

Unusual association of diseases/symptoms

Stroke preceding autoimmune encephalitis with neuronal potassium channel antibody

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Summary

Autoimmune encephalitis related to voltage-gated potassium channel (VGKC) antibodies can occur as a complication of cancer but, more frequently, as a non-paraneoplastic disorder. The prompt recognition and treatment could mitigate the morbidity associated with this entity, but the broad-spectrum of neurological manifestations often makes the diagnosis a challenge. The authors describe, here, a unique case of autoimmune encephalitis related to VGKC antibodies preceded by an ischaemic stroke. Conditions associated with the stroke (infection, seizures, metabolic disturbances) had delayed the diagnosis. The authors suggest that autoimmune encephalitis needs to be taken into consideration as part of a differential diagnosis in patients with prolonged encephalopathy following an ischaemic stroke. Infection may trigger an inflammatory response. In addition, the rupture of blood brain barrier that occurs in stroke may have a pathogenic role by allowing antibodies to gain access to the central nervous system.

BACKGROUND

Autoimmune encephalitis related to voltage-gated potassium channel (VGKC) can occur as a complication of cancer but, more frequently, as a non-paraneoplastic disorder.¹ To the best of our knowledge, this is the first case described in the context of an acute ischaemic stroke. Pneumonia, as other complications of stroke, may trigger the autoimmune response. In addition, we suggest that the rupture of blood brain barrier in ischaemic stroke might have played a pathogenic role. It is important to take into consideration this clinical entity in the differential diagnosis of encephalopathy after ischaemic stroke, since a prompt treatment could improve the prognosis.

CASE PRESENTATION

A male patient over the sixth decade was admitted to our stroke unit because of left arm paresis, facial asymmetry and speech disturbance; signs that his family noticed when he awoke of a morning.

Of note in his medical history were arterial hypertension, hypercholesterolaemia and coronary disease. His current medications were 300 mg daily of acetylsalicylic acid, 10 mg daily of simvastatin and 50 mg daily of metoprolol. He had never smoked and had not indulged in any recreational drug abuse. Neither his wife nor family members had noticed any symptoms of cognitive decline, personality changes or mood disturbance.

Clinical examination on admission identified a left visual-spatial neglect, left visual extinction and a mild left facial and brachial paresis. Brain CT scan showed a dense right middle cerebral artery (MCA) and hypodensity of the right basal ganglia. Initial blood tests were normal. Intravenous thrombolysis was not indicated, the patient having arrived at hospital beyond the therapeutic window. Two days after admission, atrial fibrillation was detected in the ECG monitoring. The diagnosis of cardioembolic infarction in

the right MCA territory was made, and he was started on intravenous sodium heparin perfusion.

The day after admission, the patient developed a respiratory infection with bronchospasm. Chest x-ray showed a right pulmonary basal infiltrate. He initially received intravenous amoxicillin-clavulanic acid, but other antibiotic regimens were needed because of persistent pneumonia.

One week later there was significant deterioration of the level of consciousness with hyponatraemia and fever.

INVESTIGATIONS

All microbiological tests performed, including blood, urinary, sputum cultures, legionella and pneumococcal urinary antigen tests were negative. Marantic and infective endocarditis was also ruled out with a transoesophageal echocardiogram. Cerebrospinal fluid (CSF) examination revealed 1 white cell/ul, 39 mg/dl protein, 101 mg/dl glucose. CSF cultures, including Mycobacteria, were sterile. CSF and blood serological tests (syphilis, Lyme, rickettsia, HIV and brucella) were negative. PCR was also negative for Herpes viridae DNA. No malignant cells were seen. Thoracic, abdominal and pelvic CT scans showed bilateral basal infiltrates, splenic and kidney infarctions. A second evaluation performed 1 month later, showed an improvement of the pulmonary infiltrates and no evidence of tumour. Bronchoscopy was negative for malignant cells. Tumour markers (including PSA) as well as paraneoplastic and autoantibody tests (anti-Hu, anti-Yo, anti-Ri, anti-amphiphysin, anti-CV2/CRMP5, anti-PNMA2, anti-nuclear, p-antineutrophil cytoplasmic antibodies (ANCA), c-ANCA, anticentromere B, antismooth muscle, antimitochondrial, anti-LKM1, antireticulin, antithyroid, antityeloperoxidase, antiproteinase 3m, antiglomerular basement membrane, anti-Jo-1, anti Ro, anti-La, anticardiolipin and rheumatoid factor) were negative.

OUTCOME AND FOLLOW-UP

Despite improvement in the respiratory symptoms and sodium level correction with water restriction, the fever and decreased level of consciousness persisted in addition to multi-focal myoclonus. A brain MRI performed on the 9th day of admission did not add any new information to the previous diagnosis (figure 1A,B). Serial EEGs showed generalised slowing. Autoimmune encephalopathy was suspected and methylprednisolone intravenously was begun on the 20th day of admission (dose of 1 g per day for 5 days, followed by oral prednisone).

The patient experienced a dramatic, but transient, improvement after the second dose of methylprednisolone. However, a few days later, the level of consciousness decreased progressively with additional postural tremor and worsening of myoclonus that required levetiracetam and valproate treatment. During the following 2 months he evolved to a state of akinetic mutism with multi-focal myoclonus. Brain MRI (figure 1C,D) showed an important frontal atrophy compared to the previous study conducted 50 days previously. In addition, he developed severe autonomic disturbances: a resistant syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH), recurrent episodes of hypotension and alternating diarrhoea and constipation. Suspicion of autoimmune or paraneoplastic encephalitis was very high but all the autoantibody tests available in our laboratory were negative. Neuronal potassium channel antibody test was solicited from another clinical centre, and five doses of intravenous immunoglobulin were administered 3 months after admission. There was an improvement in the level of consciousness, but akinetic mutism, myoclonus and tremor persisted.

Titres of neuronal potassium channel antibody of 193 pM confirmed the diagnosis. The patient died 1 month later as a result of broncho-aspiration. Autopsy was not performed because the family did not provide consent.

DISCUSSION

We describe, to the best of our knowledge the first time in the literature, a case of autoimmune encephalitis with VGKC antibodies after ischaemic stroke. Recently, a patient with a stroke-like presentation has been reported, but in that case, the diffusion restriction in MRI did not completely match a vascular territory, with typical temporal mesial hyperintensities, and was considered a stroke-mimic.²

Titres of neuronal potassium channel antibody, although not very high (laboratory reference level <100), were conclusive within the context of a subacute encephalitis with myoclonus, frontal dysfunction, tremor, SIADH and autonomic disturbances. Moreover, it should be noted that levels could have been decreased following the corticosteroid administration.³ Although the most typical abnormality in brain MRI is the T2/flair hyperintensity of mesial temporal region, cerebral atrophy exceeding that expected for age has also been reported.⁴ A paraneoplastic origin for these symptoms was carefully considered but thoracic, abdominal and pelvic CT scans, tumour markers and bronchoscopy were negative. However, confirmation was not possible because a thorough postmortem study was not performed.

A pathogenic role for VGKC autoantibodies in autoimmune encephalitis has been supported by animal passive-transfer experiments^{4 5} and invitro suppression of potassium currents.⁶ A humoral immunity hypothesis is also supported by the response to immunotherapy,³ compared with other paraneoplastic encephalitis with antibodies directed towards intraneural antigens. A recent study has shown that the target antigen of antibodies in patients with limbic encephalitis previously attributed to VGKC is, in fact, leucine-rich glioma-inactivated 1 (LGI1) protein; a neuronal secreted protein that appears to connect presynaptic and postsynaptic protein complexes for finely-tuned synaptic transmission. It has been speculated that antibody-mediated disruption of LGI1 function causes increased excitability, which results in seizures and other symptoms of encephalopathy.⁷

The rupture of blood brain barrier that occurs in stroke may have a pathogenic role by allowing antibodies to gain access to the central nervous system. Infection is the most frequent condition that precedes the development of this syndrome, probably by triggering an inflammatory response.⁸ In this sense, there is amounting evidence that inflammation plays an important role in cerebral ischaemia. Brain response to ischaemic injury is associated with an acute, and prolonged, inflammatory process characterised by the activation of glial cells, the production of inflammatory cytokines, as well as leucocyte and monocyte infiltration in the brain.⁹ In our patient, pneumonia may have triggered the autoimmune response. Furthermore, we suggest that the breakdown of the blood-brain barrier in ischaemic stroke might have been instrumental in the pathogenesis. Postischaemic autoimmune-mediated brain injury has been previously reported, and patients that develop an infection after stroke, especially pneumonia, are more likely to evidence a lymphocyte Th1 (+) response to nervous system proteins, like myelin basic protein and glial fibrillar acid protein.¹⁰

Although a good response to immunomodulatory therapies had been observed, the patient also experienced a

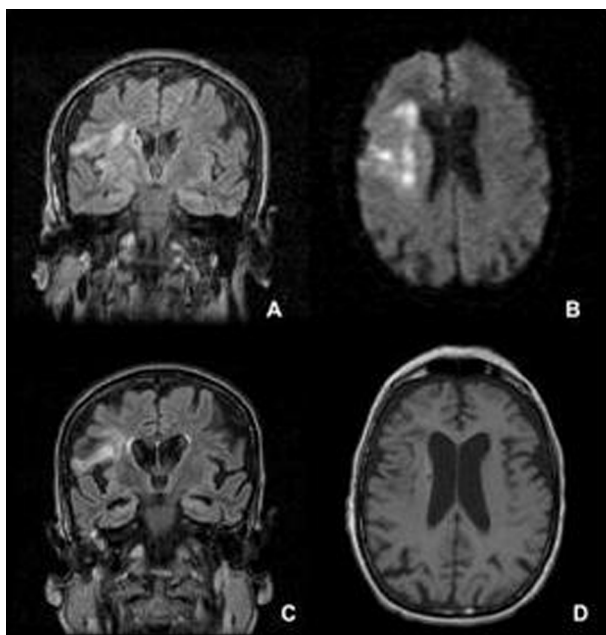


Figure 1 Brain MRI performed on the 9th day (A, B) shows right insular infarction and after 50 days important frontal atrophy (C,D).

dramatic, but transient, improvement following corticosteroid therapy. The response was milder with intravenous immunoglobulin but, since its administration had been delayed, an irreversible brain injury could have been established already by the time treatment was initiated. In a case series recently published, the response did not differ significantly between patients treated within 6 months of the neurological symptoms onset and those treated later.⁴ Cases with a poor response to immunosuppressive treatments have also been reported.¹¹ Nevertheless, most authors recommend early immunotherapy administration.⁸

Learning points

- ▶ Autoimmune encephalitis should be considered in cases of prolonged encephalopathy following an ischaemic stroke.
- ▶ Many symptoms could be wrongly interpreted as oedema, infection and metabolic complications of stroke, delaying the diagnosis.
- ▶ The prompt recognition and treatment may pre-empt the mortality associated with intractable seizures and electrolyte disturbances and might decrease the morbidity associated with cerebral atrophy.⁸

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Competing interests None.

Patient consent Not obtained.

REFERENCES

1. **Thieben MJ**, Lennon VA, Boeve BF, *et al*. Potentially reversible autoimmune limbic encephalitis with neuronal potassium channel antibody. *Neurology* 2004;**62**:1177–82.
2. **Kerney H**, Murray B, Kavanagh E, *et al*. Autoimmune encephalopathy presenting as posterior circulation stroke. *J Neurol* 2011;**258**:330–2.
3. **Pozo-Rosich P**, Clover L, Saiz A, *et al*. Voltage-gated potassium channel antibodies in limbic encephalitis. *Ann Neurol* 2003;**54**:530–3.
4. **Tan KM**, Lennon VA, Klein CJ, *et al*. Clinical spectrum of voltage-gated potassium channel autoimmunity. *Neurology* 2008;**70**:1883–90.
5. **Sinha S**, Newsom-Davis J, Mills K, *et al*. Autoimmune aetiology for acquired neuromyotonia (Isaacs' syndrome). *Lancet* 1991;**338**:75–7.
6. **Nagado T**, Arimura K, Sonoda Y, *et al*. Potassium current suppression in patients with peripheral nerve hyperexcitability. *Brain* 1999;**122**:2057–66.
7. **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**:776–85.
8. **Vincent A**, Buckley C, Schott JM, *et al*. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. *Brain* 2004;**127**:701–12.
9. **Kriz J**, Lalancette-Hébert M. Inflammation, plasticity and real-time imaging after cerebral ischemia. *Acta Neuropathol* 2009;**117**:497–509.
10. **Becker KJ**, Kalil AJ, Tanzi P, *et al*. Autoimmune responses to the brain after stroke are associated with worse outcome. *Stroke* 2011;**42**:2763–9.
11. **Fujimori J**, Endo M, Irino S, *et al*. [A recalcitrant case of encephalitis with voltage-gated potassium channel antibodies]. *Brain Nerve* 2010;**62**:1252–7.

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