CASE REPORT

Possible anti-VGKC autoimmune limbic encephalitis associated with SIADH

Nicholas Black, Hazim Hamada

Department of General and Geriatric Medicine, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK

Correspondence to
Dr Nicholas Black,
n.black@doctors.org.uk

Accepted 20 February 2018

SUMMARY

An 80-year-old woman presented with a 5-week history of increasing confusion. Examination was remarkable only for deficits in short-term memory and paranoid thoughts. Blood tests revealed hyponatraemia, and further biochemical testing was consistent with syndrome of inappropriate antidiuretic hormone (SIADH). After an exhaustive diagnostic workup for causes of SIADH, the only abnormal finding was a mildly raised antivoltage-gated potassium channel (VGKC) titre of 185 pmol/L (0–69) consistent with possible anti-VGKC autoimmune limbic encephalitis. However, other diagnostic features were absent. She is currently undergoing outpatient investigation for other causes of memory loss.

BACKGROUND

This case discusses a common and important clinical dilemma; the investigation for a cause for syndrome of inappropriate anti diuretic hormone (SIADH) when the initial screening tests are negative. It highlights an important association between antivoltage-gated potassium channel (VGKC) autoimmune limbic encephalitis and SIADH. It also emphasises the importance of interpreting mildly elevated anti-VGKC titres with caution and the difficulties of making a definitive diagnosis in this setting.

CASE PRESENTATION

An 80-year-old woman presented to hospital with a 5-week history of increasing confusion. Her medical history included anxiety, depression, reflux disease and hyperlipidaemia. Her medications are listed in table 1.

She did not smoke and drank alcohol in moderation. Her family first noticed that she was forgetful of the names of people and places. This worsened over several weeks and she had started to become disoriented to time and place. This fluctuated throughout the day. In addition she had developed some paranoid thoughts; for example, she thought that people were watching her. She had limited insight into her deterioration and it was the family who sought help by bringing her to the hospital. Her examination was remarkable for deficits in short-term memory (Montreal Cognitive Assessment score was 7/30), but her physical examination was otherwise normal.

INVESTIGATIONS

Biochemistry revealed low serum sodium of 124 mmol/L (133-146), low serum osmolality of 259 mmol/kg (275-295), inappropriately concentrated urine osmolality of 364 mmol/kg and high urinary sodium of 50 mmol/L. These findings are consistent with SIADH.

Remaining routine blood tests including full blood count, renal profile, liver function tests, B_{12} and folate were normal. Thyroid function tests and short synacthen test were also normal.

CT head showed cerebral atrophy with periventricular small vessel disease. MRI brain showed bilateral hippocampal atrophy and generalised parenchymal volume loss consistent with Alzheimer's dementia.

Electroencephalogram (EEG) was reported as normal.

CT thorax, abdomen and pelvis was performed to identify an underlying cause for SIADH such as malignancy. There were no abnormalities present.

Lumbar puncture was normal: white cell count $<3\times109$/L, protein 0.21 g/L (0.05–0.45), normal glucose and no oligoclonal bands. No organisms were grown on culture.

DIFFERENTIAL DIAGNOSIS

The first diagnostic step was deciding whether this woman had delirium or dementia. Initially, we believed that she had a delirium based on the short time course of events and her fluctuating confusion. The differential diagnosis for delirium is extremely broad and has been reviewed elsewhere.[1] In this case, the diagnosis could be narrowed down by the presence of SIADH. Its causes are summarised in table 2.

The initial workup includes a thorough history and examination, medications review, chest X-ray and blood tests including full blood count, renal profile, liver function tests, blood glucose and erythrocyte sedimentation rate/C reactive protein.[2] Thyroid function tests and a short synacthen test should also be performed to exclude hypothyroidism and adrenal insufficiency, respectively.[2] All non-essential medications associated with hyponatraemia (in this case metoclopramide, quinine, sertraline and diazepam) should be stopped. If no obvious cause is identified then the next step is to arrange for a CT head to exclude gross brain pathology and then finally a CT thorax, abdomen and pelvis to identify occult malignancy.[3] In our patient, these initial diagnostic tests were all normal.

In case series of hospitalised patients with SIADH, the percentage of patients with idiopathic SIADH varies from 15.9%[4] to 39.2%.[5] It appears

To cite: Black N, Hamada H. *BMJ Case Rep* Published Online First: [*please include* Day Month Year]. doi:10.1136/bcr-2017-223484

Table 1 List of medications

Propanolol 60 mg once daily	Sertraline 50 mg once daily
Metoclopramide 10 mg twice daily	Esomeprazole 40 mg once daily
Betahistine 16 mg twice daily	Stemetil 5 mg three times a day
Quinine 300 mg once in the evening	Diazepam 1 mg as needed
Simvastatin 40 mg once in the evening	

to be largely a disease of the elderly, with 92% of patients being 70 years or older.[4] The yield of extensive diagnostic imaging in these patients is low. In patients previously labelled as idiopathic SIADH, an underlying cause (most commonly occult malignancy) was identified in 11% of patients after extensive CT imaging.[6]

Despite the potentially low yield, we performed further tests to exclude rarer causes of subacute confusion. The patient was 80 years old and so nutritional causes of confusion, particularly B_{12}, folate and thiamine deficiency, must be considered. However, her B12 and folate levels were normal and she drank alcohol in moderation. We also considered neurological sarcoidosis, cerebral vasculitis, Lyme disease and sporadic Creutzfeldt Jakob disease as possible diagnoses. Neurological sarcoidosis is a rare condition in which non-caseating granulomas develop both within the peripheral tissues and the brain.[7] Clinical presentation is variable but may include subacute confusion, seizures, myelopathy and cranial nerve palsies.[7] Pituitary involvement can cause a wide variety of endocrine disorders including SIADH.[8] In addition, other features of systemic sarcoidosis may be present such as lymphadenopathy and lung disease. The cerebrospinal fluid (CSF) demonstrates pleocytosis and a raised protein level, and MRI shows evidence of enhancement within the brain parenchyma and/or the meninges.[7] Cerebral vasculitis is a similarly rare disease that can occur as a primary disease process or secondary to systemic vasculitis.[9] It presents clinically with subacute confusion, seizures and neurological deficits. The CSF typically demonstrates pleocytosis and a raised protein level, and MRI shows evidence of meningeal enhancement and ischaemic/haemorrhagical foci.[9] Lyme disease is caused by the tick-borne bacteria *Borrelia burgdorferi* and is most prevalent in Europe and North America.[10] If untreated, Lyme disease can involve the nervous system to cause subacute confusion and peripheral/cranial radiculopathies. CSF demonstrates a lymphocyte predominant pleocytosis and IgM/IgG antibodies against *B. burgdorferi* are often present.[10] Finally, sporadic Creutzfeldt Jakob disease is the most common of the prion diseases and is characterised by rapidly progressive dementia, myoclonus and generalised triphasic periodic complexes on the EEG.[11] In our patient, the CSF, MRI and EEG findings were inconsistent with all of these diagnoses.

The final diagnosis we considered was limbic encephalitis related to paraneoplastic or autoimmune antibodies. She had an initial mildly elevated anti-VGKC titre of 147 pmol/L (0–69) and a repeat test 1 month later showed a titre of 185 pmol/L (0–69). The remaining CSF tests were normal and paraneoplastic antibodies were negative. As discussed later on, this is an equivocal test result and must be interpreted in the broader clinical context. The evidence in favour of this diagnosis is the subacute confusion, the little known association between anti-VGKC encephalitis and SIADH,[12] the mildly elevated anti-VGKC titre and partial responsiveness to steroid therapy. The arguments against the diagnosis are the absence of seizures and the inconsistent CSF, EEG and MRI results.

The other consideration was whether this woman had dementia. Although the 5-week history of confusion is against this, on further questioning, it appears that she may have had some subtle cognitive decline preceding her presentation. Moreover, her MRI brain showed bilateral hippocampal atrophy consistent with Alzheimer's dementia.

TREATMENT

We stopped all non-essential medications particularly metoclopramide, quinine, sertraline and diazepam which have all been associated with hyponatraemia. We instigated fluid restriction and although the sodium did not normalise entirely, it did increase to 128 mmol/L (133-146) on discharge and is under outpatient follow-up.

Once a possible diagnosis of anti-VGKC autoimmune encephalitis was made, a tailing dose of prednisolone starting at a dose of 60 mg once daily was trialled for a month. The family felt that there was an improvement on therapy in terms of functioning around the house and short-term memory. There was a small rise in Montreal Cognitive Assessment score to 13/30 (7/30 on admission). It is unclear whether this was related to other changes, for example, being back in the home environment, cessation of drugs and partial resolution of hyponatraemia. On tailing down the steroids, the family felt that her short-term memory and day-to-day functioning were worse but we were unable to detect a reduction in the Montreal Cognitive Assessment score.

OUTCOME AND FOLLOW-UP

While the diagnosis is still unclear, the most probably explanation is that she has Alzheimer's dementia and experienced acute-on-chronic confusion related to SIADH. Nonetheless, the patient experienced an initial improvement with steroids. While the family feel that she has subjectively deteriorated off steroids, to date we have not recorded an objective decline in cognition. She remains under outpatient follow-up and is not being treated with steroids for the time being.

Table 2 Causes of SIADH

Neurological	Respiratory	Malignancy	Drugs	Miscellaneous
Encephalitis	Lung cancer, particularly small cell lung cancer	Lymphoma	Antiepileptics for example, carbamazepine	Pain
Meningitis	Pneumonia	Sarcoma	Antidepressants for example, SSRIs	Nausea and vomiting
Tumour	Abscess	Endometrial cancer	Antipsychotics for example, haloperidol	General anaesthesia
Intracranial haemorrhage	Tuberculosis		Chemotherapy, for example, cyclophosphamide	
			NSAIDS	
			Opiates	

NSAIDS, non-steroidal anti-inflammatory drugs; SIADH, syndrome of inappropriate anti diuretic hormone; SSRIs, selective serotonin reuptake inhibitors.

DISCUSSION

Symptomatic hyponatraemia secondary to SIADH is a common clinical problem but little information exists about how to proceed when initial screening tests are negative. This case illustrates that autoimmune limbic encephalitis should be considered when SIADH occurs alongside neurological symptoms and signs.

Limbic encephalitis is a rare diagnosis which can be made in the context of suggestive symptoms and characteristic CSF, EEG, MRI and autoantibody tests. Symptoms are non-specific and include subacute confusion (weeks to months), hallucinations, sleep disturbance and seizures.[13] In our patient, the absence of seizures and hallucinations makes the diagnosis less likely. In 80% of cases the CSF shows a raised lymphocyte count with raised protein and oligoclonal bands.[13] MRI FLAIR shows hyperintense signal in the medial temporal lobes in 70%–80% of cases.[13] EEG findings are variable but typically show epileptic activity in the temporal lobes. All these tests were normal in our patient. Patients with limbic encephalitis are positive for autoantibodies associated with paraneoplastic syndromes (anti-Hu, anti-Ma, anti-CV2 and anti-amphiphysin) or autoimmune encephalitis (anti-VGKC, anti-n-methyl-d-aspartate receptor (anti-NMDA),anti-α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (anti-AMPAR) and anti-gamma-amino-butyric acid (anti-$GABA_BR$)).[14] It is important to note that this classification is not rigid and autoimmune encephalitis can also occur secondary to occult malignancy.[14]

Anti-VGKC limbic encephalitis is the form most strongly associated with hyponatraemia. It accounts for a third of cases of autoimmune limbic encephalitis. Interestingly, autoantibodies are not directed at the potassium channel subunits themselves but rather accessory proteins which form part of the VGKC complex: LGI1 (most common), CASPR2 and Contactin-2.[14] One case series has shown that the prevalence of hyponatraemia may be as high as 59% in these patients.[12]While the exact cause of hyponatraemia remains unknown, previous case reports have identified an association between anti-VGKC limbic encephalitis and SIADH as in our case.[15 16] In a mouse model, LGI1 is expressed both within the hypothalamus and renal tubules.[17] It is possible that the autoimmune inflammatory process directly involves the hypothalamus and causes an increase in ADH secretion or there may be a direct action of autoantibodies on the kidney.[17] To our knowledge, there are no animal studies investigating the mechanisms of SIADH in autoimmune encephalitis.

Learning points

- Antivoltage-gated potassium channel (VGKC) autoimmune limbic encephalitis, most commonly caused by autoantibodies against LGI1, is associated with syndrome of inappropriate anti diuretic hormone (SIADH).
- If initial diagnostic tests for a cause of SIADH are negative, then anti-VGKC autoimmune limbic encephalitis should be considered as a possibility.
- Important diagnostic features of autoimmune limbic encephalitis include subacute confusion, hallucinations and seizures in the context of characteristic EEG, MRI and autoantibody tests.
- Low positive anti-VGKC titres (0–400 pmol/L) must be interpreted with caution. In the absence of other clinical criteria, anti-VGKC autoimmune limbic encephalitis is unlikely.

Psychogenic polydipsia has also been described with anti-VGKC limbic encephalitis.[18]

The interpretation of anti-VGKC titres can be difficult. Our samples were sent to Oxford UK and quantified using radioimmunoassay techniques. A normal result is less than 69 pmol/L and an equivocal result is 70–130 pmol/L. Nonetheless, a mildly elevated result must be interpreted with caution. For example, 1 study has shown that of 32 patients with low positive results (100–400 pmol/L), only 4 of the patients had definitive autoimmune limbic encephalitis.[19] The other clinical criteria such as seizure activity, MRI brain appearance, EEG and CSF results were all negative in our case and so this makes the diagnosis less likely.

Treatment of autoimmune limbic encephalitis is achieved using immunotherapy, corticosteroids, intravenous IG, plasma exchange and cyclophosphamide have all been used with success.[13] In our case we took a pragmatic approach, which was to trial a course of steroids to see if there was any clinical improvement.

Contributors NB is an FY2 doctor at the Manchester Royal Infirmary who was the junior doctor looking after the patient during her inpatient admission. He researched the topic and prepared this manuscript. HH is a consultant geriatrician at the Manchester Royal Infirmary. He was the consultant looking after this patient and made the initial diagnosis of anti-VGCK encephalitis. He reviewed the manuscript and provided feedback with suggestions for improvement which have been incorporated into the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet* 2014;383:911–22.
2 Hannon MJ, Thompson CJ. The syndrome of inappropriate antidiuretic hormone: prevalence, causes and consequences. *Eur J Endocrinol* 2010;162(Suppl 1):S5–S12.
3 Hoorn EJ, Hotho D, Hassing RJ, *et al*. Unexplained hyponatremia: seek and you will find. *Nephron Physiol* 2011;118:p66–p71.
4 Shepshelovich D, Leibovitch C, Klein A, *et al*. The syndrome of inappropriate antidiuretic hormone secretion: Distribution and characterization according to etiologies. *Eur J Intern Med* 2015;26:819–24.
5 Hsu CY, Chen CL, Huang WC, *et al*. Retrospective evaluation of standard diagnostic procedures in identification of the causes of new-onset syndrome of inappropriate antidiuresis. *Int J Med Sci* 2014;11:192–8.
6 Shepshelovich D, Leibovitch C, Klein A, *et al*. Yield of workup for patients with idiopathic presentation of the syndrome of inappropriate antidiuretic hormone secretion. *Eur J Intern Med* 2016;32:60–4.
7 Lacomis D. Neurosarcoidosis. *Curr Neuropharmacol* 2011;9:429–36.
8 Porter N, Beynon HL, Randeva HS. Endocrine and reproductive manifestations of sarcoidosis. *QJM* 2003;96:553–61.
9 Berlit P. Diagnosis and treatment of cerebral vasculitis. *Ther Adv Neurol Disord* 2010;3:29–42.
10 Hildenbrand P, Craven DE, Jones R, *et al*. Lyme neuroborreliosis: manifestations of a rapidly emerging zoonosis. *AJNR Am J Neuroradiol* 2009;30:1079–87.
11 Zerr I, Kallenberg K, Summers DM, *et al*. Updated clinical diagnostic criteria for sporadic Creutzfeldt-Jakob disease. *Brain* 2009;132:2659–68.
12 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;133:2734–48.
13 Tüzün E, Dalmau J. Limbic encephalitis and variants: classification, diagnosis and treatment. *Neurologist* 2007;13:261–71.
14 Vincent A, Bien CG, Irani SR, *et al*. Autoantibodies associated with diseases of the CNS: new developments and future challenges. *Lancet Neurol* 2011;10:759–72.

15 Lee JJ, Lee ST, Jung KH, *et al*. Anti-LGI1 limbic encephalitis presented with atypical manifestations. *Exp Neurobiol* 2013;22:337–40.
16 McQuillan RF, Bargman JM. Hyponatraemia caused by LGI1-associated limbic encephalitis. *NDT Plus* 2011;4:424–6.
17 Head K, Gong S, Joseph S, *et al*. Defining the expression pattern of the LGI1 gene in BAC transgenic mice. *Mamm Genome* 2007;18:328–37.
18 Harrower T, Foltynie T, Kartsounis L, *et al*. A case of voltage-gated potassium channel antibody-related limbic encephalitis. *Nat Clin Pract Neurol* 2006;2:339–43. quiz following 43.
19 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* 2014;85:625–30.