**Orthopedics**

Orthopedic complications can occur in mitochondrial disease due to a variety of causes including underlying myopathy, neuropathy, abnormalities of tone, strokes, basal ganglia or cerebellar disease. Treatment of orthopedic issues in mitochondrial disease is symptomatic. Peer reviewed data is lacking for the assessment of orthopedic interventions in the many rare diseases that collectively are referred to as mitochondrial diseases. Recommendations for adult and pediatric patient management are based on non-mitochondrial diseases. Patients are best managed by a multidisciplinary team that may include the neurologists, metabolic geneticists, physiatrists, orthopedic surgeons, and physical and occupational therapists. Orthopedic interventions may be necessary for contractures, scoliosis, hip dislocation, and limb deformities. Yearly examination of patients with mitochondrial diseases is recommended. More frequent orthopedic assessments may be needed in some patients. Additional discussion of commonly encountered orthopedic issues is discussed in the **Supplementary Material**.

**General Principles of Orthopedic Management of Mitochondrial Diseases**

1. Patients with mitochondrial disease should be examined annually for orthopedic complications including scoliosis, contractures, dislocations and limb deformities Score 4.24
2. Bracing may be required to support unstable joints. Protective pads and helmets should be a consideration for patients performing activities where there is risk of injury and falls Score 4.41
3. Activities producing significant joint impact should be avoided in those at risk of dislocations Score 4.21
4. Prostheses, walking aids, wheelchairs, and physical therapy as prescribed by a physiatrist (rehabilitation medicine specialist) are used to maintain an active lifestyle. Score 4.47
5. Occupational therapy assessment can ensure a safe home and work environment and assist in maintaining fine motor mobility Score 4,47
6. Inpatient rehabilitation may improve physical function in some patients and should be considered when needed Score 4.47
7. Orthopedic interventions, both operative and non-operative, for scoliosis, dislocations and limb deformities may be beneficial to selected patients. (Delatycki et al. 2005; PMID:15662315) Score 4.5
8. As with all procedures, life expectancy should be weighed against risks for discomfort and recovery time when considering an orthopedic procedure. Score 4.62

**Supplemental material**

**Toe walking and Achilles Tendon Contracture**

Toe walking is a gait abnormality characterized by the forefoot being used during gait with produces an absence of normal heel-to-floor contact. Toe walking has multiple etiologies including an idiosyncratic habit as well as neuromuscular diseases. The most common cause of toe walking is idiopathic. Although toe walking is commonly seen during development in children who are first learning to walk, a consistent heel-toe pattern of gait usually develops by approximately 22 months of age. (Caselli, Rzonca, and Lue 1988; PMID:3293753; Sutherland et al. 1980; PMID:7364807) Toe walking that persists beyond age 2 years may require careful assessment. (Pernet et al. 2010; PMID:20727441) Achilles tendon contracture is observed in some patients, particularly those with neuromuscular disease or spasticity.

The management of toe walking is controversial with limited comparisons of treatment modalities. Unless identifiable abnormalities are present such as fixed contractures, weakness, or spasticity, observation with monitoring at approximately 6 month intervals is appropriate for children <2 years of age. The limitations of therapeutic interventions are important to consider. Nonoperative modalities include stretching, casting, orthotics, and chemodenervation with botulinum toxin. Stretching and physical therapy are of limited efficacy and are frequently used to try and maintain range of motion. (Oetgen and Peden 2012; PMID:22553101) Botulinum toxin appears to have limited efficacy in most studies, even when combined with casting. (Engstrom et al. 2013; PMID:23467862) If nonoperative techniques are not successful after approximately 12 months, surgical options include simple heel cord tenotomy, gastrocnemius fascia lengthening, and multiple muscle lengthening within the lower extremity. Note that when significant quadriceps muscle weakness is present, the patient may be using toe walking to generate extension at the knee to compensate for a weak quadriceps. Lengthening the heel cord in this situation can cause a premature loss of ambulation. Nonoperative approaches such as bracing are preferred in these patients. For toe walking due to Achilles tendon contracture, stretching alone is ineffective. (Kranzl et al. 2013; PMID:24042745; Rattey et al. 1993; PMID:8459008) Operative intervention is generally needed in these patients. Orthosis use and stretching can delay recurrence after surgery. (Damron, Greenwald, and Breed 1994; PMID:8156683) The Ponseti method and the French method are commonly used approaches involving stretching and casting of the feet. Minor surgeries such as Achilles tendon tenotomy and anterior tibial tendon transfer may be required in some patients.

**Clubfoot (Congenital Talipes Equinovarus; CTE)**

CTE is characterized by internal rotation at the ankle, occurring in about one in every 1000 live births in the United States. Approximately half of CTE is bilateral. In most cases it is an idiopathic isolated disorder with a 2:1 male-to-female ratio. (Parker et al. 2009; PMID:19697433) No classification system is uniformly used. A widely used classification systems include the Pirani, Goldner, Di Miglio, Hospital for Joint Diseases (HJD), and Walker classifications. (Hussain 2007; PMID:17463132; Kaewpornsawan, Khuntisuk, and Jatunarapit 2007; PMID:17596049; Lejman and Kowalczyk 2002; PMID:12418398)

Although CTE is observed in some mitochondrial disease patients, it is often an unrelated disorder. Neuromuscular diseases associated with contractures (e.g MYH3, TPM2, TNNT3, TNNI2, and MYH8) and various congenital arthrogryposis syndromes are associated with an increased risk for CTE.

Approximately 90-95% of cases can be corrected without surgery or with minor procedures using a combination of stretching and casting techniques. The goal of surgery is to lengthen the heel cord and correct the forefoot and hindfoot. Surgery for children with congenital clubfoot is optimal prior to the development of walking but after 3-4 months of age. Satisfactory appearance and function are reported in approximately 75-90% of patients. (Morcuende et al. 2005; PMID:16199943; Ponseti 2000; PMID:11097239, 2002; PMID:12180612) CTE recurrence rates are reported as approximately 25%, with a range of 10-50%. (Simons 1978; PMID:709918, 1995; PMID:7719831)

**Congenital Hip Dislocation (Developmental Hip Dysplasia; DHD)**

DHD refers to a dislocation or instability of the hip resulting in hip dysplasia in some patients. Onset can be at any age ranging from conception to skeletal maturity. Four major conditions are generally recognized: (1) subluxation: incomplete contact between the femoral head and acetabulum; (2) dislocation: loss of articular surface contact; (3) instability: dislocation of the hip with passive manipulation; (4) teratologic dislocation: antenatal hip dislocation. Genetic predisposition and ethnicity influence the frequency of DHD. The frequency of DHD is approximately 10 times higher in children with affected parents. (Bjerkreim and Arseth 1978; PMID:566020) . The prevalence of hip dysplasia is higher in Native Americans and Laplanders than in other races (approximately 25-50 cases per 1000 persons) whereas the prevalence is low in southern Chinese and black populations. (Getz 1955; PMID:14375897; Hoaglund, Yau, and Wong 1973; PMID:4703218; Rabin et al. 1965; PMID:14275466; Skirving and Scadden 1979; PMID:479257) Hip dysplasia can be associated with various neuromuscular disorders, including some patients with mitochondrial disease. In general, patients with neuromuscular disorders do not benefit from surgery. Observation rather than surgical intervention appears to be the best approach. In a series of 41 patients with spinal muscular atrophy with a mean of 18 years of follow-up, the authors concluded that few patients will be symptomatic. (Sporer and Smith 2003; PMID:12499935)

**Neuromuscular Scoliosis**

Neuromuscular scoliosis (NMS) is the second most prevalent spinal deformity. Idiopathic scoliosis is first. NMS is generally most severe in nonambulatory patients. Cerebral palsy and Duchenne muscular dystrophy are the most common etiologies. Management goals include function preservation, improved daily care, and pain management. Bracing for neuromuscular scoliosis is a temporizing measure and is not definitive treatment. Surgical stabilization constitutes the mainstay of treatment for neuromuscular scoliosis. The two main indications for surgery are curve progression and deterioration in sitting ability. A preoperative assessment of respiratory competency, cardiac status, nutrition, possible feeding difficulties, seizure disorders, urologic status, and metabolic bone disease is necessary to ensure that the patient is healthy enough to tolerate surgery. The incidence of osteoporosis in severely affected patients (e.g. quadriplegic cerebral palsy) is high and can complicate surgery. (Rezende et al. 2015; PMID:26229882)

Neuromuscular scoliosis and idiopathic scoliosis have different surgical management approaches. In neuromuscular scoliosis, spinal fusion is necessary at a younger age, and the fused portion of the spine is longer. Children with neuromuscular scoliosis have higher morbidity and longer hospitalizations with surgery. (Barsdorf, Sproule, and Kaufmann 2010; PMID:20142532; Edler, Murray, and Forbes 2003; PMID:14617124; Hammett et al. 2014; PMID:24487557; Jain, Njoku, and Sponseller 2012; PMID:22426452; Modi et al. 2009; PMID:19419584; Rumbak et al. 2016; PMID:25991642; Tsirikos et al. 2008; PMID:18449049; Tsirikos and Mains 2012; PMID:21738076; Basques et al. 2015; PMID:26261918) The complexity of making evidence based recommendations for surgery in neuromuscular scoliosis is emphasized by a recent Cochran Collaboration review. (Cheuk et al. 2015; PMID:26423318) The authors concluded that since no randomized controlled clinical trials are available, evidence based conclusions were not possible. In Duchenne muscular dystrophy, the rate of scoliosis surgery declined from 2001 to 2012, possibly due to decreased progression of scoliosis with glucocorticoid treatment. (Raudenbush et al. 2016; PMID:26926354) Recently an approached termed “Minimally Invasive Scoliosis Surgery” has been proposed. (Sarwahi et al. 2015; PMID:26649305) In this publication, Minimally Invasive Scoliosis Surgery refers to preservation of tissues, utilization of the preexisting muscle planes, and less disruptive and traumatic dissection. The authors conclude that this approach is associated with less blood loss, shorter hospitalizations, more rapid mobility, and reduced pain.

Peer reviewed data suitable for evidence based decision making in mitochondrial diseases is not available. When surgery is considered for neuromuscular scoliosis, patients should be informed of the uncertainty of benefits as well as surgical risks. Despite these limitations, surgery is associated with good long term outcomes and high satisfaction rates. (Roberts and Tsirikos 2016; PMID:26966821) Although studies of patients with neuromuscular scoliosis often contain patients with a broad array of etiologies, recent studies suggest that scoliosis surgery in patients with severe neuromuscular scoliosis does not decrease the incidence of pneumonia. (Keskinen et al. 2015; PMID:26350797)

**Additional Common Orthopedic Considerations**

Pes cavus and pes planus are often associated with inward rotation at the ankle, contributing to mild ambulation difficulties, leg fatigue, and muscle cramps. Orthotics are indicated only in severe cases. Some individuals obtain benefit from arch supports. Surgical intervention is rarely indicated or fully successful. Pes cavus is usually observed in Friedreich ataxia and in Charcot-Marie-Tooth disease. Usually this deformity causes little problem for affected individuals.

**References**

Barsdorf, A. I., D. M. Sproule, and P. Kaufmann. 2010. 'Scoliosis surgery in children with neuromuscular disease: findings from the US National Inpatient Sample, 1997 to 2003', *Arch Neurol*, 67: 231-5.

Basques, B. A., S. H. Chung, A. M. Lukasiewicz, M. L. Webb, A. M. Samuel, D. D. Bohl, B. G. Smith, and J. N. Grauer. 2015. 'Predicting Short-term Morbidity in Patients Undergoing Posterior Spinal Fusion for Neuromuscular Scoliosis', *Spine (Phila Pa 1976)*, 40: 1910-7.

Berntsson, S. G., A. Holtz, and A. Melberg. 2013. 'Does intrathecal baclofen have a place in the treatment of painful spasms in friedreich ataxia?', *Case Rep Neurol*, 5: 201-3.

Bjerkreim, I., and P. H. Arseth. 1978. 'Congenital dislocation of the hip in Norway. Late diagnosis CDH in the years 1970 to 1974', *Acta Paediatr Scand*, 67: 329-32.

Caselli, M. A., E. C. Rzonca, and B. Y. Lue. 1988. 'Habitual toe-walking: evaluation and approach to treatment', *Clin Podiatr Med Surg*, 5: 547-59.

Cheuk, D. K., V. Wong, E. Wraige, P. Baxter, and A. Cole. 2015. 'Surgery for scoliosis in Duchenne muscular dystrophy', *Cochrane Database Syst Rev*, 10: Cd005375.

Damron, T. A., T. A. Greenwald, and A. L. Breed. 1994. 'Chronologic outcome of surgical tendoachilles lengthening and natural history of gastroc-soleus contracture in cerebral palsy. A two-part study', *Clin Orthop Relat Res*: 249-55.

Delatycki, M. B., A. Holian, L. Corben, H. B. Rawicki, C. Blackburn, B. Hoare, M. Toy, and A. Churchyard. 2005. 'Surgery for equinovarus deformity in Friedreich's ataxia improves mobility and independence', *Clin Orthop Relat Res*: 138-41.

Edler, A., D. J. Murray, and R. B. Forbes. 2003. 'Blood loss during posterior spinal fusion surgery in patients with neuromuscular disease: is there an increased risk?', *Paediatr Anaesth*, 13: 818-22.

Engstrom, P., A. Bartonek, K. Tedroff, C. Orefelt, Y. Haglund-Akerlind, and E. M. Gutierrez-Farewik. 2013. 'Botulinum toxin A does not improve the results of cast treatment for idiopathic toe-walking: a randomized controlled trial', *J Bone Joint Surg Am*, 95: 400-7.

Getz, B. 1955. 'The hip joint in Lapps and its bearing on the problem of congenital dislocation', *Acta Orthop Scand Suppl*, 18: 1-81.

Hammett, T., A. Harris, B. Boreham, and S. M. Mehdian. 2014. 'Surgical correction of scoliosis in Rett syndrome: cord monitoring and complications', *Eur Spine J*, 23 Suppl 1: S72-5.

Hoaglund, F. T., A. C. Yau, and W. L. Wong. 1973. 'Osteoarthritis of the hip and other joints in southern Chinese in Hong Kong', *J Bone Joint Surg Am*, 55: 545-57.

Hussain, F. N. 2007. 'The role of the Pirani scoring system in the management of club foot by the Ponseti method', *J Bone Joint Surg Br*, 89: 561; author reply 61-2.

Jain, A., D. B. Njoku, and P. D. Sponseller. 2012. 'Does patient diagnosis predict blood loss during posterior spinal fusion in children?', *Spine (Phila Pa 1976)*, 37: 1683-7.

Kaewpornsawan, K., S. Khuntisuk, and R. Jatunarapit. 2007. 'Comparison of modified posteromedial release and complete subtalar release in resistant congenital clubfoot: a randomized controlled trial', *J Med Assoc Thai*, 90: 936-41.

Keskinen, H., H. Lukkarinen, K. Korhonen, T. Jalanko, A. Koivusalo, and I. Helenius. 2015. 'The lifetime risk of pneumonia in patients with neuromuscular scoliosis at a mean age of 21 years: the role of spinal deformity surgery', *J Child Orthop*, 9: 357-64.

Kranzl, A., C. Grasl, R. Csepan, and F. Grill. 2013. 'Outcome of 23h Bracing for Tip-toe-walking Children with Cerebral Palsy', *Biomed Tech (Berl)*.

Lejman, T., and B. Kowalczyk. 2002. '[Results of treatment of congenital clubfoot with modified Goldner's technique]', *Chir Narzadow Ruchu Ortop Pol*, 67: 351-5.

Milne, S. C., E. J. Campagna, L. A. Corben, M. B. Delatycki, K. Teo, A. J. Churchyard, and T. P. Haines. 2012. 'Retrospective study of the effects of inpatient rehabilitation on improving and maintaining functional independence in people with Friedreich ataxia', *Arch Phys Med Rehabil*, 93: 1860-3.

Modi, H. N., S. W. Suh, J. H. Yang, J. W. Cho, J. Y. Hong, S. U. Singh, and S. Jain. 2009. 'Surgical complications in neuromuscular scoliosis operated with posterior- only approach using pedicle screw fixation', *Scoliosis*, 4: 11.

Morcuende, J. A., D. Abbasi, L. A. Dolan, and I. V. Ponseti. 2005. 'Results of an accelerated Ponseti protocol for clubfoot', *J Pediatr Orthop*, 25: 623-6.

Oetgen, M. E., and S. Peden. 2012. 'Idiopathic toe walking', *J Am Acad Orthop Surg*, 20: 292-300.

Parker, S. E., C. T. Mai, M. J. Strickland, R. S. Olney, R. Rickard, L. Marengo, Y. Wang, S. S. Hashmi, R. E. Meyer, and Network National Birth Defects Prevention. 2009. 'Multistate study of the epidemiology of clubfoot', *Birth Defects Res A Clin Mol Teratol*, 85: 897-904.

Pernet, J., A. Billiaux, S. Auvin, D. Rakatovao, L. Morin, A. Presedo, J. C. Mercier, and L. Titomanlio. 2010. 'Early onset toe-walking in toddlers: a cause for concern?', *J Pediatr*, 157: 496-8.

Ponseti, I. V. 2000. 'Clubfoot management', *J Pediatr Orthop*, 20: 699-700.

———. 2002. 'Relapsing clubfoot: causes, prevention, and treatment', *Iowa Orthop J*, 22: 55-6.

Rabin, D. L., C. R. Barnett, W. D. Arnold, R. H. Freiberger, and G. Brooks. 1965. 'Untreated Congenital Hip Disease. A Study of the Epidemiology, Natural History, and Social Aspects of the Disease in a Navajo Population', *Am J Public Health Nations Health*, 55: SUPPL:1-44.

Rattey, T. E., L. Leahey, J. Hyndman, D. C. Brown, and M. Gross. 1993. 'Recurrence after Achilles tendon lengthening in cerebral palsy', *J Pediatr Orthop*, 13: 184-7.

Raudenbush, B. L., C. P. Thirukumaran, Y. Li, J. O. Sanders, P. T. Rubery, and A. Mesfin. 2016. 'Impact of a Comparative Study on the Management of Scoliosis in Duchenne Muscular Dystrophy: Are Corticosteroids Decreasing the Rate of Scoliosis Surgery in the United States?', *Spine (Phila Pa 1976)*.

Rezende, R., I. M. Cardoso, R. B. Leonel, L. G. Perim, T. G. Oliveira, C. Jacob Junior, J. L. Junior, and R. B. Lourenco. 2015. 'Bone mineral density evaluation among patients with neuromuscular scoliosis secondary to cerebral palsy', *Rev Bras Ortop*, 50: 68-71.

Roberts, S. B., and A. I. Tsirikos. 2016. 'Factors influencing the evaluation and management of neuromuscular scoliosis: A review of the literature', *J Back Musculoskelet Rehabil*.

Rumbak, D. M., W. Mowrey, W. Schwartz S, V. Sarwahi, A. Djukic, J. S. Killinger, and C. Katyal. 2016. 'Spinal Fusion for Scoliosis in Rett Syndrome With an Emphasis on Respiratory Failure and Opioid Usage', *J Child Neurol*, 31: 153-8.

Sarwahi, V., T. Amaral, S. Wendolowski, R. Gecelter, M. Gambassi, C. Plakas, B. Liao, S. Kalantre, and C. Katyal. 2015. 'Minimally Invasive Scoliosis Surgery: A Novel Technique in Patients with Neuromuscular Scoliosis', *Biomed Res Int*, 2015: 481945.

Simons, G. W. 1978. 'A standardized method for the radiographic evaluation of clubfeet', *Clin Orthop Relat Res*: 107-18.

———. 1995. 'Calcaneocuboid joint deformity in talipes equinovarus: an overview and update', *J Pediatr Orthop B*, 4: 25-35.

Skirving, A. P., and W. J. Scadden. 1979. 'The African neonatal hip and its immunity from congenital dislocation', *J Bone Joint Surg Br*, 61-B: 339-41.

Sporer, S. M., and B. G. Smith. 2003. 'Hip dislocation in patients with spinal muscular atrophy', *J Pediatr Orthop*, 23: 10-4.

Sutherland, D. H., R. Olshen, L. Cooper, and S. L. Woo. 1980. 'The development of mature gait', *J Bone Joint Surg Am*, 62: 336-53.

Tsirikos, A. I., G. Lipton, W. N. Chang, K. W. Dabney, and F. Miller. 2008. 'Surgical correction of scoliosis in pediatric patients with cerebral palsy using the unit rod instrumentation', *Spine (Phila Pa 1976)*, 33: 1133-40.

Tsirikos, A. I., and E. Mains. 2012. 'Surgical correction of spinal deformity in patients with cerebral palsy using pedicle screw instrumentation', *J Spinal Disord Tech*, 25: 401-8.