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Research article

Association of circulating manganese levels with Parkinson's disease: A meta-analysis

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ABSTRACT

Whether systemic manganese (Mn) dysfunctions in Parkinson's Disease (PD) is still under ongoing debate. The recent reported studies on the circulating Mn levels in PD showed inconsistent results. A meta-analysis study was conducted to evaluate the association of circulating Mn levels with PD, and to clarify whether Mn should be considered as a potential risk factor for PD. A systematic searching was performed based on PubMed, web of science, and China National Knowledge Infrastructure (CNKI). Finally, 22 studies were identified, involving 637 PD patients and 802 health controls (HC) individuals for serum Mn, 1258 PD patients and 1304 HC individuals for peripheral blood Mn, and 195 PD patients and 196 HC individuals for cerebrospinal fluid (CSF) Mn. Forest plots were adopted to represent the comparison of the groups by assessing standardized mean difference with random effects model. This meta-analysis revealed a significantly increased serum Mn levels in PD patients (SMD = 0.78; 95% CI [0.32, 1.24]; P = 0.001), and it was further confirmed when serum, plasma and whole blood studies were analyzed together (SMD = 0.58; 95% CI [0.25, 0.91]; P = 0.001). Instead, no significant differences of CSF Mn were observed between PD patients and HC individuals (SMD = −0.09; 95% CI [−0.47, 0.29]; P = 0.644). These results supported the notion that elevated Mn level should be a potential risk factor for PD, although the high heterogeneity and methodological limitations recommended caution in the interpretations for the present findings.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease in the world [12,36,43]. It often occurred approximately 1% of those more than 60 years old of human accompanied with parallel degeneration of both central nervous system (CNS) and peripheral nervous system (PNS) [12,36,43]. It is characterized by a selective loss of dopaminergic neurons in the pars compacta of the substantia nigra (SN), and is commonly associated with motor signs such as tremor, rigidity, slowness of movement and postural instability [26]. The etiology of the disease is still largely unknown. However growing evidences suggested that a number of aetiological factors involved in the onset of PD pathology including age, dietary habits, genetic susceptibility, as well as environmental factors, like metal ions [9,14,27].

The altered homeostasis of some metal elements could be related to the progression of PD [57], and the previous meta-analysis studies have indicated that PD is associated with an imbalance of higher serum iron levels [27] and lower zinc levels [10,50]. Manganese (Mn) is an essential heavy metal for human health, and is widely found in minerals, soil and food [4,8]. It is contained in several proteins and key enzymes and required for several key physiological processes which is necessary for supporting neuronal cell development, growth and function [5,35,51]. However, Mn can accumulate in the basal ganglia region of the brain because of overexposure or decreased excretion, and further result in a state known as manganism that features symptomatology similar to PD patients [32,35]. There are also numerous common mechanistic features in Mn-induced neurotoxicity and PD such as mitochondrial impairment and oxidative stress [46]. Up to now, many original studies have investigated the circulating Mn levels in PD. However, the findings from these studies are still inconsistent. Several studies reported that Mn raised the risk of PD and indicated a significant association between PD and an increase of circulating Mn levels [1,15,18,25,30,38,56], but other studies showed no significant change or even decreased circulating Mn levels in PD patients [2,3,13,14,16,17,28,29,34,40,41,44,45,49].

Thus, due to the small sample sizes, the results of these previous studies are discrepant, and their significance with respect to PD etiology is lack of the statistical power. To better clarify the association between

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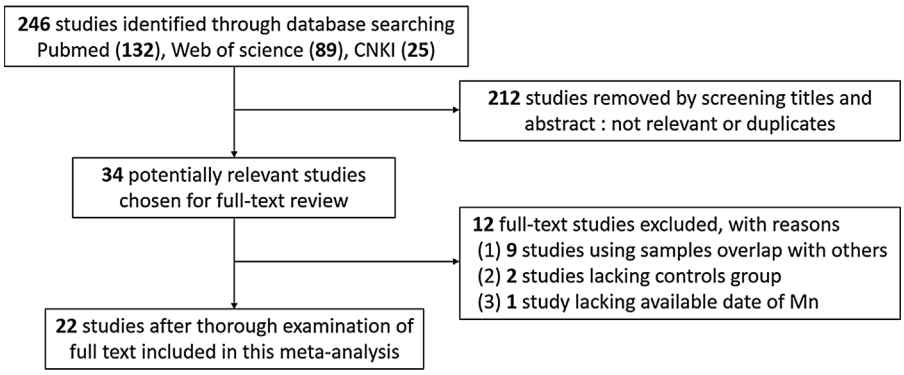

Fig. 1. Flowchart of the literature search.

circulating Mn levels and PD, we performed a meta-analysis by collecting and sorting the published studies with larger sample sizes comparing circulating Mn levels in PD patients with health controls (HC).

2. Methods

2.1. Search strategy and study selection

Our meta-analysis was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement guidelines [37]. We searched the databases of PubMed, Web of Science and China National Knowledge Infrastructure (CNKI) for publications reporting the association between circulating Mn levels and PD from inception to 2016. The search terms used were "Parkinson's disease", "manganese", "serum", "plasma", "blood", "CSF", alone and in combination. Eligible articles were retrieved from the above data. In addition, references of relevant articles were also screened for eligibility. The eligible studies were required to fulfill the following inclusion criteria: (1) human study, (2) case-control study design, (3) sample size and Mn levels of PD patients and HC individuals were provided in serum, plasma, blood or CSF. Exclusion criteria included: (1) in vitro or laboratory studies, (2) animal study, (3) review, letters, abstracts, editorials, or case reports, (4) reported on a disease other than PD, (5) overlapped publications, (5) published not in English or Chinese.

2.2. Data extraction

Two authors independently assessed the eligibility of all retrieved studies and extracted the relevant information using a unified form: last name of the first author, year of publication, sample size, the proportion of women, age, geographic locations of studied population and the technique used for measuring Mn levels. Also recorded the mean ± corresponding standard deviations (SD) on circulating Mn levels, or, a calculated data from the sample size, median and range, if they were not directly reported [24,54].

2.3. Statistical analysis

Random-effects model was used to combine study-specific Standardized Mean Difference (SMD). Heterogeneity was measured using the Chi-square and I-square test [23,48]. To explore possible explanation for high heterogeneity, we performed subgroup analysis to estimate the impact of the method used for measuring circulating Mn levels and the geographic location of studied population. Meta-regression was also performed to assess the effect of three important covariates (year of publication, mean age and gender distribution) on the circulating Mn levels in PD. Sensitivity analyses were conducted to investigate the influence of individual result on the pooled estimate by omitting one study at a time during repeated analyses. Potential publication bias was examined using Egger's and Begg's test [47]. The trim and fill analysis was also performed to further evaluate the possible effect of publication bias in the meta-analysis [11]. Temporal effect was evaluated with cumulative meta-analysis. In the present study, P-value < 0.05 was considered statistically significant for all the analyses. All data analyses were performed using STATA 12.0 (Stata, College Station, TX, USA).

3. Results

3.1. Study selection and characteristics of eligible studies

A total of 34 studies were identified after an initial searching from the Pubmed, Web of Science, CNKI and the reference list of relevant articles. After further screening, 22 studies were eventually included in our meta-analysis (total of 1453 cases and 1500 controls). The selecting process is shown in a flow diagram (Fig. 1). These studies were published from 1967 to 2016. The number of patient samples ranged from 8 to 250 individuals and the mean age was from 55.7 to 70.2 years old. The percentage of female patients ranged from 7.7% to 62.2%. The data of mean age and the percentage of female were missing in four studies. The geographic location of the studied population was in Europe of 11 studies, in Asia of 10 studies and in America of 1 study. The detailed characteristics of the included studies were listed in Table 1.

3.2. Meta-analysis: Mn in serum

Data from 10 studies was analyzed in a random-effects model to compare the serum Mn levels in PD patients and health controls (Table 1). The pooled sample size consisted of 1439 subjects including 637 PD and 802 controls. We found a significantly increased serum levels of Mn in PD patients compared with HC individuals (SMD = 0.78; 95% CI [0.32, 1.24]; $P = 0.001$; Fig. 2). However, a statistically significant amount of heterogeneity was observed among these studies ($I^2 = 93.2\%$, $P = 0.000$). Subgroup analysis by the method used for measuring Mn levels showed a high heterogeneity in each subgroup. Additionally, the subgroup analysis by geographic locations, showed that the heterogeneity was high in European populations and Asian populations. Neither the method for measuring Mn levels nor the geographic location was a main source of heterogeneity (Table 2). In meta-regression analyses, we found that none of the continuous variables including the publication years of the included studies, the age and the gender of the PD patients had moderating effects (publication years: $P = 0.158$; mean age: $P = 0.469$; gender: $P = 0.790$). Sensitivity analyses indicated that no particular study appreciably influenced our results. The temporal effect was excluded by cumulative analysis. Furthermore, although Egger's ($P = 0.012$) and Begg's ($P = 0.032$) tests raised the possibility of publication bias, the sensitivity analysis adopting the trim and fill method showed that the general result was not changed, suggesting good stability of this analysis.