Voltage-gated potassium channelopathy: an expanding spectrum of clinical phenotypes

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SUMMARY

Autoimmune voltage-gated potassium channelopathies represent a wide and expanding spectrum of neurological conditions. We present a case demonstrating the phenotypic heterogeneity of antiovoltage-gated potassium channels (VGKC)-associated disorders. Such cases may easily be dismissed as functional disorders at first presentation. We propose that there must remain a high index of suspicion for antiVGKC-associated disorders in cases where there are transient neurological disturbances in atypical spatial and temporal distributions.

BACKGROUND

Autoimmune voltage-gated potassium channelopathies represent a wide and expanding spectrum of neurological conditions. Isaac's syndrome (acquired neuromyotonia), cramp-fasciculation syndrome and Morvan's syndrome are associated with antiovoltage-gated potassium channels (VGKC) antibodies and describe variable presentations of immune-mediated peripheral nerve hyperexcitability (PNH).^{1 2} Common clinical features include: muscle twitching (myokymia or fasciculations), cramps, stiffness and delayed muscle relaxation (pseudomyotonia). However, sensory and autonomic nerves may be affected in PNH and other symptoms such as paraesthesia and hyperhidrosis can occur.² These symptoms are often dismissed as a functional disorder and this can delay reaching a diagnosis.

This case should primarily remind clinicians to have a high index of suspicion for antiVGKC-associated disorders in cases where there are transient neurological disturbances in atypical spatial and temporal distributions. However, this case also demonstrates phenotypic heterogeneity of the presentation of autoimmune channelopathies and illustrates that the effect of such antibodies can extend beyond peripheral nerve hyperexcitability.

CASE PRESENTATION

A 44-year-old woman presented with repeated episodes of involuntary and sustained contractions of the left facial muscles lasting several minutes, followed by transient ipsilateral facial droop. She returned to normal in approximately 1 h following symptom onset on each occasion. The episodes progressed to being accompanied by a left torticollis and abnormal involuntary posturing of her left upper limb. There was no loss of consciousness, her speech was unaffected and her symptoms resolved completely between attacks. She additionally described symptoms consistent with eyelid myokymia, intermittent paraesthesia and myoclonus in both upper and lower limbs over the

preceding months. The medical history included asthma and occasional palpitations. More importantly, her daughter, brother, sister, nephew and niece had epilepsy. On closer questioning, it transpired that her daughter was diagnosed with infantile hemiplegia and partial motor seizures.

On presentation the patient had generalised weakness and globally increased tone. Right arm extension and left knee flexion demonstrated fluctuating weakness over 24 h following admission. There were no other focal neurological deficits on examination.

INVESTIGATIONS

A routine blood panel was unremarkable and appropriate serology for systemic infections and malignancy were normal/negative. CT and MRI of the brain revealed no significant abnormality. Sensory and motor nerve conduction studies of upper and lower limbs were normal. Electromyography (EMG) needle examination of five limb muscles (deltoid, biceps, first dorsal interosseous, vastus medialis and tibialis anterior) showed no spontaneous muscle activity at rest. EMG needle examination of two left facial muscles, which were visibly overactive, showed myokymic EMG discharges in both orbicularis oculi and orbicularis oris. The only abnormality on the autoimmune screen was a significantly elevated titre of antibodies against VGKCs: 757pM (reference range 0–100pM).

DIFFERENTIAL DIAGNOSIS

The presence of antibodies against VGKCs strongly suggests a diagnosis of peripheral nerve hyperexcitability given myokymia, paraesthesia and torticollis. However, the abnormal involuntary posturing of the upper limb raises the possibility of concomitant partial seizures and thus effects of the antiVGKC antibodies within the central nervous system (CNS). Other diagnoses such as the Stiff Person syndrome, characterised by centrally mediated motor hyperexcitability, could also be considered but this is typically associated with antiglutamic acid decarboxylase (GAD) antibodies, not antiVGKC and does not present with sensory symptoms.³

TREATMENT

In the absence of the pending autoimmune screen results a presumptive diagnosis of partial seizures was made. The patient was therefore treated with intravenous phenytoin that resulted in rapid resolution of her symptoms. After reaching a diagnosis the patient is currently being managed with Lamotrigine.

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OUTCOME AND FOLLOW-UP

Autoimmune channelopathies can present as paraneoplastic phenomena therefore a follow-up CT chest-abdomen-pelvis was performed and did not show evidence of underlying malignancy. An EEG was also performed after resolution of symptoms and showed no abnormality.

The patient remains asymptomatic on treatment and interestingly has noticed that her palpitations have resolved with up-titration of Lamotrigine.

DISCUSSION

Autoimmune VGKC are typically associated with peripheral nerve hyperexcitability as in Isaac's syndrome (acquired neuromyotonia) or cramp-fasciculation syndrome. However, the symptom of abnormal posturing of the upper limb in this patient might not be explained by peripheral nerve hyperexcitability alone. While this posturing could represent dystonic movements caused by muscle cramps due to peripheral antibody effects, it more likely represents a partial seizure mediated via central effects of antiVGKC antibodies.¹ This assertion is made more probable considering the family history of epilepsy and raises interesting questions about the placental transfer of antiVGKC antibodies given infantile hemiplegia in the patient's daughter.

Central effects of antiVGKC antibodies have been previously characterised as limbic encephalitis, which in combination with peripheral nerve hyperexcitability is described as Morvan's syndrome.³ However, these central effects classically refer only to a subacute psychosis or severe sleep disorder. Tan *et al*¹ have demonstrated that the presence of antibodies against central VGKCs is associated with a diverse range of neurological manifestations including PNH (17%), cognitive impairment (71%), seizures (58%), hallucinations (10%), hyponatraemia (36%), insomnia (14%), hypersomnia (13%), parkinsonism (11%) and chorea (4%). Conversely, Hart *et al*⁴ have also shown that 29% of patients presenting as PNH with EMG changes have CNS symptoms. Other systemic manifestations can include: sudden death (often due to cardiac causes), intestinal pseudo-obstruction, urinary tract infections from incomplete bladder emptying, overheating due to reduced sweat function can occur in hot temperatures or with physical exertion.

Against this background, and as suggested by Tahmouh *et al*; eponymous terms such as Isaac's or Morvan's syndrome may not represent the ideal taxonomic classification for this disease spectrum while the precise molecular pathology remains an area of active research.⁵ We therefore propose a more reductionist stratification of clinical syndromes of antiVGKC antibodies into peripheral effects (PNH), central effects or both. Defining the logic of how precise combinations of antigenic targets of the

VGKC antibodies generate distinct clinical phenotypes will help to establish a more robust taxonomic reclassification of this disease spectrum. Understanding this combinatorial complexity may also raise the prospect of more targeted therapeutic strategy in the future.

More importantly, evidence of other systemic diseases should be considered and excluded by appropriate serological tests and/or biopsies. Serological markers of malignancies (eg, CEA, PSA, NSE, CA19-9, AFP, β -HCG and ProGRP, if available) can help to identify neoplastic processes not readily apparent by imaging.

Given the phenotypic heterogeneity of this autoimmune channelopathy, including a wide range of possible presentations via both centrally and peripherally mediated antibody effects, often with atypical temporal distributions, this condition may easily be dismissed as a functional disorder. We therefore recommend a high index of suspicion for this rare condition with a low threshold for performing an autoimmune screen.

Learning points

- ▶ Autoimmune channelopathies not only affect peripheral nerves but also may exhibit central effects.
- ▶ They are often dismissed as functional conditions at first presentation.
- ▶ There must remain a low threshold for performing an autoimmune screen in cases of transient neurological disturbances in atypical spatial and temporal distributions.
- ▶ Autoimmune channelopathies may form paraneoplastic phenomena and underlying malignancy should be excluded.

Competing interests None.

Patient consent Obtained.

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