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Clinical letter

Orbitofrontal syndrome and "goosebumps"—A new manifestation of autoimmune epilepsy in anti-LGI1 encephalitis

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1. Introduction

Anti–leucine-rich glioma-inactivated 1 (anti-LGI1) encephalitis is a rare autoimmune disorder that presents with a triad of cognitive and psychiatric disturbances, hyponatremia, and autoimmune epilepsy. Facial-brachial dystonic (FBD) seizures are considered a pathognomonic sign of this condition. However, more subtle seizure types can occur and should be recognized, allowing for timely diagnosis and treatment. We report a case of anti-LGI1 autoimmune encephalitis presenting as orbitofrontal syndrome with focal "goosebump" seizures.

2. Case report

A 63-year-old man was admitted due to changes in behaviour and cognition developing over months, which made him more impulsive and irritable. Those changes were noted by his family, along with indifference to important dates, increased appetite, and intermediate insomnia. This led to deteriorating work performance and two consecutive car accidents. Simultaneously, the patient developed recurrent goosebumps that travelled up his spine. These stereotypical episodes occurred multiple times a day, lasting seconds. They were preceded by a feeling of uneasiness and followed by irritation and were not followed by loss of consciousness, involuntary movements, or loss of sphincter continence. On examination, his humour was playful, with hyperfamiliar and impulsive behaviour.

The initial scores of the cognitive tests were 27/30 in the Mini-Mental State Examination (MMSE), 26/30 in the Montreal Cognitive Assessment (MoCA), and 15/18 in the Frontal Assessment Battery (FAB). These tests showed reduced phonemic fluency and errors in Luria's motor sequence, abstraction, temporal orientation, evocation, construction, visual-spatial drawing, and executive functions. He had a right palm-mentonean reflex. The neurological examination was otherwise normal. A neuropsychological evaluation documented impairments of episodic memory and inhibitory control. Due to the occurrence of an orbitofrontal syndrome, an initial diagnosis of a behavioural variant of frontotemporal dementia (FTD) was considered. However, concomitant recurrent goosebumps, suggestive of focal seizures, were atypical for this diagnosis and motivated further investigation. A blood panel with complete blood count, basic biochemistry, vitamin B12 levels, and thyroid function was normal. Sodium levels were borderline abnormal (134 mEq/L). Serologies for HIV, HBV, HCV, and syphilis were negative. The autoimmune study (with ANA, anti-dsDNA, ANCA, rheumatoid factor, and onconeural antibodies directed against intracellular neuronal proteins) was unremarkable. An interictal electroencephalogram (EEG) did not yield any epileptic activity. Brain magnetic resonance imaging (MRI) showed slight diffuse atrophy, with cortical-parietal preference, and discrete hippocampal asymmetry (left larger), without signal changes. The cerebrospinal fluid (CSF) analysis showed slight pleocytosis and protein elevation (nine cells, 0.73 mg/dL proteins), with no glucose consumption and infectious serologies were negative. CSF phospho-tau and beta-amyloid were normal. Oligoclonal bands were negative. An anti-LGI1 antibody (detected by indirect

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immunofluorescence using LGI1-transfected cells) was positive in the blood and weakly positive in the CSF. An anti-LGI1 encephalitis diagnosis was assumed. A whole-body computed tomography scan did not show any suspicious neoplastic lesions. The patient completed a five-day cycle of methylprednisolone, 1 g daily, followed by a first cycle of 32 g of intravenous immunoglobulins. The patient's seizures, which had been refractory to eslicarbazepine with daily doses of 1200 mg, completely resolved after the first administration of corticosteroids. The behavioural syndrome, which was non-responsive to sertraline, improved after immunoglobulin treatment. His insomnia, which was nonresponsive to multiple therapeutics (trazodone 150 mg, triazolam 0.25 mg and quetiapine 25 mg), also improved after immunoglobulin treatment. Two months after treatment, a neuropsychological re-evaluation showed an improvement in visual episodic memory, although his behavioural abnormalities persisted. The patient was offered a second course of immunoglobulins, with improvements in behaviour and cognitive tests, with scores of 30/30 on the MMSE, 26/30 on the MoCA and 17/18 on the FAB. He maintained stability of his clinical picture at the one-year follow-up.

3. Discussion

Limbic encephalitis associated with anti-LGI1 antibodies is a rare autoimmune disorder that can cause cognitive changes and seizures. The semiology of seizures in anti-LGI1 encephalitis is very typical, with brief episodes of FBD posture occurring multiple times per day. Other seizure semiology has been described, including impaired awareness and motor, gelastic, and focal autonomic seizures. The initial presentation of our patient, given the frontal-behavioural syndrome and his age, was very suggestive of behavioural FTD. The stereotypical goosebumps raised a red flag of possible concomitant focal seizures and led the authors to consider alternative pathways of investigation. "Goosebumps", followed by the feeling of irritation, were the only ictal semiology that made suspicion difficult. We interpreted the recurrent goosebumps as possible autonomic auras, as we did not find any objective sign in the neurological examination of autonomic involvement (such as piloerection). This is perhaps due to the short duration of the episodes. Focal pilomotor seizures and seizures with autonomic aura manifesting as goosebumps are a rare manifestation of autoimmune epilepsy that are easily underrecognized. This case was particularly challenging due to the subtlety of the clinical findings, along with the negative imaging study. In fact, MRI might be initially negative or nonspecific in such cases [1]. The surface EEG was also not informative. Although goosebumps suggest temporal activity, this might be difficult to detect, and very brief episodes may contribute to underdiagnosis, as in our case [2].

Our study provides increased evidence for other manifestations of anti-LGI1 encephalitis, indicating that the classic triad for anti-LGI1 ought to be expanded. A case report has suggested the denomination of FBDS-plus to include and raise awareness of other epileptic semiologies [3]. We support the adaptation of this terminology and add that subtle paroxysm should be systematically sought and excluded, namely, in patients with orbitofrontal syndrome.

In conclusion, anti-LGI1 encephalitis may mimic behavioural FTD with subtle focal seizures. Clinicians should maintain a high level of suspicion for anti-LGI1 before these findings, even when the initial investigation is negative. In such cases, antibodies should be assessed. If positive, patients should begin immune therapy, which may benefit behavioural and seizure control and prevent the risk of memory impairment [4].

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Ethical publication statement

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.

Declaration of Competing Interest

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