CASE REPORT

Anti-LGI1 encephalitis causing faciobrachial dystonic seizures

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SUMMARY

Anti-leucine-rich glioma inactivated protein 1 (LGI1) encephalitis has an autoimmune origin and can be reversed with immunotherapy. It is obvious that identifying and treating this condition early is of paramount importance. We present the case of a 69-year-old man who was admitted to hospital with faciobrachial dystonic seizures and was found to have antibodies to LGI1. His symptoms started approximately 3 months prior admission to the hospital. There had also been some subtle cognitive impairment. He was treated with two courses of intravenous immunoglobulin and commenced on prednisolone 50 mg daily and clonazepam 500 µg at night. Despite these treatments, his seizures were becoming progressively more frequent and severe. He then underwent treatment with a course of plasma exchange followed by an intravenous infusion of methylprednisolone and returned to his previous baseline function.

BACKGROUND

Voltage-gated potassium channel (VGKC) antibodies were detected in 1995 in patients suffering from neuromyotonia.¹

The clinical presentation of this pathology ranged significantly, and several different descriptions were given. That raised the question how such a wide range could be attributed to one antibody.

Indeed, in 2010 the identification of two proteins, the leucine-rich, glioma inactivated protein 1 (LGI1) and the contactin-associated protein2 (Caspr2), as a target of the antibodies, enabled us to understand better this autoimmune disorder.^{2,3}

Anti-LGI1 encephalitis is an antibody-associated inflammation of the limbic system of the brain. It is a rare disease. The annual incidence of this disease in the Netherlands is 0.83 per million. There have been around 300 patients, so far, reported. The clinical presentation involves a subacute onset of frequent short seizures with patients exhibiting disturbances in memory and behaviour. There is an association with tumours in 5% to 10% of the cases with the most common being thymomas.⁴

Caspr2 is a membrane protein expressed in the central nervous system (CNS) and peripheral nervous system (PNS). There is more diversity in regards to the clinical presentation of Caspr2 antibody-related disease. The majority of the cases with antibodies to Caspr2 present with Morvan syndrome, epilepsy or pain syndromes. There have been reports with positive Caspr2 antibodies

in patients with antibodies to LGI1. The clinical presentation of Caspr2 remains not well defined.⁵

According to a large clinicoserological study, it has been observed that LGI1 and Caspr2 auto-antibodies are associated with diverse neurological phenotypes that often overlap. The most common presentation is limbic encephalitis in the CNS and neuromyotonia or Morvan's syndrome in the PNS.⁶

This case highlights characteristic features such as seizures and hyponatraemia that are typical of anti-LGI1 encephalitis. The case report illustrates the importance of antibody testing and imaging in classification and identifying this condition, which is often undiagnosed.

The use of the term anti-LGI1 encephalitis is proposed, and this disorder should be classed as an autoimmune synaptic encephalopathy.

CASE PRESENTATION

A 69-year-old man complained of vague, non-specific symptoms and of 'generally not right' for 6 months. He complained of lethargy, a protracted period of soreness in the throat between March and June 2013 and then a 3-month history of abnormal movements described as spasms affecting his left face, arm and leg and occasionally, affecting the right side. The spasms lasted only for a second and he appeared to retain awareness but his speech was transiently disturbed and he lost his train of thought briefly. The spasms occurred every few minutes throughout the day but generally remitted in sleep, although his wife had witnessed this during his sleep.

The patient was a retired professor of veterinary medicine and felt that his cognition had been slightly impaired in recent months. He also reported an episode for 1 month where he had extremely cold extremities. There was a travel history of visiting Brazil including the rain forest areas in January 2013. Apart from a severe migraine with an episode of expressive dysphasia during that visit, which he attributed to jet lag, he was otherwise well. He had also visited Eastern Europe and India within the last 12 months. In India, he experienced severe gastroenteritis. There was no history of fever, rash, cough, hallucination, delusions or bleeding. However, he had lost 4 kg of body weight and had been more somnolent than usual by day and insomniac at night. He injured his left elbow in September prior admission to hospital and subsequently developed swelling, redness and tenderness at the site.

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Figure 1 MRI brain scan T2-FLAIR showing an ill-defined hyperintense signal, involving the left side of the medial temporal lobe. FLAIR, fluid attenuated inversion recovery.

Examination showed that his cognition was slightly reduced with Addenbrooke's Cognitive Examination-Revised test (ACE-R): 93/100 and Mini-Mental State Examination: 29/30 but this was not evident during general conversation.⁷ His movement disorder was observed by a neurology team, in line with the description given above. It was thought that the diagnosis might have been consistent with a faciobrachial dystonic seizure. Cranial nerve examination was normal. In the limbs, power, tone, reflexes, sensation and coordination were normal. Fasciculations were observed in both gastrocnemius muscles. The left

Figure 2 MRI brain scan coronal view showing no significant mass effect and no haemorrhagic changes.

elbow showed features consistent with an olecranon bursitis, which was initially hot, erythematous and slightly indurated.

INVESTIGATIONS

Blood investigations revealed hyponatraemia with features in keeping with the syndrome of inappropriate antidiuretic hormone secretion: Na 126 mmol/L, urine osmolality 764 mmol/kg H₂O, urine sodium 106 mmol/L and serum osmolality 267 mOsm/kg H₂O. A full blood count showed only mild lymphopaenia ($1.1 \times 10^9/L$), but indices were otherwise normal. The calcium, phosphate, magnesium, liver function tests, C-reactive protein, creatine kinase, glucose, thyroid function, ferritin, HIV serology, immunoglobulins and serum electrophoresis, serum ACE and antistreptococcal antibody titres were all normal or negative. Autoantibodies that were negative included anti nuclear, anti-double-stranded DNA, antineutrophil cytoplasmic, extractable nuclear antigens screen tests for: anti-Sm antibodies/small nuclear ribonucleoprotein antibodies/antibodies to the La antigen (anti-La)/antibodies to the Ro antigen/antitopoisomerase I antibodies/antibodies to the cytoplasmic protein.

Basal ganglia and neuronal antibodies (anti-Yo, anti-Hu, anti-Ri) were negative as well.

Antibodies against the voltage gated potassium channel (anti-VGKC) were strongly positive (1002 pM, normal <100) and antibodies to LGI1 were positive as well. Antibodies against contactin-associated protein (anti-Caspr), anti-N-methyl-D-aspartate receptor, antiglutamic acid decarboxylase, anti-amphiphysin antibodies and glycine receptor antibodies were negative. Serum ceruloplasmin and copper levels were normal.

Cerebrospinal fluid (CSF) examination showed acellular fluid, no bacterial growth, normal biochemistry and no evidence of oligoclonal bands. The opening pressure was normal. CSF cytology showed a hypocellular deposit with scanty small lymphocytes and histiocytes but no malignant cells.

Hepatitis B virus surface antigen, Hepatitis C virus IgG assay, Hepatitis B surface antibody tests were all negative or normal. Serology for American Trypanosomiasis was negative. Joint aspirations from the left olecranon bursa on two occasions, both revealed *Klebsiella oxytoca* after extended incubation.

A CT scan of the thorax showed calcified nodules in both upper lung lobes measuring 3–4 mm inside, which were reported as being benign. However, there were several other non-calcified pulmonary nodules, the largest of which was in the right lower lobe, measuring 7 mm. There was no hilar or mediastinal lymphadenopathy. Abdominal and pelvic organs were normal.

The patient had two electroencephalograms and was not felt to show any epileptiform discharges.

A consultant neuroradiologist reviewed the MRI brain scans.

T2-fluid attenuated inversion recovery (FLAIR) showed an ill-defined hyperintense signal, involving the left side of the medial temporal lobe (figure 1). There was no significant mass effect and no haemorrhagic changes in the coronal views (figure 2). The axial FLAIR showed mild asymmetrical enlargement and faint increased signal intensity in the left side of the medial temporal lobe/hippocampus (figure 3).

Nerve conduction studies showed small upper and lower limb sensory potentials but normal motor studies except for a mild reduction in lower limb motor conduction velocity. Electromyogram was normal, in particular, showing no evidence of neuromyotonia.

Echocardiogram showed dilated right heart but good left ventricular and right ventricular systolic function. There was

Figure 3 MRI brain axial FLAIR showing mild asymmetrical enlargement and faint increased signal intensity in the left side of the medial temporal lobe/hippocampus. FLAIR, fluid attenuated inversion recovery.

leaflet mitral valve prolapse with mild to moderate mitral regurgitation, and the left atrium was mildly enlarged.

DIFFERENTIAL DIAGNOSIS

It is extremely important to make the right diagnosis as early as possible, and it is necessary to exclude the presence of underlying malignancy, as it can be associated with this pathology.⁸ In this case, there was nothing to suggest the presence of neoplasia.

At the initial stage the differential diagnosis included:

- ▶ Hashimoto's encephalopathy: there was no evidence of thyroiditis and thyroid function tests were normal.
- ▶ Hepatic encephalopathy: the liver function tests were normal and radiological findings were unremarkable with no evidence of ascites.
- ▶ Wernicke-Korsakoff's encephalopathy: patient had minimal alcohol consumption.

Figure 4 Spasms of the patient per 24 hours. IVIG, intravenous immunoglobulin; OD, once daily; PLEX, Plasma Exchange

- ▶ Infectious encephalopathy: several forms of infections that could lead to encephalopathy were excluded.
- ▶ Neurosarcoidosis: the imaging and laboratory tests were not supportive of the diagnosis, ACE levels were normal.
- ▶ Wilson's disease: serum caeruloplasmin and copper levels were normal.
- ▶ Hypertensive encephalopathy: the blood pressure readings were normal throughout the admissions.
- ▶ Uraemic encephalopathy: the kidney function was normal.
- ▶ Ischaemic encephalopathy related to hypoxia: there were no changes on the MRI head scan suggestive of this diagnosis.

TREATMENT

Despite the patient being commenced on high-dose oral prednisolone at a dose of 50 mg daily and having had two 5-day courses of intravenous immunoglobulin at a dose of 0.4 g/kg/day for 5 days, there was no satisfactory clinical response.

He was commenced on clonazepam 0.5 mg at night for the seizures. While being on the ward, his hyponatraemia required ongoing monitoring without fluid restriction.

An oral course of oral amoxicillin/clavulanic acid at a dose of 625 mg three times daily for 7 days was given for left infected olecranon bursitis. Once the extended culture results were back, which showed growth of *K. oxytoca* and anaerobes, he had a course of oral ciprofloxacin 500 mg twice daily for 2 weeks, given that he was being commenced on immunomodulatory therapy and had mild ongoing symptoms of bursitis.

While being on treatment with steroids he had to be admitted to a district general hospital, as needed urgent surgery for a perforated duodenal ulcer, likely secondary to steroids. When transferred back under the neurology team, the case was discussed with surgical team that felt it was safe to restart oral steroids with proton pump inhibitor prophylaxis so he was put back on oral prednisolone 25 mg daily and omeprazole 20 mg twice daily. The patient was discharged and advised to continue steroids for the long term at the same dose until seen by the consultant neurologist at outpatients clinic after 7 days. At that point, the cognition appeared to have improved with an ACE-R score of 96/100 (previously 93). The possibility of an additional course of intravenous immunoglobulin was mentioned to the patient for the near future.

After getting expert advice on his management from the Nuffield Department of Clinical Neurosciences, University of Oxford, he finally underwent a course of plasma exchange for 5 days. After a week, this was followed by a 3-day course of intravenous infusion of methylprednisolone at a dose of 1 g daily for 3 days with very good effect (figure 4).

The patient was discharged on oral prednisolone 50 mg that was tapered over 6 months.

Interestingly, the fact that the patient suffered from infections and had surgery must have deteriorated his autoimmune disorder.

OUTCOME AND FOLLOW-UP

The patient has had regular follow-up appointments with the neurology team on an outpatient basis for 3 years. He was finally discharged back into the community. There has been no relapse of his anti-LGI1 encephalitis.

DISCUSSION

The clinical presentation of autoimmune encephalitis cases is broad. There are patients that have antibodies against LGI1,

against Caspr2 and finally patients who do not have any of these but still are VGKC positive.

This classification might enable the clinicians to perform a more accurate diagnosis and at an earlier stage which is crucial for the patient. The reason being that these antibodies cause different syndromic pictures and more specifically the patients with LGI1 antibodies present with limbic encephalitis, hyponatraemia and typical faciobrachial dystonic seizures like in our case. Caspr2 antibodies rarely cause hyponatraemia, affect older male patients with peripheral or central nervous system symptoms. Morvan's syndrome is associated with Caspr2 antibodies. Both of these two different entities might benefit from immunotherapy.⁹

The class that lacks the aforementioned antibodies affects all ages with no sex difference. The presentation includes psychiatric symptomatology, epilepsy, cognitive decline and cramp fasciculation syndromes.

The patient within this case report had characteristics of anti-LGI1 encephalitis as he was 69 years old, had faciobrachial dystonic seizures, hyponatraemia and evidence of mild cognitive decline. His seizures improved instantly with the plasma exchange another factor suggesting anti-LGI1 encephalitis. It is more than evident that nowadays there is a new subgroup of clinical syndromes with patients having positive antibodies against LGI1 and Caspr2. It is therefore necessary for the clinician to further distinguish these cases with the help of the relevant investigations and the associated characteristic clinical picture. Our case demonstrates positively how important it is to keep in mind this categorisation to reach to the right diagnosis at an early stage and give the most appropriate treatment.

A recent study which assessed the clinical relevance of a positive VGKC test in patients lacking antibodies to LGI1 and Caspr2 showed that VGKC positivity is not a clear marker for autoimmune inflammation and not clinically relevant.^{10 11}

Learning points

- A new classification for voltage-gated potassium channel-positive patients should be used: leucine-rich glioma inactivated protein 1 (LGI1) and contactin-associated protein2 (Caspr2) positive or negative.
- Anti-LGI1 encephalitis cases present with limbic encephalitis, hyponatraemia and typical faciobrachial dystonic seizures.
- Caspr2-antibody mediated disease affects predominantly older male patients with central nervous system manifestations like limbic encephalitis, peripheral nervous hyperexcitability or a combination of both such as Morvan's syndrome.
- Immunotherapy is beneficial for both anti-LGI1 and anti-Caspr2 disease. Underlying tumour has to be excluded.
- Anti-LGI1 encephalitis presents with T2 fluid attenuated inversion recovery hyperintense signal alterations in the medial temporal lobes including the hippocampus that may progress to atrophy. In many cases, basal ganglia are affected as well.

In the last few years, a variety of new antibodies targeting cell-surface proteins associated with distinct clinical syndromes have been discovered. Despite the wide range of different antibody targets, many of these syndromes present with features of limbic encephalitis and corresponding T2/FLAIR hyperintense signal alterations in the medial temporal lobes including the hippocampus. This includes patients with antibodies directed against LGI1.¹²

In conclusion, this case illustrates the need to be more specific when referring to this disease, as there is a broad spectrum of clinical presentation. In the future, when trying to describe these cases, as they are completely different clinical entities, we have to use a distinct term.

This change in the terminology will enable the better understanding and management of these syndromes, which possibly are more common than we think.

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Contributors SZ treated the patient, presented the case at a grand round, interpreted data, wrote manuscript and acted as corresponding author. JS made contribution to drafting the article and critically revised it. SRA reviewed all the CT and MRI scan images and helped with the differential diagnosis of the case. CE helped to collect the data for the manuscript.

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