Orthopaedic Complications of Myotubular Myopathy

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Abstract: Myotubular myopathy is a rare genetic disease that was uniformly fatal until recent developments in long-term ventilation. Today, however, it is not unusual for a patient to live into the second decade. The orthopaedic manifestations of the disease have not been reported in the literature. We present our experience with complications related to the spine and extremities in a series of 4 patients with this disease who have survived beyond early childhood.

Key Words: myotubular myopathy, limb deformity, spine deformity, joint contracture

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Myotubular myopathy is a rare disorder. The main pathological feature is the presence of large central nuclei in hypotrophic muscle fibers, thus resembling neonatal muscle fibers.[1] The disease is alternately referred to as *centronuclear myopathy* for this reason. Spiro et al[2] documented the first case in 1966. Since then, the gene has been mapped, the mutations sequenced, and the protein gene product studied.

The term *myotubular myopathy* covers a spectrum of disorders and genetic abnormalities with the commonality of having the nucleus of the myocyte located centrally rather than the normal peripheral location. Micropathology reveals a predominance of small type I muscle fibers, evidence of immature myotubes. Two theories on which cellular mechanism failed exist. The first postulates that the diseased tissues represent a failure of the nucleus to migrate peripherally.[3] The second postulates a failure of myogenesis.[4] The genetic mode of inheritance can be X-linked recessive or, more rarely, autosomal recessive or dominant. The X-linked form is caused by a mutation in the gene for myotubularin.[3] The exact role of myotubularin is unknown. Its gene has been mapped to the Xq28 region of the genome.[5] A variety of mutations in the gene have been identified; the severity of the mutation seems to correlate with the severity of the phenotype.[6]

Clinical manifestations of this disease include a large head with narrow elongated facies, cryptorchidism, small anterior fontanelle, hydrocephalus, hypotonia, areflexia, and large birth length and skull circumference.[7] This condition was almost always fatal in the first few months to years of life. However, with the advent of long-term mechanical ventilation, it is now possible for these children to live well into their childhood years and beyond. This presents a heretofore-unseen challenge for the orthopaedist who must manage the associated musculoskeletal complications of this disease. We present our experience in diagnosing and managing the orthopaedic manifestations of myotubular myopathy in a series of 4 patients.

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METHODS

We conducted a review of the medical records of all patients at our medical center in the past 12 years who were given a diagnosis of myotubular myopathy or centronuclear myopathy. Four patients were identified. Data sources include a review of their radiographs and medical records. Three of the 4 patients were diagnosed with myotubular myopathy by muscle biopsy shortly after birth. The fourth is the younger sibling of another patient in the study who displayed similar characteristics and was thus presumptively diagnosed with the disease.

The patients are all at least partially dependent on ventilators. The average start of ventilation is at the age of 15 months. The children all had tracheotomies placed when this occurred. Two of the 4 are fully dependent on ventilator. One is ventilated at night only, and the other can be off the ventilator for 30 to 60 min/d. When undergoing surgery, they generally are fully ventilated during the perioperative period.

One patient died at 10 years from pneumonia. It was more than 30 days after his most recent surgery when he died.

RESULTS

Our study has revealed some common manifestations among patients with myotubular myopathy. Our patients demonstrated the elongated facies typical of this disease (Fig. 1). We noted altered bone morphology on radiograph. Children with myotubular myopathy are likely to have many fractures particularly in the metaphyseal region of long bones. Also, an above-normal birth length was noted. These patients are prone to have flexion contractures and hip dysplasia. Lastly, we encountered several instances of axial skeletal deformity requiring surgery for spinal stabilization (Table 1).

The patients have characteristic bone morphology of long and thin long bones with normal cortical widths (Fig. 2). This morphology is present in all 4 cases in all extremities radiographed. This morphology likely contributes to the large number of fractures encountered in these patients. Metaphyseal fractures, particularly of the femora, are common (Fig. 3). Our patients sustained 0 to 9 fractures. Ten of 14 fractures were located in the metaphyseal region of long bones. These fractures were amenable to nonoperative

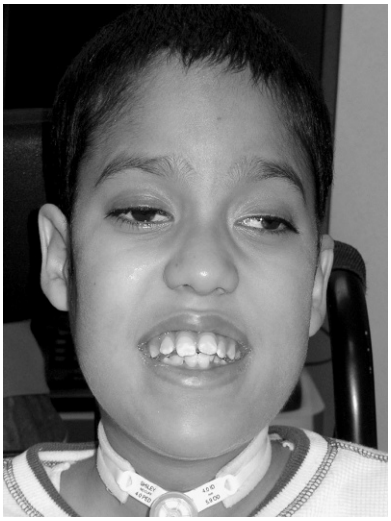

FIGURE 1. This patient demonstrates the elongated facial features typical of this disease.

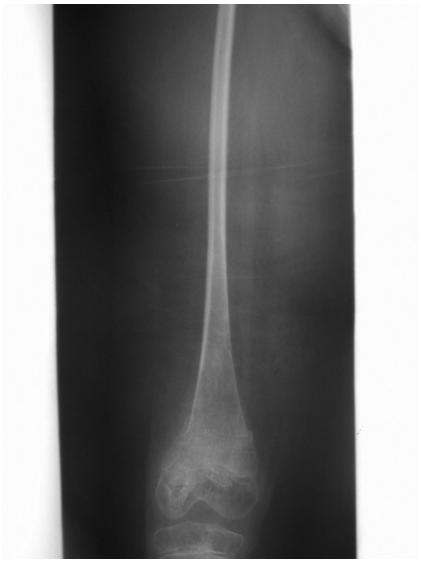

FIGURE 2. Lower extremity in a patient with myotubular myopathy demonstrating gracile bones.

treatment. Fracture healing did not seem to be altered. All 14 of the fractures encountered healed in a normal time frame. There was 1 refracture. None of the fractures were open injuries, nor did any require operative intervention.

Unlike in myelomeningocele, these patients did not develop any skin ulcers during their fracture immobilization. This may be related to the fact that sensation is maintained or because of the generous padding, frequent cast changes, and/or the use of removable splints.

As has been previously reported, these patients are generally in the upper centiles for height/length.[1,8] We found this to be true in our population as well. The average birth length was 21 in, which is in the 90th centile for birth length. Three of the 4 patients were above average in birth length; however, only 1 of the 4 was above average in birth weight.

Myotubular myopathy leads to decreased mobility, wheelchair confinement, and, inevitably, joint contractures. Three of the 4 patients had knee flexion contractures. Two patients developed bilateral ankle equinus deformity, one of whom required surgical releases despite conservative management. Bilateral elbow contractures were noted in 1 patient. All contractures and deformities were bilateral and symmetric with the exception of 1 patient who had a left-sided shoulder subluxation.

TABLE 1. Orthopaedic Complications of Myotubular Myopathy

Patient	No. Fractures	Age at Diagnosis	Age at Ventilation	Orthopaedic Problems
1	9	12 d	7 mo	Fractures
				Scoliosis
2	3	1 mo	Birth	Fractures
				Hip subluxation
				Shoulder subluxation
				Rigid lordosis
				Scoliosis
3	0	6 d	3 yrs	Joint contractures
4	3	8 d	18 mo	Fractures
				Scoliosis

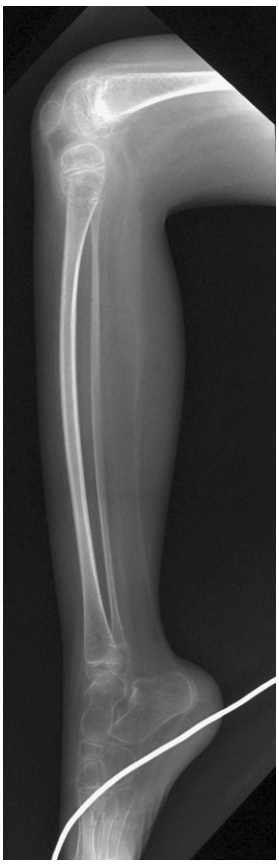

FIGURE 3. Distal femoral metaphyseal fracture.

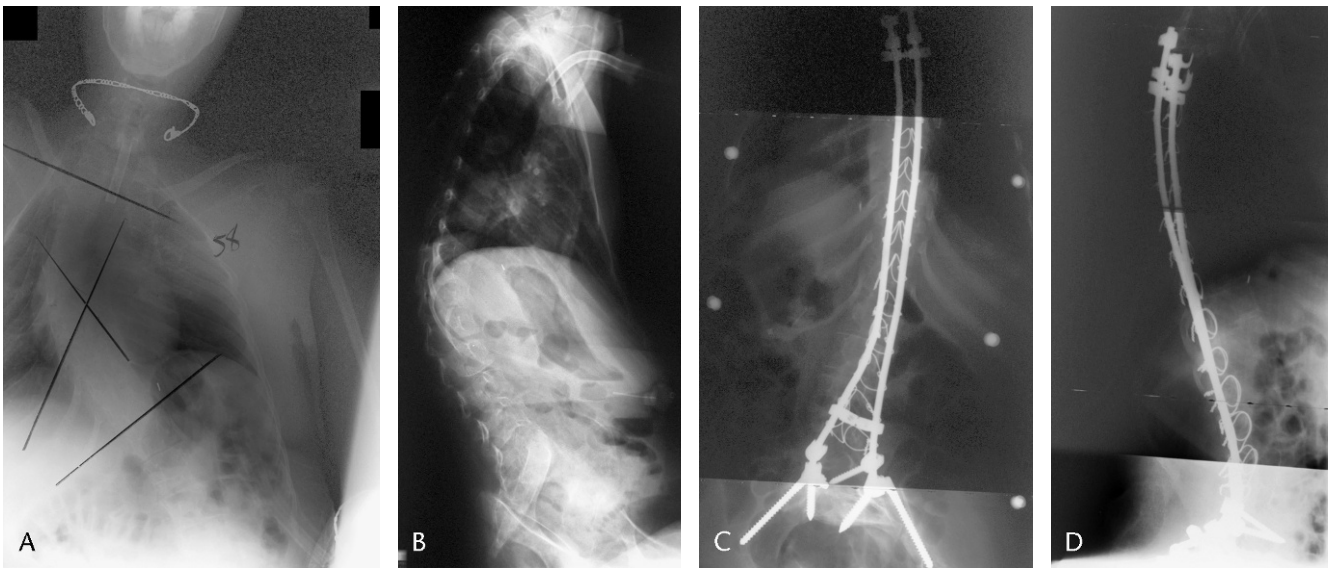

FIGURE 4. Preoperative and postoperative posteroanterior and lateral radiographs of the first patient with scoliosis.

We had 2 patients who had deformity about the hip. One patient had bilateral hip flexion and adduction contractures that were treated with sartorius and tensor fascia lata releases at age 7 years. He has not had a recurrence for the past 3 years. Another patient developed bilateral hip flexion and adduction contractures with hip subluxation by age 5 years 3 months. He progressed to frank dislocation by age 6 years 9 months. He was also experiencing ischemic changes in his lower extremities when he was placed upright in his stander. At age 7 years, he was treated with psoas and adductor releases that were sufficient to relocate the hips. However, within 6 months, he developed bilateral abduction contractures. Within 18 months of the surgery, the hip flexion contractures recurred. These led to further soft-tissue releases at age 12 years. A third patient developed bilateral hip abduction contractures by age 6 years 2 months. Within a year, one side was dislocated and the other was subluxed. He had pain and difficulty sitting.

We encouraged the parents and caregivers to perform joint mobilization exercises several times daily and integrate range-of-motion exercises to activities of daily living such as dressing and hygiene.

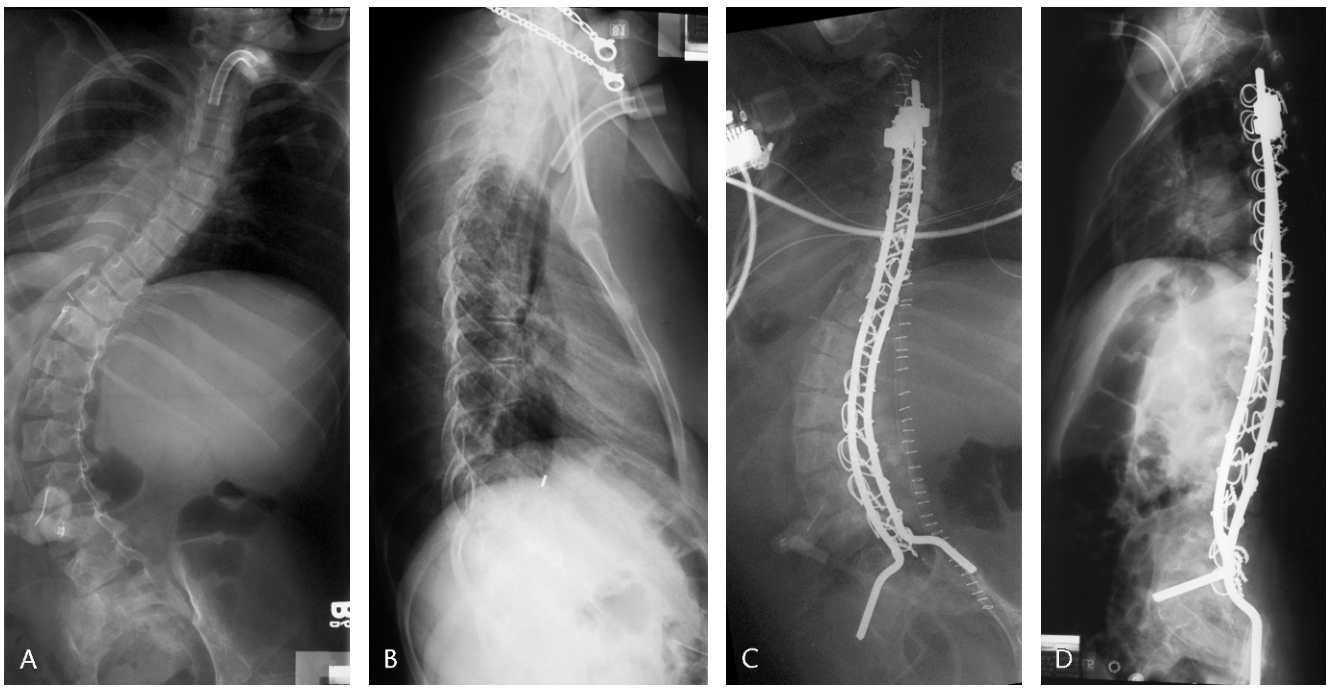

FIGURE 5. Preoperative and postoperative posteroanterior and lateral radiographs of the second patient with scoliosis.

It should be noted, however, that only 1 of the 4 patients was ever able to achieve independent ambulation. This patient was able to take a few steps independently at age 3 years but lost this ability after a few months.

Spinal deformity is another common manifestation of this disease. Three of the patients had progressive severe scoliosis that was refractory to conservative measures and required surgical stabilization. One patient had excessive lumbosacral lordosis preceding coronal deformity by almost 2 years. He had 80 degrees of lumbosacral lordosis (55 degrees in the lumbar spine). The patient was forced to discontinue use of a standing device because of ischemic changes he experienced only while using it. These ischemic events were related to his excessive lordotic deformity. The lordosis recurred quickly after a hamstring release. He subsequently developed a 58-degree right thoracic curve with compensatory lumbar curve by age 11 years 10 months.

At age 11 years 11 months, he underwent posterior fusion from T2 to the sacrum. Screws were placed at L5, S1, and the ilium. Hooks were placed on the pedicles of T2 and T3, and sublaminar wires were used at the intervening levels. His curve was reduced by approximately 50% (Fig. 4).

A second patient developed a 96-degree left thoracolumbar curve by age 6 years 6 months. This deformity resulted in rib abutment on his pelvis and left lower lobe pulmonary atelectasis. He underwent posterior spinal fusion from T2 to the pelvis using a laminar wire construct (Fig. 5).

By the age of 9 years 5 months, a third patient had also developed a progressive scoliotic deformity that was refractory to bracing. His thoracic curve measured 68 degrees. He subsequently underwent uncomplicated posterior spinal fusion from T4 to the pelvis (Fig. 6).

Complications were encountered with 2 of the 3 patients. The first patient had a comorbidity of von Willebrand disease and had a posterior spinal fusion attempt aborted because of complications with intravenous access. When the patient underwent the procedure 9 months later, he had a blood loss of 750 mL, approximately 30% of his total blood volume. He required 6 U of packed red blood cells and 1 U of fresh frozen plasma intraoperatively in addition to 400 mL of recycled autotransfusion product. Furthermore, 1 of 3 postoperative blood cultures produced growth of a *Serratia* strain that was treated with a 10-day course of intramuscular ceftriaxone without further sequela. The second patient had an intraoperative blood loss of 6000 mL, requiring 10 U of packed red blood cells in addition to his recycled autotransfusion products. This blood loss represented approximately 178% of his total blood volume. Postoperatively, he required another 3 U of packed red blood cells and a unit of fresh frozen plasma. In the postoperative period, he was diagnosed with a genetic platelet dyscrasia. Both patients were noted to have weak bone; this manifested itself in the first patient when several of the sublaminar wires pulled out intraoperatively.

None of the complications were related to general anesthesia. Both patients were discharged home within 10 days of their fusions. Both patients have radiographic evidence of fusion without progression of their deformities. Also, there does not seem to be a relationship between the patients' ambulatory status and the onset or progression of the spinal deformity.

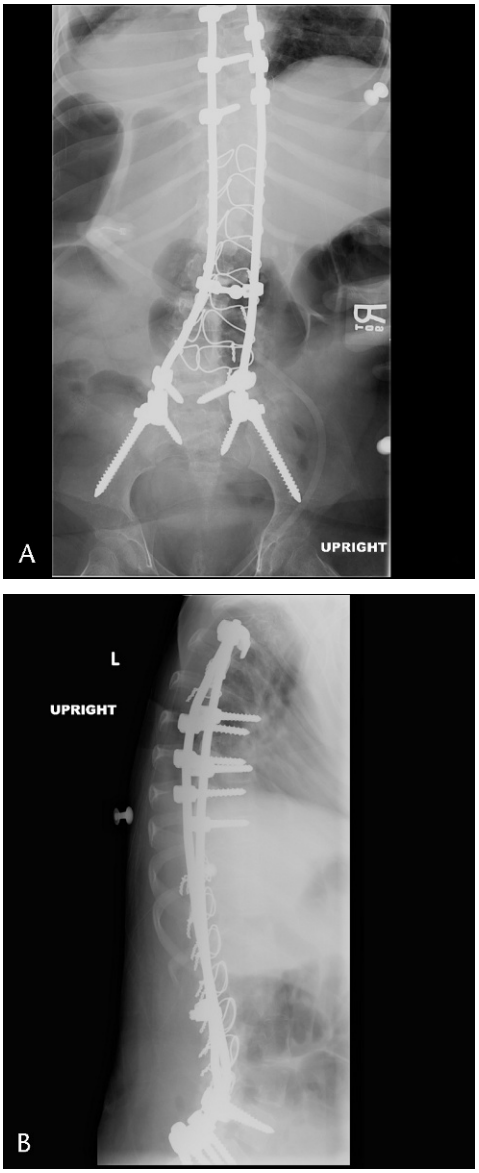

FIGURE 6. Postoperative posteroanterior and lateral radiographs of the third patient with scoliosis.

The primary goals of spinal surgery in our series were to restore balance in all planes and to achieve a stable solid fusion. Correction of deformity was a secondary goal. The correction in our treatment of scoliosis in myotubular myopathy patients varied. The earliest of these patients' spines was treated in 1997. His 96-degree thoracolumbar curve was treated with a Galveston rod attached to hooks at the cephalad end and intervening segmental wires. The main curve was corrected to 75 degrees. A 39-degree compensatory curve in the thoracic spine did not change. The remaining 2 scoliosis surgeries were performed by a specialist in spinal deformity (A.S.R.). The first surgery used a hybrid technique with iliac screws in the pelvis and hooks at the top with

sublaminar wires at the intervening levels. In this patient, a 58-degree curve was corrected approximately 50%. The most recent patient was treated in late 2005 for a 70-degree main thoracic curve. The construct involves screws in the iliac, S1, and L5; hooks at the cephalad end; pedicle screws in the thoracic curve levels; and sublaminar wires in the intervening levels. The curve reduced to 29 degrees. More importantly, his mother subjectively reported that his oxygen saturation has improved, he no longer uses his arms for support while sitting, and his lower extremity blood flow has improved. The mother of the other patients noted improved sitting balance and tolerance after their spinal surgeries. There was no change in the ventilation support in these 2 patients after their surgeries. None of the patients have had crankshaft phenomenon.

DISCUSSION

The musculoskeletal complications of myotubular myopathy have not been presented in the literature until now. However, these manifestations bear some similarities to those encountered with other neuromuscular conditions. The most notable similarity is with spinal muscular atrophy. In myotubular myopathy, the manifestations, including scoliosis, contractures, and muscle imbalances, seem to be more severe at an earlier age.

The frequency of fractures, fracture pattern, bone morphology, and fracture healing all seem to be similar to high-level myelomeningocele. In both disorders, fractures most often occur in the long bones.[9] Furthermore, fractures have a slight predilection for the metaphyseal region.[10–12] Lock and Aronson[12] have reported that 55% of long-bone fractures in children with myelomeningocele occur in the metaphysis; our series has a metaphyseal location in 8 (57%) of 14 of the long-bone fractures. Treatment of long-bone fractures in patients with myelomeningocele can lead to complications such as skin irritation and breakdown and fracture elsewhere in the immobilized extremity.[11] We thus recommend treating fractures in myotubular myopathy patients with brief period of immobilization in soft dressings or removable splints. Once there is radiographic evidence of callus formation, the immobilization should be discontinued, and weightbearing and activity should be gradually increased to normal levels.

The goals of fracture treatment were to avoid causing more fractures through stress transfer from a long immobilized segment with a heavy cast. Furthermore, as these are fairly low-demand patients, the duration of immobilization was generally shorter than for similar fractures in their healthy peers. The fractures were treated in a variety of ways. For example, a supracondylar femur fracture was treated with immobilization by a large amount of cotton padding wrapped from the supramalleolar ankle to below the hip and covered with 2 layers of soft cast. This was used for 4 weeks until there was radiographic evidence of callus. For other fractures, thermoplastic splints, made by the occupational therapist, were used. This allowed for skin inspection and hygiene.

Many of the manifestations of myotubular myopathy seem to be similar to spinal muscular atrophy. In both diseases, scoliosis is a common manifestation. We report a 75% occurrence of scoliosis in myotubular myopathy. The prevalence of scoliosis in spinal muscular atrophy is related to the subtype of the disease and the ambulatory status of the patient.[13–15] The reported age at spinal fusion in spinal muscular atrophy is 14.4 years.[12] In our series, the average age is 8.5 years. This difference may be explained by the difference between the magnitude of the deformity at the age of fusion. In the largest series of spinal muscular atrophy, the curve measured an average of 90 degrees, and the authors recommended that the patients should be fused earlier.[16]

We recommend a treatment algorithm for myotubular myopathy similar to that of spinal muscular atrophy. Bracing in spinal muscular atrophy, as in myotubular myopathy, is ineffective.[17,18] We recommend long posterior fusion over selective anterior fusion based on our own clinical results with long fusion and the poor results of short anterior fusions in spinal muscular atrophy.[16] The procedure is best performed when the curve is between 50 and 60 degrees.[12,15]

Our construct design has evolved to allow a single posterior approach that will prevent crankshaft phenomenon in a cost-effective manner. Monaxial pedicle screws were selected for the thoracic curve to provide 3-column fixation and therefore avoid crankshaft phenomenon. As a cost-saving measure, sublaminar wires are used at levels where pedicle screws are not required. Cheng et al[19] have shown equivalent correction in the coronal plane with pedicle screws and sublaminar wiring. Although we did not experience any wire cutout through the laminae, we did note that the patients did have weak bone and several transverse processes fractured when we attempted to instrument them with hooks. The surgeon who uses this construct should be prepared to insert pedicle screws at any level where lamina failure occurs.

The 2 patients with large volumes of blood loss had bleeding anomalies caused by von Willebrand disease in one and platelet dyscrasia in the other. Neither of these patients sustained damage to a major vessel; rather, a steady generalized ooze was noted throughout the surgeries. We conjecture that it was this condition, not the myotubular myopathy, that contributed to the large amount of blood loss. We have found no evidence in the literature of an association between von Willebrand disease or platelet dyscrasias and myotubular myopathy. Herman et al[20] reviewed a study of 55 men with myotubular myopathy. The only hematologic abnormality was a mild spherocytosis in 2 patients, which led to hemolysis and anemia.

With regard to soft-tissue contractures about the joints, we prefer a conservative approach. Because most of these patients will not achieve the ability to ambulate, the main goal was to accommodate seating. A secondary goal was to prevent hip subluxation. The first line of treatment was a continual involvement of physical therapy and stretching. Only when this treatment failed did we undertake operative soft-tissue releases. We believe that the treatment of contractures about the hip may decrease the patient's pain, improve sitting, and prevent exacerbation of lumbar lordosis deformity. These recommendations are again based largely on previous experience with spinal muscular atrophy and the similarities between these 2 entities.[21] Spinal muscular atrophy patients, particularly those who are nonambulatory,

often have hip deformities that lead to subluxation and even dislocation.[15]

The clinical consequences of these subluxations have recently been called into question. Recent studies have advocated not addressing these problems, citing the lack of symptoms. Sporer and Smith[22] reported that on their series of 37 of 82 subluxed or dislocated hips in children with spinal muscular atrophy, only 2 of their patients were symptomatic. Furthermore, they discuss the differences in hip muscle forces between spinal muscular atrophy and cerebral palsy. Cerebral palsy patients have a muscle imbalance combined with spasticity. Spinal muscular atrophy produces global weakness and ligamentous laxity about the hip that leads to diminished weightbearing and understimulation of the trochanteric apophysis by the gluteal muscles. This produces coxa valga and is thus a mechanical reason for femoral head migration.

In another recent study, Zenios et al[23] also reported on their experience with hip displacement in spinal muscular atrophy. Seventeen hips in 9 patients underwent surgery consisting of soft-tissue releases combined in some instances with pelvic and/or femoral osteotomies. Four (23.5%) of these resubluxed, and only 1 child reported improvement in pain and function. In their group of 42 hips in 21 patients who did not have surgery, 28 hips (67%) were subluxed in 18 patients. Only 1 child complained of hip pain.

The exception to this natural history of lower extremity contractures seems to be the foot and ankle. All of our patients developed bilateral equinovarus contractures between 4 and 6 years. All responded well to treatment with ankle-foot orthoses, with the exception of 1 patient who developed rigid equinus contractures. He was successfully treated with percutaneous Achilles tendon lengthenings followed by a course of short-leg casting.

These data on myotubular myopathy and previously published experience with similar disorders such as spinal muscular atrophy can help the orthopaedist guide treatment and counsel families of children with the disorder.

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