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Case report

A congenital myopathy with diaphragmatic weakness not linked to the SMARD1 locus

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Abstract

Severe diaphragmatic weakness in infancy is rare. Common causes include structural myopathies, neuromuscular transmission defects, or anterior horn cell dysfunction (spinal muscular atrophy with respiratory distress, SMARD1). We describe a form of infantile diaphragmatic weakness without mutations in the SMARD1 gene, in which pathological and clinical features differ from known conditions, and investigations suggest a myopathy. We identified seven cases in four families. All presented soon after birth with feeding and breathing difficulties, marked head lag, facial weakness, and preserved antigravity movements in the limbs, with arms weaker than legs. All had paradoxical breathing and paralysis of at least one hemi-diaphragm. All required gastrostomy feeding, and all became ventilator-dependent. Investigations included myopathic EMG, muscle biopsy showing myopathic changes, normal electrophysiology and no mutations in *SMN1* or *IGHMBP2*. These seven infants are affected by a myopathic condition clinically resembling SMARD1. However, its pathogenesis appears to be a myopathy affecting predominantly the diaphragm.

Keywords: Diaphragmatic weakness; Congenital myopathy; Respiratory failure

1. Introduction

Diaphragmatic weakness presents in infants or older children with life-threatening respiratory distress, can be suspected on clinical grounds by paradoxical abdominal movements during inspiration with in-drawing of the diaphragm, and can be confirmed by radiological studies. The differential diagnosis of neonatal diaphragmatic weakness includes acquired phrenic nerve injury and the following congenital neuromuscular diseases: spinal muscular atrophy with respiratory distress (SMARD1), congenital myopathies with prominent respiratory involvement (nemaline and X-linked myotubular myopathies), congenital myotonic dystrophy, and infantile myasthenia [1,2]. Autosomal recessive SMARD1 is also characterised by distal muscle weakness and by fatty pads on fingers [3]. In contrast to classic SMA in which infants become floppy before they suffer from respiratory distress, SMARD1 infants manifest in reverse order in which respiratory distress is frequently the initial

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feature. SMARD1 results from mutations in the *IGHMBP2* gene on chromosome 11q13.2. Considerable phenotypic and genetic heterogeneity has been demonstrated [3–7]. Moreover, conditions with presentations similar to SMARD1 have been described which are not linked to the SMARD1 locus [1]. We present seven children from four families with a very similar clinical presentation to SMARD1 but no mutations in the coding region of the SMARD1 gene. Investigations suggested that the diaphragmatic weakness was associated with a myopathy. This appears to be a congenital myopathy mainly characterised by diaphragmatic weakness.

2. Cases

We report seven cases from four families. Family 1 are Qatari; family 2 are Sri Lankan Tamils, family 3 are Italian Caucasian, and family 4 are English Caucasian.

2.1. Family 1 (cases 1 and 2)

These are the two female children of consanguineous (first cousin) parents with previous unaffected daughters. The first affected child was born by normal full term delivery after a pregnancy complicated by decreased fetal movements and growth retardation (birth weight <3rd centile). At birth she required resuscitation due to poor respiratory effort. Throughout the neonatal period she was tachypnoeic and had feeding difficulties necessitating nasogastric tube feeds. On examination she had a narrow bifrontal diameter, facial weakness, long fingers with finger flexor tightness, generalised thin muscles and areflexia. She walked with a rollator at 18 months of age. Her cognitive development was normal. At this time she developed an acute viral respiratory illness which progressed to respiratory failure. Chest radiography showed paralysis of the right hemi-diaphragm and this was confirmed on ultrasonography. She became ventilator-dependent via tracheostomy and underwent a gastrostomy insertion. Subsequently she developed normal speech limited by the tracheostomy and could manage up to 1 h off the ventilator. She developed severe scoliosis at the age of 4 years, with a Cobb angle of 80°. She had scoliosis surgery at the age of 6 years and died at the age of 9 years following a respiratory tract infection.

Investigations revealed a myopathic EMG with normal repetitive nerve stimulation studies and nerve conduction velocities. Echocardiogram, serum lactate, pyruvate, amino, and organic acids were all normal. Muscle biopsy from her left deltoid showed mild variability in fibre size (Fig. 1A). A subsequent biopsy of her quadriceps showed mild variability in fibre size with no rods or ragged red fibres although there was some evidence of increased lipid staining in type 1 fibres.

Case 2, her younger sister, now 30 months old, was born by elective Caesarean section at 36 weeks due to placental insufficiency (birth weight 3rd centile). No resuscitation was required but she was admitted to the special care unit for one week due to respiratory distress and feeding difficulties. She had a cleft palate and was hypotonic with marked head lag but had antigravity limb movements.

At the age of 6 months she was failing to thrive with a weight below the 0.4th centile. She developed a respiratory infection and became ventilator-dependent via tracheostomy from the age of 7 months. She sat with support at the age of 13 months but has not achieved any additional motor milestones. Her cognitive development is normal. She can tolerate up to 10 min off the ventilator.

On examination at 13 months her weight was <0.4th centile, height 9th centile. She had generalised thin musculature with pectus excavatum and paradoxical breathing when lying down. She appeared alert but had facial weakness and a narrow bifrontal diameter. She had full extra-ocular movements and no tongue fasciculation or myotonia. Bilateral dimpling over the extensor surfaces of the elbows suggested in utero inactivity, also confirmed by the presence of single palmar creases and poorly developed dermatoglyphics on the soles.

There was axial weakness and she was unable to sit unsupported. She had antigravity power in her proximal limbs with upper limbs weaker than lower, but marked weakness distally. Reflexes were not elicitable. Her fine motor skills were age appropriate.

Investigations: serum CK (75 IU/l), echocardiogram, and nerve conduction velocities and single fibre EMG studies were normal, while her EMG was myopathic. Chest X-ray showed paralysis of the right hemi-diaphragm. Muscle biopsy (quadriceps) showed minimal fibre size variability with no rods or ragged red fibres, normal oxidative enzyme and lipid staining. Respiratory chain enzyme studies were normal. She had no response to a trial of neostigmine. SMN1 and SMARD1 mutation analysis were normal.

2.2. Family 2 (cases 3 and 4)

These two siblings were born to non-consanguineous parents of Sri Lankan Tamil origin with no other family history.

Case 3, the elder daughter was delivered at term by Caesarean section following a pregnancy complicated by reduced fetal movements and breech presentation. Her birth weight was on the 50th centile. At birth she required suction and was noted to be floppy with contractures of her finger flexors. She had evidence of bulbar dysfunction with excessive secretions and feeding difficulties and required nasogastric feeding. Despite this she failed to thrive and coughed with feeds. At 5 months