■ Case vignette

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Epileptic Disorders

# Anti-Ma2-associated limbic encephalitis presenting with transient epileptic amnesia

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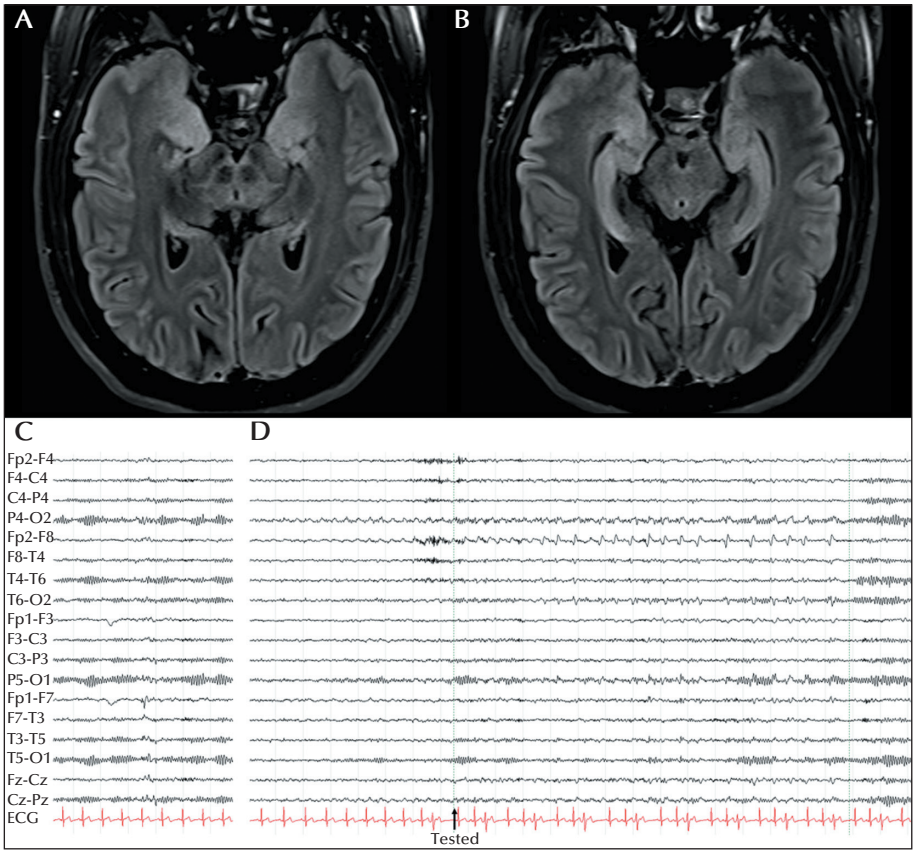
Autoimmune limbic encephalitis (LE) is defined by subacute-onset working memory deficits, seizures or psychiatric symptoms, associated with T2/FLAIR hyperintensity of the mesial temporal lobes, CSF pleocytosis or EEG abnormalities in the temporal regions, when alternative causes are excluded [1]. Transient global amnesia (TGA) is a syndrome characterized by the sudden onset of anterograde amnesia lasting up to 24 hours [2, 3]. Its differential diagnosis includes ischaemic amnesia and transient epileptic amnesia (TEA); a focal epilepsy syndrome in which amnestic attacks are the primary ictal manifestation [2, 4]. Herein, we describe a patient with anti-Ma2-associated LE presenting with an amnestic episode mimicking TGA, eventually diagnosed as TEA.

A 43-year-old man with an unremarkable past medical history was brought to the emergency department as his son found him in the afternoon confused and with repetitive questioning. Vitals, physical examination, routine blood tests and brain CT were within the norm. Neurological examination was unremarkable except for severe anterograde amnesia. The patient was admitted overnight and was asymptomatic upon awakening. He displayed incomplete amnesia for the events immediately prior to or during the episode, with patchy recollection of moments across the hospital stay. An EEG performed the following morning showed no abnormalities, and the patient was dismissed with a diagnosis of possible TGA. Since then, the patient reported the onset of episodes lasting a few seconds, characterized by a burning feeling in the upper abdomen, rising up to the chest. Two weeks after the amnestic spell, he underwent brain MRI which revealed right-predominant T2/FLAIR hyperintensity of the mesial temporal lobes (*figure 1A, B*). Sleep-deprived EEG showed interictal temporal spikes and an electrographic seizure involving the right fronto-temporal region (*figure 1C, D*). On the basis of these findings, the patient was admitted to our neurology unit. Cognitive testing revealed impaired short-term recall and slightly reduced verbal fluency (Montreal Cognitive Assessment: 25/30). CSF analysis was unremarkable, including oligoclonal banding. A panel for neuronal autoantibodies (intracellular antigens: Hu, CV2, Yo, Ma2, Ri, SOX1, Zic4, Tr, Titin, GAD65, and amphiphysin; surface antigens: NMDAR, CASPR2, AMPAR, LGI1, DPPX, and GABAbR) led to the detection of high serum and CSF titres of anti-Ma2 antibodies. The patient was diagnosed with anti-Ma2-associated LE [5], receiving high-dose methylprednisolone (1,000 mg/day for five days) and lacosamide 200 mg daily. A comprehensive neuropsychological examination and EEG, repeated following treatment, were within the norm. Tumour screening was performed; contrast-enhanced thoraco-abdominal CT was unremarkable, whereas testicular ultrasound revealed a subcentimetric left testicular mass. The patient was subsequently referred to the urology service and underwent orchifunicolectomy. Histopathology was consistent with a regressed ("burned-out")




■ **Figure 1.** Brain MRI and EEG findings. (A, B) Brain MRI (fluid attenuated inversion recovery; axial view) shows right-predominant hyperintensity of the mesial temporal lobes, specifically the amygdala (A) and hippocampus (B). (C, D) EEG shows an interictal left fronto-temporal spike (C) and an electrographic seizure arising during relaxed wakefulness, predominantly involving the right fronto-temporal region, lasting for 22 seconds, with postictal return to physiological, symmetric, posterior alpha rhythm (D); the patient remained asymptomatic during the discharge and answered without language errors to the neurophysiology technician; ECG shows frequent extrasystoles, which also occurred interictally. Sensitivity: 7.0 µV/mm.

germ cell tumour. Notwithstanding, in the months following surgery, the epigastric sensations recurred weekly, and the patient experienced two further amnestic spells that were shorter than the former, lasting for a few hours. Brain MRI was unchanged after three months, while EEG revealed bilateral fronto-temporal epileptiform abnormalities. Anti-Ma2 antibodies in serum were still positive. A total-body FDG-PET ruled out malignancies. The patient was treated with intravenous immunoglobulin (2 g/kg in five days) and started on lamotrigine 200 mg daily, leading to seizure freedom after five months of follow-up. He is currently undergoing regular cancer surveillance.

Our patient with anti-Ma2-associated LE presented with reversible sudden-onset anterograde amnesia, initially diagnosed as possible TGA. Discriminating between TGA and TEA can be tricky. Amnestic seizures in TEA may associate with other symptoms proper to temporal lobe seizures, but can present with pure isolated amnesia in up to 30% of cases [4]. Repetitive questioning, originally described for TGA, is reported in up to 50% of TEA cases [4]. Duration of more than an hour reverberates in the literature as a discriminating criterion, but is frequent in TGA [6], and cases of TEA lasting for hours/days have been reported [4, 7]. Patchy memory recollection (remembering not being able to remember) might provide some insight, being rather more common in TEA than in TGA [6]. Non-convulsive status epilepticus may also mimic TGA [8], yet it is most commonly associated with altered awareness. In our patient, the atypical features of the episode and the development of epigastric auras prompted further investigations, including brain MRI and sleep-deprived EEG, which were consistent with LE. An isolated short-term memory deficit was demonstrated with neuropsychological testing, and might otherwise have passed unnoticed.

The diagnosis of TEA was confirmed by the clinical evolution of our patient, including the response to antiseizure medications, in compliance with Zeman's criteria [4]. Our report highlights that an in-depth neurological assessment is crucial to identify atypical features of TGA. These cases should be investigated by brain MRI, EEG and cognitive testing to spot subtle memory deficits and their cause. As in our patient, the diagnosis becomes accurate as we scratch the surface. Overall, TEA may represent the first manifestation of hippocampal epileptogenic changes that are known to occur at very early stages of autoimmune encephalitis [4, 9]. Since LE may even precede cancer diagnosis, early recognition impacts long-term prognosis. ■

**Supplementary material.**
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

**Disclosures.**
The authors report no relevant disclosures or conflicts of interest for this manuscript.

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## TEST YOURSELF

**(1) Which of the following does not represent a differential diagnosis of transient global amnesia?**
A. Transient epileptic amnesia
B. Ischaemic amnesia
C. Convulsive status epilepticus
D. Non-convulsive status epilepticus

**(2) Which of the following findings would support a diagnosis of transient epileptic amnesia instead of transient global amnesia?**
A. Complete amnesia for the episode
B. Epileptiform discharges on EEG
C. Repetitive questioning
D. Small vessel disease on brain MRI

**(3) Which of the following statements regarding autoimmune limbic encephalitis is wrong?**
A. Some patients with anti-Ma2 antibody positivity have a testicular tumour
B. CSF analysis always shows elevated WBC count
C. Brain MRI may show T2 hyperintensity of the mesial temporal lobes
D. Transient epileptic amnesia is a possible manifestation at onset

*Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.*