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Unusual association of diseases/symptoms

VGKC positive autoimmune encephalopathy mimicking dementia

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Summary

Voltage gated potassium channel antibodies (VGKC Abs) are known to cause three rare neurological syndromes- neuromyotonia, Morvan's syndrome and limbic encephalitis although an increasing array of other associated neurological symptoms are becoming recognised. The authors describe the case of a 60-year-old female who presented to the neurology clinic with an apparent early onset dementing process. She was noted to have both extrapyramidal and frontal release signs on examination and was admitted for further evaluation. Her dementia investigation including a neoplastic screen was negative except for VGKC antibody positivity. Her symptoms dramatically improved with commencement of immunosuppression. A non-paraneoplastic VGKC antibody associated dementia-like syndrome has rarely been described. The authors add to the few existing reports of what represents an important reversible cause of cognitive impairment.

BACKGROUND

This interesting case demonstrates a rare but important treatable dementia mimic syndrome. It is unknown to date whether voltage gated potassium channel (VGKC) antibody positivity is pathological in this disorder or merely a marker of autoimmunity. Initiation of immunosuppressive treatment in these patients can produce a prompt and sustained recovery of cognitive function and independent living. VGKC antibodies should be considered in all young onset cases of cognitive impairment particularly those cases without a family history of dementia, where the initial dementia screen is negative and who have features of a movement disorder.

CASE PRESENTATION

A 60-year-old right handed lady presented to the neurology clinic accompanied by her daughter in a May 2009 with deterioration in gait and cognition over a 6 month period. Her daughter reported that the patient was increasingly forgetful, had reduced mobility and a tremor in her right upper limb. Falls were not a major feature but the patient did have urinary frequency, urgency and occasional incontinence. There were no reports of hallucinations.

Her medical history was notable for hypothyroidism and bipolar affective disorder (BPAD) diagnosed 30 years previously. She had been on many different psychotropic agents in the past including a number of antipsychotics but was stable from a psychiatric perspective for many years. She was recently assessed at the psychiatric clinic. An mini–mental state examination (MMSE) performed in 2008 by psychiatry noted mild cognitive impairment (27/30).

Medications included eltroxin 100 mcg once daily (OD), quetiapine 600 mg nocte, valproate 800 mg twice daily, lithium 800 mg nocte and procyclidine 5 mg OD.

The patient had a strong family history of psychiatric disease with BPAD in her father and major depression in her mother. She was an active retired primary school teacher who was an ex- smoker and did not consume alcohol or unprescribed drugs.

On examination, the patient was euthymic but disinhibited. No psychotic or manic symptoms were noted. Cognition was severely impaired with disorientation in time and place. The patient scored 15/30 on MMSE, 9/18 on a frontal assessment battery and 54/100 on the Addenbrook's cognitive assessment. There was evidence of an asymmetrical resting tremor of the right upper limb but no myoclonus. Glabellar tap was positive. The patient demonstrated a stooped posture and festinant gait without retropulsion. A grasp reflex was present bilaterally. Cranial nerve examination was normal. Tone, power, reflexes were normal in all four limbs and plantars were flexor bilaterally. The initial impression was of an early onset neurodegenerative process with both frontal and extrapyramidal features. It was felt that some of the parkinsonian features could be part of the underlying process or as a side effect of previous psychiatric medication. A preliminary dementia panel was performed.

Six months later at follow-up, a significant deterioration was noted. The patient was now unable to stand without assistance, was wheelchair dependant and doubly incontinent. She required assistance with all activites of daily living and hoisting for transfers. Extrapyramidal and frontal release features were ongoing. She was admitted urgently for further evaluation and management.

INVESTIGATIONS

Blood testing demonstrated normal full blood count, urea and electrolytes, liver function tests, erythrocyte sedimentation rate, C-reactive protein, thyroid function tests, lyme, venereal disease research laboratory, HIV, B12, folate, ferritin and autoantibodies. Lithium and valproate levels were normal. Antineuronal and thyroid peroxidase antibodies

were negative. Voltage gated potassium channel antibodies were positive at a titre of 1:256 (ref <1:128) on two separate occasions.

Electrocardiogram and echocardiogram were normal. Chest x-ray demonstrated scarring consistent with old or latent tuberculosis (TB). This was further evaluated with high-resolution CT thorax abdomen and pelvis where widespread lymphadenopathy was noted. Mantoux test was positive. A lymph node biopsy was performed and was reported as consistent with latent TB. She was commenced on a course of rifampicin, isoniazid, pyrazinamide and pyridoxine.

An electroencephalogram (EEG) showed diffuse slow wave activity consistent with a widespread encephalopathy but no seizure activity was noted. Cerebrospinal fluid (CSF) analysis was consistent with a traumatic tap only. CSF protein 14-3-3 was negative. MRI scan showed mild generalised atrophy with some micro- haemorrhages in the region of the basal ganglia bilaterally. single-photon emission CT (SPECT) showed bilateral non-specific diffuse cortical reduction in perfusion. DaT (ioflupane iodine-123 injection) scan showed normal symmetrical tracer uptake.

Psychiatry were closely involved in her care throughout her stay and it was felt that she was not clinically depressed. Lithium levels were therapeutic. After her investigations were completed it was felt that the results were most in keeping with a non-paraneoplastic VGKC antibody associated autoimmune encephalopathy. Her case was discussed with psychiatry and infectious diseases given the complicating factors of her underlying bipolar disorder and latent TB with regards to commencing a trial of steroid therapy.

DIFFERENTIAL DIAGNOSIS

Initial differential diagnosis included:

1. Pseudo- dementia in the context of possible decompensation of BPAD.
2. Medication related syndrome in the context of lithium, anticholinergic (procyclidine) and atypical antipsychotic treatment (quetiapine).
3. Neurodegenerative disease (eg, Creutzfeldt–Jakob disease, frontotemporal dementia, lewy body dementia, Alzheimer's disease).
4. Autoimmune syndrome (eg, Hashimotos encephalopathy, paraneoplastic/non-paraneoplastic limbic encephalitis, vasculitides).
5. Infectious cause (eg, HIV, lyme, syphilis, viral encephalitis, TB, Whipple's).
6. Toxic/metabolic (eg, B12/folate deficiency, liver toxicity in context of chronic valproate use, electrolyte disturbances).
7. Endocrine (thyroid dysfunction, adrenal dysfunction).
8. Neoplastic (eg, metastases, glioblastoma, central nervous system lymphoma).

TREATMENT

Because of her history of BPAD it was decided not to give the patient bolus intravenous methylprednisolone but instead to commence 1 mg/kg (60 mg) daily of oral prednisolone. The patient developed a steroid related mania such that her steroids had to be weaned relatively rapidly over the course of the next 3 months while azathioprine was introduced and maintained at a dose of 75 mg twice daily. Her psychiatric medications also required dose adjustments and the addition initially of benzodiazepines during this period under the guidance of psychiatry for the management of her steroid induced mania.

OUTCOME AND FOLLOW-UP

One month post steroid introduction, MMSE had improved to 21/30. Mobility also improved and continence returned. Four months post initiation of therapy, in October 2010, the patient was mobilising independently and conducting all ADLs unaided, her steroid related mania had completely settled. VGKC titres had normalised (reported as 'negative' on two occasions). MMSE had further improved at this time to 29/30. The patient has been successfully discharged home and currently continues on azathioprine therapy, TB therapy and her psychiatric medications. It is unclear at present what the optimal duration of therapy should be. We will continue surveillance for an underlying neoplasm periodically.

DISCUSSION

We report a case of reversible VGKC antibody associated encephalopathy mimicking a dementing process. Prompt response and resolution of deficits was noted post introduction of immunosuppression. This presentation is different to the classically reported VGKC antibody associated syndromes such as neuromyotonia, Morvan's syndrome and limbic encephalitis although it shares some features in common with the latter.

Limbic encephalitis (LE) refers to the subacute onset of episodic memory impairment, disorientation and agitation commonly associated with seizures, hallucinations, sleep disturbance and histological and/or MRI evidence of medial temporal lobe inflammation. It has been described in association with VGKC antibodies as both a paraneoplastic and non-paraneoplastic phenomenon. Although our patient was cognitively impaired she did not demonstrate definite seizure activity, hyponatraemia or an abnormal MRI scan. In addition, her evaluation for an underlying neoplasm was negative. VGKC antibodies were first reported in the context of acquired neuromyotonia in 1995[1] and later with Morvan syndrome and in 2001 Buckley and colleagues reported VGKC antibodies in two cases of LE.[2]

Ten cases of VGKC associated LE were reviewed by Vincent *et al* in 2004. Early confusion, memory impairment and strongly positive VGKC antibody titres were typical. Ninty per cent of cases had seizures and 20% reported gait disturbance. Hyponatremia was a striking feature in 80%. EEG showed non-specific slowing in most as in our case. Eighty per cent of patients had MRI abnormalities in the temporal lobes. Plasma exchange/intravenous immunoglobulin (IVIG) was initiated prior to steroids in nearly all patients. A definite and sustained improvement was reported in 6 of 10 patients.[3] A later review of antiVGKC syndromes[4] reported 37 cases of LE with similar findings although hyponatraemia and MRI changes were not as common as in the first report. In comparison our case did not demonstrate definite seizure activity, hyponatraemia or an abnormal MRI scan.

In 2007 Mc Keon *et al* reported the first case of VGKC encephalopathy mimicking frontotemporal dementia. MRI in this case was normal but positron emission tomography

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scan showed bilateral frontal hypometabolism. VGKC abs were positive and syndrome of inappropriate antidiuretic hormone hypersecretion was noted along with slow wave activity on EEG. Oral prednisolone 1 mg/kg with subsequent taper was initiated with a sustained beneficial response.[5] Our case is similar clinically although lacking hyponatraemia and focal SPECT abnormalities. In addition our case was parkinsonian.

Later in 2008 Tan *et al* reported the spectrum of neurological symptoms described in association with VGKC antibodies in 72 patients. In particular fronto-subcortical features were described in 13% manifesting as personality change, executive dysfunction or disinhibition. Extrapyramidal features were noted in 21% and included parkinsonism. Autonomic features such as urinary difficulties were noted in 33.[6]

Various treatment regimes have been used in VGKC antibody related disorders. The use of high dose steroids, IVIG, plasma exchange, azathioprine and other immunomodulating drugs have all been reported. The appropriate regime, period of treatment and follow-up remains unclear.[3 7]

With regard to VGKC titres in relation to prognosis and response to treatment,[3] (previously referenced, Brain 2004), titres ranged from 450 pM (ref<100) to 5128 pM. Treatment was associated with dramatic reduction in titres in half of the cases with marked clinical improvement. The others had slower reductions to between 17% and 88% had clinical improvement that was more variable. An association was noted between fall in titres and improvement in percentile memory scores. Wong *et al*[7] noted in their study of treatment response in nine patients, that all patients with titres ranging from 210 to 4102 pM showed a rapid decline in titres within 1–4 months. The two patients who developed hippocampal atrophy had the highest titres (>4000 pM).

In 2008, Dalmau reported that paraneoplastic antibodies against neuronal surface antigens (VGKC antibodies) occur frequently, along with with antibodies against intracellular antigens (Lg1 and Caspr) and that it is the latter that are pathogenic. Such cases are frequently refractory to immunotherapy alone but symptoms typically improve when the primary neoplasm is removed. Non-paraneoplastic conditions associated with with VGKC antibodies in contrast, often respond to immunomodulatory therapies although the ideal treatment regime is unclear. The false positive rate of VGKC assay has been shown as 1.7%.[8]

Learning points

- VGKC antibody mediated disease constitutes range of clinical presentations, we report a case with atypical features only rarely described previously including extrapyramidal and frontotemporal features.
- Any patient presenting with a dementia like syndrome especially should have VGKC antibodies sent.
- It is one of the rare treatable causes of dementia- like illness and symptoms may be completely reversible with prompt initiation of immunosuppression.

Competing interests None.

Patient consent Obtained.

REFERENCES

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**:714–22.
2. **Buckley C,** Oger J, Clover L, *et al*. Potassium channel antibodies in two patients with reversible limbic encephalitis. *Ann Neurol* 2001;**50**:73–8.
3. **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):701–12.
4. **Merchut MP**. Management of voltage-gated potassium channel antibody disorders. *Neurol Clin* 2010;**28**:941–59.
5. **McKeon A,** Marnane M, O'connell M, *et al*. Potassium channel antibody associated encephalopathy presenting with a frontotemporal dementia like syndrome. *Arch Neurol* 2007;**64**:1528–30.
6. **Tan KM,** Lennon VA, Klein CJ, *et al*. Clinical spectrum of voltage-gated potassium channel autoimmunity. *Neurology* 2008;**70**:1883–90.
7. **Wong SH,** Saunders MD, Larner AJ, *et al*. An effective immunotherapy regimen for VGKC antibody-positive limbic encephalitis. *J Neurol Neurosurg Psychiatr* 2010;**81**:1167–9.
8. **Apiwattanakul M,** McKeon A, Pittock SJ, *et al*. Eliminating false-positive results in serum tests for neuromuscular autoimmunity. *Muscle Nerve* 2010;**41**:702–4.