Hong Kong College of Physicians
Case Report for Interim Assessment
Specialty Board of Advanced Internal Medicine (AIM)

For AIM Training, case reports should be submitted in the prescribed format together with the application form for Interim Assessment at least EIGHT Weeks before the date of Interim Assessment

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Date(s) and place (hospital) of patient encounter: Feb 2020, Oct 2022
Date of report submission: March 2024

Case report

Note: Failure to follow the prescribed format (including the number of words) results in a FAILURE mark (score between 0 and 4) for the Case Report.

Title: Uncontrollable seizures, hyponatremia, and cognitive decline - A case of anti-LGI-1 antibody autoimmune encephalitis

Case History:

A 70-year-old man with hypertension and lower urinary tract symptoms was admitted for suspected focal seizures presenting as involuntary movements affecting the right upper extremity. The symptoms started 1 month prior to admission and manifested as sudden and brief episodes of lateralized tonic contractions involving the right upper extremity. Each episode lasted for a few seconds, and were associated with dystonic posturing of the hand, ipsilateral "spasms" of the face and occasionally sudden cessation of speech. Consciousness was fully preserved in all episodes, without preceding auras or prodromal symptoms, nor any incontinence or tongue biting. There were no preceding head injuries or stroke-like symptoms in the past. There was no fever, neck pain, or constitutional symptoms. These occurrences had occurred around 1-2 times per day for once or twice per week, and the patient was subjectively well between episodes.

Upon admission, patient was self-ambulatory and fully alert. An episode of

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the described 'attack' occurred during the initial assessment, but the patient was able to continue with the assessment promptly afterwards. Further history was supplemented by the patient's accompanying wife, and was unrevealing for any illicit drug use, mental illness, or family history of neurological disorders. On physical examination, the blood pressure and pulse rate, temperature, and oxygen saturation were within normal limits. A point-of-care capillary blood glucose measurement showed a random blood glucose of 6.0 mmol/L. The Glasgow Coma Scale (GCS) was full at 15/15. An abbreviated mental test (AMT) was conducted, which scored 10/10. There were no focal neurological deficits with full limb powers and preserved sensation over the upper and lower extremities. Cranial nerves examination was unremarkable. The rest of the physical examination including the cardiovascular, respiratory, and abdominal systems was unrevealing.

A computed tomography (CT) of the brain was performed which was unrevealing. Basic biochemistry panel including electrolytes, thyroid function test, and inflammatory markers were within normal limits. An electroencephalogram (EEG) was done, which identified 'features suggestive of cortical myoclonus, with intermittent interictal epileptiform discharges of polyspike or polyspike-wave'. A magnetic resonance imaging (MRI) of the brain was reported to mainly show mild age-related cerebral atrophy, but otherwise no acute ischaemic changes, intra-cranial bleed, space-occupying mass nor abnormal enhancement. A lumbar puncture examination was discussed but was declined by the patient at that juncture. The neurology team was consulted, and the patient was started on Valproate 300mg twice per day with planned outpatient monitoring. The dose was increased two weeks later to 300mg (morning dose) and 500mg (evening dose) due to persistent and frequent 'attacks'.

Two months after the commencement of anti-epileptic drug, the patient was re-admitted for increasing frequency of seizures. Blood tests upon admission revealed hyponatremia of 123 mmol/L, with further urine pattern compatible with 'syndrome of inappropriate anti-diuretic hormone release' (SIADH). In view of possible drug-related SIADH, the patient was placed on fluid restriction and low-dose sodium chloride tablet at 900mg daily with normalization of sodium levels. Clonazepam 0.25mg twice per day was added-on, with initial improvements in terms of seizure frequencies. A positron-emission tomography-computed tomography (PET-CT) for the

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exclusion of occult malignancies giving rise to SIADH was also unrevealing.

Three months after initial presentation, the patient was reviewed at the neurology clinic during which the patient reported further increase in frequencies of seizures to twice per hour, severely impairing his ability to write or eat. There was a subtle change in seizure semiology, with increased involvement of facial and lower limb musculature. In addition, the patient's wife reported the patient to be more agitated and forgetful than usual. The patient was admitted for further management, with oral levetiracetam added on top of valproate and clonazepam. Upon review of the patient's latest video-recording of the seizure attacks, a specific type of seizure – 'faciobrachial dystonic seizure (FBDS)' was identified. Combined with prior features of SIADH, cognitive decline and resistance to anti-epileptic therapy, anti-leucine-rich-glioma-inactivated 1 (LGI1) autoimmune encephalitis was suspected. A lumbar puncture was eventually agreed by the patient and was performed. Cerebral spinal fluid (CSF) analysis showed a total cell count of less than 1×10^6/L, with a slightly elevated CSF protein at 0.63 g/L, CSF/plasma glucose ratio of 2.8/5.8mmol/L. CSF microbiological workup including bacterial and fungal smears, cultures and multiplex polymerase chain reaction (PCR) for viruses were negative. While serum autoimmune encephalitis panel testing returned to be negative, a CSF sample for autoimmune encephalitis antibody screen returned to be positive for anti-LGI1-antibodies (figure 1). A diagnosis of anti-LGI1-antibody autoimmune encephalitis was made. The patient was then treated with 5 doses of intravenous methylprednisolone at 1 gram followed by a tapering course of oral prednisolone starting at 35mg daily. Azathioprine was later introduced and increased to a dose of 100mg daily after TPMT/NUDT15 genotyping confirmed the absence of thiopurine intolerance alleles. There was marked improvement in the frequency of seizures, with complete abatement of clinical seizures 6 weeks after initiation of immunosuppressive therapy. Residual cognitive deficits remained with subjectively poor short-term memory, although this had considerably improved compared to pre-immunosuppression state. Oral steroids were eventually tapered off after 9 months, and the patient was maintained on oral azathioprine at 100mg daily. His baseline anti-epileptic therapy was streamlined to valproate 300mg twice per day, and he remained seizure-free for the past 3 years.

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Discussion & literature review

Anti-leucine-rich glioma-inactivated 1 (anti-LGI1) autoimmune encephalitis (AIE) is a rare type of AIE, with a reported incidence rate of less than 1 per million people across various ethnicities (1). Average age of onset is typically 50-60 years of age (range 22-92), with slight male predominance in the reported literature (1). It is a subtype of AIE characterized by the presence of antibodies, either in the serum and/or in the cerebrospinal fluid (CSF), against LGI1, a neuronal-synapse cell surface protein (2). The condition is associated with a tumour in around 10% of cases, typically thymoma, but tumours including pancreatic neuroendocrine tumours, mesothelioma had been described as well (3).

Cardinal features of anti-LGI1 AIE include seizures, hyponatremia, and neuro-psychiatric disturbances; all of which are observed in our patient. Seizures are seen in the 75-90% of patients, which may take the form of focal seizures, generalized tonic-clonic seizures (GTCS), complex partial seizures, status epilepticus, and autonomic seizures (4,5). The frequency of seizure typically increases along the disease course, and seizure semiology may evolve with time (4,5). Of the various seizure types described with anti-LGI1 AIE, a specific type of "seizure" - faciobrachial dystonic seizure (FBDS) - is present in 25-70% of patients, which is considered pathognomic for the condition and often precedes other symptoms of anti-LGI1 AIE such as cognitive impairments, neuropsychiatric manifestations, and hyponatremia (4,5). It is classically described as a spasm that affects the arm in all cases, with the face and legs less commonly involved; it may also be associated with impaired awareness and vocalizations (4). Either side of the body may be affected but is always unilateral on any occasion. Episodes are often brief lasting less than 3 seconds each, and may occur up to 360 times per day (range 6-360) (5). Despite its designation as a "seizure", there had been reports showing lack of corresponding EEG anomalies during episodes of FBDS, thus questioning the nature of this distinct movement pattern (6). Another classical feature of anti-LGI1 AIE is hyponatremia, which is seen in the majority of patients and may be severe (less than 120 mmol/L) in some (2). Biochemically, the pattern resembles that of SIADH, which is postulated to be due to antibodies interacting with LGI1 antigens expressed at the hypothalamic paraventricular nucleus and possibly with kidney tubules (2). Neuro-psychiatric manifestations are also common, as

was observed in our patient. Memory deficits are common with reported rates of 68-100%, and may be attributed to anti-LGI1 antibodies disrupting ligand-receptor interaction of LGI1 with ADAM22/23 transmembrane proteins, which are essential for regulation of AMPA receptor-mediated synaptic transmission in the hippocampus (2,5). Other features such as personality changes, hallucination, sleep disturbances, mood disorders are more variable in prevalence (5). The occurrence of the various forms of neuropsychiatric lends its designation as a form of limbic encephalitis by some experts.

The diagnosis of anti-LGI1 AIE, similar to other subtypes of AIE, requires a combination of compatible clinical symptomatology, imaging or CSF findings, and reasonable exclusion of alternative causes (fig. 2) (7,8). Further subclassification of AIE requires the demonstration of specific autoimmune encephalitis-specific antibodies, such as anti-LGI1, anti-CASPR2, anti-$GABA_A$-R antibodies (8). While a similar approach in the diagnosis of AIE is proposed, significant differences exist with regards to investigation findings. A systematic analysis of CSF findings from patients with AIE revealed that basic CSF findings are profoundly different across various subtypes of AIE. In this study CSF pleocytosis (defined as a CSF total cell count of more than 5 cells per cubic millimeter) was rare in anti-LGI1 AIE at 16% of cases, whereas CSF pleocytosis was present in more than 50% of patients with anti-NMDA-R, anti-AMPA-R, anti-$GABA_B$R and anti-DPPX AIE. Elevated CSF protein levels, although present in only around 25% of anti-LGI1 AIE, had a had a relatively high median pathological protein level compared to other subtypes of AIE when present. CSF oligoclonal band, a feature present in more than 50% of patients with anti-GAD, anti-$GABA_B$R and anti-NMDA-R AIE, is rare in patients with anti-LGI1 AIE at only 5% (9). Findings of brain MRI are also variable as well, with rates of normal MRI reported at 30-70% (5,10). When abnormal, abnormalities on T2-weighted fluid-attenuated inversion recovery MRI sequence may be seen over the medial temporal lobe region, mostly with bilateral distributions (5).

With regards to treatment of anti-LGI1 AIE, early immunosuppressive therapy is key to better outcomes. No guidelines currently exist on the treatment of anti-LGI1 AIE; most case series or case reports in the existing literature reported drastic improvements with the use of systemic steroids, frequently in the form of pulse intravenous methylprednisolone at doses

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ranging from 250 to 1000mg for 3 to 5 days, followed by a tapering course of oral predniso(lo)ne (5,10). Other adjunctive treatments that have been described to be used in conjunction with systemic steroids include intravenous immunoglobulin, plasma exchange, rituximab, mycophenolate mofetil, and azathioprine (5). Response to immunosuppression is generally favorable, and cessation of seizures (including FBDS) is typically seen within 3 months in almost 88% of patients (1,10). Improvement in neuro-psychiatric manifestations including cognition is seen with immunosuppression, but residual cognitive impairment often remained especially in patients where immunosuppressive therapy was delayed (10). Anti-epileptic drugs are frequently co-prescribed prior to initiation of immunosuppressive therapy, but is frequently ineffective (5). In the long term, relapses can occur even after long intervals, but may remain responsive to steroids (10).

In conclusion, this case illustrates the possible diagnostic complexities in approaching a patient with new-onset seizure. In patients who failed to improve or had suboptimal seizure control despite anti-epileptic drugs at reasonable doses, the initial diagnosis should be revisited. The case also demonstrated that in certain types of autoimmune encephalitis such as anti-LGI1-antibody encephalitis, initial evaluations including MRI and CSF analysis may be largely unremarkable. As such normal CSF or MRI results do not exclude a diagnosis of autoimmune encephalitis. This is particularly important as cases of autoimmune encephalitis may respond well to early immunosuppressive therapy with drastic improvements without being subjected to the detriments of multiple, possibly ineffective anti-epileptic agents and their side effects.

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Tables and figures (where applicable) (no more than two figures)

Figure 1 – autoimmune encephalitis antibody screen (panel)

Autoimmune Encephalitis Ab Panel (CSF)	
Anti-CASPR2	Neg
Anti-AMPA1/2	Neg
Anti-LGI1	WP
Anti-DPPX	Neg
Anti-GABAR B1/B2	Neg

Autoimmune Encephalitis Ab Panel	
Anti-CASPR2	Neg
Anti-AMPA1/2	Neg
Anti-LGI1	Neg
Anti-DPPX	Neg
Anti-GABAR B1/B2	Neg

Footnotes:
WP - Weak POSITIVE

Figure 2 – Diagnostic crtieria for definite autoimmune encephalitis

Diagnosis can be made when all four of the following criteria have been met:
(1) Subacute onset (rapid progression of less than 3 months) of - Working memory deficits (short-term memory loss), or - Altered mental status (decreased /altered level of consciousness, lethargy, personality changes), or - Psychiatric symptoms suggesting involvement of the limbic system
(2) At least one of the following: - New focal central nervous system findings - Seizures not explained by a previously known seizure disorder - CSF pleocytosis (white blood cell count > 5 cells/mm^3) - MRI features suggestive of encephalitis*
(3) Reasonable exclusion of alternative causes
(4) Autoimmune encephalitis-specific antibody (e.g. LGI1 encephalitis, CASPR2 encephalitis)
Footnote: *MRI features of encephalitis: hyperintense signal on T2-weighted fluid-attenuated inversion recovery sequences highly restricted to one or both medial temporal lobes, or in multifocal areas compatible with demyelination or inflammation

Modified from references 7,8

Reference (not more than 10)

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2. Li W, Wu S, Meng Q, Zhang X, Guo Y, Cong L, et al. Clinical characteristics and short-term prognosis of LGI1 antibody encephalitis: a retrospective case study. BMC Neurology. 2018 Jul 6;18(1)
3. van Sonderen A, Roelen DL, Stoop JA, Verdijk RM, Haasnoot GW, Thijs RD, et al. Anti-LGI1 encephalitis is strongly associated with HLA-DR7 and HLA-DRB4. Annals of Neurology. 2017 Jan 27;81(2):193–8
4. Yang X, Li AN, Zhao XH, Liu XW, Wang SJ. Clinical features of patients with anti-leucine-rich glioma inactivated-1 protein associated encephalitis: a Chinese case series. International Journal of Neuroscience. 2019 Feb 15;129(8):754–61
5. Irani SR, Michell AW, Lang B, Pettingill P, Waters P, Johnson MR, et al. Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. Annals of Neurology [Internet]. 2011 Mar 17;69(5):892–900
6. van Sonderen A, Thijs RD, Coenders EC, Jiskoot LC, Sanchez E, de Bruijn MAAM, et al. Anti-LGI1 encephalitis. Neurology. 2016 Sep 2;87(14):1449–56
7. Orozco E, Valencia-Sanchez C, Britton J, Dubey D, Flanagan EP, A. Sebastian Lopez-Chiriboga, et al. Autoimmune Encephalitis Criteria in Clinical Practice. Neurology Clinical Practice. 2023 Jun 1;13(3)
8. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. The Lancet Neurology [Internet]. 2016 Apr;15(4):391–404.
9. Blinder T, Lewerenz J. Cerebrospinal Fluid Findings in Patients With Autoimmune Encephalitis—A Systematic Analysis. Frontiers in Neurology. 2019 Jul 25;10
10. Li L, Ma C, Zhang H, Lian Y. Clinical and electrographic characteristics of seizures in LGI1-antibody encephalitis. Epilepsy & Behavior. 2018 Nov;88:277–82

No of words in Case History and Discussion (excluding references): 1873.

(should be between 1000-2000)

Declaration

I hereby declare that the case report submitted represents my own work and adheres to the prescribed format. I have been in clinical contact with the case selected. The case report has not been submitted to any assessment board or publication and it is NOT related to my second specialty(ies), if any. My consent is hereby given to the College to keep a copy of my case report, in written and/or electronic, at the College Secretariat and allow the public to have free access to the work for reference.

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(signature of Trainee)

Endorsed by Supervisor *

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(signature of Supervisor)

* Supervisors must go over the Case Report with the Trainees, advise Trainees whether further amendments are necessary, review the Originality/ Similarity Report prepared by Trainees, adherence to the required format, sign on the report and remind Trainees on issues related to copyright and plagiarism.