Clinical commentary

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A case of anti-NMDA receptor encephalitis revealed by insular epilepsy

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ABSTRACT – Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune disorder of the central nervous system that typically manifests predominantly as a psychiatric disorder. However, other manifestations such as epileptic seizures, abnormal movements, and memory or language complications are not unusual. Here, we report the case of a young man who presented with a new-onset epilepsy, with ictal semiology suggestive of insular involvement; this hypothesis was supported by a PET-CT study. Anti-NMDAR antibodies were found in the CSF, confirming the diagnosis of anti-NMDAR encephalitis. A review of the literature reveals that epilepsy can be the first manifestation of NMDAR encephalitis, with a clear male predominance. Despite its rarity, neurologists should consider this diagnosis for any young patient developing a new-onset epilepsy with temporal or insular features, particularly if the patient is male. Other cognitive or behavioural signs, even very subtle, should also prompt diagnosis.

Key words: encephalitis, NMDA receptor antibodies, insula, focal epilepsy

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an immune-mediated inflammatory disorder involving the central nervous system that was first described in 2007 (Dalmau *et al*., 2007). The typical clinical presentation includes, after a prodromal flu-like phase (Bayreuther *et al*., 2009), psychosis with delusions and hallucinations, behavioural disorders, amnesia, quickly evolving aphasia, epilepsy, dysautonomia, and progressive decrease of consciousness (Cooray *et al*., 2015; Hegen *et al*., 2016). Abnormal movements are another frequent manifestation, especially dyskinesia involving the orofacial area and tongue, as well as writhing movements of the limbs, that may be more obvious during the comatose phase (Cooray *et al*., 2015; Lancaster, 2016).

NMDAR encephalitis is more frequent in women and can be paraneoplastic in approximately 50% of cases, mainly associated with ovarian teratoma (Dalmau *et al*., 2011). It can also occur as a relapse after herpetic encephalitis (Graus *et al*., 2016).

Paraclinical investigations, such as brain MRI, F18-FDG-PET, and EEG, may contribute to establishing the diagnosis, but do not provide formal evidence. Brain MRI is normal in 50 to 90% of the patients (Hegen *et al*., 2016) or shows very discrete

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abnormalities, not correlated to the length or the severity of the affection (Novy *et al.*, 2016). Regarding F18-FDG-PET, an increased glucose uptake has been observed in frontotemporal regions, cerebellum, brainstem, thalamus, and basal ganglia (Hegen *et al.*, 2016; Novy *et al.*, 2016). A few studies also highlighted a specific pattern of hypermetabolism in the anterior frontotemporal areas, contrasting with relative posterior hypometabolism (Leypoldt *et al.*, 2012; Novy *et al.*, 2016).

A clinical diagnosis should be confirmed by the presence of antibodies directed against the NR1 subunit of the NMDA receptor in the cerebrospinal fluid (CSF); this test appears to be less specific when serum is used (Graus *et al.*, 2016; Kreye *et al.*, 2016).

In this study, we focus on epilepsy as an unusual early manifestation of NMDAR encephalitis. We report a case with an interesting and rare ictal semiology revealing the disease.

Case study

A 26-year-old, right-handed male patient, with a past history of autoimmune hepatitis and haemorrhagic ulcerative colitis, was admitted for a first epileptic seizure. The seizure occurred after several weeks of recurrent hemicranial pulsatile headaches with photophobia, phonophobia, and nausea. Several febrile peaks had been noted during the previous month. The patient also reported a bad taste that had started at the same time, and a tinnitus that was compared to the sound of flowing water by the patient, which was occurring almost constantly at the time of consultation. The seizure that brought him to the hospital started with a painful numbness of the left arm, naming difficulties, and drooling. Shortly after, the patient yelled, lost consciousness, and fell on the ground. No abnormal movement was reported. The postictal phase showed a slow recovery with a prolonged reduction of fluency. Neurological examination during hospitalization, brain MRI, and EEG, were normal. The patient was discharged with an appointment for a 24-hour EEG.

During the following days, he developed difficulties in reading or remembering his friends' names. Three days later, in the morning, the patient felt very anxious due to the recurrence of a seizure that started with pain in the left arm, extending quickly to the left leg. This was followed by a state of confusion (he was unable to recognize his wife), as well as marked verbal perseverations and paraphasias. The patient then developed a tonic posture with a diffuse fine tremor, but neither clear dyskinesia nor impairment of awareness. The seizure lasted approximatively 20 minutes. The neurological examination was unremarkable, except for the presence of left V1 dysesthesias, triggered by tactile stimulation. The 24-hour video-EEG monitoring revealed an interictal epileptiform activity characterized by generalized slow theta and delta waves, sometimes associated with a spike morphology, appearing on a preserved background activity. Three seizures were reported by the patient, but only one led to an ictal discharge that was located on the left temporal region with late contralateral hemispheric propagation (*figure 1*). Clinically, this seizure presented as a somatosensitive and painful phase involving the left arm and, to a lesser extent, the right arm.

Based on CSF analysis, 104 white blood cells/µl (84% lymphocytes) and two specific oligoclonal IgG bands were identified in the CSF. Herpes virus PCR was negative. Anti-NMDAR antibodies were found in the CSF, confirming the diagnosis of anti-NMDAR encephalitis (test performed in Saint-Luc University Hospital, Brussels, using a validated recombinant immunofluorescence assay [Wandinger *et al.*, 2009]). Brain PET-CT highlighted a hypermetabolism of the left insular cortex (*figure 2*), which was likely to be due to the encephalitis itself. Indeed, at the time PET-CT was obtained, epilepsy was under control, as confirmed by further video-EEG monitoring.

Immunomodulatory treatment was promptly started, including five days of high-dosage IV corticosteroids (1 g methylprednisolone/day), followed by oral methylprednisolone and eight plasma exchange sessions. Epilepsy was controlled with levetiracetam (1,500 mg/day) and later replaced by valproic acid to improve tolerance.

The evolution was marked by an initial deterioration of language (reduction in speech output and semantic paraphasias), as well as memory deficits (predominantly regarding short and long-term verbal memory). We noted some dysautonomic manifestations, such as persistent tachycardia. Dysthymia was especially remarkable in this patient; he first showed a euphoric behaviour, but progressively developed paranoid and delirious ideas, associated with major anxiety, requiring neuroleptic medication. The patient then improved slowly. CSF analysis, one week after treatment initiation, showed 25 white blood cells/µl. A second brain MRI scan remained normal. CSF analysis was normalized at discharge one month later. The patient left the hospital with a slow tapering scheme of corticoids, until termination after eight weeks.

Four weeks after discharge, the patient was doing much better, however, he described tension headaches, insomnia, and a persistent reduction in speech output. There was no recurrence of seizure. The neuropsychological examination performed at that time confirmed decreased lexical access, and revealed a weakness of short-term visuospatial and verbal memory.

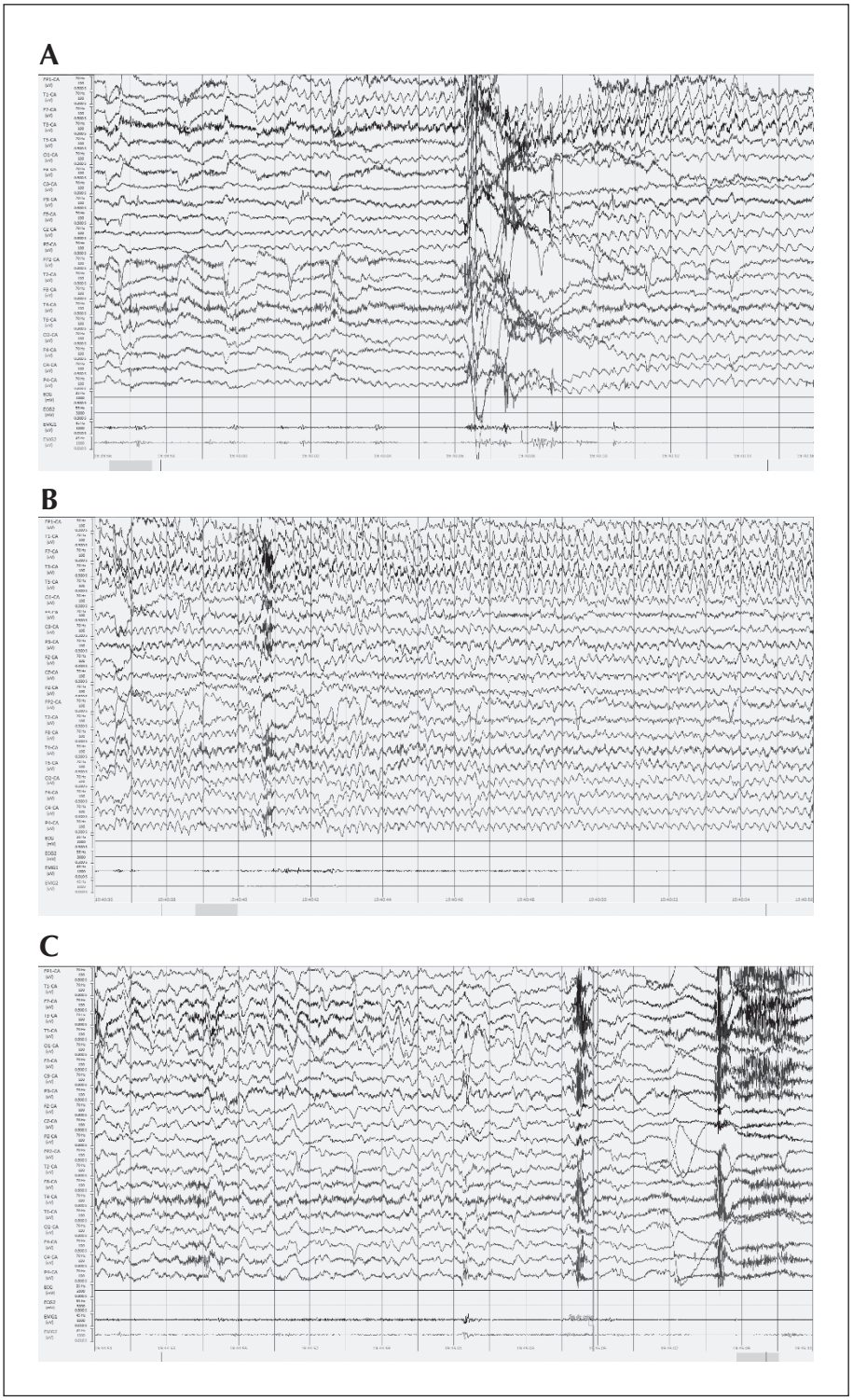

Figure 1. Three non-contiguous epochs of the ictal EEG pattern (longitudinal referential montage [common average]; 20 seconds/page; 70-Hz filter; 75 μV/cm). (A) Rhythmic delta (3-Hz) and theta activity (4-5-Hz) appearing simultaneously in left frontotemporal derivations (Fp1, F7, T1). (B) Temporal and spatial recruitment of the ictal discharge, presenting as sharp rhythmic temporal theta waves diffusing to the contralateral hemisphere. (C) Theta and delta waves becoming less rhythmic up to the end of the discharge.

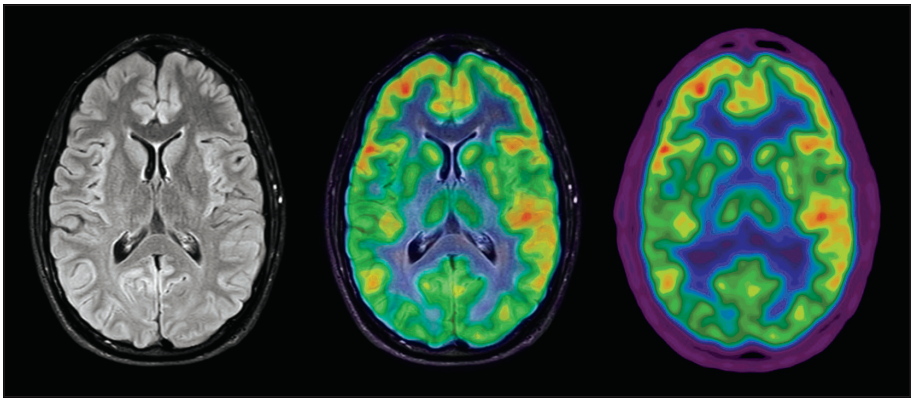

Figure 2. Brain F18-FDG PET-CT (coregistered with MRI), showing significant relative hypermetabolism of the left insular cortex, compared to the contralateral insula, with a globally preserved cortical signal.

Discussion

Our case report of a young man with epilepsy as a presenting symptom of NMDAR encephalitis is consistent with the literature. Several semiological features are remarkable and suggest an insular ictal onset. The unpleasant sensation was distributed to a large cutaneous area, without clear somatotopia or Jacksonian march, suggesting the involvement of the posterior and superior part of the insula. The fact that somatosensitive symptoms were ipsilateral to ictal discharge (and to FDG-PET hypermetabolism) further supports this hypothesis. Drooling suggests anterior insulo-opercular involvement. Finally, prolonged initial symptoms without impairment of awareness are also compatible with insular onset. Indeed, all these semiological features were described as orientating towards the insula in the study of Isnard *et al*. (2004). The aphasia that develops later suggests an implication of the dominant hemisphere in this right-handed patient. To our knowledge, this is the first case of a well-established insular epilepsy revealing NMDAR encephalitis.

Seizures may be part of the initial presenting symptoms of NMDAR encephalitis. NMDA receptors are ligand-gated cation channels, composed of one NR1 subunit that binds to glycine and one NR2 (A, B, C, or D) subunit that has affinity for glutamate. As a result, there are different types of receptors depending on the combination of subunits. Hyperactivity of NMDA receptors that cause excitotoxicity is a proposed mechanism to explain the occurrence of epilepsy in NMDAR encephalitis (Dalmau *et al*., 2008). In the study of Dalmau *et al*., it was noticed that 76 of 100 patients with NMDAR encephalitis presented with epileptic seizures during the first three weeks of symptoms. Among them, 46/76 were generalized tonic-clonic seizures and 10/76 were focal secondary generalized seizures. Status epilepticus was reported in only 6%, without further precision. Titulaer and Dalmau (2014) reported that adult men presented more frequently (27%) with seizures than adult women (11%). Female patients initially presented abnormal behaviour and psychiatric symptoms. The inaugural seizures in men were frequently focal (5/8), while in women they were usually generalized. The authors suggested hormonal factors and selection bias for the different sex-related symptom presentations (Titulaer and Dalmau, 2014; Kim *et al*., 2015).

EEG has previously been shown to reveal generalized or fronto-temporal delta or theta slow waves in 77% of patients, and epileptic activity in 23% of patients (Dalmau *et al*., 2008; Kim *et al*., 2015). A particular pattern of "extreme delta brush" was also associated with NMDAR encephalitis (Schmitt *et al*., 2012; Veciana *et al*., 2015). A previous study highlighted the fact that rhythmic delta waves on scalp EEG were not associated with cyclic spike or spike-wave activity on invasive EEG. A crucial differential diagnosis should be assessed between EEG slowing linked to encephalitis and a form of non-convulsive status epilepticus in NMDAR encephalitis. Moreover, in the event of rhythmic delta activity persisting in prolonged NMDAR encephalitis, despite anaesthetic-induced burst suppression and immune therapy, the use of depth electrodes has been proposed to formally distinguish this from focal status epilepticus. Finally, brain FDG PET hypermetabolism in mesiotemporal structures has been reported in autoimmune limbic encephalitis and has been correlated with focal slow activity on surface EEG in NMDAR encephalitis (Probasco *et al*., 2014).

In conclusion, the diagnosis of autoimmune encephalitis, including anti-NMDAR encephalitis, should be considered for any young patient developing a new-onset epilepsy, with temporal or insular features, especially if cognitive or behavioural signs, even very subtle, are present. A history of systemic autoimmune disorder should also raise suspicion of an inflammatory cause of new-onset epilepsy. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) What are the main semiological characteristics of insular epilepsy?

(2) What is the difference in clinical presentation between men and women suffering from NMDAR encephalitis?

(3) What tests should be performed to confirm the diagnosis of NMDAR encephalitis?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".