Neonatal Spinal Muscular Atrophy With Bone Fractures and Heart Defect

ABSTRACT

We present an infant girl with severe generalized weakness, multiple bone fractures, and a heart defect. She needed mechanical ventilation from birth. Radiographs showed mid-diaphyseal fractures of both humeri and the right femur, as well as generalized osteopenia. Electroneuromyography showed spontaneous fibrillations at rest, with no active movements. Motor response to a stimulus could not be registered. A systolic heart murmur was detected; echocardiography showed a large atrial septal defect and an additional membrane in the left atrium. DNA analysis confirmed the diagnosis of spinal muscular atrophy on the third day of life. Histology of the muscle showed both hypertrophic and atrophic fibers. Degenerating swollen neurons were found in the ventral horns of the spinal cord and in the mesencephalic red nucleus, which have not been described before. Humeral bone showed only partly formed cortical bone. The spectrum of spinal muscular atrophy is very diverse, and atypical clinical findings do not always rule out chromosome 5q spinal muscular atrophy. The SMN1 gene should still be investigated. (J Child Neurol 2007;22:000–000; DOI 10.2310/7010.2006.00248).

Neonatal (type I) spinal muscular atrophy represents a severe autosomal recessive disorder leading to progressive symmetric muscular atrophy of limb and trunk muscles. This neuromuscular disease is the second most common lethal autosomal recessive disorder, with an overall incidence of 1 in 10,000 live births. Ninety-six percent of spinal muscular atrophy type I cases are caused by deletions or mutations in the survival of the motor neuron gene (SMN1) on chromosome 5q11.2-q13. Several atypical spinal muscular atrophy forms (spinal muscular atrophy plus types) have been described: spinal muscular atrophy with joint contractures, bone fractures, congenital heart defects, and respiratory distress. These forms are often not linked to the SMN1 gene region. We present a newborn girl with severe generalized hypotonia and weakness, multiple fractures, a heart defect, and deletion of the SMN1 gene.

Case Report

The patient was the first sibling of a nonconsanguineous healthy couple. The father had healthy children from a previous marriage. There was no history of neuromuscular or any other neurologic disorders in the parents' families. During the first half of the pregnancy, ureaplasmosis was treated repeatedly. Amniocentesis was performed at 17 weeks of gestation because of increased fetal nuchal translucency found on ultrasonography and a positive triple test. The fetal karyotype was normal (46,XX). Two weeks before delivery, the mother detected a significant decrease in fetal movements.

A baby girl was born at 38 weeks of gestation by cesarean section owing to breech presentation and the mother's narrow pelvis. A cracking sound of fracturing bones was reported during the delivery of the child, although no powerful manipulations were used. Her birthweight was 2850 g. The Apgar scores were 1, 4, and 6 at the first, fifth, and tenth minutes of life. She needed mechanical ventilation immediately after birth and was transported to the neonatal intensive care unit of the Children's Hospital of Tartu University Hospital.

Physical examination of the newborn revealed severe generalized muscle hypotonia and weakness. She was lying in a froglike position, with the legs abducted and laterally rotated, flexed from the hips and knees, and the arms flexed and abducted. No limb deformities or joint contractures were present; instead, joint laxity was noted. Tendon reflexes were absent. She showed no spontaneous movements, and there was no active response to painful stimulus at first. On the third day, minimal movement in the toes and facial grimace as a response to stimulus were noticed. Her chest was small and asymmetric, with the left side of the body slightly smaller and wider at the level of the lower ribs. There was no visible chest movement during breaths. She was conscious and opened her eyes; sclerae were of a normal color. There were signs of bulbar paralysis. Fasciculations of the tongue could be seen. A systolic heart murmur was detected at the first examination.

Because of the tongue fasciculations, severe weakness and hypotonia spinal muscular atrophy I were suspected. DNA analysis confirmed the diagnosis on the third day of life. Owing to the brittle bones and fractures, osteogenesis imperfecta was also suspected. She died at the age of 20 days owing to respiratory failure. The mother gave permission for a postmortem examination.

Laboratory and Neuroradiologic Studies

Mid-diaphyseal bilateral humeral and right femoral fractures were seen on radiographs taken on the first day of life. All were fresh fractures without any periosteal reaction or callus formation. There were no signs of former fractures or rib or skull deformities. Radiographs also showed generalized osteopenia: thin cortical bone and the difference between cortical and trabecular bone was not very clear (Figure 1). Control radiographs on day 15 showed adequate callus formation at all three fracture sites. No new fractures were seen, although subchondral osteoporosis at the proximal metaphyseal area of the fibula and tibia had developed. The findings were not characteristic of osteogenesis imperfecta.

A brain computed tomographic scan on the first day of life showed normal-sized symmetric ventricles. The cerebral cortical sulci were not fully developed, and the white-matter density was slightly lower than normal. These findings were explained by the immaturity of the brain. There were no signs of trauma to the cervical spinal cord.

Only the child's left leg was suitable for electromyography, done on day 8. The findings supported the diagnosis of spinal muscular atrophy. Spontaneous fibrillations were seen at rest, with no active movements. The tibial and peroneal nerve motor responses to a stimulus could not be registered. Sensory responses were unobtainable.

Echocardiography showed a large atrial septal defect (~10 mm) and an additional membrane in the left atrium. The ductus arteriosus was open, leading to hypervolemia in the pulmonary circulation.

Calcium and phosphate levels were within normal limits, 1.97 mmol/L (normal 1.8–2.8 mmol/L) and 2.66 mmol/L (normal 1.6–3.1 mmol/L), respectively. The same was true with the blood serum creatine kinase level and lactate dehydrogenase values, 370 U/L (normal < 652 U/L) and 1030 U/L (normal < 1732 U/L), respectively. Specific bone metabolism markers—osteocalcin and alkaline phosphatase as bone formation markers and deoxyypyridinoline as a bone resorption marker—were also investigated. The activity of bone-specific alkaline phosphatase was two to three times below that of a normal newborn; however, the alkaline phosphatase isoenzyme ratio was normal (98% bone isoenzyme). The activity of osteocalcin was approximately two times higher (27.9 ng/mL), the DPD/creatinine index in the urine was two to three times higher (174 nmol/mmol) than in the normal newborn. Metabolic screening tests were negative. Polymerase chain reaction and enzyme restriction analysis of...
the DNA samples showed homozygous deletion of the SMN1 gene exons 7 and 8.

**Autopsy Findings**

Histology of the muscle showed hypertrophy of both fiber types and small rounded atrophic fibers between the hypertrophic fibers (Figure 2A). Degenerating swollen neurons with central chromatolysis and eosinophilic cytoplasm among the normal motoneurons were found in the ventral horns of the spinal cord (Figure 2B), evident particularly in the cervical segments. Two thirds of the neurons of the mesencephalic red nucleus were degenerated (Figure 2C). Histologic analysis of the humeral bone showed only partly formed cortical bone, present as a compact zone in the deeper layers. Superficial bone layers, beneath the periosteum, were of the trabecular type, and in two thirds of the circumference, these trabeculae extend to the central part of the bone without forming any compacta (Figure 2D). In the most superficial layers beneath the periosteal fibrous tissue, trabeculae were surrounded by extensive numbers of osteoblasts (evidence of intensive bone synthesis in this area), and only occasional osteoclasts were found (Figure 2E). In the areas where compacta was forming, only single attenuated osteoblastic cells could be seen. Most of the cells present here were osteoclasts, forming small clusters in some areas (evidence of active bone remodeling in this area) (Figure 2F). These morphologic changes represent extensive periosteal new bone formation following trauma (fracture).

**Discussion**

We presented a girl with long bone fractures from birth and typical clinical features of type I spinal muscular atrophy with prenatal onset and an early lethal outcome. Several cases of spinal muscular atrophy with bone fractures and joint contractures have been published in the literature. A case without contractures, similar to our patient, has also been described. Additional findings in our proband were nuchal translucency, an atrial septal defect, and loss of neurons in the mesencephalic red nucleus.

The development of contractures, as well as fragile bones, fractures, and osteopenia, in patients with spinal muscular atrophy has been associated with the absence of muscular strength and decreased fetal movements during pregnancy. Movements are reduced owing to the decreased function and number of motoneurons in the spinal cord already in utero.

It is possible that in our case, the time interval for the development of contractures was too short as the decrease in fetal movements was
noticed only a couple of weeks before birth. At the same time, changes in the bone structure were already present that made them vulnerable and easy to fracture.\textsuperscript{2}

Kelly et al and Courtens et al found in their cases that the serum chemistry values were within the normal range, including the level of total alkaline phosphatase.\textsuperscript{5,6} We found low bone formation and mineralization activity markers, as well as increased bone resorption activity. The rise in the activity of the bone resorption markers can be explained by the inactivity of the child, but in that case, an increase in calcium excretion in the urine should also be expected.

The first five patients described in the literature were all males. Our patient was female, as was the newborn described by Courtens et al.\textsuperscript{6} In the latter case, the parents were first cousins, but in our case, no consanguinity was reported. Molecular studies were not reported in the two cases by Borochowitz et al.\textsuperscript{4} In the patients with spinal muscular atrophy described by Greenberg et al with joint contractures and bone fractures, the gene was mapped to chromosome Xp11.3-q11.2.\textsuperscript{10,11} The SMN1 gene deletion was found in one case only.\textsuperscript{7} All other reports show no homozygous deletion or point mutations in the SMN1 gene.\textsuperscript{5,6,8,12} Our proband had the SMN1 gene exons 7 and 8 homozygously deleted, confirming the diagnosis of spinal muscular atrophy and suggesting a link between typical and different variants.

The association of spinal muscular atrophy and congenital heart defect is usually considered coincidental. Atrial and ventricular septal defects have most commonly been described in association with spinal muscular atrophy.\textsuperscript{6,13,14} Atrial septal defect is a common congenital malformation that is part of many autosomal recessive syndromes, as well as chromosomal abnormalities. Our patient had normal chromosomes, and no other reason for the septal defect could be found.

Congenital heart defect, bone fractures, and arthrogryposis are considered exclusion criteria of spinal muscular atrophy. These spinal muscular atrophy plus types have been accepted as separate entities not related to the spinal muscular atrophy chromosome 5q13 region.\textsuperscript{3} But some cases of spinal muscular atrophy I associated with these findings and the SMN1 gene mutation have been described.

In addition to the loss of spinal ventral and medullary motoneurons, neuropathology in our case revealed degeneration and loss of neurons of the mesencephalic red nucleus. Neuronal degeneration in a red nucleus has not been reported before in association with spinal muscular atrophy and obviously represents a secondary phenomenon rather than a primary spinal muscular atrophy-related event, evolving as a result of retrograde axonal degeneration owing to the damage to and loss of spinal ventral motoneurons. Neuronal loss in the red nucleus evoked by retrograde axonal degeneration has been described in spinal cord injury, as well as under experimental conditions after cervical axotomy of the rubrospinal tract.\textsuperscript{15,16} Kwon and coauthors observed significant atrophy of rubospinal neurons 2 months after injury in experimental animals, indicating that a certain time period is necessary to develop such damage.\textsuperscript{15} These data indirectly point to the possible prenatal onset of spinal muscular atrophy in the case described by us. It is possible that the changes in the red nucleus were partly responsible for the severe course of the disease in our patient.

Increased nuchal translucency is often associated with chromosomal abnormalities. Nuchal translucency in association with spinal muscular atrophy has also been reported.\textsuperscript{17} In our case, the karyotype of the patient was normal (46,XX). Increased nuchal translucency, together with a normal karyotype, could be an early finding of spinal muscular atrophy and should be a reason for further prenatal investigation.

In conclusion, atypical clinical findings do not always rule out chromosome 5q spinal muscular atrophy. The spectrum of spinal muscular atrophy is diverse, and the SMN1 gene should still be investigated when a child has spinal muscular atrophy with atypical clinical findings. The effects of the changes in the mesencephalic red nucleus on disease severity also need further investigation.

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References


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