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Contents

Thrice Monthly Volume 10 Number 24 August 26, 2022

EDITORIAL

8432 Evolution of *World Journal of Clinical Cases* over the past 5 years

Muthu S

OPINION REVIEW

8436 NF-κB: A novel therapeutic pathway for gastroesophageal reflux disease?

Zhang ML, Ran LQ, Wu MJ, Jia QC, Qin ZM, Peng YG

MINIREVIEWS

8443 Obligate aerobic, gram-positive, weak acid-fast, nonmotile bacilli, *Tsukamurella tyrosinosolvens*: Minireview of a rare opportunistic pathogen

Usuda D, Tanaka R, Suzuki M, Shimozawa S, Takano H, Hotchi Y, Tokunaga S, Osugi I, Katou R, Ito S, Mishima K, Kondo A, Mizuno K, Takami H, Komatsu T, Oba J, Nomura T, Sugita M

8450 Diffusion tensor imaging pipeline measures of cerebral white matter integrity: An overview of recent advances and prospects

Safri AA, Nassir CMNCM, Iman IN, Mohd Taib NH, Achuthan A, Mustapha M

8463 Graft choices for anterolateral ligament knee reconstruction surgery: Current concepts

Chalidis B, Pitsilos C, Kitridis D, Givissis P

8474 Overview of the anterolateral complex of the knee

Garcia-Mansilla I, Zicaro JP, Martinez EF, Astoul J, Yacuzzi C, Costa-Paz M

8482 Complication of lengthening and the role of post-operative care, physical and psychological rehabilitation among fibula hemimelia

Salimi M, Sarallah R, Javanshir S, Mirghaderi SP, Salimi A, Khanzadeh S

ORIGINAL ARTICLE

Clinical and Translational Research

8490 Pyroptosis-related genes play a significant role in the prognosis of gastric cancer

Guan SH, Wang XY, Shang P, Du QC, Li MZ, Xing X, Yan B

Retrospective Study

8506 Effects of propofol combined with lidocaine on hemodynamics, serum adrenocorticotropic hormone, interleukin-6, and cortisol in children

Shi S, Gan L, Jin CN, Liu RF

8514 Correlation analysis of national elite Chinese male table tennis players' shoulder proprioception and muscle strength

Shang XD, Zhang EM, Chen ZL, Zhang L, Qian JH

8525 Clinical value of contrast-enhanced ultrasound in early diagnosis of small hepatocellular carcinoma (≤ 2 cm)

Mei Q, Yu M, Chen Q

8535 Identification of predictive factors for post-transarterial chemoembolization liver failure in hepatocellular carcinoma patients: A retrospective study

Yuan M, Chen TY, Chen XR, Lu YF, Shi J, Zhang WS, Ye C, Tang BZ, Yang ZG

8547 Clinical significance of half-hepatic blood flow occlusion technology in patients with hepatocellular carcinoma with cirrhosis

Liu D, Fang JM, Chen XQ

8556 Which octogenarian patients are at higher risk after cholecystectomy for symptomatic gallstone disease? A single center cohort study

D'Acapito F, Solaini L, Di Pietrantonio D, Tauceri F, Mirarchi MT, Antelmi E, Flamini F, Amato A, Framarini M, Ercolani G

Clinical Trials Study

8568 Computed tomography combined with gastroscopy for assessment of pancreatic segmental portal hypertension

Wang YL, Zhang HW, Lin F

Observational Study

8578 Psychological needs of parents of children with complicated congenital heart disease after admitting to pediatric intensive care unit: A questionnaire study

Zhu JH, Jin CD, Tang XM

Prospective Study

8587 Quantitative differentiation of malignant and benign thyroid nodules with multi-parameter diffusion-weighted imaging

Zhu X, Wang J, Wang YC, Zhu ZF, Tang J, Wen XW, Fang Y, Han J

Randomized Controlled Trial

8599 Application of unified protocol as a transdiagnostic treatment for emotional disorders during COVID-19: An internet-delivered randomized controlled trial

Yan K, Yusufi MH, Nazari N

8615 High-flow nasal cannula oxygen therapy during anesthesia recovery for older orthopedic surgery patients: A prospective randomized controlled trial

Li XN, Zhou CC, Lin ZQ, Jia B, Li XY, Zhao GF, Ye F

SYSTEMATIC REVIEWS

8625 Assessment tools for differential diagnosis of neglect: Focusing on egocentric neglect and allocentric neglect

Lee SH, Lim BC, Jeong CY, Kim JH, Jang WH

World Journal of Clinical Cases

Thrice Monthly Volume 10 Number 24 August 26, 2022

Contents

CASE REPORT

8634 Exome analysis for Cronkhite-Canada syndrome: A case report

Li ZD, Rong L, He YJ, Ji YZ, Li X, Song FZ, Li XA

8641 Discrepancy between non-invasive prenatal testing result and fetal karyotype caused by rare confined placental mosaicism: A case report

Li Z, Lai GR

8648 Paroxysmal speech disorder as the initial symptom in a young adult with anti-N-methyl-D-aspartate receptor encephalitis: A case report

Hu CC, Pan XL, Zhang MX, Chen HF

8656 Anesthetics management of a renal angiomyolipoma using pulse pressure variation and non-invasive cardiac output monitoring: A case report

Jeon WJ, Shin WJ, Yoon YJ, Park CW, Shim JH, Cho SY

8662 Traumatic giant cell tumor of rib: A case report

Chen YS, Kao HW, Huang HY, Huang TW

8667 Analysis of two naval pilots' ejection injuries: Two case reports

Zeng J, Liu XP, Yi JC, Lu X, Liu DD, Jiang YQ, Liu YB, Tian JQ

8673 Beware of the DeBakey type I aortic dissection hidden by ischemic stroke: Two case reports

Chen SQ, Luo WL, Liu W, Wang LZ

8679 Unilateral lichen planus with Blaschko line distribution: A case report

Dong S, Zhu WJ, Xu M, Zhao XQ, Mou Y

8686 Clinical features and progress of ischemic gastritis with high fatalities: Seven case reports

Shionoya K, Sasaki A, Moriya H, Kimura K, Nishino T, Kubota J, Sumida C, Tasaki J, Ichita C, Makazu M, Masuda S, Koizumi K, Kawachi J, Tsukiyama T, Kako M

8695 Retinoblastoma in an older child with secondary glaucoma as the first clinical presenting symptom: A case report

Zhang Y, Tang L

8703 Recurrent herpes zoster in a rheumatoid arthritis patient treated with tofacitinib: A case report and review of the literature

Lin QX, Meng HJ, Pang YY, Qu Y

8709 Intra-abdominal ectopic bronchogenic cyst with a mucinous neoplasm harboring a *GNAS* mutation: A case report

Murakami T, Shimizu H, Yamazaki K, Nojima H, Usui A, Kosugi C, Shuto K, Obi S, Sato T, Yamazaki M, Koda K

8718 Effects of intravascular photobiomodulation on motor deficits and brain perfusion images in intractable myasthenia gravis: A case report

Lan CH, Wu YC, Chiang CC, Chang ST

World Journal of Clinical Cases

Thrice Monthly Volume 10 Number 24 August 26, 2022

Contents

8728 Spontaneous acute epidural hematoma secondary to skull and dural metastasis of hepatocellular carcinoma: A case report

Lv GZ, Li GC, Tang WT, Zhou D, Yang Y

8735 Malignant melanotic nerve sheath tumors in the spinal canal of psammomatous and non-psammomatous type: Two case reports

Yeom JA, Song YS, Lee IS, Han IH, Choi KU

8742 When should endovascular gastrointestinal anastomosis transection Glissonean pedicle not be used in hepatectomy? A case report

Zhao J, Dang YL

8749 *VARS2* gene mutation leading to overall developmental delay in a child with epilepsy: A case report

Wu XH, Lin SZ, Zhou YQ, Wang WQ, Li JY, Chen QD

8755 Junctional bradycardia in a patient with COVID-19: A case report

Aedh AI

8761 Application of 3 dimension-printed injection-molded polyether ether ketone lunate prosthesis in the treatment of stage III Kienböck's disease: A case report

Yuan CS, Tang Y, Xie HQ, Liang TT, Li HT, Tang KL

8768 High scored thyroid storm after stomach cancer perforation: A case report

Baik SM, Pae Y, Lee JM

8775 Cholecystitis-an uncommon complication following thoracic duct embolization for chylothorax: A case report

Dung LV, Hien MM, Tra My TT, Luu DT, Linh LT, Duc NM

8782 Endometrial squamous cell carcinoma originating from the cervix: A case report

Shu XY, Dai Z, Zhang S, Yang HX, Bi H

8788 Type 2 autoimmune pancreatitis associated with severe ulcerative colitis: Three case reports

Ghali M, Bensted K, Williams DB, Ghaly S

8797 Diffuse uterine leiomyomatosis: A case report and review of literature

Ren HM, Wang QZ, Wang JN, Hong GJ, Zhou S, Zhu JY, Li SJ

LETTER TO THE EDITOR

8805 Comment on "Posterior reversible encephalopathy syndrome in a patient with metastatic breast cancer: A case report"

Kunić S, Ibrahimagić OĆ, Kojić B, Džananović D

World Journal of Clinical Cases

Thrice Monthly Volume 10 Number 24 August 26, 2022

Contents

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The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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The *WJCC* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJCC* as 1.534; IF without journal self cites: 1.491; 5-year IF: 1.599; Journal Citation Indicator: 0.28; Ranking: 135 among 172 journals in medicine, general and internal; and Quartile category: Q4. The *WJCC*'s CiteScore for 2021 is 1.2 and Scopus CiteScore rank 2021: General Medicine is 443/826.

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CASE REPORT

Paroxysmal speech disorder as the initial symptom in a young adult with anti-N-methyl-D-aspartate receptor encephalitis: A case report

Chuan-Chen Hu, Xiao-Ling Pan, Mei-Xia Zhang, Hong-Fang Chen

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Abstract

BACKGROUND

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a treatable but frequently misdiagnosed autoimmune disease. Speech dysfunction, as one of the common manifestations of anti-NMDAR encephalitis, is usually reported as a symptom secondary to psychiatric symptoms or seizures rather than the initial symptom in a paroxysmal form. We report a case of anti-NMDAR encephalitis with paroxysmal speech disorder as a rare initial manifestation, and hope that it will contribute to the literature.

CASE SUMMARY

A 39-year-old man with anti-NMDAR encephalitis initially presented with paroxysmal nonfluent aphasia and was misdiagnosed with a transient ischemic attack and cerebral infarction successively. The patient subsequently presented with seizures, but no abnormalities were found on brain magnetic resonance imaging or electroencephalogram. Cerebrospinal fluid (CSF) analysis revealed mild pleocytosis and increased protein levels. Anti-NMDAR antibodies in serum and CSF were detected for a conclusive diagnosis. After immunotherapy, the patient made a full recovery.

CONCLUSION

This case suggests that paroxysmal speech disorder may be the presenting symptom of anti-NMDAR encephalitis in a young patient.

Key Words: Anti-N-methyl-D-aspartate receptor encephalitis; Autoimmune disease; Paroxysmal speech disorder; Seizure; Immunotherapy; Case report

Core Tip: Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a treatable but often misdiagnosed autoimmune disease. In this paper, we describe a 39-year-old man with anti-NMDAR encephalitis who initially presented with paroxysmal speech disorder and was subsequently misdiagnosed with a transient ischemic attack and cerebral infarction. The definitive diagnosis was made based on the detection of anti-NMDAR antibodies in serum and cerebrospinal fluid. The patient recovered completely after immunotherapy. This case suggests that paroxysmal speech disorder may be the first symptom of anti-NMDAR encephalitis in a young patient without risk factors for cerebrovascular disease.

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INTRODUCTION

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis was initially reported as a paraneoplastic immune-mediated syndrome associated with ovarian teratoma[1]. Since Dalmau *et al*[2] discovered antibodies against N-methyl-D-aspartate receptor (NMDAR) in 2007, anti-NMDAR encephalitis has been gradually recognized worldwide. The exact incidence of the disease was unknown. A multicenter, population-based prospective study suggested that anti-NMDAR encephalitis accounts for 4% of all causes of encephalitis[3]. Data from the California Encephalitis Project regarding the cause of encephalitis revealed that the frequency of anti-NMDAR encephalitis surpassed that of individual viral etiologies in young individuals[4]. Anti-NMDAR encephalitis is a treatable but often misdiagnosed autoimmune disease[5]. It primarily affects children and young adults (a median age of 21 years), with a higher incidence among females (4:1) but a similar incidence between women and men after the age of 45 years[6]. We present a case of anti-NMDAR encephalitis with paroxysmal speech disorder as the presenting symptom. The patient was initially misdiagnosed with cerebrovascular disease due to a transient ischemic attack (TIA)-like onset, but anti-NMDAR antibodies in serum and cerebrospinal fluid (CSF) eventually validated the diagnosis.

CASE PRESENTATION

Chief complaints

A 39-year-old man presented to the emergency department of our hospital complaining of repeated episodes of speech impediment for one day. In addition, he experienced a generalized tonic-clonic seizure an hour before the visit.

History of present illness

The patient's symptoms began with paroxysmal speech disorder one day prior. Each attack lasted for dozens of seconds to several minutes and was not accompanied by other neurological deficits. The patient experienced convulsion with loss of consciousness during his first visit to another hospital. The epileptic attack lasted for two minutes and the patient regained consciousness after ten minutes. He was diagnosed with TIA and treated with 200 mg aspirin and 20 mg atorvastatin. Then, he presented to our hospital with persistent slurred speech lasted for more than one hour.

History of past illness

Except for a headache one month prior, the patient had no significant medical history and no drug in use.

Personal and family history

The patient's personal and family history was unremarkable.

Physical examination

The patient's temperature was 36.5 °C, heart rate was 89 beats per minute, respiratory rate was 18 breaths per minute, blood pressure was 18.1/9.8 KPa and oxygen saturation in room air was 98%. No obvious abnormality was found on neurological examination when he was admitted to another hospital. However, we found nonfluent aphasia and deviation of the tongue to the right on neurological

examination.

Laboratory examinations

Routine laboratory studies, including a complete blood count, hepatic and renal function, blood glucose, glycosylated hemoglobin, coagulation testing, autoantibodies, autoantibody spectrum associated with anti-cardiolipin antibodies, thyroid function, homocysteine, serum tumor markers, human immunodeficiency virus antibody test and treponema pallidum hemagglutination assay, were all unremarkable.

Imaging examinations

An initial brain computed tomography (CT) scan showed no significant abnormalities. Brain computed tomography angiography (CTA) showed no intracranial hemorrhage, aneurysm, vascular malformation, or intracranial arterial stenosis. Brain magnetic resonance imaging (MRI) further excluded lesions that were easily overlooked on CT. Based on the above imaging findings, ischemic stroke was ruled out.

Electrophysiological detection

Routine and ambulatory electroencephalogram (EEG) showed no epileptic discharges, and the diagnosis of epilepsy was untenable.

Further diagnostic work-up

Lumbar puncture revealed a CSF pressure of 2.21 kPa. CSF analysis revealed a nucleated cell count of 28/μL (normal < 5/μL), which was dominated by lymphocytes (85% lymphocytes, 10% monocytes, 4% neutrophils, 1% eosinophils), lactate dehydrogenase of 56 U/L (normal < 40 U/L), and protein levels of 662 mg/L (normal 120-600 mg/L). The concentrations of glucose, chlorine and adenosine deaminase in the CSF were normal. Anti-NMDAR antibodies were detected in the CSF and serum by indirect immunofluorescence testing using a commercial kit (Euroimmune, Germany). The titer of anti-NMDAR antibody IgG was 1:10 (++) in CSF and 1:32 (++) in serum. Anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid 1, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid 2, gamma-aminobutyric acid-B, leucine-rich glioma-inactivated protein 1, contactin-associated protein-like 2 and glutamic acid decarboxylase-65 antibodies IgG in CSF and serum were negative. No tumor was found on chest CT or abdominal ultrasound.

FINAL DIAGNOSIS

The presence of anti-NMDAR antibodies in serum and CSF led to a final diagnosis of anti-NMDAR encephalitis in the presented case.

TREATMENT

The patient was initially misdiagnosed with TIA and treated with 200 mg aspirin and 20 mg atorvastatin at another hospital. The patient was subsequently misdiagnosed with cerebral infarction and received intravenous thrombolytic therapy with 50 mg of recombinant tissue plasminogen activator at the emergency department of our hospital. Twenty-four hours after thrombolytic therapy, aspirin (200 mg/d) and atorvastatin (20 mg/d) were administered orally in the ward until the final diagnosis was reached.

Ultimately, the patient was diagnosed with anti-NMDAR encephalitis and treated with intravenous immunoglobulin (25 g/d × 5 d) and intravenous methylprednisolone (1000 mg/d × 3 d to 500 mg/d × 3 d to 240 mg/d × 3 d to 120 mg/d × 3 d). Then the patient was discharged with slowly tapered oral methylprednisolone (48 mg qd × 2 wk to reduction of the dosage by 4 mg every 2 wk) (Figure 1).

OUTCOME AND FOLLOW-UP

The patient's speech disorder recovered after immunotherapy, and he no longer had seizures. No adverse effect was observed during the treatment. At the follow-up six months after discharge, he was asymptomatic.

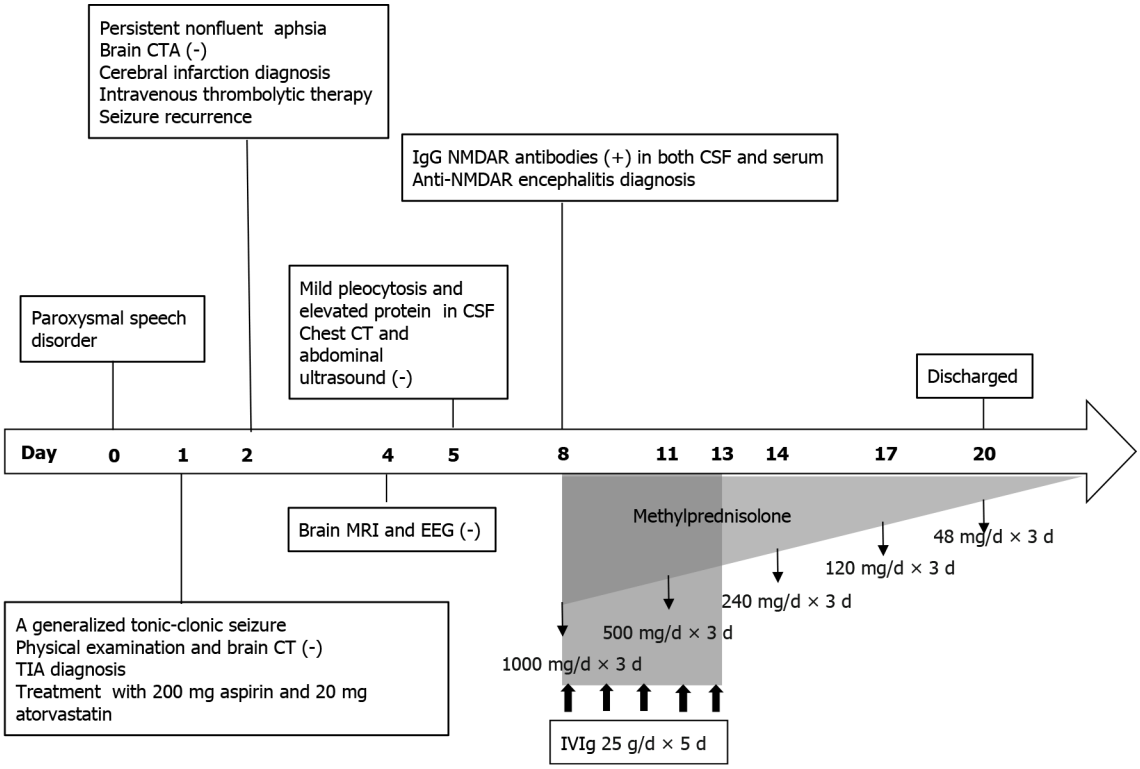

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Figure 1 The timeline of the patient's clinical course. The rectangle represents the time at which the patient received intravenous immunoglobulin; and the triangle represents the time at which the patient received intravenous and oral methylprednisolone. CTA: Computed tomography angiography; NMDAR: N-methyl-D-aspartate receptor; CSF: Cerebrospinal fluid; CT: Computed tomography; MRI: Magnetic resonance imaging; EEG: Electroencephalogram; TIA: Transient ischemic attack; IVIg: Intravenous immunoglobulin.

DISCUSSION

The NMDAR is a member of the ionotropic glutamate receptor family, which plays a crucial role in neuronal communication[7]. NMDAR-mediated signals control diverse processes across the life course, including synaptogenesis and synaptic plasticity, and contribute to excitotoxic processes in neurological disorders[8]. NMDAR overactivity is the proposed underlying mechanism in epilepsy, dementia, and stroke, whereas decreased NMDAR activity results in symptoms of schizophrenia[9]. The antibodies in patients with anti-NMDAR encephalitis lead to selective and reversible loss of cell-surface NMDARs by capping and internalization, resulting in abrogation of NMDAR-mediated synaptic function, which can cause patients' symptoms, such as psychotic behavior, signs of involvement of dopaminergic pathways (rigidity, dystonia, orofacial movements, tremor) and autonomic dysfunction (cardiac dysrhythmia, hypertension, hypersalivation)[10,11].

Anti-NMDAR encephalitis is the most common cause of treatable autoimmune diseases and is characterized by prominent neuropsychiatric symptoms[12]. The clinical symptoms of the disease are mainly classified into eight groups: Psychiatric and behavioral symptoms, seizures, motor dysfunctions/involuntary movements, memory deficits, speech disorders, decreased levels of consciousness, autonomic dysfunctions and central hypoventilation[13]. Symptom presentations vary between children and adults; neurologic symptoms occur more often in children, while psychiatric symptoms are prevalent in adults[14], but in most cases, the progression of symptoms evolves toward a similar syndrome in days or weeks[6].

According to literature evaluations, over half of the patients with anti-NMDAR encephalitis had abnormal speech, including reduced verbal output or mutism, abnormal content, mumbling, echolalia, increased output or perseveration[15,16]. Speech dysfunction is one of the common symptoms of anti-NMDAR encephalitis but is frequently described as a symptom secondary to psychiatric symptoms or seizures rather than the main or initial symptom[17]. To our knowledge, paroxysmal speech disturbance as the first presentation has rarely been reported in anti-NMDAR encephalitis. Finke *et al*[18] described a patient with anti-NMDAR encephalitis who presented with recurrent aphasia. Episodes were accompanied by headache, hemianopia, and hemiparesis with pleocytosis, mimicking the syndrome of headache with neurological deficits and CSF lymphocytosis (Table 1). The patient in our report had recurrent speech dysfunction at onset but without typical psychiatric symptoms or movement disorders. Therefore, he was originally misdiagnosed with TIA and then with cerebral infarction due to his symptom lasting for more than one hour. Since brain MRI showed no structural abnormalities, we

Table 1 Comparing the present case with that from Finke *et al*[18]

Item	The present case	Finke *et al*[18]
Age (yr)	39	67
Gender	Male	Male
History of past illness	No	Migraine with aura
Vascular risk factors	No	No
Initial paroxysmal symptoms	Nonfluent aphasia	Right homonymous hemianopia, global aphasia and right hemiparesis
Accompanying symptoms	Generalized tonic-clonic seizures	Throbbing bilateral headaches, confusion and agitation
CSF analysis	Mild pleocytosis (28 cells/μL) dominated by lymphocytes (85%) and elevated protein (662 mg/L)	Lymphocytic pleocytosis (95 cells/mL) with few activated lymphocytes and plasma cells and elevated protein (96 mg/dL)
Brain MRI	No lesions	Mild frontoparietal microangiopathic leucoencephalopathy
EEG	No epileptic discharges	First: Moderate generalized slowing; r: Normal
Tumor screening	Negative	Negative
Testing for anti-NMDAR antibodies	IgG NMDAR antibodies in both CSF (titer, 1:10) and serum (titer, 1:32)	IgG NMDAR antibodies in CSF (titer, 1:32), but not serum
Treatment	Intravenous immunoglobulin and methylprednisolone, followed by oral methylprednisolone	Oral corticosteroids and plasma exchange, followed by azathioprine
Outcome	Asymptomatic	No further episodes occurred, but verbal long-term memory deficit persisted

MRI: Magnetic resonance imaging; CSF: Cerebrospinal fluid; EEG: Electroencephalogram; NMDAR: N-methyl-D-aspartate receptor.

considered that paroxysmal speech disorder might be a form of seizure. However, subsequent EEG recorded no epileptic discharges. The hypothesis was disproved.

This case deserves our attention as we consider the diagnostic and treatment options. First, this patient was a young adult with no risk factors for cerebrovascular disease (*e.g.*, hypertension, diabetes, cardiopathy, *etc.*) and no abnormalities on brain CTA. Furthermore, this patient had a headache a month before onset, which is exactly one of the common prodromal symptoms of anti-NMDAR encephalitis. Finally, the patient had a seizure during the visit, which is seldom observed in ischemic stroke but is a common symptom of anti-NMDAR encephalitis.

To date, the pathophysiological mechanism of speech impairments caused by anti-NMDAR encephalitis remains unclear. Hébert *et al*[17] reported a case of adult-onset anti-NMDAR encephalitis presenting primarily as progressive nonfluent aphasia. The patient's EEG showed the left frontotemporal slow wave activity, suggesting that the function of left frontal and opercular structures might be affected. Constantinides *et al*[19] described a case of an adult patient with anti-NMDAR encephalitis presenting with isolated, abrupt-onset aphasia. The patient's EEG revealed paroxysmal left temporal theta and delta waves. Deiva *et al*[20] reported a child with anti-NMDAR encephalitis who presented sudden and isolated Broca's aphasia following partial seizures and whose sleep EEG showed a repetitive pattern of focal theta rhythms spreading through the left hemisphere(Table 2). Similar electrical patterns were also described in previous anti-NMDAR encephalitis studies[21,22]. These studies suggested that these patterns did not necessarily correlate with seizures[17,21] but were probably the result of an increased frontotemporal-to-occipital gradient in cerebral glucose metabolism due to impaired NMDAR function[22]. Unfortunately, similar EEG abnormalities were not found in our case. However, the EEGs of the reported cases of anti-NMDAR encephalitis with aphasia provided neurophysiological evidence of left focal cortical dysfunction. Finke *et al*[18] speculated that cortical spreading depression (CSD) might be related to the patient's transient neurological symptoms. According to their hypothesis, CSD can be experimentally induced by glutamate, and it is assumed that an antibody-mediated decrease in NMDAR leads to increased glutamatergic activity by inactivating GABAergic neurons[10,18].

From previous observations, approximately 90% of anti-NMDAR encephalitis patients had at least four symptoms by the fourth week of disease onset[6], and mono- or oligosymptomatic presentations of anti-NMDAR encephalitis were rare[6,10]. The atypical manifestations of our case might be due to early initiation of immunotherapy, which prevented the development of the complete clinical phenotype of anti-NMDAR encephalitis[18].

Table 2 Reported cases of anti-N-methyl-D-aspartate receptor encephalitis with aphasia as the sole or dominant manifestation

Item	Constantinides *et al*[19]	Hébert *et al*[17]	Deiva *et al*[20]
Age (yr)	29	29	4
Gender	Female	Female	Female
Presenting symptoms	Isolated, abrupt-onset aphasia	A progressive nonfluent aphasia; simple partial seizures; confusion and emotional lability	Fever; repeated right partial motor seizures; sudden and isolated Broca's aphasia
Description of language difficulties	With a 6-mo history of aphasia; her prominent impairment, namely, non-fluent aphasic disturbances (effortful, halting speech with sound errors), had progressed rapidly and reached a peak in 72 h, at which point she was unable to speak and had difficulties in writing, but her ability to perceive verbal stimuli was relatively preserved	6-d history of progressive word-finding difficulties	The patient suddenly presented isolated speech difficulties; speech evaluation showed that her receptive language was preserved but that expressive language was affected associated with anomia, and anarthria suggestive of Broca's aphasia
EEG	Paroxysmal left temporal theta and delta waves	Abundant intermittent polymorphic slow wave activity over the left lateral fronto-temporal area	Waking EEG was characterized by unilateral left hemispheric slowing, and sleep EEG showed a repetitive pattern of focal theta rhythms over 10-15 s in the postero-temporal region which then spread to the whole left hemisphere for 45-60 s
Brain MRI	Normal	Normal	Normal
CSF analysis	Within normal limits (3 white blood cells × 10^6/L, protein 420 g/L), with negative cytology	Within normal limits (2 white blood cells × 10^6/L, 95% lymphocytes, protein 0.20 g/L, glucose 3.7 mmol/L) with normal cytology	19 leukocytes, with 0.22 g/L of protein and no oligoclonal bands
Testing for anti-NMDAR antibodies	Positive in both serum and CSF	Positive in CSF	Positive (1:100) in both serum and CSF
Screening for ovarian teratoma	Negative	A 5.3 cm right adnexal cystic teratoma (confirmed by pathology)	Negative
Immunotherapy	A 5-d course of intravenous methylprednisolone 1 g/d, followed by slowly tapered oral methylprednisolone 1 mg/kg per day; six courses of plasmapheresis; azathioprine 50 mg bid	A 2d course of 2 mg/kg intravenous immunoglobulin	Intravenous rituximab (375 mg/m^2)
Prognosis	Aphasia eventually resolved at the 1 yr follow-up	10 mo after symptom onset, her language impairments completely resolved, but she had impaired recollection of the events surrounding her hospitalization	After 20 mo of follow-up, the child had completely recovered and was free of seizures

EEG: Electroencephalogram; MRI: Magnetic resonance imaging; CSF: Cerebrospinal fluid; NMDAR: N-methyl-D-aspartate receptor.

On physical examination, the patient's tongue deviated to the right when he was asked to extend it. As no involuntary movements of the patient's jaw, mouth, tongue, or lower face were observed, the phenomenon was thought to be functional or central hypoglossal palsy rather than oromandibular dystonia or orofacial dyskinesia.

No lesion was found on our patient's brain MRI scan. A systematic review indicated that MRI scans showed abnormal findings in less than 50% of patients with anti-NMDAR encephalitis[23]. The CSF test revealed a slight increase in cell count and protein. Dalmau *et al*[11] reported that 95% of patients had CSF abnormalities, 91% had a mild-to-moderate lymphocytic increase, and 32% had a mildly elevated level of protein. Anti-NMDAR encephalitis was diagnosed based on the clinical manifestations, evidence of CSF, brain MRI, EEG and the antibodies against the NR1 subunit of the NMDAR in CSF and/or serum[13]. Speech impairment and seizures, as well as positive anti-NMDAR IgG antibodies in CSF and serum, led to the patient's ultimate diagnosis. Despite the severity of anti-NMDAR encephalitis, patients tend to have a good prognosis after immunotherapy[6]. Our patient made a full recovery after intravenous immunoglobulin and steroid administration. Therefore, early diagnosis and immunotherapy are important to patients with anti-NMDAR encephalitis.

The present report describes a young patient with a peculiar initial manifestation, and it demonstrates that a patient with anti-NMDAR encephalitis can present solely paroxysmal speech dysfunction with no additional symptoms of limbic encephalitis at onset. This case may also help us to further understand

the manifestation of speech dysfunction in patients with anti-NMDAR encephalitis. The likelihood of anti-NMDAR encephalitis should be considered in a young adult with paroxysmal speech disorder and clinical features of limbic encephalitis, such as psychiatric disorders, seizures, and cognitive impairment.

CONCLUSION

This case suggests that paroxysmal speech disorder may be the first symptom of anti-NMDAR encephalitis in a young patient without risk factors for cerebrovascular disease. Recognizing that is vital to early diagnosis and more timely treatment for future cases.

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FOOTNOTES

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