European Review for Medical and Pharmacological Sciences 2019; 23: 10970-10975

Focus on autonomic dysfunctions in anti-NMDAR encephalitis: a case report

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Abstract. – OBJECTIVE: We hope it will provide a reference for early detection, early diagnosis, and early treatment of atypical Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis with non-typical autonomic dysfunctions as the first symptom.

PATIENTS AND METHODS: We present a 15-year-old girl with the repetition of conscious disturbance at different levels, but no abnormal movements. Initially, there were no positive findings on routine electroencephalography (EEG) and dynamic video-electroencephalography (V-EEG), but the head-up tilt test (HTT) suggested neurocardiogenic syncope (vascular rejection type), which seemed to be the final diagnosis. However, the patient later experienced several episodes of disturbance of consciousness with unexplained abdominal pain. Abnormalities were discovered on EEG, which indicated the possibility of "epileptic seizures with autonomic-gastrointestinal features". Based on these findings, we finally tested the autoimmune encephalitis-related antibodies for the patient after the literature search and review.

RESULTS: The patient was finally diagnosed with anti-NMDAR encephalitis. Her symptoms were fully controlled after glucocorticoid and gamma globulin treatment, and she left the hospital with complete recovery.

CONCLUSIONS: Although autonomic nervous dysfunction occurred in our patient, her prognosis was good because she did not have respiratory or (and) circulatory failure. Exclusive diagnosis and early treatment are important in patients with anti-NMDAR encephalitis. Abdominal pain with positive HTT may be a manifestation of autonomic dysfunction in this disease.

Key Words:
Anti-NMDAR encephalitis, Head-up tilt test, Neurocardiogenic syncope, Epilepsy, Abdominal pain, Autonomic nervous system dysfunction.

Abbreviations

AE: autoimmune encephalitis; anti-NMDAR: Anti-N-methyl-D-aspartate receptor; CSF: cerebrospinal fluid; CT: computed tomography; ECG: electrocardiography; EEG: electroencephalography; GTCS: generalized tonic-clonic seizure; HTT: head-up tilt test; LOS: length of stay; MRI: magnetic resonance imaging.

Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is the most common type of autoimmune encephalitis (AE), and it is associated with NMDAR antibodies[1-3]. The clinical symptoms are variable, but headache, fever, and other prodromal flu-like symptoms are frequent. If not treated in time, these symptoms are aggravated, and severe mental and behavioral abnormalities, seizure, cognitive impairment, disturbance of consciousness, autonomic nervous system dysfunction, and other symptoms can occur[4-6], which lead to a poor therapeutic outcome and increased length of stay (LOS), hospitalization costs, mortality rate, and disability rate. Therefore, early diagnosis and early treatment

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are of paramount importance in patients with anti-NMDAR encephalitis. Due to its complex clinical presentation and the necessity for reasonable exclusion of other causes, anti-NMDAR encephalitis is often misdiagnosed. In particular, mild or incomplete phenotypes are difficult to detect, and deserve a comprehensive diagnostic workup[5,7]. Furthermore, some examinations can indicate other diseases, making the diagnosis even more difficult. In such cases, a comprehensive analysis by clinicians is needed. Here, we report a case of such a dilemma in a teenage girl, in an attempt to further improve our knowledge on atypical anti-NMDAR encephalitis.

Case Report

The patient was a 15-year-old girl suffering from the repetition of conscious disturbance at different levels. She was absence of schizophrenia-like symptom and generalized convulsion and her auxiliary examination results, such as brain magnetic resonance imaging (MRI; GE, Boston, MA, USA), routine electroencephalography (EEG; Nicole, Madison, WI, USA), ambulatory video EEG, routine cerebrospinal fluid (CSF) examination (routine biochemical, etiological and cellular examinations), abdominal and pelvic computed tomography (CT; Philip, Amsterdam, NY, USA), and tumor markers, were all normal. At the onset, no clear clinical symptoms and epileptiform abnormalities suggesting seizure activity were detected, and the initial diagnosis was functional neurological symptom disorder, cardiac disturbance, or syncope. Color Doppler echocardiography (TOSHIBA, Tokyo, Japan), dynamic electrocardiography (ECG: Philip, Amsterdam, NY, USA), and ambulatory blood pressure examinations were all negative, while the head-up tilt test (HTT) (Beijing Standley Technology Co., Ltd., Beijing, China) suggested neurocardiogenic syncope (attention please, she had not syncope episodes before the onset). However, the patient subsequently developed abdominal pain that could be relieved by herself. Disturbingly, abdominal examinations were all still negative. In addition, abnormalities on EEG (Figure 1) were detected during an attack of disturbance of consciousness after an episode of abdominal pain relieved, which resulted in a diagnosis of autonomic epilepsy with abdominal discomfort. Possible diagnoses were epilepsy with autonomic seizures of unknown etiology, or autonomic seizures and autonomic dysfunction due to AE. Based on these assumptions, autoimmune encephalitis-related examinations (serum and CSF) were performed, and the final diagnosis was confirmed to be anti-NMDAR encephalitis. The patient received immunotherapy consisting of intravenous pulses of methylprednisolone (Pfizer, New York, NY, USA) (1000 mg/d) combined with intravenous immunoglobulins (Shandong Taibang Biological Products Co., Ltd., Tai'an City, Shandong Province, China) (20 g/d) for 3 d, 500 mg/d methylprednisolone for 3 d, and 60 mg/d prednisone (Zhejiang Xianju Pharmaceutical Co., Ltd., Taizhou City, Zhejiang Province, China) with a dose reduction of 5 mg every 2 weeks (the maintenance period of prednisone was approximately 6 months). She was discharged when all her symptoms were completely resolved; meanwhile, episode of positive HTT and EEG disappeared after treatment. At the 3-month and 6-month follow-up visits, there was no recurrence of disease, and pelvic ultrasound examinations were normal.

Discussion

Anti-NMDAR encephalitis has received increased clinical attention. It often produces prodromal flu-like symptoms such as headache, fever, and fatigue. When these symptoms are aggravated due to disease progression and abnormal mental status, it may manifest as consciousness disturbance, insufficient ventilation, and autonomic nervous system disorder. Moreover, the motor disorder is also an important clinical feature of this disease. Neuroimaging and CSF examinations are usually normal in patients with anti-NMDAR encephalitis, and EEG mostly shows a diffuse slow-wave, in which the appearance of "extreme delta brush" is helpful in the clinical diagnosis of this disease[8,9]. At present, there is no unified standard for the diagnosis of anti-NMDAR encephalitis. Clinicians generally use the standard proposed by Graus et al in 2016[10] as a reference, which is dependent on the clinical symptoms and the presence of anti-NMDAR antibodies in the serum and CSF, and a definite diagnosis can be confirmed when anti-NMDAR antibodies are detected in CSF. It has been reported[6,11-15] that this disease is often seen in young women, with a median age at onset of 23 years (4-76 years). Over half of patients have a teratoma, mainly in the ovaries and occasionally in the mediastinum and the testis. Tumors are identified in most patients 3 weeks

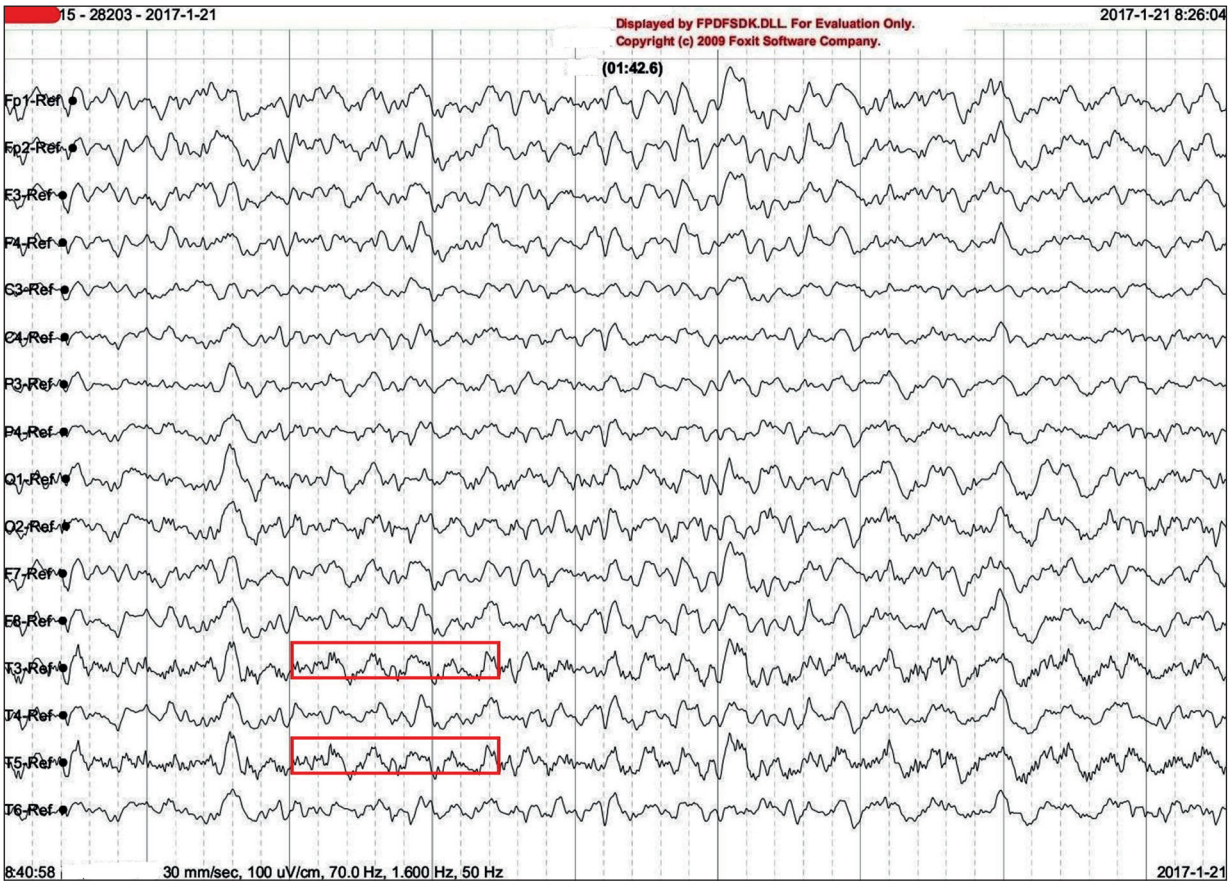

Figure 1. An atypical performance of delta brush. The fast wave superimposed on the basic slow wave in the left temporal region was detected on EEG during episodes of altered consciousness.

to 4 months after the appearance of neurologic symptoms. Although some patients are positive for anti-NMDAR antibodies, no tumor is found. Anti-NMDAR encephalitis has the following clinical presentations. (1) Mental and behavior disorders and disturbance of consciousness: during the early period of the disease, evident mental abnormalities, including bizarre behavior, delusions or paranoia and visual or auditory hallucinations are observed. The patient soon develops disturbance of consciousness, often in an unresponsive state. (2) Epileptic seizures: 76% of patients develop seizures within 3 weeks, which can present as any type[16]. Generalized tonic-clonic seizure (GTCS) is most common, followed by complex partial seizure. (3) Movement disorders: most commonly orofacial involuntary movements, grimace and mandatory opening, and closure of the mandible[17]. Athetosis, myoclonus, muscle fasciculation, and loss of muscle tension may also occur. (4) Hypoventilation: patients often have insufficient ventilation. Most cases require mechanical ventilation and ventilator-assisted respiration. (5) Autonomic nervous system dysfunction: arrhythmia, mydriasis, shortness of breath, sweating, hypertension or hypotension, salivary hypersecretion, high fever, urinary and intestinal dysfunction, and erectile dysfunction, which are mainly caused by low or hyperactivity of the autonomic nervous system. Based on the above clinical features, anti-NMDAR encephalitis is classified into 3 types[18]: Type I has a disease course < 60 days, with comatose symptoms; Type II mainly presents as mental and behavior disorders; Type III has a disease course of ≥ 60 days, mainly with mental stress. According to the different clinical manifestations in different periods, the disease is roughly divided into 5 stages[19]. (1) Prodromal stage: 2 weeks before disease onset, a series of non-specific symptoms may occur, including fever, cough, diarrhea, nausea, and vomiting. (2) Neuropsychiatric stage: with headache, convulsion, and mental and behavior

disorders. (3) Non-responsive stage: with speech disorder, difficulty in eye-opening, and even coma. (4) Dyskinesia stage: with involuntary movements of the mouth/face/tongue, and other dysfunctions include dance-like movement and foot movement, small hand and foot movements, and opisthotonus. (5) Recovery stage: recovery process is slow. Symptoms that appear later recover earlier[5].

With an increasing number of clinical cases and the formulation of a consensus among experts, most clinicians are aware of the possibility of anti-NMDAR encephalitis when diagnosing young female patients with new-onset psychiatric symptoms associated with seizures, memory impairment, reduced consciousness, and ventilation disorder, and perform the relevant examinations for early diagnosis and treatment. However, when the patient's symptoms are mild or incomplete, the diagnosis is very difficult. Furthermore, some examinations may indicate other diseases, and patients can easily be misdiagnosed. In the present case, the patient initially presented simple disturbance of consciousness, which could be attributed to common diseases such as epilepsy, syncope, and pseudo-epilepsy. The HTT test suggested neurocardiogenic syncope. At this time, the patient could have been discharged after consultation with the Department of Cardiology. However, the patient subsequently suffered several attacks of disturbance of consciousness, accompanied by inexplicable abdominal pain. As abdominal pain is a frequent complaint in childhood and adolescence, it may be a non-specific and difficult to define symptom. Therefore, the differential diagnosis in our patient could have included somatic disorders, abdominal migraine, familial Mediterranean fever, and porphyria. However, abnormalities on EEG were found during an attack of disturbance of consciousness, which suggested a diagnosis of autonomic epilepsy with abdominal discomfort. Another possible diagnosis was epilepsy with autonomic seizures of unknown etiology, or autonomic seizures and autonomic dysfunction due to AE. Based on this uncertainty, we tested for AE-related antibodies and found anti-NMDAR antibodies. Thus, the patient received standard treatment for anti-NMDAR encephalitis, was recovered, and discharged from the hospital. It is suggested that repeated EEG examinations play an important role in patients with anti-NMDAR encephalitis and mild or incomplete clinical manifestations. Accordingly, Freri et al[7] even recommend that in mild or incomplete oligosymptomatic cases of anti-NMDAR encephalitis, a complete diagnostic workup including long-term V-EEG-polygraphy monitoring is of paramount importance.

During the diagnosis and treatment of our patient, we realized that the abdominal pain and neurocardiogenic syncope identified by the HTT could both be due to an atypical presentation of autonomic nervous system dysfunction caused by anti-NMDAR encephalitis. Therefore, in addition to the common autonomic nervous system dysfunction presentation of anti-NMDAR encephalitis previously described in the literature[4-6,20-22], such as central hyperthermia/hypothermia, arrhythmia (sinus tachycardia/sinus bradycardia), abnormal blood pressure (hypertension/hypotension), central hypoventilation/hyperventilation, sexual dysfunction (erectile dysfunction), hypersecretion and urinary incontinence, attention should also be focused on the rare and newly reported clinical manifestations. The specific mechanism underlying the development of autonomic nervous system dysfunction in anti-NMDAR encephalitis patients is unclear. It is generally believed to be associated with a disorder of neurotransmitter balance in the brain caused by the production of anti-NMDAR antibodies, which affects the dopaminergic, adrenergic and cholinergic systems[5,23,24]. Currently, the NMDAR hypofunction hypothesis has become popular[25]. This is because non-competitive NMDAR antagonists such as phencyclidine and ketamine can induce similar autonomic dysfunction symptoms to those in patients with anti-NMDAR encephalitis, while NMDAR agonists can improve these symptoms[26,27]. Irrespective of the mechanism, when the clinical manifestations of autonomic nervous system dysfunction appear, this suggests that the patient is at the non-responsive stage, and the mortality rate is very high. Patients mainly die of respiratory and circulatory dysfunction and failure[19]; therefore, critical patients usually require cardiac pacemaker implantation or respiratory assistance at this time. Hence, attention should be paid to the discrimination of such autonomic nervous system dysfunction to ensure early diagnosis and early treatment. Although autonomic nervous dysfunction occurred in our patient, her prognosis was good because she did not occur respiratory or (and) circulatory failure.

Iizuka et al[28] reported that the clinical damage caused by anti-NMDAR encephalitis was reversible after a long-term study and observation. Approximately 75% of patients completely

recovered or had slight disability; the outcome of patients with anti-NMDAR encephalitis is often reported as "good", but many patients can have residual cognitive problems[29] and subtle long-lasting deficits that impact the quality of life. Clinicians should be aware of these sequelae to address early counseling and assessment[30,31]. In addition, follow-up should be continued in order to monitor the possible development of delayed occult malignancies in non-tumor patients[4,5]. Tumor surveillance should be performed for at least 4 years, and the possibility of tumor recurrence should be considered in patients with relapse[6].

Conclusions

In summary, when its clinical manifestation is atypical, paying attention on identifying the manifestations of autonomic nervous dysfunctions may be very important for anti-NMDAR encephalitis patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Yantai Yuhuangding Hospital Affiliated to Qingdao University. The patient's father signed the informed consent. The case report has been approved by the parents of the child.

Availability of Data and Material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Funding

This study was funded by Yantai Science and Technology Planning Project (grant No. 2018SFGY091; 2017WS105), Promotive Research Fund for Science and Technology Development Plan Project of Yantai (grant number 2013WS209; 2016WS017), Medicine and Health Science and Technology Development Plan Project of Shandong Province (grant number 2016WS0717), and Initial Scientific Research Fund of Yantai Yuhuangding Hospital (grant number 201624; KJ0160).

Authors' Contribution

CR and YN found references and drafted the manuscript. WL and HL read the literature. QC and ZW S summarized information of the case. JH W helped to draft the manuscript. LN G disposed figures. XT W, LG, and CR evaluated the data of patient, designed literature retrieval strategy, and modified the manuscript. XT W and CR did a lot of work in word edit. All authors read and approved the final manuscript.

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