Review of Duchenne Muscular Dystrophy (DMD) for the Pediatricians in the Community

Sumit Verma, Yaacov Anziska and Joan Cracco

CLIN PEDIATR 2010 49: 1011 originally published online 19 August 2010
DOI: 10.1177/0009922810378738

Review of Duchenne Muscular Dystrophy (DMD) for the Pediatricians in the Community

Clinical Pediatrics
49(11) 1011–1017

DOI: 10.1177/0009922810378738
http://clp.sagepub.com
SAGE

Sumit Verma, MD[1], Yaacov Anziska, MD[1], and Joan Cracco, MD[1]

Introduction

Duchenne muscular dystrophy (DMD), an inherited X-linked recessive disorder, is characterized by progressive symmetric muscle weakness and gait disturbance, with onset in early childhood.[1] DMD is the most common muscular dystrophy in children, and incidence ranges from 1 in 3600 to 4700 live male births.[2] Early diagnosis (screening, confirmation, and genetic counseling), treatment, and long-term follow-up of affected individuals in routine pediatric practice can be challenging and are the focus of this review.

Natural History and Clinical Features

Infant boys with DMD are often asymptomatic. Although the clinical manifestations may be present by the end of the first year, first symptoms are usually noted during the toddler and preschool years (2-5 years). In spite of increased awareness, there is an average delay of 2.5 years from the onset of symptoms, and mean age of definitive diagnosis is 5 years.[3] Affected children usually present with gait problems (waddling, toe walking, and lordotic posture), calf hypertrophy, positive Gower's sign (difficulty arising from the floor, spreading their legs, and using their hands to climb up their thighs to help them to an upright position), and difficulty climbing stairs. Pediatricians should be aware of the importance of having preschoolers get up from a sitting position on the floor, walk, and run so as to detect early signs of muscle weakness. Motor status may appear to plateau between 3 and 6 years; deterioration begins between 6 to 8 years. Affected children lose the ability to climb stairs and rise from the floor and also develop Achilles tendon contractures. They may be able to self-propel for some time and maintain posture, but lordosis and scoliosis become obvious. Between ages 9 and 12 years, the majority of DMD patients become wheelchair bound (Figure 1). Upper-limb function is preserved until a later period. Decreased pulmonary function as a result of respiratory muscle weakness and chest deformity (kyphoscoliosis), along with respiratory infections, predisposes to respiratory failure. Cardiomyopathy and arrhythmia result in cardiac failure. Cardiorespiratory complications appear during the second decade and eventually lead to death.[4]

Screening With Creatine Kinase (CK)

CK is a good screening test for muscle disease in clinical practice because levels rise in conditions with active muscle fiber necrosis and injury.[5] In DMD patients, CK levels are usually very elevated and are between 5000 and 150 000 IU/L (normal is less than 200 IU/L). Reversible causes of elevated CK include drugs, trauma, crush injury, recent bacterial/viral infections, and hypothyroidism. However, the CK elevation in these circumstances rarely approaches that of DMD. Newborn screening using CK levels is not done routinely, and such screening has been restricted to research settings because of limited data on the impact of early diagnosis and initiation of (steroid) therapy in DMD.[6]

Disease Confirmation and Genetic Counseling

Those with DMD are deficient in dystrophin, an important muscle structural protein. The gene that codes for dystrophin is large, with 79 exons.[7] Approximately one-third of new cases in children are the result of new mutations.[8] Dystrophin gene mutation testing should be done in all suspected cases. Large deletions or duplications on

[1]State University of New York (SUNY) Downstate Medical Center, Brooklyn, New York, NY, USA

Corresponding Author:
Yaacov Anziska, Department of Neurology, 450 Clarkson Avenue, Box 1213, Brooklyn, NY 11023
Email: Yaacov.Anziska@downstate.edu

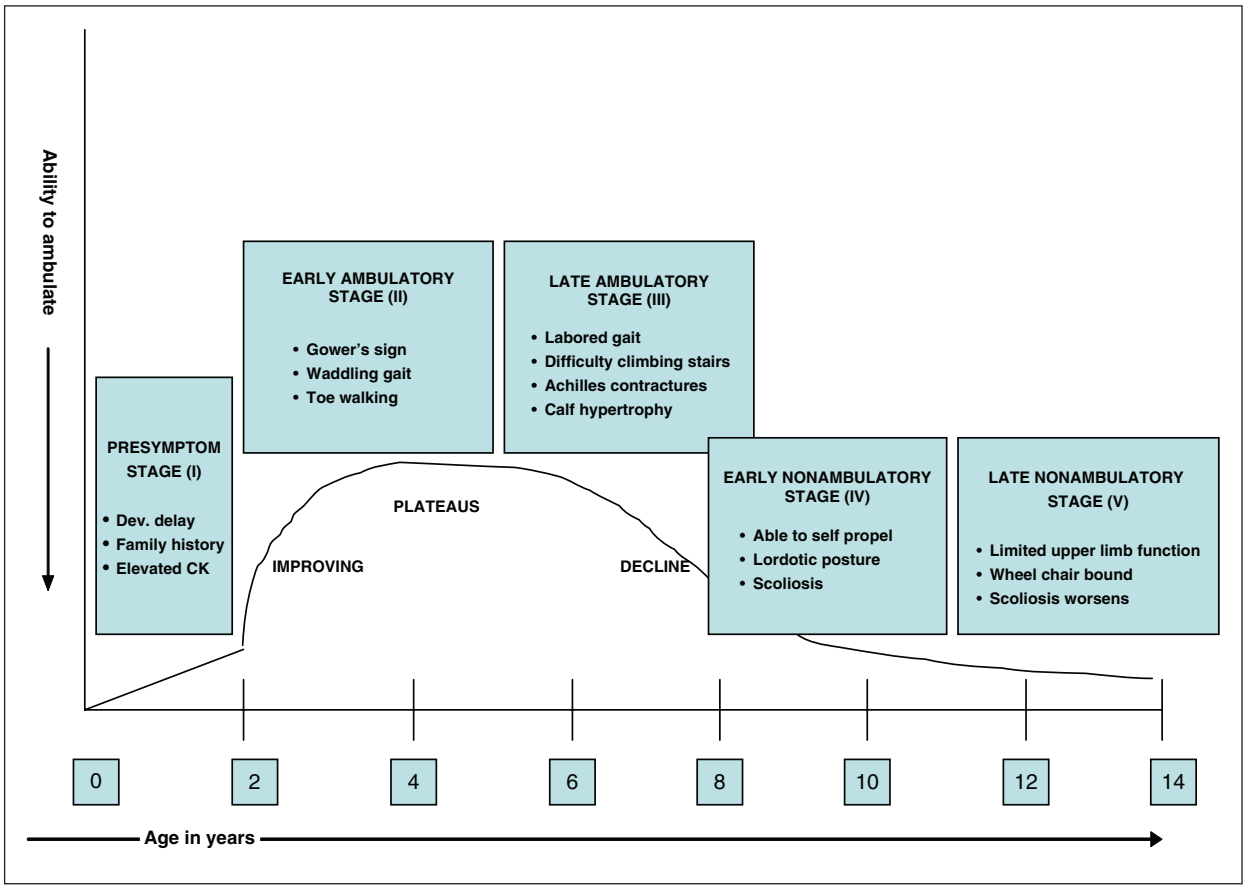

Figure 1. Musculoskeletal course in Duchenne muscular dystrophy

Xp21 locus account for 72% of the mutations among all cases; another 20% are point mutations (amino acid substitution, premature stop mutation, splice mutation), and 7% are small insertions or deletions; entire gene deletions are very rare.[9,10] Disruption or preservation of the reading frame by deletion mutations accounts for the phenotype severity. The mRNA formed by joining the ends of exons has to be in phase to maintain the correct translational open reading frame for the ribosome. Deletions that shift the translational reading frame (frameshift deletion) result in severely truncated dystrophin molecules. In-frame deletions lead to production of semifunctional protein, which can persist in small quantities, and this results in Becker Muscular Dystrophy (BMD), a milder, later onset muscular dystrophy.[11] EMG has no role in the diagnosis of DMD. Muscle biopsy can be considered in suspected children with negative family history and inconclusive or nonavailable genetic testing.[12] In DMD, dystrophin is absent in the muscle on immunostaining. Clinically asymptomatic siblings and the mother of the index case should be tested for disease and carrier state. Most carrier females are asymptomatic; however, up to 20% of carrier females may develop some degree of muscle weakness or cardiomyopathy.[13] A carrier mother has a 50% risk of having a boy with DMD and a 50% risk of her daughters being carriers. In sporadic cases, with no known family history and negative DNA deletion testing in the mother, germ line mosaicism cannot be excluded. These families have a 7% to 10% recurrence risk. Before planning the next pregnancy, mothers with a carrier state or sporadic germline mutations with previously affected male babies must have genetic counseling and prenatal testing (Southern blot or polymerase chain reaction with chorionic villus sampling or amniocentesis).[14]

Differential Diagnosis

The majority of childhood and adult onset inherited muscular disorders involve defects in the dystrophin axis (Figure 2). The axis comprises an actin–dystrophin–dystroglycan–sarcoglycan–laminin complex that connects

the sarcolemma and extracellular basal lamina and provides the mechanical stabilization of the sarcolemma during contraction and relaxation of muscle fibers.[15] Common differential diagnosis for DMD include BMD, limb girdle muscular dystrophies (subtypes 2D, 2E, 2C, 2F, 1C and 2B), Emery-Dreifuss disease, congenital muscular dystrophies with and without brain involvement, congenital myopathies, motor neuron disease (spinal muscular atrophy, type III), dermatomyositis, and acid maltase deficiency (Table 1). Most neuromuscular diseases occurring at similar ages as DMD do not have the striking increase in CK levels. In BMD, CK levels are generally lower but at times may approach those of DMD. CK levels may also be significantly elevated in the autosomal recessive sarcoglyconopathies. Therefore, patients presenting with DMD but having normal dystrophin levels should be evaluated for sarcoglycans on the muscle biopsy. Pediatricians should also consider DMD in children with persistently elevated liver enzymes (aspartate aminotransferase/alanine aminotransferase) with negative workup for liver disease.[16] Dystrophinopathies should be considered in children with unexplained dilated cardiomyopathy. In summary, diagnosis of muscular dystrophy can be made by taking a complete history and pedigree, determining CK levels, and carrying out a thorough neuromuscular exam.

Treatment of DMD: Role of Glucocorticoids

Glucocorticoids are the first line therapy in the treatment of DMD. Steroids decrease inflammation, prevent fibrosis, improve muscle regeneration, improve mitochondrial function, decrease oxidative radicals, and stop abnormal signaling of pathways and apoptosis. The 2 most commonly used corticosteroids are prednisone and deflazocort. Oral prednisone 0.75 mg/kg/d (max 80 mg/d) improved muscle strength and function for 6 months to 2 years as shown in Cochrane meta-analysis.[17] Daily scheduling is more effective than alternate-day or intermittent dosing. In those with intolerable side effects, the glucocorticoid dose should be decreased by 25% each month. The minimum effective dose is 0.3 mg/kg/d for prednisone.[18] Deflazocort 0.9 mg/kg/d is another alternative with fewer side effects (less weight gain and behavior problems) but has limited availability.[19] Age of initiation for corticosteroids is debatable. Many experts advocate beginning between 2 and 5 years, when gait difficulty develops. Bone density measurement and up-to-date immunization is a prerequisite for steroid initiation. Children on corticosteroids need calcium and vitamin D supplementation. Vertebral fractures are a well-known complication associated with steroid use and should be aggressively treated with bisphosphonate therapy.[20] Glucocorticoids should be continued even in nonambulatory patients to prevent scoliosis and heart and lung failure. Parents should be informed about the side effects and limitations of steroid therapy and made aware that this form of therapy is not curative.

Novel Therapies for DMD

Emerging treatment options for DMD include gene repair or replacement. These therapies include the use of recombinant adeno-associated viral vectors (rAAVs) for dystrophin gene delivery.[21] Studies in dystrophin double-knock-out mice have shown that rAAV/ microdystrophin can be used to deliver dystrophin genes in adult dystrophic mice. It is safe and effective for up to 2 years with improvement in phenotype and 5-fold extension in life span in these mice.[22] Encouraging early data of rAAV/microdystrophin delivery in dog models has been reported.[23] Another treatment modality is causing exon skipping (avoiding deletions that disrupt the codon reading frame) with antisense oligonucleotides.[24] This approach has shown promising results in both mice and dog models of DMD and is currently under investigation in humans. A recent Phase 2b trial with overreading of premature stop codons in dystrophin transcription did not achieve clinical significance (PTC Therapeutics). Other treatment strategies include upregulation of compensatory proteins like utrophin, α-dystrobrevin, and α7integrin. Blocking the downstream effects of muscle degeneration by the use of creatine, CoQ10, MYO-029, IGF (insulin-like growth factor), glutamine, arginine-like drugs, TNF (tumor necrosis factor)-α antagonists, and antifibrotics have been tried without benefit.[25]

Comorbid Conditions and Their Long-Term Management

DMD is a multisystem disease. Pediatricians caring for these children need to coordinate with specialists in the field of neurology, cardiology, pulmonology, orthopedics, physical medicine, and rehabilitation. At each pediatric office visit, weight, height, and blood pressure (BP) should be checked and plotted on age- and sex-appropriate anthropometric and BP percentile charts.[26] Intellectual impairment with average intelligence quotient <–1 standard deviation below the mean is common. Verbal ability is more affected than performance skills.[27] A team approach with parents, school teachers, child psychologists, and speech and occupational therapists can

Table 1. Differential Diagnoses of Childhood-Onset Inherited Neuromuscular Disorders

Dystrophin Axis Level Affected	Name of Disorder	Gene Location/Pattern of Inheritance	Clinical Features	CK Levels/Pathology
Dystrophinopathies	Duchenne muscular dystrophy (DMD)	Xp21/XR	Onset 2 to 5 years, calf hypertrophy, cognitive dysfunction, wheel-chair bound by 10 to 20 years; cardiorespiratory failure with death in second to third decade	CK level markedly elevated (10-20×), absent dystrophin in muscle on immunostaining
	Becker muscular dystrophy (BMD)	Xp21/XR	Variable age of onset, benign course, wheel-chair bound by end of second decade	CK moderately elevated (5×), reduced dystrophin on muscle biopsy immunostaining
Sarcoglycanopathies	Limb girdle muscular dystrophy (LGMD) 2D/C/E/F	Autosomal recessive: 2C—13q12 2D—17q21 2E—4q12 2F—5q33	Weakness first in hip and proximal leg muscles, progressing onto shoulder and proximal arm weakness. No cognitive impairment, rare cardiac disease	Very high CK (>10× normal), absent sarcoglycan on staining of muscle biopsy, degeneration and regeneration of muscle fibers, increased endomysial connective tissue
Caveolin	LGMD1C	Autosomal dominant, mutations in caveolin-3		Absent caveolin-3 on Western blot, muscle biopsy degenerating and regenerating fibers
Laminin	Emery-Dreifuss disease	Emerin xq28, x-linked: laminin A/C 1q21.2, autosomal dominant or recessive	Paravertebral rigidity; tendon and joint contractures, including neck; conduction defects and bradycardia; humeroperoneal weakness	Loss of emerin or laminin staining on muscle biopsy, mildly elevated CK, EKG-junctional escape rhythm, absent P waves
Extracellular matrix defect: congenital muscular dystrophies (CMDs) without brain involvement	Merosin-positive CMD		Moderate severity, neonatal onset, hypotonia, weakness, arthrogryposis, 90% ambulate by 4 years	CK level modestly elevated, immunostaining for dystrophin helps differentiate
	Merosin-negative CMD	Deletion or mutation of LAMA2 (laminin) gene on 6q22-q23	Severe weakness, hypotonia, may have arthrogryposis, respiratory failure common	MRI: extensive high-signal-intensity white matter
Dystroglyconopathies: CMD with brain involvement	Fukuyama-type CMD	Autosomal recessive, chromosome 9	Moderate severity (progressive) polymicrogyria, lissencephaly, neuronal heterotopia, seizures	CK levels, EMG, and muscle biopsy finding similar to CMD without brain involvement
	Walker-Warburg CMD	May be allelic with Fukuyama	Moderate severity polymicrogyria, lissencephaly, neuronal heterotopia, seizures	CK levels, EMG, and muscle biopsy finding similar to CMD without brain involvement

(continued)

Table 1. (continued)

Dystrophin Axis Level Affected	Name of Disorder	Gene Location/Pattern of Inheritance	Clinical Features	CK Levels/Pathology
	Muscle–eye–brain disease	Links to 1p34-p32	Developmental delay, neuronal heterotopia, hypomyelination, optic nerve hypoplasia	Ocular dysplasia, pyramidal tract dysplasia
Congenital myopathy	Myotubular myopathy	X-linked,Xq28, AD 11q22	Ptosis, joint contractures, micognathia	Centrally placed large nuclei, immunochemical increased signal of myofibers against desmin
	Nemaline myopathy	NEB, ACTA1: autosomal dominant or recessive	Muscle wasting, rarely cardiomyopathy	Thread-like inclusions on Gomori trichrome staining
Motor neuron disease	Spinal muscular atrophy (SMA)	SMN1 mutation, phenotype depends on number of SMN2 genes	Varies based on severity of disease, ranges from death at 1 month from respiratory weakness to living >18 years	Grouped muscle fiber atrophy, mainly type I fibers
Inflammatory	Dermatomyositis		Proximal muscle weakness, helitrope rash on upper eyelids, Gottron's papules	Vasculitis on biopsy, perifascicular, CK elevated
Metabolic	Acid maltase deficiency	AR (chromosome 17)	Proximal muscle weakness, childhood onset <5 years with calf hypertrophy in some cases	CK not elevated, EMG is characteristic

NOTE: AR = autosomal recessive.

address this problem. To monitor decline in ejection fraction and the onset of dilated cardiomyopathy, a baseline echocardiogram should be performed at diagnosis or by age 6; it should be repeated every 2 years up to the age of 10 and annually thereafter.[28] ACE (angiotensin-converting enzyme) inhibitors are the first line therapy in DMD patients with cardiac failure to aid in cardiac remodeling. β-Blockers and diuretics are also used. Pulmonary involvement from respiratory muscle weakness and chest wall deformity (kyphoscoliosis) needs close monitoring.[29] Annual forced vital capacity (FVC) measurement at an age when the child can cooperate is essential. During office visits, pulse oximetry and peak flow should be documented. In the late nonambulatory stage, end-tidal CO_2 can be measured with a capnograph. Pulmonary insufficiency (FVC < 30% predicted, SpO_2 < 95%, end-tidal CO_2 > 45 mm Hg) warrants volume recruitment and deep lung inflation (FVC < 40% predicted) with noninvasive ventilation, including CPAP (continuous positive airway pressure) or BiPAP (bilevel positive airway pressure). This may begin with nighttime ventilation, with full-time ventilation if hypoventilation persists. Tracheostomy is required if noninvasive ventilation cannot be done successfully or 3 extubation failures are recorded. A cough assist device may be useful to prevent respiratory infections, which should be treated aggressively. Orthopedic evaluation of the spine and X rays every 6 months between 10 and 16 years are advised. Although scoliosis incidence has decreased with the use of glucocorticoids, spine stabilization surgery may be useful for curvature as little as 15° to 20° to prolong ambulation. A physical medicine and rehabilitation specialist must be involved early in care to emphasize exercise and contracture prevention. Stretching and positioning exercises at the hip, knee, and ankle should be performed daily at home or at school. Aquatic therapy may also be helpful. Use of night ankle bracing has been shown to prevent Achilles contractures. Children on oral steroids also need screening for mood disorder and reflux disease. Diet and swallowing evaluation is

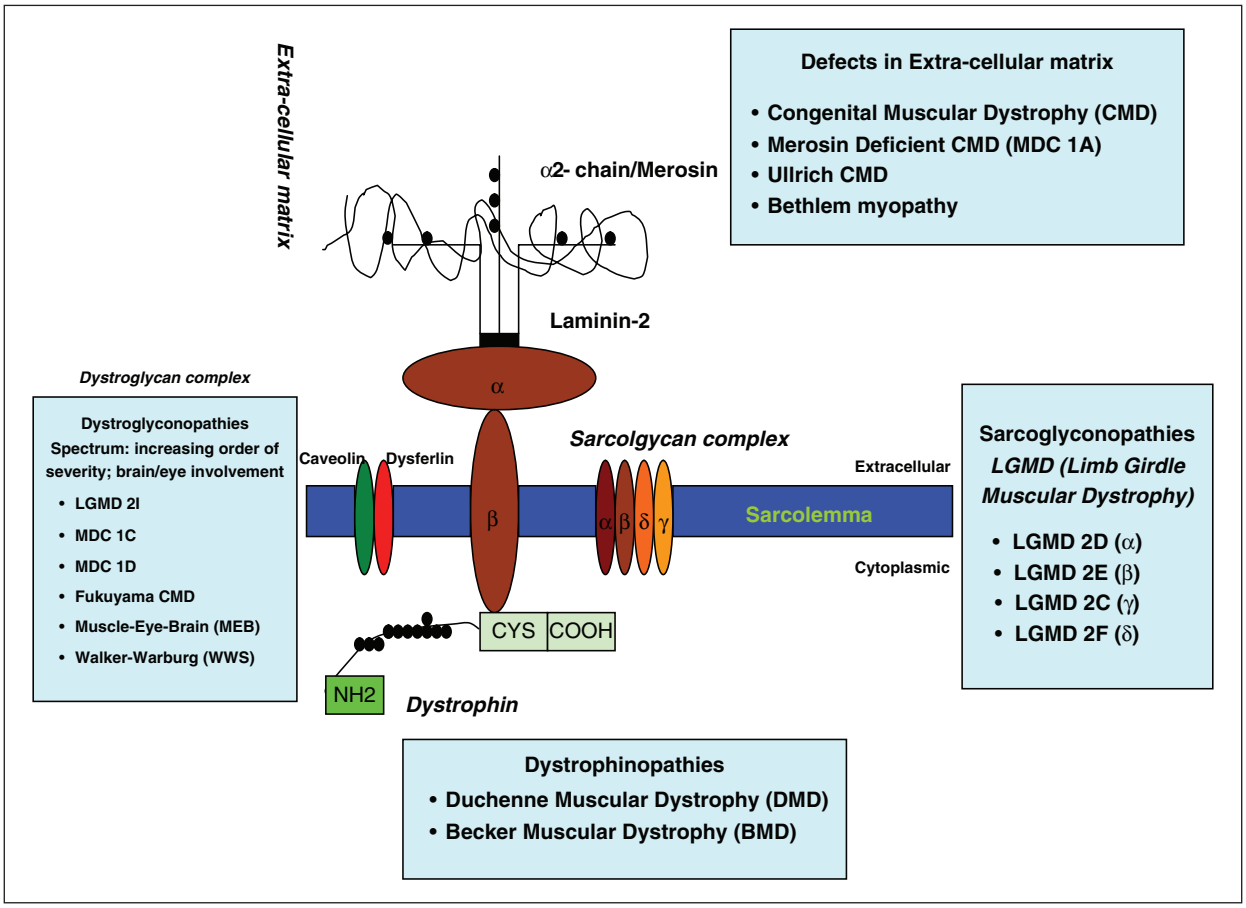

Figure 2. Dystrophin axis and its defects

helpful for those with rapid weight gain or weight loss from swallowing difficulty. Gastrointestinal hypo motility secondary to smooth muscle involvement can be seen as acute gastric distension, vomiting, abdominal pain, and distension. The current management approach has dramatically improved life expectancy, and patients may now survive into their late 20s and 30s.[30]

Summary

DMD is a life-limiting disorder. Pediatricians can play a vital role in screening, diagnosis, and management of the affected children. Observing young children walk and squat during well-child examination, CK level testing in suspicious cases, and referral to muscular dystrophy clinics, if available, can help decrease the delay in diagnosis of DMD. Pediatricians can play an important role in coordinating treatment and follow-up of affected patients with a multidisciplinary team. Pediatricians can also be a great resource in encouraging genetic testing and counseling, prenatal diagnosis, and newborn screening for affected families.

Author's Note

SV conceived the idea and wrote the manuscript; YA and JC reviewed the article and would act as guarantors.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research and/or authorship of this article.

References

1. Darras BT, Menache CC. Dystrophinopathies. In: Katriji B, ed. *Neuromuscular Disorders in Clinical Practice*. 1st ed. Newton, MA: Butterworth-Heinemann; 2002:1028-1048.
2. Dooley J, Gordon KE, Dodds L, MacSween J. Duchenne muscular dystrophy: a 30-year population-based incidence study. *Clin Pediatr (Phila)*. 2010;49:177-179.
3. Ciafaloni E, Fox DJ, Pandya S, et al. Delayed diagnosis in Duchenne muscular dystrophy: data from the Muscular

Dystrophy Surveillance, Tracking, and Research Network (MD STARnet). *J Pediatr*. 2009;155:380-385.
4. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurol*. 2010;9:77-93.
5. Brooke MH, Fenichel GM, Griggs RC, et al: Clinical investigation in Duchenne dystrophy: 2. Determination of the "power" of therapeutic trials based on the natural history. *Muscle Nerve*. 1983;6:91-103.
6. Kemper AR, Wake MA. Duchenne muscular dystrophy: issues in expanding newborn screening. *Curr Opin Pediatr*. 2007;19:700-704.
7. Stockley TL, Akber S, Bulgin N, Ray PN. Strategy for comprehensive molecular testing for Duchenne and Becker muscular dystrophies. *Genet Test*. 2006;10:229-243.
8. Online Mendelian Inheritance in Man. Muscular dystrophy, Duchenne type; DMD. http://www.ncbi.nlm.nih.gov/omim/310200. Accessed July 13, 2010.
9. Gillard EF, Chamberlain JS, Murphy EG, et al. Molecular and phenotypic analysis of patients with deletions within the deletion-rich region of the Duchenne muscular dystrophy (DMD) gene. *Am J Hum Genet*. 1989;45:507-520.
10. Bushby KM. Genetic and clinical correlations of Xp21 muscular dystrophy. *J Inherit Metab Dis*. 1992;15:551-564.
11. Monaco AP, Bertelson CJ, Liechti-Gallati S, et al. An explanation for the phenotypic differences between patients bearing partial deletions of the DMD locus. *Genomics*. 1988;2:90-95.
12. Darras BT, Jones HR. Diagnosis of pediatric neuromuscular disorders in the era of DNA analysis. *Pediatr Neurol*. 2000;23:289-300.
13. Hoogerwaard EM, Bakker E, Ippel PF, et al. Signs and symptoms of Duchenne muscular dystrophy and Becker muscular dystrophy among carriers in The Netherlands: a cohort study. *Lancet*. 1999;353:2116-2119.
14. Abbs S. Prenatal diagnosis of Duchenne and Becker muscular dystrophy. *Prenat Diagn*. 1996;16:1187-1198.
15. Ozawa E, Yoshida M, Hagiwara Y, et al. Dystrophin-associated proteins in muscular dystrophy. *Hum Mol Genet*. 1990;4:11711-11716.
16. Morse RP, Rosman NP: Diagnosis of occult muscular dystrophy: importance of the "chance" finding of elevated serum aminotransferase activities. *J Pediatr*. 1993;122:254-256.
17. Manzur AY, Kuntzer T, Pike M, Swan A. Glucocorticoid corticosteroids for Duchenne muscular dystrophy. *Cochrane Database Syst Rev*. 2008;(1):CD003725.
18. Moxley RT III, Ashwal S, Pandya S, et al. Practice parameter: corticosteroid treatment of Duchenne dystrophy: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2005;64:13-20.
19. Biggar WD, Gingras M, Fehlings DL, Harris VA, Steele CA. Deflazacort treatment of Duchenne muscular dystrophy. *J Pediatr*. 2001;138:45-50.
20. Bothwell JE, Gordon KE, Dooley JM, MacSween J, Cummings EA, Salisbury S. Vertebral fractures in boys with Duchenne muscular dystrophy. *Clin Pediatr (Phila)*. 2003;42:353-356.
21. Blankinship MJ, Gregorevic P, Chamberlain JS. Gene therapy strategies for Duchenne muscular dystrophy utilizing recombinant adeno-associated virus vectors. *Mol Ther*. 2006;13:241-249.
22. Arnett AL, Chamberlain JR, Chamberlain JS. Therapy for neuromuscular disorders. *Curr Opin Genet Dev*. 2009;19:290-297.
23. Gregorevic P, Schultz BR, Allen JM, et al. Evaluation of vascular delivery methodologies to enhance rAAV6-mediated gene transfer to canine striated musculature. *Mol Ther*. 2009;17:1427-1433.
24. Yokota T, Duddy W, Partridge T. Optimizing exon skipping therapies for DMD. *Acta Myol*. 2007;26:179-184.
25. Nelson SF, Crosbie RH, Miceli MC, Spencer MJ. Emerging genetic therapies to treat Duchenne muscular dystrophy. *Curr Opin Neurol*. 2009;22:532-538.
26. Rosner B, Prineas RJ, Loggie JM, Daniels SR. Blood pressure nomograms for children and adolescents, by height, sex, and age, in the United States. *J Pediatr*. 1993;123:871-886.
27. Cyrulnik SE, Fee RJ, De Vivo DC, Goldstein E, Hinton VJ. Delayed developmental language milestones in children with Duchenne's muscular dystrophy. *J Pediatr*. 2007;150:474-478.
28. American Academy of Pediatrics Section on Cardiology and Cardiac Surgery. Cardiovascular health supervision for individuals affected by Duchenne or Becker muscular dystrophy. *Pediatrics*. 2005;116:1569-1573.
29. Finder JD, Birnkrant D, Carl J, et al. Respiratory care of the patient with Duchenne muscular dystrophy: an official ATS consensus statement. *Am J Respir Crit Care Med*. 2004;170:456-465.
30. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. *Lancet Neurol*. 2010;9:177-189.