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**Title:** CASPR2 antibody encephalitis presenting as transient epileptic amnesia

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## 1 Highlights

- 2 • Isolated **transient amnesia** can be of epileptic origin
- 3 • The epileptic origin may be suggested by a short duration of the episodes (< 1h)
- 4 • Interictal cognitive complaints are highly suggestive of the diagnosis
- 5 • Both interictal and ictal features can be of autoimmune origin (here, anti-CASPR2)

6

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9 **Keywords:** transient epileptic amnesia, autoimmune encephalitis, anti-CASPR2, case report

## 10 Case report

11 **Transient epileptic amnesia** (TEA) is an underrecognized form of late-onset temporal lobe  
12 epilepsy, generally occurring between the ages of 50 and 70, and manifesting as ictal episodes of  
13 transient amnesia, either retro- and/or anterograde, of variable duration. The episodes are mostly  
14 short ( $\leq 1$  h), but can last for hours and thereby mimic benign transient global amnesia (TGA) [1]. In  
15 addition to episodic amnesia, the diagnosis of TEA may be suggested by complaints of interictal  
16 cognitive problems. These typically involve memory and consist in autobiographical deficits,  
17 accelerated forgetting, and, to a lesser extent, topographical amnesia. This symptom profile indicates  
18 hippocampal dysfunction, which can be of autoimmune origin [1,2]. Here, we present the case of a  
19 patient in whom the first and only amnestic attack was appropriately diagnosed because of the  
20 nature of his subjective cognitive impairment. The diagnosis of TEA, in turn, led to the secondary  
21 identification of CASPR2 antineuronal antibodies, most likely involved in the aetiology of the clinical  
22 picture.

23 The patient was 60 years old when an episode of TEA occurred **after he had been awake for**  
24 **several hours**. He was an ex-smoker (stopped 4 months prior to presentation) with a history of mild  
25 traumatic brain injury at the age of 22, dyslipidemia and hypertension. The patient gave a good  
26 description of the first 5 min of the TEA because he recollected that he was unable to remember  
27 anything at that time: He did not recognize a cheque he had signed 30 min earlier **(in the early**

28 **afternoon**) and experienced a strange feeling of “jamais vu” without any dysautonomic aura or  
29 indicators of a confusional state. The retrograde amnesia was followed by anterograde amnesia for  
30 3.5 h described by his wife, with repetitive questioning but no other accompanying signs **or**  
31 **automatisms**. The patient reported that for the past 4 years he had been suffering from a blunted  
32 sense of smell and fluctuating mood, in combination with “panic attacks” (weekly to monthly  
33 unexplained and unpredictable spells **lasting 30 s to 2–3 min** with upper limb piloerection and  
34 sudden tachycardia, sometimes followed by fear and subsequent loss of contact with speech arrest  
35 for a few seconds). Besides, two similar episodes occurred in the 5 days after the transient amnesic  
36 attack. Moreover, the patient had been complaining about his memory for the past 2 years: He gave  
37 a clear account of accelerated forgetting from one week to the next (**e.g., he was unable to**  
38 **remember details of a party at a friend’s house 10 days before attending our clinic**), and patchy  
39 autobiographical amnesia over the past 4–5 years (**e.g., he could not remember clearly what he had**  
40 **done with his colleague on the day of his retirement 18 months before presentation, nor did he**  
41 **remember his wedding that took place 6 months before the TEA**). He also reported occasional word-  
42 finding difficulties and attentional lapses. **Since the patient’s history and clinical presentation met the**  
43 **recommended diagnostic criteria for TEA**, we immediately suspected TEA: The patient’s Mini-Mental  
44 State Examination (MMSE) score was 29/30 at baseline and routine neuropsychological assessment  
45 showed a dysexecutive profile with impaired attention (i.e. faulty retrieval in verbal memory task,  
46 failed the Trail-Making Test [TMT]-B and short-term memory tasks). **Accelerated forgetting or**  
47 **autobiographical amnesia were not specifically tested**. A standard electroencephalogram (EEG; 40-  
48 min awake session) was normal. Since a computed tomography (CT) scan of the brain performed in  
49 the emergency room was normal, we carried out magnetic resonance imaging (MRI) of the brain: It  
50 revealed scattered cortical and juxta-cortical hyperintensities, as well as increased T2 signal in both  
51 hippocampi but more marked on the right (figure 1). We therefore carried out an autoimmune work-  
52 up: Antinuclear and antiphospholipid antibody levels were normal, anti-thyroid antibody levels were  
53 slightly increased (anti-TPO = 64 UI/ml, antithyroglobulin = 357 UI/ml, N < 34 UI/ml and 115 UI/ml,

54 respectively), and antineuronal antibody samples were positive (immunofluorescent-positive  
55 neuropil staining on monkey cerebellum slices). On cell-based assays, serum anti-CASPR2 antibody  
56 samples were positive (the test employed provided no titer of the anti-CASPR2 or of the anti-VGKC-  
57 complex antibodies). Whole-body CT scan did not reveal any malignancy. Treatment with lamotrigine  
58 at 2 mg/kg/day (150 mg once daily) was progressively initiated, which led to the immediate cessation  
59 of dysautonomic spells and prevented recurrence of amnesia for the following 12 months. The  
60 patient refused **sleep-EEG**, lumbar puncture, and intravenous immunoglobulin treatment because he  
61 felt better (improved sense of smell, better mood, and fewer memory complaints). **Repeat MRI after**  
62 **6 months of treatment with lamotrigine showed no significant change from the initial scan.**

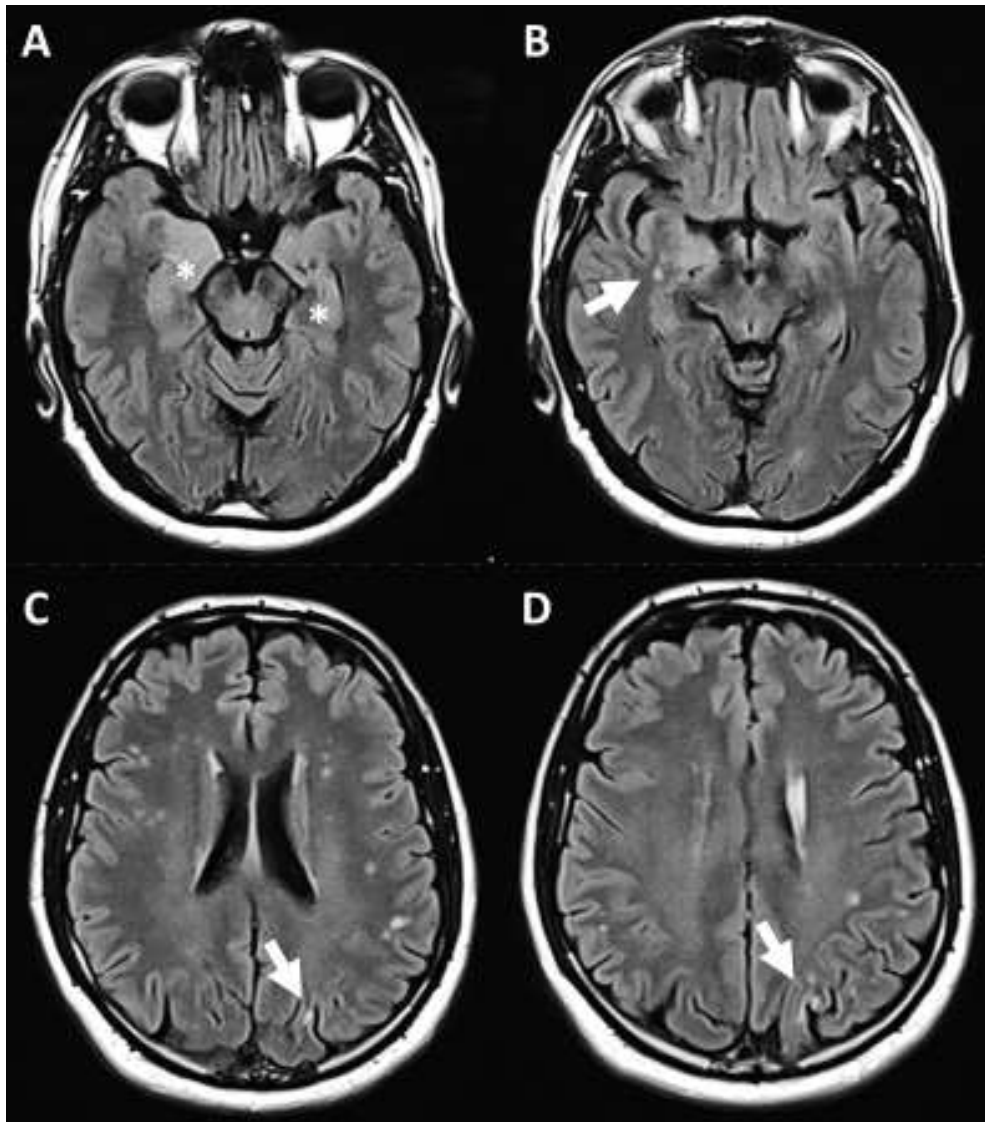
63         This case is the second, to our knowledge, to report TEA in association with a well-identified  
64 antineuronal antibody. The first patient described had anti-NMDA antibodies: He was younger at  
65 disease onset (44 years) than our patient, whose age was more typical of TEA. Not only the age but  
66 also the other characteristics of our patient encompass the syndromic features of non-paraneoplastic  
67 limbic encephalitis with CSF-positive anti-CASPR2: median age = 64.5 years, focal seizures with  
68 typically normal EEG (in more than 75% of cases), episodic memory impairment, increased T2  
69 hippocampal signal on brain MRI, and positive serum CASPR2 antibodies [3]. However, because our  
70 patient refused CSF analysis, we could not definitively categorize his condition as this type of  
71 autoimmune encephalitis. Nevertheless our report suggests that, in some cases, TEA may be due to a  
72 subtle form of autoimmune encephalitis and that TEA should be considered part of the clinical  
73 spectrum autoimmune encephalitides may present with [1,2]. In combination with the rare  
74 degenerative forms reported, our case therefore highlights the etiological heterogeneity of TEA.  
75 Moreover, we wish to stress the fact that the diagnosis of TEA was strongly suspected, and thereafter  
76 quickly made, in this patient because he complained of chronic memory disturbances: these  
77 complaints were suggestive of the diagnosis, as were the other episodes with dysautonomic signs,  
78 despite the isolated antero-retrograde amnesic attack.

79 In conclusion, substantial progress has been made in the understanding of TEA. The  
80 refinement of the ictal and interictal characteristics of TEA since the 1990s, now allows for an  
81 accurate and quick recognition of the syndrome: not only in light of repetitive and stereotyped  
82 transient amnesic episodes, but also in view of the peculiar and highly suggestive other memory  
83 complaints [4]. As illustrated by our case, this scenario has therapeutic implications: First, antiseizure  
84 medications can be prescribed; second, an early and correct aetiological diagnosis can be made with  
85 subsequent appropriate follow-up and management (which should now include autoimmune  
86 conditions).

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101

102 Note: A = bi-hippocampal hypersignal (stars) predominating on the right side; B = unusual white  
103 matter hyperintensities close to the right hippocampus (thick arrow); C–D = scattered juxta-cortical  
104 round-shaped white matter hyperintensities with cortical hypersignal (thick arrows)