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Muscular dystrophy with large mitochondria associated with mutations in the CHKB gene in three British patients: Extending the clinical and pathological phenotype

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Abstract

Three patients with CHKB deficient muscular dystrophy are described which broadens the previously described phenotype. Blood smear in one patient showed Jordans anomaly (vacuolated leukocytes). Gastrointestinal features occurred in two patients and there appeared to be acute deterioration with infection/general anaesthesia. Brain imaging showed no structural changes but brain magnetic resonance proton spectroscopy (MRS) demonstrated significant reduction in choline:*N*-acetyl aspartate and choline:creatine ratios in keeping with a general decrease in the amount of choline and phosphocholine-based substrate. Muscle pathology showed either myopathic or dystrophic features, uneven oxidative enzyme staining, COX deficient fibres and peripherally located large mitochondria. CHKB activity was reduced in all three patients and complex 1 activity was significantly reduced in one patient.

Keywords: Muscular dystrophy; Cardiomyopathy; Ichthyosis; Choline kinase beta; Mitochondria

1. Background

In 1998 four children presenting with a severe form of autosomal recessive congenital muscular dystrophy with unusual muscle biopsy features, showing large mitochondria with crystalline inclusions, were described [1]. Mutations in the gene encoding choline kinase beta (CHKB) in these and 11 other children were identified by the same group in 2011 [2]. Onset was in infancy or early childhood, learning difficulty and microcephaly were significant features, most never acquired expressive speech and some had seizures. Four patients had ichthyosiform skin changes, six had dilated cardiomyopathy and two had congenital cardiac anomaly. Serum creatine kinase (CK)

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varied from 190 iu/l to 2676 iu/l and notably varied within individuals on different occasions. Dysmorphic features were not described in this cohort, although more recently an affected child presenting with developmental delay and dysmorphic facial features including: a broad flat face with long philtrum, wide nasal bridge and low set ears was described [3].

Phospholipids and triglycerides are essential lipid molecules both are esters from glycerol and fatty acids. Abnormalities occurring in either metabolic pathway can lead to muscle disease. Phospholipids are the main component of plasma membranes while triglycerides function to facilitate long term energy storage [4–6]. Phosphatidyl choline, also known as lecithin, is highly abundant and is an essential component of the outer layer of plasma membranes. Phosphatidyl choline is also involved in circulating lipoproteins (LDL), sphyngomyelin production and it may play a role in stabilising chromatin structure [5]. Choline is ingested as an essential nutrient and once absorbed by cells is immediately phosphorylated to phosphocholine. There are three isoforms of the choline kinase enzyme: CHKA1, CHKA2 and CHKB which are involved in the phosphorylation of choline [5]. Mice that lack CHKA1 and CHKA2 die during embryogenesis [7], while mice with mutations in CHKB develop a neonatal onset 'rostro-caudal muscular dystrophy with hind limb deformity'. Studies of this mouse model suggest that membrane defects are the cause of the muscular dystrophy [8].

The combination of learning disability, ichthyosiform skin changes and myopathy is uncommon and can also be a feature of a multi-system triglyceride storage disorder (TAG) caused by a defect of intracellular TAG metabolism resulting in accumulation of lipid droplets in most tissues including: muscle, skin, leucocytes and bone marrow [9]. The condition neutral lipid storage disorder with ichthyosis (NLSDI) presents with myopathy in association with hepatomegaly, ophthalmic abnormalities (cataracts, nystagmus and squint), mental retardation, microcephaly, hearing loss, short stature and gastrointestinal involvement. Muscle biopsy shows extensive abnormal deposition of intracellular lipid droplets. Skin biopsy usually reveals lipid droplets in epidermal keratinocytes. It is caused by homozygous mutations in *ABHD5*, which encodes for a protein of the esterase/lipase/thioesterase subfamily [10,11]. A second form of neutral lipid storage disorder presents with an early onset myopathy, hepatomegaly and cardiomyopathy in association with diabetes but without ichthyosis and is caused by mutations in *PNPLA2* [12,13]. Muscle biopsy features are similar to NLSDI, although autophagic vacuoles can also be seen. A pathognomonic feature of both conditions is the finding of Jordans anomaly which refers to vacuolation of leukocytes and may also be seen in carriers [14].

In this report we describe clinical and pathological features of three patients with myopathy due to homozygous mutations in CHKB. The clinical phenotype was broader than previously described and one patient had clinical features suggestive of NLDSI.

2. Clinical material

Informed written consent was obtained from the parents and, where relevant, the patients. Patient two was included in the original cohort described by Mitsuhashi et al. [2] but is described here in more detail.

3. Patient one

A young female adult, who had always been viewed as a clumsy child, was followed for progressive limb girdle weakness of unknown origin. Her perinatal period and first year of life were unremarkable and she was walking by 13 months of age. Her mother first became concerned because of frequent falls around the time of her second birthday. She showed speech delay and was only speaking fluently by about 5 years of age, having received speech therapy from 3 years. At school she required learning support, but more significant learning difficulties became apparent from around 12 years of age. She never acquired the ability to run and always had difficulty climbing stairs. She never learned to ride a bicycle, even with stabilizers, and she was never able to hop or jump. Her clumsiness had always been viewed as more severe than could be accounted for by her muscle weakness, and her gross motor skills remained relatively stable during childhood. Fine motor function was reported to be impaired but improved to normal at around 12 years of age although she had become clinically obese (weight >90th centile). Her head circumference was proportionate to her height with no evidence of microcephaly.

On examination at 9 years, she had muscle weakness affecting hip flexion and shoulder flexion (MRC 4), she developed a Gowers' manoeuvre (8 s) and there was no evidence of facial weakness. She had no dysmorphic features. At 12 years of age weakness was restricted to the proximal limb muscles and her timed function tests were unchanged. During puberty, muscle weakness progressed considerably.

At 14 years shoulder girdle muscle weakness became more apparent and she could no longer comb her hair. Timed Gowers' manoeuvre had increased to 20 s (Fig. 1). By 18 years of age she could no longer climb stairs (hip muscles MRC power grade 2–3); quadriceps muscles were more severely affected than her hamstring muscles. She had calf hypertrophy, no scapular winging and apart from bilateral TA tightening there were no joint contractures. She did not develop a scoliosis. At the same age she developed cardiomyopathy with left ventricular dilatation and started treatment with beta blockers and angiotensin-converting enzyme inhibitors. Her skin appeared normal. Muscle MRI imaging at 22 years of