Two different presentations, one diagnosis

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Abstract

Acute confusion and hyponatraemia are common presentations in acute medicine. We report two cases of anti-voltage gated potassium channel (VGKC) antibody-related limbic encephalitis highlighting the variable presentation of this condition. Both patients were thoroughly investigated with MRI scan of brain, lumbar puncture, EEG as well as infective and autoimmune screens for encephalitis. Anti-VGKC antibodies were positive for both patients and prompt treatment with immunotherapy yielded good recovery. Patients presenting with confusion and seizures who have no demonstrable infectious or metabolic cause should have investigation for an autoimmune cause expedited. In addition, psychiatric presentations with atypical features such as drowsiness should prompt similar investigations. The outcome of anti-VGKC-related limbic encephalitis is improved with early treatment employing steroids or immunotherapy.

Keywords

Limbic encephalitis, confusion, psychiatric symptoms, hyponatraemia, voltage-gated potassium channel antibodies.

Key Learning points

- Autoimmune encephalitis should be considered in the differential diagnosis with any of the following clinical features: confusion, acute psychiatric symptoms, and seizures.
- Potentially reversible causes of psychoses should be considered when patients have features suggestive of organic disease such as rapid onset, changes in level of consciousness and/or an abnormal neurological examination.
- The presence of an unusual condition can cause prolonged diagnostic delay. Prompt recognition and treatment can improve outcome from voltage-gated potassium channel antibody-related encephalitis.
- While hyponatraemia can cause encephalopathy in its own right, it is occasionally associated with a distinct pathology and should be investigated promptly.

Case Reports

Patient 1

A 72 year old previously independent woman presented to hospital with a three week history of increasing confusion and a fall. She had a history of type 2 diabetes mellitus and hypertension. She lived alone. Her only medications were metformin and bendroflumethiazide. Examination was unremarkable apart from confusion (acute mental test score - 6/10) and poor short term memory. She was euvolaemic. Her blood pressure was 150/70.

Investigations on admission to hospital revealed hyponatraemia (110 mmol/L), serum osmolality 237mOsmol/kg and urine osmolality 645 mOsmol/kg. The last recorded serum sodium level 60 days prior to admission was 136mmol/l. Liver, thyroid and adrenal function tests were normal and given her euvolaemic status this was felt to be consistent with a syndrome of inappropriate anti-diuretic hormone (SIADH) secretion. There was no evidence of a systemic inflammatory response syndrome and her white cell count, serum bicarbonate and C-reactive protein were in the normal range; she was afebrile.

Bendroflumethiazide was stopped. In accordance with local guidelines 2.7% hypertonic saline was carefully administered.[1] Once serum sodium level was above 120mmol/l, fluid restriction was instigated. Neuroimaging with CT and MRI brain was performed on day 4 of her hospital admission. Bilateral medial temporal changes were identified on MRI brain scan, consistent with limbic encephalitis (Figure 1A and B). She was empirically treated with intravenous aciclovir (10mg/kg TDS). Lumbar puncture revealed normal white cell count, glucose and protein in the cerebrospinal fluid (CSF). Polymerase chain reaction (PCR) testing of CSF for HSV 1, 2 and varicella zoster viruses was negative. Whilst CSF PCR has high sensitivity for detecting HSV there are reported cases of PCR negative HSV encephalitis and so aciclovir was continued.[2] In accordance with guidelines for suspected encephalitis, autoimmune and paraneoplastic antibody screens (anti-NMDA-receptor, anti-voltage-gated potassium channel and a paraneoplastic antibody panel) were requested.[3] An electroencephalogram showed a diffusely slow pattern consistent with an encephalopathy. Plasma

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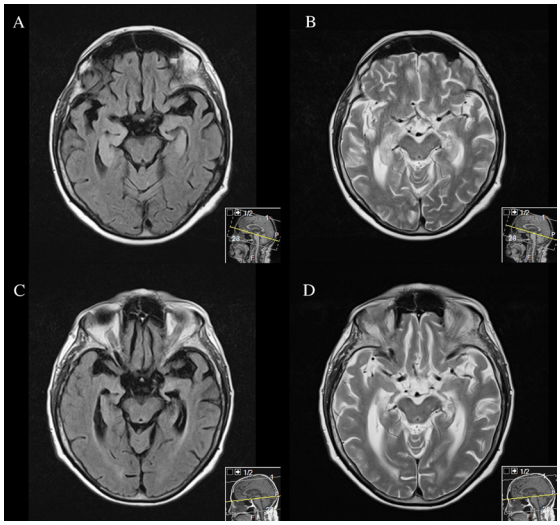

Figure 1. Axial MRI brain scans showing medial temporal signal change on FLAIR (A) and T2 (B) images shortly after admission. Ten weeks later signal changes had resolved but atrophy was present on follow-up MRI brain scans (C and D).

sodium levels remained below the normal range (see Figure 2). On day 11 of her admission she had a tonic clonic seizure. She was transferred to the intensive care unit for management of status epilepticus. Propofol and lamotrigine were added to the benzodiazepine and phenytoin therapy to control seizure activity. Her serum sodium at that stage was 123 mmol/L and had been stable in the preceding days.

After correction of the serum sodium on day 18 (Figure 2), her general delirium had developed into a more specific problem with short term memory in keeping with the temporal lobe changes identified on MRI. An Addenbrooke's cognitive score was 51/100 on day 47. On day 45 an elevated anti-VGKC antibody titre was reported (1144 pM); anti-NMDA receptor antibodies were not detected. Empirical steroid therapy (60mg per day) was started. A transient neutropenia was observed and the anti-epileptic medication was switched to sodium valproate. She had no further seizures following her initial seizure on day 11 and the Addenbrooke's cognitive score had improved to 61 by day 75 with the patient still having deficits in short term memory. Follow-up MRI brain scan demonstrated resolution of the medial temporal signal change and atrophy (Figure 1C and D). There was no evidence of a thymoma or other malignancy on a CT scan of her chest, abdomen and pelvis. Repeat anti-VGKC titres performed immediately prior to (1763 pM) and then six weeks after steroid initiation (1526 pM) were obtained. Neither of the two commonly tested subtypes, contactin-associated protein-2 (CASPR2) or leucine-rich glioma inactivated 1 protein (LGI1), was detected on any of these three samples. Discharge home with an extensive care package was arranged five months after initial presentation.

Patient 2

A 50 year old vehicle breakdown patrolman presented to the emergency department of a general hospital with a rapid-onset of confusion, encompassing insomnia, auditory hallucinations, agitation, disorientation and labile mood. This followed a one week history of a 'flu'-like viral illness. He recently had an amicable separation from his long-term partner. His past medical history included a spontaneous pneumothorax in his early 20s, and a possible episode of optic neuritis a year earlier; MRI

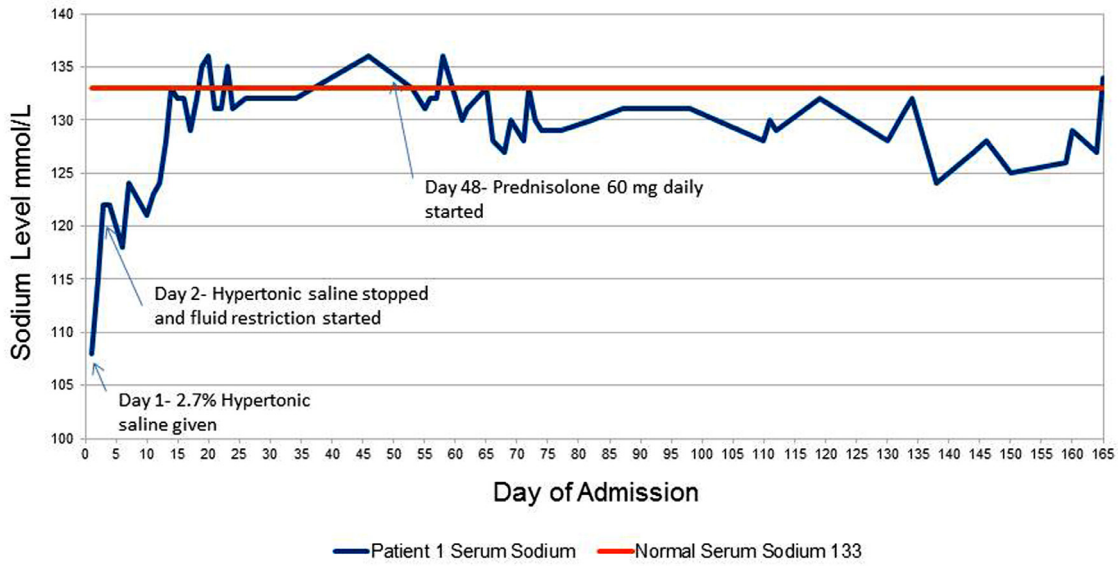

Figure 2. Serum sodium levels of admission along with therapeutic interventions.

Table Key differences between NMDA receptor and VGKC receptor encephalitis.

Variable	VGKC receptor encephalitis	NMDA receptor encephalitis
Sex	M:F 2:1	M:F 2.5:1
Age range	>40 years	15 years- 40 years
Associated Tumours	Approximately 20% small cell lung cancers; thymomas	Ovarian teratomas
CSF changes	Common (lymphocytic pleocytosis)	Rare
MRI findings	Common (hyperintensity in medial temporal lobe)	Rare
Predominant CSF symptoms	Confusion, memory deficits (visual), sometimes seizures e.g. facio-brachial dystonic	Psychosis (delusions, hallucinations), Autonomic dysfunction, dyskinesias, seizures
Behavioural symptoms	Apathy, irritability	Anxiety, agitation, mutism
Differential diagnosis	Wernicke-Korsakoff syndrome, infective encephalitis, overdose (drug e.g. gold/manganese), Creutzfeldt-Jakob disease, Hashimoto's encephalopathy, non-convulsive status epilepticus Motor neuron disease, prion diseases	Motor neuron disease, prion diseases, neuropsychiatric lupus, Encephalitis lethargica, Sydenham's chorea, Infective, non-convulsive status epilepticus, Hashimoto's encephalopathy, neuropsychiatric lupus
Disease course	Orofacial, limb dyskinesias	Reduction in consciousness; dysautomnia
Treatment	Immunotherapy/spontaneous resolution	Early immunotherapy- responds well

brain and CSF oligoclonal bands had been negative on that occasion. He was on no regular medications. There was no evidence of illicit drug use.

Physical examination revealed no abnormalities. He was initially referred to the psychiatry team for suspected new-onset psychosis. However due to an altered level of consciousness (drowsiness) and degree of disorientation, an organic cause was suspected. Urinary toxicology, an unenhanced CT brain and lumbar puncture for microscopy, protein and glucose showed no abnormalities; CSF PCR was negative for HSV-1, HSV-2 and VZV. Over a 3 day period, the agitation became increasingly problematic and he required 24 hour security and sedation. Despite the initial negative PCR he was commenced empirically on intravenous aciclovir on the suspicion of infective encephalitis, and he received levetiracetam for suspected non-convulsive status epilepticus as on-site EEG facilities were not available. He underwent an MRI brain with gadolinium and a magnetic resonance venogram, and blood was sent for a vasculitic screen, hepatitis virus serology, HIV serology and antibodies against neuronal surface antigens (NMDA receptor and VGKC antibodies).

A neurology review was sought on day 7 of admission: he was noted to exhibit stereotypical rhythmic movements of the right arm with variable tone. An EEG showed paroxysmal frontal sharpened slow waves suggestive of encephalitis. The clinical impression was that this was autoimmune encephalitis, probably of the anti-NMDA receptor type, and that he required empirical plasmapheresis. He was transferred to the regional tertiary neurology centre, where he required sedation for five days to enable plasmapheresis to be performed safely. Neuroimmunology results were negative for NMDA receptor antibodies but voltage-gated potassium channel (VGKC) antibodies were positive at a level of 339 pmol/l (LGI1 positive, CASPR2 negative), and 334 pmol/l on repeat testing. On withdrawal of sedation, his behavioural disturbance had significantly improved and he was alert and orientated but with profound amnesia for events leading up to and during the hospital admission. After discussion with the patient, a decision was made to commence oral steroids with a tapering dose plus azathioprine in order to reduce the potential risk of relapse.

Discussion

This report highlights the importance of fully investigating previously well and independent patients presenting with altered mental status. The abnormal investigations in our first patient (hyponatraemia and MRI brain changes suggestive of limbic encephalitis but negative PCR testing for the common herpes viruses) prompted a thorough evaluation of non-infective causes for the presentation. This is in contrast to the second patient in whom the clinical importance of the multidisciplinary assessment prompted the team to consider neurological disorders as a cause for the psychiatric presentation. First presentation of psychosis, movement disorder and disorientation are recognised features of antibody-mediated encephalitis.[4]

Patient 1 presented following a fall associated with confusion - a common reason for admission

to hospital. Her short history of confusion was initially attributed to hyponatraemia secondary to thiazide diuretic treatment. Hyponatraemia work-up, however, was more consistent with an evolving SIADH picture. This informed the correct initial management of fluid restriction. Despite improvement in her serum sodium concentration the confusion and memory impairment did not improve. Radiological evidence of temporal lobe pathology was suggestive of viral encephalitis but there was no response to full dose antiviral treatment.

Patient 2 had quite a different presentation with prominent psychiatric features in the history. However, the rapid onset of psychosis, altered consciousness and drowsiness prompted investigation for an organic cause. This patient had no biochemical abnormality. This patient's MRI scan of brain showed no signs of encephalitis, but the EEG was compatible with encephalitis. Interestingly, the case bears many similarities to one of the first reported cases of anti-VGKC encephalitis, where rapid onset insomnia, confusion and hallucinations were important features and the patient had recently separated.[5] The clinical phenotype of patient 2 was thought to be more in keeping with NMDA receptor encephalitis (comparisons shown in table), which usually presents with psychiatric symptoms, memory problems, seizures, decreased consciousness, dyskinesias and autonomic instability.[6]

Both patients had similarities in their initial management. Once encephalitis was suspected, they both had lumbar punctures which were non-diagnostic. As HSV is the most common cause of encephalitis, both patients were treated with intravenous aciclovir. It has been estimated that 40-85% of cases of encephalitis have no identifiable cause despite extensive investigation.[7] In the absence of confirmed HSV infection, confirmatory tests for less common diagnoses such as anti-VGKC and anti-NMDA receptor antibody associated autoimmune encephalitis were performed.

Autoimmune limbic encephalitis due to VGKC antibodies has been recognised since 2001 as a potentially reversible cause of encephalitis.[5] In a study of almost 55000 patients with unexplained neurological symptoms, 4% tested positive for VGKC antibodies.[8] Higher VGKC antibody titres (over 400 pM) are more often associated with autoimmune disease than lower titres (100-400pM).[9] The response to treatment in patient 2 (with a lower VGKC antibody titre) was suggestive of an underlying autoimmune process. Subtypes of this condition exist due to antibodies directed at proteins closely associated with VGKCs in brain tissue, including leucine-rich glioma inactivated 1 protein (LGI1), which frequently presents with amnesia, confusion, seizures and hyponatraemia with medial temporal lobe signal change. Patient 1, while exhibiting all these features, was negative for both LGI1 and for another VGKC antibody subtype, contactin-associated protein-2 (CASPR2) antibody which can be associated with a thymoma or other malignancy.[10-12] Patient 2, however exhibited prominent psychiatric features often found in anti-NMDA receptor antibody encephalitis. However the positive anti-VGKC antibody result (with a positive LGI1 subtype antibody and negative anti-NMDA antibody) emphasises that anti-VGKC –mediated encephalitis is an important differential diagnosis in these patients. The normal neuroimaging is not unusual in patients with anti-VGKC antibodies.[10]

There was delay in obtaining the VGKC antibody result for patient 1 as testing is performed in one UK centre in Oxford and samples run as a batch every few weeks. As early treatment is associated with better overall outcomes, timely diagnosis is important.[11] A recent advance in testing for VGKC antibodies may reduce the reporting time to within one week.[13] In patient 1 the diagnosis was made prior to immunotherapy. In case 2 however, the patient was treated empirically with plasmapheresis as his presentation was thought to be due to an autoimmune encephalitis. This leads to the difficult question of whether it is more appropriate to confirm the diagnosis and potentially miss a window when appropriate treatment would lead to the greatest benefit or to treat empirically and risk harm through treating the wrong disease process. Patient 2 showed a more marked clinical improvement than patient 1. Patient 1 after treatment still had severe memory impairment and amnesia confirming other reports that these are sequelae of this condition.[14] Patient 2 has no significant persistent memory problems but experiences some residual dysexecutive function.

The evidence base for treatment of this condition is evolving. The options include steroids, plasma exchange and intravenous immunoglobulin.[15] In a case series of 50 patients, 39 had a good clinical outcome following immunotherapy.[16] As the cognitive scores and functional testing were improving in patient 1 only prednisolone was used. VGKC antibody titres usually decrease with successful treatment over three to six months.[15,17] Most cases reported in the literature exhibit a monophasic course with no relapse after successful treatment.

Conclusion

Autoimmune encephalitis due to anti-VGKC antibodies is increasingly recognised. Many causes of confusion, altered mental state and memory impairment are irreversible and progressive. However, there is the potential for resolution of

symptoms after treating limbic encephalitis associated with anti-VGKC antibodies. An autoimmune cause should be considered in the differential diagnosis of encephalitis, particularly if there are features such as an acute onset of delirium, psychiatric symptoms, confusion, hyponatraemia or seizures with negative viral work up. Recent advances in testing for antibodies associated with autoimmune encephalitis will aid the acute physician in timely diagnosis. Early treatment with steroids or immunotherapy maximises the chances of recovery in these patients.

Declaration of competing interests

Nothing to declare.

References

1 The Guidelines and Audit Implementation Network (GAIN) (Northern Ireland) Guidance on hyponatraemia in adults (on or after 16th birthday) February 2010. Available at: http://www.gain-ni.org/Publications/Guidelines/Hyponatraemia_guideline.pdf (last accessed 15 March, 2014).

2 Denes E, Labach C, Durox H, *et al.* Intrathecal synthesis of specific antibodies as a marker of herpes simplex encephalitis in patients with negative PCR. *Swiss Med Wkly* 2010; **140**:w13107.

3 Solomon T, Michael BD, Smith PE, *et al.* Management of suspected viral encephalitis in adults-Association of British Neurologists and British Infection Association National Guidelines. *J Infect* 2012; **64(4)**:347-373.

4 Lennox BR, Coles AJ, Vincent A. Antibody-mediated encephalitis: a treatable cause of schizophrenia. *Br J Psychiatry* 2012 Feb;200(2):92-94.

5 Buckley C, Oger J, Clover L, *et al.* Potassium channel antibodies in two patients with reversible limbic encephalitis. *Ann Neurol* 2001; 50(1):73-78.

6 Parthasarathi UD, Harrower T, Tempest M, *et al.* Psychiatric presentation of voltage-gated potassium channel antibody-associated encephalopathy. Case report. *Br J Psychiatry* 2006; **189**:182-183.

7 Ambrose HE, Granerod J, Clewley JP, *et al.* Diagnostic strategy used to establish etiologies of encephalitis in a prospective cohort of patients in England. *J Clin Microbiol* 2011; **49(10)**:3576-3583.

8 Klein CJ, Lennon VA, Aston PA, *et al.* Insights from LGI1and CASPR2 potassium channel complex autoantibody subtyping. *JAMA Neurol* 2013; **70(2)**:229-234.

9 Paterson RW, Zandi MS, Armstrong R, *et al.* Clinical relevance of positive voltage-gated potassium channel (VGKC)-complex antibodies: experience from a tertiary referral centre. *J Neurol Neurosurg Psychiatry* 2013 Jun **11** (epub ahead of print)

10 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; **133(9)**:2734-2748.

11 Irani SR, Vincent A. Autoimmune encephalitis -- new awareness, challenging questions. *Discov Med* 2011; **11(60)**:449-458.

12 Alcantara M, Bennani O, Verdure P, *et al.* Voltage-gated potassium channel antibody paraneoplastic limbic encephalitis associated with acute myeloid leukemia. *Case Rep Oncol* 2013; **6(2)**:289-292.

13 Sadalage G, Karim A, Jacob S. Autoimmune encephalitis screen-a review of rapid diagnostic screening in 600 patients over 5 years. *J Neurol Neurosurg Psychiatry* 2013; **84(11)**:e2.

14 Butler CR, Miller TD, Kaur MS, *et al.* Persistent anterograde amnesia following limbic encephalitis associated with antibodies to the voltage-gated potassium channel complex. *J Neurol Neurosurg Psychiatry* 2014 (epub ahead of print) doi:10.1136/jnnp-2013-206724.

15 Mittal M, Hammond N, G Lynch S. Immunotherapy responsive autoimmune subacute encephalitis: a report of two cases. *Case Rep Med* 2010; **2010**:837371.

16 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. *Lancet Neurol* 2010; **9(8)**:776-785.

17 Vincent A, Buckley C, Schott JM, *et al.* Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. *Brain* 2004; **127(Pt 3)**:701-712.