Full clinical cases submission template

TITLE OF CASE
Anti-LGI1-encephalitis causing faciobrachial dystonic seizures

SUMMARY

Anti-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 leucine-rich glioma inactivated protein 1 (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 milligrams daily and clonazepam 500 micrograms 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 ***Why you think this case is important – why did you write it up?***

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 attriuted to one antibody.
Indeed, in 2010 the identification of two proteins, the leucine-rich, glioma inactivated 1 protein (LGI1) and the contactin-associated protein-2 (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 is 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]

Contactin-associated protein-like 2 (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 antibodies 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]

There is an association between Caspr2 and other proteins in the PNS and in CNS and more specifically the transiently-expressed axonal glycoprotein (TAG1), the post synaptic density Protein-Drosophila disc large tumour suppressor-zonula occludens-1 protein (PDZ), and the ankyrin-spectrin protein.

According to a large clinicoserologic study it has been observed that LGI1 and Caspr2

autoantibodies are associated with diverse neurologic phenotypes that often overlap. The commonest presentation is limbic encephalitis(LE) in the CNS and neuromyotonia or Morvan's syndrome in the PNS.[6]

This case highlights characteristic features such as seizures and hyponatremia 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 ***Presenting features, medical/social/family history***

A 69-year-old man complained of vague, non-specific symptoms and of "generally not right" for six 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 one 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 jetlag, 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 kilograms 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.

Examination showed that his cognition was slightly reduced with Addenbrooke's Cognitive Examination-Revised test (ACE-R): 93/100 and Mini–Mental State Examination (MMSE): 29/30 but this was not evident during general conversation.[7] His movement disorder was observed by Neurology team, in line with the description given above. It was thought that the diagnosis may have been consistent with a faciobrachial dystonic seizure. Cranial nerve examination was normal. In the limbs, power, tone, reflexes, sensation and co-ordination was normal. Fasciculations were observed in both gastrocnemius muscles. The left elbow showed features consistent with an olecranon bursitis, which was initially hot, erythematous and slightly indurated.

INVESTIGATIONS ***If relevant***

Blood investigations revealed hyponatraemia with features in keeping with the syndrome of inappropriate antidiuretic hormone secretion (SIADH): Na 126 mmol/L, urine osmolality 764 mmol/kg H_2O, Urine sodium 106 mmol/L and serum osmolality 267 mOsm/kg H_2O. A full blood count showed only mild lymphopaenia (1.1×10^9/L) but indices were otherwise normal. The calcium, phosphate, magnesium, liver function tests, c-reactive protein (CRP), creatine kinase (CK), glucose, thyroid function, ferritin, human immunodeficiency virus (HIV) serology, immunoglobulins and serum electrophoresis, serum angiotensin converting enzyme (ACE) and antistreptococcal antibody titres

(ASOT) were all normal or negative. Autoantibodies that were negative included anti nuclear (ANA), against double stranded DNA (anti ds-DNA), antineutrophil cytoplasmic (ANCA), extractable nuclear antigens screen tests (ENA) for: Anti-Sm antibodies (anti-Sm)/ small nuclear ribonucleoprotein (anti-RNP) antibodies / antibodies to the La antigen (anti-La)/ antibodies to the Ro antigen (anti-Ro)/ anti-topoisomerase I antibodies (anti-Scl70)/ antibodies to the cytoplasmic protein (anti-Jo-1).

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 leucine-rich glioma inactivated protein 1 (LGI1) were positive as well. Antibodies against contactin-associated protein (anti-CASPR), anti-*N*-methyl-d-aspartate receptor (anti-NMDA), antiglutamic acid decarboxylase (anti GAD), anti-Amphiphysin antibodies and Glycine receptor antibodies were negative. Serum Caeruloplasmin 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 (HBV), Hepatitis C virus IgG assay, Hepatitis B surface antibody (anti-HBs) tests were all negative or normal. Serology for American Trypanosomiasis was negative. Joint aspirations from the left olecranon bursa on two ocassions, 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-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 assymetrical 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 (EMG) 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 leaflet mitral valve prolapse with mild to moderate mitral regurgitation and the left atrium was mildly enlarged.

DIFFERENTIAL DIAGNOSIS ***If relevant***

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.
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.
Uremic 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 ***If relevant***

Despite the patient being commenced on high dose oral Prednisolone at a dose of 50 mg daily and having had two five day courses of intravenous immunoglobulin (IVIg) 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. Whilst 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 seven days was given for left infected olecranon bursitis. Once the extended culture results were back, that showed growth of Klebsiella oxytoca and anaerobes, he had a course of oral Ciprofloxacin 500 mg twice daily for two weeks, given that he was being commenced on immunomodulatory therapy and had mild ongoing symptoms of bursitis.
Whilst 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 50 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 seven 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 IVIg 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 (PLEX) for five days. After a week this was followed by a three-day course of intravenous infusion of methylprednisolone at a dose of 1 gram daily for three days with very good effect. (figure 4).
The patient was discharged on oral Prednisolone 50mg that was tapered over six 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 three years .He was finally discharged back into the community. There has been no relapse of his anti-LGI1 encephalitis.

DISCUSSION ***Include a very brief review of similar published cases***

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, hyponatremia and typical faciobrachial dystonic seizures like in our case. Caspr2-antibodies rarely cause hyponatremia, 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 pshychiatric 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 (FBDS), hyponatremia 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 is to keep in mind this categorization in order 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 voltage-gated potassium channel (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]

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.

LEARNING POINTS/TAKE HOME MESSAGES ***3 to 5 bullet points – this is a required field***

- A new classification for VGKC-positive patients should be used: LGI1 & Caspr2 positive or negative.
- Anti-LGI1-encephalitis cases present with limbic encephalitis, hyponatremia 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-Flair 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. .

REFERENCES ***Vancouver style (Was the patient involved in a clinical trial? Please reference related articles)***

1. Shillito P, Molenaar PC, Vincent A, et al. Acquired neuromyotonia: evidence for autoantibodies directed against K+ channels of peripheral nerves. Ann Neurol 1995; 38:714 – 722.
2. Lai M, Huijbers MG, Lancaster E, et al. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. The Lancet Neurology. 2010 Aug 31;9(8):776-85.
3. Irani SR, Alexander S, Waters P, et al .Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. Brain. 2010 Jul 27;133(9):2734-48.
4. Van Sonderen A, Thijs RD, Coenders EC, et al. Anti-LGI1 encephalitis Clinical syndrome and long-term follow-up. Neurology. 2016 Oct 4;87(14):1449-56.
5. Van Sonderen A, Ariño H, Petit-Pedrol M, et al. The clinical spectrum of Caspr2 antibody–associated disease. Neurology. 2016 Aug 2;87(5):521-8.
6. Klein, CK, Lennon VA, Aston, PA, et al. (2013) Insights from LGI1 and CASPR2 Potassium Channel Complex Autoantibody Subtyping. JAMA Neurology, 70, 229-234.
7. Ariño H, Armangué T, Petit-Pedrol M, et al. Anti-LGI1–associated cognitive impairment Presentation and long-term outcome. Neurology. 2016 Aug 23;87(8):759-65.
8. Van Sonderen A, Petit-Pedrol M, Dalmau J, et al. The value of LGI1, Caspr2 and voltage-gated potassium channel antibodies in encephalitis. Nature Reviews Neurology. 2017 Apr 18.
9. Irani SR, Stagg CJ, Schott JM, et al. Faciobrachial dystonic seizures: the influence of immunotherapy on seizure control and prevention of cognitive impairment in a broadening phenotype. Brain. 2013 Oct;136(Pt 10):3151-62. doi: 10.1093/brain/awt212. Epub 2013 Sep 6
10. Lang B, Makuch M, Moloney T, et al. Intracellular and non-neuronal targets of voltage-gated potassium channel complex antibodies. J Neurol Neurosurg Psychiatry.

2017 Apr 1;88(4):353-61.
11. Van Sonderen A, Schreurs MW, Wirtz PW, et al. From VGKC to LGI1 and Caspr2 encephalitis: The evolution of a disease entity over time. Autoimmun Rev. 2016 Oct;15(10):970-4.
12. Heine J, Prüss H, Bartsch T, et al. Imaging of autoimmune encephalitis–Relevance for clinical practice and hippocampal function. Neuroscience. 2015 Nov 19;309:68-83.

- **FIGURE/VIDEO CAPTIONS** ***figures should NOT be embedded in this document***

Figure 1 : MRI brain scan T2-Flair showing an ill-defined hyperintense signal, involving the left side of the medial temporal lobe.
Figure 2 : MRI brain scan coronal view showing no significant mass effect and no haemorrhagic changes.
Figure 3 : MRI brain axial flair showing mild assymetrical enlargement and faint increased signal intensity in the left side of the medial temporal lobe/hippocampus .
Figure 4 : Spasms of the patient per 24 hours

PATIENT'S PERSPECTIVE ***Optional but strongly encouraged – this has to be written by the patient or next of kin***

"From my perspective plasmapheresis seemed to be spectacularly effective at controlling the spasms. The side effects of the corticosteroids were so wide ranging and life changing that I wonder if alternatives to this aspect of treatment should be researched? Perhaps they are?"

Copyright Statement

Date: 29/08/2017

PLEASE SAVE YOUR TEMPLATE WITH THE FOLLOWING FORMAT:

Corresponding author's last name and date of submission, eg,

Smith_September_2014.doc

BMJ Case Reports

We cannot process your article until you can check all these boxes

- **HAVE YOU READ THE INSTRUCTIONS FOR AUTHORS?**
  This important information presents the types of case reports we're interested in reviewing as well as details on patient consent, preparing your submission, etc

- **ARE YOU USING THE CORRECT WORD TEMPLATE?**
  All case reports MUST be submitted using one of our Word templates

  Full cases

  Images in …

  Global Health

  This document provides detailed guidance on how to write your case report

- **HAVE ALL AUTHORS (MAXIMUM 4 ALLOWED) APPROVED THE SUBMISSION?**
  Important information on authorship

- **DO YOU HAVE PATIENT CONSENT?**
  You must have signed informed consent from patients (or relatives/guardians) before submitting to BMJ Case Reports. **For living patients this is a legal requirement under the UK's Data Protection legislation; we will not send your article for review without explicit consent from the patient or guardian**. Further information is available online and Consent forms are available in several languages

- **IS YOUR ARTICLE ORIGINAL?**
  BMJ takes publication ethics very seriously and abides by the best practice guidance of the Committee on Publication Ethics. Every article is screened using iThenticate on submission and any that is deemed to overlap more than trivially with other publications will be rejected automatically with no right of appeal. Do not copy paragraphs from other sources

- **DO YOU OR YOUR INSITUTION HAVE A VALID FELLOWSHIP?**