Non-paraneoplastic immune-mediated calcium channel chorea

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ABSTRACT

Antibodies to the N-type voltage-gated calcium channel have rarely been reported in association with chorea. Prior reported cases have been either paraneoplastic in nature or presented in the setting of other concurrent antibody elevations. Moreover, the identified studies showed only mild elevation of calcium channel antibodies. We present a case of chorea in association with an isolated serum elevation in N-type calcium channel antibodies and clinical improvement with intravenous immunoglobulin.

KEYWORDS Autoimmune; calcium channel; chorea; movement disorder; N-type

Voltage-gated calcium channels (VGCCs) are ion channels dispersed throughout the peripheral and central nervous systems. Several subtypes exist, each of which has a specific pharmacologic motif and anatomic distribution. A variety of clinical syndromes are associated with antibodies to VGCCs, most commonly the P/Q and N subtypes. Antibodies to the N-type VGCC have classically been associated with Lambert-Eaton myasthenic syndrome and small cell lung carcinoma. The P/Q subtype is even more highly associated with Lambert-Eaton myasthenic syndrome.¹ Prior reports have implicated N-type VGCC antibodies in paraneoplastic and non-paraneoplastic cerebellar degeneration² as well as autoimmune encephalitis.³ Chorea occurring in association with N-type VGCC antibodies has been reported but is quite rare.^{4–6} In these cases, N-type VGCC antibody titers were above the reference range, but all were either paraneoplastic in nature or presented with other concurrent antibody elevations. In addition, the titer levels were of relatively modest elevation for all cases in which the titer level was reported.^{5,6} The case described here, a non-paraneoplastic, isolated N-type VGCC antibody elevation of high titer that presented with chorea, is, to the best of our knowledge, a presentation not previously reported.

CASE DESCRIPTION

A 68-year-old woman with a history of hypothyroidism presented to the movement disorders clinic with a 10-year

history of involuntary movements and mild cognitive impairment. Her family history was notable for dopa-responsive dystonia in her daughter and two grandchildren. Her father and paternal grandmother were described as having a tremor. She had a history of psychiatric disease and was previously on aripiprazole. Several previous diagnoses had been suggested, including drug-induced parkinsonism and idiopathic Parkinson disease, but neither withdrawal of antipsychotics nor a trial of dopaminergic agents improved her symptoms. She had several emergency department visits for episodes of generalized shaking that responded well to benzodiazepines. She was subsequently seen in our clinic, where generalized involuntary, arrhythmic movements that appeared forcible, rapid, and jerky were observed, consistent with broadly accepted definitions of chorea.⁷ In addition, she was noted to demonstrate myoclonic jerks, tremor, and slowed cognition. Tetrabenazine was started but her chorea and psychiatric symptoms worsened. She was subsequently transitioned to quetiapine, which helped control her chorea.

Tests including thyroid-stimulating hormone, anti-thyroid and anti-thyroid peroxidase antibodies, antinuclear antibody, anti-SSA/SSB, anti-DNA antibody, anti-cardiolipin immunoglobulin (Ig) G/IgM, rheumatoid factor, HIV 1/2 antigen and antibody, and serum copper/ceruloplasmin were within normal limits. Hematological studies were not suggestive of polycythemia vera or neuroacanthocytosis. Huntington's disease repeat expansion analysis did not reveal

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a mutation. Electromyography/nerve conduction studies did not reveal a large-fiber neuropathy. The serum paraneoplastic panel was positive at a high titer level for the N-type calcium channel antibody (2.36 nmol/L, reference range <0.03 nmol/L). An extensive malignancy workup including computed tomography of the chest was negative. Given the suggestion in the literature for aggressive immunomodulation of paraneoplastic disorders due to N-type VGCC antibodies,⁸ the patient was given intravenous immunoglobulin infusions for 5 days and then monthly. This was done despite lack of evidence of malignancy. She had complete resolution of her tremor and myoclonus and near resolution of her chorea. This improvement persisted while she was maintained on monthly intravenous immunoglobulin treatments.

DISCUSSION

There have been a few previous case reports of chorea in association with N-type calcium channel antibodies. However, many of these cases had coexisting autoimmune antibodies. In the study by O'Toole et al,⁴ a patient in the idiopathic group was noted to be positive for N-type VGCC, yet also had a concurrently positive antiphospholipid antibody. In the same study, a patient in the paraneoplastic group who was positive for the N-type VGCC had several anti-neuronal antibodies, including ANNA-1, ANNA-2, CRMP-5, and VGCC P/Q.⁴ The N-type calcium channel-related chorea cases documented by Zalewski et al and Chang et al both had mildly elevated serum titers and no response to immunotherapy.^{5,6} It has previously been noted that low or medium serum titers for VGCC antibodies may be relatively nonspecific and can even be seen in healthy controls, but a higher titer (defined in the study by Zalewski et al as >1.00 nmol/L) is more specific for an autoimmune neurologic disorder.⁵ Our patient had a high serum titer at 2.36 nmol/L and no other associated serum antibodies.

A pathophysiologic basis for the development of chorea in relation to N-type VGCC antibodies could be posited by extrapolating from a mouse model study of Huntington disease, where mutant huntingtin protein expression was shown to affect N-type calcium channel function.⁹ In humans, movement disorders have been observed with a mutation of the *CACNA1B* gene, which encodes the neuronal VGCC. Clinically this has been described as a unique myoclonus-dystonia syndrome.¹⁰ Further studies would be needed to elucidate the mechanisms underpinning the relationship between antibodies to the N-type calcium channel and clinical manifestations.

Two of the previously reported cases of calcium channel-related chorea responded to immunotherapy,⁴ but in both cases other neuronal or serum autoantibodies were present, which obfuscated the relationship of the N-type VGCC antibodies and chorea. The present case demonstrates not only a clear relationship between a high titer of serum

N-type calcium channel antibodies and clinical phenomenology but also substantial clinical improvement with immunomodulation. This latter point is germane when working up chorea, because immune-mediated chorea is potentially treatable with immunotherapy. Factors associated more highly with the presence of an underlying neoplasm include male sex, older age, peripheral neuropathy, and weight loss,⁴ none of which were present in our patient. Even without such risk factors, in most cases it would seem prudent to assess for an underlying neoplasm, because this could significantly change management if found. Even without the presence of a neoplasm, testing for the presence of VGCC antibodies should be considered in cases of chorea with unknown cause, because the treatment differs significantly from the conventional symptomatic management of chorea.

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