Central core disease: clinical, pathological, and genetic features

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Central core disease (CCD) is a dominantly inherited congenital myopathy allelic to malignant hyperthermia (MH) caused by mutations in the RYR1 gene on chromosome 19q13.1. Eleven individuals with RYR1 mutations are described. Four index cases showed features consistent with a congenital myopathy (hypotonia, delayed motor milestones, and skeletal abnormalities including congenital hip dislocation and scoliosis). All four cases and subsequently seven other family members were found to possess novel mutations in the RYR1 gene. The degree of disability varied from one clinically normal individual, to another who had never achieved independent ambulation (the only patient with a de novo mutation). Four cases showed a mild reduction in vital capacity, repeated nocturnal polysomnography showed hypoxaemia in one case. A variety of muscle biopsy features were found; central cores were absent in the youngest case, and the biopsy specimens from two others were more suggestive of mini-core myopathy. In all cases missense mutations in exons 101, 102, and 103 of the RYR1 gene were found. Central cores were absent in the youngest case, and the biopsy specimens from two others were more suggestive of mini-core myopathy. In all cases missense mutations in exons 101, 102, and 103 of the RYR1 gene were found. 

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A 5 year old schoolboy of Asian origin (table 1, B1) presented with a scoliosis at 3½ years of age (fig 2). His mother reported reduced fetal movements and commented that he had been floppy as an infant when compared with his peers and was described as clumsy with a tendency to fall frequently.

On examination, his vital capacity was 0.77 l (50% of that expected for his age and height). He had mild facial weakness. Neck flexion weakness was evident but his upper limb power was normal. He had a positive Gower’s manoeuvre with moderate hip flexion and extension weakness (MRC 4/5). Deep tendon reflexes were absent. His serum creatine kinase was normal (50 iu/l). Muscle biopsy taken from the vastus lateralis showed a mild degree of fibre size variability. With oxidative enzyme stains, focal areas devoid of stain were seen. These resembled mini-cores in both transverse and longitudinal sections (fig 1A). Oxidative stains showed a uniform pattern, indicating uniformity of fibre typing, with well defined central cores.

Examination of the parents and younger sister showed a mild degree of facial weakness only in the mother (A2). Molecular analysis of the RYR1 gene showed a mutation Ala4940Thr in exon 103 in both the child and her mother. However, in the child the aberrant single strand conformation polymorphism band was of the same intensity as the normal band, while in the mother the aberrant band was much fainter than the normal “G” peak in the mother (data not shown). We have interpreted these results to suggest that the mother has somatic mosaicism for the gene mutation.

**Family 2**

A 5 year old schoolboy of Asian origin (table 1, B1) presented with a scoliosis at 3½ years of age (fig 2). His mother reported reduced fetal movements and commented that he had been floppy as an infant. He walked at 15 months but at 5 years was unable to hop or jump. He was slow at running stairs only with support and had never been able to run, jump, or hop. On examination, she had reduced muscle tone and deep tendon reflexes. She had mild facial weakness and upper limb power was normal. His elder sister (table 1, B2) was referred to the muscle clinic at 15 years of age. She had been followed up in a paediatric clinic between 2 and 12 years of age because of “poor motor skills”. At 12 years of age she developed a scoliosis which required bracing. Her mother reported that she had been floppy as an infant when compared with her clinically normal sister. She was walking by 13 months of age, but had always been poor at motor skills; she climbed stairs only with support and had never been able to run, jump, or hop. On examination, she had reduced muscle tone and deep tendon reflexes. She had mild facial weakness and mild scoliosis (MRC 4/5); upper limb power was normal. Gower’s manoeuvre was positive; there was moderate weakness of all of her hip girdle muscles (MRC 3/5). Her thoraco-lumbar scoliosis was controlled by bracing until she was 16 years of age; thereafter no further treatment was required. At 18 years, respiratory insufficiency was noted; forced vital capacity (FVC) was 1.14 litres (32% of predicted) and nocturnal hypoxaemia was detected on repeated polysomnography studies. Echocardiography was normal. Her serum creatine kinase was less than 20 iu/l. Muscle biopsy taken from the vastus lateralis showed similar features to her brother.

Examination of both parents and the younger sibling revealed the father and child to be clinically normal. The mother (B3), however, showed evidence of mild facial weakness together with weakness of neck flexion and hip

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**Table 1 Summary of affected individuals, clinical, pathological, and genetic findings**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>MH</th>
<th>Sex</th>
<th>CDH</th>
<th>Spine</th>
<th>Facial weakness</th>
<th>Skeletal weakness</th>
<th>Respiratory impairment</th>
<th>Biopsy</th>
<th>DNA</th>
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<tr>
<td>A1</td>
<td>13 m</td>
<td>+</td>
<td>F</td>
<td>+</td>
<td>Scoliosis</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Marked increase in connective tissue, central cores, type 1 fibre uniformity</td>
<td>Not done</td>
</tr>
<tr>
<td>A2</td>
<td>30 y</td>
<td>–</td>
<td>F</td>
<td>–</td>
<td>Normal</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Not done</td>
<td>Ala4940Thr exon103</td>
</tr>
<tr>
<td>B1</td>
<td>6 y</td>
<td>–</td>
<td>M</td>
<td>–</td>
<td>Scoliosis</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Multiple mini-cores, type 1 fibre uniformity</td>
<td>Arg4893Trp exon 102</td>
</tr>
<tr>
<td>B2</td>
<td>16 y</td>
<td>–</td>
<td>F</td>
<td>–</td>
<td>Scoliosis</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Multiple mini-cores, type 1 fibre uniformity</td>
<td>Arg4893Trp exon 102</td>
</tr>
<tr>
<td>B3</td>
<td>38 y</td>
<td>–</td>
<td>F</td>
<td>–</td>
<td>Scoliosis</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Central cores, type 1 fibre uniformity</td>
<td>Arg4893Trp exon 102</td>
</tr>
<tr>
<td>C1</td>
<td>3 m</td>
<td>–</td>
<td>F</td>
<td>+</td>
<td>Normal</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>No cores, type 1 fibre uniformity</td>
<td>Tyr4864Cys exon 102</td>
</tr>
<tr>
<td>C2</td>
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<td>+</td>
<td>M</td>
<td>–</td>
<td>Lordosis</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Central and peripheral cores, type 1 fibre uniformity</td>
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</tr>
<tr>
<td>C3</td>
<td>33 y</td>
<td>–</td>
<td>F</td>
<td>–</td>
<td>Scoliosis</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Multiple mini-cores, type 1 fibre predominance</td>
<td>Tyr4864Cys exon 102</td>
</tr>
<tr>
<td>C4</td>
<td>42 y</td>
<td>–</td>
<td>F</td>
<td>–</td>
<td>Scoliosis</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Not done</td>
<td>Tyr4864Cys exon 102</td>
</tr>
<tr>
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<td>–</td>
<td>M</td>
<td>–</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>Not done</td>
<td>Tyr4864Cys exon 102</td>
</tr>
<tr>
<td>D</td>
<td>11 y</td>
<td>–</td>
<td>M</td>
<td>+</td>
<td>Lordosis</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Central cores, type 1 fibre uniformity</td>
<td>Arg4861His exon 101</td>
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extension (MRC 4/5). Her upper limb power was normal. She had a positive Gower’s manoeuvre but unlike the children, she was able to jump and hop. She had no evidence of any joint contracture or scoliosis. Her deep tendon reflexes were diminished. There was a mild reduction in FVC (2.01 litres; 72% predicted). Serum creatine kinase was less than 20 iu/l. Muscle biopsy taken from left vastus lateralis showed a spectrum of abnormal oxidative staining with well defined cores. These were single or multiple, peripheral, central, and eccentric in position (fig 1, B3).

Molecular genetic analysis revealed a mutation in RYR1 at Arg4893Trp in exon 102 in the mother and two affected children. The mutation segregated with the disease and was not found in the father or younger sibling.

Family 3
A white female infant (table 1, C1), the third child of unrelated parents, presented with bilateral congenital hip dislocation and hypotonia noted from birth. A muscle biopsy was taken from the adductor longus at the time of open hip surgery at 4 months of age. Subsequently her motor milestones were delayed; she rolled from supine to prone at 12 months and sat unsupported at 13 months. She did not walk until 22 months. She had no joint contractures or scoliosis. Deep tendon reflexes were absent. Her muscle biopsy showed a mild variation in fibre size, no internal nuclei or fibrosis. Oxidative stains revealed uniform fibre typing but no cores (fig 1, C1).

Her brother (table 1, C2) was examined in the muscle clinic at the time of his sister’s referral. He had been under follow up in a paediatric clinic for developmental delay but a muscle disorder had not been suspected. He sat independently at 11 months but did not walk until 2 years. By 3 years of age, he was unable to run or jump. He had facial weakness and a high arched palate. He had a moderate lumbar lordosis with waddling gait and positive Gower’s sign. His deep tendon reflexes were present except for the ankle jerks which were absent. Immediately following routine ear, nose, and throat surgery he developed a pyrexia of unknown origin, although there were no other features to suggest a malignant hyperthermia reaction.

Muscle biopsy taken from the vastus lateralis, showed a mild variation in fibre size, no internal nuclei or fibrosis. Oxidative stains showed uniform fibre typing and abundant peripheral and central cores (fig 1, C2). The father and older sibling were examined and found to be clinically normal.

The mother of the two children (table 1, C3) did not walk independently until 21 months of age. She had never been able to run, jump, or hop and had difficulty climbing stairs. On examination at 33 years of age, she was noted to have facial weakness, and a mild reduction in FVC (2.39 litres, 75% predicted for height and age). She had weakness of neck flexion, shoulder adduction (MRC 4/5), and moderate weakness of the hip flexors, extensors, adductors, and abductors (MRC 3–4/5). She had a mild thoracic scoliosis. Her deep tendon reflexes were absent. Muscle biopsy from the vastus lateralis showed a mild variation in fibre size with internal nuclei and type 1 fibre predominance. Oxidative enzymes showed small cores in some fibres and unevenness in many fibres, but unlike the children there was no fibre type uniformity (fig 1, C3). She underwent a second muscle biopsy for in vitro contracture testing to exclude MH which proved negative (Dr Halsall, Leeds, UK).

Figure 3 summarises the family tree; we were informed that the paternal grandfather, who had since died, developed a progressive muscle wasting disease in the sixth decade. His elderly sister was also affected by progressive muscle weakness, apparently beginning in her sixth decade, although we did not have the opportunity to examine her or arrange for molecular genetic testing. We were invited to examine the mother’s remaining first degree family members.

The mother’s older sister was examined and found to be clinically normal. At her request, she underwent a muscle biopsy for in vitro contracture studies which proved negative for both MH and CCD.

Figure 1  Muscle biopsies stained for NADH-TR. A: normal two fibre pattern. A1: type 1 fibre uniformity (all dark fibres), central cores, and increased adipose and connective tissue. B1 (B2 similar): type 1 fibre uniformity with uneven staining and small core-like areas. B3: type 1 fibre uniformity and multiple central and eccentric cores. C1: type 1 fibre uniformity. C2: abundant well defined central and eccentric cores with type 1 fibre uniformity. C3: type 1 fibre predominance, uneven stain, and small eccentric cores. D1: type uniformity, with cores in most fibres, a wide variability in fibre size, and excess adipose tissue.

Figure 2 Case B1, showing mild facial weakness with an inability to bury the eyelashes and early onset scoliosis.
A second maternal sister (table 1, C4) required scoliosis surgery at 14 years of age. On examination at 42 years of age, she was found to have facial weakness and mild weakness of the hip adductors.

Two maternal brothers were also examined and found to be clinically normal, although one of the brothers (C5) had a son with mild congenital foot deformities (not examined). The maternal grandmother was examined and found to be clinically normal.

Molecular genetic analysis undertaken in all of these individuals showed a Tyr4864Cys mutation in exon 102 of RYR in the two children (C1 and C2), their mother (C3), maternal aunt (C4), and clinically normal uncle (C5).

**Family 4**

A white schoolboy (table 1, D1) was referred at 11 years of age with a diagnosis of hereditary spastic paraplegia. The pregnancy was normal; he was born by Ventouse delivery, and no resuscitation was required. He was admitted to the neonatal unit at 1 day of age because of poor feeding. His mother informed us that at the time he was noted to be hypotonic and his legs appeared weak. He acquired head control at the normal time and sat independently at 10 months. Subsequently his motor skills were significantly delayed; he did not roll from supine to prone until 13 months and could not pull himself to stand until 16 months. He was unable to pull himself from a lying to sitting position until 18 months of age. At 3.5 years he walked with a Kaye walker and by 5 years he could walk only with the aid of two sticks; following a period of stability, his gait has become more laboured in recent years and he has not achieved independent ambulation. He underwent bilateral hip flexor releases at 4 years of age following delayed diagnosis of bilateral congenital hip dislocation. He had no family history of neuromuscular disease.

On examination, his vital capacity was normal at 2.3 litres. He had mild facial weakness and a high arched palate. He was hypotonic and had marked distal joint laxity. There were no joint contractures; he had bilateral scapular winging and a marked lumbar lordosis, but no scoliosis. He walked on his toes with difficulty using two walking sticks for support. His reflexes were present in the upper limbs with facilitation and absent in the lower limbs. His plantar responses were flexor. Sensation for all modalities was normal.

Power in the neck flexors, shoulder girdle muscles, and triceps was reduced (MRC 2–3/5). There was severe muscle weakness in the hip girdle muscles: flexion and abduction (MRC 2–3/5), extension and adduction (MRC 1/5). Power in the quadriceps was also reduced (MRC 4/5). Examination of both parents was normal.

Investigation showed a normal serum creatine kinase (40 iu/l) and 12 lead ECG. Hip x-rays confirmed high posterior dislocation of the femoral heads bilaterally; x-rays and MRI of the whole spine (undertaken at 5 years of age) were normal.

Muscle biopsy taken from the vastus lateralis, showed a variation in fibre size, fibre-type uniformity, and abundant central cores (fig 1, D).

Molecular genetic studies showed a heterozygous mutation in RYR1 in exon 101: 14582G>A replacing Arg4861 by His. Both parents were tested and found not to possess the mutation, thus representing a spontaneous de novo mutation in this child.

**DISCUSSION**

The 11 cases summarised in table 1 show a wide spectrum of phenotypic expression of CCD, ranging from apparently clinically normal (C5) to an inability to attain aid-free independent ambulation (D1). In each of these families the index cases were born with, or developed orthopaedic deformities, namely congenital dislocation of the hips and/or scoliosis. Facial weakness was a feature in 10 cases. Weakness involving the neck flexors and proximal limb muscles was present in all except two (A2 and C5). The upper limbs were stronger than the lower limbs in all cases. An interesting finding was that the children were more severely affected than their parents. This could be explained by a relative improvement in the condition occurring with advancing age; however, the possibility of anticipation cannot be excluded and long term follow up studies of affected families will be needed to resolve this question.

Respiratory insufficiency is not generally recognised as a feature of CCD and patient B2 might, therefore, be considered to be unusual; in conjunction with her muscle biopsy findings, this could have led to the incorrect diagnosis of mini-core myopathy, a condition with autosomal recessive inheritance, no linkage with MH, but an association with nocturnal hypoventilation. Examination of the mother suggested an autosomal dominant disorder in this family; her muscle biopsy and subsequent unambiguous DNA results confirmed the diagnosis of CCD.

The diagnosis of CCD could also have been missed in family C in which all of the cases were detected as a consequence of a suspected diagnosis in C1. However, the muscle biopsy taken from C1 showed no cores with histochemical stains, the only abnormality being type 1 fibre atrophy. Type 1 fibre uniformity in the absence of cores is a rare but recognised feature in CCD. Careful examination of the other family members together with a positive muscle biopsy in the mother and sibling led to the correct diagnosis, subsequently confirmed with molecular DNA analysis. The families described in this series highlight the importance of taking a detailed family history and examining the parents of “floppy infants”; CCD may be rare but it is not the only dominantly inherited neuromuscular disorder to present with floppy infant syndrome.

The DNA analysis in our cases, together with those reported recently, indicate a new hot spot for CCD in region 3 of the RYR1 gene, involving exons 95–103. Two of the amino acid substitutions reported here, Arg4861His and Arg4893Trp, have been assayed at the functional level. The RYR1 protein, previously considered to be muscle specific, is expressed at considerable level in B lymphocytes and lymphoblastoid cells. When calcium release via RYR1 was studied in B cells from CCD patients carrying either one of these mutations, a significant spontaneous release of Ca²⁺ was recorded in the absence of any RYR1 trigger. This may be interpreted as a permanent leakiness of the mutated RYR1, an observation which could well explain the chronic...
muscle weakness in CCD. It is therefore highly likely that these mutations are the genetic cause of the disease.

It is interesting to note that the most severely affected individual in this series (D1) was a spontaneous de novo mutation. Manzur et al reported a severe CCD phenotype in two children from unaffected parents and suggested the possibility of recessive inheritance; DNA analysis was not available to the authors at the time. Recently, however, DNA analysis has shown such sporadic cases to possess heterozygote mutations in the RYR1 gene, and has suggested that de novo mutations are relatively common among CCD cases.

Testing for MH involves an in vitro contracture test (IVCT) developed by the European and North American malignant hyperthermia groups. The test requires a large fresh muscle biopsy and is not easily performed in children. It is based on the tendency of MH muscle to be abnormally sensitive to stimuli that induce sarcoplasmic reticulum calcium release. The degree of muscle contraction is measured on flooding or gradually increasing concentrations of halothane or caffeine. In general, the correlation between the results of the two tests is good and the test shows a high sensitivity (99%) and specificity (93%). The results can, however, be equivocal and discrepancies, both false positive and false negative results, compared to DNA results have been reported. Patient C3 had a negative IVCT, but was subsequently shown to possess a mutation in the RYR1 gene. The contradictory nature of her results could represent a false negative IVCT, or alternatively, it could be that mutations in this part of the RYR1 gene are less likely to be associated with MH. None of our patients experienced a fulminant MH reaction although this would not necessarily exclude MH, since about one half of all MH reactions can be preceded by up to 13 previously uneventful general anaesthetics. It has been suggested that mild episodes of MH could go unnoticed, especially if anaesthesia is conducted without end tidal CO₂ monitoring. Prior to the diagnosis of CCD, two patients, A1 and C2, developed high fever immediately following general anaesthesia. Even though there was no evidence of MMR or metabolic disturbance in either case and although we did not have information relating to the perioperative monitoring, the possibility of mild MH cannot be completely excluded. Until further IVCT studies are undertaken in individuals with mutations in this region of the RYR1 gene, all confirmed cases of CCD should be considered to be at risk for MH.

In summary, CCD is thought to be rare but because of the variability in phenotypic expression and its non-progressive nature, it seems likely that as yet undiagnosed cases exist within the general population. Paediatricians and orthopaedic surgeons should be aware of the condition because of the genetic implications and the close association with MH, especially as new cases are likely to present to those specialty clinics. The diagnosis should be considered in any child or young adult presenting with weakness, hypotonia in infancy, and/or skeletal abnormalities. A careful family history and examination of the parents may be useful and should be done routinely for investigation of all floppy infants. The diagnosis of CCD can be confirmed by muscle biopsy (creatine kinase and electromyogram may be normal), but exceptions will include cases showing only type 1 fibre predominance, or multiple small cores resembling mini-core myopathy especially in the very young. The finding of a new hot spot for CCD at the C-terminal RYR1 receptor gene, with mutations occurring in exons 95–103, is likely to resolve these difficulties and improve diagnostic accuracy in the future.

**References**