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ORIGINAL RESEARCH

Emerging role of prodromal headache in patients with anti-N-methyl-D-aspartate receptor encephalitis

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Background: Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis patients often present with psychiatric symptoms, cognitive dysfunction, epilepsy and memory deficits. A previous study has suggested that headache can occurr during the early stages of anti-NMDAR encephalitis. However, the exact association between headache and anti-NMDAR encephalitis has hardly been investigated, apart from a few case studies. This is probably due to the severity of encephalitis symptoms, and the mechanism underlying headache-associated anti-NMDAR encephalitis remains largely unclear.

Objective: This study aimed to investigate the role of prodromal headache in 28 patients diagnosed with anti-NMDAR encephalitis.

Methods: Clinical data related to the prodromal headache characteristics of anti-NMDAR encephalitis patients were prospectively collected from January first 2017 to June first 2018. Autoimmune antibodies in the cerebrospinal fluid (CSF) of anti-NMDAR encephalitis patients were detected by an indirect immunofluorescence staining kit. The differences between age, sex, clinical symptoms (fever, epilepsy, psychiatric symptoms, cognitive impairment, disturbance of consciousness), CSF, brain MRI abnormalities, and modified Rankin Scale (mRS) score were compared between patients with and without headache. In addition, the association of headache severity with brain MRI abnormalities, antibody titers, and mRS score was examined.

Results: Twenty-eight patients with anti-NMDAR encephalitis (median, 29 years; range, 15–62 years) reported headache. Among them, 18 (64%) were female, 24 (86%) had fever, 21 (75%) were positive for serum virus antibody, 19 (68%) had severe pain intensity (scored 4–7 out of 10 on the visual analog scale), 18 (64%) presented with pulsating character, and 5 (18%) patients accompanied by vomiting. Moreover, headache was detected in the frontal lobe of 14 (50%) patients and temporal lobe of 12 (43%) patients. Encephalitic symptoms (psychiatric symptoms, cognitive dysfunction, epilepsy, and memory deficits) appeared in 23 patients at average 5.5 days (range, 1–21 days) followed by headache attack. In five patients, the headache was lasted for 21 days.

Conclusion: Prodromal headache is commonly found in the temporal lobe and frontal lobe of young patients, and hardly accompanied by vomiting. Headache is rapidly substituted by encephalitis symptoms in the majority of patients, while gradually relieved in a few patients after the recovering from encephalitis symptoms. The results strongly suggest that the NR1 subunit of NMDAR is involved in prodromal headache. In sum, the symptom of prodromal headache is crucial for the diagnosis of anti-NMDAR encephalitis.

Keywords: headache, autoimmune encephalitis, immunology

Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is recognized as a multi-stage disease, in which encephalitis symptoms may appear after prodromal symptoms (headache, fever, nausea, and vomiting).[1–5] Previous studies have reported that prodro-

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mal symptoms occurred in 70%–86% of the patients with anti-NMDAR encephalitis.[2,5] However, there is a lack of studies that examine the characteristics of prodromal headache in patients with anti-NMDAR encephalitis.[6] Moreover, few studies have suggested that the mechanism of encephalitis may be related to the NR1 subunit of NMDAR.[1,2,7] Nevertheless, the mechanism underlying headache-associated encephalitis remains largely unclear. Therefore, this study aimed to examine the characteristics of prodromal headache in this disease and the underlying pathogenic mechanism of headache-associated anti-NMDAR encephalitis.

Methods

Patients

Demographics characteristics and clinical data of 42 patients with anti-NMDAR encephalitis were prospectively collected from The First Affiliated Hospital of Zhengzhou University between January 1, 2017 and June 1, 2018. These patients were diagnosed according to the diagnostic criteria for "definite anti-NMDAR encephalitis".[8] Autoimmune antibodies in the cerebrospinal fluid (CSF) were detected using an indirect immunofluorescence staining kit (German EU, FAIl2d-6). A total of 42 patients were positive for anti-NMDAR antibodies. Among them, nine patients without prodromal headache and five adolescent patients younger than 14 years (because we could not get their detailed headache information) were excluded from this study. Ultimately, 28 patients were included in the analysis. Written informed consent was obtained from all participants, parent(s), or a legal guardian of the participant under 18 years of age. This study was conducted in accordance with the Declaration of Helsinki.

Data collection

The demographic characteristics and clinical data such as the clinical features of prodromal headache, serum and CSF, brain MRI, treatment response, and modified Rankin Scale (mRS) score were collected. According to the Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. (ICHD-III), the presence of prodromal headache was examined by an attending physician through a set of standard questions.[9]

Assessment of clinical features

The definition of prodromal headache is referred to the symptoms that appear before encephalitis symptoms. Thus, headache, fever, and/or other related symptoms that occur before the onset of encephalitis are considered prodromal symptoms, whereas headache or fever after encephalitis symptoms is not included in the symptoms of prodromal headache.

The clinical features of prodromal headache (initial 2 months of disease onset) were assessed, including position, character, visual analog scale, simultaneous phenomenon, frequency of attacks, duration of attacks, and treatment response[6] (Table 1). In addition, clinical symptoms, serum and CSF, brain MRI, and treatment response of anti-NMDAR encephalitis patients were analyzed. To determine the interval time from onset of prodromal headache symptoms to anti-NMDAR encephalitis, all patients were followed-up prospectively for 3–9 months by telephone contact.

The differences between age, sex, clinical symptoms (fever, epilepsy, psychiatric symptoms, cognitive impairment, disturbance of consciousness), CSF, brain MRI abnormalities, and mRS score were compared between anti-NMDAR encephalitis patients with and without headache (Table 2). In addition, the association of headache severity with brain MRI abnormalities, antibody titers, and mRS score was examined (Tables 3 and 4).

Statistical analysis

Statistical analysis was performed using SPSS software, version 21.0. Categorical variables were analyzed by Fisher's exact test, whereas continuous variables were analyzed using Mann–Whitney test. Kruskal–Wallis test was used for single-factor multiclassification. *P*-values of 0.05 were considered statistically significant.

Ethical approval

This prospective study was approved by the Ethics Committee of First Affiliated Hospital of Zhengzhou University.

Results

Prodromal headache features

Thirty one of 89 patients diagnosed with autoimmune encephalitis (AE) have prodromal headache, and 28 of them were positive for anti-NMDAR antibodies. The average age of 28 patients is 29 years (range, 15–62 years); 18 (64%) of them were female, 24 (86%) had fever, 19 (68%) were of severe pain intensity (scored 4–7 out of 10 on the verbal rating scale), 18 (64%) presented with pulsating character, 5 (18%) patients accompanied by vomiting. In addition, headache was detected in the frontal lobe of 14 (50%) patients and temporal lobe of 12 (43%) patients. Encephalitic symptoms appeared in 23 patients at average 5.5 days (range, 1–21 days), followed by headache attack. In five patients, the headache lasted for 21 days. Besides, prodromal headache without encephalitic symptoms was observed in one patient and initially confirmed with viral encephalitis. Finally, the patient was successfully

Table 1 The characteristic of headache in 28 patients with anti-NMDAR encephalitis

Sex	Antibody level	Parietal lobe	Character	Additional symptoms	VAS	Duration	Frequency/ days	Age	MRI	mRS
F	1/3.2	The whole brain	Stuffy	Fever	1–3	<4 hours	15–21	28	Normal	1
M	1/3.2	Temporal lobe, parietal lobe	Pulsating	Nausea, phonophobia, fever	4–7, 8–10	<4 hours	>21	17	Temporal lobe, insular lobe, hippocampus	1
F	1/3.2	Laterality	Stuffy	Phonophobia, fever	4–7	Seconds to minutes	4–7	14	Frontal lobe, temporal lobe	2
F	1/3.2	Frontal lobe, laterality, occipital lobe, the whole brain, temporal lobe	Pulsating, pressing	Nausea, vomiting, fever, phonophobia, photophobia	4–7	<1 hour	1–3	35	Normal	2
M	1/32	The whole brain, temporal lobe	Pulsating	Fever	4–7	<1 hour	4–7	14	Normal	1
M	1/3.2	Frontal lobe, laterality	Swollen, pulsating	Nausea	4–7	<4 hours	8–14	48	Frontal lobe, temporal lobe	0
M	1/3.2	Laterality, parietal lobe, frontal lobe	Swollen, pulsating	Fever	8–10	<4 hours	8–14	41	Parietal lobe, occipital lobe, frontal lobe	0
M	1/3.2	Laterality, parietal lobe	Stuffy, pulsating	Nausea, phonophobia, fever	4–7, 8–10	<4 hours	8–14	45	Hippocampus, basal ganglia, parietal lobe	1
F	1/3.2	Laterality	Swollen	Fever	1–3	<4 hours	4–7	32	Normal	1
M	1/3.2	The whole brain	Swollen	Nausea, fever	4–7	<1 hour	15–21	15	Normal	0
M	1/3.2	Occipital lobe	Pressing	Fever	1–3	Seconds to minutes	15–21	27	Not checked	1
F	1/32	Frontal lobe, temporal lobe	Pulsating	Fever	4–7	<4 hours	4–7	33	Frontal lobe	0
F	1/3.2	Occipital lobe	Stuffy	Fever	1–3	<1 day	8–14	25	Cerebellum	0
F	1/3.2	Frontal lobe, temporal lobe	Pulsating	Fever, nausea, vomiting	4–7	<4 hours	4–7	21	Normal	0
M	1/3.2	Laterality, frontal lobe	Stuffy, pulsating	Nausea	4–7	<1 day	15–21	16	Frontal lobe, parietal lobe, temporal lobe, insular lobe	0
F	1/3.2	Laterality, frontal lobe	Stuffy	Nausea, fever	1–3	<1 day	>21	23	Frontal lobe, hippocampus, insular lobe, temporal lobe	0
F	1/3.2	Laterality	Pulsating	Nausea, fever	4–7	<4 hours	4–7	57	Temporal lobe	0
M	1/3.2	Laterality	Pulsating	Nausea, fever, vomiting, phonophobia	4–7	<4 hours	4–7	21	Normal	2

(*continued*)

Table 1 (*continued*)

Sex	Antibody level	Parietal lobe	Character	Additional symptoms	VAS	Duration	Frequency/ days	Age	MRI	mRS
F	1/3.2	Frontal lobe, parietal lobe, temporal lobe	Pulsating	Nausea, fever	4–7	<4 hours	4–7	30	Cerebral hemisphere, frontal lobe	0
F	1/3.2	Frontal lobe, temporal lobe	Stuffy	Fever, nausea, vomiting	4–7	<1 hour	1–3	62	Frontal lobe, temporal lobe	0
F	1/3.2	Laterality	Stuffy	Nausea, fever	4–7	Seconds to minutes	1–3	57	Temporal lobe, hippocampus	2
M	1/3.2	Temporal lobe, frontal lobe	Pulsating	Nausea, fever	4–7	Seconds to minutes	4–7	21	Frontal lobe, parietal lobe	0
F	1/3.2	Frontal lobe, temporal lobe, occipital lobe, parietal lobe	Pulsating	Nausea, fever, phonophobia, photophobia	8–10	<4 hours	>21	23	Frontal lobe, occipital lobe, parietal lobe	0
F	1/3.2	Laterality, parietal lobe	Pulsating	Nausea	4–7	Seconds to minutes	4–7	21	Parietal lobe, temporal lobe	1
F	1/3.2	Frontal lobe, temporal lobe	Pulsating, stuffy	Nausea, fever	4–7	Seconds to minutes	>21	16	Frontal lobe, cerebellum	0
F	1/3.2	Frontal lobe, parietal lobe, temporal lobe	Swollen, pulsating	Nausea, fever	4–7	<1 hour	4–7	27	Frontal lobe	1
F	1/32	Frontal lobe, temporal lobe	Swollen, pulsating	No	8–10	<1 hour	>21	30	Normal	0
F	1/3.2	The whole brain, temporal lobe, occipital lobe	Swollen, pulsating	Nausea, vomiting, fever	8–10	<1 hour	4–7	47	Not checked	0

Abbreviations: mRS, modified Rankin Scale, NMDAR, N-methyl-D-aspartate receptor; VAS, visual analog scale.

Table 2 Comparison of clinical features between patients with and those without headache in anti-NMDAR encephalitis

Clinical features	Patients with headache (n=28)	Patients without headache (n=9)	*P*-value
Gender female	18 (64%)	4 (44%)	0.252
Median age at symptoms onset (years)	29.5 (range, 15–62)	27 (range, 17–42)	0.848
Fever	24 (86%)	2 (22%)	0.001
Psychiatric symptoms	27 (96%)	8 (89%)	0.432
Cognitive impairment	27 (96%)	8 (89%)	0.432
Epilepsy	23 (82%)	6 (67%)	0.373
Disturbance of consciousness	26 (93%)	7 (78%)	0.244
Comorbid migraine	4 (14%)	0	0.554
mRS	3.6	3	0.059
Brain MRI abnormalities	18 (69%)	2 (22%)	0.22
CSF			
Median white blood cells (mg/μL)	21 (75%)	6 (67%)	0.679
Median protein (mg/dL)	17 (%)	6 (67%)	1.000
Antibody titers	0.21	0.23	0.876
Lymphocyte (%)	23 (82%)	8 (89%)	0.5

Notes: Patients with headache had more frequent fever and higher cerebrospinal fluid (CSF) lymphocyte than those without headache.
Abbreviations: mRS, modified Rankin Scale, NMDAR, N-methyl-D-aspartate receptor.

Table 3 Comparison of headache severity with antibody titers and patient prognosis modified Rankin Scale (mRS)

Auxiliary inspection	Severity VAS (1–10)			*P*-value
	1–3	4–7	8–10	
Antibody titers	1/3.2	1/3.2	1/3.2	0.198
Patient prognosis mRS	1	0	0	0.653

Abbreviation: VAS, visual analog scale.

Table 4 Comparison of headache severity with brain MRI abnormalities, antibody titers, and patient prognosis modified Rankin Scale (mRS)

Statistical results	Severity VAS (1–10)		
	a	b	c
P-value	0.557	0.524	1

Notes: a: 1–3 vs 4–7; b: 1–3 vs 8–10; c: 4–7 vs 8–10.
Abbreviation: VAS, visual analog scale.

treated by immunotherapy instead of antiviral therapy. All patients were recovered from anti-NMDAR encephalitis using immunotherapy or immunoglobulin, and three of them had recurrence during the follow-up period of 3–9 months.

The headache symptoms were lasted from 1 to 21 days in 23 patients and often improved spontaneously and rapidly prior to the appearance of encephalitic symptoms or relieved after consuming a simple analgesic drug (tramadol, ibuprofen). The remaining patients (n=5) exceeded 21 days of headache, in which the primary headache symptoms gradually worsened and immediately substituted by encephalitis and ultimately improved using immunotherapy. Besides, the included patients had a past medical history of hypertension (n=6), migraine (n=4), diabetes (n=2), and depression (n=1). One patient was allergic to penicillin and another one was alcohol intolerant.

Encephalitis symptoms included mental disorder or memory deficits (n=27), seizure (n=23), altered level of consciousness (n=26), involuntary movements (n=20), and epilepticus (n=5). Additionally, mechanical ventilation was found in three patients, whereas two patients presented with ovarian teratoma. These encephalitis symptoms appeared at average 5.5 days (range, 1–21 days), followed by headache attack in 23 patients (Table 1).

Due to the altered level of consciousness and mental illness, detailed information on headache, such as its location, quality, severity, duration, and/or accompanying symptoms, is not available for some patients.

Fever was more common in patients with headache than without headache (24/28 vs 2/9, $P<0.001$). However, there were no significant differences in age, gender, clinical symptoms (eg, epilepsy, psychiatric symptoms, cognitive impairment, disturbance of consciousness), white blood cells in CSF, brain MRI abnormalities at the time of symptom onset, mRS score, and comorbid migraine between patients with and without headache (Table 2).

Laboratory inspection

All patients underwent lumbar puncture examination. Among them, the CSF pressures and CSF white blood cells of 17 patients were in the range of 208–400 mmH2O and 6–50×10^6/L (normal, 0–5×10^6/L), respectively. In addition, the CSF protein levels were elevated in 11 patients (range, 455–920.8 mg/L; normal range, 150–450 mg/L). High levels of pleocytosis (range, 68%–93%; normal range, 60%–70%)

were observed in 24 patients. Furthermore, serum tumor markers were abnormal in five patients, whereas the serum virus antibody was not detected in nine patients.

Brain MRI

Twenty six patients underwent brain MRI examination. The abnormalities included frontal lobe in 11 patients (39%), temporal lobe in nine patients (32%), parietal lobe in six patients (21%), occipital lobe in two patients (7%), and hippocampus and cerebellum in three patients (11%) (Table 1).

Discussion

The present study demonstrated that in most patients, prodromal headache relieved spontaneously and rapidly prior to the appearance of encephalitic symptoms, whereas in few patients, headache gradually improved after the treatment of encephalitis symptoms. The headache was commonly found in the temporal lobe and frontal lobe of patients, with severe pain intensity, pulsating character, and hardly accompanied by vomiting. As well as, we speculate that prodromal headache is primarily related to anti-NMDAR, especially the NR1 subunit of NMDAR.

A previous report has suggested that the new-onset headache is probably related to anti-NMDAR-associated encephalitis (7/9, 78%).[6] Tominaga et al[10] found that prodromal headache is a distinctive symptom in anti-NMDAR encephalitis patients. Moreover, a previous study reported that headache can present at the prodromal stage of anti-NMDAR encephalitis. Consistently, our study indicated that the levels of NMDAR antibodies were significantly higher than other antibodies in patients with AE. Therefore, we postulate that prodromal headache is associated with anti-NMDAR antibodies in AE.

Another study has reported that most patients stopped complain about headache, rapidly followed psychiatric symptoms.[3] Similarly, this study found that headache (80%) improved spontaneously and rapidly prior to the appearance of psychiatric symptoms. Some studies have revealed that the disappearance of headache is due to the activation of NMDAR via NR1 antibodies.[2,10,11] However, a previous study shows that there is no obvious connection between headache and NR1 antibodies.[6] In contrast, we are not in agreement with their findings. NMDAR is largely made up of three subunits: NR1, NR2, and NR3, in which the mechanism of headache is mainly associated with NR2B subunit,[12,13] while the pathogenesis of anti-NMDAR encephalitis is more related to NR1 subunit.[14,15] Thus, we speculated that the more the antagonists bind to the corresponding autoantibodies target of NR1 subunit, the severe the destruction of NMDAR (NR2B subunit) structure and function. Finally, prodromal headache gradually improved and rapidly accompanied by psychiatric symptoms. Collectively, we speculate that headache disappearance is related to the mechanism of both headache and anti-NMDAR encephalitis, especially, the destruction of NMDAR structure and function (eg, NR1 and NR2B subunits). Besides, headache (20%) is gradually attenuated after relieving encephalitis symptoms. We propose that such prodromal headache may involve hyperexcitability of the brain or activation of anti-NMDAR by antibodies,[15] which triggers the inhibition of GABAergic neurons,[16,17] and ultimately leads to cortical spreading depression.[18] However, there is no biological study using patients' serum or CSF samples on the NMDAR subunit changes in vitro or in vivo until now; this is only our speculation. Hence, further investigation is needed to confirm these speculations.

Indeed, fever and elevated CSF lymphocytes were commonly found in headache group compared to nonheadache group (Table 2). Some studies classify this headache as "7.3.2 sterile (noninfectious) meningitis headache", sterility. Meningitis can occur in a variety of systemic inflammatory diseases.[19] Therefore, we cannot rule out that headache may be caused by intracranial infections.[10,19] There were no significant differences in age, gender, mental disorder, recognition disorders, epilepsy, disturbance of consciousness, comorbid migraine, mRS score, brain MRI abnormalities, and CSF parameters (eg, white blood cells, protein quantification, antibody titers, and lymphocytes) between headache group and nonheadache group. Moreover, headache severity was not significantly associated with mRS, antibody titers, and brain MRI abnormalities (Tables 3 and 4).

Nonetheless, the mechanism of prodromal headache remains largely unclarified. Few studies have reported that the patients with herpes simplex encephalitis (HSE) or vaccination may subsequently develop anti-NMDAR encephalitis.[20–22] Another study shows that anti-NMDAR antibodies are detected in patients with post-HSE.[23] In the present study, one patient exhibited similarly phenomenon; previous research speculated that prodromal viral infection may switch on the response of autoimmune in anti-NMDAR encephalitis,[24] However, prodromal symptoms were absent in 24% of patients, indicating that the disease can still occur without prominent viral infection. It may be possible that NR2B subunit has not been activated in some patients, due to the relatively low proportion (60%–70%) of NR2B subunit among the three subunits.[15]

Through an accurate imaging of prodromal headache, it is observed that headache was primarily occurred in both

temporal lobe and frontal lobe, suggesting that NMDAR is highly expressed in the frontal lobe and hippocampal neurons.[25] However, the location of initial headache does not obviously represent the onset position of brain MRI scanning.[10]

Interestingly, the results showed a significantly lower prevalence of headache accompanied by vomiting in patients with anti-NMDAR encephalitis compared to virus encephalitis (16.7% vs 75.4%).[26] It has been reported that the mechanism of anti-NMDAR encephalitis is likely to be associated with the dysfunction of neuron and neurotransmitter rather than the changes in anatomic structure.[27] Noticeably, intracranial pressure is rarely increased in patients with anti-NMDAR encephalitis; therefore, less vomiting is observed. Besides, the mechanism of viral encephalitis may be associated with inflammation, as indicated by the diffuse brain tissue swelling and elevated intracranial pressure.[28]

Although this research has reached its aims, there were few unavoidable limitations. First, the sample size was relatively small in this study. Moreover, several patients were unable to provide their clinical information due to severe encephalitis symptoms, leading to the incomplete data on prodromal headache features. Additionally, few patients were failed to recall headache information after recovering from encephalitis symptoms.

Conclusion

This study reveals that prodromal headache commonly occurs in the temporal lobe and front lobe, with severe pain intensity, pulsating character, and hardly accompanied by vomiting. Patients with this headache and followed by encephalitic symptoms should be considered for the possibility of anti-NMDAR encephalitis. Taken altogether, prodromal headache is crucial for the early diagnosis of anti-NMDAR encephalitis.

Disclosure

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