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Multiple Sclerosis and Related Disorders

Low serum uric acid levels in patients with multiple sclerosis and neuromyelists opticis: An updated meta-analysis

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ABSTRACT

Objectives: To evaluate the association between serum uric acid (UA) levels and patients with MS and NMO.
Methods: The PubMed, Web of Science and Cochrane Library database were searched for relevant studies. Pooled standardized mean difference (SMD) and 95% confidence interval (CI) were used as effect size. Subgroup analysis was performed by gender, country, disease durations, scores of EDSS, detection method and clinical classification.
Results: A total of 10 case-control studies involving 1537 patients (1308 MS patients, 229 NMO patients) and 908 healthy controls were included. We found the serum UA levels of patients with MS and NMO were significantly lower compared to those of healthy controls (SMD= −0.52, 95%CI, −0.81 to −0.24). In the subgroup analysis, there was no significant difference between serum UA levels in patients and healthy controls in European subgroup (SMD= −0.32, 95%CI, −0.78 to 0.14). Additionally, we found that serum UA levels were higher in MS and NMO patients than in healthy controls in EDSS > 3.5 subgroup (SMD= −0.38, 95%CI, −0.58 to −0.19), but not in EDSS ≤ 3.5 subgroup (SMD= −0.35, 95%CI, −0.97 to 0.27). Patients of relapsing group had significant lower serum UA levels than patients of remitting group (SMD=0.70, 95%CI, 0.19-1.21).
Conclusion: Patients with MS and NMO showed lower serum UA levels when compared with healthy controls. Serum UA might be a potential diagnostic biomarker for MS and NMO.

1. Introduction

Multiple sclerosis (MS) and neruomyelists opticis (NMO) are autoimmune-mediated diseases of the central nervous system (CNS). The lesions of MS include the optic nerves, periventricular white matter, brain stem, cerebellum, and spinal cord white matter, while NMO selectively targets the optic nerves and spinal cord (McDonald et al., 2001; Wingerchuk et al., 1999). Reportedly, the process of demyelination and axonal injury in MS and NMO disease induces the excessive formation of reactive oxygen (ROS) and nitrogen species (RNS) (Peng et al., 2012). Recently, uric acid, the end of purine metabolism, is considered to be a scavenger of ROS and RNS (Hooper et al., 1998). Experimental investigation showed that uric acid administration exerted neuroprotective effects on EAE-induced mice in a dose-dependent fashion (Hooper et al., 1998). However, clinical studies have conflicted conclusions of the association of serum uric acid level with MS. Some case-control studies found lower (Peng et al., 2012; Min et al., 2012), while others reported higher (Salemi et al., 2010; Tavazzi et al., Amorini), and even some work revealed no difference between the MS and healthy controls (Mostert et al., 2005; Kastenbauer et al., 2005). Recently, Liu B et al. conducted a meta-analysis on serum UA levels and MS patients and revealed the serum UA levels were lower than controls (Liu et al., 2012; B. Liu et al., 2012). However, their study did not include NMO patients. In addition, the controls in their study were other neurological disease patients and healthy subjects. Furthermore, two recent studies were not included in their meta-analysis. Therefore, a systematic analysis is required to assess the association between NMO, MS and the level of serum UA. Basing on these investigations, we perform an updated meta-analysis to evaluate the correlation between serum uric acid levels in MS and NMO with healthy controls, which contribute to the prevention and treatment of the disease.

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2. Methods

2.1. Search strategy and selection criteria

We searched PubMed, Web of Science and Cochrane Library database from January 1, 1970 to October 31, 2015 using MeSH terms or key words "uric acid or urate" and "multiple sclerosis or neruomyelists opticis". No language restrictions were imposed. Additionally, we obtained the articles through the introduction of retrieved trials and previous meta-analysis on the uric acid levels with MS and (or) NMO.

Two investigators (Lijun Wang and Wei Hu) reviewed all the abstracts of articles and decided the inclusion of the articles. A third investigator (Jun Wang) anticipated discussion and made decisions when discrepancies occurred. Studies were eligible for inclusion if: 1) a case-control study; 2) reported serum uric acid or serum urate concentration; 3) diagnosis of MS according to Poser's criteria (Poser et al., 1983) or McDonald criteria (McDonald et al., 2001) and diagnosis of NMO according to Wingerchuk et al."s NMO criteria (Wingerchuk et al., 1999); 4) age and gender-marched healthy controls. Newcastle-Ottawa Scale (NOS) was used for quality control (Stang, 2010).

2.2. Data collection and analysis

We collected data variables from studies including the first author, countries, publication date, the number, average age, the mean and SD of UA levels and detection method of cases and healthy controls, disease duration, EDSS score of patients. Some studies used the conventional units (mg/dl) to report serum UA levels. Therefore, we converted these different units to the International System of units (μmol/l) using a conversion rate of 16.81 (1 mg/dl=59.48 μmol/l). Pooled standardized mean difference (SMD) with 95% confidence interval (CI) was used as effect size. Heterogeneity was tested through I-square (I^2) tests. According to the method of Cochrane Handbook for Systemic Review of Interventions, we considered I^2 of less than 40% as milder heterogeneity, while more than 70% as considerable heterogeneity. If I^2 was less than 40%, we pooled data using fixed effect models on the inverse variance method; on the contrary, we used random effect model on the DerSimonian and Laird (D-L) method. Subgroup analysis was performed by gender, country, durations of disease, scores of EDSS, detection method and Clinical classification. Sensitivity analysis was conducted by excluding one study each time to investigate the effect of individual study on the pooled SMD. Funnel plots were applied to evaluate publication bias. All the analyses were done with STAT (12.0).

3. Results

3.1. Flow of study selection was shown in Fig. 1

We identified 30 associated articles through literature search. Two studies were excluded due to lack of reporting serum UA levels (Kanabrocki et al., 2008; Miller et al., 2012), twelve studies for absence of healthy controls (Kastenbauer et al., 2005; Guerrero et al., 2011; Dujmovic et al., 2009; Rentzos et al., 2006; Ljubisavljevic et al., 2013; Koutoula et al., 2007; Masera et al., 2013; Yoldas et al., 2010; Tsakiri et al., 2008; Przybek et al., 2010; Mamarabadi et al., 2010; Liu et al., 2012), three studies for lacking of full texts (Keklikoglu et al., 2009; Kuracka et al., 2010; Xu et al., 2009), 2 studies due to the same authors(Peng et al., 2008; Peng et al., 2010), and one was the prospective study (Massa et al., 2009). Finally, 10 case-control studies were included (Peng et al., 2012; Min et al., 2012; Tavazzi et al., Amorini; Mostert et al., 2005,

2014; Ashtari et al., 2013; Zoccolella et al., 2012; You et al., 2010; Ramsaransing et al., 2005; Toncev et al., 2002).

3.2. Characteristics of studies

Of the ten studies, two were conducted in China, two in The Netherland, one in Iran, three in Italy, one in Korea, and one in Yugoslavia. Our studies included 1537 patients (1308 MS patients, 229 NMO patients) and 908 healthy controls. Table 1 shows baseline characteristics of studies (Fig. 1).

3.3. Serum uric acid in patients with MS and NMO

In our meta-analysis, the influence of the serum UA levels on MS and NMO patients were investigated using the random effects model for the evidence of the heterogeneity(I^2=91.6, P=0.000). We found that the serum UA levels of patients with MS and NMO were significantly lower compared to those of healthy controls (SMD=−0.52, 95%CI,−0.81 to −0.24). Among MS patients group, serum UA levels were significant lower compared to those of healthy controls (SMD=−0.40, 95%CI, −0.73 to −0.07). Similarly, the significantly differences between NMO and healthy controls were also observed (SMD=−0.85, 95%CI,−1.24 to −046) (Fig. 2). Fig. 2 Overall pooled estimate of standardized mean difference (SMD) and 95% CI of serum uric acid levels in patients with MS and NMO and healthy controls.

3.4. Subgroup analysis of serum uric acid levels in patients with MS and NMO

As significant heterogeneity, subgroup analyses were performed by gender, country, disease duration, scores of EDSS, detection method and Clinical classification. In the gender-stratified subgroup analysis, we found both male patients and female patients had significant lower SUA levels than healthy controls for men (SMD=−1.07, 95%CI,−1.39 to −0.74) and women (SMD=−0.68, 95%CI,−1.21 to −0.15). The ethnicity-stratified subgroup analysis displayed that MS and NMO patients were associated with decreased serum UA levels compared to healthy controls in the Asian subgroup (SMD=−0.65, 95%CI,−0.96 to −0.35), however, there was no significant difference between SUA levels in patients and healthy controls in European subgroup (SMD=−0.32, 95%CI,−0.78 to 0.14). Additionally, we compared serum UA between patients with MS and NMO and healthy controls in EDSS score subgroup and found that SUA levels were higher in MS and NMO patients than in healthy controls in EDSS > 3.5 subgroup (SMD=−0.38, 95%CI,−0.58 to −0.19), but not in EDSS ≤ 3.5 subgroup (SMD=−0.35, 95%CI,−0.97 to 0.27). Then, in the method subgroup analysis, we demonstrated that MS and NMO patients had significant lower serum UA levels than healthy controls in both Enzymatic method subgroup (SMD=−0.61, 95%CI,−1.04 to −0.17) and PAP method subgroup (SMD=−0.43, 95%CI,−0.65 to −0.22). Finally, in clinical classification-stratified analysis, significant lower SUA levels were observed in remitting cases group (SMD=−0.32%CI,−0.58 to −0.06) and relapsing cases group (SMD=−0.96, 95%CI,−1.49 to −0.44). Patients of relapsing group had significant lower serum UA levels than patients of remitting group (SMD=0.70, 95%CI, 0.19 to 1.21) (Table 2).

3.5. Sensitivity analysis and publication Bias

We further conducted sensitivity analyses to determine whether the results of our analysis were affected by the choice of any single study. Only the study by Tavazzi et al. showed significant departure from the meta-analysis (Fig. 3). Fig. 3 Sensitivity analysis