Infantile spinal muscular atrophy variant with congenital fractures in a female neonate: evidence for autosomal recessive inheritance

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We read with great interest the article published in this journal in 1991 by Borochowitz *et al*,[1] describing a new lethal syndrome consisting of infantile spinal muscular atrophy (SMA) and multiple congenital bone fractures in two sibs. Recently, another infant with a form of SMA and congenital fractures was reported by Kelly *et al*,[2] thus validating the suggestion of a distinct and rare form of SMA associated with congenital bone fractures. Autosomal recessive inheritance was suggested in the original report,[1] but no history of consanguinity was noted in the second.[2] X linked inheritance could, however, not be excluded since these three affected infants were male. Greenberg *et al*[3] reported four cases with infantile SMA, neonatal death, congenital joint contractures, and the presence of bone fractures in three of the four cases; these cases seem clinically to be similar to the originally reported cases,[1] but the pedigree in this report was consistent with X linked recessive inheritance and the gene in this family was mapped to Xp11.3-q11.2.[4]

Here, we report on a female neonate with a severe, acute, lethal form of SMA and congenital bone fractures, thus excluding X linked inheritance. Furthermore, since this girl was born to first cousin parents, this suggests autosomal recessive inheritance in this rare variant of SMA type 1 with congenital fractures.

CASE REPORT

The girl was born to a 35 year old, G5 P5 mother and a 41 year old father. The parents, of Moroccan origin, were consanguineous, as were the maternal grandparents. They had one healthy son and two healthy daughters, and another son who had died at the age of 3 months in Morocco. The pregnancy was not medically followed but reported by the mother as uneventful. Delivery, recorded as normal by both gynaecologist and mother, occurred spontaneously at 40 weeks of gestation with cephalic presentation. The Apgar scores were 3, 4, and 5 at one, five, and 10 minutes, respectively. Birth weight and length were normal (3700 g, 51 cm, respectively). She was severely hypotonic and was intubated and ventilated as soon as the paediatrician arrived (10 minutes after birth). A 4/6 pluriorificial heart murmur was noted. She was immediately transferred to the University Children's Hospital for ventilatory support and further evaluation. An abnormal position of the upper and lower limbs (in abduction) with swelling of the left upper arm and the left thigh and pain on mobilisation of the limbs were noted. She was very hypotonic and showed no spontaneous movements. Tendon reflexes were absent. She also had a prominent forehead, generalised oedema, an apparent accumulation of fat in the lower limbs, generalised hypertrichosis, a swollen abdomen, and camptodactyly of the fingers and toes (fig 1). Her sclerae were not blue. Head circumference could initially not be measured because of the presence of an important haematoma of the skull, but at the age of 13 days, it was 37.5 cm (>90th centile). Radiographs showed a mid-diaphyseal fracture of the left humerus and of the left femur. Ossification was normal. There were, however, abnormally straight femora with modelling defect, abnormally dense metaphyses of the lower limbs, dislocated hips, a

Figure 1   Clinical photograph of the proband.

thickening of subcutaneous tissue with loss of muscle density, and an impression of marked infiltration by fat (fig 2A, B). This fatty infiltration, confirmed by ultrasound, was also visible in the abdominal region extending into the mid-thoracic region (fig 2C). The ribs were thin and the skull was normal (no Wormian bones) except for the presence of a large parietal haematoma. Control *x* rays of the left femur and humerus at the age of 3 weeks showed the formation of a normal and large callus.

Nerve conduction studies, performed on the 13th day of life, showed normal sensory and motor values. Electromyography of the biceps brachii, pectoralis major, and tibialis anterior muscles, done at 13 days, showed the presence of spontaneous fibrillations and positive sharp waves at rest and reduced interference pattern during contraction, changes compatible with a neurogenic disorder. The EMG of muscles innervated by cranial nerves (M orbicularis oris, M genioglossus) was normal.

A muscle biopsy from the quadriceps, performed at 16 days, showed almost exclusively atrophic fibres, with a small cluster of large fibres in only one area. The larger fibres were mostly of type 1; the atrophic fibres were of both histochemical types. The range of diameter fluctuations was 4-20 μm. There was no evidence of necrosis with myophagia. In order to ascertain the diagnosis, a second biopsy was performed at 32 days from the thenar muscle (fig 3), in a still moving hand, and confirmed the pronounced fibre size variation (diameters varied from 5 to 10 μm for type 2 and from 5 to 40 μm for type 1), but showed

Figure 2 X rays of the proband showing (A) the upper limbs, with mid-diaphyseal fracture of the left humerus; (B) the lower limbs, with diaphyseal fracture of the left femur, abnormally straight femora with modelling defect, abnormally dense metaphyses, dislocated hips, a thickening of subcutaneous tissue with loss of muscle density, and an impression of marked infiltration by fat; (C) a marked fatty infiltration is also visible in the abdominal region extending into the mid-thoracic region; the ribs are thin.

less atrophy and more clumps of large fibres in comparison with the more proximal muscle.

Immunocytochemistry showed no deficit of dystrophin or merosin. There was no evidence of a mitochondrial disease. Electron microscopic findings showed a disorganised myofibrillar network in some fibres. The muscle biopsy findings were thus compatible with a severe and acute form of SMA.

Blood chemistry tests including calcium, phosphorus, alkaline phosphatase, electrolytes, viral serology, TORCH, and metabolic screening (including amino acids and very long chain fatty acids) were all within normal limits except for severe anaemia resulting from bleeding from the fractures and requiring red blood cell transfusions, severe neonatal asphyxia, and at birth a slightly raised CK level which normalised completely at the age of 25 days. Ultrasonography of the heart showed persistence of the arterial canal, moderate pulmonary hypertension, and a small ventricular septal defect. A haemodynamic exploration by cardiac catheterisation excluded a vascular malformation. Brain magnetic resonance imaging showed minor cortical atrophy and a slight delay of myelinisation. A CT scan confirmed the absence of intracerebral calcifications. Other examinations including eye fundus, ophthalmological examination, renal ultrasounds,

and microscopic examination of the skin were normal. Her karyotype on high resolution banding was normal, 46,XX. DNA studies on a blood sample showed the absence of homozygosity for a deletion of exons 7 and 8 of the *SMNt* gene; congenital myotonic dystrophy or Steinert disease could also be excluded. Further molecular studies in the proband with 5q markers excluded homozygosity for the *SMN* region. Flanking markers used were D5S823 at less than 1 cM on the proximal side and D5S557 at less than 1 cM on the distal side. A hemizygous deletion of this region was also excluded by quantitative analysis of *SMN* by competitive PCR as described.[5] Point mutation analysis of the *SMN1* gene is continuing (HS).

During her stay in the neonatal unit, the proband continued to be dependent on a ventilator, furthermore requiring increasing ventilatory conditions. She had many bronchopulmonary infections. She showed no spontaneous movements, except some infrequent small movements of her fingers and face, even with treatment with strong analgesic drugs and even after healing of her fractures. There was, however, good visual contact. She developed decubitus wounds and had persistent generalised oedema. Parenteral feeding was needed throughout her life; enteral feeding by tube was tried at the
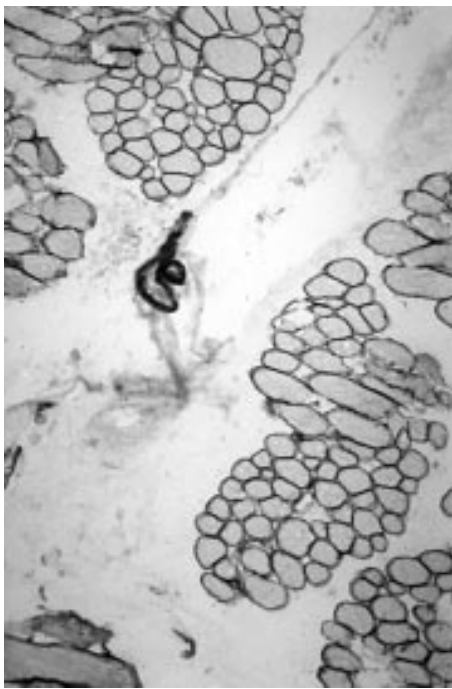
Figure 3 Muscle biopsy specimen of the thenar muscle of the proband at the age of 32 days, performed in order to ascertain the diagnosis, showed atrophic and hypertrophic fibres and confirmed the pronounced fibre size variation. It showed less atrophy and more clumps of large fibres, in comparison with the more proximal muscle (Spectrin, ×330).

age of 6 days but had to be stopped after three days because of ventilatory problems. She finally died at the age of 34 days from a cardiorespiratory arrest owing to massive bronchopneumonia. The family would not authorise a necropsy.

DISCUSSION

This female infant presented with a severe, acute form of SMA, confirmed by neurophysiological and muscle biopsy findings, with prenatal onset and early lethal outcome, together with congenital bone fractures, camptodactyly, bilateral hip dislocation, and a heart murmur resulting from persistence of the arterial canal, moderate pulmonary hypertension, and a small VSD. A distinct and very rare form of SMA associated with congenital bone fractures was proposed recently.[2] Three infants, similar to our case, have been reported so far.[1][2] Similarities between these three infants and our proband are a severe infantile form of SMA, profound hypotonia requiring artificial ventilation at birth, bone fractures (of the humerus/femur), joint contractures, normal sclerae, severe generalised oedema, and early death (all died before the age of 3½ months). Normal ossification and thin ribs, as present in the proband, have also been described in both originally described cases.[1] Additional findings in the proband are the presence of bilateral hip dislocation, abnormally straight femora with modelling defect, hypertrichosis, and a congenital heart defect. The association of SMA and hip dislocation, SMA and abnormally straight femora with modelling defect, and the association of SMA and hypertrichosis have not been described previously. To exclude the presence of abnormal collagen bundles, a skin biopsy was performed that did not show any alteration in collagen or elastin fibres. The hypertrichosis present in the proband could be familial. The association of SMA and congenital heart defect is usually seen as coincidental, but three sibs with SMA type 1 combined with atrial septal defect have been reported.[6] One of these sibs was a boy described as

having a long bone fracture, arthrogryposis, distal oedema, and very early death from respiratory failure. The second and third sib, both girls, did not have long bone fractures, but presented with profound hypotonia at birth requiring artificial ventilation, early death owing to respiratory failure/bronchopneumonia, and other malformations, including valvular aortic stenosis with hypertrophic right ventricle (sib 2) and prenatal pleural effusion and brain malformation (sib 3). We think that the clinical features of these sibs, especially sib 1, resemble those of the proband and could belong to the same SMA variant we have described and reviewed here. A variable expression of this SMA variant seems probable. Additional cases with SMA and congenital fractures are needed for further delineation of the clinical phenotype. We suggest that the association of a congenital heart defect with SMA should prompt a search for additional anomalies.

In the differential diagnosis, a neonatal form of adrenoleucodystrophy[7][8] has been excluded.

Concerning the molecular studies, it is well known that homozygous deletions of exons 7 and 8 within the telomeric copy of the survival motor neurone (*SMN*) gene are detectable in about 95% of patients with early onset SMA.[9] It was not present in the proband or in the infant reported by Kelly *et al*.[2] Molecular studies were not reported in the two originally described cases.[1] We propose that all SMA patients, including variants, should be carefully investigated for *SMN* deletion because deletions of the *SMN* gene have also been shown in various "atypical" SMA patients with congenital joint contractures and in SMA patients with congenital heart disease.[10][11] Also, patients with severe SMA type 1, presenting at birth with asphyxia and severe weakness, characterising a new SMA type 0,[12] similar to our patient, have been reported with deletions of the telomeric survival motor neurone gene.[13] In our proband, we could exclude homozygosity for the *SMN* region (5q13) with DNA markers flanking the SMA locus, and we could also exclude a hemizygous deletion of this region. This supports non-linkage of SMA to chromosome 5 in this family, as was the case in a consanguineous family with two affected male sibs with SMA and arthrogryposis.[14] The probability of finding a *SMN* compound heterozygous genotype of two point mutations in this region is very low. However, further studies are continuing to rule out this possibility.

It seems probable that this variant with congenital fractures might be more common than the description of the three cases reported so far.[1][2] There are, indeed, the cases published by Möller *et al*,[6] discussed above, and the letter by Garcia-Alix *et al*,[15] briefly reporting six infants who were similar to the two originally described patients,[1] except that they had hypomineralised long bones. Osteopenia in SMA patients could occur secondary to the decreased load placed on the fetal skeleton owing to decreased fetal movement.

In conclusion, autosomal recessive inheritance should be considered in a rare and severe acute form of congenital SMA type 1, requiring early artificial ventilation and with early lethal outcome, and associated with congenital bone fractures, congenital joint contractures, generalised oedema, and sometimes also cardiopathy. Variable expression of this SMA variant seems probable. Since the primary defect is so far unknown, additional cases are needed to delineate the clinical spectrum further and to confirm the probability that this SMA variant is not linked to 5q.

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