

# Limbic encephalitis with LGI1 antibodies in a 14-year-old boy

M. Schimmel<sup>a,\*</sup>, M.C. Frühwald<sup>a</sup>, C.G. Bien<sup>b,c</sup>

<sup>a</sup> Children's Hospital Augsburg, Section of Neuropediatrics, Klinikum Augsburg, Germany

<sup>b</sup> Epilepsy Centre Bethel, Krankenhaus Mara, Bielefeld, Germany

<sup>c</sup> Laboratory Krone, Bad Salzuflen, Germany

## 1. Introduction

Limbic encephalitis (LE) with antibodies against leucine-rich glioma-inactivated 1 protein (LGI1) is an auto-antibody mediated disorder with characteristic symptoms as faciobrachial dystonic seizures,<sup>4</sup> temporal lobe seizures, dysfunction of memory, and neuropsychiatric symptoms as emotional lability. It has been described in adults so far.<sup>3,6,7</sup> Within the existing series with >10 cases, the youngest patient has been 21 years old.<sup>7</sup>

We present the case of a 14-year-old boy with typical symptoms of limbic encephalitis as dysfunction of memory and detection of LGI1 antibodies.

To the best of our knowledge, this is the youngest patient with this condition described to date.

## 2. Case study

We present the case of a 14-year-old boy with subacutely evolving dysfunction of recent memory. The first signs of memory problems became obvious with therapy of his pre-existing diabetes mellitus. Having been familiar with the insulin injection system, he forgot simple details on how to use it. He became emotionally labile, had suicidal thoughts and developed kleptomania. In the course of the disease, the boy

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\* Corresponding author. Children's Hospital Augsburg, Section of Neuropediatrics, Stenglinstr. 2, 86156 Augsburg, Germany.  
E-mail address: [mareike.schimmel@freenet.de](mailto:mareike.schimmel@freenet.de) (M. Schimmel).

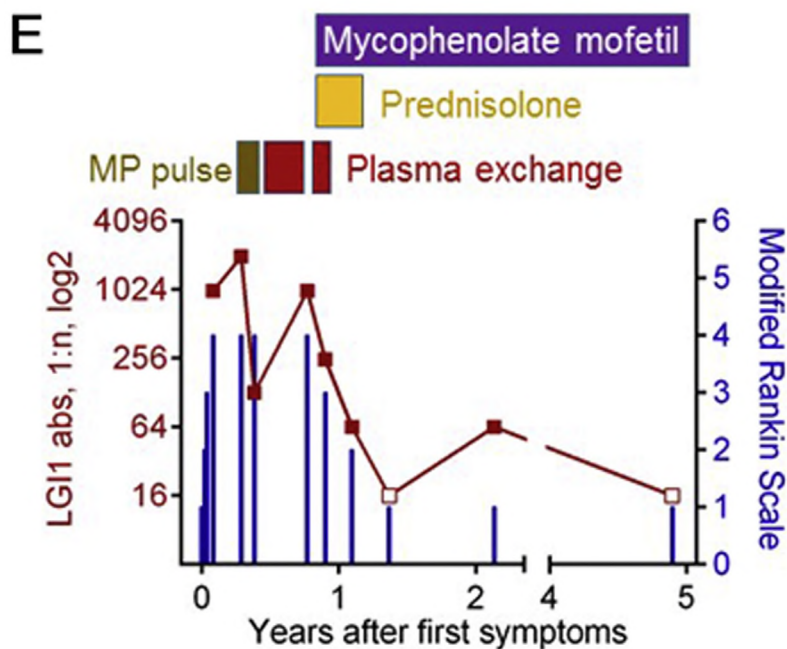
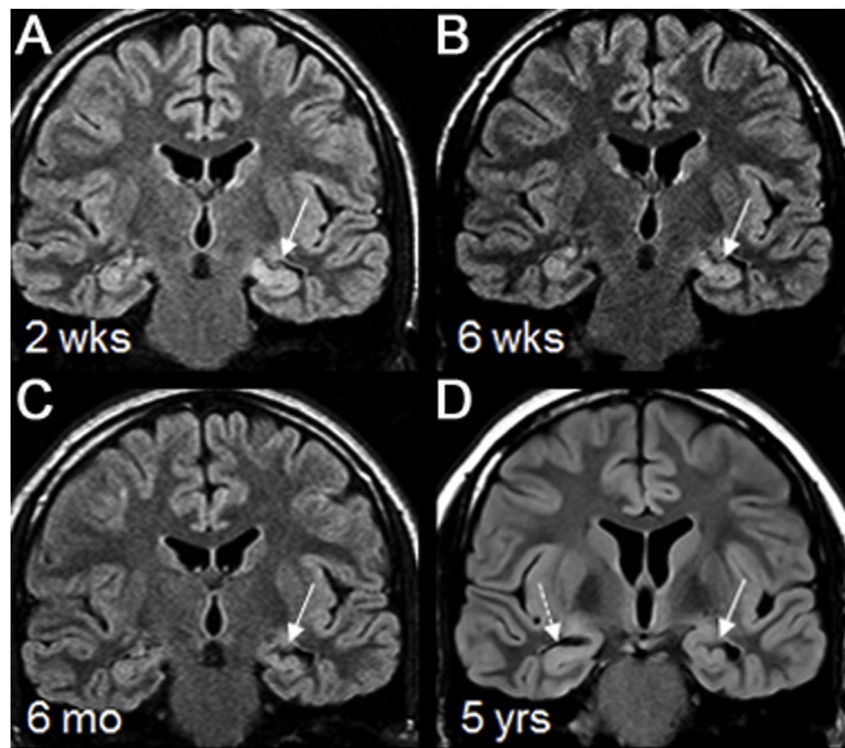


Fig. 1 – A–D: Serial fluid-attenuated inversion recovery magnetic resonance imaging revealing development of left sided hippocampal sclerosis (arrows). In D, the loss of the internal structure of the right hippocampus and a slightly increased signal suggests that the right hippocampus, too, has become sclerotic (dashed arrow). E: LGI1 antibody titres over time in relation to the immunological therapies and disability as measured by the modified Rankin Scale. Yellow: methylprednisolone pulse. Red: plasma exchanges. Orange: oral prednisolone. Blue: mycophenolate mofetil. Open squares: LGI1 serum antibody titres <1:16 (“negative”). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

suffered from episodes with half-side pallor and paraesthesia of the face with ptosis. The episodes lasted for 40–60 s. None of these signs and symptoms occurred in parallel to abnormal blood glucose concentrations. No faciobrachial dystonic seizures were observed.

One month following onset, he was investigated as an inpatient. EEG was normal and remained non-pathologic over time. CSF had a normal cell count but autochthonous oligoclonal bands indicating intrathecal IgG synthesis. Brain MRI showed swelling of the left hippocampus (Fig. 1A). Serum and CSF were tested by cell based assays (Euroimmun, Lübeck/Germany) for a broad panel of neural antibodies. Immunoglobulin G (IgG) against leucine-rich glioma inactivated protein 1 was detected at a titre of 1:1000; these antibodies were not found in undiluted CSF. Since the total IgG concentration in serum was about 400 times higher than in CSF, this suggested a slight measuring inaccuracy and in any case a peripheral production of the anti-LGI1-IgG. All other tested antibodies – against glutamic acid decarboxylase or the receptors for N-methyl-D-aspartate, gamma-aminobutyric acid B, alpha-amino-3-hydroxy-5-methyl-4-isoazolpropionacid or glycine, those against contactin-associated protein 2, amphiphysin, CV2, PNMA2 (Ma2), Hu, Ri, Yo and thyroid antigens – were negative. ANA were found at a borderline titre of 1:100. Sodium levels were within the normal range at all times.

A tumour was not detected, MRI of the thorax and abdomen were normal.

Upon the diagnosis of limbic encephalitis with LGI1 antibodies, one methylprednisolone pulse (1 g/day for 5 days intravenously) was given without beneficial effect. We escalated therapy to plasmapheresis (3 times/week, in total 10 times, 50 ml/kg, against albumin) with subsequent oral prednisolone treatment for 3 months. Treatment success was consolidated with immunosuppressive therapy with mycophenolate mofetil (MMF, 2 × 1 g/day) for 4 years. LGI1 antibodies disappeared. The swelling of the left hippocampus resolved (Fig. 1B and C).

The patient's memory and behaviour started improving after the second round of plasmapheresis, but the impairment was not completely reversible at most recent follow-up, five years after disease onset. Serial brain MRI showed development of left (and potentially right) sided hippocampal sclerosis over time (Fig. 1D). For a graphical summary of the antibody titre course and disability symptoms measured by modified Rankin Scale, see the Fig. 1E.

### 3. Discussion

Adults with limbic encephalitis (LE) due to LGI1 antibodies present with memory impairment, temporal lobe seizures, affective symptoms or combinations. Mediotemporal MRI changes are common.<sup>3,6,7</sup> In the existing large series, all patients were  $\geq 21$  years old. The average age at disease onset is in the seventh decade.<sup>7</sup> Most patients improve clinically, but are left with residual memory deficits and hippocampal atrophy.<sup>1</sup>

To the best of our knowledge, this is the youngest patient reported so far. His symptoms, MRI course, antibody findings and treatment response are indistinguishable from the adult cases. The case satisfies the recent criteria of definite limbic encephalitis.<sup>2</sup> We conclude that LE with LGI1 antibodies may be a differential diagnosis in adolescents with subacutely evolving deficits of recent memory.

In this patient, the pre-existing diabetes and the antinuclear antibodies at a serum titre of 1:100 may suggest a predisposition for autoimmune diseases, even though Hashimoto encephalitis, thyroid disease or lupus erythematosus do not explain his presentation. Recently, the predilection for certain HLA types in patients with anti-LGI1 encephalitis has been reported.<sup>5</sup>

LGI1 is mainly expressed in the central nervous system (CNS) and may regulate presynaptic VGKCs and so affect transmitter release. Post-synaptically, LGI1 interacts with ADAM22 proteins and may maintain AMPA receptors at synaptic sides. Antibodies may interfere with this.<sup>8</sup> The diversity of symptoms associated with LGI1 antibody mediated encephalitis is not well understood. In our case, we could not observe the typical faciobrachial dystonic seizures which often precede the onset of limbic encephalitis.<sup>4</sup> The boy told us about episodes of half-side pallor and paraesthesia of the face with ptosis but we could not verify them. The classification of this symptom is unclear. It could be autonomic seizures, potentially pilomotor seizures that have been found repeatedly in patients with limbic encephalitis.<sup>10</sup> We could not observe hyponatraemia that is common in adults. In our case the main symptom was the memory dysfunction, especially of short-term memory. Autoimmune disorders linked to antibodies targeting synaptic proteins such as LGI1 respond well to immunomodulatory treatment. In our case, upon a combination of immunotherapies, there was improvement of memory deficits in parallel with a decrease of the antibody titre. As a residual symptom, the boy continued to have memory problems explained by irreversible hippocampal atrophy and sclerosis. In accordance to recent data hippocampal atrophy and poor memory recovery is common in patients with LGI1 antibodies and suggests permanent functional damage.<sup>1</sup> It may be speculated that very early diagnosis and rapid immunomodulatory treatment could help to prevent a progression resulting in irreversible lesions.

It is tempting to speculate that the rarity of anti-LGI1 encephalitis in paediatric patients relates to a lower expression of this protein in younger age as described in mice.<sup>9</sup> Our case shows that in the paediatric population, LGI1 antibody mediated limbic encephalitis should be considered as a differential diagnosis in patients with subacutely evolving, otherwise unexplained memory dysfunction.

### Funding

No. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Conflict of interests

MS received travel support from Actelion (Freiburg, Germany) and Desitin (Hamburg, Germany).

CGB gave scientific advice to Eisai (Frankfurt, Germany) and UCB (Monheim, Germany), undertook industry-funded travel with support of Eisai (Frankfurt, Germany), UCB (Monheim, Germany), Desitin (Hamburg, Germany), and Grifols (Frankfurt, Germany), obtained honoraria for speaking engagements from Eisai (Frankfurt, Germany), UCB (Monheim, Germany), Desitin (Hamburg, Germany), diamed (Köln, Germany), Fresenius Medical Care (Bad Homburg, Germany), and received research support from diamed (Köln, Germany) and Fresenius Medical Care (Bad Homburg, Germany). He is a consultant to the Laboratory Krone, Bad Salzfluren, Germany, regarding neural antibodies and therapeutic drug monitoring for antiepileptic drugs.

MCF has received a travel grant and honorarium for a talk by Yakult (Neuss, Germany).

## Acknowledgements

The authors would like to thank Mrs Jutta Potthoff, Antibody Research Laboratory at Krankenhaus Mara, Bielefeld-Bethel, and Mrs Simone Reimann, Laboratory Krone, Bad Salzfluren/Germany, for excellent technical assistance. They are grateful to Dres. Johannes Demharter and Kurt Vollert, Dept. of Radiology, Klinikum Augsburg/Germany, and Dr. Friedrich Wörmann, Bielefeld/Germany, for providing and interpreting the MR images.

## REFERENCES

1. Bien CG, Vincent A, Barnett MH, et al. Immunopathology of autoantibody-associated encephalitides: clues for pathogenesis. *Brain* 2012;135:1622–38.
2. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016;15:391–404.
3. Irani SR, Alexander S, Waters P, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. *Brain* 2010;133:2734–48.
4. Irani SR, Michell AW, Lang B, et al. Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. *Ann Neurol* 2011;69:892–900.
5. Kim TJ, Lee ST, Moon J, et al. Anti-LGI1 encephalitis is associated with unique HLA subtypes. *Ann Neurol* 2017;81:183–92.
6. Lai M, Huijbers MG, Lancaster E, et al. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. *Lancet Neurol* 2010;9:776–85.
7. Navarro V, Kas A, Apartis E, et al. Motor cortex and hippocampus are the two main cortical targets in LGI1-antibody encephalitis. *Brain* 2016;139:1079–93.
8. Ohkawa T, Fukata Y, Yamasaki M, et al. Autoantibodies to epilepsy-related LGI1 in limbic encephalitis neutralize LGI1-ADAM22 interaction and reduce synaptic AMPA receptors. *J Neurosci* 2013;33:18161–74.
9. Ribeiro PA, Sbragia L, Gilioli R, et al. Expression profile of Lgi1 gene in mouse brain during development. *J Mol Neurosci* 2008;35:323–9.
10. Rocamora R, Becerra JL, Fossas P, et al. Pilomotor seizures: an autonomic semiology of limbic encephalitis? *Seizure* 2014;23:670–3.