HC, MSA vs HC, PSP vs HC, CBS vs HC, DLB vs HC, MSA vs PD, PSP vs PD, CBS vs PD, and DLB vs PD)

Sensibility analysis: To examine whether overall results were influenced by a single study, sensitivity analyses will be performed.

Language: English.

Country(ies) involved: China.

Keywords: Parkinson's disease; parkinsonism; neurofilament light chain; meta-analysis; blood.

Dissemination plans: Once the meta-analyses are complete, it will be published in conferences or a peer-reviewed journal.

Contributions of each author:
Author 1 - HongZhou Wang - Author 1 drafted the manuscript
Author 2 - WanHua Wang - The author provided statistical expertise.
Author 3 - HaiCun Shi - The author contributed to the development of the selection criteria, and the risk of bias assessment strategy.
Author 4 - LiJian Han - The author read, provided feedback and approved the final manuscript.
Author 5 - PingLei Pan - The author read, provided feedback and approved the final manuscript.