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Clinical letter

Olfactory stimulus-induced temporal lobe seizures in limbic encephalitis

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1. Introduction

Limbic encephalitis (LE) is a recently defined clinical entity, which might be associated with autoantibodies targeting either intracellular or neuronal surface antigens, with or without evidence of an underlying malignancy. Typical features of LE consist of subacute amnestic syndrome, psychiatric symptoms and focal seizures, which usually reflect the ictal involvement of the temporo-mesial structures and often represent the most striking manifestation at disease onset [1]. However, not only could the complex and elusive immune-mediated mechanisms underlying LE cause seizures during the acute phase, but also lead to the development of chronic epilepsy. Here we describe a patient suffering from a non-paraneoplastic LE who presented peculiar reflex temporal seizures induced by various intense olfactory stimuli, and particularly by his wife's perfume.

2. Case report

A 55-year-old previously healthy man, suddenly developed hypertension, insomnia and low-grade fever, persistent for about a month despite a course of ceftriaxone. He started complaining of altered perception of tastes and smells, leading to severe inappetence (except for chocolate) and a consequent remarkable weight loss (around 10 kg). A few months later, mild memory deficits, mood and behavioral changes also appeared. When the patient came to our attention, he was experiencing daily episodes, lasting 2–3 minutes, characterized by "anxiety…an abdominal sensation…chills and fear". Interestingly, these phenomena were often induced by intense smells such as his wife's perfume, as he clearly recalled. The neurological examination was normal, except for a mild attention deficit and a mood disorder. A brain MRI scan showed T2-FLAIR hyperintensities bilaterally involving hippocampus and amygdala but more evident on the left side, with minimal diffusion restriction and no contrast enhancement (Fig. 1).

Given the suspicion of encephalitis, a lumbar puncture was performed, and cerebrospinal fluid (CSF) analysis revealed mild pleocytosis (28/mm3 mononucleate cells) and slightly increased protein level (48 mg/dL). Neither viruses or bacteria were found in CSF (HSV-1, HSV-2, VZV, JCV, HHV-6, BKV, EBV, CMV were researched). Considering the high frequency of the paroxysmal phenomena, we managed to record several episodes through video-EEG monitoring, which confirmed their epileptic nature. The recorded seizures were characterized by tachycardia, rising epigastric sensation, asymmetrical horripilation, fear, sweating, olfactory and gustatory hallucinations, followed by staring and speech arrest; awareness impairment with gestural and oral automatisms were sometimes observed. On the basis of anamnestic data, we also performed targeted activation tasks during Video-EEG: more specifically, we had the patient sniff his wife's perfume, alcohol and solvents, which consistently evoked his typical seizures, lasting from 20 s to 1–2 minutes and arising from both temporal lobes with left predominance (Fig. 2, Supplemental figures). Thorough clinical examinations and imaging studies performed at baseline and at scheduled time-points during a 5-year follow-up ruled out the presence of underlying malignancies. The search for typical autoantibodies (anti-NMDAR, anti-VGKC/LGI1 and anti-VGKC/CASPR2, anti-GAD, anti-AMPAR, anti-$GABA_BR$, anti-ganglioside, onconeural) on serum and CSF samples was negative, except for the positivity of serum sample for anti-SOX1 antibodies.

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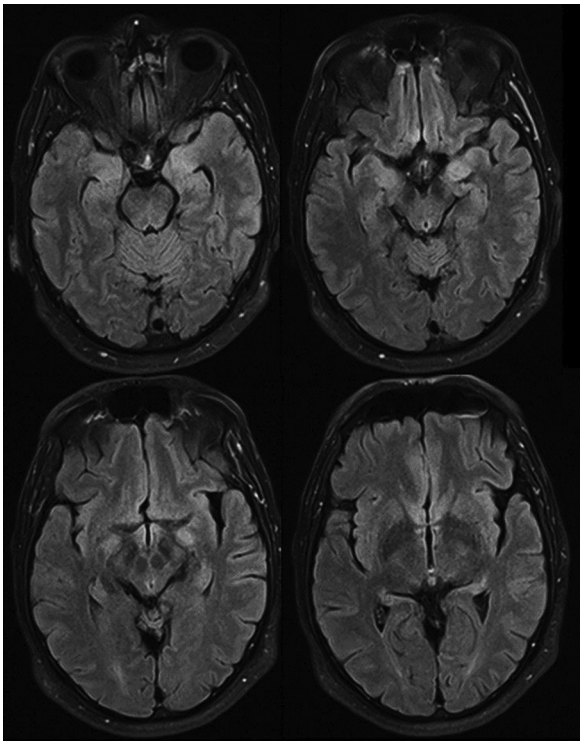

Fig. 1. Brain MRI scan (T2-weighted fluid-attenuated inversion recovery - FLAIR - axial images) showing hyperintensity involving bilateral temporo-mesial structures with left predominance.

On the basis of the currently accepted criteria, the diagnosis of autoimmune encephalitis was made and an immunosuppressive therapy was started (intravenous methylprednisolone 1 g/die for five days, followed by oral prednisone 50 mg daily and then intravenous immunoglobulins). Because of the unsatisfactory clinical response to therapy (with only a slight, transitory improvement in terms of seizure frequency and smell/taste disturbance severity), a subsequent therapeutic up-grade with azathioprine and then cyclophosphamide was attempted, unsuccessfully, for a period of 19 and 8 months respectively.

As to the antiepileptic treatment, countless drugs were used, including levetiracetam, carbamazepine, perampanel, zonisamide, valproate, rufinamide, brivaracetam and topiramate, without any significant effect on seizure control.

3. Discussion

The classic presentation of LE includes the rapid development of cognitive and psychiatric disorders, sleep disturbances, autonomic alterations and epileptic seizures. Seizures with acute/subacute onset, high frequency and electro-clinical features reflecting the involvement of temporo-mesial structures are highly suggestive of this peculiar condition.

The pathophysiological mechanisms underlying the generation of seizures in LE include different factors: indeed, antibody-mediated damage, inflammation cascade, low epileptic threshold of specific areas (such as the temporo-mesial regions) and microstructural tissue alterations can produce determinant changes in the neural excitation-inhibition balance.

From a semiological point of view, the clinical core of our patient's seizures primarily suggests the involvement of temporo-mesial structures, as previously stated, but several symptoms can reflect the contribution of a more complex and integrated network that includes different cortical and subcortical regions belonging to the limbic system. In particular, some ictal features (horripilation, epigastric sensation, fear, tachycardia, sweating, olfactory/gustatory hallucinations), may point to the involvement of extra-temporal regions, e.g. insula, fronto-basal and orbital cortices. The variability of ictal manifestations in LE has been particularly described in patients suffering from anti-LGI1 LE, who, indeed, may present seizures characterized by heterogeneous signs/symptoms [2], including a peculiar seizure type known as facio-brachial dystonic seizures (FBDS), which suggests the existence of a wide network also involving primary motor areas and basal ganglia [1,3].

The novel finding observed in our case was that the patient's seizures were consistently induced by the exposure to intense olfactory stimuli. This specific mode of activation gave us the opportunity to speculate about the pathophysiological basis of reflex seizures in a peculiar condition such as LE. Indeed, in our patient the immune-mediated process likely affects the cerebral areas contributing to the olfactory processing, as suggested by his persistent smell impairment. Therefore, in a disrupted network already made "vulnerable" (that is, hyperexcitable) by the ongoing inflammatory process, the physiological sensorial input could facilitate a further unbalance between excitation and inhibition and eventually lead to seizure generation. Considering the complexity of the specific sensorial modality, it can be argued that the triggering factors might include, beside pure olfactory inputs, also emotional, cognitive and autonomic components. However, similarly to other, widely studied types of reflex seizures, the exact mechanisms underlying the rarely reported olfactory stimulus-induced seizures are not fully understood to date [4]. In our case, the occurrence of seizures evoked by this specific stimulus highlights, once more, the involvement

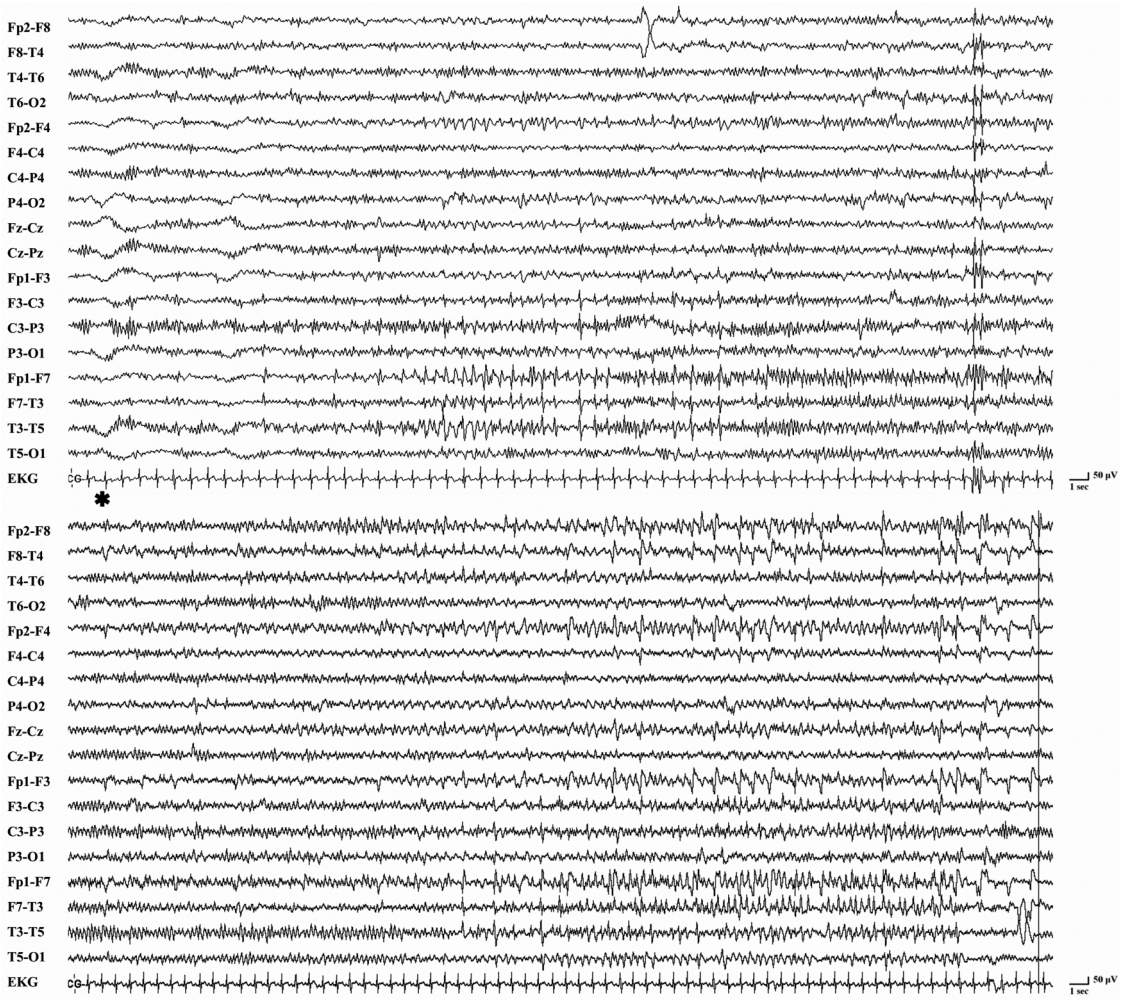

Fig. 2. Video-EEG recording showing a focal seizure, induced by the patient's olfactory stimulation with his wife's perfume (*), arising from the left temporal regions with subsequent spreading to contralateral temporal structures. The ictal pattern, starting 5–6 seconds after the stimulus, is characterized by a focal amplitude reduction on the left anterior temporal derivations followed by rhythmic spikes, and then a 5–6-Hz monomorphic theta activity involving a wide left temporal area with prompt spreading to contralateral fronto-temporal electrodes. The described monomorphic theta activity is finally replaced by a 3-Hz sharp wave activity located on the above mentioned regions. Clinically, the seizure, lasting about 75 s, was characterized by piloerection, tachycardia, anxiety and impairment of awareness.

of highly interconnected limbic structures, and also emphasizes the crucial concept of LE as a network disease.

Note

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure

Neither of the authors has any conflict of interest to disclose.

References

[1] Thompson J, Bi M, Murchison AG, Makuch M, Bien CG, Chu K, et al. The importance of early immunotherapy in patients with faciobrachial dystonic seizures. Brain 2018;141:348–56.
[2] Aurangzeba S, Symmondsa M, Knighta RK, Kennetta R, Wehnerc T, Irani SR. LGI1-antibody encephalitis is characterised by frequent, multifocal clinical and subclinical seizures. Seizure 2017;50:14–7.
[3] van Sonderen A, Petit-Pedrol M, Dalmau J, Titulaer MJ. The value of LGI1, Caspr2 and voltage-gated potassium channel antibodies in encephalitis. Nat Rev Neurol 2017;13:290–301.
[4] Ilik F, Pazarli AC. Reflex epilepsy triggered by smell. Clin EEG Neurosci 2015;46(3):263–5.