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9 year old girl with progressive weakness: Com july 2009 case 1

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9 YEAR OLD GIRL WITH PROGRESSIVE WEAKNESS

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CLINICAL HISTORY

A 9-year old girl presented with a 6 month history of progressive shoulder and back discomfort associated with generalized weakness and exercise intolerance.

Her past medical history was complicated by spina bifida in association with a Chiari type II malformation and hydrocephalus. She had undergone a myelomeningocele repair, tethered cord release and placement of a VP shunt. Developmental motor milestones were delayed (walking began at age 2) but she eventually walked unassisted. She had mild bowel and bladder dysfunction.

On physical exam, muscle bulk and tone were normal in the upper limbs but shoulder adduction was weak, graded 4/5. Shoulder abduction and elbow flexion were graded 4+/5. Muscle bulk in the lower limbs was decreased. Tone was normal. Hip flexion and knee flexion were graded as 4+/5. When asked to lie supine then rise to a standing position she demonstrated a partial Gower's maneuver.

Nerve conduction studies were normal, but electromyography demonstrated myopathic units in the shoulder girdle muscles and quadriceps. A muscle biopsy was performed.

MICROSCOPIC PATHOLOGY

Perimysial and endomysial connective tissues were found to be generous and fibre size variation was markedly increased on the basis of scattered hypertrophic and atrophic fibres. Individual and small clusters of degenerating and regenerating fibres were present and associated with light adjacent mononuclear infiltrates. Internal nuclei were increased and scattered rounded, hypereosinophilic (hypercontracted) fibres were present.

Dystrophin immunohistochemistry (N-terminus, rod domain and C-terminus) identified a highly variable expression pattern from fibre to fibre with approximately half of the fibres showing normal expression and the remainder having markedly reduced, patchy or no expression. Dystrophin expression levels were highly variable from fascicle to fascicle. Figure 1 shows the skeletal muscle biopsy reveals endomysial and perimysial fibrosis and increased fiber size variation. Internal nuclei are increased in frequency and there centrally in the field of view are degenerating and regenerating fibers, while Figure 2 shows scattered hyperstaining, rounded (hypercontracted) fibers. Figure 3 shows spectrin immunostains and in figure 4 immunostains for dystrophin were used.

What is the diagnosis?

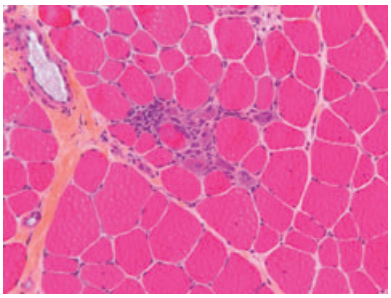

Figure 1.

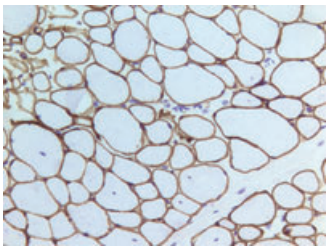

Figure 3.

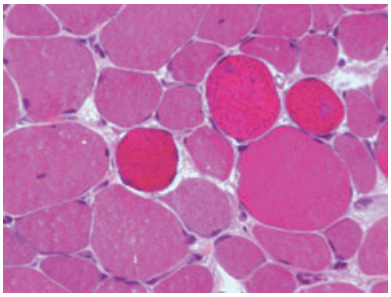

Figure 2.

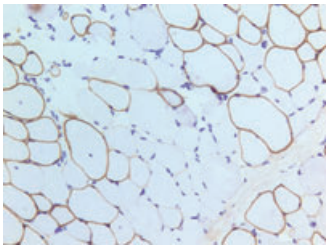

Figure 4.

DIAGNOSIS

Manifesting carrier of a dystrophinopathy.

She has a duplication noted in exon 5–11 of the dystrophin gene. Her X-inactivation studies showed marked skewing, with 95% inactivation of the wild-type allele.

DISCUSSION

The present case is an uncommon example of a manifesting Duchenne carrier presenting with myalgias and proximal muscle weakness. Although symptomatic pediatric cases are rare, there are several reported cases of manifesting female Duchenne Muscular Dystrophy (DMD) and Becker's Muscular Dystrophy (BMD) carriers presenting between 20 and 40 years of age. Typically the such cases have mild proximal weakness and dilated cardiomyopathy (4). Muscular weakness can be demonstrated in 19% of female DMD carriers and 14% of female BMD carriers (3). Myalgia and muscle cramps, however, are only present in 4–7% of this patient group. Furthermore, the mean age of onset of symptoms in these carriers is 33 years and signs do not tend to occur before age 16 (3).

There have been two previous case reports describing the presentations of young female dystrophinopathy carriers (2, 8). In addition to skewed X-inactivation, there are several additional rare circumstances in which a female carrier may manifest with earlier and more severe dystrophy (1, 5, 7).

In our case, non-randomized X-inactivation or unfavourable lyonization was the mechanism for marked dystrophin underexpression. X-inactivation is considered non-randomized or "skewed" if 80% or more lymphocytes in the blood have the same active X-chromosome (6). In one study all female manifesting carriers studied showed skewed X-inactivation while all unaffected carriers studied showed symmetrical X-inactivation (10). However, there are examples where symptomatic patients do not display significant X-inactivation (2). The gold standard for diagnosis remains immunostaining for dystrophin with a mosaic distribution of positive and negative fibers in both cardiac and skeletal muscles. However, immunostaining has not been shown to correlate accurately with the severity of diseases(4, 9). While predicting progression is difficult, diagnosis is essential to genetic counseling. (The full text for this discussion can be found at: http://path.upmc.edu/divisions/neuropath/bpath/cases/case190/dx.html).

REFERENCES

1. Boyd Y, Buckle V, Holt S, Munro E, Hunter D, Craig I (1986) "Muscular dystrophy in girls with X; autosome translocations." *Journal of Medical Genetics* **23**:484–490.
2. Ceulemans BP, Storm K, Reyniers E, Callewaert L, Martin JJ (2008) "Muscle pain as only presenting symptom in a girl with dystrophinopathy." *Pediatric Neurology* **38**(1):64–66.
3. Hoogerwaard EM, Bakker EM, Ippel PF, Oosterwijk JC, Majoor-Krakauer DF, Leschot NJ, Van Essen AJ, Brunner HG, van der Wouw PA, Wilde AAM, de Visser M (1999) "Signs and symptoms of Duchenne muscular dystrophy and Becker muscular dystrophy among carriers in the Netherlands: a cohort study." *The Lancet* **353**:2116–2119.
4. Hoogerwaard EM, Ginjaar IB, Bakker E, de Visser M (2005) "Dystrophin analysis in carriers of Duchenne and Becker muscular dystrophy." *Neurology* **65**(12):1984–1986.
5. Katayama Y, Tran VK, Hoan NT, Zhang Z, Goji K, Yagi M, Takeshima Y, Saiki K, Nhan NT, Matsuo M (2006) "Co-occurence of mutations in both dystrophin- and androgen-receptor genes is a novel cause of female Duchenne muscular dystrophy." *Human Genetics* **119**:516–519.
6. Naumova AK, Olien L, Bird LM, Slamka C, Fonseca M, Verner AE, Wang M, Leppert M, Morgan K, Sapienza C (1995) "Transmission-ratio distortion of X chromosomes among male offspring of females with skewed X-inactivation." *Developmental Genetics* **17**(3):198–205.
7. Quan F, Janas J, Toth-Fejel S, Johnson DB, Wolford JK, Popovich BW (1997) "Uniparental Disomy of the Entire X Chromosome in a Female with Duchenne Muscular Dystrophy." *American Journal of Human Genetics* **60**:160–165.
8. Romero NB, De Lonlay P, Llense S, Leturcq F, Touati G, Urtizberea J, Saudubray JM, Munnich A, Kaplan JC, Recan D (2001) "Psuedo-metabolic presentation in a Duchenne muscular dystrophy symptomatic carrier with 'de novo' duplication of dystrophin gene." *Neuromuscular Disorders* **11**:494–498.
9. Sewry CA, Sansome A, Clerk A, Sherratt TG, Hasson N, Rodillo E, Heckmatt JZ, Strong PN, Dubowitz V (1993) "Manifesting carriers of Xp21 muscular dystrophy; Lack of correlation between dystrophin expression and clinical weakness." *Neuromuscular Disorders* **3**(2):141–148.
10. Yoshioka M, Yorifuji T, Mituyoshi I (1998) "Skewed X inactivation in manifesting carriers of Duchenne muscular dystrophy." *Clinical Genetics* **53**:102–107.

ABSTRACT

A 9-year-old female patient experienced progressive weakness and myalgias of shoulders and back of several months duration. Her medical history was notable for spina bifida in association with a Chiari type II malformation and hydrocephalus. Developmental motor milestones were delayed whereby walking began at age 2. She had mild bowel and bladder dysfunction. At presentation, her neurological exam was notable for weak shoulder adduction, hip and knee flexion and she demonstrated a partial Gower's maneuver. A muscle biopsy showed dystrophic changes and immunohistochemical findings of a Duchenne's mosaic which was confirmed by DNA analysis. The proposed pathogenesis in this case is unfavourable lyonization, which was corroborated by X-inactivation studies.