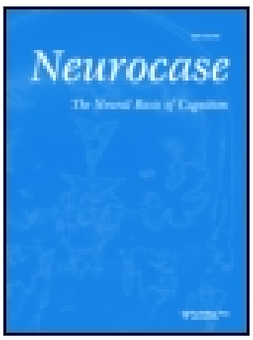

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Anti-NMDA receptor encephalitis presenting as isolated aphasia in an adult

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ABSTRACT

Anti-NMDA receptor (NMDA-r) encephalitis is a relatively rare cause of autoimmune encephalitis with divergent clinical presentations. We report a case of an adult patient with anti-NMDA-r encephalitis presenting with isolated, abrupt-onset aphasia. Her condition remained unaltered over a period of 6 months. The patients' electroencephalogram findings were typical for NMDA-r encephalitis; however, her magnetic resonance imaging and cerebrospinal fluid analysis were normal. She responded well to immunotherapy, and aphasia eventually resolved. The natural course of the present case contradicts the rapidly progressive nature of typical NMDA-r encephalitis. Furthermore, it broadens the clinical spectrum of anti-NMDA-r encephalitis, to incorporate isolated, nonprogressive aphasia.

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Anti-NMDA-r encephalitis; aphasia; immunotherapy; language; cognitive decline

Introduction

Autoimmune encephalitis is a term used to describe diverse antibody-mediated diseases of the central nervous system. These diseases usually present acutely or subacutely with alterations in cognition and level of consciousness, neuropsychiatric symptoms, epilepsy, movement disorders, dysautonomia, and sleep disorders. Robust epidemiologic data are lacking, although some support that autoimmune encephalitis is more common than herpes related encephalitis (Dubey et al., 2018; Gable, Sheriff, Dalmau, Tilley, & Glaser, 2012).

A case of limbic encephalitis in the presence of ovarian teratoma in a young girl was first reported in 1997 (Nokura et al., 1997). In 2005 emerged the first case series, and the pathogenic antigen was preliminary characterized (Ances et al., 2005). In 2007, anti-NMDA antibodies were first recognized as the cause of this limbic encephalitis (Dalmau et al., 2007). Over the last decade, the phenotypical expression of these antibodies has expanded wildly, incorporating such diverse symptoms as neuropsychiatric disorders (Lebon et al., 2012; Perogamvros, Schnider, & Leemann, 2012; Sacré et al., 2011; Tidswell, Kleinig, Ash, Thompson, & Galletly, 2013; Wilson, Shuster, & Fuchs, 2013; Yuan & Glezer, 2013), cognitive decline (Finke et al., 2012; Marques, Teotónio, Cunha, Bento, & Sales, 2014; Nath, Warren, & Ali, 2011; Sawamura et al., 2014; Vahter, Kannel, Sorro, Jaakmees, & Talvik, 2014), epilepsy (Goldberg, Taub, Kessler, & Abend, 2011; Johnson, Henry, Fessler, & Dalmau, 2010; Kadoya, Onoue, Kadoya, Ikewaki, & Kaida, 2015; Kim, Ryu, & Kang, 2015), movement disorders (Baizabal-Carvallo, Stocco, Muscal, & Jankovic, 2013; Kadoya, Kadoya, Onoue, Ikewaki, & Kaida, 2015; Li et al., 2015; Uchino et al., 2011), and autonomic dysregulation (Byun et al., 2015; Hinson, Takahashi, Altowaijri, Baguley, & Bourdette, 2013; Lee, Lawn, Prentice, & Chan, 2011; Vural, Arsava, Dericioglu, & Topcuoglu, 2012).

A recent, large multi-institutional observational study helped to better characterize anti-NMDA receptor (NMDA-r) encephalitis as a disease mainly presenting with behavioral problems, seizures, and movement disorders, affecting young women (Titulaer et al., 2013). A tumor—in the vast majority of the cases is an ovarian teratoma—is present in ~40% of such patients. The vast majority (97%) of patients with an underlying tumor are female. Ovarian teratoma is most often (94%) the underlying tumor. The frequency of an underlying ovarian teratoma reaches 58% in women >18 years old (Titulaer et al., 2013).

The disease course is rapidly progressive but generally responds well to immunotherapy (corticosteroids, IVIG, plasmapheresis as first-line and rituximab and cyclophosphamide as second-line options), though a minority of patients has a poor outcome. Most patients exhibit electroencephalogram (EEG) (slow waves or epileptic features) and cerebrospinal fluid (CSF) abnormalities (pleocytosis and elevated CSF protein), and less than half of the patients have magnetic resonance imaging (MRI) lesions. CSF detection of the antibodies seems to be more sensitive compared to serum (100% vs. 80%) (Titulaer et al., 2013).

As clinicians become more aware of this entity, its' clinical spectrum expands rapidly. Rare cases of ophthalmoplegia with flaccid paraparesis (Ishikawa et al., 2013), optic neuritis (Cobo-Calvo et al., 2014), and a neuromyelitisoptica phenotype (Kruer et al., 2010) have been described. Recently, a case of a child with seizures followed by aphasia has also been reported (Deiva et al., 2014). In this paper, we present a case of an adult with abrupt-onset, isolated, persistent aphasia.

Case presentation

A 29-year-old woman with no prior medical or family history presented at our clinic with a 6-month history of aphasia. Her

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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. She visited a neurologist, and MRI, magnetic resonance arteriography, and magnetic resonance venography were performed and found to be normal. She was tested for thrombophilia (fibrinogen, antithrombin III, protein C, and S), with negative results. An EEG, with the exception of slow wave activity, more prominent in the left hemisphere, was otherwise normal.

During the following few weeks, her symptoms slowly improved and remained stable thereafter. However, after the aforementioned short period, the patient started to notice a slowly progressive difficulty using her right arm that affected fine movements. Furthermore, she complained of intermittent numbness of her right leg. A brain and cervical spine MRI were performed 1 month prior to admission, which were also normal.

First neurological assessment

On admission (6 months from disease onset—first neuropsychological assessment), her general physical examination was unremarkable. Her reflexes were slightly brisker on her right side, and she had a right Hoffman sign. Her plantar reflexes were flexor. Muscle strength and tone were normal. There was slight bradykinesia on her right upper and lower extremity. Sensory examination was normal. She demonstrated impaired speech output. Cognitive screening was performed using the Frontal Assessment Battery (FAB; Flanagan, MDDubois, Slachevsky, Litvan, & Pillon, 2000) and the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975). She scored 23/30 on MMSE and 8/18 on FAB (conceptualization: 1/3; inhibitory control: 0/3; mental flexibility: 0/3). Her overall performance indicated a prominent executive dysfunction, with particular difficulty in conceptualization, inhibitory control, and mental flexibility, as well as mildly impaired memory and intact visuospatial abilities. A thorough neuropsychological examination revealed severe aphasia (for details, see "Neuropsychological assessment" section).

Laboratory studies included normal complete blood count, electrolyte panel, liver function, thyroid function, and a slightly increased erythrocyte sedimentation rate. Antithyroid, antinuclear, and antiphospholipid syndrome antibodies (ACA, anti-β2-GPI) as well as lupus anticoagulant, serum angiotensin converting enzyme, HIV, HBV, HCV, vitamin B12, and folic acid were within normal limits. On protein electrophoresis, she exhibited mild hypergammaglobulinemia, with negative protein immunofixation.

A repeat brain MRI on admission, which included axial T1, T2, Flair, PD, DWI and ADC sequences, coronal GRE, and sagittal T1 sequences, was normal. Her EEG was abnormal, with paroxysmal left temporal theta and delta waves, without evident delta brush (see Figure 1). CSF analysis was within normal limits (3 WBC, protein 42 mg/dl), with negative cytology. An extensive workup for infectious (both viral and bacterial) agents in the CSF was also negative.

A complete workup for paraneoplastic and autoimmune encephalitis, including anti-Hu, anti-Ri, anti-Yo, anti-CRMP5, anti-Ma2, anti-amphiphysin, anti-NMDA-r, anti-VGKC, anti-LGI1, anti-Caspr2, anti-GABA and anti-AMPA, was ordered. The patient tested positive for anti-NMDA-r antibodies both in serum and in CSF via immunostaining in cultured cerebellar neurons, thus confirming the diagnosis of anti-NMDA-r encephalitis. She underwent abdominal ultrasound and MRI, which were negative for an underlying ovarian teratoma.

Second neurological assessment

The patient received a 5-day course of IV methylprednisolone 1 g/day, followed by slowly tapered oral methylprednisolone 1 mg/kg/day. A second neuropsychological assessment indicated marginal improvement of language functions (for details, see "Neuropsychological assessment" section). She was released and a Tc-99m HMPAO-Spect was scheduled, which was within normal limits.

Third neurological assessment

Forty-five days after treatment initiation, the patient was readmitted for reevaluation. She reported improved fluency, which was evident on neurological examination during spontaneous speech. A third neuropsychological assessment indicated that her speech output was evidently improved; however, naming deficits persisted (for details, see "Neuropsychological assessment" section). Her neurologic examination was unaltered compared to the patient's first admission.

Fourth neurological assessment

Due to the remaining deficits, initiation of six courses of plasmapheresis was decided. Upon completion of plasmapheresis, the patient underwent a fourth neuropsychological assessment. She exhibited further improvement and was released. Due to her good clinical response, the patient was started on azathioprine 50 mg b.i.d. At her 1-year follow-up, she was symptom-free. Neurological examination was within normal limits. A repeat EEG was not performed.

Neuropsychological assessment

The patient underwent four consecutive neuropsychological assessments: first assessment at 6 months post-onset (Day 180), second assessment 1 day after 5-day cortisone infusion completion (Day 200), third assessment 40 days after cortisone infusion completion (prior to plamapheresis) (Day 240), and fourth assessment 3 days post-plasmapheresis completion (Day 250). The measures used were the short form of the Boston Diagnostic Aphasia Examination (BDAE-SF; Goodglass & Kaplan, 1972), adapted in Greek (Tsapkini, Vlahou, & Potagas, 2009/2010), the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983) and the Peabody Picture Vocabulary Test—Revised (PPVT-R; Dunn & Dunn, 1981), both standardized in Greek (Simos, Kasselimis, & Mouzaki, 2011a, 2011b), the Comprehension of Instructions in Greek (CIG; Simos, Kasselimis, Potagas, & Evdokimidis, 2014), the

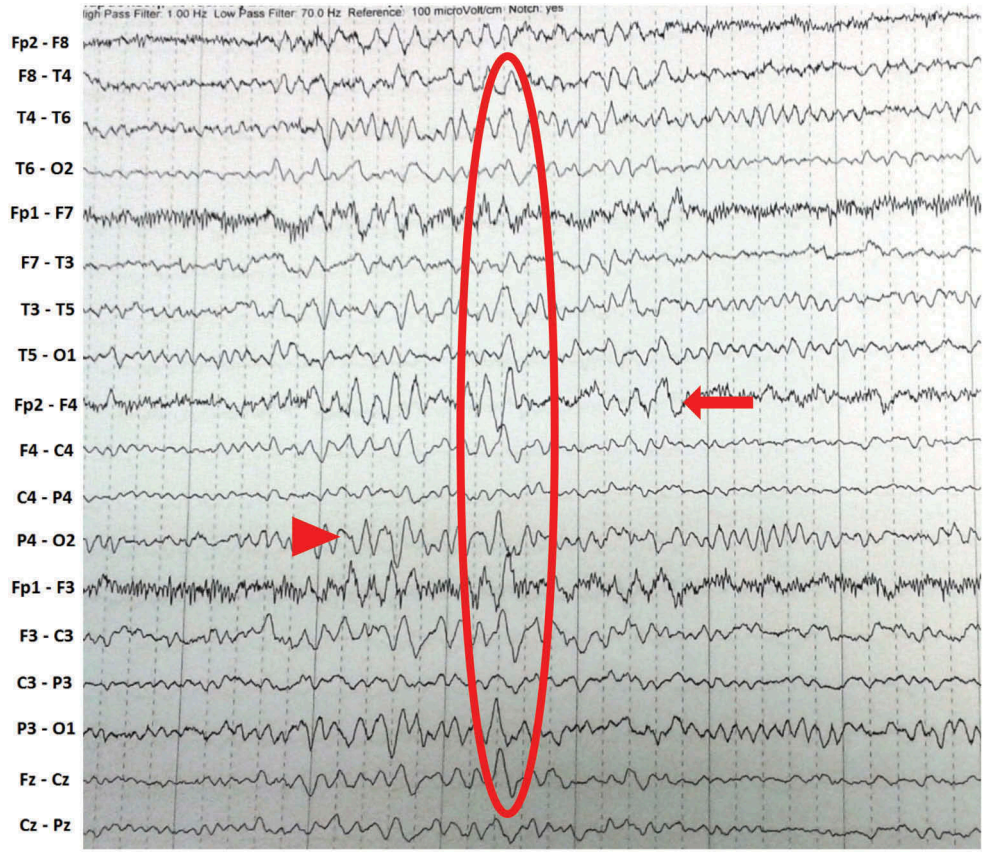

Figure 1. EEG of the patient 6 months after disease onset.

EEG of the patient 6 months after disease onset. The EEG exhibits paroxysmal delta waves (circle), single theta (arrowhead), and delta waves (arrow).

Controlled Oral Word Fluency (COWF; Kosmidis, Vlahou, Panagiotaki, & Kiosseoglou, 2004), two standardized word and pseudoword reading fluency measures (WRF and psWRF, respectively; Simos, Sideridis, Kasselimis, & Mouzaki, 2013), and a digit span task (DS; Simos, Papastefanakis, Panou, & Kasselimis, 2011) with two conditions, forward and backward, in order to assess verbal short-term and working memory, respectively (see Table 1). BDAE-SF and BNT were administered in all assessment sessions. The specifics with regard to the rest of the psychometric tools are discussed in the following paragraphs. The fact that particular measures were not administered during all assessment sessions was partly due to time and practical constraints and partly based on clinical judgment (e.g., there was no point in administering the demanding reading fluency tasks in the first session, since the patient demonstrated severe reading difficulties in the much easier BDAE-SF subscale).

First assessment (Day 180)

BDAE-SF, BNT, and CIG revealed severe linguistic deficits, including reduced speech rate, apraxia of speech, phonemic paraphasias, impaired writing and reading, anomia, and word finding difficulties during conversational speech. Her speech output was sparse, effortful, characterized by prominent phonemic errors and subsequent auto-correction attempts (i.e., the patient was fully aware of her impairment), and consisting of short phrases with poor grammatical structure. Auditory comprehension was found to be relatively preserved (in contrast with comprehension of written stimuli which was impaired) based on the Comprehension of Commands BDAE-SF subscale, although she demonstrated poor performance on CIG. This can be explained in terms of task difficulty, given that CIG is supposed to pose increased demands on patients, due to its suggested working memory component (for a discussion, see Simos et al., 2014). She was unable to repeat three-syllable words short sentences, write or read aloud, even single words. A zero score at BNT revealed severe anomia. It should be noted that her overall performance indicated possible short-term/working memory impairment, although formal testing to confirm this assumption was not implemented.

Second assessment (Day 200)

The evaluation was more comprehensive (the patient was able to perform on all BDAE-SF subscales, although poorly in some cases) and included one additional test (PPVT-R). Performance on the BDAE-SF indicated slight improvement with regard to speech rate (30.4 words per minute compared to 21 words per minute at initial assessment), reading aloud, reading comprehension, and repetition. Word finding issues were at some degree (however far from fully) resolved, as indicated by the naming subscale. Further neuropsychological testing revealed a marginally low score on the short form of PPVT-R (18/32), which, combined with the deficient BNT

Table 1. Performance of the patient on language and neuropsychological measures across assessments.

BDAE subscales		First assessment	Second assessment	Third assessment	Fourth assessment
Speech output	Stroke story	Moderately impaired fluency, phonemic paraphasias, elements of apraxia of speech	Although speech rate was somewhat improved, the deficits with regard to speech output persisted	Fluent speech with rare phonemic paraphasias	Fluent, intelligible speech with no paraphasias or signs of word finding difficulties
	CTP	Inability to describe the picture, partly due to speech output impairment, but mainly due to word-finding difficulties	Moderately non-fluent speech output, word finding difficulties	Fluent speech with no phonemic paraphasias. Mild word finding difficulty	Fluent, intelligible speech with no paraphasias; mild anomia
Oral comprehension	Words (max: 16)	–	16	16	16
	Commands (max: 10)	10	9	10	10
	Complex material (max: 6)	–	4*	6	6
Repetition	Words (max: 5)	2*	3*	4	4
	Sentences (max: 2)	0*	1*	2	2
Reading	Words (max: 15)	0*	12	14	12
	Sentences (max: 5)	0*	0*	4	4
	Comprehension (max: 4)	0*	2*	4	4
Writing	Words (max: 9)	0*	0*	6	–
	CTP	Inability to write. Grapheme selection was impaired even for automated word strings (e.g., her own name)	Inability to write. Grapheme selection was impaired even for automated word strings (e.g., her own name). Writing was restricted to a few words with noted paragraphias	Recovered writing ability, semantically and syntactically correct output, a few orthographic errors noted	–
BNT (max: 45)		0 < 5%	1 < 5%	27	29
PPVT-R (max: 32)		–	17	–	23
CIG		4 (−3.56 SDs)	4 (−3.56 SDs)	–	6 (−2.60 SDs)
DS	Forward span	–	–	–	3 < 5%
	Backward span	–	–	–	3 < 5%
COWF	Semantic	–	–	–	47
	Phonemic	–	–	–	24
Reading fluency	Words	–	–	–	46 (−2.60 SDs)
	Pseudowords	–	–	–	10 (−4.90 SDs)

*Impaired score based on the normative data provided by Tsapkini et al. (2009/2010) and clinical judgment. Deficient scores on neuropsychological measures are indicated by either "<5%" (below the fifth percentile), or reporting of SDs below the mean, based on normative data provided by the corresponding studies (see methods).

BDAE: Boston Diagnostic Aphasia Examination; CTP: Cooke Theft Picture; BNT: Boston Naming Test (confrontational naming); PPVT-R: Peabody Picture Vocabulary Test-Revised (receptive vocabulary); CIG: Comprehension of Instructions in Greek (oral comprehension of complex commands); DS: digit span (verbal short-term/working memory); COWF: controlled oral word fluency (semantic and phonemic verbal fluency).

score, indicates impaired access to lexical/semantic representations.

Third assessment (Day 240)

The BDAE-SF and the BNT were administered. Significant improvement was marked in all BDAE-SF subscales; the patient was fluent and demonstrated relative ease in reading aloud, oral and reading comprehension, repetition, and writing (with only few paragraphias noted). Performance on the BNT was improved but remained impaired (27/45). The rationale of excluding additional, more sensitive neuropsychological tests was based on precaution with regard to possible learning effects. Due to the time proximity of the consecutive assessments, learning effects concerning the items of the PPVT-R and the CIG could arise. Therefore, these tests were not administered during the particular testing session. One could however argue about the same phenomenon (i.e., learning effects) affecting performance on BDAE-SF and BNT. Nevertheless, the administration of these two tests was considered to be mandatory for several reasons. First, the BDAE-SF is the only aphasia battery standardized in Greek, therefore the only measure which could provide a useful aphasia profile. The same stands for the BNT. Second, clinical practice indicates that anomia is demonstrated via random errors, and repetitive testing cannot improve performance, especially when the examiner is not providing the correct answer after patient's failure to communicate the correct answer.

Fourth assessment (Day 250)

It included the following tests: BDAE-SF, BNT, PPVT-R, CIG, COWF, WRF, and psWRF. Additionally, a DS task was administered in order to assess possible short-term and working memory deficits. BNT score was found to be slightly improved, however marginally low (29/45). Overall, basic testing revealed only mild anomic and apraxic disturbances, thus indicating rapid resolution of the initial aphasic syndrome. On the basis of further neuropsychological testing, access to lexical/semantic representations was found to be recovered (PPVT-R score: 23/32), and semantic and phonological fluency indices as measured by COWF were within normal range. In contrast, reading fluency was impaired, with regard to both recognition (WRF) and decoding (psWRF). Verbal short-term and working memory deficits were prominent (as indicated by a forward DS of 3 and a backward DS of 3). This finding may explain the low performance on CIG (6/14), given that the latter has a working memory component.

Discussion

We present a case of anti-NMDA-r encephalitis that manifested as abrupt-onset, isolated, and persistent aphasia in an adult. Our patient fulfilled the recently proposed criteria for definite autoimmune encephalitis and more specifically for definite anti-NMDA-r encephalitis (Graus et al., 2016).

To our knowledge, this is the first report of such a presentation. A similar case has been described in a 4-year-old child by Deiva et al. (2014), who had fever at disease onset, followed by partial seizures which responded to antiepileptic treatment. Non-fluent aphasia then followed, which resolved after rituximab administration. Furthermore, Finke et al. (2012) described a patient with NMDA-r encephalitis who presented with recurrent episodes of aphasia. These episodes however had concomitant headache, further neurological deficits (hemianopia and hemiparesis), and CSF lymphocytosis, mimicking the HaNDL syndrome.

The course of our patient's disease is strikingly atypical. Anti-NMDA-r encephalitis is a rather rapidly progressive disease, presenting most commonly with behavioral problems, movement disorders, or epilepsy, with the rapid admixture of further symptoms such as aphasia, cognitive decline, memory deficits, loss of consciousness, and dysautonomia if left untreated. In the largest described cohort as of yet, Titulaer et al. (2013) concluded that about 90% of their patients had at least four symptoms by the fourth week of disease onset, and only 1% had remained with one symptom. Although aphasia is one of the cardinal manifestations of anti-NMDA-r encephalitis, its isolated presence for a 6-month period is highly uncommon.

Adding to the atypical presentation of our patient is the normal MRI and CSF analysis throughout the disease course. MRI is positive in 33% and CSF analysis (with either pleocytosis or elevated CSF protein) in 80% of patients with anti-NMDA-r encephalitis. A possible explanation is that the CSF analysis was performed 6 months after disease onset. However, she exhibited rather typical EEG abnormalities.

The normal HMPAO-SPECT in our patient suggests that no hypo- or hyperperfusion was present at the time of the examination. Our finding is in agreement with a single report (Llorens et al., 2010). They reported multiple focal areas of increased uptake in the striatum and frontal lobes at presentation in the HMPAO-SPECT of a 14-year patient with anti-NMDA-r encephalitis presenting with neuropsychiatric symptoms, movement disorders, and dysautonomia. A repeat HMPAO-SPECT after recovery of their patient following IVIG administration was normal. It is plausible that anti-NMDA-r encephalitis causes hyperperfusion during the acute phase of the disease and perfusion normalizes with symptom improvement. Further studies are required to elucidate this matter.

A theoretical concern is the possibility of a false-positive NMDA-r antibody test. However, the presence of the anti-NMDA-r antibodies both in the serum and in the CSF measured by cell based assays is considered nearly pathogenic in the literature. A recent study found 100% specificity for the combined immunohistochemistry and CBA with fixed cell-based NMDA-r antibody test (Gresa-Arribas et al., 2014). Other studies also exhibited extremely low false-positive NMDA-r antibody test results, ranging from 0.4% to 3% (Hammer et al., 2013; Viaccoz et al., 2014).

The atypical presentation raises the possibility of the coexistence of another as of yet unknown antibody, which is actually pathogenic for the encephalitis. The presence of the anti-NMDA-r antibodies could represent an epiphenomenon of an immunologic response targeted against another antibody. However, the rapid and significant improvement of our patient, indicated by both clinical and neuropsychological examination, after IV cortisone infusion and plasmapheresis,

is indicative of an immune-based underlying mechanism. A decrease in NMDA-r antibody titers, especially after treatment and clinical improvement, would strengthen the pathogenic role of the antibodies (Gresa-Arribas et al., 2014). However, titer determination was not available and a repeat lumbar puncture to reevaluate the antibody titer was not performed.

Conclusion

Anti-NMDA-r encephalitis is an entity with a rapidly expanding phenotype. To the best of our knowledge, the present study is the first description of such an oligosymptomatic, nonprogressive disease course due to anti-NMDA-r encephalitis. The importance of our report lies in the broadening of the clinical spectrum that could encompass isolated focal deficits, with a fluctuating or stable clinical course. Considering testing for autoimmune encephalitis in patients with measurable, focal neurologic deficits in the absence of an underlying structural lesion seems to be reasonable. These findings remain to be proven by further such reports.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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