Introduction
Congenital myopathy is a heterogeneous group of inherited neuromuscular disorders categorised by characteristic histopathological features on muscle biopsy. Among different types, central core myopathy was the first described congenital myopathy in humans in 1956.\(^1\) The clinical phenotype is highly variable, ranging from asymptomatic or mild muscle weakness to severe neuromuscular involvement leading to lack of independent ambulation and early infant death.\(^2,3\) Central core myopathy is a rare disease, and is usually inherited in an autosomal dominant manner resulting from the ryanodine receptor type 1 (\textit{RYR1}) gene mutation on chromosome 19q13.1.\(^4\) Autosomal recessive inheritance has also been reported.\(^5,6\) Classically it manifests as a slowly or non-progressive symmetrical proximal muscle weakness and infantile hypotonia that can persist into adulthood. Affected patients usually have delayed milestones for motor development and reduced muscle bulk. Orthopaedic manifestations such as congenital hip dislocation or kyphoscoliosis commonly coexist.\(^2,7\) Here, we report a case of central core myopathy with atypical clinical presentations. The diagnosis is based on the histopathological findings of characteristic cores on muscle biopsy and molecular genetic testing for the \textit{RYR1} gene mutation.

Case report
A 14-year-old Chinese boy was referred because of lower limb muscle atrophy and foot deformity. There was no family history of neuromuscular disease. He presented with delayed motor milestones and could not walk independently until 22 months old. He had always been poor at motor skills, never being able to squat and described as exhibiting clumsiness with easy falling. Aged 11 years, he had an episode of left knee injury with dislocation of patella, which was treated with a plaster for 2 months. Later, left thigh muscle atrophy was noted. He started to walk with a tip-toe gait and manifested bilateral foot deformities. There were no features of disordered sensory, bladder or bowel functions.

Examination revealed left lower limb muscle atrophy and bilateral pes cavus. He walked with tip-toe gait and an exaggerated lumbar lordosis. There was bilateral Achilles tendon tightness and weakness of ankle dorsiflexion, more severe on the left side. Deep tendon reflexes were normal, there was no abnormality in the upper limbs, and there was no ptosis, ophthalmoplegia or facial weakness. Investigations—including complete blood count, erythrocyte sedimentation rate, and tests for antinuclear antibody and thyroid disorders—yielded nil abnormal. Nerve conduction studies and magnetic resonance imaging (MRI) of the spine were entirely normal. However, his serum creatine kinase level was 2259 U/L. In view of the clinical features and the moderately elevated serum creatine kinase level, diagnoses including muscular dystrophies (such as the limb-girdle type) or other hereditary myopathies were suspected.

Muscle biopsy from the left vastus lateralis revealed skeletal muscle fibres with generally enlarged size, in the range of 120 to 130 µm (Fig 1). Internalised and central nuclei were readily seen. ATPase enzyme histochemistry showed indistinct fibre type discrimination, in keeping with myopathic changes. Staining for oxidative enzymes (NADH...
known disease-causing mutation of the RYR1 gene arginine-to-histidine substitution at codon 2508 (NM_000540.2:c.7523G>A; NP_000531.2:p.R2508H) was identified in the index patient, while in the parents, such a specific mutation was absent.

The patient’s clinical condition was stable. Genetic counselling together with the possibility of malignant hyperthermia susceptibility (MHS) were explained to the patient and the family.

Discussion

Central core myopathy is a rare neuromuscular disease with a wide phenotypic spectrum, and is considered an allelic disease of malignant hyperthermia (MH). The diagnosis depends on the presence of characteristic core areas devoid of mitochondria and oxidative enzyme stains in muscle biopsy specimens, and is confirmed by molecular genetic testing for an RYR1 gene mutation. These gene mutations were firstly discovered in 1990 as the cause of MH, and were subsequently detected in central core disease, multi-minicore disease, congenital myopathies with cores and rods, and congenital neuromuscular disease with uniform type 1 fibre. To date, over 280 RYR1 mutations have been identified. These gene mutations were firstly discovered in 1990 as the cause of MH, and were subsequently detected in central core disease, multi-minicore disease, congenital myopathies with cores and rods, and congenital neuromuscular disease with uniform type 1 fibre. To date, over 280 RYR1 mutations have been identified. These gene mutations were firstly discovered in 1990 as the cause of MH, and were subsequently detected in central core disease, multi-minicore disease, congenital myopathies with cores and rods, and congenital neuromuscular disease with uniform type 1 fibre. To date, over 280 RYR1 mutations have been identified.

RYR1 is one of the largest described genes in humans. The ryanodine receptor is the principal sarcoplasmic reticulum calcium release channel. The mutated codons giving rise to central core disease are clustered in three restricted regions of proteins
or ‘hot-spots’: N-terminal (amino acids p.M1-p.R614),
central (p.R2163-p.R2458), and C-terminal (p.R4136-
p.P4973). Most of the central core disease mutations
are clustered in the C-terminal region. Because of the
large size of the RYR1 gene, most routine screenings
have been limited to the three ‘hot-spots’ or even
to the C-terminal region alone (containing 47-67%
RYR1 mutations). 2,11,12 In 2006, Wu et al13 sequenced
all the 106 exons encoding RYR1 among 27 unrelated
Japanese central core disease patients, of whom
more than 90% had RYR1 mutations, which was a
much higher mutation detection rate than previously
reported. Most mutations outside the usual ‘hot-spots’
are localised in exons 47 and 48 that neighbour
the central region (exon 39-46). By screening the C-terminal
region alone and the three ‘hot-spots’ together, the reported mutation detection rates
are about 59% and 67%, respectively. However, by
including exons 47 and 48, the mutation detection rate
could be increased up to 89%.14 Our analysis
followed this approach; one of the mutations we
found was reported in Wu et al’s study7 and localised
at exon 47. This seems a more practical and efficient
genetic screening approach than sequencing the
entire RYR1 gene, and has yielded the first case with
an RYR1 gene mutation identified in our locality.

The genotype-phenotype correlations
associated with the RYR1 gene are complex and
may be partly explained by the degree of functional
differentiation conferred onto the large protein for
which it is responsible.15 In general, patients with
C-terminal mutations usually have classical clinical
features3,7 and a characteristic pattern of selective
muscle involvement on MRI imaging.14 In contrast,
patients with non-C-terminal mutations have only
mild musculoskeletal abnormalities such as joint
contracture and scoliosis, and are more liable to
have MHS.7,16 Notably, MHS is a pharmacogenetic
disorder in which seemingly normal individuals are
prone to develop serious adverse reactions upon
exposure to certain inhalational anaesthetics and
depolarising muscle relaxants.15 The most frequent
manifestation is isolated masseter muscle rigidity.16
Other reactions include fever, tachycardia,
hypertension, electrolyte disturbances, and
rhabdomyolysis leading to acute renal failure.
Malignant hyperthermia is predominantly reported
in western populations, and central core disease
has been largely reported in patients from western
Europe.17 The majority (96%) of the mutations
detected in association with MH and central core
disease are missense changes.17 MHS-related RYR1
mutations are predominantly located in the N-
terminal and central portions of the RYR1 protein.13
The association of MHS and central core disease is
strong but not invariable. All cases of central core
disease, however, should be considered at risk
of MHS.18 Any putative triggering anaesthetic (eg
halothane) or succinylcholine should be avoided,
in order to avoid possible MH.

In our case, the patient’s clinical presentation
was compatible with a non-C-terminal mutation
resulting in a later onset and milder phenotype
disorder. There were also some atypical features
however. Firstly, the clinical course of central core
disease is usually static,2 whereas rapid progression
from muscle atrophy after trivial knee injury to
pes cavus deformity within such a short period is
not typical. Secondly, the serum creatine kinase
concentration is usually normal or only mildly
elevated in congenital core disease.19 Thus, the
finding of a moderately elevated serum creatine
kinase level may suggest an alternative diagnosis
such as limb-girdle muscular dystrophy. Limb-girdle
muscular dystrophies are a heterogeneous group
of disorders characterised by weakness and wasting
of the pelvic and shoulder girdle muscles. There are
currently 19 subtypes, and patients with subtypes 1B
and 1C may have only distal muscle involvement.20
Both the clinical and biochemical findings may not
assist in differentiating muscular dystrophies from
central core myopathies. In addition, core formation
may also be observed in other clinical conditions
such as tenotomy, denervation21 (“target-fibres”) or
MHS individuals without other features of congenital
myopathy.22 This highlights the importance of
molecular genetic confirmation to make a definitive
diagnosis in this patient.

Conclusion
The phenotype of central core myopathy is
relatively heterogeneous, with variable age of onset,
different degrees of muscle weakness, spinal or
limb deformity and joint problems. Similar to other
congenital myopathies, biochemical tests including
serum creatine kinase is of limited diagnostic value.
Targeted molecular study after muscle biopsy is
helpful for the confirmation of the diagnosis, defining
the phenotype and prediction of MHS.

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