Clinical commentary

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Surgical control of limbic encephalitis associated with LGI1 antibodies

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ABSTRACT – Limbic encephalitis with LGI1 antibodies may cause drug-resistant temporal lobe epilepsy. We report a case of a young man with progressive drug-resistant focal epilepsy, hyperhidrosis, and memory impairment associated with a left mesial temporal lesion. Epilepsy surgery was performed with the provisional diagnosis of cortical dysplasia or tumour. A neuropathological study following amygdalohippocampectomy revealed limbic encephalitis and LGI1 antibodies were identified in the serum. Two and a half years after surgery, the patient remains seizure-free without medication, with normal memory and without hyperhidrosis. Although immunosuppression is the first-line therapy for autoimmune limbic encephalitis, this case suggests that, in selected cases, a lasting response can be achieved with surgery.

Key words: autoimmune epilepsy, hyperhidrosis, pilomotor, limbic encephalitis, LGI1 antibodies, voltage-gated potassium channel (VGKC), epilepsy surgery

Leucine-rich glioma inactivated 1 (LGI1) antibodies are, together with contactin-associated protein-like 2 (CASPR2) and contactin-2 antibodies, part of the voltage-gated potassium channel (VGKC) antibody complex associated with immune disorders of the nervous system (Irani *et al*., 2010). They are the most frequently identified antibodies in patients with autoimmune limbic encephalitis (LE) and temporal lobe epilepsy (TLE) (Irani *et al*., 2011).

Limbic encephalitis typically presents with acute or subacute onset of epilepsy, neuropsychiatric symptoms, and loss of episodic memory. MRI usually shows bilateral or unilateral mesial temporal lobe hyperintensity (Irani *et al*., 2010).

Contrasting with other immune disorders of the nervous system, LGI1

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antibodies are rarely associated with paraneoplastic syndromes and immunosuppression is the first-line treatment with an overall good response (Lai *et al.*, 2010; Irani *et al.*, 2010).

Herein, we describe a case of autoimmune epilepsy in a patient with symptomatic TLE, whose lesionectomy resulted in epilepsy control. Following surgery, a neuropathological diagnosis of LE was made along with the identification of LGI1 antibodies.

Case study

A 19-year-old, right-handed male developed seizures after an ankle surgery due to a traumatic bone fracture. The seizures were described as pilomotor, beginning in the left hand and spreading to both arms and to the face bilaterally, followed by intense skin pallor of these regions. They occurred almost every day and lasted 5 to 10 seconds.

Over time, he developed other types of focal seizures: dystonic posture of the right hand with right eye deviation, *déjà vu* phenomena, clonic seizures of the right hemiface, and aphasic seizures. Concomitantly, he reported some problems associated with memory. Six months later, severe hyperhidrosis was noted but no other autonomic symptoms, sleep changes or psychiatric symptoms were reported.

Ten months post-onset, he experienced several secondary generalised tonic-clonic seizures and was admitted to our department. His medical history revealed hepatitis A and post-infectious glomerulonephritis. There was no history of febrile seizures, head trauma or infection. The family history was significant for epilepsy (an uncle with transient, unspecified epilepsy) and systemic tumours (lung, colon, and bladder). The neurological examination was unremarkable.

The patient was initially treated with valproic acid at 2,000 mg/day but on the fifth day of admission, carbamazepine, titrated to 400 mg/day, was added due to the lack of focal seizure control.

Two EEGs showed left frontotemporal electrographic seizures. Brain MRI (*figure 1A-B*) disclosed a slight diffuse hyperintensity in T2 and FLAIR-weighted images along the left medial temporal lobe (amygdala, uncus, and hippocampus), accompanied by expansion of these structures, mainly in the amygdaloid complex, without signal change in T1 or contrast enhancement. Low-grade glioma or a dysplastic lesion was considered.

Focal and secondary generalised tonic-clonic seizures recurred during the following months and

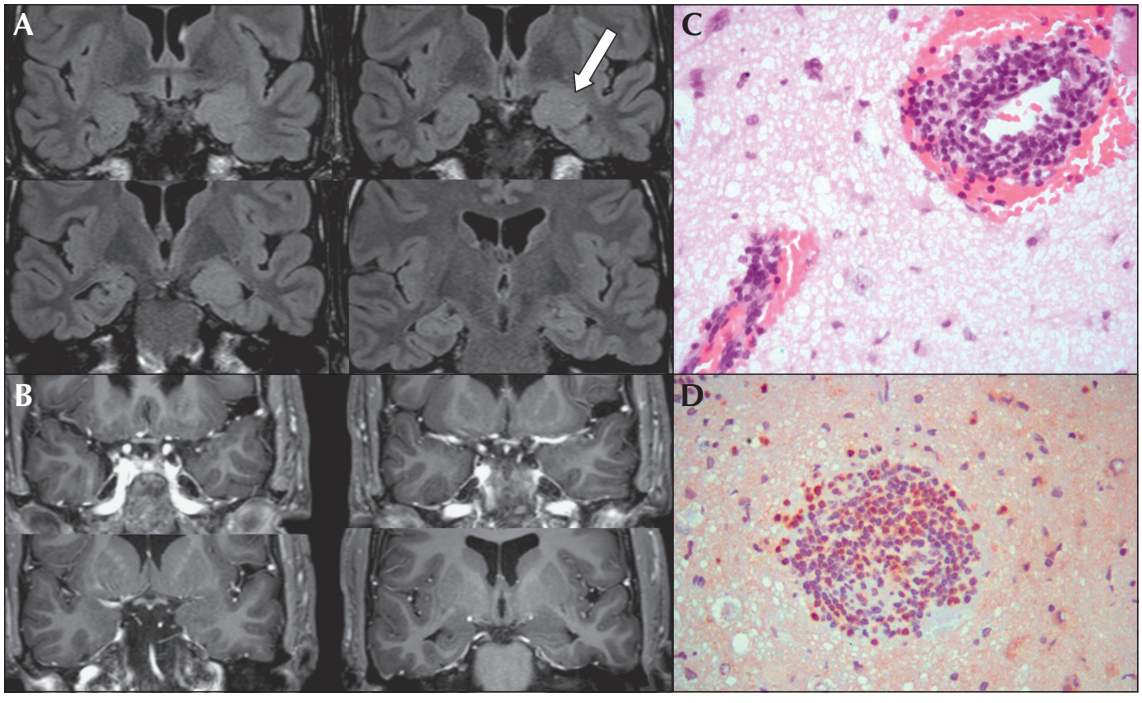

Figure 1. (A) 3T MRI coronal FLAIR showing slight diffuse hyperintensity and expansion mainly affecting the amygdaloid complex (white arrow) and also the hippocampus (B) 3T MRI T1 gadolinium image showing no obvious signal change or contrast enhancement of the lesions (C) Haematoxylin and eosin staining (x40) showing perivascular inflammatory infiltrate composed of lymphocytic mature elements (original magnification) (D) CD3 immunostaining (x40) showing perivascular lymphocytic infiltration consisting mainly of T cells.

carbamazepine was switched to lamotrigine (titrated to 250 mg/day) with improvement of generalised seizures only.

Video-EEG monitoring recorded 46 focal simple seizures with autonomic symptoms and for 19, it was possible to identify a left frontotemporal and temporal inferior onset.

Given the fact that epilepsy was refractory to pharmacological treatment and the lesion aetiology was uncertain, the patient agreed to undertake surgery. A left anterior amygdalohippocampectomy (AHC) was performed 15 months after the onset of epilepsy. The neuropathological examination (*figure 1C-D*) showed perivascular polyclonal (predominantly T-cells; CD3 immunoreactive) lymphocytic infiltration, intense astrocytic gliosis, and scarce microglial activation, in accordance with LE.

Due to this new diagnosis, his medical history was carefully reviewed but no other symptoms suggesting autoimmune LE, associated infection, or systemic tumour, were found. A second MRI scan showed only postsurgical changes and cytochemical evaluation of CSF was unremarkable. The workup for systemic autoimmune disease and neoplasm was negative. Hyponatraemia was not found. A panel of serum and CSF antineuronal antibodies (indirect fluorescent antibody test) disclosed LGI1 antibodies in the serum (1/320) and a final diagnostic test for LE associated with LGI1 antibodies was performed.

A single seizure occurred in the immediate postoperation period. The patient decided to stop medication a few months later, remaining seizure-free two and half years after surgery and without hyperhidrosis.

Cognitive assessments were performed five and two months before, and 22 months after surgery. The first evaluation disclosed age- and education-adjusted normal scores in tests of verbal memory (immediate and delayed story recall) but a low score (<-2 sd) in visual memory and working memory (digit span backwards). Although verbal learning was within normal range (California Verbal Learning Test total [CVLT] recall) (Delis *et al*., 1987), he presented with many perseverations and intrusions. In the second assessment, there was a decline in verbal learning (CVLT total recall: -1.5 sd below mean), visual memory (-2 sd), and divided attention scores. Postsurgical evaluation showed a complete cognitive recovery with a normal performance on tests of verbal memory (story recall), divided attention, and visual memory.

Discussion

We report a young patient with drug-resistant TLE associated with memory loss and hyperhidrosis due to LE associated with LGI1 antibodies, who responded to surgery, remaining seizure-free and without cognitive impairment.

Autoimmune LE should be considered in the differential diagnosis of unexplained subacute TLE in adults (Irani *et al*., 2011). Diagnosis is straightforward when other symptoms of LE are present and when the MRI shows bilateral FLAIR/T2 hyperintensity in the limbic structures. The characterisation of the associated antibodies is a valuable aid for its early and correct identification.

The autoantigen LGI1 was recently shown to be one of the three accessory antigens comprising part of the dendrotoxin-labelled VGKC immunoprecipitate using patient antibodies (Lai *et al*., 2010). It is a neuronal secreted protein, strongly expressed in the hippocampus and is known to interact with two epilepsy-related proteins; the presynaptic ADAM23 and postsynaptic ADAM 22 (Lai *et al*., 2010). The neuropathology of LE is relatively non-specific, consisting of perivascular lymphocytic infiltration, microglia hyperplasia, neuronal loss, and reactive gliosis (Scaravilli *et al*., 1999).

Two series of patients with epilepsy associated with LGI1 antibodies have been previously published (Irani *et al*., 2010; Lai *et al*., 2010). One series with 57 patients included only cases positive for LGI1 antibodies (Irani *et al*., 2010), with a mean age of 60 years (range: 30-80) and a male predominance. Hence, the present case is the youngest reported patient with LE associated with LGI1 antibodies. In the reported series, LE and rarely Morvan's disease or isolated epilepsy were the forms of presentation (Irani *et al*., 2010; Lai *et al*., 2010). Acute or subacute onset of mediotemporal lobe seizures, episodic memory loss, confusion, agitation, and other psychiatric features were part of the typical clinical picture. Hyponatraemia and sleep disorders were also common. Unilateral or bilateral medial temporal lobe signal changes on MRI were seen in up to 82% of the cases. An associated tumour was identified in 0-11% of the cases. In both series, the large majority of the patients were treated with different immunomodulatory therapies. Most of them experienced a good recovery but some were left with residual memory deficits, with no or limited impact on daily living. Relapse was reported in a few cases. Faciobrachial dystonic seizures, consisting of brief dystonic limb movements of the face and arms, have also been associated with these antibodies (Vincent *et al*., 2011). Seizures usually have a poor response to antiepileptic drugs but have a good response to immunotherapy (Vincent *et al*., 2011). Clinical improvement is usually associated with a fall in the serum antibody titre (Bien and Elger, 2007), although in some cases it persists or reappears in patients with slow improvement or relapse (Vincent *et al*., 2011). The most frequent MRI evolution in LE is a progressive decrease in

hippocampal swelling over several months with persistence of hyperintense T2/FLAIR signal and later development of hippocampal atrophy, indistinguishable from hippocampal sclerosis (Bien and Elger, 2007). Lesions of the mesial aspect of the temporal lobe are usually resected by selective or anterior AHC, and high rates of seizure control are reached and maintained for years (Pimentel *et al*., 2010). The efficacy of temporal lobe surgery has been shown in a wide range of pathologies (Tassi *et al*., 2009), however, to the best of our knowledge, it has only been performed in one patient with LE (Muehlebner *et al*., 2010). A left, two-third anterior temporal lobectomy was performed in a 15-year-old girl with drug-resistant epilepsy, one and a half years after disease onset, resulting in epilepsy control with one antiepileptic drug. This case contrasts with ours because there was evidence, both on MRI (performed nine months after disease onset) and neuropathological examination, that evolution to hippocampal atrophy had occurred. Although we only performed one MRI scan (10 months after disease onset and 5 months before surgery), the neuropathological examinations did not show hippocampal sclerosis.

In our patient, seizure control, resolution of hyperhidrosis, and lack of cognitive deterioration, suggest that the progression of LE is, so far, interrupted. Nevertheless, the patient should not be considered to be cured because a recurrence in the contralateral hippocampus may occur. LGI1 antibodies were identified in the serum several weeks after surgery, although the absence of presurgical levels precludes any assurance of improvement or stability of the immune process.

With the limitation of a single case, this report suggests that TLE surgery may help control intractable seizures in cases with unilateral mesial temporal involvement, even for inflammatory pathologies where surgery is most likely to be ineffective.

In conclusion, this case underlines the need to consider the diagnosis of LE, particularly for any case of TLE with sudden onset in adults and drug-resistant epilepsy. In selected cases, surgery could be considered a rescue treatment when immunosuppression is ineffective or not tolerated. □

Disclosure.
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