

A rare case of limbic encephalitis with anti leucine-rich glioma inactivated-1 (LGI1) antibodies

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Abstract

We report a case of limbic encephalitis with LGI1 antibodies and cranial MRI abnormality. A 41-year-old woman who presented with confusional state that had started 1 month ago. Brain magnetic resonance imaging revealed hyperintense signal in right basal ganglia followed by hyperintense signals in left hippocampus and bilateral basal ganglia half a month later. This case expands the spectrum of limbic encephalitis to include LGI1 antibodies and cranial MRI changing process.

INTRODUCTION

Limbic encephalitis (LE) is characterized by a subacute onset of episodic memory impairment, disorientation, agitation, seizures and histological evidence of mesial temporal lobe inflammation. It is usually considered to have a paraneoplastic origin and is associated with specific autoantibodies in various cancers (Didelot *et al.* 2009). The non-paraneoplastic form has similar clinical and neuroradiological presentation. In these cases antibodies usually target voltage-gated potassium channels (VGKC) or glutamic acid decarboxylase and are, therefore, accepted as immunotherapy responsive syndromes. Potassium channel antibodies were reported in two patients with reversible LE for the first time in 2001 (Buckley *et al.* 2001). Since this is a relatively rare condition, there have been very few publications on the clinical findings, treatment and follow-up results in this group of patients (Lai *et al.* 2010; Thieben *et al.* 2004) and the optimum treatment regimen is still unknown. Potassium channel antibodies are now recognized to bind to different components of VGKC complexes such as leucine-rich glioma

inactivated-1 (LGI1) (Lai *et al.* 2010; Irani *et al.* 2010) or contactin-associated protein 2 (Caspr2) (Irani *et al.* 2010) and we will refer to them as VGKC-complex Abs. Herein, we describe a case of LE with anti LGI1 antibodies.

CASE REPORT

A 41-year-old woman was admitted for confusional state and left face grimacing and arm posturing that started 1 month ago. She had fever, vomiting and headache at the onset. Concomitantly, she reported some problems associated with memory. Her past medical history was unremarkable. Physical and neurological examinations were normal apart from confusion, seizure attack and short-term memory deficits. Cranial MR-DWI (magnetic resonance diffusion weighted imaging) revealed hyperintense signal in right basal ganglia (Figure 1A).

Electroencephalography revealed ictal 2 to 4Hz spike-wave activity was noted over the right frontotemporal region. MRS indicated right hyperintense signals as inflammatory process. In our hospital, blood studies including complete

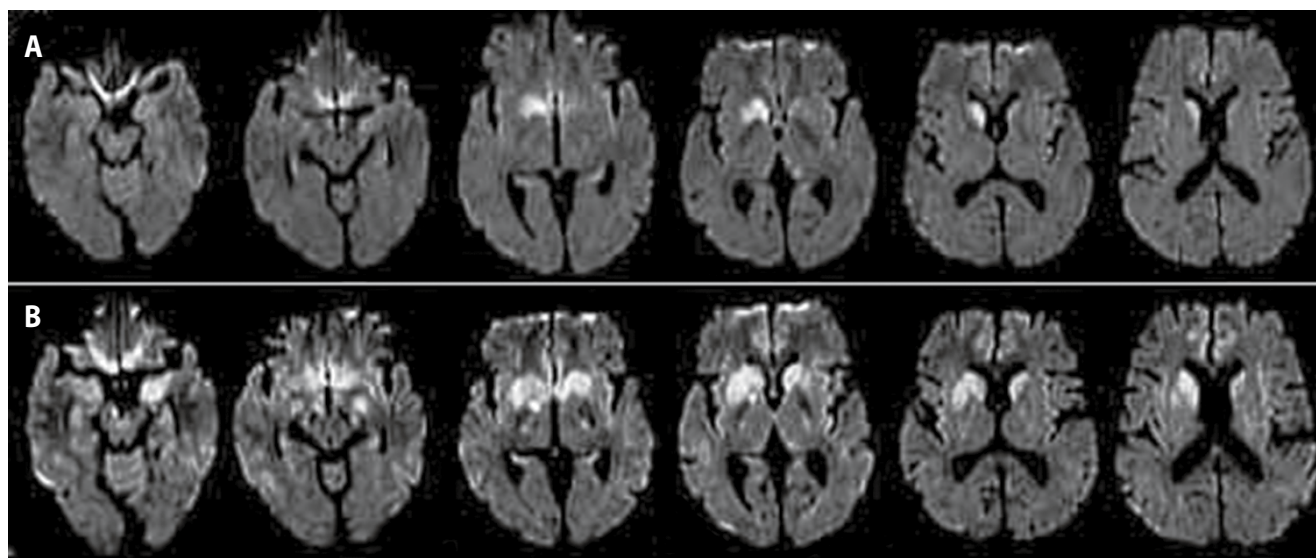


Fig. 1. A: DWI (2013-07-02 top six slices) showed hyperintense signal in right basal ganglia. **B:** DWI (2013-07-17 bottom six slices) showed hyperintense signals in left hippocampus and bilateral basal ganglia.

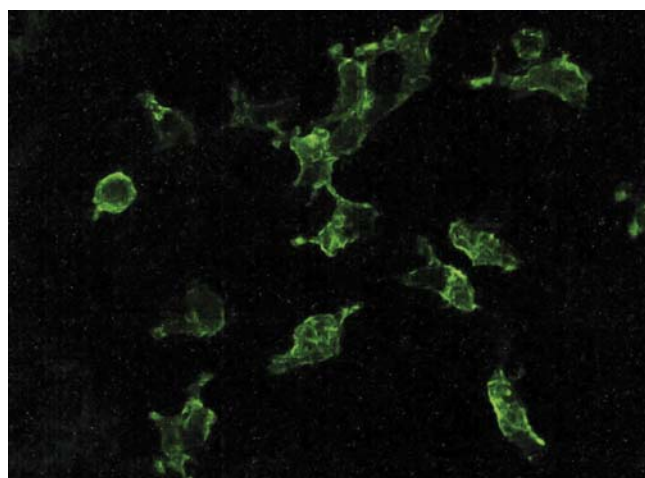


Fig. 2. The patient's serum reacted positively with LGI1 transfected HEK293 cells (indirect fluorescence staining $\times 40$).

blood count, liver and renal function tests, NMDAR-Abs, tumor markers and paraneoplastic antibody analysis (anti-Hu, -Yo, -Ri, -Ma, -CV2) were all normal. Serum electrolyte analysis revealed mild hyponatremia (132 mEq/L). Serum and CSF LGI1 antibodies were positive (Figure 2). At the onset of her complaints she was admitted to another hospital where she was diagnosed with herpes encephalitis and was given acyclovir without any benefit. A second cranial MRI revealed hyperintense signals in left hippocampus and bilateral basal ganglia (Figure 1B). The patient started treatment with 500 mg methylprednisolone intravenous (IV) bolus for 3 days, followed by oral prednisolone (1 mg/kg per day) and IV immunoglobulin (Ig) (0.4 g/(kg·d) over 7 days). Carbamazepine was administered. Dramatic clinical improvement was observed within 1 week. Monthly

IV Ig infusions were continued while oral corticoids were gradually decreased. MRI revealed morphologic improvement. Three months later the patient had no clinical abnormalities. Memory deficits had improved overall, particularly short-term memory.

DISCUSSION

LE was characterized as an inflammatory disorder involving the hippocampi, amygdala, frontobasal and insular regions, with a spectrum of symptoms, most commonly characterized by a subacute progressive impairment of short-term memory, psychiatric features and seizures (Machado *et al.* 2012). While in some cases it appears to exclusively involve limbic regions, it has become clear that several clinical features implicate involvement of areas other than the limbic system. For this reason, LE was also called autoimmune encephalitis (Irani *et al.* 2011). The diagnosis of autoimmune LE is difficult and often delayed. Time between first symptoms and treatment onset usually ranges from 6 months to 9 months (Merchut *et al.* 2010). Diagnosis is made when other symptoms of LE are present and when the MRI shows bilateral hyperintensity in the limbic structures.

Since the early 2000s, many Abs implied in central nervous system autoimmune disorders have been identified (Vincent *et al.* 2011). The characterization of the associated antibodies is a valuable aid for its early and correct identification. LGI1 is a unique human epilepsy-related gene in that it does not encode an ion channel subunit, but is a neuronal secreted protein (Kegel *et al.* 2013). LGI1 antibodies are directed against VGKC and have been recently identified as associated with LE (Lai *et al.* 2010).

The clinical findings and cranial MRI results were compatible with LE in this patient. Prodromal symptoms consisting of fever, headache, nausea and vomiting first led to the erroneous diagnosis of herpes encephalitis. However, failure in response to antiviral treatment, the very symmetrical appearance of mesial temporal lobe involvement and the presence of mild hyponatremia were somewhat atypical, necessitating further investigation for the presence of paraneoplastic or non-paraneoplastic LE. Extensive search for malignancy revealed negative results. On the other hand, the presence of LGI1 autoantibodies in serum and CSF confirmed the diagnosis of non-paraneoplastic LE. She displayed almost complete recovery soon after treatment with IV Ig.

LGI1 related LE (also known as LGI1 antibody associated LE) is characterized by amnesia, behavioral and psychiatric disturbances, seizures, hyponatremia due to SIADH, and in some cases autonomic dysfunction and sleep abnormalities. Age of the patients varies between 30 and 80 (mean 60) years and it seems to have a higher predilection for males (Lai *et al.* 2010). Imaging abnormalities include increased T2W or DWI hyperintensities involving the medial temporal lobes. Cerebrospinal fluid protein may be elevated and there may be lymphocytic pleocytosis in some patients.

There are limited data on optimal treatment of LE with LGI1 (Thieben *et al.* 2004). Although no consensus treatment standard exists, immunotherapy, including high doses of steroids associated with another immunosuppressive agent (for example, IV Ig, plasma exchange, mycophenolate) yields promising results. Earlier diagnosis of this rare disease is important.

In conclusion, recognition of these brief seizures and their association with VGKC-complex/LGI1 Abs should

prompt consideration of immunotherapies because early treatment of the LE syndrome may limit the duration or severity of the illness and the degree of cognitive disability. Recognition of these seizures should offer a window of opportunity for early treatment and possible prevention of permanent disability.

Conflict of interests. None

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