Unusual association of diseases/symptoms

Voltage-gated potassium channel antibody-related encephalopathy: a case which may extend the documented phenotype of this condition

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Summary

A 51-year-old man presented with a focal epileptic, fluctuating encephalopathy. Antibodies to voltage-gated potassium channels (VGKC-Abs) were detected in his serum. Several features of this case were different from those previously reported in VGKC-Ab-associated encephalitis, illustrating that it may have a broader phenotype than previously documented. These features were: excess hepatic iron deposits without cirrhosis, reduced consciousness and fluctuating neurological signs. Previous history included personality change, depression, type 2 diabetes mellitus, pupil sparing third nerve palsy and epilepsy secondary to a head injury. He had never drunk alcohol and had recovered from a similar episode 4 years previously. Both episodes resolved after approximately 2 months. The cerebrospinal fluid had a raised protein content but no organisms. The patient was heterozygous for C282Y and negative for H63D mutations excluding classical idiopathic haemochromatosis. He recovered with supportive care to his premorbid level of health.

BACKGROUND

The current case most closely resembles voltage-gated potassium channel antibody (VGKC-Ab) encephalopathy, which is a reversible auto-immune limbic encephalitis responsive to immunomodulatory treatments such as corticosteroids, plasma exchange or intravenous immunoglobulin.^{1–4} The better known, paraneoplastic form of limbic encephalitis is not reversible and carries a poor prognosis.² VGKC-Ab encephalopathy is characterised by VGKC-Abs in serum and cerebrospinal fluid (CSF), personality changes, seizures, memory impairment, hyponatraemia secondary to a syndrome of inappropriate antidiuretic hormone secretion, MRI signal change in the temporal lobe and a raised white cell count and protein in CSF.^{2–7}

VGKC are a group of membrane-bound proteins which repolarise the nerve terminal after an action potential. Antibodies to VGKC are detected with a radioimmuno-precipitation assay using ¹²⁵I-labelled α -dendrotoxin, which is extracted from the green mamba snake (*Dendroaspis angusticeps*).⁸ ¹²⁵I-labelled α -dendrotoxin preferentially blocks some types of VGKC: Kv1.1, Kv1.2 and Kv1.6^{6,7}, which are found throughout the brain, but are strongly expressed in the molecular layer of the hippocampus.⁸ In contrast to other antibodies associated with paraneoplastic syndromes, VGKC-Abs are thought to be pathogenic^{2,9,10} although this view has been challenged.^{11,12} Antibody titres typically fall to near-normal levels as the patients recover.² VGKC-Abs have been documented in a

number of syndromes including cramp, fasciculation, Movat's and Isaac's syndromes^{2,8} and epilepsy.¹³

VGKC-Ab encephalopathy may be more common than it is usually thought to be, and it is probable that cases are misdiagnosed as other types of encephalopathy such as *Herpes simplex* (HS) encephalitis, Creutzfeldt-Jakob or Wernicke-Korsakoff syndromes.^{1,7} The incidence of VGKC-Ab encephalopathy is therefore difficult to ascertain; however, between 1 and 3 patients fitting the accepted case definition present annually in the west of Scotland (a population of 2.5 million).⁶ In one series, 10 patients were identified in 15 months. During the same period, only one case of paraneoplastic encephalopathy was identified.

This case illustrates some classical characteristics of VGKC-Ab encephalopathy such as seizure, hyponatraemia and personality change although other features such as MRI changes were not present. In addition, some aspects of the case were unique to our knowledge: a reduced consciousness (Glasgow Coma Score (GCS) dropped to 3) and fluctuating neurological signs sometimes indicating a right and sometimes a left hemiparesis despite no accompanying CT abnormalities. The patient also had excess iron deposits in the liver in combination with an anaemia and type 2 diabetes mellitus. The full extent of clinical presentations of VGKC-Ab disease is yet to be elucidated.^{1,6} This case further extends documentation of the phenotype and highlights the importance of recognising and diagnosing this reversible condition.

CASE PRESENTATION

Presenting complaint and clinical course

A 51-year-old man presented with the clinical picture of a focal epileptic, fluctuating encephalopathy. He had never drunk alcohol or used recreational drugs. He had suffered a similar incident 4 years ago which resolved after approximately 2 months concurrent with treatment with high-dose steroids. The diagnosis at the time was 'encephalopathy of unknown aetiology'. Corticosteroids were used empirically on the assumption that there was an underlying autoimmune mechanism. The two episodes were remarkably similar including seizures, coma and fluctuating focal signs, but no measured memory loss (in either episode). The investigation findings were also similar. For brevity the second episode, which was the best documented, has been included here; however, information about the initial episode is available on request. Of note the brain biopsy documented in this report occurred during the initial episode and was not repeated.

Between episodes, the patient led an independent life, had no intellectual or memory impairment and was mobile with two walking sticks. His mobility problem was due to muscle wasting after prolonged immobility; he did not have a gait abnormality. He had a history of epilepsy previously attributed to a head injury when aged 16 years, drug refractory depression treated with electroconvulsive therapy in his 20s (at least 20 years prior to the onset of encephalopathy), reversible personality change, long-standing poorly controlled type 2 diabetes mellitus, a pupil sparing third nerve palsy and hypertension. The personality change was documented in outpatient letters. He appeared, to his friends' family and doctors, to be acting abnormally and took on a different persona. This lasted several months and spontaneously resolved but did occur in the months prior to the first hospital admission for encephalopathy and so may have been related.

On this occasion he presented to the Accident and Emergency wing with reduced consciousness, fluctuating confusion and a generalised tonic-clonic seizure lasting less than 30 s. He was apyrexial and clinically anaemic (haemoglobin 100 g/l) with a GCS of 11 (eyes 4, verbal 2, and motor 5). His temperature was 36.5°C, heart rate was 90 bpm, respiratory rate was 22, blood pressure was 130/60 and his SpO₂ was 98% in room air.

His neurological examination was documented as otherwise normal but he had bilateral crepitations on respiratory examination with a white cell count of $15\,900 \times 10^6/l$ and a C-reactive protein (CRP) of 36 mg/l. His blood glucose was 25.7 mmol/l, arterial pH and bicarbonate were normal and he was hyponatraemic (sodium 129 mmol/l). Liver function tests were normal. Initial impression was of a post-ictal state following a seizure secondary to a respiratory tract infection. He was commenced on ceftriaxone, aciclovir and an insulin sliding scale. Blood glucose normalised quickly. He was already taking phenytoin but the serum level was markedly subtherapeutic (<1 mg/l). This was titrated up to the therapeutic level. His antiepileptic was subsequently changed to levetiracetam by a consultant neurologist.

The patient's condition improved over the first 12 h and his GCS soon reached 15; however, over the next 3 days

he deteriorated. He began to visually hallucinate and his haemoglobin dropped >10 g/l over 6 h, stabilising in the low 70s where it remained despite transfusion for the next 2 months. He developed aspiration pneumonia which fulfilled criteria for severe sepsis. On day 3 he was pyrexial, with a respiratory rate of 52 breaths per minute, a heart rate of 110/min, BP 99/40 mm Hg GCS 8 (E1 N5 V2) and elevated white cell count ($21\,900 \times 10^6/l$) and his chest x-ray showed a dense opacity consistent with consolidation throughout the right lung. This was treated initially with intravenous amoxicillin and metronidazole and subsequently intravenous piperacillin and tazobactam. On day 6 he was transferred to the intensive care unit (ICU) for artificial ventilation when his GCS dropped to the extent that it could no longer support his own airway. He remained in the ICU for 14 days, where he had further short-lived (<5 min) witnessed seizures and received treatment for an aspiration pneumonia.

The seizure activity was with one exception in the first 7 days of admission. On day 1 he had a <30 s tonic-clonic self-limiting generalised seizure and then no further seizures activity until day 5, when he had an additional two self-limiting <30 s seizures. On days 6 and 7, he had a series of short-lived self-limiting seizures, until on the evening of day 7 he had two seizures, which were controlled with 2 mg lorazepam. These lasted between 1 and 5 min; he was never in *status epilepticus*. His care was stepped down via a high-dependency unit (HDU) and then to a general ward. There was no further seizure activity until day 24 and then he had a 1-min generalised tonic-clonic seizure, which was controlled with 7.5 mg intravenous diazepam.

On the ward he developed diarrhoea during a norovirus outbreak although he never had positive stool cultures and was apyrexial. Two days later he developed a fever (38.3°C) and had a respiratory rate of 22/min. He was readmitted to the HDU the following day where he spent a further 17 days.

A septic screen revealed that his urine contained protein, nitrites and leukocytes. Coagulase-negative *Staphylococcus* resistant towards meropenem but sensitive to vancomycin was isolated from blood cultures from both peripheral and central lines. His central line was removed and he was commenced on intravenous vancomycin. He continued to exhibit signs of sepsis including pyrexia, tachycardia and raised white cell count for most of the following 2 weeks. Further positive microbiological findings were trachea site swabs, which were positive for *Enterobacter aerogenes*, *Klebsiella* and methicillin-resistant *Staphylococcus aureus*. These infections were treated according to their sensitivities and local antibiotic guidelines.

His seizures with one exception stopped after the first week, and he was no longer septic after the second week. His blood glucose was controlled with insulin—either intravenous via a sliding scale or subcutaneously with daily endocrine review. However, he remained anaemic, and continued to have a fluctuating GCS between 3 and 11, and in addition, he developed changing neurological signs without concurrent CT changes. An attempt was made to correlate both haemoglobin and neurological status with GCS, but no clear pattern could be ascertained. The patient's speech was incoherent and he did not appear

to understand commands for most of his admission up until day 43 when he began to improve. The phenomenon of fluctuating neurology was best documented in his previous hospital admission 4 years previously, although a similar pattern was observed in 2010. In 2006, he had normal power on admission (the sensation in the context of his reduced consciousness would have been difficult to assess). Thirteen days later, he developed a left hemiparesis, and then 10 days after that a flaccid right-sided weakness. By day 33, he turned his head and eyes to the right, indicating left face and arm weakness, and then by day 44 he was noted to exhibit right inattention, turning his head only to the left. The next day he had left upper and lower limb weakness. Neurological signs were noted to 'continue fluctuating' until his eventual recovery.

By day 43 of his admission in 2010 his haemoglobin began to recover, his GCS improved and the fluctuating neurological signs began to dissipate. After a period in a rehabilitation unit he was discharged back into the community. All focal neurological signs including the third nerve palsy that was noted prior to admission, and attributed to his diabetes mellitus, resolved. He continues to attend follow-up in out-patient neurology, ophthalmology and diabetes clinics, where he was initially treated with oral prednisolone that was gradually reduced and he is now maintained on azathioprine 100 mg daily.

INVESTIGATIONS

Anti-VGKC-Abs: Negative just after the previous episode, during the current episode 389 pmol on day 89, 171 pmol by day 140, and negative the following year, after the episode had resolved.

Lumbar puncture: Opening pressures in lumbar punctures performed early in the previous admission were raised to 30–36 cm H₂O, but in the most recent admission opening pressures were normal. Protein levels were elevated, reaching a maximum of 1.49 g/l. Example result: protein 0.8 g/l (0.2–0.4), glucose 4.1 mmol/l (concurrent plasma glucose 8.6 mmol/l), white cell count <1, red cell count 24, no organisms. PCR was negative for *Herpes simplex* virus (HSV) I and II and Varicella zoster virus (VZV).

Imaging: Several CT scans taken when focal neurological deficits were present indicated no abnormality including ischaemic change. An MRI suggested small-vessel ischaemic change and a CT cerebral angiogram indicated the left internal carotid artery occluded at its origin, but the circle of Willis was patent and filled the left anterior and middle cerebral arteries. On discussion with the neurologist and radiologist, these changes did not correspond to the neurological deficits exhibited (he had a left hemiparesis at the time; this deficit would have been consistent with the right hemiparesis). Even with a drop in the systolic blood pressure. There were no changes in the limbic area. Ultrasound imaging of the thyroid indicated no thyroiditis.

Haematology: Anaemia was present. Haematinics were as follows: lactate dehydrogenase 1010 IU/l (raised), reticulocytes 44 per film (not elevated), platelets, 400 × 10⁹/l, serum ferritin 2862 µg/l (42–262), serum folate 13.7 µg/l (2.1–14), vitamin B₁₂ 240 ng/l (180–900), total iron-binding capacity 27 µg/dl (45–72) and iron 10 µmol/l (11–29). The patient was septic when the sample was taken. Blood films indicated spherocytes, nucleated red

blood cells and polychromatic possibly erythroblastic change. Direct Coombs tests were at different times both positive and negative. Examination of serial blood films did not show evidence of either red blood cell fragmentation (Schistocytes) or reticulocytes, and were not considered to be typical of a haemolytic anaemia. A bone marrow biopsy indicated reactive, hypercellular, megakaryocytes, abundant iron and no sideroblasts.

One year after resolution of the episode, serum ferritin remained high (1422 µg/l). At this time haemoglobin was 165 g/l, mean corpuscular volume 90 fl, TIBC 40 µg/dl, iron 12 µmol/l, serum folate >20 µg/l and vitamin B₁₂ 514 ng/l. He was well and not septic.

Investigations excluding other differential diagnoses

Infection: The following infections were tested for and excluded: HIV, HSV, cytomegalovirus, human herpesvirus 6, VZV, Epstein-Bar virus, viral hepatitis, *Syphilis* tested using VDRL.

Neoplasia: Carcinoembryonic antigen, alpha fetoprotein and cancer antigen 125 (CA125) were unremarkable. There was no other indication of neoplasia on examination or imaging.

Non-convulsive status epilepticus: Background EEG indicated low-voltage non-specific changes. There were no changes to suggest non-convulsive status epilepticus.

Wilson's disease: Serum copper, 23.4 mg/dl (10–22); Ceruloplasmin, 0.29 mg/l (0.2–0.6); urine copper, 0.78 µmol/l; and urine copper extraction, 1.05 µmol/24 h (0.2–0.6). The concurrent CRP when these samples were collected was 23 mg/l; the patient was recovering from sepsis. Kayser-Fleischer rings were not visible on mobile slit lamp examination. Subsequent liver biopsy found no copper deposits.

Liver biopsy: The live parenchymal cells did not contain any copper-associated protein; however, they did contain an excess of stainable iron which was assessed as grade 2+. Stainable iron was confined to hepatocytes and there was no staining of the portal tracts. There was no fibrosis, cirrhosis or fatty change. No inflammatory infiltrate of portal tracts or parenchyma is seen. The histology appearance suggested haemochromatosis.

Haemochromatosis: The patient was heterozygous for C282Y and negative for H63D mutations. Although serum ferritin was high during periods of sepsis he was consistently anaemic.

Porphyria: Normal urinary total porphyrin and porphobilinogen excretion on a sample taken during acute illness.

Autoantibodies negative: Antinuclear antibody/rheumatoid factor/antineutrophil cytoplasmic antibody/antimitochondrial/antismooth muscle/parietal/liver-kidney microsomal/anti hi, ro, ri/antithyroid peroxidase/antiglutamic acid decarboxylase/anti-N-methyl-D-aspartate receptor antibody.

Mitochondrial disease: Negative MTT1 (mitochondrially encoded tRNA leucine 1), NARP (neuropathy, ataxia and retinitis pigmentosa) and MTTK (mitochondrial thymidine kinase). Light and electron microscopy of a muscle biopsy showed only diffuse atrophy with mild disruption of myofibrils and no evidence of mitochondrial disease.

Transmissible spongiform encephalopathy: A brain biopsy was performed during the previous admission. Large samples of right temporal dura and parenchyma showed no pathological abnormality.

DIFFERENTIAL DIAGNOSIS

This patient's condition bore the closest resemblance to a VGKC-Ab encephalopathy but there were some important differences that made this case different from previously published descriptions (discussed below). The characteristic changes in MRI in the temporal lobe were absent. The more common form of limbic encephalitis is the paraneoplastic phenomenon, but there was no indication of an underlying neoplasia. A previous test for VGKC-Abs from the previous incident was negative, and the positive result in the second incident was not received until some months after the patient had recovered. During both hospital admissions, a variety of differentials for a relapsing remitting encephalopathy associated with seizures was therefore considered and excluded, for example:

Wernicke-Korsakoff's encephalopathy—he has never drunk alcohol.

Hashimoto's encephalopathy—thyroid peroxidase antibody negative and no thyroiditis on ultrasound.

Hepatic encephalopathy—no cirrhosis on liver biopsy.

Infectious encephalopathy—a variety of infections were excluded including HSV.

Hypertensive encephalopathy—no acutely increased blood pressure.

Wilson's disease—no copper deposits in liver and negative slit light examination.

Mitochondrial encephalopathy—negative DNA analysis for MTTL1, NARP and MTTK.

Hypoxic ischaemic encephalopathy—no ischaemia on head CT, but possibly some abnormalities on MRI and CT cerebral angiogram.

Uremic encephalopathy—creatinine normal on admission.

Transmissible spongiform encephalopathy—no spongy-form or prion change on brain biopsy and the patient recovered.

Symptoms were related to hyperglycaemia and hyperosmolar state. Hyperglycaemia was modest and rapidly reversed, while neurological problems were ongoing for months.

TREATMENT

Once the positive VGKC-Ab results were confirmed, although the patient was already showing significant clinical improvement he was treated with oral corticosteroids for 1 year and was subsequently maintained on azathioprine 100 mg daily.

OUTCOME AND FOLLOW-UP

The patient was discharged back into the community where he is independent and attends regular outpatient follow-up in neurology, diabetes and ophthalmology clinics.

DISCUSSION

VGKC-Ab encephalopathy or non-paraneoplastic limbic encephalitis has been documented in individual case reports and case series.^{2–6} Case definitions have been proposed; however, the consensus opinion is that the phenotype might be wider than currently accepted.^{2–8} Indeed, according to a recent review, 'traditional distinctions between "encephalitis" and "encephalopathy" ... may be blurred in such patients'.⁸

This patient shows characteristic features of VGKC-Ab encephalopathy in terms of his age at presentation,

psychiatric features, seizures, no neoplasia, protein in the CSF, hyponatraemia, encephalopathy and VGKC-Abs in serum. VGKC-Abs are considered positive when above 100 pM.² The samples for this patient were taken about 1 month after he had recovered from the acute episode, but remained at high levels (329 pM) and dropped thereafter, in keeping with patterns documented in other patients.² Should another episode occur it would be reasonable to repeat the test immediately on presentation.

Sepsis was the dominant feature of this patient's episode, precluding earlier treatment with steroids, and possibly resulting in a more severe presentation. Four out of 10 patients in a previous case series had a prodromal illness preceding their episode: of these, 2 had flu-like symptoms, 1 had diarrhoea and 1 had an eye infection suggesting an infectious trigger for their auto-immune disease.²

Whereas serial blood films were not considered typical of haemolytic anaemia, other factors (the raised ferritin, intermittently positive Coomb's test, spherocytes, polychromasia and occasional nucleated cells) might suggest such a process. Where the causative autoantibody is directed against very early erythroid precursors, haemolytic anaemia can occur in the absence of a peripheral reticulocytosis, and we cannot exclude the possibility that this was the case here.

This patient also had type 2 diabetes mellitus. VGKC have been implicated in having a control function for both insulin secretion and peripheral sensitivity; however, the presence of functioning potassium channels would appear to increase the chances of having diabetes rather than decrease it. Kv1.1 and Kv1.2 limit insulin secretion¹⁴ and Kv1.3 gene deletion and channel inhibition increases peripheral insulin sensitivity in vivo in mice.¹⁵ Indeed, blocking VGKC has been proposed as a potential therapy for diabetes.¹⁶

There are some characteristic features of VGKC-Ab encephalitis that were not seen in this case. This patient had no MRI signal changes in the temporal lobe. As 39/47 reported cases had MRI changes, this is unusual but not unique. Even in classical paraneoplastic limbic encephalitis, the MRI signal change was not an invariable finding^{8–17} (28/44 patients). No memory impairment was noted on full outpatient assessment by a consultant neurologist either before or after admission to hospital. During his admission his consciousness level was such that mental status examination or formal memory testing was not appropriate.

To our knowledge, no patient with VGKC-Ab disease has been reported previously to have iron deposits in the liver, a reduced consciousness to the extent of requiring intubation or anaemia. These may be incidental or previously undocumented manifestations of VGKC-Ab-associated disease. That this patient's ferritin remained high even 1 year after the episode may imply that this is a feature of his disease. This should become clear as more cases are identified. This patient improved concurrently with high-dose steroids, from his first episode and spontaneously from his second. Spontaneous improvement has been reported previously once.⁷

Our challenge in the case of this patient was to advise on how best to avoid such episodes in future and to be better equipped to treat such an episode if it happens

again. Steroids have been found to be beneficial^{2 18} and plasma exchange and intravenous immunoglobulin have also been proposed, but their efficacy is less well-documented.² Long-term steroids make it extremely difficult to control this patient's type 2 diabetes; he is therefore being managed now with azathioprine.

In conclusion, although this case is similar to previous descriptions of VGKC-Ab-associated encephalopathy, there are differences that make it distinct. VGKC-Ab disease may have a broader phenotype than currently documented and may be a relatively common and treatable condition. It is worth reiterating that the unusual features documented here, such as iron deposits in the liver, may be incidental—future cases should help elucidate this point. This case highlights the importance of considering an autoimmune differential for encephalopathy. We would propose testing similar patients for VGKC-Abs earlier in the disease process.

Learning points

- This report illustrates a case of VGKC-Ab disease that had some unique features: excess hepatic iron deposits without cirrhosis, reduced consciousness and fluctuating neurological signs and anaemia, further illustrating the wide clinical spectrum of VGKC-Ab disease.
- It is vital that VGKC-Ab disease is included in the differential diagnosis of patients presenting with an encephalopathic disorder since it is reversible and treatable.^{3 8} This patient demonstrates the difficulties which may be encountered in making a diagnosis despite the undertaking of multiple investigations, including brain biopsy, if VGKC-Ab disease is not considered in the differential.
- VGKC-Ab disease may be relatively common.^{2 6}
- It is a differential diagnosis for other encephalopathies such as *Herpes simplex* encephalitis, Creutzfeldt-Jakob or Wernicke-Korsakoff syndromes.^{2 3}

Competing interests None.

Patient consent Obtained.

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