Neurochemistry International 108 (2017) 34–39

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/nci

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

Yaqing Shu [1], Yuge Wang [1], Tingting Lu [1], Rui Li, Xiaobo Sun, Jing Li, Yanyu Chang, Xueqiang Hu, Zhengqi Lu, Wei Qiu*

Department of Neurology, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

ARTICLE INFO

Article history:
Received 26 November 2016
Received in revised form
25 January 2017
Accepted 8 February 2017
Available online 10 February 2017

Keywords:
Uric acid
Autoimmune disorders
Anti-*N*-Methyl-D-aspartate receptor encephalitis

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.

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.

* Corresponding author. Department of Neurology, The Third Affiliated Hospital, Sun Yat-sen University, 600 Tianhe Road, Guangzhou, Guangdong 510630, China. Tel.: +86 020 85252327.

E-mail addresses: shuyaqing@126.com (Y. Shu), wangyuge1228@163.com (Y. Wang), lutingting_sysu@163.com (T. Lu), waterlr886@126.com (R. Li), sister_555@163.com (X. Sun), wendy_lij81@163.com (J. Li), changyyu@163.com (Y. Chang), huxueqiangqm@aliyun.com (X. Hu), lzq1828@aliyun.com (Z. Lu), qw9406@gmail.com (W. Qiu).

[1] These authors are first co-authors.

http://dx.doi.org/10.1016/j.neuint.2017.02.005
0197-0186/

(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.

Table 1
Demographic features of patients with anti-NMDAR encephalitis and age- and sex-matched healthy controls.

	Anti-NMDAR encephalitis (n = 58)	Age- and sex-matched CTLs (n = 58)
Age (y, mean ± SD)	28.9 ± 14.5	28.8 ± 14.6
Sex (male:female)	27:31	27:31
BMI (mean ± SD)	20.4 ± 3.2	21.0 ± 3.7
UA level (μmol/L, median, range)	241.8 (81.0–695.0)	347.0 (110.8–540.7)
mRS (median, range)	4.0 (1–5)	–
CSF routine		
CSF WBC (× 10^6, median, range)	17 (0–142)	–
CSF TP (g/L, mean ± SD)	0.40 ± 0.47	–
CSF Glu (mmol/L, mean ± SD)	3.46 ± 0.96	–
CSF CL (mmol/L, mean ± SD)	122.7 ± 6.43	–
Symptom onset (n, %)		
Prodromal symptoms	16 (27.6)	–
Psychiatric symptoms	26 (44.8)	–
Memory deficits	5 (8.6)	–
Speech disturbances	9 (15.5)	–
Seizures	25 (43.1)	–
Movement disorders	8 (13.8)	–
Loss of consciousness	13 (27.6)	–
Sleep disorder	3 (5.1)	–
Central hypoventilation	5 (8.6)	–
Tumour comorbidity (n, %)	12 (20.6)	–
Ovarian teratoma	9 (15.5)	–
Ovarian cysts	2 (3.4)	–
Colon carcinoma	1 (1.7)	–
Treatment (n, %)		
First line treatment	42 (72.4)	–
First line combined with second line treatment	16 (27.6)	–
Tumour removal	9 (15.5)	–

Anti-NMDAR, anti-*N*-Methyl-D-aspartate receptor; CTLs, healthy controls; UA, uric acid; mRS, modified Rankin Scale; CSF, cerebrospinal fluid; WBC, white blood cells; TP, total protein; Glu, glucose; CL, chlorine; SD, standard deviation; BMI, body mass index.

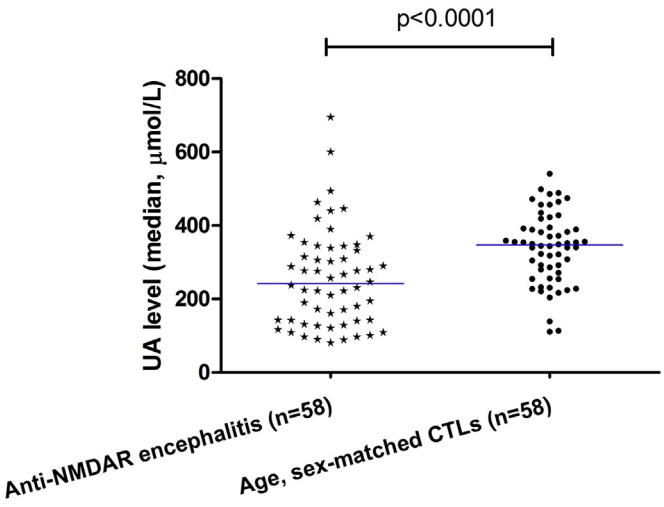

Fig. 1. Serum UA levels in patients with anti-NMDAR encephalitis and in age- and sex-matched CTLs. Serum UA levels in anti-NMDAR encephalitis patients at initial admission were significantly lower than those in age- and sex-matched CTLs ($p < 0.001$).

Thirty anti-NMDAR encephalitis patients (14 males, 16 females) with follow-up evaluation showed in Table 3. The changes in serum UA levels and mRS scores are shown in Fig. 2. Following anti-NMDAR encephalitis treatment, serum UA levels significantly increased (326.8 ± 119.8 vs. 230.5 ± 123.4 μmol/L, $p < 0.001$), and mRS scores significantly decreased (0.5 vs. 4, $p < 0.001$) (Fig. 2A and B). Although the changes in mRS scores appeared to be negatively associated with the changes in UA levels ($r = -0.314$), this association was not statistically significant ($p = 0.091$; Fig. 2C).

Table 2
UA levels in patients with anti-NMDAR encephalitis.

Variables	Median (nmol/L)	Range (nmol/L)	P Value
Sex			
Male (n = 27)	277.0	97.0–446.0	
Female (n = 31)	210.0	81.0–695.0	0.170
Age			
<18 years (n = 15)	302.0	81.0–600	
≥18 years (n = 43)	222.0	89.0–695.0	0.062
mRS			
<4 (n = 28)	304.0	101.0–600.0	
≥4 (n = 30)	152.0	81.0–695.0	0.0004
Brain MRI			
Normal (n = 28)	251.5	89.0–600.0	
Abnormal (n = 30)	234.3	81.0–695.0	0.570
Prodromal symptoms			
With (n = 16)	257.3	89.0–600.0	
Without (n = 42)	235.0	81.0–695.0	0.503
Tumour			
With (n = 12)	160.9	89.0–695.0	
Without (n = 46)	277.0	81.0–600.0	0.072
Response to therapy			
Favourable (n = 43)	280.0	81.0–695.0	
Limited (n = 15)	128.7	89.0–345.0	0.0011

Anti-NMDAR, anti-*N*-Methyl-D-aspartate receptor; UA, uric acid; mRS, modified Rankin Scale; MRI, magnetic resonance imaging; SD, standard deviation.

3.5. Association between serum UA levels and clinical characteristics or CSF parameters in patients with anti-NMDAR encephalitis

The relationships between serum UA levels and clinical characteristics or CSF parameters in patients with anti-NMDAR encephalitis were evaluated (Fig. 3). There was a significant negative correlation between serum UA levels and mRS scores ($r = -0.463$, $p < 0.001$). However, correlations between serum UA levels and age, sex, BMI, or CSF parameters (WBC, TP, GLU, and CL) were not significant.

Table 3
Changes in serum UA and mRS scores in anti-NMDAR encephalitis after treatment.

	Anti-NMDAR encephalitis (n = 30)		p Value
	Before treatment	After treatment	
Sex (male:female)	14:16	14:16	
UA level (μmol/L, median, range)	208.5 (81–695)	295.5 (101–677)	<0.001
mRS (median, range)	4 (1–5)	0.5 (0–4)	<0.001

Anti-NMDAR, anti-*N*-Methyl-D-aspartate receptor; UA, uric acid; mRS, modified Rankin Scale.

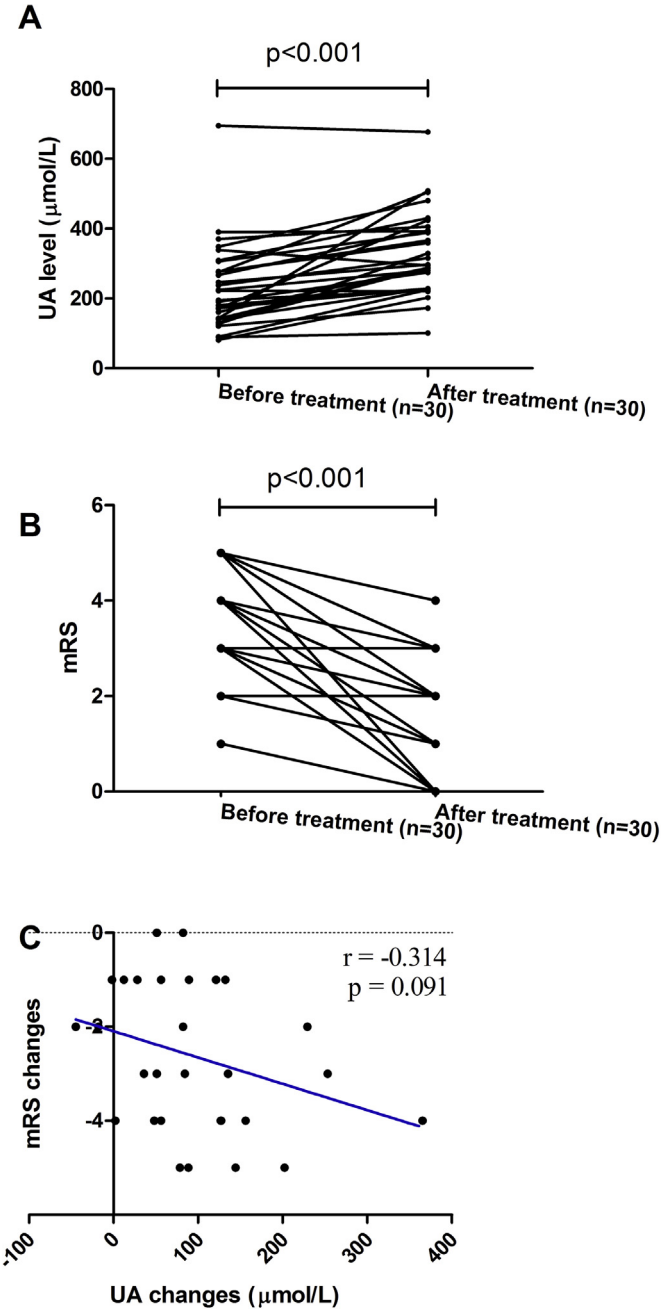

Fig. 2. (A) Changes in serum UA levels in patients with anti-NMDAR encephalitis between initial admission and follow-up after treatment. (B) Improvement in mRS scores in anti-NMDAR encephalitis patients between initial admission and follow-up after treatment. (C) Although changes in mRS scores appear negatively associated with the UA level changes (r = −0.314), this result is not statistically significant (p = 0.091).

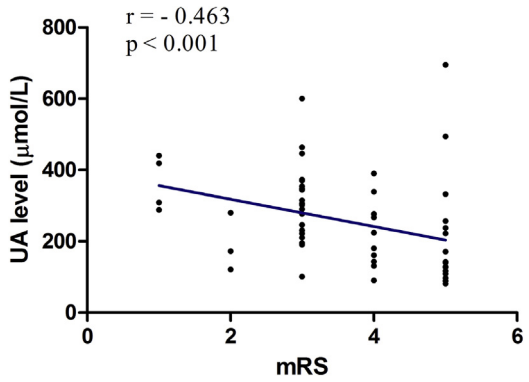

Fig. 3. Association between serum UA levels and mRS scores in patients with anti-NMDAR encephalitis (n = 58). Serum UA level versus mRS score, $r = -0.463$, $p < 0.001$.

4. Discussion

Our results showed that patients with anti-NMDAR encephalitis have significantly lower levels of serum UA than CTLs. Low UA levels have been reported in patients with NMO, MS, and PD (Drulovic et al., 2001; Min et al., 2012; Peng et al., 2008; Sampat et al., 2016), and our results suggested that this also occurs in patients with anti-NMDAR encephalitis. In the follow-up evaluation of 30 patients with anti-NMDAR encephalitis, increased serum UA levels and decreased mRS scores were found after treatment. Furthermore, low levels of UA were associated with a worse prognosis. To the best of our knowledge, this is the first study to analyse serum UA levels in patients with anti-NMDAR encephalitis.

The role of UA in anti-NMDAR encephalitis remains poorly understood. Increasing evidence suggests that immune cells are important effectors and regulators of inflammation and autoimmunity in anti-NMDAR encephalitis (Camdessanche et al., 2011; Hachiya et al., 2013; Martinez-Hernandez et al., 2011; Simma et al., 2014). Analysis of the inflammatory infiltrates in brain samples from patients with anti-NMDAR encephalitis has suggested that oxidative stress caused by inflammation occurs in the active autoimmune CNS processes of anti-NMDAR encephalitis. Because UA is a known antioxidant, a reduced UA concentration could impair the ability to prevent peroxynitrite and other free radicals from acting on cellular components and damaging the cell (Ames et al., 1981). In animal models of MS, treatment suppresses the inflammatory cascade, blood–brain barrier permeability changes, and CNS tissue damage (Hooper et al., 2000). In the present study, serum UA levels in patients with anti-NMDAR encephalitis were significantly lower than those in healthy controls. This result is similar to that described in other neuroinflammatory disorders, such as MS and NMO (Drulovic et al., 2001; Ashtari et al., 2013; Sotgiu et al., 2002; Min et al., 2012). Drulovic et al. and Ashtari et al. have both shown that patients experiencing MS relapse have significantly lower serum UA levels than controls (Drulovic et al., 2001; Ashtari et al., 2013). A study by Min et al. (2012). suggested

that serum UA levels decrease in patients with NMO during relapse compared with those in healthy subjects. We speculate that there are two plausible explanations for these results. First, low serum UA levels may be caused by a secondary effect of inflammatory oxidation in anti-NMDAR encephalitis. Second, low serum UA levels may contribute to relatively less protection against inflammatory oxidative damage in anti-NMDAR encephalitis. However, although the average serum UA levels in our patients with anti-NMDAR encephalitis were lower than those in our CTLs, we observed two patients (outliers) with serum UA levels that were higher than those in CTLs. We speculate that serum UA levels that are too high may also be associated with anti-NMDAR encephalitis disease risk. Further studies will be required to clarify the role of excessive UA levels in anti-NMDAR encephalitis.

Uncertainties exist whether low serum UA is a cause or a consequence of anti-NMDAR encephalitis-related activity. It has been suggested that a decrease in UA levels is due to the potent UA peroxynitrite scavenging activity and accompanying increased oxidative stress in MS (Squadrito et al., 2000). Our results showed that anti-NMDAR encephalitis patients with worse prognosis, who may have more oxidative stress, had lower serum UA levels. Thus, we speculate that decreased serum UA levels in anti-NMDAR encephalitis may be associated with increased oxidative demand leading to UA depletion. However, further studies investigating the association between low serum UA levels and anti-NMDAR encephalitis will be required.

In the present study, we also found that patients with favourable treatment outcomes had significantly higher serum UA levels than patients with limited treatment responses. We speculate that higher UA levels may help to ameliorate the disease attack through an antioxidative role. Thus, serum UA is likely to be a potential target for treatment agents in patients with anti-NMDAR encephalitis.

Furthermore, the reduced UA levels observed during an attack of anti-NMDAR encephalitis were normalized after treatment, and there was a significant difference between serum UA levels before and after treatment. Serum UA levels could be influenced by a number of factors, including treatment, disease duration, and diet. Thus, we speculate here on the plausible explanations for the elevated serum UA levels after treatment. First, elevated serum UA levels may be associated with reduced CNS inflammation and tissue damage after treatment. Second, Toncev et al. suggested that increasing UA concentrations may be one of the possible mechanisms of action associated with methylprednisolone administration in MS (Toncev et al., 2002). In our study, the 30 patients followed up were all treated with methylprednisolone, which could affect UA levels. Third, because the patients' conditions were improved after treatment, they were eating enough food and absorbing sufficient nutrients to elevate their serum UA levels. Nevertheless, further studies will be required to clarify the underlying mechanisms.

We acknowledge that there were some limitations in our study. First, the patient sample size was small (58 patients). In our study, the relatively low number and frequency of symptoms (44.8% psychiatric symptoms and 8.6% memory deficits) and relatively low proportion of females (31/58), which differed from previous larger cohort series, may be related to our sample size. Second, because encephalitis is in the brain and almost all patients showed considerable intrathecal antibody synthesis, the most apparent change in UA levels would likely be observed in the CSF. However, we did not test CSF UA levels. Third, we did not investigate the association between serum UA levels and acute phase proteins, so we could not confirm whether serum UA changes could be a general inflammatory effect in anti-NMDAR encephalitis patients.

In conclusion, our results showed that serum UA levels in patients with anti-NMDAR encephalitis were lower during attacks than those in CTLs, were normalized after treatment, and were associated with disease severity. Certainly, more extensive epidemiological studies and more thorough studies regarding the role of UA in the genesis of the disease will be required.

Funding

This study was supported by Guangdong Science Foundation of Guangdong Province (No. 2014A030313014).

Competing interests

The authors declare that they have no competing interests.

References

Ames, B.N., Cathcart, R., Schwiers, E., Hochstein, P., 1981. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc. Natl. Acad. Sci. U. S. A. 78, 6858–6862.
Ashtari, F., Bahar, M., Aghaei, M., Zahed, A., 2013. Serum uric acid level in patients with relapsing-remitting multiple sclerosis. J. Clin. Neurosci. 20, 676–678.
Bowman, G.L., Shannon, J., Frei, B., Kaye, J.A., Quinn, J.F., 2010. Uric acid as a CNS antioxidant. J. Alzheimers Dis. 19, 1331–1336.
Camdessanche, J.P., Streichenberger, N., Cavillon, G., Rogemond, V., Jousserand, G., Honnorat, J., et al., 2011. Brain immunohistopathological study in a patient with anti-NMDAR encephalitis. Eur. J. Neurol. 18, 929–931.
Drulovic, J., Dujmovic, I., Stojsavljevic, N., Mesaros, S., Andjelkovic, S., Miljkovic, D., et al., 2001. Uric acid levels in sera from patients with multiple sclerosis. J. Neurol. 248, 121–126.
Florance, N.R., Davis, R.L., Lam, C., Szperka, C., Zhou, L., Ahmad, S., et al., 2009. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann. Neurol. 66, 11–18.
Hachiya, Y., Uruha, A., Kasai-Yoshida, E., Shimoda, K., Satoh-Shirai, I., Kumada, S., et al., 2013. Rituximab ameliorates anti-N-methyl-D-aspartate receptor encephalitis by removal of short-lived plasmablasts. J. Neuroimmunol. 265, 128–130.
Hooper, D.C., Scott, G.S., Zborek, A., Mikheeva, T., Kean, R.B., Koprowski, H., et al., 2000. Uric acid, a peroxynitrite scavenger, inhibits CNS inflammation, blood-CNS barrier permeability changes, and tissue damage in a mouse model of multiple sclerosis. Faseb J. 14, 691–698.
Hughes, E.G., Peng, X., Gleichman, A.J., Lai, M., Zhou, L., et al., 2010. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. J. Neurosci. 30, 5866–5875.
Ishiura, H., Matsuda, S., Higashihara, M., Hasegawa, M., Hida, A., Hanajima, R., et al., 2008. Response of anti-NMDA receptor encephalitis without tumor to immunotherapy including rituximab. Neurology 71, 1921–1923.
Maetzler, W., Stapf, A.K., Schulte, C., Hauser, A.K., Lerche, S., Wurster, I., et al., 2011. Serum and cerebrospinal fluid uric acid levels in lewy body disorders: associations with disease occurrence and amyloid-beta pathway. J. Alzheimers Dis. 27, 119–126.
Martinez-Hernandez, E., Horvath, J., Shiloh-Malawsky, Y., Sangha, N., Martinez-Lage, M., Dalmau, J., 2011. Analysis of complement and plasma cells in the brain of patients with anti-NMDAR encephalitis. Neurology 77, 589–593.
Min, J.H., Waters, P., Vincent, A., Lee, S.,Y.,S.H.,H.,L.K., et al., 2012. Reduced serum uric acid levels in neuromyelitis optica: serum uric acid levels are reduced during relapses in NMO. Acta Neurol. Scand. 126, 287–291.
Peng, F., Zhang, B., Zhong, X., Li, J., Xu, G., Hu, X., et al., 2008. Serum uric acid levels of patients with multiple sclerosis and other neurological diseases. Mult. Scler. 14, 188–196.
Sampat, R., Young, S., Rosen, A., Bernhard, D., Millington, D., Factor, S., et al., 2016. Potential mechanisms for low uric acid in Parkinson disease. J. Neural Transm. (Vienna) 123, 365–370.
Schiess, M., Oh, I., 2008. Serum uric acid and clinical progression in Parkinson disease: potential biomarker for nigrostriatal failure. Arch. Neurol. 65, 698–699.
Sevanian, A., Davies, K.J., Hochstein, P., 1991. Serum urate as an antioxidant for ascorbic acid. Am. J. Clin. Nutr. 54, 1129S–1134S.
Simma, N., Bose, T., Kahlfuss, S., Mankiewicz, J., Lowinus, T., Luhder, F., et al., 2014. NMDA-receptor antagonists block B-cell function but foster IL-10 production in BCR/CD40-activated B cells. Cell Commun. Signal 12, 75.
Sotgiu, S., Pugliatti, M., Sanna, A., Sotgiu, A., Fois, M.L., Arru, G., et al., 2002. Serum uric acid and multiple sclerosis. Neurol. Sci. 23, 183–188.
Squadrito, G.L., Cueto, R., Splenser, A.E., Valavanidis, A., Zhang, H., Uppu, R.M., et al., 2000. Reaction of uric acid with peroxynitrite and implications for the mechanism of neuroprotection by uric acid. Archives Biochem. Biophy. 376, 333–337.
Titulaer, M.J., McCracken, L., Gabilondo, I., Armangue, T., Glaser, C., Iizuka, T., et al.,

2013. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 12, 157–165.

Toncev, G., Milicic, B., Toncev, S., Samardzic, G., 2002. High-dose methylprednisolone therapy in multiple sclerosis increases serum uric acid levels. Clin. Chem. Lab. Med. 40, 505–508.

van Swieten, J.C., Koudstaal, P.J., Visser, M.C., Schouten, H.J., van Gijn, J., 1988. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 19, 604–607.

Waugh, W.H., 2008. Inhibition of iron-catalyzed oxidations by attainable uric acid and ascorbic acid levels: therapeutic implications for Alzheimer's disease and late cognitive impairment. Gerontology 54, 238–243.