

1 **Acquired neuromyotonia in children with CASPR2 and LGI1 antibodies**

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**Abstract**

**Introduction:** Acquired neuromyotonia 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 in some cases of this syndrome in adults.

**Objective:** To describe three children with acquired neuromyotonia and CASPR2 and LGI1 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 immunotherapy on presentation and remained immunotherapy-dependant.

**Conclusion:** Acquired neuromyotonia is rare in children and although not fatal, can be quite disabling and affect quality of life. It is amenable to symptomatic treatment or may undergo spontaneous recovery, while more severe cases may require rational immunotherapy.

What this paper adds:

1. CASPR2 and LGI1 antibody should be tested in children presenting with acquired neuromyotonia
2. Symptoms may resolve spontaneously or may require sodium channel blockers. Patients with debilitating symptoms, refractory to symptomatic therapy, may require immunotherapy.

1 **Introduction**

2 Neuromyotonia is a condition of spontaneous muscle activity occurring as a result of peripheral nerve  
3 hyperexcitability<sup>1</sup>. Isaac's syndrome or acquired neuromyotonia manifests with muscle twitching (myokymia),  
4 cramps, hypertrophy, weakness, wasting and sometimes excessive sweating. When autonomic and central  
5 changes such as confusion, agitation and sleep disturbance are also present, the term Morvan's syndrome is  
6 applied. These syndromes are rare and mostly seen in adults<sup>1</sup>.

7  
8 Antibodies to the Voltage gated potassium channels (VGKC) were the first to be reported in association with  
9 neuromyotonia<sup>2</sup>. It is now well established that the antibodies do not bind to the potassium channel directly but  
10 to one of the associated proteins; contactin-associated protein-like 2 (CASPR2) in patients with neuromyotonia,  
11 leucine-rich, glioma inactivated 1 protein (LGI1) in patients with limbic encephalitis, and both CASPR2 and LGI1  
12 in patients with Morvan's syndrome.<sup>3, 4</sup>

13  
14 Since 2011, when antibody testing became clinically available for LGI1 and CASPR2, three children from our  
15 three paediatric neurology centres in the UK with acquired neuromyotonia had their serum tested. All were  
16 positive for both CASPR2 and LGI1 antibodies. Here we describe their clinical presentation, disease course and  
17 treatment response. Written informed consent for the publication of the case descriptions was obtained for all  
18 three patients.

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20 **CASE 1**

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

26  
27 On examination he was lethargic. His blood pressure was raised (both when awake and asleep) at 150-160/90-  
28 100 mm Hg, (over the 99<sup>th</sup> centile). Cranial nerve examination was normal with no papilloedema. Myokymia was  
29 observed in both lower limbs, more predominant over the calves. He had normal tone and power in all limbs. His  
30 lower limb reflexes were reduced. He had a burning sensation in his legs over the calves. Mobility was limited  
31 due to lower back muscle pain.

32  
33 Brain and spine magnetic resonance imaging (MRI) with contrast was normal. Cerebrospinal fluid (CSF) analysis  
34 was acellular with normal glucose, lactate and protein. ECG was normal, but his echocardiogram suggested mild  
35 left ventricular hypertrophy. No cardiac or renal cause of the arterial hypertension was found.

36 EMG demonstrated spontaneous activity as fasciculation potentials (singles, doublets, triplets) representing  
37 spontaneous depolarization of motor axons, with evidence of peripheral nerve hyperexcitability (Figure 1).

1  
2 He was treated with the antihypertensive medication amlodipine, with lisinopril added on as second agent. He  
3 required regular paracetamol, codeine and gabapentin for his pain management. He was started on  
4 carbamazepine for his neuromyotonia. A night time dose of amitriptyline was started to aid sleep and pain  
5 overnight. At four weeks, his symptoms had markedly subsided, with the myokymia completely resolved and  
6 normal blood pressure.

7  
8 CASE 2

9 A 14-year-old boy of Indian ethnicity presented with leg weakness and leg twitching one week following a trip to  
10 India and a diarrhoeal illness. There was no recent immunisation. The muscle twitching was initially over the  
11 thighs and calves, then spread to involve the biceps and suprascapular areas. He had muscle cramps which  
12 were precipitated by activity, and painful leg cramps. He lost 3kgs in weight. There was no change in his  
13 cognition or school performance.

14  
15 There was a history of autoimmune disease with Type1 diabetes diagnosed at the age of 4.5 years for which he  
16 was well controlled on an insulin pump, and membranous glomerulonephritis diagnosed at 13years of age with  
17 stable renal function. There was no other significant medical history and his development was age appropriate.

18  
19 On examination he was alert and oriented. He had a normal gait. Cranial nerve examination was unremarkable.  
20 Neurological examination showed bilateral myokymia in the thighs, calves and in the suprascapular area. He had  
21 normal tone, power and reflexes in his upper and lower limbs.

22  
23 EMG/Nerve conduction studies and spinal MRI scan were normal. His symptoms resolved spontaneously without  
24 any treatment. On follow-up, four weeks from symptoms onset, his myokymia had all but disappeared except for  
25 minimal residual myokymia overlying the right scapula.

26  
27 CASE 3

28 A four-year-old Caucasian boy presented with motor regression associated with leg pain and the inability to walk  
29 short distances without a wheelchair. He had a diagnosis of medium-chain acyl-CoA dehydrogenase (MCAD)  
30 deficiency detected in the urinary neonatal metabolic screen, and an additional diagnosis of Hyper IgE syndrome  
31 (IgE levels >5000) diagnosed at the age of one year presenting with severe eczema and red, swollen hands and  
32 feet.

33  
34 On examination he was found to have proximal muscle weakness, widespread myokymia (Video 1) and  
35 telangiectasia on his nose, hands and feet.

36 Muscle biopsy prior to treatment showed multiple foci of chronic perivascular inflammation occasionally  
37 extending between muscle fibres. Surface EMG demonstrated myokymia.

1  
2 He was treated with immunosuppressive therapy, and received intravenous methylprednisolone 30mg/kg for 3  
3 days and oral prednisolone starting at 20mg/kg reducing by 5mg/dose each month. He was also given IV  
4 immunoglobulin 1g/kg over 2 days every month. Methotrexate was added as a steroid sparing agent. At 12  
5 months the neuromyotonia had resolved. His eczema, swollen hands and feet had also improved, and he was  
6 able to walk and run over long distances. Immunoglobulins were stopped and he remained controlled on low  
7 dose steroids and methotrexate for three years. On discontinuation of steroids his symptoms (myokymia,  
8 weakness and muscle pain) recurred and he was re-commenced on monthly immunoglobulin infusions.  
9

10 A summary of the clinical and paraclinical features seen in all three cases is illustrated in Table 1. Serum  
11 antibody testing in all patients was performed using cell-based assays (fixed commercial assays in Cases 1 and  
12 2; a live cell based assay was performed in Case 3 as this was the only available test in the UK at this time). All  
13 patients were empirically investigated by their physicians to exclude a range of infective, alternative inflammatory  
14 and neurometabolic aetiologies. Occult malignancy screening was negative in all patients.  
15

## 16 DISCUSSION

17 In adults, antibody-mediated diseases of the peripheral nervous system are now well defined, promptly  
18 recognised, and appropriately investigated with EMG and testing of LGI1 and CASPR2 antibodies. However,  
19 these antibodies are not commonly seen or evaluated in children. A recent case series from the Mayo clinic in  
20 the United States identified 13 positive LGI1 and CASPR2 antibody paediatric patients over seven years,  
21 significantly less than adults.<sup>5</sup> Similar to our series, three patients were double antigen positive (LGI1 and  
22 CASPR2); two of these were diagnosed with Morvan's syndrome and one had neuromyotonia. In our cases,  
23 apart from Case 1 with insomnia, no other features suggestive of Morvan's syndrome were seen. Additionally,  
24 they did not display any central nervous symptoms associated with LGI1 antibodies (e.g. encephalopathy,  
25 cognitive dysfunction, neuropsychiatric symptoms, limbic encephalitis and seizures).<sup>5</sup>  
26

27 Myokymia was the predominant feature in case 1 and 2, whereas in case 3 there was significant muscle  
28 weakness along with myokymia. Other symptoms associated with CASPR2 antibodies seen in our case series  
29 included pain and weight loss<sup>6-9</sup>. In case 1 and case 3, pain was an important feature which resulted in limitation  
30 of activity. This is in keeping with a recent report of pain hypersensitivity in animal models of both immune and  
31 genetic disruption of CASPR2.<sup>10</sup>  
32

33 Up to 28% of adult patients with LGI1 or CASPR2 antibodies are reported to have co-existent autoimmune  
34 conditions as seen in two out of three patients here.<sup>11</sup> Recent investigations using human leucocyte antigen  
35 (HLA) analysis have identified strong HLA associations in LGI1 positive and more recently, CASPR2 positive  
36 patients.<sup>11,12</sup> Interestingly, unique HLA associations have also been described in double antigen positive  
37 patients, inferring a rare genetic predisposition to developing both neuronal antibodies.<sup>11</sup>

1  
2 The association of CASPR2-Abs with malignancies particularly thymoma is well described in adults and the  
3 incidence of tumor in these patients ranges from 0 to 32%<sup>6-8</sup>. Tumours have not been reported in children and  
4 were not seen in our cases.<sup>5</sup> In adults, treatment of an underlying cancer is usually associated with resolution of  
5 symptoms<sup>1</sup>; the neuromyotonia responds well to symptomatic treatment. Sodium channel blockers such as  
6 carbamazepine, phenytoin, sodium valproate and lamotrigine can be used, if necessary in combination.<sup>13</sup> As  
7 seen here, case 1 responded well to carbamazepine which could be weaned after symptom resolution or as  
8 seen in case 2, symptoms may resolve without treatment. However, some patients, like case 3, with debilitating  
9 symptoms refractory to symptomatic therapy, may need immunomodulatory therapy. This may include plasma  
10 exchange, intravenous immunoglobulin and oral immunosuppression with prednisolone, with or without  
11 azathioprine or methotrexate, all have been tried in varying combinations with success in selected patients.<sup>13</sup>

12  
13 Treatment of most antibody mediated conditions, particularly with concurrent or sequential immunotherapy  
14 requires knowledge and careful consideration of the risk of toxicity and adverse events. The potential for long-  
15 term sequelae, including impact of childhood immunosuppression on subsequent fertility, malignancy risk, and  
16 possibility of premature immune senescence requires careful consideration for each patient.

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1 Figure 1: EMG studies in patient 1 at the time of presentation. Supramaximal stimulation of the tibial nerve at the  
2 ankle and recording from abductor hallucis muscle shows consistent after-discharges (marked with black arrow)  
3 seen immediately after the compound muscle action potentials following seven consecutive stimulations  
4 consistent with neuromyotonia.  
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1 Table 1: Clinical and paraclinical features of the three patients with acquired 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	++	-	-
Sleep disturbance	+	-	-
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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- 1 Video 1
- 2 Video clip demonstrating myokymia in the lower limbs and face of Case 3.

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