

Round 1

We are very grateful to the detailed and constructive review comments that this manuscript has received. We have revised the manuscript according to all reviewers' comments. All revised sentences are marked in **red**. Below we address each of the reviews' comments, and our responses are shown in **blue**.

Reviewer #1:

There are numerous data about NMDAR encephalitis. The present report describes a young patient with a peculiar initial manifestation. Evidently, the correct diagnosis was made timely, so that the outcome until now seems to be favorable. I have only minor concerns.

1. On page 6, the authors use several abbreviations that are unknown for many readers.

Response:

Thank you for pointing this out. We have added the full names of the abbreviations you mentioned on page 6 of the manuscript. (Page 6 Line 5-Line 9)

2. For a reader who is not so familiar with this disease, it would be helpful to include some remarks about the physiological function of the NMDA receptor (maybe only a hypothesis) and some ideas about the link between the symptoms and the disturbed function of this receptor.(are there hypotheses?).

Response:

Thank you for your advice. "The NMDAR is a member of the ionotropic glutamate receptor (iGluR) family, which plays a crucial role in neuronal communication^[1]. NMDAR-mediated signals control diverse processes across

the life course, including synaptogenesis and synaptic plasticity, and contribute to excitotoxic processes in neurological disorders^[2]. NMDAR overactivity is the proposed underlying mechanism in epilepsy, dementia, and stroke, whereas decreased NMDAR activity results in symptoms of schizophrenia^[3]." We have added these descriptions in the discussion part. (Page 7 Line 15-Line 20)

Reviewer #2:

The case report submitted by Chuanchen Hu et al. is interesting, and it is helpful for the diagnosis of anti-NMDAR encephalitis. However, a couple of minor issues need to be fixed.

1. On page 2, in CASE SUMMARY, the sentence of "Anti-NMDAR antibodies in serum and CSF were required for a conclusive diagnosis" is not a descriptive statement of this case report. It should be "Anti-NMDAR antibodies in serum and CSF were detected for a conclusive diagnosis".

Response:

We apologize for our inaccurate expression. We have revised this sentence in our manuscript. (Page 2 Line 17-Line 18)

2. On page 3, in Core tip, "The definitive diagnosis depended on the detection of anti-NMDAR antibodies in serum and CSF" is not a clear statement. A better statement is "The definitive diagnosis was made based on the detection of anti-NMDAR antibodies in serum and CSF".

Response:

Thank you for your comments. We have revised this sentence in the manuscript. (Page 3 Line 9-Line 10)

3. NMDAR's normal function and the autoantibody induced damage of NMDAR should be discussed in the manuscript.

Response:

Thanks for your suggestion. "The NMDAR is a member of the ionotropic glutamate receptor (iGluR) family, which plays a crucial role in neuronal communication^[1]. NMDAR-mediated signals control diverse processes across the life course, including synaptogenesis and synaptic plasticity, and contribute to excitotoxic processes in neurological disorders^[2]." "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)^[4,5]." We have added these descriptions in the discussion part. (Page 7 Line 15-Line 18, Line 20-Line 26)

Reviewer #3:

1. Abstract: Describe "what was the paroxysmal speech disorder encountered?"

Response:

Thank you for your comments. In this case, the patient's initial symptom was paroxysmal nonfluent aphasia. We have replaced the inaccurate phrase "paroxysmal speech disorder" with "paroxysmal nonfluent aphasia". (Page 2 Line 10)

2. There are some misspellings throughout the manuscript. 'associated with ovarian teratom'

Response:

We apologize for it, the mistake has been corrected ("teratom"→"teratoma") in our manuscript. (Page 3 Line 17)

3. Could the authors provide a video of the individual speech abnormality?

Response:

Thank you for your comments. It is a great pity that we did not videotape the patient's speech abnormality at the onset of the symptom.

4. History of past illness. Please include medications in use.

Response:

Thank you for your comments. This patient had not taken any medication. We have added this information to the manuscript. (Page 4 Line 21)

5. "tongue deviated to the right" ◇ oromandibular dystonia? Orofacial dyskinesia? Functional?

Response:

Thank you for your comments. We were also puzzled by this phenomenon. "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." We have added this question to the discussion in the revised manuscript. (Page 10 Line 4-Line 6)

6. It would be interesting a table comparing the present case with that from Finke et al.

Response:

Thanks for your suggestion. We have added the table comparing the present case with that from Finke et al. to the manuscript. (Table 1)

Table 1 Table comparing the present case with that from Finke et al.

Item	The present case	The case from Finke et al.^[18]
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Age	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/ μ l) 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; Reexamination: 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.

7. Why did the authors believe that the patient presented with only this clinical manifestation?

Response:

Thank you for your comments. It has been reported that approximately 90% of anti-NMDAR encephalitis patients had at least four symptoms by the fourth week of disease onset, and only 1% had remained with one symptom^[7]. In addition to paroxysmal non-fluent aphasia, our patient had seizures. However, mono- or oligosymptomatic presentations of anti-NMDAR encephalitis were still rare^[4]. The atypical or incomplete 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. We have added this issue to the discussion. The details are as follows:

“From previous observations, approximately 90% of anti-NMDAR encephalitis patients had at least four symptoms by the fourth week of disease onset^[7], and mono- or oligosymptomatic presentations of anti-NMDAR encephalitis were rare^[4,7]. 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^[6].” (Page 9 Line 25-Line 28; Page 10 Line 1-Line 2)

8. What are the mechanisms for explaining this presentation? How could NMDAR affect speech?

Response:

Thank you for your comments. So far, the mechanism of speech disorders caused by anti-NMDAR encephalitis remains unclear. EEGs of the reported cases of anti-NMDAR encephalitis with aphasia showed left focal slow wave activity^[8-10], suggesting that the function of the left focal cortex might be affected. The previous studies suggested that these electrical

patterns did not necessarily correlate with seizures^[8,11] but were probably the result of an increased frontotemporal-to-occipital gradient in cerebral glucose metabolism due to impaired NMDAR function^[12]. Dalmau et al. suggested that reduction of synaptic NMDAR could lead to inactivation of GABAergic neurons, resulting in most clinical manifestations of the disease^[4]. Finke et al. speculated that cortical spreading depression might be associated with the patient's transient neurological symptoms^[6]. In accordance with their hypothesis, spreading depression can be induced by glutamate in experiments, and it is assumed that NMDAR antibodies lead to glutamatergic hyperactivity by inactivating GABAergic neurons^[6]. We have added the relevant content to the discussion section. (Page 9 Line 3-Line 10; Page 9 Line 17-Line 24) The details are as follows:

"To date, the pathophysiological mechanism of speech impairments caused by anti-NMDAR encephalitis is unknown. Hébert et al. 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^[8]. Constantinides et al. described 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^[9]." "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. speculated that cortical spreading depression (CSD) might be related to the patient's transient neurological symptoms^[6]. According to their hypothesis, CSD can experimentally be induced by glutamate, and it is assumed that an antibody-mediated decrease of NMDAR increases glutamatergic activity by inactivating GABAergic neurons^[4,6]."

9. Could the authors provide a table with only the speech abnormalities already reported in the literature? This would greatly impact the quality of the manuscript.

Response:

Thank you for your comments. By reviewing the literature, there was only one reported case of anti-NMDAR encephalitis presenting as isolated aphasia and two other cases with speech disturbance as the dominant symptom. We have provided a table with these cases (Table 2).

Table 2 Reported cases of anti-NMDAR encephalitis with aphasia as the sole or dominant manifestation.

Item	The case from Constantinides <i>et al.</i>^[19]	The case from Hébert <i>et al.</i>^[17]	The case from Deiva <i>et al.</i>^[20]
Age	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-month 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-day 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 frontotemporal 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 CSF analysis	Normal Within normal limits (3 white blood cells $\times 10^6/L$, protein 420 g/L), with negative cytology	Normal Within normal limits (2 white blood cells $\times 10^6/L$, 95% lymphocytes, protein 0.20 g/L, glucose 3.7 mmol/L) with	Normal 19 leukocytes, with 0.22 g/l of protein and no oligoclonal bands

Testing for anti - NMDAR antibodies	Positive in both serum and CSF	normal cytology 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 5d 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 1y 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.

Reviewer #4:

The authors are requested to work and correct the highlighted and marked reviewer comments.

1. INTRODUCTION: Mention incidence, commonest age and Gender

wise distribution of this disease.

Response:

Thank you for your comments. "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^[13]. 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^[14]." "Anti-NMDAR encephalitis 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^[7]." We have added these in the INTRODUCTION section of the revised manuscript. (Page 3 Line 19-Line 27)

2. On page 4, in INTRODUCTION: Correct spelling mistake: teratom.

Response:

Thank you for your comments. We apologize for our carelessness and the mistake has been corrected ("teratom"→"teratoma") in our manuscript. (Page 3 Line 17)

3. On page 4, in *Chief complaints*: Please phrase this sentence: "During his first visit to another hospital, he experienced a generalized tonic-clonic

grand mal seizure". Not looking good.

Response:

Thank you for your comments. The manuscript has been thoroughly revised in grammar and syntax. We have revised this sentence as follows:

"In addition, he experienced a generalized tonic-clonic seizure an hour before the visit." (Page 4 Line 7-Line8)

4. On page 4, in *History of present illness*: Please simplify the sentence:

"At the onset of the symptoms, the patient had no alteration of consciousness, no headache or dizziness, no blurred vision, no mental or behavioral abnormalities, no numbness or weakness of limbs."

Response:

Thank you for your comments. We have revised this sentence as follows:

"Upon symptom onset, there were no other neurological deficits." (Page 4 Line 12-Line 13)

5. On page 4, in *History of present illness*: Paraphrase and simplify the sentence "Initially, the patient went to another hospital, where he had a sudden convulsion with loss of consciousness, froth at the mouth, and upturned eyes."

Response:

Thank you for your comments. We have revised this sentence as follows:

"The patient experienced a sudden convulsion with loss of consciousness during his first visit to another hospital." (Page 4 Line 13-Line 14)

6. On page 5, in *Physical examination*: No need of these words "After seizure cessation". Remove these.

Response:

Thank you for your comments. We have removed these words.

7. On page 5, in *Imaging examinations*: No need to mention this "from another hospital".

Response:

Thank you for your comments. We have deleted these words.

8. On page 7, in OUTCOME AND FOLLOW-UP: Mention the follow up duration.

Response:

Thank you for your comments. We have replaced "At the follow-up visit" with "At the follow-up six months after discharge". (Page 7 Line 11-Line 12)

9. On page 7, in DISCUSSION: This should be mention in introduction section not in discussion section. "It primarily affects children and young

adults (median age of 21 years) with a higher incidence among females (4:1) but similar between women and men after the age of 45 years."

Response:

Thank you for your comments. We have moved this sentence in the introduction section. (Page 3 Line 25-Line 27)

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Round 2

We are very grateful for the detailed re-review comments that this manuscript has received. We have revised the manuscript according to the comments of reviewer # 05755592. Below we address each review comment, and our responses are shown in [blue](#).

Reviewer #05755592:

I have reviewed the manuscript and have marked the deficiencies. The authors are requested to make the corrections. The introduction and discussion section quite improved while the case presentation section needs major improvement.

1. On page 2, in BACKGROUND: Replace the sentence with “will contribute to the literature”.

[Response:](#)

[Thank you for your comments. We have replaced the sentence “it will](#)

contribute to the diagnosis of this disease” with “it will contribute to the literature”. (Page 2 Line 8-Line 9)

2. On page 2, in CONCLUSION: Replace the marked words with “Presenting symptom”.

Response:

Thank you for your comments. We have replaced “first indication” with “presenting symptom”. (Page 2 Line 22)

3. On page 3, in INTRODUCTION: Replace word with “presenting symptom”.

Response:

Thank you for your comments. We have replaced “first symptom” with “presenting symptom”. (Page 3 Line 28)

4. On page 4, in History of present illness: Rephrase these words “Upon symptom onset”. Not appropriate.

Response:

Thank you for your comments. We have deleted these word “Upon symptom onset,” and revised the sentence as follows: “Each attack lasted for dozens of seconds to several minutes and was not accompanied by other neurological deficits.” (Page 4 Line 12-Line 13)

5. On page 4, in History of present illness: No need of these words. Authors are requested to remove.

Response:

Thank you for your comments. We have removed these words “a sudden”.

6. On page 4, in History of present illness: Rephrase the sentence “The convulsion stopped after 2 min, and the patient awoke 10 min later”. Appropriate sentence will be “the epileptic attack lasted for two minutes and the patient regain consciousness after 10 minutes”

Response:

Thank you for your comments. We have revised this sentence as suggested.

(Page 4 Line 14-Line 15)

7. On page 4, in History of present illness: Replace the word “lasting” with “lasted”.

Response:

Thank you for your comments. We have replaced “lasting” with “lasted”.

(Page 4 Line 17)

8. On page 4, in History of past illness: Rephrase the marked sentence “had not taken any medication”.

Response:

Thank you for your comments. We have revised the sentence as follows:

“Except for a headache one month prior, the patient had no significant medical history and no drug in use”. (Page 4 Line 20-Line 21)

9. On page 5, in Physical examination: Rephrase the marked sentence to “However, we found nonfluent aphasia and deviation of the tongue to the right on neurological examination”.

Response:

Thank you for your comments. We have revised this sentence as suggested.

(Page 5 Line 1-Line 2)

10. On page 5, in Imaging examinations: Seems awkward. Remove these marked words “in our hospital”.

Response:

Thank you for your comments. We have deleted these words “in our hospital”.

11. On page 5, in Imaging examinations: MRI was done for brain lesion exclusion? CT already done can exclude brain lesion. Rephrase and explain the marked sentence: “Brain magnetic resonance imaging (MRI) after admission showed no lesions. Due to the above imaging findings, ischemic

stroke was excluded”.

Response:

Thank you for your comments. Routine diagnostics with multimodal computed tomography (CT) has limited capacity for differentiating ischemic stroke from stroke mimics within the first hours after the event. CT has a significantly lower sensitivity, compared to MRI, to depict acute ischemic stroke, with an overall sensitivity of 57–71% in the first 24 h, and only 12% in the first 3 h^[1-3]. Small ischemic lesions in patients with mild stroke are difficult to identify on CT^[4]. In addition, CT sensitivity is very low in posterior fossa and deep infarcts^[5]. MRI has better accuracy for identification of the intraluminal thrombus, small petechial haemorrhagic transformation and previous chronic lobar hematomas and/or microbleeds^[1-3]. Diffusion-weighted imaging (DWI) and the corresponding apparent diffusion coefficient (ADC) maps is the most sensitive imaging modality to depict brain ischemia, with a sensitivity up to 73–92% in the first 3 h and up to 95–100% in the first 6 h^[1-3]. In acute ischemic stroke, the ADC values show an early decrease (from minutes to less than 1 h) due to cell depolarization and cytotoxic oedema, when CT and T2WI imaging are still normal^[5]. DWI provides most benefit in identifying patients with hyperacute, small volume or atypical infarcts since these are more likely to be overlooked using non-contrast CT^[4]. So MRI was done for brain lesion exclusion.

We have revised the sentence as follows: “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.”
(Page 5 Line 14-Line 16)

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10.1016/j.ejrad.2017.08.014]

12. On page 5: No need of this heading.

Response:

Thank you for your comments. We have removed the headings “CASE PRESENTATION” on page 5 and 6.

13. On page 6, in TREATMENT: Rephrase this sentence “due to the acute onset, rapid remission of symptoms, and lack of abnormal findings on physical examination and brain CT”.

Response:

Thank you for your comments. We have removed this sentence.

14. On page 6, in TREATMENT: This is redundancy. This has already mentioned in respective headings. No need of this.

Response:

Thank you for your comments. We have removed these sentences: “The patient experienced a recurrence of slurred speech that lasted for more than one hour. Neurological examination revealed nonfluent aphasia and deviation of the tongue to the right. Brain CTA showed no intracranial hemorrhage.”

15. On page 6, in TREATMENT: Was the patient labelled a case of cerebral infarction? Was it a diagnosis of exclusion?

Response:

Thank you for your comments. The patient was initially misdiagnosed with cerebral infarction in our hospital. The diagnosis of cerebral infarction was not ruled out until MRI was negative after admission.

16. On page 11, in CONCLUSION: Replace with may be the “first symptom”

Response:

Thank you for your comments. We have replaced “first indication” with “first symptom”. (Page 10 Line 19)