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Serum uric acid and anti-*N*-methyl-D-aspartate receptor encephalitis

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ABSTRACT

Background: Uric acid (UA) levels are associated with autoimmune and neurodegenerative disorders, but their relationship with anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is unknown.
Methods: UA levels were evaluated in 58 patients with anti-NMDAR encephalitis, and 58 age- and sex-matched healthy controls (CTLs). Follow-up evaluations of 30 out of the 58 patients with anti-NMDAR encephalitis were conducted 3 months after admission. Modified Rankin scale (mRS) scores and clinical and cerebrospinal fluid parameters were evaluated in all anti-NMDAR encephalitis patients.
Results: Serum UA levels were significantly lower in patients with anti-NMDAR encephalitis than those in CTLs ($p < 0.001$), and this was especially evident in patients with severe impairments (mRS ≥ 4 vs. <4, $p = 0.004$) or with limited response to treatment (vs. favourable outcome, $p = 0.002$). Follow-up evaluations revealed that serum UA levels normalized after treatment, with significantly increased serum UA levels ($p < 0.001$), and that mRS scores were significantly lower ($p < 0.001$) than those before treatment. In addition, serum UA levels were significantly associated with mRS scores ($r = -0.463$, $p < 0.001$).
Conclusion: Our results showed that serum UA levels in patients with anti-NMDAR encephalitis are reduced during attacks compared with those in CTLs, are normalized after treatment, and are associated with disease severity.

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1. Introduction

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is form of encephalitis that develops through the action of NMDAR antibodies (immunoglobulin G) against the GluN1 subunit of the NMDAR (Hughes et al., 2010). It is a severe and rare disorder that can affect patients of all ages, but it usually occurs in young women and children (Florance et al., 2009). It has been increasingly recognized that these patients often have comorbid ovarian teratoma, but it may occur without any associated tumour. Some patients respond to tumour removal and immunotherapies, including corticosteroids and intravenous immunoglobulins or plasmapheresis, whereas others require treatment with second-line agents, such as cyclophosphamide or rituximab (Ishiura et al., 2008; Titulaer et al., 2013).

Uric acid (UA) is a natural product of the purine metabolic pathway. However, the role of UA in the central nervous system (CNS) remains poorly understood. Most studies have suggested that UA is a strong peroxynitrite scavenger and natural antioxidant (Ames et al., 1981; Bowman et al., 2010; Hooper et al., 2000; Sevanian et al., 1991; Waugh, 2008). UA has been found to be able to suppress the inflammatory cascade, decrease blood–brain barrier permeability, and diminish central nervous tissue damage and neuronal death (Hooper et al., 2000). Thus, a reduction in UA could impair the ability to prevent peroxynitrite and other free radicals from acting on cellular components and damaging the cell (Ames et al., 1981).

At present, UA is associated with a variety of neurological diseases, including autoimmune disorders, such as multiple sclerosis

Abbreviations: anti-NMDAR, Anti-*N*-methyl-D-aspartate receptor; UA, uric acid; IgG, immunoglobulin G; MS, multiple sclerosis; NMO, neuromyelitis optica; PD, Parkinson's disease; CTLs, healthy controls; CNS, central nervous system; CSF, cerebrospinal fluid; mRS, modified Rankin scale; WBC, white blood cells; TP, total protein; Glu, glucose; CL, chlorine; MRI, magnetic resonance imaging; Gd-DTPA, gadopentetate dimeglumine; BMI, body mass index.

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(MS), neuromyelitis optic (NMO) (Ashtari et al., 2013; Drulovic et al., 2001; Min et al., 2012; Peng et al., 2008; Sotgiu et al., 2002), and neurodegenerative disorders, such as Parkinson's disease (PD), dementia with Lewy bodies, and Alzheimer's disease (Bowman et al., 2010; Maetzler et al., 2011; Sampat et al., 2016; Schiess and Oh, 2008). However, the importance of UA in anti-NMDAR encephalitis is unknown. Here, we analysed serum UA levels in patients with anti-NMDAR encephalitis and investigated the associations between serum UA and clinical parameters in these patients.

2. Methods

2.1. Patients and controls

We recruited patients with anti-NMDAR encephalitis hospitalized from August 2014 to August 2016 as well as age- and sex-matched healthy controls (CTLs) for comparison. For each case, one control participant was randomly selected and matched to the age and sex of the index case. The patients with anti-NMDAR encephalitis were followed up 3 months after treatment.

Serum and CSF samples from all patients with anti-NMDAR encephalitis were analysed by indirect immunostaining using a commercially available kit (EUROIMMUN Medizinische Labordiagnostika, Lübeck, Germany) to detect IgG antibodies against NMDAR, according to the manufacturer's instructions.

Symptoms were categorized into the following groups: prodromal symptoms (such as headache and fever), psychiatric symptoms, memory deficits, speech disturbances, seizures, movement disorders, loss of consciousness, sleep disorders, and central hypoventilation. Brain magnetic resonance imaging (MRI) and CSF examinations were reviewed. All patients were screened with computed tomography (CT) or MRI or B-scan ultrasonography at least once for systemic tumours. Treatments included first-line immunotherapy, second-line immunotherapy, and tumour removal. First-line immunotherapies included the use of steroids, intravenous immunoglobulins, or plasma exchange alone or combined; and second-line immunotherapy included rituximab, azathioprine, or cyclophosphamide treatment alone or combined. Each patient's neurological status was assessed using the modified Rankin Scale (mRS) (van Swieten et al., 1988). The initial treatment was recorded as a failure if no sustained improvement occurred within 1 month of initiation of immunotherapy or tumour removal, and if the mRS score remained at 4 or higher.

2.2. Ethics statement and consent to participate

This research was approved by the ethics committee of the Third Affiliated Hospital of Sun Yat-sen University. Informed written consent was obtained from the patients or their representatives.

2.3. Biochemical assays

Serum UA concentrations were measured by the direct enzymatic method, as described in our previous paper (Peng et al., 2008). In our hospital, serum UA is measured using a Clinical Analyzer 7 180-ISE (Hitachi High-Technologies, Tokyo, Japan), and the reference range of serum UA values is 150–360 μmol/L in women and 210–430 μmol/L in men.

2.4. Follow-up evaluations

Patients who were followed up received repeated assessments of mRS scores and serum UA levels in our hospital.

2.5. Statistical analysis

All statistical analyses were performed using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). The UA levels, mRS scores, and CSF white blood cell (WBC) counts are presented as the median (range). Age, BMI, and CSF factors, including total protein (TP), glucose, Glu, and chlorine (CL), are presented as the mean (±standard deviation as indicated). Mann–Whitney U tests were performed to determine the differences in serum UA levels between patients with anti-NMDAR encephalitis and CTLs, and between subgroups of patients with encephalitis. Correlations between serum UA and age, BMI, mRS score and CSF factors (WBC, TP, Glu, and CL) were analysed using Spearman's rank test. Values of $p < 0.05$ were considered statistically significant.

3. Results

3.1. Demographic and clinical features

Table 1 shows the demographic features for the recruited 58 anti-NMDAR patients with encephalitis (mean age, 28.9 years; mean BMI, 20.40; female:male = 27:31) and the 58 age- and sex-matched CTLs (mean age, 28.8 years; mean BMI, 21.0; female:male = 27:31). The median UA levels and mRS scores for the patients with anti-NMDAR encephalitis were 241.8 μmol/L (range, 81.0–695.0 μmol/L) and 4.0 (range, 1–5), respectively. Of the 58 patients with anti-NMDAR encephalitis, 16 (27.6%) had prodromal symptoms (such as headache, fever), 26 (44.8%) had psychiatric symptoms, 5 (8.6%) had memory deficits, 9 (15.5%) had speech disturbances, 25 (43.1%) had seizures, 8 (13.8%) had movement disorders, 13 (27.6%) had loss of consciousness, 3 (5.1%) had sleep disorders, and 5 (8.6%) had central hypoventilation. Twelve patients (20.6%) had complications, including ovarian teratoma (n = 9, 15.5%), ovarian cysts (n = 2, 3.4%), colon carcinoma (n = 1, 1.7%). Forty-two patients (72.4%) received first-line treatment, 16 (27.6%) received combined first- and second-line treatment, and 9 (15.5%) received tumour removal treatment.

3.2. Comparison of serum UA levels between patients with anti-NMDAR encephalitis and CTLs

As shown in Fig. 1, serum UA levels in patients with anti-NMDAR encephalitis were significantly lower than those in age- and sex-matched CTLs ($p < 0.001$).

3.3. Comparison of serum UA levels between subgroups of patients with anti-NMDAR encephalitis

We subdivided the anti-NMDAR encephalitis patients into subgroups according to sex, age, mRS, brain MRI, with or without prodromal symptoms, with or without tumour, and response to therapy (Table 2). Patients with mRS scores <4 had significantly higher serum UA levels than those with mRS scores ≥4 ($p = 0.0004$). Serum UA levels in patients with favourable treatment outcomes were significantly higher than in patients with limited responses to treatment ($p = 0.0011$). No other factors differed significantly (Table 2).

3.4. Follow-up evaluation of serum levels in anti-NMDAR encephalitis patients following treatment

Of the 58 patients recruited with anti-NMDAR encephalitis, 30 had a follow-up evaluation 3 months after admission, while the remaining 28 patients did not return to our hospital after being discharged.

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