DUCHENNE MUSCULAR DYSTROPHY

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Duchenne muscular dystrophy (DMD), an X-linked disorder, is the second most common single gene disorder in children presenting in early childhood. Duchenne defined the disease as being characterized by: progressive weakness of movement, first affecting the lower limbs and then later the upper limbs; a gradual increase in the size of many affected muscles; an increase in interstitial connective tissue in affected muscles with the production of abundant fibrous and adipose tissue in the later stages.
Fig. 3.2 Extensive muscle enlargement (pseudohypertrophy) in a case of DMD. (Reproduced by kind permission of Dr Sarah Bundey.)
The most common presentation is delay in walking and unsteady gait, with a tendency to walk on tiptoes. Patients usually become wheelchair-bound by the age of 12 years, and die of cardiorespiratory complications in their late teens to early twenties.
It is unlikely that an experienced physician would have any difficulty in suspecting Duchenne muscular dystrophy (DMD) in an otherwise healthy young boy who presents with a waddling gait, pseudohypertrophic calves, and a positive Gower’s sign.
Fig. 3.3  A 5-year-old with DMD showing the typical Gowers’ manoeuvre while rising from the floor.
The expression of dystrophin (a direct protein test) allows a confident diagnosis to be made of DMD. However, it is not always possible to predict with precision the phenotype resulting from the mutations in the dystrophin gene by DNA analysis alone. The diagnosis of DMD can be established in all cases on the basis of the clinical findings, SCK level, muscle biopsy for histology and dystrophin studies and DNA testing.
Advances in the management of DMD, including treatment with corticosteroids and the use of intermittent positive pressure ventilation have provided improvements in function, ambulation, quality of life and life expectancy, although novel therapies still aim to provide a cure for this devastating disorder.
The incidence of DMD is approximately 1 in 3500 live male births. The majority of female DMD carriers are asymptomatic. However, 2-20% of carriers have clinically evident muscle weakness. DMD is caused by mutations in the DMD gene, one of the largest known genes in humans. This gene encodes the protein dystrophin
Molecular genetic testing is now the mainstay of diagnosis. A multiplex polymerase chain reaction (PCR), covering 18 exons at the deletion hotspots developed by Chamberlin and Beggs detected 90-98% of all deletions. Complex segregation analysis in a large number of families with the disease indicates that the gene for DMD is always fully penetrant.
Gowers recognized the familial nature of Duchenne muscular dystrophy very early. He also noted that the disorder was limited to males and transmitted by healthy females, a mode of inheritance now recognized to be that of an X-linked recessive trait.
Palliative treatment therefore represents an essential tool to enhance affected boys’ quality of life. Although DMD is not curable, effective treatments are available that can improve the quality of life and survival of affected boys.
Paramount is the maintenance of good general health with emphasis on good nutrition and weight control, the prevention of deformities, and the preservation of respiratory function. There are now good reasons to entertain cautious optimism that an effective treatment for DMD may well be found in the not too distant future.
There is currently no known cure for Duchenne muscular dystrophy. However, the location of the defective gene and the recent isolation of dystrophin, the protein encoded by that gene, raises the possibility that this disease may eventually be cured by gene splicing and by the replacement of the genetic deletion.
Description of Genetic Case

• 19 year-old non ambulatory male with pneumonia

• James, a 19-year old male, is immobile and hospitalized for pneumonia. He has a long history of progressive weakening of his muscles. In the first year of his life, James reached many gross motor skill milestones, such as holding his head up, rolling over, sitting, and standing, at normal times. However he did not walk until age 16 mos,
and by age two, started to assume a lordotic Posture while standing but not while sitting. A Gower’s sign was noted by age four, as well as a Trendelenberg gait. Over the next several years, he suffered progressive muscle weakness, most notably in the proximal musculature of the arms, pelvis, and legs. By age 9, he required orthotic braces to assist his walking, and by age 11, he was confined to a wheelchair ambulation.
In his early teen years, James was still able to use eating utensils, write, and type on a keyboard, though these functions have declined over the past year. At 16, he was hospitalized with bronchitis requiring antibiotic treatment, but recovered. Throughout the years, James has had no history of muscle pain or spasm, chest pain, or irregular heartbeat. He was diagnosed
with a learning disability in the fourth grade, but has progressed through the grades with tutorial assistance. The only medications that he normally takes are calcium and fluoride supplements. James has a younger sister in good health and a younger brother (age 10) who is confined to a wheelchair with problems similar to James’s. Mom is now pregnant with a confirmed male child. No other immediate or distant
family members have any musculoskeletal difficulties.
Ethical Dilemma/Situation

SHOULD ALL NEWBORN MALES BE SCREENED FOR DUCHENNE MUSCULAR DYSTROPHY?
Facts of the Case

• James suffers from a condition called Duchenne Muscular Dystrophy
• James has gradual weakening of the respiratory muscles, and therefore has a difficult time completely expanding his lungs
• DMD is an X-linked disorder
• DMD is caused by mutations in the DMD gene, this gene encodes the protein dystrophin
• Screening is the identification, in an apparently healthy population, of those people who are at risk for a specific disorder

• Often takes more than two years for a diagnosis of DMD to be confirmed
Clinical/Psychosocial Issues Influencing Decision

• Wealth, crime, occupational choice and legitimate inequalities in society
• The role of social, cultural and political forces in structuring science and scientific medicine
• Increase human knowledge and make a substantial impact on the burden of such a disease
• Guilt and remorse-proper information appears to be the only way to prevent this from happening
Initial Plan

• Whether it is a prenatal screening by ultrasound, newborn screening or carrier screening, the information gained empowers individuals to make decisions and shape an informed future for themselves.
Policies & Ethical Code Directive

- Professional Duty to Care
- WHO guidelines - voluntary not mandatory, preceded by adequate information about the purpose and possible outcomes of the screen
Ethical Principle Analysis

• Should all newborn males be screened for Duchenne muscular dystrophy?
  – The question of informed consent
• “A New Test for Baby Boys: Do You Want It?”
• MORAL RESPONSIBILITY IN MEDICINE: BENEFICENCE OR AUTONOMY?
• It is the practical application of these two apparently conflicting philosophical frameworks that will be explored in the context of newborn screening for DMD
• Should the physician be servant of the “art” or servant of the “client?”
Possible Legal Issues

- American Medical Association, E-2.137 Ethical Issues in Carrier Screening of Genetic Disorders, 1994: The Association recommends that all carrier testing must be voluntary, and informed consent from screened individuals is required.
- Carrier testing should be available uniformly among the at-risk population being screened.
Issues Cont’d

• If testing is offered to some patients, it should be offered to all patients within the same risk category

• Discrimination should not be permitted against carriers of genetic disorders through policies about testing and reproduction
QUESTIONS??????????