

CLINICAL QUIZ

How much do you know about Duchenne Muscular Dystrophy?

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WHAT IS DUCHENNE MUSCULAR DYSTROPHY?

Muscular dystrophies are a group of diseases characterized by the following obligate criteria:

- 1) They are primary myopathies.
- 2) Degeneration and death of muscle fibers occurs at some stage in the disease.
- 3) They have a genetic basis.
- 4) They follow a progressive course.

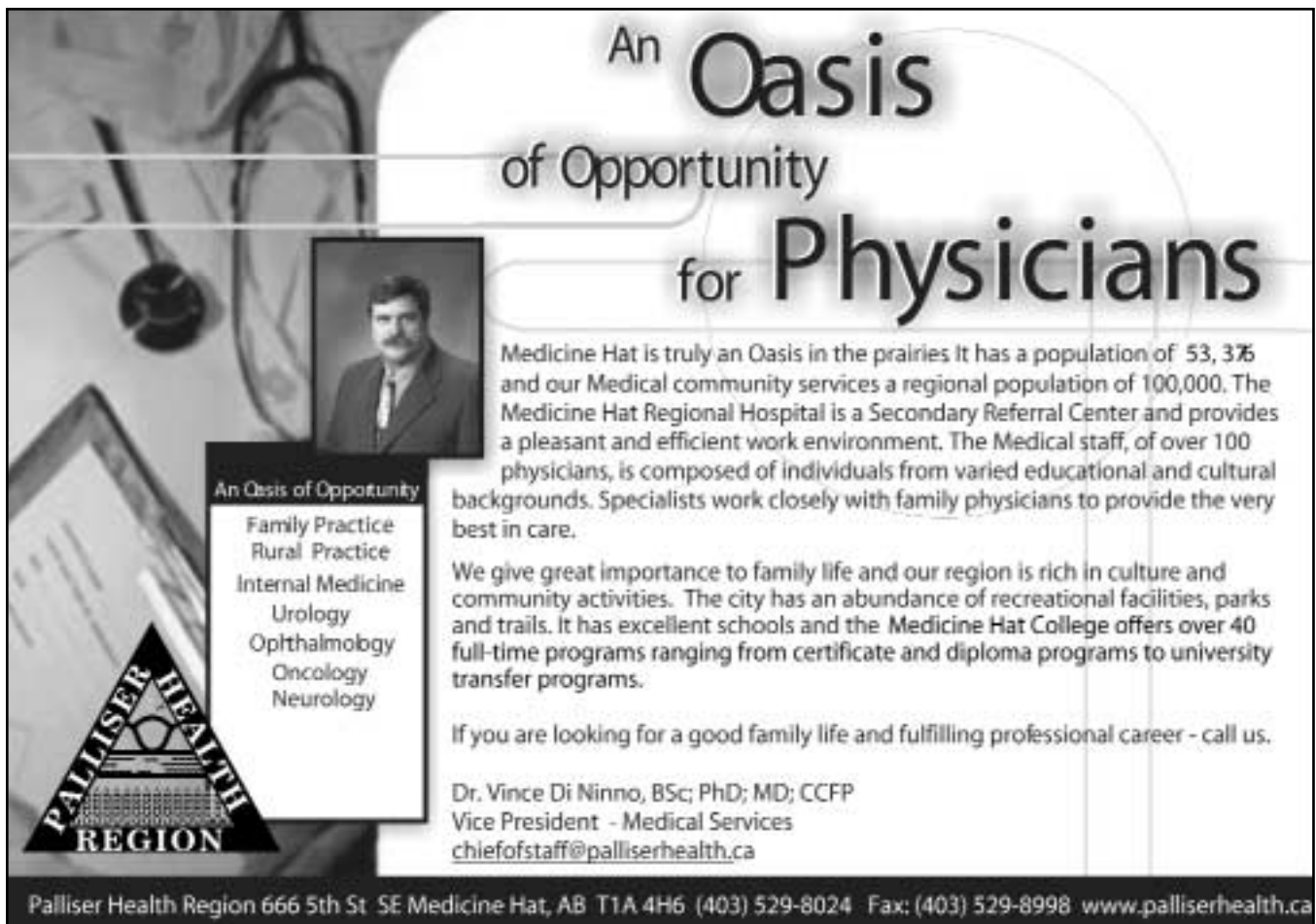
Duchenne muscular dystrophy (DMD) is one of the most common hereditary neuromuscular diseases, affecting all races and ethnic groups. One of every 3,500 live infant boys will be born with DMD. Duchenne first described the characteristic clinical features in 1861 after seeing boys with progressive weakness, hypertrophy of the calves, intellectual impairment and proliferation of connective tissue in muscle.

Precise diagnosis of DMD is crucial, as it carries both genetic and prognostic implications. Once a diagnosis of DMD is made, appropriate management may be instituted and family members may be screened for the dystrophic mutation. As well, advances in molecular genetics are providing new means of evaluating patients with this condition. Appropriate awareness and treatment of the cardiovascular and respiratory aspects of DMD also allow for a better prognosis for DMD patients. As the pathogenesis of DMD includes many systemic complications, promoting an interdisciplinary approach to these patients' care will help maximize their quality of life.

This quiz is designed to evaluate your knowledge of DMD. Answers along with explanations are located at the end of the quiz.

- 1) **DMD is most commonly inherited in the following pattern:**
 - a) Autosomal dominant
 - b) Autosomal recessive
 - c) X-lined recessive
 - d) Sporadic mutation
- 2) **What role does dystrophin play in the muscle cell?**
 - a) Dystrophin works to increase the ability of actin and myosin to bind together.
 - b) Dystrophin is a transport protein that helps control the intracellular environment of the myocyte.
 - c) Dystrophin works to link the cytoskeleton with the extracellular matrix.
 - d) None of the above.
- 3) **Which of the following is true of female carriers of the dystrophin mutation?**
 - a) Creatine Kinase (CK) levels are elevated in 80% of carriers.
 - b) CK levels are highest between the ages of eight and twelve.
 - c) Clinically apparent muscle weakness occurs in 2.5 - 20% of female carriers.
 - d) All of the above.
- 4) **Most patients with DMD exhibit clinical signs of muscle weakness between:**
 - a) 0-2 years
 - b) 2-5 years
 - c) 5-7 years
 - d) 7-9 years
- 5) **The pattern of weakness that predominates in the early stages of DMD is:**
 - a) Proximal muscles and lower extremities.
 - b) Distal muscles and upper extremities.
 - c) Proximal muscles and upper extremities.
 - d) Distal muscles and lower extremities.
- 6) **Which of the following is NOT a common finding on physical exam?**
 - a) Trendelenburg (waddling) gait
 - b) Pseudohypertrophy of calves
 - c) Hyperreflexia
 - d) Lumbar lordosis

- 7) **Pseudohypertrophy is characterized by:**
- An initial increase in number of muscle cells to compensate for the degenerating muscle cells.
 - Local interstitial edema.
 - An increase in muscle bulk to compensate for proximal muscle weakness.
 - An initial increase in the size of muscle fibers, followed by an increase in muscle volume due to deposits of fat and connective tissue.
- 8) **All of the following tests are helpful in diagnosing DMD except:**
- Pelvic X-Ray
 - Electromyography
 - Serum levels of muscle enzymes
 - Muscle Biopsy
- 9) **Associated conditions of DMD include:**
- Tendon and muscle contractures
 - Kyphoscoliosis
 - Intellectual impairment
 - Obesity
 - All of the above
- 10) **Patients with DMD have sensory disturbances and autonomic dysfunction:**
- True
 - False
- 11) **Which of the following therapies is recommended for treating select DMD patients?**
- Oxandrolone
 - Aziathioprine
 - Cyclosporine
 - Prednisone
- 12) **The most common cause of death in DMD patients is:**
- Arrhythmia secondary to cardiomyopathy
 - Cardiorespiratory insufficiency and its ensuing complications
 - Heart failure
 - Toxicity from muscle fiber breakdown products
- 13) **What is the most likely life expectancy of someone with DMD?**
- 20-25 years old
 - 30-35 years old
 - 35-40 years old
 - 15-16 years old



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ANSWERS

- 1) **C**
DMD is an X-linked trait. It is located in the Xp21 region and encodes the protein dystrophin. Seventy percent of cases are male offspring of female carriers of the gene mutation. However, up to 30 percent of cases are new mutations.
- 2) **C**
Dystrophin is an essential component of the dystrophin-glycoprotein complex (DGC) and links the cytoskeleton with the extracellular matrix. The DGC strengthens the sarcolemmal membrane and protects it against mechanical injury during contraction. The absence or decreased level of dystrophin in DMD patients weakens and disrupts the sarcolemmal membrane, thus allowing calcium entry and an ensuing process which causes muscle fiber necrosis.
- 3) **D**
Carrier detection of at-risk females is possible after the detection of a DNA deletion or duplication in an affected family member. Although mild (three times the upper limit of normal), elevations in CK are noted in up to 80% of female carriers. Most carriers of the dystrophin mutation are asymptomatic, and those symptomatic carriers often present with higher CK levels. Female carriers will demonstrate highest CK levels between eight and twelve years of age.
- 4) **B**
Patients born with DMD will be normal at birth and will often achieve all normal motor milestones in infancy. Walking is often delayed in DMD patients, and the first clinical signs manifest around age two or three, when the child finally begins to walk. Patients usually exhibit marked clumsiness and instability, and parents often complain that their child has frequent falls. The child may also have difficulty puckering their lips or may be less able to change their facial expressions. By age eight, the child has difficulty walking up stairs and by the age of twelve, most DMD patients are in a wheelchair.
- 5) **A**
The pattern of weakness in DMD first begins in the pelvic girdle muscles then extends to the shoulder girdle. Weakness is more predominant in proximal muscles and, and this is reflected in the child's compensation for weakness in the pelvic and shoulder girdles. One of the classic signs demonstrating this compensation is Gower's sign. To stand up, the child rolls from his back to his stomach, pushes himself up on all fours and then "walks" up his legs and thighs with his hands until he's in standing position.
- 6) **C**
Deep tendon reflexes remain normal or are decreased in patients with DMD. Ankle jerks are relatively preserved until the terminal stages, while the knee jerk reflex is less brisk than the ankles by age six, but is eventually lost. As well, it is common to find a stronger brachioradialis reflex compared to either the biceps or triceps reflex. A waddling gait and lumbar lordosis typically result from proximal muscle weakness.
- 7) **D**
Muscle biopsy of DMD patients demonstrates degeneration and regeneration of muscle fibers, isolated hypertrophic fibers, and significant replacement of muscle by fat and connective tissue. Muscle fiber necrosis and subsequent fibrous changes are intertwined with the inflammatory response, which also causes the initial enlargement of individual muscle fibers. However, the calves appear large due to an increase in deposits of fat and collagen, not due to the inflammatory response or an increasing number of muscle fibers.
- 8) **A**
Elevated serum levels of creatinine kinase and a muscle biopsy revealing minimal dystrophin are diagnostic of muscular dystrophy; however muscle biopsy remains the gold standard. Biopsy reveals the pathological process that involves both the consequence of the genetic mutation and the involvement of the immune system: there is a decrease or absence of dystrophin (<3% of the normal dystrophin [< 365 U/L] concentration) as determined by immunocytochemistry. CD8+ and macrophages are also found, both of which contribute to the eventual destruction of the cell. An electrodiagnostic consultation from a neuromuscular specialist is important to exclude motor neuron or peripheral nerve disorders.
- 9) **E**
With the atrophy of muscle fibers resulting in weakened muscle strength, the pressure on joints shifts. There are two common complications due to the lack of muscular support: contractures and scoliosis. More than 95% of children with DMD will develop scoliosis, which progresses at a rate of approximately 10 degrees for each year that a child is in a wheelchair. Varying degrees of intellectual impairment are found in DMD patients, though rarely a child presents with average or above average intelligence. Obesity is a frequent problem because of the decreased ability to move therefore a decreased use of calories. This lowers the child's caloric requirement to a point where even a normal diet can lead to obesity.
- 10) **B**
Patients with myopathies do not have sensory disturbances or autonomic dysfunction as the peripheral nerves and the autonomic nervous system are spared.
- 11) **D**
The pathophysiology of DMD is driven by the lack of the protein dystrophin which, in the normal person, contributes to the strength and longevity of muscle cells. Although the lack of dystrophin 'weakens' the cell, the final stage in the death of the cell involves an inflammatory response, whereby the immune system recognizes the damaged cell, then proceeds to destroy it. A recent study by Griggs *et al.* (1993) has shown that the use of immunosuppressants can slow the rate of muscle atrophy and its associated weakness, at least in the short term.
- This prospective double-blind study examined the effects of prednisone on DMD patients. Compared to placebo, those randomized to high dose prednisone (1.5 mg/kg/d) showed significant improvement in walking, standing, lifting weights, and arising from a supine to standing position. These benefits appeared within 10 days and peaked by three months. However, significant side effects included weight gain, hypertension, behavioural changes, growth retardation and cataracts. Prednisone at lower doses (75 mg/kg/d) is therefore recommended for ambulatory DMD patients older than 5 years. Immunosuppression with azathioprine has not been shown to be beneficial. Cyclosporine has been shown to improve clinical function in children with DMD, however due to rare reports of myopathies associated with other drugs (e.g. statins), its use remains controversial. Pilot studies with

oxandrolone, an anabolic steroid, have shown improved quantitative muscle strength with fewer side effects. However, this effect only lasted for 6 months. As DMD has a high incidence in all populations, there is a significant amount of ongoing research investigating novel therapies to improve the morbidity and mortality of the disease.

12)B

In the adult phase of DMD, scoliosis, weakened respiratory muscles, inactivity and obesity compromise both lung expansion and function. By age 14, the patient's vital capacity can be reduced to up to half of the original vital capacity. The muscle weakness also limits the cough reflex, thus predisposing the patient to pneumonia. Cardiomyopathy is a common feature in DMD patients, occurring in a significant percentage of patients. Together, these respiratory and cardiac complications eventually lead to cardiorespiratory insufficiency.

13)A

Although DMD is a relatively common disease, there have been few breakthroughs in the treatment and management of these patients. Historically, DMD patients lived on average, until their late teens, and rarely past the age of 20. With the recent recognition of DMD's cardiopulmonary complications and the availability of more respiratory support, patients now live to approximately 20 – 25 years, and sometimes beyond that. At the moment, however, the prognosis continues to be poor, with minimal functional ability and death before age 30.

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AUTHOR BIOGRAPHIES

Rahima Nenshi and Kelly Strode are both in their final year of the McMaster Undergraduate MD Program.

REFERENCES

1. WebMD Scientific American Medicine, 2001. Neurology: III, Diseases of Muscle and the Neuromuscular junction.
2. Darras, BT. (2003). Duchenne and Becker Muscular Dystrophies. UpToDate online version 11.3. Retrieved from the January 2, 2004 from the World Wide Web : www.uptodate.com
3. De Giralami, U, Anthony DC and Frosch, MP. (1999). "Peripheral nerve and skeletal muscle". In: Robbins: Pathologic basis of disease, 6th ed. Cotran RS, Kumar, V and Collins T. W.B. Saunders: Philadelphia. 1269-1291.
4. Fenichel, GM, Griggs, RC, Kissel, J, et al. (2001). A randomized efficacy and safety trial of oxandrolone in the treatment of Duchenne dystrophy. Neurology. 56(8): 1075-9.
5. Fenichel G, Pestronk A, Florence J, et al. (1997). A beneficial effect of oxandrolone in the treatment of Duchenne muscular dystrophy: a pilot study. Neurology. 48(5): 1225-6.
6. Griggs, RC. (2001). "Muscle Diseases". In: Cecil Essentials of Medicine, 5th ed. Andreoli TE, et al. (eds.) W.B. Saunders: Philadelphia. 988-997.
7. Griggs RC, Moxley RT, Mendell JR, et al. (1993) Duchenne dystrophy: randomized, controlled trial of prednisone (18 months) and aziathioprine (12 months). Neurology. 43(3 Pt 1): 520-7.
8. Jennekens, F.G.I., Ten Kate, L.P., De Visser, M., and Wintzen, A.R. (1991). Diagnostic criteria for Duchenne and Becker muscular dystrophy and myotonic dystrophy. Neuromuscular Disorders. 1: 389-391.
9. Mendell JR, Moxley RT, Griggs RC, et al. (1989).

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