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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.**

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[a]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.

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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.

Uric 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

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

Characteristics	VM [*n* (%)]	VE [*n* (%)]	HC	P_1 value	P_2 value
N	73	84	179		
Age (mean ± SD)	34 ± 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 (89.3)	–	–	0.142
Headache	73 (100)	43 (51.2)	–	–	< 0.001*
Meningeal irritation sign	44 (60.3)	38 (45.2)	–	–	0.078
Acute upper respiratory infection history	7 (9.6)	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)					
CSF pressure (mmH_2O)	180 (20–300)	200 (100–400)	–	–	0.127
WBC count ($\times 10^6$)	64 (5–620)	26 (6–980)	–	–	0.003*
Protein (mg/l)	610 (100–2729)	605 (100–3704)	–	–	0.668
Glucose (mM)	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.
P_1 value: each group.
P_2 value: VM versus VE.
*$P < 0.05$.

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 $> 5 \times 10^6$/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 $> 5 \times 10^6$/l
Other parenchymatous disease of the brain unlikely

CSF, cerebrospinal fluid.

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

	Total		Male		Female	
Groups	*N*	SUA (mean ± SD) (mM)	*N*	SUA (mean ± SD) (mM)	*N*	SUA (mean ± SD) (mM)
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	256 ± 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.

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

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 continuous 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

	SUA (mean ± SD) (mM)		
Characteristics	Yes	No	*P* value
Fever	207 ± 79	207 ± 52	0.882
Headache	211 ± 74	195 ± 86	0.271
Meningeal irritation sign	208 ± 84	206 ± 71	0.681
Acute upper respiratory infection history	190 ± 76	210 ± 78	0.269
Behavioral changes	199 ± 72	207 ± 78	0.597
Neurological abnormalities	181 ± 82	225 ± 69	0.001*
Cognitive dysfunction	188 ± 81	208 ± 77	0.307
Seizures	183 ± 84	218 ± 72	0.006*
ICU treatment	123 ± 56	218 ± 73	< 0.001*
EEG abnormal	174 ± 75	222 ± 73	< 0.001*
MRI abnormal	158 ± 69	226 ± 71	< 0.001*
Poor outcome	147 ± 56	208 ± 77	0.003*

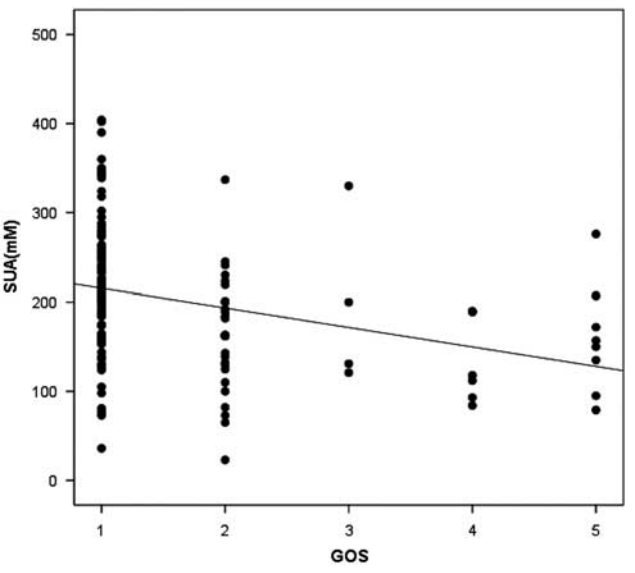
The Mann–Whitney *U*-test was performed.
EEG, electroencephalogram; SUA, serum uric acid.
*$P < 0.05$.

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	59	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.
*$P < 0.05$.

Fig. 1



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

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

	Value	CSF pressure	CSF WBC count	CSF protein	CSF glucose	CSF chloride	GOS
CNS virus infections	*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.
*$P < 0.05$.

Discussion

The pathology of CNS infections can include infiltration of mononuclear cells and lymphocytes around the meninges and cerebral vessels, microglial proliferation, neuronal edema and damage, nerve demyelination, and degeneration and death of cerebral vascular endothelial cells. These pathological changes can sometimes cause severe brain damage [14], although the precise pathophysiological mechanisms of meningitis and meningoencephalitis are not fully understood. In addition to direct damage to nervous tissue caused by invasive viruses, abundant oxygen free radicals resulting from inflammation, ischemia, hypoxia, and abnormal metabolism are important factors that aggravate brain injury in VE and VM. NO and its toxic metabolite PN are critical mediators of neurological damage [15]. PN is involved in the pathogenesis of CNS inflammatory diseases [9], and can cause DNA cleavage, lipid peroxidation, and oxidation 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 prostaglandins, 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, $CO_3^{\bullet -}$ and $NO_2^{\bullet}$, which are produced following the rapid reaction of PN with CO_2 [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 meningoencephalitis, cryptococcal meningitis or meningoencephalitis, 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 functional 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

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.

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Conflicts of interest

There are no conflicts of interest.

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