Acquired neuromyotonia in children with CASPR2 antibodies

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What this paper add:

1. Casper2 and LGI1 antibody should be tested in children presenting with acquired neuromyotonia
2. Symptoms my resolve spontaneously or may require sodium channel blockers. Patients with with debilitating symptoms, refractory to symptomatic therapy, may require immunotherapy.

Abstract

Introduction: Acquired neuromyotonia (Isaac's Syndrome) is a form of peripheral nerve hyperexcitability. Pathogenic antibodies, targeting the extracellular domains of leucine-rich glioma-inactivated 1 (LGI1) and contactin-associated protein-like 2 (CASPR2) have been reported as the cause of this syndrome in adults.

Objective: To describe three children with acquired neuromyotonia with CASPR2 antibodies.

Case reports: Three children (13-year-old boy; 14-year-old boy; and 4-year-old boy), presented with acute onset myokymia and pain in the lower limbs. Case 3 in addition had significant muscle weakness. EMG was suggestive of peripheral nerve hyperexcitability. All patients had positive serum antibodies to CASPR2 and LGI1. Two cases improved without immunotherapy; case 1 was treated with Carbamazepine and gabapentin while case 2 received no treatment. Case 3 was treated with steroids, immunoglobulins and methotrexate with improvement but relapsed on on discontinuation of immunotherapy and remained immunotherapy-dependant. Screening for occult malignancy was negative in all.

Conclusion: Acquired neuromyotonia is rare in children and although not fatal, can be quite disabling and affect quality of life. This condition may be associated with underlying tumours (e.g thymoma) which mandates investigation. It is amenable to symptomatic treatment or may undergo spontaneous recovery, while more severe cases may require rational immunotherapy.

Introduction

Ion-channel antibodies associated with neuromuscular disease are known to be pathogenic in disorders such as myasthenia gravis, where the removal of antibodies against the acetylcholine receptor is directly associated with improvement of the patient's clinical symptoms[1]. This led to the postulation of ion channel antibodies associated with other neuromuscular disorders. Neuromyotonia is a condition of spontaneous muscle activity occurring as a result of peripheral nerve hyperexcitability[2]. Isaac's syndrome or acquired neuromyotonia manifests with muscle twitching (myokymia), cramps, hypertrophy, weakness, wasting and sometimes excessive sweating. When autonomic and central changes such as confusion, agitation and sleep disturbance are also present, the term Morvan's syndrome is applied. These syndromes are rare and mostly seen in adults[2].

Antibodies to the Voltage gated potassium channels (VGKC) were the first to be reported in association with neuromyotonia[3]. More recently, it has become apparent that the antibodies do not bind to the potassium channel directly but to one of the associated proteins; contactin-associated protein-like 2 (CASPR2) in patients with neuromyotonia[3], leucine-rich, glioma inactivated 1 protein (LGI1)[4] in patients with limbic encephalitis, and sometimes both CASPR2 and LGI1 in patients with Morvan's syndrome[5].

Here, we describe three paediatric patients who presented with acquired neuromyotonia and were positive for CASPR2 and LGI1 antibodies. Written informed consent for the publication of the case descriptions was obtained for all three patients.

CASE 1

A previously healthy 13-year-old Caucasian boy presented to his local hospital with complaints of muscle twitching in his legs, pain in lower back, gluteal and posterior thigh muscles, and cramps. He had no other medical problems and was performing well at school. His symptoms followed 2-3 days of exertion whilst playing competitive football. His weight bearing activities were reduced due to pain, he was unable to attend school and also had insomnia.

On examination he was lethargic. His blood pressure was raised (both when awake and asleep) at 150-160/90-100 mm Hg, over the 99th centile. Cranial nerve examination was normal with no papilloedema. Myokymia was observed in both lower limbs, more predominant over the calves. He had normal tone and power in all limbs. His lower limb reflexes were reduced. He had a burning sensation in his legs over the calves. Mobility was limited due to lower back muscle pain.

Brain and spine magnetic resonance imaging (MRI) with contrast was normal. Cerebrospinal fluid (CSF) analysis was acellular with normal glucose, lactate and protein. ECG was normal, but his echocardiogram suggested mild left ventricular hypertrophy. No cardiac or renal cause of the arterial hypertension was found.

EMG demonstrated spontaneous activity as fasciculation potentials (singles, doublets, triplets) representing spontaneous depolarization of motor axons, with evidence of peripheral nerve hyper excitability (Figure 1). Antibodies to CASPR2 and LGI1 antibodies were detected in the serum (CSF was not tested). MRI of the abdomen and chest to exclude thymoma and other neoplasms was normal.

He was treated with antihypertensive medication, amlodipine with lisinopril added on as second agent. He required regular paracetamol, codeine and gabapentin for his pain management. He was started on carbamazepine for his neuromyotonia. A night time dose of amitriptyline was started to aid sleep and pain overnight. At 4 weeks, his symptoms had markedly subsided. His myokymia had completely resolved and his blood pressure had returned to the baseline.

CASE 2

A 14-year-old boy of Indian ethnicity presented with leg weakness and leg twitching one week following a trip to India and a diarrhoeal illness. There was no recent immunisation. Over the next few days the twitching which initially was over the thighs and calf spread to involve the biceps and suprascapular area. He had muscle cramps which were precipitated by activity. He had leg cramps and associated pain. He lost 3kgs in weight. There was no change in his cognition or school performance.

There was a history of autoimmune disease with Type1 diabetes diagnosed at the age of 4.5 years for which he was well controlled on insulin pump, and membranous glomerulonephritis diagnosed at 13years of age with stable renal function. There was no other significant medical history and his development was age appropriate.

On examination he was alert and oriented. He had a normal gait. Cranial nerve examination was unremarkable. Neurological examination showed bilateral myokymia in the thighs, calves and in the suprascapular area. He had normal tone, power and reflexes.

EMG/Nerve conduction and MRI scan of the spine were both normal. Serum antibodies to CASPR2 and LGI1 were both positive. Whole body MRI was conducted at a later date to rule out any tumours and came back negative. His symptoms resolved spontaneously without any treatment. On follow-up, 4 weeks from symptoms onset, his myokymia had all but disappeared except for minimal residual myokymia overlying the right scapula.

CASE 3

A 4-year-old Caucasian boy presented with motor regression associated with leg pain and the inability to walk short distances without a wheelchair (he started walking at 10months). He had a diagnosis of medium-chain acyl-CoA dehydrogenase (MCAD) deficiency detected in the urinary neonatal metabolic screen and an additional diagnosis of Hyper IgE syndrome (IgE levels >5000) diagnosed at the age of 1year when he developed severe eczema and red, swollen hands and feet.

On examination he was found to have proximal muscle weakness, widespread muscle twitching and telangiectasia on his nose, hands and feet.

Genetic tests showed no evidence of SMA or myotonic dystrophy. Muscle biopsy prior to treatment showed multiple foci of chronic perivascular inflammation occasionally extending between muscle fibres. There was no evidence of fibre necrosis and no upregulation of MHC class 1. Normal dystrophin panel. Normal fat and glycogen stains. Surface EMG demonstrated myokymia. Serum antibodies for both CASPR2 and LGI1 antibodies were detected.

He was treated with immunosuppressive therapy and received intravenous methylprednisolone 30mg/kg for 3 days and oral prednisolone starting at 20mg/kg reducing by 5mg/dose each month. He was also given IV immunoglobulin 1g/kg over 2 days every month. Methotrexate was added as a steroid sparing agent. At 12months the neuromyotonia resolved along with improvement in his mood, appetite, eczema and swollen hands and feet also improved. He was able to walk and run over long distances. Immunoglobulins were stopped and he remained controlled on low dose steroid and methotrexate for 3 years. On discontinuation of steroids, 6 months later his symptoms (myokymia, weakness and muscle pain) recurred and he was re-commenced on immunoglobulins every 4 weeks.

A summary of the clinical and paraclinical features is illustrated in Table 1. All three patients were empirically investigated by their physicians to exclude a range of infective, alternative inflammatory and neurometabolic aetiologies, of which none were identified. All three patients were screened for occult malignancies which were negative.

DISCUSSION

Antibody-mediated neuromyotonia has rarely been reported in children[6]. In these three children it was the acquired myokymia and evidence for peripheral nerve hyperexcitability seen on EMG that prompted the investigations for antibodies to CASPR2 and LGI1. These antibodies are associated with peripheral and central nervous system syndromes but mainly in older males. Antibody-mediated diseases of the peripheral nervous system in adults are now being promptly recognised, investigated with EMG and serum antibodies, and treated. However, these antibodies are not commonly seen or evaluated in children.

In our patients, myokymia was the predominant feature in case 1 and 2, whereas in case 3 there was significant muscle weakness along with myokymia. Other symptoms associated with CASPR2 antibodies are pain and weight loss[4, 7, 8]. In case 1 and case 3, pain was an important feature which resulted in limitation of activity. This is in keeping with a recent report of pain hypersensitivity in animal models of both immune and genetic disruption of CASPR2[9].

CASPR2 is a member of the neurexin superfamily, a cell adhesion molecule localised to the juxtaparanodal region of the axons of both the central nervous system (CNS) and peripheral nervous system (PNS)[10]. CASPR2 is necessary for the clustering of voltage-gated potassium channels (VGKC)[11]. By contrast, LGI1 is a protein found mostly in the hippocampus and temporal lobe and acts by binding to proteins of the ADAM (A disintegrin and metalloproteinase) family. This modifies synaptic transmission by reducing LGI1-VGKC-commplex and LGI1-ADAM interactions[12] which may explain the CNS phenotype typically associated with these antibodies.

Antibodies against voltage gated potassium channel (VGKC)-complex can be misleading. Most VGKC-complex antibodies in adults bind specifically to LGI-1 and CASPR2, and are typically associated with clinical syndromes such as limbic encephalitis with faciobrachiodystonic seizures (LGI1 antibodies), or neuromyotonia with or without limbic encephalitis (CASPR2 antibodies). The clinical relevance of VGKC complex antibodies that do not bind LGI1 and CASPR2, is not clear and some may be binding to antigens in the complex that are not cell-surface antigens[13]. Importantly, most VGKC-complex antibodies in children do not bind to LGI1 or CASPR2[13]. A study of 39 children with VGKC-complex antibodies found that these antibodies were present in paediatric patients with highly variable clinical symptoms, and the presence of these VGKC antibodies did not correlate with severity of neurological impairment. Treatment with immunosuppressive therapy was not clearly beneficial.[13] As such, in the paediatric context, detection of VGKC-complex antibodies has limited diagnostic value.

The association of CASPR2-Abs with malignancies particularly thymoma is well described in adults and the incidence of tumor in these patients ranges from 0 to 32%[4, 7, 8]. Some of the patients with thymoma may also suffer from myasthenia gravis[5]. Other tumors, such as lung tumor and endometrial carcinoma have also been reported[4, 14, 15]. In adults, treatment of an underlying cancer is usually associated with resolution of symptoms[2]; the neuromyotonia responds well to symptomatic treatment. Sodium channel blockers such as carbamazepine, phenytoin, sodium valproate and lamotrigine can be used, if necessary in combination[16, 17]. As seen here, case 1 responded well to carbamezapine which could be weaned after symptom resolution or as seen in case 2, symptoms may resolve without treatment. However, some patients, like case 3, with debilitating symptoms refractory to symptomatic therapy, may need immunomodulatory therapy. This may include plasma exchange, intravenous immunoglobulin and oral immunosuppression with prednisolone, with or without azathioprine or methotrexate, all have been tried in varying combinations with success in selected patients[17].

Treatment of most antibody mediated conditions, particularly with concurrent or sequential immunotherapy requires knowledge and careful consideration of the risk of toxicity and adverse events. The potential for long-term sequelae, including impact of childhood immunosuppression on subsequent fertility, malignancy risk, and possibility of premature immune senescence requires careful consideration for each patient.

Figure 1: EMG studies in patient 1 at the time of presentation. Supramaximal stimulation of the tibial nerve at the ankle and recording from abductor hallucis muscle shows consistent after-discharges seen immediately after the compound muscle action potentials following 7 consecutive stimulations consistant with neuromyotonia.

Table 1: Clinical and paraclinical features of the three patients with aquired neuromyotonia

Case	1	2	3
Age	13 years	14 years	4 years
Sex	Male	Male	Male
Demographic	Caucasian	Indian	Caucasian
Neuromyotonia	++	++	++
Muscle weakness	-	-	++
Muscle cramps	+	+	-
Pain	++	-	+
Weight loss	++	++	+
Autonomic changes	-	-	-
Hypertension	++	-	-
Hyponatremia	-	-	-
CNS symptoms- (limbic encephalitis)	-	-	-
EMG findings	Myokymia	Normal (done during asymptomatic phase)	Myokymia
Antibodies in the serum	CASPR2 LGI 1	CASPR2 LGI 1	CASPR2 LGI 1
Other co-morbidities	-	Type I Diabetes Mellitus Membranous glomerulonephritis	MCAD deficiency Hyper IgE syndrome
Associated tumours	No	No	No
Drugs found useful	Carbamazepine Gabapentin	No	Steroids Immunoglobulins Methotrexate
Spontaneous or immunotherapy-independent improvement	Yes	Yes	No

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