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ORIGINAL COMMUNICATION

A novel late-onset axial myopathy associated with mutations in the skeletal muscle ryanodine receptor (*RYR1*) gene

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Abstract Mutations in the skeletal muscle ryanodine receptor (*RYR1*) gene are a common cause of inherited neuromuscular disorders and have been associated with a wide clinical spectrum, ranging from various congenital myopathies to the malignant hyperthermia susceptibility (MHS) trait without any associated weakness. *RYR1*-related myopathies are usually of early-childhood onset. Here we present 11 patients from 8 families with a late-onset axial myopathy associated with *RYR1* variants. Patients presented between the third and seventh decade of life to neuromuscular centres in Norway, the Netherlands and the United Kingdom with predominant axial muscle involvement, comprising variable degrees of lumbar hyperlordosis, scapular winging and/or camptocormia. Marked myalgia was commonly associated. Serum creatine kinase levels were normal or moderately elevated. Muscle imaging showed consistent involvement of the lower paravertebral muscles and the posterior thigh. Muscle biopsy findings were often discrete, featuring variability in fibre size, increased internal nuclei and unevenness of oxidative enzyme staining, but only rarely overt cores. *RYR1* sequencing revealed heterozygous missense variants, either previously associated with the MHS trait or localizing to known MHS mutational hotspots. These findings indicate that MHS-related *RYR1* mutations may present later in life with prominent axial weakness but not always typical

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histopathological features. We propose a combined effect of RyR1 dysfunction, aging and particular vulnerability of axial muscle groups as a possible pathogenic mechanism. *RYR1* is a candidate for cases with "idiopathic" camptocormia or bent spine syndrome (BSS).

Keywords Skeletal muscle ryanodine receptor (*RYR1*) gene · *RYR1* mutations · Malignant hyperthermia susceptibility (MHS) · Axial myopathy · Camptocormia

Introduction

Mutations in the skeletal muscle ryanodine receptor (*RYR1*) gene cause a wide range of inherited muscle disorders, ranging from the malignant hyperthermia susceptibility (MHS) trait, a pharmacogenetic predisposition to adverse reactions in response to volatile anaesthetics and muscle relaxants (for review, [1]), to various congenital myopathies, comprising mainly dominantly inherited central core disease (CCD) and recessively inherited forms of multi-minicore disease (MmD) (for review, [2]), centronuclear myopathy (CNM) [3] and congenital fibre-type disproportion (CFTD) [4]. The clinical phenotypes are variable from mild and non-progressive to severe and fatal. Whilst most dominant *RYR1* mutations give rise to relatively mild symptoms with weakness pronounced in the proximal lower limb, recessive *RYR1* mutations are associated with more variable features, comprising generalized muscle weakness and wasting, extraocular muscle involvement, and respiratory impairment [5].

The vast majority of patients with *RYR1*-related myopathies present in the neonatal period, infancy or early childhood. Here we report 11 patients from 8 families with a novel *RYR1*-related axial myopathy of late-onset, previously only reported in one isolated case [6].

Patients and methods

Patients

Patients presented with features of a late-onset axial myopathy to tertiary neuromuscular referral centres in Norway, the Netherlands and the United Kingdom. Detailed medical histories and neurological examinations were obtained from all index cases and, where applicable, their relatives (outlined in detail in Supplemental File S1). All human studies have been approved and were performed under the ethical guidelines issued by the appropriate ethics committee for clinical studies and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all subjects (or, where applicable, their legal guardians) for genetic studies. Written informed consent was obtained for photographs of any recognizable patient.

Muscle histology and histochemistry

All patients had muscle biopsies, mostly taken from the quadriceps. We reviewed the standard histological (hematoxylin and eosin, H&E; Gomori trichrome, GT; periodic acid-Schiff, PAS) and histochemical (nicotinamide adenosine dinucleotide-tetrazolium reductase, NADH-TR; myosin adenosine triphosphatase, ATPase, preincubated at pH 9.4, 4.6 and 4.3; cytochrome C oxidase, COX) stains in all patients.

Molecular genetic studies

The entire *RYR1* coding regions (exons 1–106) including splice sites were screened at the genomic level in all patients. Similarly affected relatives were investigated for

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the presence of the *RYR1* variant identified in the proband by direct sequencing. Novel *RYR1* variants identified were interrogated by in silico analysis using Alamut v1.5 (Interactive Biosoftware) as previously described [5]. Additional negative genetic investigations performed prior to *RYR1* sequencing included screening for facioscapulohumeral dystrophy (FSHD) in most cases, as well as *DM1*, *DM2*, *GAA*, *LMNA*, *MYOT*, *DES*, *FKRP* and *CAV3* sequencing in selected patients.

Results

The main clinical, histopathological and genetic findings from 11 patients from 8 families presenting with *RYR1*-related late-onset axial myopathy are summarized in Table 1.

Clinical features

Patients presented between the 3rd and 7th decade without any preceding neuromuscular symptoms. On examination (Fig. 1), axial involvement was the most prominent feature and variably affected the lumbar region, neck muscles and shoulder fixators. Some patients presented with lumbar hyperlordosis exaggerated when they were asked to raise their arms, whilst others developed marked camptocormia on standing and walking but had a normal bedside examination. Although in some patients there was also a degree of proximal muscle weakness, this was much milder than axial involvement. Before the onset of axial muscle weakness, many patients had been particularly athletic or had engaged in intense physical labour, resulting in hypertrophy of unaffected muscle groups. In all cases there this information could be obtained, early motor developmental milestones had been within normal limits. One patient (Patient 6) had some features of proximal muscle involvement in childhood, suggesting early onset of symptoms despite normal motor developmental milestones.

Marked myalgia was prominent and often preceded clinically overt muscle weakness by many years. The myalgia was mainly exercise-related, although in some instances a considerable interval between physical activity and onset of myalgia was noted. Myalgia mainly affected the lower (thigh, calves) and upper limb (upper arm, shoulders) but also the axial muscles. Lower back pain was a common complaint, often out of proportion to the degree of axial weakness. Some individuals with myalgia also had significant CK increases (up to 1,407 IU/l), leading to the erroneous suspicion of an underlying muscular dystrophy in some instances.

There was no personal or familial malignant hyperthermia (MH) history. However, not all individuals included in this study had undergone general anaesthesia, and in those who had it could not always be established with certainty if or if not potentially MH triggering agents had been used. Despite absence of a clinical MH history, MH susceptibility was formally confirmed by in vitro contracture (IVCT) testing in Patient 1.

Muscle imaging findings (Fig. 2) were consistent between patients, with prominent involvement of the paravertebral muscles, the gluteus muscles and the posterior thigh in cases with lower limb involvement.

Other medical features included cataracts, present in three individuals (Patients 1, 2 and 10) from two families, and associated with staphyloma in one family (Family 1, Patients 1 and 2). In one family (Family 8) there was a strong history of Gilles de la Tourette syndrome.

Histopathological features

In many patients, histopathological features (Fig. 3) were considered non-specific, often resulting in a prolonged diagnostic process and involving several muscle biopsies to clarify the diagnosis. Subtle but consistent histopathological features comprised increased variability in fibre size, increased internal nuclei and uneveneness of oxidative enzyme staining. Only one patient had overt cores on muscle biopsy. Electron microscopy was not routinely performed in our cohort.

Genetic results

The heterozygous dominant *RYR1* missense mutations identified in Patients 1, 2, 3, 10 and 11 were all previously reported MHS mutations [7–9], whereas variants identified in Patients 4, 5 and 6 have not been reported previously but localize to known MHS mutational hotspots within the *RYR1* gene. The *RYR1* p.Glu3583Gln variant identified in Family 6 (Patients 7, 8 and 9) has been found in a number of MHS families from the United Kingdom [7] and has been considered a common and possibly neutral variant. The *RYR1* p.Lys1393Arg mutation identified in mother and son (Family 1, Patients 2 and 1) from a Norwegian family is a Scandinavian MHS mutation [8] that has been functionally characterized.

Parental testing was not always possible, particularly in families where the index case had presented late in life. In the two families (Family 1, Family 6) where a detailed clinical and genetic multigenerational assessment could be performed, the *RYR1* mutation was parentally inherited. We did not find any evidence for *de novo* occurrence.

There was marked phenotypical variability associated with the same familial *RYR1* mutation: In Family 1 and Family 6, 1st and 2nd degree relatives harbouring the same

Table 1 Main clinical, histopathological and genetic features from 11 patients with *RYR1*-related late-onset axial myopathy

F	P	Onset	Myalgia	Scapula alata	Lumbar hyperlordosis	Camptocormia	Limb weakness	CPK (IU/l)	Muscle imaging	Muscle biopsy	*RYR1* variant
1	1	20 s	Y	+	+++	–	+	857	Lumbar paraspinals, glutei, posterior thigh	Increased fibre size variability, Unevenness of oxidative enzyme staining	c.4178A > G; p.Lys1393Arg
	2	20 s	Y	+	+++	–	++	N	Thoracic and lumbar paraspinals, glutei (thighs not imaged)	Few basophilic fibres; fibre type grouping; perivascular lymphocytic infiltrates	c.4178A > G; p.Lys1393Arg
2	3	30 s	Y	++	+++	–	+	213	ND	Type 1 predominance; unevenness of oxidative enzyme staining	c.7025A > G; p.Asn2342Ser
3	4	60 s	N		–	+++	–	300	Posterior thigh, soleus (paraspinals not imaged)	Increased fibre size variability; few regenerative fibres; central cores	c.9713A > G; p.Glu3238Gly
3	5	40 s	Y	++	–	–	+	1,407	Thoracic and lumbar paraspinals; posterior thigh	Increased fibre size variability; unevenness of oxydative enzyme and COX staining; few cores	c.10354A > C; p.Lys3452Gln
4	6	40 s	N	+	+++	–	–	1,000	ND	Mild central reduction of oxidative enzyme stains	c.10621G > A; p.Ala3541Thr
6	7	20 s	Y	+	+	–	(+)	591	Lumbar paraspinals; posterior thigh	Type 1 atrophy	c.10747G > C p.Glu3583Gln
	8	40 s	Y	–	++	–	+	262	Lumbar paraspinals; posterior thigh	Non-specific myopathic changes	c.10747G > C p.Glu3583Gln
	9	30 s	Y	–	–	–	(+)	475	Lumbar paraspinals; posterior thigh	Normal	c.10747G > C p.Glu3583Gln
7	10	70 s	N	N		+++	–	204	ND	Increased variability in fibre size, unevenness of stain, core, lobulated fibres	c13513G > C; p.Asp4505His
8	11	40 s	Y	+++	++	–	++	512	ND	Few atrophic fibres, Increased internal nuclei	c.14545G > A; p.Val4849Ile

F family, *P* patient, *ND* no data

familial *RYR1* mutation as the index case had either developed similar features of an axial myopathy or were still asymptomatic. However, lower back pain was a common finding in *RYR1* mutation–positive individuals with or without associated axial weakness. In Family 8, the *RYR1* mutation–positive sister of the index case was probably similarly affected as her brother (Patient 11), but was not included in our series as her assessment was still incomplete. In Family 5, where only the index case (Patient 6) had been genetically investigated, dominant inheritance with variable expression was suggested by a history of exaggerated lumbar lordosis in his mother, maternal grandmother and a maternal great aunt, none of whom were available for clinical or genetic assessment.

Discussion

Myopathies associated with mutations in the *RYR1* gene are usually of early onset and associated with proximal or generalized muscle weakness. Neuromuscular manifestations of *RYR1* mutations in adulthood have been reported in isolated cases only, in one instance associated with prominent axial muscle involvement [6].

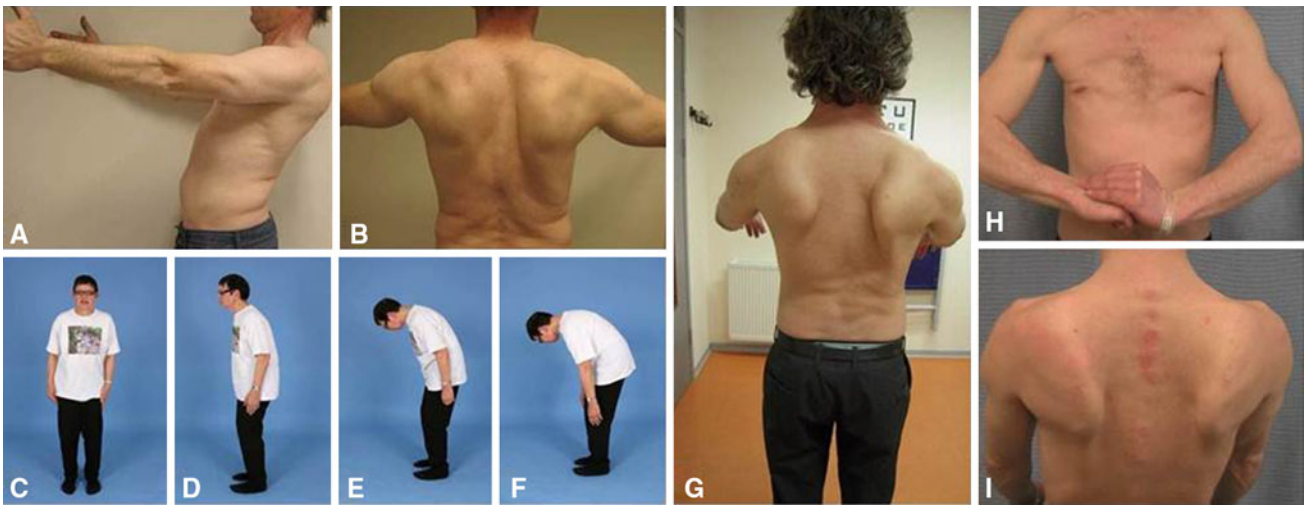

Fig. 1 Clinical features, Patients one (**a**, **b**), four (**c**–**f**), six (**g**) and seven (**h**, **i**). Note exaggerated lumbar lordosis, wasting of the paravertebral muscles, scapular winging (**a**–**b**, **g**) and asymmetrical atrophy of the pectoralis muscles (**h**). Patient four shows marked camptocormia (**c**–**f**)

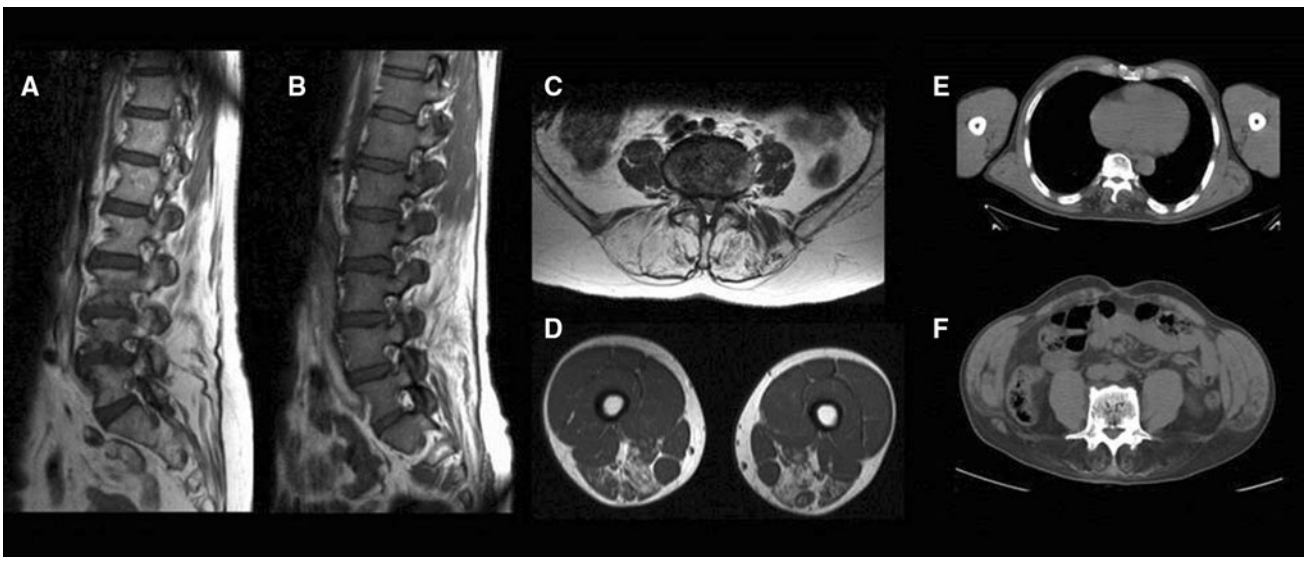

Fig. 2 Muscle MR (**a**–**d**) and CT (**e**–**f**) imaging findings, Patients one (**b**, **d**), two (**a**, **c**) and five (**e**–**f**). There is marked involvement of the thoracic and/or lumbar paravertebral muscles (**a**–**c**, **e**–**f**). Patient one shows additional posterior thigh involvement (**d**)

Here we report consistent evidence for a novel, *RYR1*-related myopathy of late onset and with prominent involvement of the axial musculature. Corresponding to clinical findings, muscle imaging revealed prominent paravertebral and posterior thigh involvement, in contrast to early-onset *RYR1*-related myopathies, where the most severe changes are seen in the medial and anterior thigh compartments [10, 11]. In most patients, histopathological features were subtle, emphasizing that *RYR1* involvement has to be excluded in unresolved myopathies with suggestive clinical features, even if muscle biopsy findings are considered to be non-specific and do not suggest a specific histopathological diagnosis.

Before the possibility of a *RYR1*-related myopathy was considered, most patients had undergone a lengthy diagnostic process, in some instances extending over years. The differential diagnosis in these patients had included all known causes of late-onset axial myopathies and camptocormia ("bent spine syndrome", BSS), namely myofibrillar myopathies [12] inflammatory conditions, FSHD, myotonic dystrophy, various limb girdle muscular dystrophies, neurological conditions, mitochondrial and other metabolic myopathies (for review [13]). Apart from cases secondary to psychogenic, neurological or other neuromuscular causes, BSS is now considered a distinct late-onset axial myopathy [14] whose genetic basis remains currently

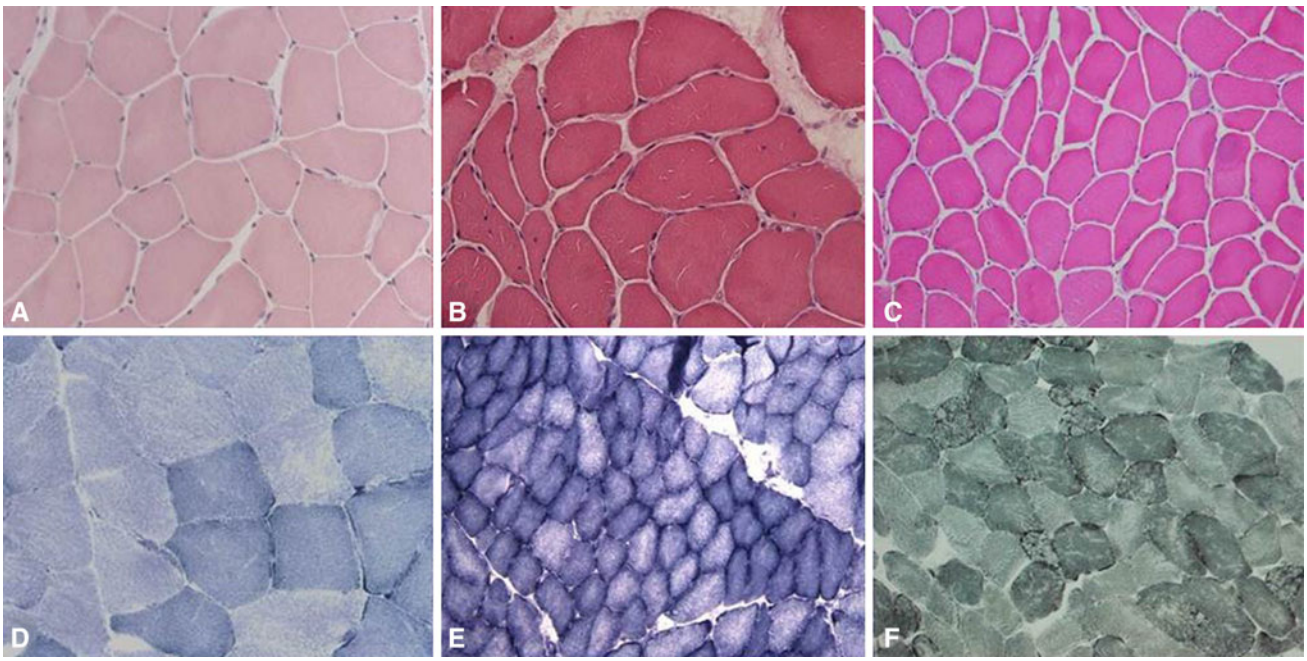

Fig. 3 Histopathological features, Patients one (**a**, **d**), five (**b**, **e**) and seven (**c**, **f**), transverse muscle biopsy sections, H&E (**a–c**), NADH-TR (**d–f**). Note increased fibre size variability and oxidative enzyme staining abnormalities, ranging from subtle unevenness (**d–e**) to overt cores and lobulated fibres (**f**)

uncertain. Some patients with BSS do have a positive family history, hyperCKaemia, radiological and histopathological features very similar to those observed in our series [15], suggesting the *RYR1* gene as a plausible candidate at least for a proportion of unresolved BSS cases.

Our findings also indicate that the axial myopathy reported in this paper is a specific late manifestation of *RYR1* mutations associated with the MHS trait. Although MHS and clinically manifest *RYR1*-related myopathies have been considered distinct entities, a continuum is indicated by the early observation of central cores in patients with MHS, and of MHS in some patients with CCD, respectively. Other distinct myopathic manifestations of MHS mutations include the King–Denborough syndrome (KDS) [16], an early-onset myopathy associated with dysmorphic features, skeletal abnormalities and MHS, as well as exertional rhabdomyolysis, episodes of muscle breakdown provoked by exercise in MH susceptible individuals [17]. A continuum with the MHS trait is also suggested by the additional observation of muscle hypertrophy, heat intolerance, myalgia and hyperCKaemia in our cohort, recognized features in patients and animal models of MHS but unusual in the context of other myopathies. Conversely, late-onset mild lumbar weakness has been reported in some individuals from a large MHS pedigree [18]. Lastly, despite an obvious association, the MHS trait with an estimated incidence of 1 in 2,000–3,000 [19] is much more prevalent than *RYR1*-related late-onset axial myopathy, suggesting variable expression of myopathic manifestations, probably due to the presence of additional genetic and other modifiers.

The cause for the late and predominantly axial involvement seen in our patients is uncertain, but may reflect a combination of RyR1 dysfunction, normal aging and particular vulnerability of the axial musculature to both processes; mouse models carrying *RYR1* mutations associated with "leaky" RyR1 channels show changes in oxidation and nitrosylation similar to those observed in aged wild-type animals [20], suggesting that aging and co-existing RyR1 dysfunction may exert a synergistic detrimental effect on muscle structure and function. Oxidative stress in particular increases with age and has recently been suggested as an important pathophysiological mechanism in *RYR1*-related myopathies [21], with potential therapeutic implications for patients. In addition, axial muscles may be particularly vulnerable to oxidative stress, as illustrated by the predominant axial involvement in patients and animal models of *SEPN1*-related myopathies, neuromuscular disorders with defects in redox regulation and substantial clinico-pathological overlap with *RYR1*-related disorders [22].

These findings expand the clinical spectrum of *RYR1*-related disorders. In sporadic patients presenting with isolated axial weakness without limb involvement, a specific diagnosis remains often elusive, as in this clinical setting limb muscle biopsies are rarely helpful and axial muscle biopsies usually show only endstage changes. We conclude that *RYR1* mutations should be considered in such patients, even if histopathological features are mild or non-specific.

Muscle MR imaging of the paravertebral muscles and the lower limb may inform genetic testing in selected cases.

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Conflicts of interest The authors do have no conflict of interest to declare.

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