Autoimmune encephalitis presenting with cognitive decline and hyponatraemia

Introduction

The clinical presentation of subacute cognitive decline with behavioural disturbance in an older patient presenting with severe hyponatraemia can be a diagnostic challenge as the differential diagnosis is broad. This article presents a case in which identification of typical clinical features and laboratory findings guided investigations, culminating in a diagnosis of limbic encephalitis with positive leucine-rich glioma inactivated 1 (LGI1) antibodies, not associated with malignancy. The patient made a good recovery with a course of rituximab, following initial unsuccessful treatment with corticosteroids, intravenous immunoglobulin and plasma exchange.

Discussion

The differential diagnosis of subacute cognitive decline is broad. Lack of improvement despite correcting sodium levels ruled out hyponatraemia as the only cause of the symptoms, while normal magnetic resonance imaging ruled out central pontine myelinolysis, a neurological complication of rapid sodium correction and other metabolic disturbances. Other toxic and metabolic causes (vitamin B_{12} deficiency, Wernicke's and Hashimoto's encephalopathy) as well as infections (HIV, neurosyphilis and herpes simplex virus encephalitis) were ruled out through extensive investigations.

Creutzfeldt–Jakob disease can cause rapid cognitive decline, unsteadiness and myoclonus. However, this patient lacked typical synchronous bi- or triphasic sharp wave complexes on electroencephalogram and had no basal ganglia abnormalities on magnetic resonance imaging.

Frontotemporal dementia can progress rapidly and is often preceded by neuropsychiatric disturbance (Geschwind et al, 2007). However, hyponatraemia, mildly inflammatory CSF and lack of frontal or temporal lobe atrophy on magnetic resonance imaging made this diagnosis unlikely.

Dr Gillian Chin, Foundation Year 2 Doctor, Department for Older People, Whiston Hospital, Prescot L35 5DR

Dr Stephen Allsup, Consultant in Geriatrics and General Medicine, Department for Older People, Whiston Hospital, Prescot

Dr Lauren Fratalia, Consultant Neurologist, Department of Neurology, The Walton Centre, Liverpool

Correspondence to: Dr G Chin (Gillian.chin@doctors.org.uk)

CASE REPORT

A 69-year-old man presented with a 5-month history of increasing confusion, memory loss, unsteadiness, and repetitive, brief body spasms.

There was no past or family history of psychiatric or neurological conditions, or any history of alcohol or substance misuse. Comorbidities included ischaemic heart disease, hypertension and hypercholesterolaemia.

Initial investigation revealed significant hyponatraemia (120 mmol/litre), prompting admission to hospital.

On examination, cranial nerve and cerebellar examinations were normal, as well as tone, power, reflexes and sensation in all limbs. He had an unsteady shuffling gait, frequent facial grimaces and body spasms affecting the arms and legs. On Addenbrooke's Cognitive Examination (ACE-III), he scored 87/100, losing marks in fluency and memory, and was unable to write simple sentences. He had fluctuating confusion and would repeatedly attempt to leave the ward, becoming verbally and occasionally physically aggressive against staff and relatives.

In hospital, baseline investigations revealed a hyponatraemia consistent with syndrome of inappropriate antidiuretic hormone. Blood counts, renal function, C-reactive protein, liver function test, thyroid function tests, electrolytes and vitamin B_{12} levels were normal. He tested negative for hepatitis C virus antibody, hepatitis B virus surface antigen, human immunodeficiency virus (HIV) 1 and 2 antibody, p24 antigen, syphilis and connective tissue disease autoantibodies.

Magnetic resonance imaging of the head showed minor chronic ischaemia as expected for age but the temporal lobes in particular appeared normal. A computed tomography scan of the thorax abdomen and pelvis with contrast showed no lymphadenopathy or evidence of malignancy.

CSF studies showed mild inflammatory changes with raised white blood cell count of 8 cells/mm^3 (>5 cell/mm^3 is abnormal) and normal protein 0.33 g/litre (>0.45 g/litre is abnormal). Viral polymerase chain reaction was negative for varicella zoster virus, herpes simplex virus type 1 and 2, and parechovirus. No organism was found on Gram staining.

Several electroencephalogram assessments were undertaken including a 24-hour ambulatory study and prolonged video-electroencephalogram, none of which showed any epileptiform change.

Screening for autoimmune encephalitis found highly positive voltage-gated potassium channel antibodies at 2017 pmol/litre (>69 pmol/litre is abnormal) and positive leucine-rich glioma inactivated 1 (LGI1) antibodies, an immunological subgroup of voltage-gated potassium channel antibodies. Anti-CASPR2 (contactin-associated protein 2), anti-VGCC (voltage-gated calcium channels) and anti-NMDAR (N-methyl-D-aspartate receptor) were negative.

He was diagnosed with anti-LGI1 limbic encephalitis with associated faciobrachial dystonic seizures and hyponatraemia.

Treatment with high-dose steroids did not lead to any improvement, while benefit from intravenous immunoglobulin was modest and transient. Subsequently, he failed to respond to plasma exchange and was transferred to a tertiary neurological centre where treatment with rituximab, given 10 months after disease onset, was highly effective.

The patient made a steady improvement over months. His working memory, long-term memory and concentration are now within normal limits, with mild short-term memory impairment. The neuropsychiatric disturbance, aggression and abnormal movements have subsided completely. He engages in meaningful conversation and is independent in all activities of daily living. Repeat testing of LGI1 antibodies following immunotherapy showed a weak positive result.

A diagnosis of autoimmune encephalitis was made on the basis of a typical clinical presentation and positive LGI1 antibodies. Autoimmune encephalitis is a rapidly progressing, debilitating, autoantibody-mediated inflammatory condition of the CNS (Graus et al, 2016). Dubey et al (2018) found the prevalence (14 per 100 000 population) and incidence (0.8 per 100 000 person-year) of autoimmune encephalitis comparable to that of infective encephalitis.

Limbic encephalitis is a common manifestation of various autoimmune encephalitides or paraneoplastic processes, and is characterized by subacute deterioration of short-term memory, disorientation and seizures (Graus et al, 2016). Differentiation between immunological subgroups is important as subgroups associated with paraneoplastic conditions are less responsive to immunotherapy (Graus et al, 2016). Anti-LGI1 limbic encephalitis is usually monophasic and is generally quickly responsive to immunotherapy. It is often non-paraneoplastic, with only 5–10% associated with cancers, usually thymomas (Graus et al, 2016; Wang et al, 2017). Anti-LGI1 limbic encephalitis frequently presents with mild-to-moderate pleocytosis (60–80%) (Graus et al, 2016; Wang et al, 2017). Hyponatraemia is common, and can be severe in up to 60% of cases (Lai et al, 2010).

Faciobrachial dystonic seizures are characteristic of anti-LGI1 limbic encephalitis (72–78%) and consist of frequent, brief, dystonic movements involving the face, arm and, occasionally, leg (Irani et al, 2011; Gastaldi et al, 2016; Wang et al, 2017). They respond poorly to antiepileptic drugs, but usually respond to immunotherapy (Irani et al, 2011, 2014).

Characteristically, limbic encephalitis presents with hippocampal T2 hyperintensity on magnetic resonance imaging of the brain, but imaging may be normal in 26–58% of cases at disease onset (Navarro et al, 2016; van Sonderen et al, 2016).

First-line treatment is single or combination therapy with corticosteroids, intravenous immunoglobulin or plasmapheresis. In a limited number of refractory cases, steroid-sparing agents such as rituximab, tacrolimus or azathioprine have been used with highly variable results (Gastaldi et al, 2016). In this patient, rituximab was administered 10 months after symptom onset with excellent response. He had no adverse effect from rituximab and had no relapses on 6-month follow up. **BJHM**

LEARNING POINTS

- Anti-leucine-rich glioma inactivated 1 (LGI1) encephalitis is a clinically recognizable and treatable condition.
- Hyponatraemia and episodes suggestive of faciobrachial dystonic seizures should raise suspicion for limbic encephalitis in a patient presenting with cognitive symptoms.
- Anti-LGI1 limbic encephalitis generally responds well to immunosuppressive treatment, although residual cognitive impairment is common and relapses may occur.
- Rituximab may be an effective treatment when first-line agents have failed.

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