Agrypnia excitata as the main feature in anti-leucine-rich glioma-inactivated 1 encephalitis: a detailed clinical and polysomnographic semiological analysis

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Abstract

Background and purpose: The core manifestations of leucine-rich glioma-inactivated 1 (LGI1) autoantibody-mediated encephalitis are limbic encephalitis and faciobrachial dystonic seizures. Agrypnia excitata (AE) is a rare syndrome characterized by sleep–wake cycle disruption, autonomic hyperactivation and episodes of oneiric stupor. Only a few diseases are known to present with AE. An autoimmune etiology must be considered when accompanied by neuromyotonia. A case of anti-LGI1 encephalitis presenting with AE is reported.

Methods: Detailed clinical, video-polysomnographic, laboratory, radiological and long-term follow-up assessments were performed.

Results: A previously healthy 58-year-old man was referred for a rapidly progressive change in mental status, characterized by persistent drowsiness and confusion, accompanied by frequent episodes of unconscious gestures ranging from simple stereotyped movements to more complex actions mimicking various daily activities. Other symptoms included tachycardia, hyperhidrosis, mild hyponatremia, rare faciobrachial dystonic seizures, and a single generalized tonic–clonic seizure, but no neuromyotonia. Prolonged video-polysomnography excluded epileptic activity and showed continuous monomorphic slowing of background activity not consistent with a regular wakefulness or sleep state. A brain magnetic resonance imaging scan was unremarkable. Brain fluorodeoxyglucose positron emission tomography revealed hypermetabolism of the hippocampi, amygdala and basal ganglia. Anti-LGI1 antibodies were detected in the cerebrospinal fluid. The sleep disorder resolved progressively after starting immunotherapy.

Conclusions: Agrypnia excitata can be a dominant, treatable manifestation of anti-LGI1 encephalitis. Oneiric stupor episodes are a useful clinical feature for establishing diagnostic suspicion and could provide a window to understanding the mechanisms behind some movement disorders in autoimmune encephalitis.

KEYWORDS
electroencephalography, immunotherapy, limbic encephalitis, positron emission tomography, sleep initiation and maintenance disorders

INTRODUCTION

Anti-leucine-rich glioma-inactivated 1 (LGI1) encephalitis is prevalently a primary central nervous system autoimmune disease mediated by antibodies against a secreted synaptic protein functionally linked to the voltage-gated potassium channel complex (VGKC) [1,2].

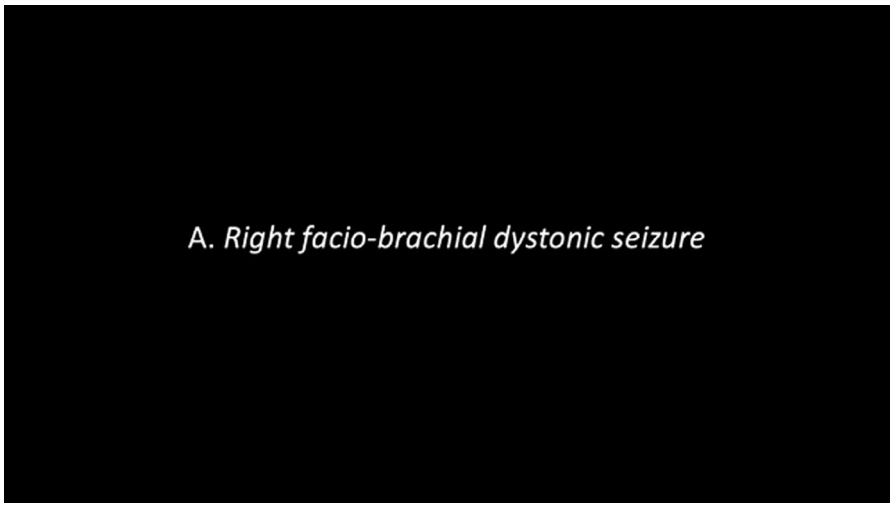
The typical clinical presentation is limbic encephalitis. With decreasing prevalence, focal seizures with mainly sensory, dyscognitive or subtle autonomic semiology, memory deficits, behavioral changes, faciobrachial dystonic seizures (FBDS) and sometimes generalized tonic–clonic seizures constitute its symptoms of presentation and major manifestations [2], usually in different combinations, with FBDS as its hallmark.

Using detailed video-polysomnographic recordings, a 58-year-old man affected by autoimmune LGI1 encephalitis with an unusual presentation, showing sleep–wake cycle disruption, autonomic hyperactivation and episodes of oneiric stupor (OS) [3], which define a unique electroclinical syndrome known as agrypnia excitata (AE) [4] is reported.

No ethical approval was required by our institution for this retrospective case description, once informed consent had been obtained, since no diagnostic or therapeutic intervention used in the management of this patient fell outside standard practice.

CASE REPORT

The patient was a healthy tradesman with no significant previous medical history. He presented at the emergency room with confusion and a single generalized tonic–clonic seizure. During the previous month, his relatives had noted the onset of restless sleep marked by various frequent movements, including muscle spasms in his face and arms, causing sleep fragmentation and subsequently severe insomnia. They also reported a behavioral change with mild confusion in daily activities and anxiety. Neurological examination revealed a deficit in episodic memory, but no sensory-motor deficits or signs of peripheral nerve hyperexcitability and no complaints of paroxysmal dizziness spells or neuropathic pain. During his hospital stay the patient showed only a few FBDS, sometimes with bilateral face involvement (Video 1, segment a). More significantly, he presented complete loss of the physiological sleep–wake cycle and dysautonomia, with persistent tachycardia (heart rate between 100 and 110 beats per minute), mild persistent hypertension (systolic values between 140 and 160 mmHg) and hyperhidrosis, without clear-cut breathing rhythm abnormalities. Throughout the day, he fluctuated between an alert and a drowsy state, frequently presenting unconscious episodes of motor activity, ranging from simple movements to complex gestures mimicking daily activities, suggestive of OS. For example, one night whilst lying in bed with his eyes closed he was seen handling an imaginary object with the fingers of both hands. Then, on realizing that he was holding nothing, he looked around as though in search of the object, whilst describing it to onlookers. Several other episodes of OS were observed, for example he was seen using imaginary objects such as a TV remote control or pencil sharpener, chewing, putting something unreal in his mouth, performing bipedal locomotor activities, or, independently with both hands, making simple, rapidly alternating thumb–finger movements, resembling pill-rolling tremor (Video 1, segments b–d). Prolonged video-polysomnography (10-channel electroencephalogram (EEG) plus electrooculogram, electrocardiogram and electromyogram of the mylohyoideus, bilateral deltoid and tibialis anterior muscles) performed during episodes of OS showed continuous, mildly slow



VIDEO 1 Faciobrachial dystonic seizure and episodes of oneiric stupor (OS). A. Brief right faciobrachial dystonic seizure lasting 3 s. B. Episodes of OS characterized by "over-learned" activities mimicking patient's habitual daily-life activities, including the use of imaginary objects (e.g., sharpening a pencil, using the TV remote control). C. Episodes of OS characterized by simple oro-alimentary activities and hand-to-mouth behaviors. D. Episodes of OS characterized by inborn motor patterns, possible expression of central pattern generators (e.g., alternating leg muscle activation, resembling bipedal locomotor activity, and hand pill-rolling automatism). File format: .mov.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1111/ene.15152

background activity and brief intermittent diffuse delta wave bursts, with no reactivity to sensory stimuli, no recognizable wakefulness and no sleep state pattern (see Figure 1 and Video 1, segments c and d). No epileptiform discharges were observed. Unfortunately, long-term video-EEG monitoring could not be recorded overnight for technical reasons. Extensive laboratory blood and cerebrospinal fluid (CSF) tests and brain magnetic resonance imaging (MRI) were unremarkable, except for persistent mild hyponatremia. Total body positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose (^{18}F-FDG PET) showed pathological bilateral hypermetabolism of the hippocampus, amygdala and basal ganglia (see Figure 1). Laboratory and radiological screening showed no evidence of a coexisting tumor, particularly thymoma. Lastly, recombinant cell indirect immunofluorescence assay for several antibodies against neuronal cell-surface proteins, ion channels or receptors, including those against contactin-associated protein 2 (CASPR2) and LGI1, detected only anti-LGI1 antibodies in the CSF. Unfortunately serum data were not available for antibodies against CASPR2 and LGI1.

Initial treatment with symptomatic drugs, such as valproic acid, neuroleptics and benzodiazepines, was ineffective in improving the main clinical manifestations. Improvement in the sleep–wake cycle was obtained only after first-line (including high-dose corticosteroids, eight sessions of plasma exchange) and second-line immunotherapy (cyclophosphamide and rituximab). After 6 months the patient almost completely regained autonomy in activities of daily living but still had residual cognitive impairment, mainly in executive functions, and a marked depressive mood. Six months after hospital discharge he died from accidental causes.

DISCUSSION

Anti-LGI1 encephalitis has been described as a homogeneous clinical syndrome, with insomnia being reported at onset in only 3% of cases [2]. Although our case showed all the common clinical features of anti-LGI1 encephalitis, the patient had AE as the prominent presenting manifestation. AE is attributed to dysfunction in the thalamo-limbic circuits and was originally observed in three different disorders: fatal familial insomnia, delirium tremens and Morvan's syndrome, an autoimmune disease characterized by neuromyotonia and associated mainly with a second class of anti-VGKC antibodies: the anti-CASPR2 antibodies [1]. Reports of AE and status dissociatus in anti-LGI1 encephalitis are rare but have recently gained increasing recognition, supporting the presence of a spectrum of central nervous system involvement shared by the two anti-VGKC antibody-mediated diseases [5–7]. In the present case, the absence of anti-CASPR2 antibodies has been demonstrated in CSF only, but no data are available on serum. Nonetheless, various factors suggest that diagnosis of this case can reasonably be based on anti-LGI1 antibodies alone. First, it is recommended in the literature to search for anti-CASPR2 antibodies in CSF to support the pathological significance of serum positivity [8]. Secondly, recent studies report the presence of anti-CASPR2 antibodies in the CSF of patients with limbic encephalitis without evidence of peripheral nerve hyperexcitability, and almost only in the serum of patients with peripheral nerve hyperexcitability, particularly in Morvan's syndrome [9,10]. Thirdly, thymoma, which was absent in our patient, has been reported in patients with neuromyotonia or Morvan's syndrome associated with anti-CASPR2 antibodies [9,10], especially in those with double serum positivity for anti-LGI1 and anti-CASPR2 antibodies [10].

As shown in our case, AE primarily represents an extreme form of status dissociatus [11], where the three common electroclinical states of being (wakefulness, rapid eye movement [REM] sleep and non-REM sleep) are replaced by an intermediate, admixed electroclinical state [11]. As described by Lugaresi et al., AE is characterized behaviorally by a state of somnolence or mental confusion accompanied by hallucinations, delirium and OS, and electrically by a mixture of brief, unstable, partial REM sleep (even limited to REM on the electrooculogram, see Figure 1). Stage 1 non-REM sleep (with low-amplitude theta rhythm and slow eye movements) is also present, typically accompanied by the disappearance of physiological non-REM sleep features (like spindles, K-complexes and delta activities) [4].

Oneiric stupor episodes define the characteristic motor hyperactivity of AE. They can range from simple stereotyped gestures to more complex, apparently purposeful mimicking of daily activities. According to Guaraldi et al., these reflect the content of the dream experience, which, as observed in our case, can be recalled by patients upon awakening [3]. They differ from the unconscious movements of REM sleep behavior disorders, which arise instead from lack of muscle atonia during normal REM sleep in patients with a regular sleep–wake cycle [3]. REM sleep behavior disorders are usually less frequent and shorter than OS episodes and show typically violent, complex, wide behavior patterns that seem to mimic the content of a dream rather than a daily activity [3].

Several OS episodes were observed, which can be grouped by decreasing levels of complexity as (i) OS mimicking complex daily activities, (ii) oro-alimentary activity, including chewing and hand-to-mouth movements, and (iii) simple motor patterns (Video 1, segments b–d). Amongst the latter, bipedal, rhythmic alternating movements in our patient, resembling alternating leg muscle activation during sleep (Video 1, segment d1) [12] were repeatedly recorded by video-polysomnography. Some authors consider this phenomenon to be due to transient facilitation of a spinal central pattern generator (CPG) for locomotion [12,13]. Similarly, a CPG disinhibition mechanism [14] could be assumed to underlie the masticatory activity observed in our patient. Hence, albeit speculatively, this hypothesis supports the “carillon theory” [13] which postulates that “automatic” motor phenomena could be the result of CPG release, independently of the different etiologies. From this perspective, autoimmune encephalitis can be added to the list of triggers able to induce episodes of automatic fictive locomotion and mastication. Likewise, in the absence of an ictal pattern on EEG, multiple episodes of unilateral, rapid, repetitive thumb–finger movements resembling hand pill-rolling tremor were documented. This has been described amongst ictal motor

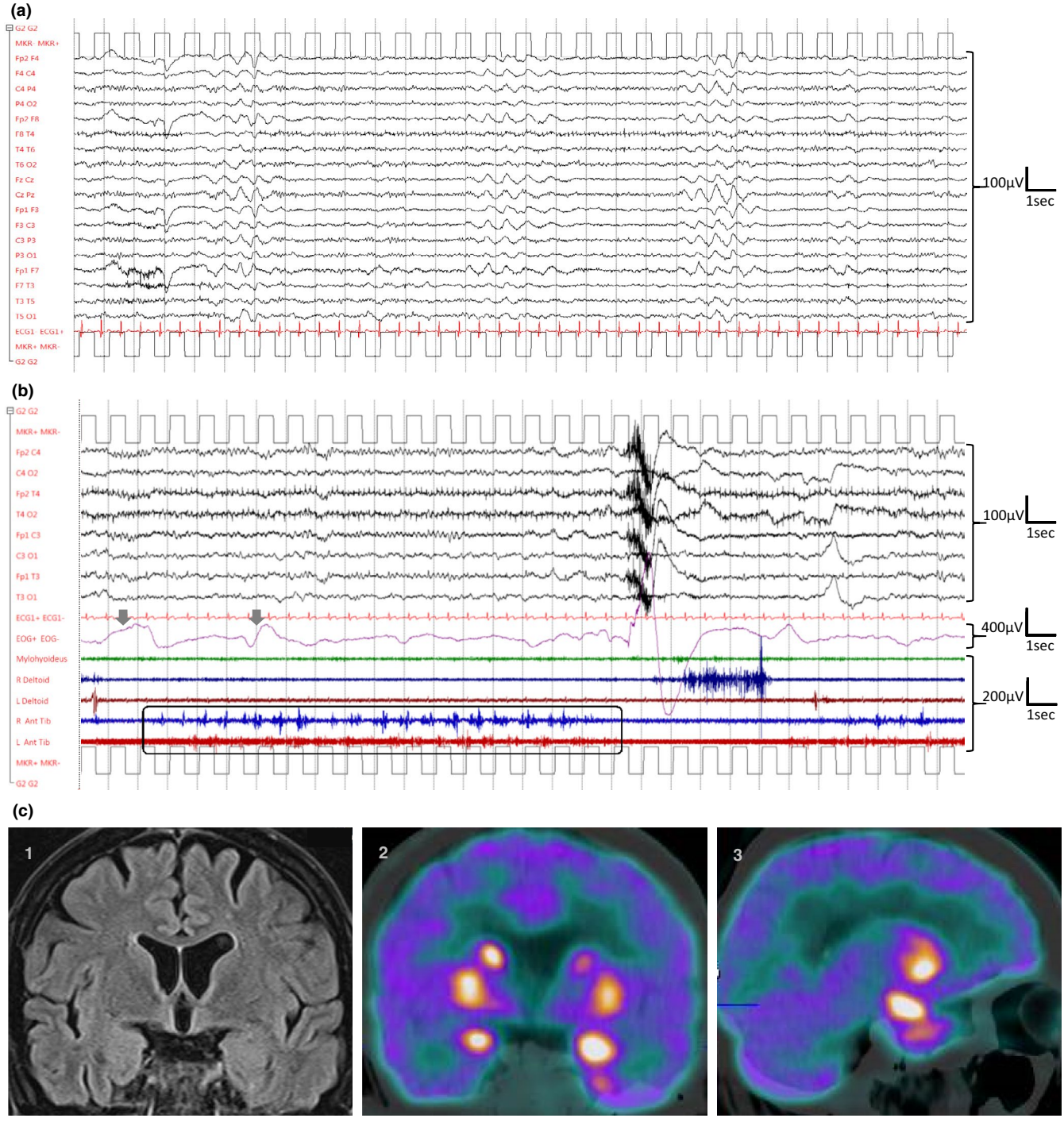


FIGURE 1 Electroencephalogram (EEG) and videopolygraphy of agrypnia excitata, brain magnetic resonance imaging (MRI) and positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose (^{18}F-FDG PET). (a) EEG shows background activity characterized by continuous low-amplitude theta-delta rhythm with superimposed fast activities and intermittent sequences of diffuse high-amplitude delta waves, without epileptiform abnormalities. (b) Prolonged video-polysomnography during which the patient lay calmly on a bed with his eyes closed. The EEG has the same features shown in (a) for the entire recording time, unchanged during rest and activity, even during an episode of oneiric stupor (OS). Sometimes rapid eye movements (REM, arrows) are evident on the electrooculogram (EOG). Electromyogram channels from the anterior tibialis muscles show alternating rhythmic activations (rectangle) during an episode of OS characterized by bipedal locomotor activity, similar to the sleep-related phenomenon described as alternating leg muscle activation. (c) Brain MRI did not show clear-cut abnormalities, although a mild hyperintense signal in fluid-attenuated inversion recovery sequences can be noted in both the anterior mesial temporal structures and hypothalamus (the coronal plane image is shown in (c1)). (c2), (c3) ^{18}F-FDG PET shows pathological hypermetabolism of the hippocampus bilaterally, amygdala (left > right), and basal ganglia (right > left). Ant Tib, anterior tibialis muscle; Deltoid, deltoid muscle; ECG, electrocardiogram; L, left; MKR, marker; Mylohyoideus, mylohyoid muscle; R, right [Colour figure can be viewed at wileyonlinelibrary.com]

phenomena in temporal lobe seizures, classified as rhythmic ictal non-clonic hand motions (Video 1, segment d2) [15]. Speculatively, our observations could suggest that hand pill-rolling movements may also be considered a simple, inborn motor pattern, observed in different etiological entities (namely epilepsy and AE).

Finally, sympathetic overactivity, the third criterion for AE, was a dominant clinical manifestation in our patient, who presented persistent tachycardia and hyperhidrosis during the first weeks of hospital stay.

CONCLUSIONS

Agrypnia excitata without neuromyotonia could be the dominant clinical feature of anti-LGI1 encephalitis. The OS episodes represent a useful electroclinical factor for diagnostic suspicion at the bedside, permitting prompt treatment. Furthermore, Agrypnia excitata represents a possible window to understanding the mechanisms of some movement disorders observed in autoimmune encephalitis.

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CONFLICT OF INTEREST

No authors declare any disclosures.

AUTHOR CONTRIBUTIONS

Silvio Piffer: Conceptualization (lead); data curation (lead); formal analysis (lead); investigation (lead); methodology (lead); project administration (lead); writing—original draft (lead); writing—review and editing (lead). Gaetano Cantalupo: Conceptualization (lead); data curation (lead); formal analysis (lead); investigation (supporting); methodology (supporting); project administration (supporting); supervision (lead); writing—original draft (lead); writing—review and editing (lead). Stefania Filipponi: Data curation (supporting); supervision (supporting). Valentina Poretto: Data curation (supporting); supervision (supporting). Maria Pellegrini: Data curation (supporting); supervision (supporting). Raffaella Tanel: Data curation (supporting); supervision (supporting). Manuela Buganza: Data curation (supporting); supervision (supporting). Bruno Giometto: Supervision (supporting); writing—original draft (supporting); writing—review and editing (supporting).

PATIENT CONSENT

The patient's family consented to publication of all documents forming this work since the patient died before the first submission.

DATA AVAILABILITY STATEMENT

All data relevant to this study are included in the article or uploaded as supplementary information.

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