Low serum uric acid levels in patients with acute central nervous system viral infections

Xiang Li\(^{a,b,*}\), Qiaowen Tong\(^{c,*}\), Dewei Xie\(^b\), Zhibo Chen\(^b\), Sipei Pan\(^b\), Xu Zhang\(^b\) and Wanli Dong\(^a\)

Most acute central nervous system (CNS) viral infections lead to either encephalitis or meningitis. Many neurotropic viruses may cause CNS dysfunctions through various mechanisms including oxidative stress. Serum uric acid (SUA) levels, which are associated with oxidative stress and antioxidant status, are reduced in patients with various neurological disorders, including multiple sclerosis. We investigated the possible correlation between SUA levels and clinical disease status in patients with acute CNS viral infections. We measured SUA concentrations in 336 individuals, including 179 healthy individuals and 157 patients with acute CNS viral infections. We found that the patients had lower SUA levels than the healthy individuals did irrespective of sex. Effective therapy significantly increased SUA levels. The patients' SUA levels were correlated inversely with outcomes as measured with the Glasgow Outcome Scale. SUA levels may be a biomarker for predicting treatment outcomes and prognoses for patients with acute CNS viral infections with inflammatory components. NeuroReport 28:1250–1254 Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc.

Keywords: outcome, oxidative stress, uric acid, viral encephalitis, viral meningitis

*Department of Neurology, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu Province, \(^b\)Department of Neurology, The First Affiliated Hospital of Wenzhou Medical University and \(^c\)Department of Neurology, Wenzhou People’s Hospital, Wenzhou, Zhejiang Province, China

Correspondence to Wanli Dong, PhD, Department of Neurology, The First Affiliated Hospital of Soochow University, 188 Shizi Street, Suzhou 215006, Jiangsu Province, China

Tel: + 86 512 65223637; fax: + 86 577 55579318; e-mail: szdongwl@126.com

*Xiang Li and Qiaowen Tong contributed equally to the writing of this article.

Received 14 September 2017 accepted 21 September 2017

Introduction

Central nervous system (CNS) viral infections can lead to inflammation in different anatomical regions, such as the meninges (meningitis), brain (encephalitis), and spinal cord (myelitis). The clinical manifestations of inflammation are associated closely with the location and severity of illness and include fever, headache, meningeal irritation, seizures, focal neurological signs, disturbed consciousness, mental disorders, and other symptoms outside the CNS [1]. Many neurotropic viruses cause CNS dysfunctions by various mechanisms including oxidative stress, apoptosis [2], and immunomodulation [3].

Accumulating evidence suggests that oxidative stress is related closely to viral infections, during which clinicians observe increased levels of oxidants including peroxynitrite (PN), nitric oxide (NO) free radicals, and hydroxide radicals. These oxidants all contribute toward viral pathogenesis, regulation of cellular responses, and modulation of virus replication and host defenses [4,5]. Several studies indicate that antioxidants may be effective antiviral agents. For example, Valero et al. [6] found that antioxidants, including curcumin, melatonin, minocycline, and ascorbic acid, can reduce oxidative stress and viral titers and increase survival rates in mice with Venezuelan equine encephalitis. Zhang et al. [5] concluded that several antioxidants, such as minocycline, arctigenin, fenofibrate, and curcumin, can protect against the Japanese encephalitis virus.

Uronic acid (UA) is a selective scavenger of radicals formed by the reactive oxygen and nitrogen species and can alleviate PN-induced tissue injury [7,8]. Hooper et al. [9] proposed that UA might suppress increased blood–brain barrier (BBB) permeability by protecting against PN-induced damage and directly scavenging PN. Epidemiologic studies show that increased serum uric acid (SUA) levels indicate better prognoses and lower morbidity in patients with CNS diseases, such as multiple sclerosis (MS) [10], Alzheimer’s disease [8], and Parkinson’s disease [11]. However, few studies have focused on UA’s role in acute CNS viral infections, such as viral encephalitis (VE) or viral meningitis (VM).

We aimed to explore the correlation between SUA levels and clinical disease status in patients with acute CNS viral infections. Our findings may provide novel insights into disease assessment, prognosis evaluation, and clinical therapy of CNS viral infections.

Patients and methods

The patients for this cross-sectional study were selected on the basis of records from the Department of
Neurology or ICU at the First Affiliated Hospital of Wenzhou Medical University. Between June 2013 and June 2016, serum samples were collected from 336 individuals. Of these, 157 had CNS viral infections, including 73 with VM (51 men and 22 women) and 84 with VE (47 men and 37 women). There were 179 healthy controls (HCs) (108 men and 71 women). Our participants’ demographic characteristics are shown in Table 1. The HCs and patients did not differ significantly in age ($P=0.304$).

To clinically diagnose acute CNS viral infections, we considered patient history, clinical symptoms and signs, cerebrospinal fluid (CSF) findings, neuroradiology findings (i.e. cranial MRI), and electroencephalography (EEG) results (Table 2) [1]. All patients who fulfilled the diagnostic criteria [1] received intravenous acyclovir after admission to our hospital. The exclusion criteria were as follows: (i) renal failure, gout, diabetes, liver disease, tumors, or autoimmune disorders; (ii) use of aspirin, diuretics, antibiotics, or other drugs that could affect SUA levels; and (iii) presence of other infections, fever, or, in HCs, other complaints. The participants’ clinical characteristics are presented in Tables 1 and 3.

We used a five-grade scale derived from the Glasgow Outcome Scale (GOS) [12] to estimate the CNS viral infection outcomes 6–12 months after discharge by questioning the patients or their family members. To identify the prognostic factors for the CNS viral infections, the patients were assigned to a ‘favorable outcome’ category for patients with good recovery or mild or moderate disability (GOS grades I–III) or a ‘poor outcome’ category for patients with severe disability or those who died (GOS grades IV and V).

Venous blood was drawn from an antecubital vein after overnight fasting at about 6 a.m. on the day after

---

**Table 1** Demographic and clinical characteristics of acute central nervous system virus infections and the healthy control group

| Characteristics     | VM [n (%)] | VE [n (%)] | HC [n (%)] | $P_1$ value | $P_2$ value |
|---------------------|------------|------------|------------|-------------|-------------|
| $N$                 | 73         | 84         | 179        |             |             |
| Age (mean ± SD)     | 73 ± 13.9  | 37 ± 16.9  | 35.1 ± 9.7 | 0.304       |             |
| Sex (male/female)   | 51/22      | 47/37      | 108/71     | 0.188       |             |
| Fever               | 70 (95.9)  | 75 (93.3)  | –          | –           | –           |
| Headache            | 73 (100)   | 43 (51.2)  | –          | –           | 0.142       |
| Meningeal irritation sign | 44 (60.3)  | 38 (45.2)  | –          | –           | 0.078       |
| Acute upper respiratory infection history | 7 (9.8) | 16 (19) | – | – | 0.115 |
| Behavioral changes  | 0          | 15 (17.9)  | –          | –           | $<0.001^*$  |
| Neurological abnormalities | 0 | 64 (76.2) | – | – | $<0.001^*$ |
| Cognitive dysfunction | 0 | 10 (11.9) | – | – | 0.002* |
| Seizures            | 0          | 51 (60.7)  | –          | –           | $<0.001^*$  |
| ICU treatment       | 0          | 18 (21.4)  | –          | –           | $<0.001^*$  |
| EEG abnormal        | 11 (15.1)  | 57 (67.9)  | –          | –           | $<0.001^*$  |
| MRI abnormal        | 0          | 53 (63.1)  | –          | –           | $<0.001^*$  |
| Poor outcome        | 0/64 (0)   | 14/72 (19.4)| – | – | $<0.001^*$ |
| Median (range)      | 180 (20–300) | 200 (100–400) | – | – | 0.127 |
| CSF pressure (mmH2O) | 610 (100–2729) | 605 (100–3704) | – | – | 0.668 |
| Protein (mg/L)      | 3 (2.2–5.3) | 3.7 (2.4–9.4) | – | – | $<0.001^*$ |
| Chloride (mM)       | 119 (112–130) | 120 (105–140) | – | – | 0.361 |

CSF, cerebrospinal fluid; EEG, electroencephalogram; HC, healthy control; VE, viral encephalitis; VM, viral meningitis; WBC, white blood cell.

---

**Table 2** Definitions of possible viral meningitis and encephalitis

Possible viral meningitis

- Symptoms and/or signs consistent with meningitis such as fever, headache, nausea/vomiting, neck stiffness, and sensitivity to light and noise
- Lack of symptoms and signs consistent with encephalitis
- Bacterial etiology unlikely
- CSF leukocytes > $5 \times 10^6/\mu L$

Possible viral encephalitis

- Symptoms and/or signs of parenchymatous disease of the brain such as focal neurological signs, seizures, decreased consciousness, or disorientation, often concomitant with fever and pathological neuroradiology or neurophysiology findings
- CSF leukocytes > $5 \times 10^6/\mu L$
- Other parenchymatous disease of the brain unlikely

---

**Table 3** Serum levels of serum uric acid in acute central nervous system virus infections patients and the healthy control group

| Characteristics     | Total (mean ± SD) | Male (mean ± SD) | Female (mean ± SD) |
|---------------------|------------------|-----------------|-------------------|
| SUA (mM)            |                  |                 |                  |
| Groups N            | VM 73 227 ± 68*  | 51 240 ± 72*    | 22 197 ± 47**     |
| VE 84 189 ± 82**    | 47 207 ± 86**    | 37 167 ± 70**   |
| HC 179 313 ± 69     | 108 350 ± 59     | 71 266 ± 37     |

The covariance analysis was carried out.

HC, healthy control; SUA, serum uric acid; VE, viral encephalitis; VM, viral meningitis.

* $P<0.001$, VM vs. HC in both sexes.

** $P<0.001$, VE vs. HC in both sexes.

* $P<0.05$, male vs. female in each group.
admission and at the first follow-up visit within 1 month after hospital discharge. SUA levels were measured using a clinical analyzer (AU5831; Beckman Coulter Inc., Brea, California, USA). In our hospital, the normal SUA range is 208–428 mM for men and 155–357 mM for women.

Statistical analysis
All noncontinuous variables are presented as mean±SD. All noncontinuous variables are presented as medians (with ranges). We used analysis of variance analysis of variance for three-group comparisons and Student’s t-test for between-group comparisons. To analyze nonparametric data, we used Fisher’s exact tests for qualitative variables and the Mann–Whitney U-test for quantitative variables. We compared the SUA levels of patients and HCs through covariance analysis with age as the covariant. SUA levels are sex dependent [13], and thus we explored the effect of sex by dividing the patients in each group into subgroups. We analyzed differences between same-patient SUA measurements at different timepoints using the Wilcoxon matched-pairs signed rank test. We used Spearman’s rank correlation to investigate associations between SUA levels and GOS scores, CSF pressure, white blood cell counts, and protein levels. We carried out all analyses in SPSS, version 21.0 (IBM Corp., Armonk, New York, USA). We defined statistical significance as a P value less than 0.05.

Results
The SUA levels in the VM group were significantly lower than those in the HCs (P<0.001), and those in the VE group were in turn significantly lower than those in the VM group (P<0.001) (Table 3). The SUA levels in the female HCs were significantly higher than those in female VM and VE group patients (P<0.001 for both comparisons, Table 3). The same observation was made in men (P<0.001 for both comparisons, Table 3). Furthermore, we observed significantly lower SUA levels in patients who had neurological abnormalities (P=0.001), seizures (P=0.006), abnormal EEG results (P<0.001), abnormal MRI findings (P<0.001), or a need for ICU treatment (P<0.001) than in patients who did not have these conditions (Table 4).

Alterations in the different groups’ SUA levels across timepoints are shown in Table 5. The patients’ SUA levels were significantly increased after treatment (VM: P<0.001; VE: P=0.001). The patients’ SUA levels correlated negatively with their GOS scores (r=−0.399, P<0.001) (Fig. 1 and Table 6), but did not correlate with their CSF findings, such as CSF pressure (r=−0.136, P=0.089), white blood cell counts (r=−0.1, P=0.212), protein levels (r=−0.037, P=0.646), glucose levels (r=−0.125, P=0.12), or chloride levels (r=0.031, P=0.699) (Table 6).

### Table 4 Serum levels of serum uric acid in clinical characteristics of acute central nervous system virus infections patients

| Characteristics                                      | SUA (mean ± SD) (mM) |
|------------------------------------------------------|----------------------|
| Fever                                                | 207 ± 79             |
| Headache                                             | 211 ± 74             |
| Meningeal irritation sign                            | 208 ± 84             |
| Acute upper respiratory infection history            | 190 ± 76             |
| Behavioral changes                                   | 199 ± 72             |
| Neurological abnormalities                           | 181 ± 82             |
| Cognitive dysfunction                                | 188 ± 81             |
| Seizures                                             | 183 ± 84             |
| ICU treatment                                        | 123 ± 56             |
| EEG abnormal                                         | 174 ± 75             |
| MRI abnormal                                         | 158 ± 69             |
| Poor outcome                                         | 147 ± 56             |

The Mann–Whitney U-test was performed.

### Table 5 Serum uric acid levels in the patients studied according to the period of treatment

| n | Before treatment (mean ± SD) (mM) | After treatment (mean ± SD) (mM) | P value |
|---|----------------------------------|----------------------------------|---------|
| VM | 37                               | 223 ± 57                         | 285 ± 78 | <0.001* |
| VE | 58                               | 205 ± 96                         | 261 ± 100 | 0.001* |

The Wilcoxon matched-pairs signed rank sum test was used to compare serum uric acid levels before and after treatment in central nervous system virus infections groups.

VE, viral encephalitis; VM, viral meningitis.

*P<0.05.

Glasgow Outcome Scale (GOS) with serum uric acid (SUA) levels in acute central nervous system viral infections. There was a negative correlation between the GOS score and SUA levels in patients with central nervous system viral infections (r=−0.399, P<0.001).
downstream radicals of PN CNS virus infections

CNS, central nervous system; CSF, cerebrospinal fluid; GOS, Glasgow Outcome Scale; WBC, white blood cell.

PN exerts its neuroprotective effects not only by eliminating important neuroprotective antioxidant in humans. UA vicious cycle [18].

taglandins, which aggravate inflammation and induce a the production of inflammatory mediators such as pros-
motion and nitration of amino acid residues and guanine.

This results in cytochrome C release and finally induces cytotoxicity or apoptosis [16]. PN releases active matrix metalloproteinase from its proenzyme forms and metalloproteinase then splits the tight junctions between the BBB's endothelial cells [17]. PN is also an important modulator of cyclooxygenase, which is a key enzyme for the production of inflammatory mediators such as pros-taglandins, which aggravate inflammation and induce a vicious cycle [18].

UA, which is an oxidative metabolite of purine, is an important neuroprotective antioxidant in humans. UA exerts its neuroprotective effects not only by eliminating PN's oxidative toxicity but also by effectively scavenging downstream radicals of PN – that is, CO3^-2 and NO2^-, which are produced following the rapid reaction of PN with CO2 [19]. Hooper et al. [9] found that UA not only reduced BBB disruption but also alleviated inflammatory responses and tissue injury in a myelin basic protein-induced experimental allergic encephalomyelitis model. The same group later observed that UA inhibited the onset of symptoms in Borna disease virus-infected adult rats and prevented elevated BBB permeability and CNS inflammation [20]. This suggests that CNS inflammation because of neurotropic virus infections may be dependent on PN activity at the BBB. A 2-year follow-up study showed that the ability to repair tissue damage induced by PN and other free radicals was impaired in patients with relapsing-remitting MS and low SUA levels.

Therefore, SUA may be a biomarker for relapse risk, disability progression, and cognitive function in MS [21]. Liu et al. [22] observed recently that patients with different CNS infection types, including VM or meningoencephalitis, cerebral cysticercosis, tuberculous meningitis or meningocencephalitis, cryptococcal meningitis or meningoen-ccephalitis, and bacterial meningitis or meningoencephalitis, had lower SUA levels than HCs. Effective therapy increased SUA levels in these patients. UA may thus be used to evaluate clinical treatments in patients with CNS infections.

SUA levels are naturally lower in healthy females of child-bearing age than males. This difference is not limited to individuals with diseases. We observed that patients with VM or VE showed obviously depressed SUA levels compared with HCs after eliminating the influence of age and sex. This finding is consistent with the results of a previous study of patients with VM by Liu et al. [22]. Peng et al. [23] also found that SUA levels in patients with MS and those with VM or VE were obviously lower than those in HCs. Previous studies [12,23] have shown that female patients with MS or other neurological diseases have lower SUA levels than male patients. We found that SUA levels were clearly lower in patients with VM or VE than in HCs irrespective of sex and that there were no significant sex-related differences in SUA levels in patients with VM or VE. However, SUA levels were significantly decreased in patients with nervous func-tional disorders, seizures, ICU stays, EEG abnormalities, and MRI abnormalities, which implies that SUA levels are associated closely with disease severity. Kutzing et al. [24] analyzed the possible causes for decreased SUA levels and found that inflammation induces the consumption of UA, which is used to scavenge excess free radicals. This is turn reduces SUA levels. SUA levels were also correlated with CNS injury, especially BBB disruption. SUA protects the BBB's integrity and reduces its permeability. It also reduces inflammatory cell infiltration and thereby relieves brain inflammation.

This study was designed to follow up the patients and determine their prognoses with the GOS. The GOS scores of patients correlated negatively with SUA levels and SUA levels in patients with poor prognoses were lower than those in patients with favorable prognoses. These results suggest that SUA might be a useful

### Table 6 Correlation coefficients generated between serum uric acid and cerebrospinal fluid findings, Glasgow Outcome Scale in acute central nervous system virus infections

| CNS virus infections | Value | CSF pressure | CSF WBC count | CSF protein | CSF glucose | CSF chloride | GOS |
|----------------------|-------|--------------|---------------|-------------|-------------|--------------|-----|
| Pirin-related virus   | r     | -0.136       | -0.1          | -0.037      | -0.125      | 0.031        | -0.399 |
|                     | P     | 0.089        | 0.212         | 0.646       | 0.120       | 0.699        | <0.001* |

The Spearman's rank correlation was performed.
CNS, central nervous system; CSF, cerebrospinal fluid; GOS, Glasgow Outcome Scale; WBC, white blood cell.

*P < 0.05.
biomarker for assessing prognoses in patients with CNS infections. In addition, SUA levels were clearly increased in patients with VM or VE after antiviral treatment. This is consistent with the findings of Collazos et al. [25], who reported that hypouricemia is common in patients with AIDS and CNS infections, but that the patients’ SUA levels were increased after successful treatment of the CNS infections. This suggests that UA may be a predictive biomarker for evaluating therapeutic outcomes.

**Conclusion**

SUA levels were evidently decreased in patients with viral CNS infections, but effective treatments restored them. More importantly, lower SUA levels may be related to several phenomena indicative of disease severity, including neurological abnormalities, seizures, abnormal EEG results, abnormal MRI findings, and a need for ICU treatment. Furthermore, lower SUA levels were correlated closely with poor prognoses. Therefore, SUA levels may be a useful biomarker of acute CNS viral infections with inflammatory components and may be useful indicators for prognoses and treatment outcomes.

**Acknowledgements**

This study was supported by the Wenzhou Municipal Sci-Tech Bureau Program (grant no. Y20140278).

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Studahl M, Lindquist L, Eriksson BM, Günther G, Bengner M, Franzén-Röhl E, et al. Acute viral infections of the central nervous system in immunocompetent adults: diagnosis and management. Drugs 2013; 73:131–158.

2. Aravalli RN, Hu S, Lokensgard JR. Toll-like receptor 2 signaling is a mediator of apoptosis in herpes simplex virus-infected microglia. J Neuroimmunol 2007; 4:11.

3. Nair S, Diamond MS. Innate immune interactions within the central nervous system modulate pathogenesis of viral infections. Curr Opin Immunol 2015; 36:47–53.

4. Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. Nature 2000; 408:239–247.

5. Zhang Y, Wang Z, Chen H, Chen Z, Tian Y. Antioxidants: potential antiviral agents for Japanese encephalitis virus infection. Int J Infect Dis 2014; 24:30–36.

6. Valero N, Mosquera J, Alcocer S, Bonilla E, Salazar J, Alvarez-Mon M. Melatonin, minocycline and ascorbic acid reduce oxidative stress and viral titers and increase survival rate in experimental Venezuelan equine encephalitis. Brain Res 2015; 1622:368–376.

7. Hooper DC, Spitsin S, Kean RB, Champion JM, Dickson GM, Chaudhry I, et al. Uric acid, a natural scavenger of peroxynitrite, in experimental allergic encephalomyelitis and multiple sclerosis. Proc Natl Acad Sci USA 1998; 95:675–680.

8. Bowman GL, Shannon J, Frei B, Kaye JA, Quinn JF. Uric acid as a CNS antioxidant. J Alzheimers Dis 2010; 19:1331–1336.

9. Hooper DC, Scott GS, Zborek A, Mikheeva T, Kean RB, Kropowski H, et al. 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 2000; 14:691–698.

10. Moccia M, Lanzillo R, Palladino R, Russo C, Carotenuto A, Massarelli M, et al. Uric acid: a potential biomarker of multiple sclerosis and of its disability. Clin Chem Lab Med 2015; 53:753–758.

11. Pakpoor J, Seminog OO, Ramagopalan SV, Goldacre MJ. Clinical associations between gout and multiple sclerosis, Parkinson’s disease and motor neuron disease: record-linkage studies. BMC Neurol 2015; 15:16.

12. Raschias F, Wolff M, Delatour F, Chaffaut C, de Broucker T, Chevret S, et al. Outcome of and prognostic factors for herpes simplex encephalitis in adult patients: results of a multicenter study. Clin Infect Dis 2002; 35:254–260.

13. Zoccoliella S, Tortorella C, Iaf baldano P, Direnzo V, D’Onghia M, Lucianelli et al. Low serum urate levels are associated to female gender in multiple sclerosis patients. PLoS One 2012; 7:e40608.

14. Shankar SK, Mahadevan A, Kowoor JM. Neuropathology of viral infections of the central nervous system. Neuroinming Clin N Am 2008; 18:19–39.

15. Kruuij L, Noroozian M, Akhondzadeh S, Abdollahi M, Javadi MR. Anti-inflammatory activity of melatonin in patients with multiple sclerosis and other neurological diseases. J Neurol 2010; 257:308–314.

16. Akaike T, Suga M, Maeda H. Free radicals in viral pathogenesis: molecular mechanisms involving superoxide and NO. Proc Soc Exp Biol Med 1998; 217:64–73.

17. Akaike T, Maeda H. Nitric oxide and virus infection. Immunology 2000; 101:300–308.

18. Landino LM, Crews BC, Timmons MD, Morrow JD, Marnett LJ. Peroxynitrite, a reactive nitrogen and oxygen radical that mediates neuronal injury. J Neuroimmunol 2001; 125:11–17.

19. Squadrito GL, Cueto R, Splenser AE, Valavanidis A, Zhang H, Uppu RM, et al. Reaction of uric acid with peroxynitrite and implications for the mechanism of neuroprotection by uric acid. Arch Biochem Biophys 2000; 376:333–337.

20. Hooper DC, Kean RB, Scott GS, Spitsin SV, Mikheeva T, Morimoto K, et al. The central nervous system inflammatory response to neurotropic virus infection is peroxynitrite dependent. J Immunol 2001; 167:3470–3477.

21. Moccia M, Lanzillo R, Costabile T, Russo C, Carotenuto A, Sasso G, et al. Uric acid in relapsing-remitting multiple sclerosis: a 2-year longitudinal study. J Neurovirol 2015; 21:959–967.

22. Liu J, Li M, Wang X, Yi H, Xu L, Zhong XF, et al. Serum uric acid levels in patients with infections of central nervous system. Acta Neurol Belg 2016; 116:303–308.

23. Peng F, Zhang B, Zhong X, Li J, Xu G, Hu X, et al. Serum uric acid levels of patients with multiple sclerosis and other neurological diseases. Mult Scler 2008; 14:189–196.

24. Kutzing MK, Firestein BL. Altered uric acid levels and disease states. J Pharmacol Exp Ther 2008; 324:1–7.

25. Collazos J, Blanco MS, Guerra E, Mayo J, Martinez E. Sequential evaluation of serum urate concentrations in AIDS patients with infections of the central nervous system. Clin Chem Lab Med 2000; 38:1293–1296.