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IVIG treatment in non-paraneoplastic Lambert-Eaton myasthenic syndrome with elevated voltage-gated calcium channels antibodies and subacute cerebellar ataxia

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Abstract

Non paraneoplastic Lambert Eaton myasthenic syndrome (LEMS) is rare and only very few cases have been reported to date. Besides that, LEMS is rarely associated with cerebellar ataxia. Here, we described a case of middle age gentleman who presented with subacute onset of cerebellar ataxia and subsequently found to have remarkably elevated voltage-gated calcium channels (VGCC) antibodies serum titre and LEMS. Repeated screenings for malignancies remained negative. He improved significantly with intravenous immunoglobulin (IVIG) treatment. In conclusion, even with negative malignancy screen, investigation for LEMS and measurement of VGCC level should be considered in patients with subacute cerebellar ataxia. Our case demonstrated good initial response towards IVIG treatment and hence early and timely initiation of treatment with IVIG may lead to clinical improvement. However, more clinical trials will be required in the future to further determine the long term prognosis of non-paraneoplastic cerebellar ataxia and LEMS towards IVIG treatment.

INTRODUCTION

Lambert-Eaton myasthenic syndrome (LEMS) is a disorder of the neuromuscular junction due to a decrease in acetylcholine release from the presynaptic nerve terminals. LEMS is related to antibodies directed against the voltage-gated calcium channel (VGCC) and is classically known to be a paraneoplastic syndrome attributed to the expression of VGCC on the surface membrane of small cell lung cancer (SCLC) cells. While autoimmune non-paraneoplastic LEMS has also been described, the specific trigger of the immune response and treatment options remain unclear.

Subacute cerebellar ataxia is a neurological presentation that typically progresses over weeks to months and the underlying aetiologies include atypical infections, chronic toxins or medications exposure, alcohol dependence and vitamin deficiencies, autoimmune disorders and paraneoplastic cerebellar degeneration. While the association of cerebellar ataxia and paraneoplastic LEMS has been well described, non-paraneoplastic LEMS and subacute cerebellar ataxia are less commonly reported.

Here, we report a patient with a non-paraneoplastic subacute cerebellar ataxia and LEMS in whom VGCC were detected at high titre in serum and responded well to intravenous immunoglobulin (IVIG) treatment.

CASE REPORT

A 46 years old Chinese man with background history of fully treated nasopharyngeal carcinoma (NPC) in 2018, presented in March 2019 with history of vertiginous giddiness. Magnetic resonance imaging (MRI) of paranasal sinuses (PNS) and nasal endoscopy did not show any recurrence of tumour. Unfortunately, he declined further investigations at this point and was discharged against medical advice.

Subsequently, his symptoms progressed rapidly over the next 2 months. He had severe incoordination which resulted in recurrent falls and hence, he required wheelchair assistance for his mobility. In addition, he also had dysphagia on drinking fluids. Neurological examination revealed multidirectional nystagmus, cerebellar dysarthria and bilateral limb and gait ataxia. Power were full and reflexes were normal at all limbs. The cranial nerves examination was normal. Systemic examinations were also unremarkable. An impression of subacute cerebellar syndrome

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was made and investigations were performed to exclude possible metabolic cause, immune-mediated and paraneoplastic aetiologies of subacute cerebellar syndrome.

Lumbar puncture was performed and the cerebrospinal fluid (CSF) cell count, CSF protein and cytology were negative. Serum thyroid function test, vitamin E and IgA levels were unremarkable. Peripheral blood film was normal. Paraneoplastic panel including antibodies against Hu, Yo, Ri, CV2, Ampiphysin, PNMA2/Ta, Recoverin, SOX1, Titin, Zic4 were negative. Serum autoimmune encephalitis panel including NMDA, CASPR2, LGI1, AMPAR 1/2, DPPX, GABA and anti-GAD was negative. Anti-ganglioside antibodies were not evaluated.

In view of previous history of malignancy, a short exercise test during nerve conduction study was also performed which showed significant incremental response of the right ulnar nerve (pre-exercise amplitude 0.7mV, post exercise amplitude 9.3mV), consistent with a diagnosis of LEMS. There is no electrodiagnostic evidence of peripheral neuropathy, sensory neuronopathy and myopathy. A nasal endoscopy was repeated and was normal. A MRI brain with contrast was performed and unremarkable. Total body [^{18F}] flurodeoxyglucose positron emitted tomography was unremarkable for systemic malignancy. Serum anti-VGCC antibodies was markedly elevated at 2640 pmol/L (normal value 0-45).

A diagnosis of immune-mediated cerebellar ataxia and LEMS was made and he received a course of IVIG (2g/kg for 5 days) and he was treated with 3,4- diaminopyridine 5mg TDS. In addition, he underwent an intensive rehabilitation program. Eight weeks after the first course IVIG treatment, he showed remarkable functional improvement. He could walk independently without assistance and apart from mild cerebellar dysarthria, there was resolution of bilateral dysmetria. He was also able to perform activities of daily living (ADL) independently. He continued to improve clinically after a second course of IVIG and he was scheduled for monthly IVIG and regular review in outpatient setting. Since the first dose of IVIG treatment in 2019, patient's symptoms remained stable and his malignancies screen and systemic radiological imaging remained negative. Follow up VGCC level after IVIG treatment, was not performed as patient declined further testing.

DISCUSSION

We describe a middle age gentleman presented with non-paraneoplastic subacute cerebellar ataxia and LEMS with elevated VGCC level which responded well to IVIG treatment.

The association of LEMS and cerebellar ataxia with elevated VGCC level had been reported in the past and classically linked to an underlying paraneoplastic syndrome attributed to small cell lung cancer.[1,2] This group of patients with paraneoplastic aetiology of LEMS and cerebellar ataxia had been reported to have poorer prognosis or partial response to IVIG treatment.[3,4] This observation is also described in a review article by Höftberger *et al*. which commented that paraneoplastic cerebellar degeneration generally does not respond to treatment including tumour-directed therapy and immunotherapy. In their review, most patients became wheelchair-bound with only small group of patients had some meaningful functional recovery with intensive inpatient rehabilitation.[5]

On the other hand, the association of non-paraneoplastic LEMS and cerebellar ataxia, is less common[2] since Eaton and Lambert described a case in 1957.[6] While one of the postulated aetiologies include autoimmune disorders, the underlying pathophysiology and the treatment options remain unclear. The presence of significantly elevated VGCC level in our case and the fact that our patient responded to IVIG treatment supports the possible pathogenesis of immune mediated process for his LEMS and cerebellar ataxia.

Unfortunately, due to the limited number of cases reported, the long-term prognosis of non-paraneoplastic cerebellar ataxia and LEMS remain inconclusive. A review paper by Giannocccaro *et al*. suggested that IVIG as first line treatment for LEMS, based on several case reports. However, even though there was initial response towards IVIG, the long-term prognosis was variable.[7] This finding is similar to another case described by McKasson *et al*. who presented with non-paraneoplastic progressive cerebellar ataxia and LEMS with elevated VGCC level. The patient reported initial significant improvement with IVIG, however later deteriorated and passed away 18 months later.[8]

A review of 10 cases of non-paraneoplastic LEMS by Lorenzoni *et al*. reported that immunotherapy including IVIG lead to a short-term benefit, but it did not change the disease course of the patients. This further strengthened

the point that evidence of IVIG long term effect and prognosis in non-paraneoplastic LEMS patients were still scanty and the response was still variable.[9]

Occasionally, patients with cerebellar ataxia will have LEMS and vice versa. Cerebellar ataxia sometimes is the predominant symptom and so the presence of LEMS is often overlooked.[2] In our patient, he presented with subacute history of cerebellar ataxia and LEMS. His predominant symptoms and signs were that of cerebellar ataxia. VGCC level was significantly elevated and he responded well to IVIG treatment. Repeated systemic radiological investigations since symptom onset did not reveal any malignancies.

Our case suggested the importance of investigating for presence of LEMS and measurement of VGCC level in patients who present with subacute cerebellar ataxia. The presence of significantly elevated VGCC level and the fact that our patient rapidly responded to IVIG treatment support the pathogenesis of immune mediated process for his LEMS and cerebellar ataxia. His initial response towards IVIG treatment was consistent with some of the previous cases reported, however, the long-term prognosis of non-paraneoplastic LEMS and cerebellar ataxia towards IVIG treatment was variable and more clinical trials will be needed in the future.

In conclusion, even with negative malignancy screen, investigation for LEMS and measurement of VGCC level should be considered in patients with subacute cerebellar ataxia. Our case demonstrated good initial response towards IVIG treatment and hence early and timely initiation of treatment with IVIG may lead to clinical improvement. However, more clinical trials will be required in the future to further determine the long-term prognosis of non-paraneoplastic cerebellar ataxia and LEMS towards IVIG treatment.

DISCLOSURE

Ethics approval: Written informed consent was obtained from patient for publication of this case report and accompanying investigation results.

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