CASE REPORT

Double trouble in a patient with myotonia

Michael K Hehir,[1] Eric Logigian,[2] Dipa L Raja Rayan,[3] Emma Ciafaloni[2]

[1]Department of Neurology, University of Vermont, Burlington, Vermont, USA
[2]Department of Neurology, Neuromuscular Disease Center, University of Rochester, Rochester, New York, USA
[3]MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London, UK

Correspondence to
Dr Michael K Hehir,
Michael.Hehir@vtmednet.org

To cite: Hehir MK, Logigian E, Raja Rayan DL, *et al*. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2012-008167

SUMMARY

Non-dystrophic myotonias (NDM) are characterised by muscle stiffness during voluntary movement owing to delayed skeletal muscle relaxation caused by mutations in the chloride (CLCN1) and sodium (SCN4A) skeletal muscle channel genes. Late onset acid maltase deficiency (AMD) is characterised by progressive respiratory and proximal muscle weakness; electrical but not clinical myotonia can be observed. Case report of a unique patient with concurrent NDM and AMD. We describe the clinical presentation and management of a patient with two rare neuromuscular disorders. This case illustrates the importance of reopening the differential diagnosis in patients who do not conform to the typical natural history of a specific disease.

BACKGROUND

Non-dystrophic myotonias (NDM) and late onset acid maltase deficiency (AMD) are distinct clinical entities. NDM is characterised by muscle stiffness during voluntary movement owing to delayed skeletal muscle relaxation caused by mutations in the chloride (CLCN1) and sodium (SCN4A) skeletal muscle channel genes.[1 2] Patients with NDM can develop mild proximal weakness and typically exhibit widespread electrical and clinical myotonia.[1 2] Late onset AMD is an autosomal recessive neuromuscular disorder caused by a deficiency of lysosomal enzyme acid α-glucosidase which breaks down lysosomal glycogen.[3 4] AMD is characterised by progressive respiratory and proximal limb-girdle muscle weakness; electrical but not clinical myotonia can be observed.[3–5] These conditions are managed with different therapeutic agents. We will describe a patient with concurrent NDM and AMD.

CASE PRESENTATION

A 31-year-old man with NDM diagnosed in his teens presented after a hiatus with severe dyspnoea, orthopnea and progressive limb-girdle weakness since the age of 27. The patient began to develop progressive stiffness of his legs around age 12. This symptom limited his ability to compete in ice hockey. The diagnosis of probable sodium channel NDM was established at the age of 13 based on autosomal dominant inheritance pattern (mother and maternal grandmother similarly affected), clinical myotonia without clear warm-up, not exacerbated by cold/potassium/high carbohydrate meals and the absence of weakness. Needle electromyography (EMG) showed diffuse electrical waxing and waning myotonia. Short and long exercise nerve conduction tests with and without cooling to 32°C did not reveal an electrical decrement in CMAP area or amplitude (Fournier Pattern III)[6 7] which can be consistent with sodium channel myotonia. Serum creatine kinase (CK) ranged from 1000 to 1500. A deltoid muscle biopsy was normal. At that time, limited mutation analysis of CLCN1 and SCN4A (T1313M, R1448C) and DNA testing for myotonic dystrophy types 1 and 2 were negative. The patient's mother has widespread electrical myotonia and fluctuating clinical myotonia. She has less pain than her son. The patient's maternal grandmother has fluctuating clinical myotonia.

In his mid-20s, the patient developed stiffness in his lower back, shoulders, neck and hands. He began to experience handgrip myotonia when attempting to release objects. His neurological examination was significant for eyelid/grip myotonia, percussion myotonia in his forearms and normal strength testing. He was treated with the sodium channel antagonist, mexiletine, which improved his clinical myotonia. The patient and his mother were both enrolled in the CINCH trial in NDM. Gene sequencing of the SCN4A (exons 13, 22, 24) and CLCN1 genes for NDM was performed at the age of 31. The patient and his mother are heterozygous for a single splice site point mutation (c.774+1G>A in intron 6) on the CLCN1 gene; this mutation is recessive and in isolation may not be consistent with the phenotype of chloride channel NDM.

At the age of 31, the patient reported difficulty climbing stairs owing to weakness and dyspnoea with exertion and difficulty in performing his job with the highway department. His neurological examination revealed grade 4 shoulder and hip strength as well as persistent clinical myotonia. He presented to the emergency department 1 month later with continued dyspnoea. His chest x-ray showed reduced lung volumes and arterial blood gas showed pH 7.38, pCO_2 56 mm Hg, pO_2 71 mm Hg, O_2 saturation 90%. He had an urgent evaluation by a pulmonologist 1 month later. The patient reported worsening dyspnoea and began sleeping at a 30–45° incline owing to orthopnea. He was described by the pulmonologist to be somnolent and to have significant lower extremity oedema. Pulmonary function testing in the seated position showed forced vital capacity (FVC) 2.04 litre (34% predicted); forced expiratory volume1 1.64 litre (34% predicted). Nocturnal BiPAP therapy was initiated and the patient underwent an additional neuromuscular evaluation.

The patient's neurological examination showed eyelid and grip myotonia, percussion myotonia, lordotic gait and symmetric grade 4 limb-girdle weakness. Ultrasound-guided phrenic nerve conduction revealed absence of diaphragmatic movement and

unevokable diaphragmatic motor responses. Repeat short-exercise nerve conduction protocol with cooling did not show an electrical decrement (Fournier Pattern III). Needle EMG continued to show widespread electrical waxing and waning myotonia. Serum CK was 1600. Muscle biopsy showed central vacuoles and increased periodic acid-Schiff (PAS) and acid-phosphatase staining; it was interpreted as consistent with AMD (figure 1). Muscle acid maltase levels were measured at 0.4 μmol/g (normal 1.74–9.98 μmol/g). The patient was diagnosed with late-onset AMD (Pompe's disease). Genetic testing for AMD showed a heterozygous single nucleotide change in the first intron of the GAA gene (c. −32–13 T>G) and a heterozygous single nucleotide change (c.2619 C>G) in exon 18; these findings are described in late-onset AMD.

Therapy with intravenous alglucosidase α (Lumizyme) began 4 months after presentation. After 3 months of therapy, the patient reported stabilisation in weakness with continued orthopnea, somnolence and dyspnoea. His hip girdle strength reached NADIR at less than antigravity (2). Supine FVC: 1.52 L (32% predicted); pCO_2: 61 mm Hg. Five months post-treatment, the patient was able to play nine holes of golf and ambulate at the state fair. He showed improved limb-girdle strength. He also showed reduced $PaCO_2$ 48 mm Hg; FVC was unable to be measured owing to dental injury. At the time of his last visit to the neuromuscular clinic (8 months post-treatment) the patient's strength exam was stable (figure 1). His FVC was improved to 2.18 litre (45% predicted). He continues on BiPAP therapy at home and continues to sleep with head elevated at 30°s.

DISCUSSION

NDM and late onset AMD are rare neuromuscular conditions. We describe a patient with clinical and electrodiagnostic features of both conditions.

The NDM are skeletal muscle channelopathies owing to mutations in the SCN4a muscle sodium channel (paramyotonia congenita/sodium channel myotonia) and CLCN1 muscle chloride channel (myotonia congenita).[1 2] A separate set of mutations in the SCN4a gene results in hyperkalaemic periodic paralysis.[2] The clinical diagnosis of sodium channel NDM was established in our patient at the age of 13 based on autosomal dominant inheritance pattern, clinical myotonia, widespread electrical myotonia and the absence of weakness. However, gene sequencing later in life revealed a heterozygous single splice site mutation in the CLCN1 gene in the patient and his mother; this finding in isolation is not necessarily consistent with the phenotype of myotonia congenita (CLCN1, chloride channel) NDM. The limited analysis of the three exons in the SCN4a gene performed in this patient account for 60–70% of known pathological mutations; the negative findings do not fully exclude sodium channel NDM. A normal short exercise protocol (Fournier Pattern III) has been described in both sodium channel NDM and myotonia congenital.[6 7]

Development of permanent proximal weakness is described in 60–90% of patients with NDM and periodic paralysis.[1] However, these patients rarely develop severe respiratory weakness requiring ventilatory support. The development of rapidly progressive respiratory and proximal extremity weakness in our patient led us to reopen the differential diagnosis and ultimately discover evidence of concurrent late onset AMD.

Late onset AMD is an autosomal recessive, progressive neuromuscular condition marked by progressive limb-girdle and respiratory weakness owing to an inability to break down glycogen.[3 4] Phenotype is variable but many patients require ventilatory support; respiratory failure is a major cause of mortality.[4 5] Although not checked in this patient, muscle MRI can reveal muscle atrophy and fatty replacement in late onset AMD; changes are most common in the paraspinal muscles, hip flexors and quadriceps.[8 9] In contrast, limited case series have illustrated normal standard muscle MRI in NDM; specialised-MRI techniques in research settings have shown sodium accumulation in muscle in NDM.[10–12] Muscle biopsy in AMD shows centrally located PAS positive vacuoles indicative of glycogen accumulation.[4 13] α-Glucosidase α (acid maltase) levels can be obtained from muscle or peripheral blood. Our patient's muscle acid maltase was 0.4 μmol/g (normal 1.74–9.98 μmol/g) confirming the diagnosis of late-onset AMD. Subsequent genetic analysis was also consistent with late-onset AMD.

We propose that our patient developed two separate, rare, neuromuscular conditions. The prevalence of NDM is estimated to be 1–10/100 000 (NDM).[1] The incidence of AMD is estimated at 1/40 000.[3 4 14] Although not comparable statistics, the probability of developing both conditions is small.

IMPLICATIONS FOR THERAPY

The myotonia experienced by patients with NDM is typically mitigated by treatment with sodium channel blockade (mexiletine) and with carbonic anhydrase inhibition (acetazolamide).[1 15] Medical therapies to address the late proximal myopathy has not been identified. Enzyme replacement with alglucosidase α (Lumizyme) has been shown to slow the progression of respiratory decline and development of weakness in patients with AMD.[3] Identification of AMD in this patient led to enzyme replacement therapy. Although he continues to require BiPAP therapy, our patient's pulmonary function studies have remained stable and possibly improved over the 8 months since instituting the therapy.

CONCLUSIONS

We describe a patient with the novel presentation of two rare neuromuscular disorders (AMD and NDM). This case illustrates the importance of reopening the differential diagnosis in patients who do not conform to the typical natural history of a specific disease.

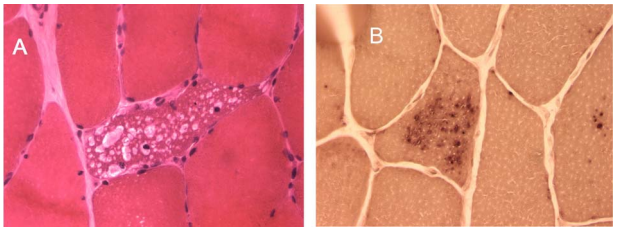

Figure 1 Muscle biopsy of quadriceps. (A) H&E staining with evidence of a vacuolar myopathy. (B) Acid phosphatase staining with increased uptake in areas of vacuoles.

Learning points

- Non-dystrophic myotonia (NDM) and acid maltase deficiency (AMD) are two rare neuromuscular disorders which can present with electrical myotonia on electromyography testing.
- Atypical progressive weakness and respiratory dysfunction led to a concurrent diagnosis of AMD in a patient with NDM.
- AMD is treated with enzyme replacement whereas NDM is treated with sodium channel blockers and acetazolamide.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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