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Coincidence or connection?

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## Sodium and chloride channelopathies with myositis: coincidence or connection?

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### Abstract

**Introduction**—A proximal myopathy develops in some patients with muscle channelopathies, but the causative molecular mechanisms are unknown.

**Methods**—We reviewed retrospectively all clinical and muscle biopsy findings of three patients with channelopathy and additional myositis. Direct DNA sequencing was performed.

**Results**—Pathogenic mutations were identified in each case. Biopsies illustrated inflammatory infiltrates.

**Conclusions**—Clinicians should consider muscle biopsy in channelopathy patients with severe myalgia and/or subacute weakness and accompanying elevated CK. Chance association of myositis and channelopathy is statistically unlikely. An alternative hypothesis suggests that inflammatory insults could contribute to myopathy in some patients.

### Keywords

neuromuscular; channelopathy; myositis; histopathology; treatment

### Introduction

The skeletal muscle channelopathies are a group of episodic neuromuscular disorders that include the periodic paralyses and the non-dystrophic myotonias. Causative mutations occur in genes that code for voltage-gated skeletal muscle ion channels which regulate muscle

membrane excitability. Disturbed ion channel function results in altered sarcolemmal excitability. The resulting symptoms of episodic muscle weakness (due to an inexcitable membrane) and/or muscle stiffness (myotonia due to a hyperexcitable membrane) reflect this. The natural history of these disorders is not described extensively, although there is evidence, particularly in the periodic paralyses, that a significant proximal myopathy can develop<sup>1,2-8</sup>. In addition there are reports of moderate to severe myalgia<sup>8-13</sup> and elevated creatine kinase (CK)<sup>2, 6, 11, 12</sup> in muscle channelopathy patients although the cause of this is not fully understood.

We examined retrospectively three cases of genetically confirmed skeletal muscle channelopathy who underwent muscle biopsies to investigate variable combinations of proximal weakness, myalgia and significantly elevated CK. All three biopsies showed inflammatory infiltrates. Each patient received long-term prednisone and various combinations of other immunosuppressive agents.

## Methods

All patients were referred to our national diagnostic service for skeletal muscle channelopathies in the UK funded by the Department of Health, National Commissioning Group (NCG). We confirmed a genetic diagnosis in each case. Each patient was examined personally by one of the authors. The muscle biopsy pathology was reviewed by J.I. (cases 1 and 2) and J.L.H. (cases 2 and 3).

## Genetic Analysis

We performed direct automated DNA sequencing of all 23 exons of CLCN1 in the patient with a diagnosis of myotonia congenita. For the patients with hyperkalemic periodic paralysis (case 1) and paramyotonia congenita (case 3) we performed sequencing of SCN4A hotspots, exon 13 and a portion of exon 24 (c.4289–4524). All primers were tagged with M13 tails. See supplemental data for primer sequences. PCR reactions to amplify each exon of CLCN1 and SCN4A using the following reagents and conditions were performed: A 25µL reaction contained 200ng genomic DNA, 2.5µL of 10×PCR buffer without MgCl<sub>2</sub> (Applied Biosystems), 2µL of 25mM MgCl<sub>2</sub>, 2.5µL of 2mM dNTPs, 10pmol of each primer (forward and reverse), and 2.5 units of AmpliTaq Gold polymerase (Applied Biosystems). Cycling conditions consisted of an initial denaturing step of 95°C for 10 minutes followed by 30 cycles of 95°C for 30 seconds, 58°C for 30 seconds (CLCN1) or 60°C for 30 seconds (SCN4A), 72°C for 30 seconds, and a final extension step of 72°C for 7 minutes.

Samples were sequenced (bidirectionally) using the ABI Big Dye Terminator Sequencing Kit version 1.1, M13 universal primers, and an ABI Model 3730xl Automated DNA Sequencer. Data were analyzed using version 2.5 SeqScape Analysis software (ABI).

## Histopathology

Each patient had undergone a muscle biopsy in another center, and tissue sections stained for hematoxylin and eosin (H&E), Gomori trichrome method, lipid and glycogen in addition to enzyme histochemical preparations for succinic dehydrogenase, cytochrome oxidase and nicotinamide adenine dinucleotide dehydrogenase tetrazolium reductase were available for review. Immunohistochemical preparations available for review were: Case 1: CD3 and MHC class I; Case 2: CD3, CD20, spectrin, dystrophin, merosin, dysferlin, sarcoglycans, emerin and desmin; and Case 3: MHC Class I, CD3, CD68 and CD20.

## Results

### Case One

An 80 year old man complained of episodes of muscle weakness after periods of prolonged rest from the age of four years. Initially only the lower limbs were affected, but by his late teens the upper limbs were also involved. The episodes usually lasted hours and occasionally days. A clinical diagnosis of familial periodic paralysis was made when he was aged 21 following reports of similar episodes of weakness in his mother and sister.

From his early 50s, mild proximal muscle weakness was noted on examination. At the age of 56, following a positive potassium challenge, his diagnosis was revised to hyperkalemic periodic paralysis, and he was treated with salbutamol. A CK at this time was noted to be 436U/L. At the age of 65 he began complaining of progressive difficulties over 12 months of rising from a low chair and climbing stairs. Examination confirmed limb weakness greater proximally than distally. Clear difficulty rising from a chair without using his hands for leverage was observed, and a degree of thigh atrophy was noted. EMG showed polyphasic motor unit potentials intermixed with some short duration simple units and spontaneous activity including fibrillation potentials, fasciculation potentials and myotonic discharges. His CK was 2729 U/L. Muscle biopsy showed internal nuclei, fiber atrophy, fiber hypertrophy with occasional split fibers, some regenerating fibers and an increase in endomysial connective tissue. In addition, there was a dense inflammatory cell infiltrate focused around small capillaries and necrotic fibers, which was demonstrated by immunohistochemistry to consist mainly of T-lymphocytes. There was expression of MHC 1 on occasional skeletal muscle fibers. The biopsy findings and overall clinical picture were consistent with a diagnosis of polymyositis, and he was started on prednisone 60mg once daily. A few hours after the initial dose of steroids he suffered a severe attack of paralysis lasting 48 hours. Following recovery from this he was restarted on prednisone 10mg once daily with gradual improvement of his muscle weakness.

Ten years later he re-presented with further complaints of leg weakness and difficulties in mobilization progressing sub-acutely over a six week period. At this time he was on 5mg of prednisone daily although it is not clear if this had been continuous since commencement ten years earlier. Azathioprine, 50mg twice daily was added to his therapy, but he continued to deteriorate and was admitted to hospital where proximal lower limb power was documented to range from 3+/5 to 4+/5. The azathioprine dose was further increased to 100mg twice daily, and he was discharged from hospital. When he was reviewed in clinic two months later he reported his mobility difficulties fluctuated in severity and self-postulated they were contributed to by his periodic paralysis. Improved proximal leg strength was recorded. Genetic analysis confirmed the presence of the common T704M point mutation in the SCN4A gene associated with hyperkalemic periodic paralysis<sup>14</sup>.

### Case Two

A 42 year old woman complained of daily muscle cramps from early childhood. This was confirmed to be myotonia on EMG. The family history revealed similar symptoms in her mother and two maternal aunts, and a clinical diagnosis of myotonia congenita was made. The patient complained of severe cramps with increasing age and began to experience episodes of muscle weakness after exertion, although between episodes she reported normal muscle power. Examination was generally unremarkable, but a CK level was found to be 1109 U/L. Muscle biopsy was performed and demonstrated increased variation in fiber size, evidence of fiber regeneration and 1 necrotic fiber. Foci of inflammation composed of CD3 immunoreactive T lymphocytes were noted in the perimysium and endomysium (Fig 1A). Invasion of intact myofibers by T cells was not evident, and MHC Class I

immunohistochemistry was not available for review. There was no evidence of a vacuolar myopathy, and tubular aggregates were not present. She was started on prednisone, and there was a resultant reduction in CK to 300–400 U/L. All attempts to reduce the prednisone dose were unsuccessful, and the patient was unable to tolerate other immunosuppressants. Genetic sequencing confirmed the presence of the F167L mutation in the CLCN1 gene associated with myotonia congenita<sup>15</sup>.

### Case Three

A 38 year old man complained of episodes of muscle stiffness when exposed to the cold that affected predominantly his tongue, hands and feet from early childhood. This was confirmed by EMG to be myotonia. There was no family history of note. Myotonia occurred daily, but symptoms remained fairly static until his late teens. He then noted episodes of acute muscle swelling predominantly affecting his forearms and thighs. Initially these were non-painful, and CK and muscle power were normal. Later however he complained of myalgia accompanying the episodes of swelling which occurred 2–3 times per month and lasted up to a week. Examination between episodes continued to demonstrate normal muscle power. Ultrasound examination confirmed hypoechoic regions within the muscles but normal subcutaneous tissue. An intermittent peripheral eosinophilia was noted in conjunction with the episodes of myalgia. No specific cause for the eosinophilia was identified. MRI scans of the lower limbs performed during symptomatic episodes confirmed widespread edema that was not present during asymptomatic periods (Fig 2). A muscle biopsy showed no evidence of regeneration, necrosis, vacuolation of fibers, or tubular aggregates. Inflammatory infiltrates composed of a mixture of T lymphocytes and macrophages were present in the perimysium, and there was a single endomysial cluster (Fig 1B and 1C). Invasion of intact muscle fibers by T cells was not apparent. Immunohistochemical staining for MHC Class I demonstrated an increase in sarcolemmal and sarcoplasmic expression (Fig 1D). The biopsy findings were interpreted as being compatible with polymyositis, although the clinical history and normal CK were not typical.

He had an excellent response to prednisone, 20 mg on alternate days that was reduced to 5 mg on alternate days. The frequency and severity of the muscle swelling and myalgia were reduced, although he unfortunately developed osteopenia. Attempts to introduce other steroid-sparing immunosuppressive agents were unsuccessful, as he did not respond to methotrexate, cyclosporine, imatinib or hydroxyurea and did not tolerate azathioprine. Genetic analysis confirmed the presence of the L1436P mutation in the SCN4A gene associated with sodium channel myotonia<sup>5</sup>.

### Statistical Considerations

The prevalences of both skeletal muscle channelopathies and idiopathic inflammatory myopathy are each estimated to be 1 in 100 000<sup>16–18</sup>. We initially took a null hypothesis that the development of both diseases in our 3 cases was coincidental. Considered statistically, if the likelihood of developing a skeletal muscle channelopathy and an IIM is independent, then the chance of having both is one in  $10^{-10}$ . The probability of observing UK patients with both diseases (if this association were by chance alone) can be calculated using the Poisson distribution, since  $p$  is small and the UK population is large; Poisson  $\lambda = 10^{-10}$  (independent probability of 2 events in an individual)  $\times 6.5 \times 10^6$  (UK population) = 0.0065, and the probability of observing 3 or more patients with both diseases (assuming independence) is  $4.5 \times 10^{-8}$ . This small  $p$  value indicates that the occurrence of both diseases in the same individual is highly unlikely to be independent.

## Discussion

The precise natural history of the skeletal muscle channelopathies is not extensively documented, but development of a proximal myopathy is recognized, especially in the periodic paralyses. Whether the myopathy is related to the severity and frequency of paralytic attacks is unclear<sup>6, 19</sup>. There is some evidence that development of myopathy may be associated with increasing age<sup>6, 20</sup>. In addition, moderately elevated CK (1000–2000 U/L) and moderate to severe myalgia are reported in the skeletal muscle channelopathies, although there is no evidence to link these directly to the presence of myopathy or to explain their pathogenesis.

A characteristic history in conjunction with specialized neurophysiologic techniques<sup>21</sup> allows a diagnosis in the majority of cases of skeletal muscle channelopathy, and it is rare that a muscle biopsy is now performed in the UK.

In our three cases a clinical diagnosis of skeletal muscle channelopathy had been made prior to the muscle biopsy and was later confirmed genetically. Biopsy was performed due to additional clinical features that were deemed unusual or severe for a muscle channelopathy. In case 1 the proximal myopathy could have been attributed to the myopathy that is reported in periodic paralysis, but the very high CK (2729 U/L) was considered to be atypical. The severe myalgia and moderate elevation of CK (1109 U/L) reported in case 2 are also described features of the channelopathies, and we cannot exclude the possibility that at least some of the myalgia is due to myotonia. However, as the myalgia became severe enough to be the patient's primary complaint a biopsy was performed. The initial complaint of muscle swelling in case 3 is not a typical feature of the muscle channelopathies, and with the later development of significant myalgia, a biopsy was felt to be warranted. We suggest that the clinical features of weakness, myalgia and significantly elevated CK in these three cases are secondary, at least in part, to the observed inflammatory process.

The biopsy findings in these cases do not fulfil all morphological criteria for IIM, particularly the lack of invasion of intact fibers. However upregulation of MHC class I expression (cases 1 and 3) is supportive, and it is not unreasonable that a diagnosis of IIM had been made in these cases, especially when each was considered in isolation. There are numerous examples of other genetic muscle disorders in which inflammatory infiltrates have been observed and even diagnosed as IIM<sup>22</sup>. We cannot exclude the possibility that the observed inflammatory process is a coincidental finding, and two independent pathologies (channelopathy and IIM) are present in each of the three individuals. This seems to be statistically unlikely.

Whether this inflammatory response plays a potential pathogenic role in the development of the myopathy is not known. Morphology data is reported for the skeletal muscle channelopathies, especially the periodic paralyses, but in many cases it pre-dates the availability of genetic testing. A vacuolar myopathy and/or tubular aggregates support the diagnosis of periodic paralysis. With improved electrophysiologic and genetic diagnostic methods, muscle biopsy is now less common. Without a larger number of biopsy samples from similar cases it is not possible to know how accurately inflammatory muscle infiltrates may correlate with the clinical presentation.

Although there was some improvement in symptoms and a reduction in CK with prednisone in two cases, in one case high dose prednisone induced a severe paralytic attack, although low dose steroids were better tolerated. Worsening of the paralytic symptoms of periodic paralysis with glucocorticoids has been reported<sup>23</sup>. Other immunosuppressive agents had no clear additional benefit.

Based on these observations, we suggest that a diagnostic muscle biopsy should be considered in cases of skeletal muscle channelopathy that present with the symptoms of severe myalgia and/or subacute weakness and an accompanying elevated CK (>1000 U/L) to ascertain the presence of any inflammatory infiltrates. The therapeutic benefit of immunosuppressants is not established, but our cases may indicate that steroids could have a role. The optimal dose is undetermined, and higher doses may be detrimental such that caution with their use is recommended.

The statistical evidence indicates that the coexistence of an inflammatory process and skeletal muscle channelopathy is very unlikely to be purely coincidental. The possible implications this may have for our understanding of the mechanisms of muscle damage in the skeletal muscle channelopathies remains to be explored.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

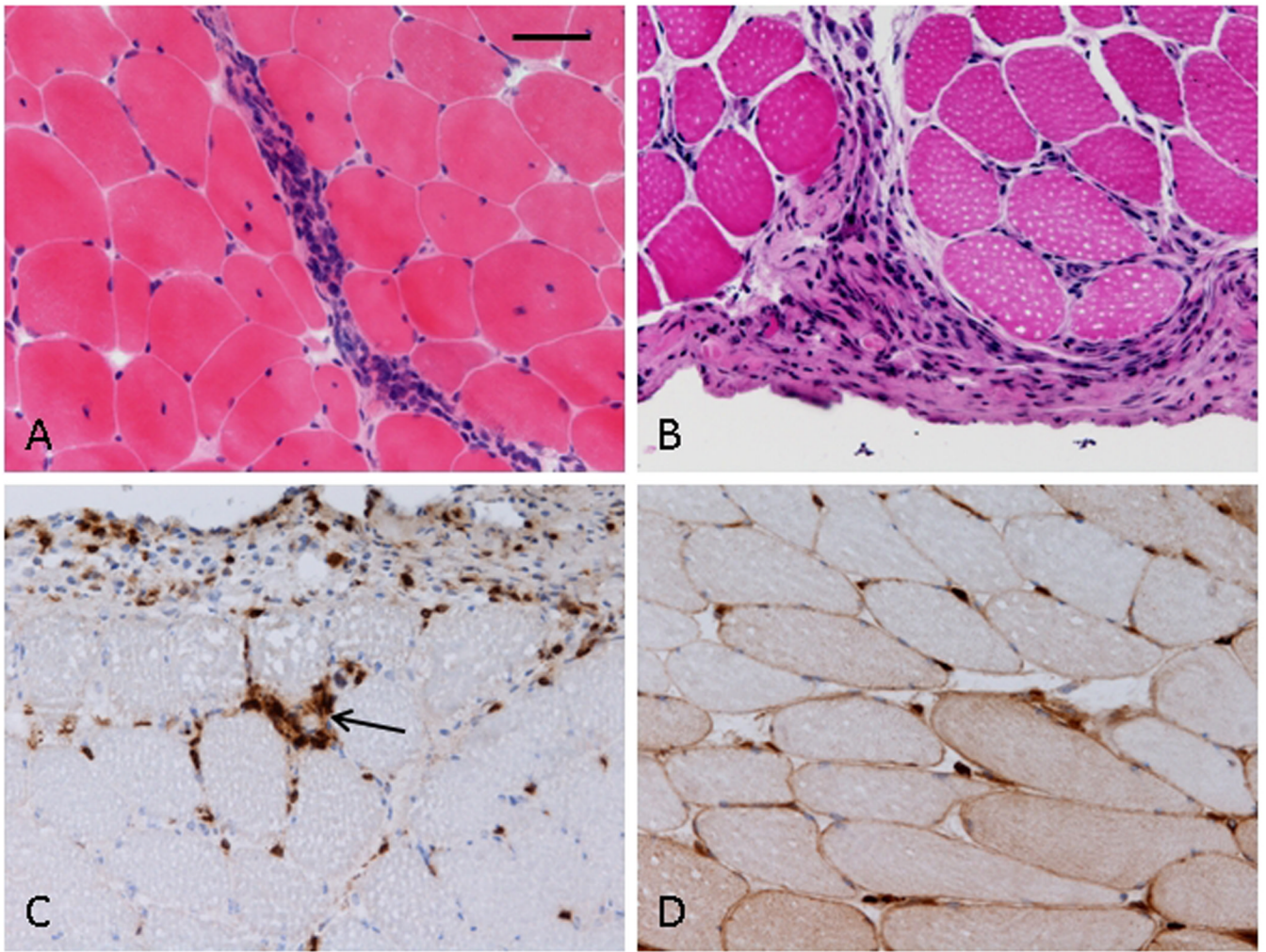
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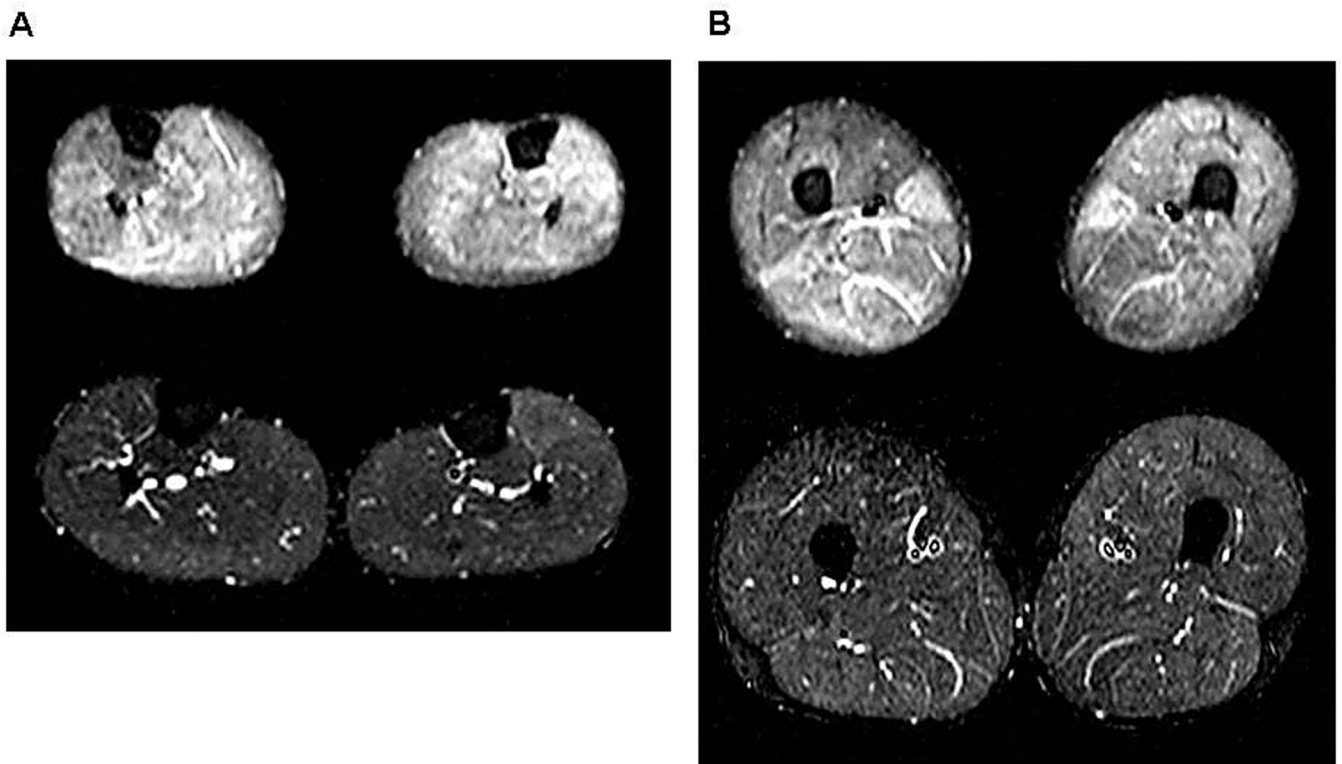
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**Figure 1.**

In case 2 a prominent focus of perimysial inflammation was found (A). Similarly the inflammation in case 3 was predominantly perimysial (B) with focal extension into the perimysium (arrow in C). The inflammatory cells included abundant T lymphocytes (C) and increased expression of MHC Class I at the sarcolemma and within the sarcoplasm of fibers (D). A: case 2; B – D: case 3. A & B: hematoxylin and eosin, C: CD3 immunohistochemistry; D: MHC Class I immunohistochemistry. Bar in A represents 50 $\mu$ m in A – D.



**Figure 2.** STIR images of the calves (A) and thighs (B) of Case 3 illustrating widespread edema during a symptomatic period of myalgia and muscle swelling compared with normal imaging when asymptomatic.

**Table 1**  
Summary of clinical, biochemical, neurophysiological and histological findings in each case.

Case	Predominant clinical features	Examination findings	Investigations	Biopsy Findings	Response to steroid therapy
1	Episodic muscle paralysis Progressive proximal limb weakness	Proximal limb weakness, MRC grade 3+/5 to 4+/5	CK 2729U/L EMG: polyphasic units + short duration units, fibrillations, fasciculations and myotonic discharges	Internal nuclei, fibre atrophy, fibre hypertrophy with occasional split fibres, some regenerating fibres and an increase in endomysial connective tissue. Dense inflammatory cell infiltrate focused around small capillaries and necrotic fibres composed mainly of T-lymphocytes. MHC I upregulation on occasional muscle fibres.	High dose prednisone (60mg) led to severe paralytic attack lasting 48hrs 10mg better tolerated with improved muscle strength
2	Muscle cramps and severe myalgia	Myotonia Normal muscle power	CK 1109U/L EMG: massive myotonic discharges at every insertion point that precluded analysis of MUAP configuration, voluntary recruitment or interference pattern.	Increased variation in fibre size, evidence of fibre regeneration and 1 necrotic fibre. Two foci of inflammation composed of CD3 immunoreactive T lymphocytes noted in perimysium and endomysium. Immunohistochemistry unavailable for review.	Reduction in CK to 3-400.
3	Muscle cramps and episodic limb oedema with myalgia	Myotonia Normal muscle power	CK normal EMG: myotonic discharges	Inflammatory infiltrates composed of a mixture of T lymphocytes and macrophages were present in the perimysium with a single endomysial cluster (Fig 2). Immunohistochemical staining for MHC Class I demonstrated an increase in sarcolemmal and sarcoplasmic expression	Excellent response with significant reduction in symptoms of oedema and myalgia