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Opercular myoclonic-anarthric status epilepticus due to glutamic acid decarboxylase antibody-associated encephalitis

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ABSTRACT – We report a patient who was diagnosed with opercular myoclonic-anarthric status epilepticus and found to have glutamic acid decarboxylase antibody (GADA)-associated encephalitis, a previously unrecognised aetiology of this condition. The patient was a 23-year-old female admitted for investigation of focal myoclonic status epilepticus in the right side of the face and glossopharyngeal area. Intravenous corticosteroid was administered and improvement was observed in seizure activity and overall general health. A video sequence of opercular myoclonia is included. Due to the presence of inflammatory elements based on brain MRI and CSF studies, a decision to investigate autoimmune encephalitis was undertaken. Anti-GAD65 radioimmunoassay was markedly positive. This case study highlights the need for awareness of the clinical presentation of GADA-associated encephalitis. [*Published with video sequences*]

Key words: glutamic acid decarboxylase, antibody, encephalitis, status epilepticus, opercular myoclonia

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In the last few years, awareness of autoimmune encephalitis has increased, and in particular, voltage-gated potassium channel (VGKC), N-methyl-D-aspartate receptor (NMDAR) and glutamic acid decarboxylase (GAD) antibodies have been reported. Typically, the clinical picture associated with these conditions is similar to that of limbic encephalitis, of mainly complex partial seizures and psychiatric comorbidities. We present a female found to have GAD antibody (GADA)-associated encephalitis, presenting with opercular myoclonic-anarthric status epilepticus (OMASE). Of note, this was an adult patient with no history of diabetes. Brain MRI and seizure semiology are presented.

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Case report

A 23-year-old female was admitted to the epilepsy monitoring unit for evaluation of refractory status epilepticus. The patient was bedridden with a naso-enteral feeding tube. She was referred from an intensive care unit in another city, as local treatment protocols for status epilepticus were ineffective. On arrival, there was continuous twitching of the right side of her face. Eventually, twitching of the left side of the face was observed, but was clearly much less frequent. She was torporous and presented with significant laborious breathing, no gag reflex, and diffuse hyperreflexia. No hemiparesis was found. She presented with clinical status epilepticus for three months, and was recovering from nosocomial pneumonia. Her speech was slow and dysarthric.

Her problems started four years before admission. As a previously healthy girl, she had an unprovoked generalised tonic-clonic seizure during sleep. After this event, treatment with carbamazepine was started. Four months later, daily partial complex seizures initiated and persisted, in spite of increasing doses of carbamazepine. Two years later, she became pregnant. Even though there was no increase in seizure frequency, she developed post-partum depression, with rejection of the baby. Three months before admission, after a generalised tonic-clonic seizure, she developed continuous twitching in the right side of her face. She was admitted to a local institution for treatment of focal status epilepticus, reportedly with induced coma, but no improvement was observed. There was no family history of epilepsy. She was referred for evaluation and treatment.

Previous investigations revealed normal CSF results and progressive lesions on brain MRI. The first scan obtained eight months before admission demonstrated increased T2 signal changes in the left hippocampal formation associated with decreased volume and signs were interpreted as hippocampal sclerosis. A follow-up study performed one month before admission demonstrated asymmetric bilateral hippocampal sclerosis, more marked on the right side.

During long-term monitoring in the epilepsy unit, EEG was obscured by muscle artefacts. The diagnosis of OMASE was suggested by continuous and irregular twitching of the right side of the lower face involving the tongue and dysphagia/dysarthria, which was not associated with dysmetria. There was no propagation of muscle twitching to other segments of the body and the patient could easily follow commands, even though she appeared to be somewhat somnolent. She demonstrated clear difficulty in pronouncing words, but no weakness in the right arm (the patient was dextrous). Infrequent twitching of the left side of the face was noted.

During the night, when the twitching was less intense, left and right temporal and left frontal sharp waves were observed. Continuous, 4-5-Hz focal myoclonic seizures of the right side of her face and tongue were observed (see *video sequence*). There was no ictal pattern on scalp EEG, which was, for most of the time, obscured by movement artefact.

After two days of monitoring, CSF was obtained for analysis. There was a high IgG index with suspicion of inflammatory disease. Immunological investigation excluded lupus. Repeat brain MRI revealed bilateral hippocampal sclerosis and multiple lesions with hyperintensity on T2/FLAIR sequences, involving the temporal and parietal lobes in both hemispheres, markedly in the left perisylvian region (*figure 1*).

Due to the supposed inflammatory nature of the disease, a workup for autoimmune antibodies was conducted, revealing 7,990 U/mL serum anti-GAD65 antibodies (normal range: <0.90 U/mL). Tests for other autoantibodies were negative. Antibody testing for HIV in serum was negative. Further immunological investigation excluded lupus and vasculitis, primarily based on negative tests for ACA and ANA antibodies and normal inflammatory markers such as VHS and C-reactive protein.

The patient was placed on a five-day regimen of intravenous methylprednisolone at 1 g/day. She regained independence, but continued to present with facial myoclonia, even though it was much improved. She had no history of diabetes and her glycaemic levels remained normal, except for brief periods during the corticosteroid treatment. Finally, no evidence of ovarian teratoma was found.

Discussion

Here, we report a patient with OMASE. Due to the multitude of T2/FLAIR hyperintense lesions on brain MRI, the decision to investigate probable encephalitis was taken. Rasmussen's encephalitis was not considered due to the presence of bilateral lesions and the absence of progressive brain atrophy and hemiparesis. An increased CSF IgG index raised the suspicion of autoimmune encephalitis and a diagnosis of GADA-associated encephalitis was made.

Anti-GAD autoantibodies are increasingly being recognised as an aetiology for encephalitis. GAD is the rate-limiting enzyme for the synthesis of γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the CNS (Liimatainen *et al*., 2009). Most reports associate anti-GAD autoantibodies with limbic encephalitis (Olson *et al*., 2002; Saiz *et al*., 2008; Korff *et al*., 2011; Mirabelli-Badenier *et al*., 2012) or temporal lobe epilepsy (Stagg *et al*., 2010). However no complex partial seizures were recorded in our patient during

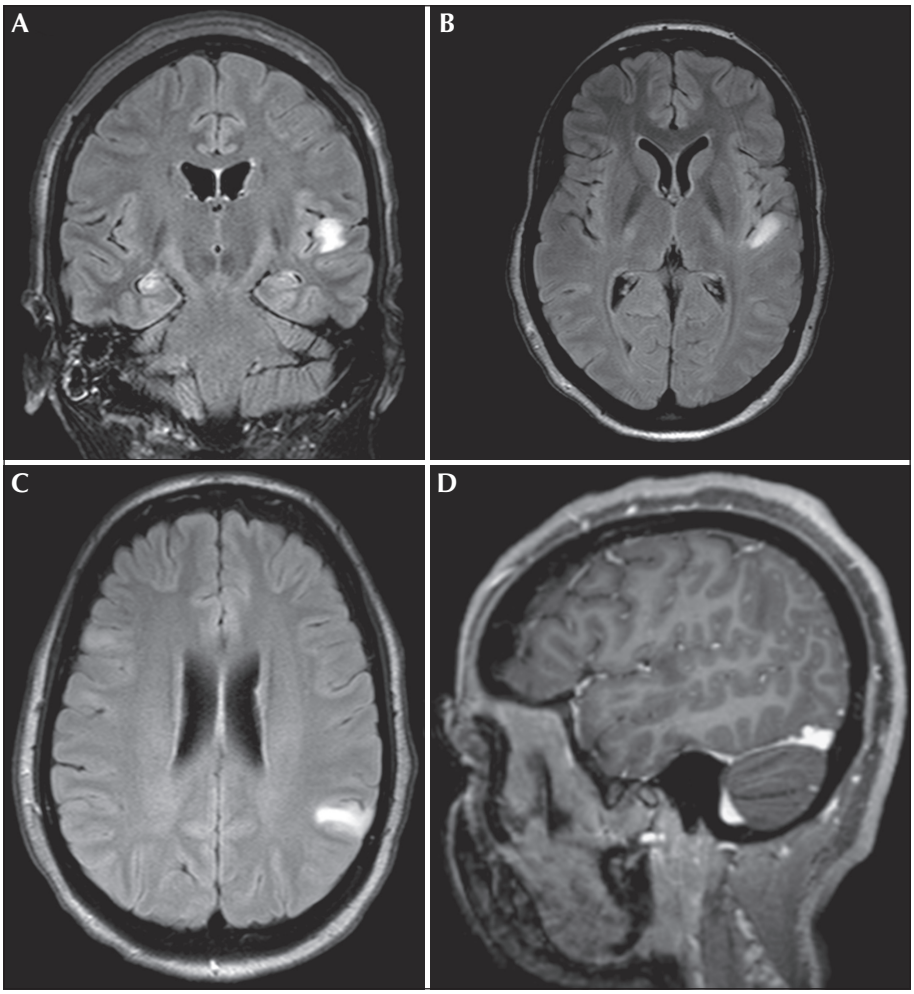

Figure 1. Magnetic resonance imaging shows multifocal brain lesions.
A) Hyperintense lesion in the left superior temporal gyrus (FLAIR sequence); B) the same lesion in an axial view (FLAIR sequence);
C) hypertense lesions in the left parietal operculum and the right frontal lobe (FLAIR sequence); and
D) hypointense lesions in the left parietal operculum and superior temporal gyrus (T1-weighted sequence).

long-term video-EEG monitoring. Moreover, most patients had diabetes mellitus type I, which was not evident in our patient.

Treatment consists mainly of immunotherapy using glucocorticoids, plasmapheresis, intravenous immunoglobulin, and cyclophosphamide (Olson *et al.*, 2002; Saiz *et al.*, 2008; Kanter *et al.*, 2008; Korff *et al.*, 2011) with variable results. In our patient, methylprednisolone IV significantly improved the opercular syndrome during hospitalisation. No further treatment was offered, and the patient regained independence at home, even though minor myoclonic seizures persisted in the right side of her lower face.

The few reported cases of OMASE in the literature (Thomas *et al.*, 1995) are associated with stroke or tumour. Patients presented with facial twitching and fluctuating cortical dysphasia which improved with treatment for status epilepticus. The myoclonia also involved the tongue and palate. As in our case, the EEG may not be suggestive of cortical ictal epileptic activity (*figure 2*), which can be seen in 80% of patients with simple partial seizures (Devinsky *et al.*, 1988). The presence of bilateral motor expression in a strictly unilateral epileptiform discharge was attributed to the bilateral projections of the inferior cortico-nuclear pathways. This presentation of non-convulsive status epilepticus was recognised in a recent review (Sutter and Kaplan, 2012).

An adult patient presenting with pseudobulbar syndrome and anarthria was previously diagnosed with Foix-Chavany-Marie opercular syndrome (FCMS) due to non-convulsive status epilepticus (Steiner-Birmanns *et al.*, 2006), possibly caused by oxycodone use. A third report related FCMS with chronic herpes simplex encephalitis (Sasaguri *et al.*, 2002), and extensive bilateral damage was observed on brain MRI, including atrophy. Neither had myoclonia.

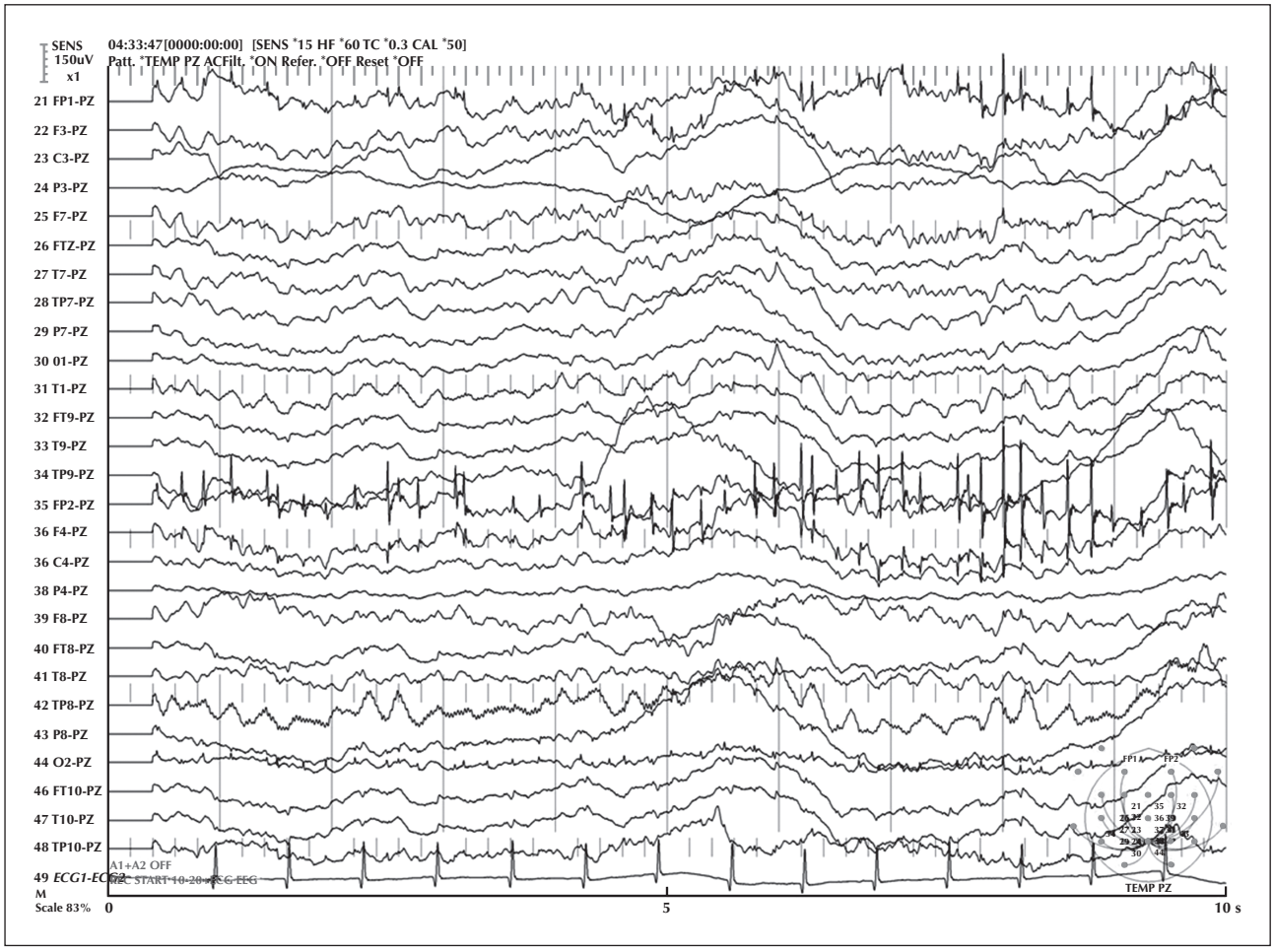

Figure 2. Sleep EEG tracing (NREM) depicting muscle artefact (myoclonia) in the right frontal region. No EEG ictal activity is observed.

In conclusion, OMASE can occur when the inferior rolandic areas are involved in epileptogenic lesions associated with epilepsia partialis continua, such as GADA-associated encephalitis.

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The authors have no conflicts of interests to declare.

Legends for video sequences

Myoclonia in the right side of the face during sleep

Key words for video research on www.epilepticdisorders.com

Syndrome: Epilepsia partialis continua
Etiology: encephalitis
Phenomenology:
status epilepticus (non convulsive);
myoclonic seizure
Localization: Operculum (left)

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