Duchenne's muscular dystrophy in six siblings

The case for early diagnosis and neonatal screening

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Summary

Six brothers aged from 15 months to 13 years with confirmed Duchenne's muscular dystrophy are described. The serum creatine kinase levels ranged from 2420 IU/l in the youngest boy to 769 IU/l in the eldest. The diagnosis of Duchenne's muscular dystrophy was only made when the eldest boy was 13 years old, despite the fact that his parents had sought medical advice when he was 5.

The importance of early diagnosis, detection of carriers and neonatal screening is discussed in relation to the prevention of Duchenne's muscular dystrophy.

Of the chronic neuromuscular disorders of childhood, Duchenne's muscular dystrophy is one of the commonest forms. It is characterized by the onset of symptoms of proximal muscle weakness when the child is between 3 and 5 years of age, a progressive course with loss of ambulation between 10 and 12 years of age and death due to respiratory or cardiac causes in the late teens. It is an X chromosome-linked recessively inherited disease. Because most of the affected boys present with symptoms for the first time only after the age of 2 years, it is not unusual to have 2 and sometimes even 3 affected boys in the same family. Between 13 and 18% of children with Duchenne's dystrophy are born into families in which there is already an affected child who has not been diagnosed. This article describes a unique family in which 6 of 7 brothers suffer from Duchenne's dystrophy.

Case histories

Case 1

The eldest son, aged 13 years, has had difficulty in walking since the age of 3. Apparently he first walked at a normal age, but had been unable to run or climb stairs and until a few months before presentation used to walk on his toes. He is now unable to walk or stand.

On examination he had proximal muscle weakness and wasting of his pelvic and shoulder girdle muscles, this being more severe in the pelvis. All reflexes were absent. There was no pseudohypertrophy. He had flexion contractures of his knees, hips and elbows. The serum creatine kinase (CK) level was 769 IU/l and an ECG showed evidence of left ventricular strain. He is in the 2nd-year class at school.

Case 2

This 11-year-old was unable to run or climb stairs. He walked on his toes and had difficulty in getting up from the floor. On examination he had marked lumbar lordosis, pseudohypertrophy of the calves and tongue and a positive Gower's sign. Reflexes in the lower limbs were absent. The serum CK level was 989 IU/l and an ECG showed evidence of biventricular hypertrophy. He is in the beginners' class at school.

Case 3

This 8-year-old boy had meningitis as a baby and only started walking at 4 years of age. He walked on his toes with a waddling gait and lumbar lordosis. He also had pseudohypertrophy of the calves and a positive Gower's sign. Reflexes were absent. The CK level was 1136 IU/l, and an ECG showed biventricular hypertrophy. He does not yet attend school.

Case 4

This son, aged 6 years, had difficulty getting up stairs and was unable to run. He first walked at the age of 2 years. On examination he had pseudohypertrophy of the calves and thighs, lumbar lordosis, a waddling gait and a positive Gower's sign. The upper limb reflexes were absent, the knee jerks depressed and the ankle jerks normal. The serum CK level was 1209 IU/l and an ECG showed right ventricular hypertrophy.

Case 5

This 2-year-old boy was not yet able to walk, stand or pull himself up on his own. He sat at 1 year of age and shuffled on his bottom. He was able to sit without support, but was unable to stand or bear weight on his legs. He was hypotonic. The upper limb reflexes were absent but those in the lower limbs were present and equal. There was no pseudohypertrophy of the muscles. The serum CK level was 1036 IU/l. The ECG showed nonspecific T-wave flattening over the left precordial leads.

Case 6

The youngest affected son, aged 15 months, was unable to stand or walk. He sat at the age of 9 months and shuffled on his bottom. He was able to sit up from the supine position. He had wasting of the shoulder girdle and lower limb muscles. He kicked his legs and was able to lift up his arms. His hips abducted to 180°. The reflexes were all present and equal, and there was no pseudohypertrophy of the muscles. The serum CK level was 2420 IU/l, and an ECG showed evidence of severe right ventricular hypertrophy.

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**Family history (Figs 1 and 2)**

There are 2 other siblings (a boy aged 4 months and a girl aged 15 years), both of whom are clinically and biochemically normal. The mother had 3 brothers, 1 of whom died of muscular dystrophy at the age of 16 years. She is therefore definitely a carrier.

**Muscle biopsies**

Muscle biopsies were carried out in all 6 siblings and they showed the typical changes of muscular dystrophy, ranging from variation in fibre size, internalization of nuclei, mild fibro-fatty replacement, degeneration of fibres and clusters of basophilic fibres in the youngest patient, to increasing fibro-fatty replacement, fibre splitting and disintegration of fibres in the older children.

**Discussion**

This family illustrates several points of interest in Duchenne's dystrophy:

**Genetics**

The X-linked nature of the inheritance in the family is confirmed by the affected brothers and an affected maternal uncle. In female carriers the risk of giving birth to an affected male is 1-in-2, but it is important to realize that this risk applies to each pregnancy. It does not mean that if the family has 6 boys, 3 will have the disease and the other 3 will not be affected. In this family the odds were against the mother for each of 6 pregnancies and in her favour for the last pregnancy. She was therefore most unfortunate to have 6 affected sons.

**Onset of symptoms**

The diagnosis of Duchenne's dystrophy was made exceedingly late in this family, by which stage the eldest sibling was no
longer ambulant; yet, 4 of the affected siblings had delayed motor milestones — 3 had not walked by 2 years of age and the other was not yet able to stand at 15 months. The 2 youngest affected children, aged 15 months and 2 years, were also hypotonic, whereas the unaffected 4-month-old infant had normal tone.

The parents had sought medical advice when the eldest child was about 3 years old, but were reassured that his 'laziness' would improve with time. Gardner-Medwin reported a mean age of 5.8 years at the time of diagnosis in a series of isolated and first affected cases in northern England, in spite of the fact that half of the patients had had symptoms before the age of 2½ years and all by 5 years. The fact that the diagnosis was not made in this family until the mother had borne 6 affected sons is a serious reflection of the provision of health care to this family.

Progression of disease

The inexorable progression of the disease from infancy to later childhood with delayed motor milestones, increasing difficulty with walking, and eventually total loss of ambulation is illustrated in these children.

CK levels

The serum CK level was elevated in all 6 affected brothers, the highest value being found in the youngest boy and the lowest value in the eldest. This is a well-recognized phenomenon, the explanation being that with advancing disease muscle bulk decreases, thus lowering the CK level. It also means that in presymptomatic affected infants the CK level will be markedly elevated, i.e. by 50- to 100-fold. A mild elevation of CK rules out Duchenne's dystrophy; such an elevation is not uncommon in otherwise normal infants in the first few days after birth.

Prevention

Could this tragedy have been avoided in this family?

Early diagnosis. The potential for prevention of this tragedy existed in this family. Health care professionals failed in two major respects:

1. The mother was not identified as a carrier. She had an affected brother, and had estimations of the serum CK level been performed there would have been a 70% chance of identifying her as a carrier.

2. There was an inordinate delay in diagnosing the affected brothers. The difference in age between the two eldest siblings was 2 years. The eldest affected child apparently began walking at a normal age, and it is therefore unlikely that the diagnosis could have been made by the time the second affected child was born (except if the mother had been identified as a carrier and then had heeded our genetic counselling). About 13-18% of children with Duchenne's muscular dystrophy are born into families in which there is already an affected child who has not yet been diagnosed. There is, however, no excuse for the diagnosis not having been made by the time the third son was born. By that time the oldest sibling was 5 years old and, as mentioned above, by this time all affected children have symptoms. The mother had sought medical advice at this stage but had been mistakenly reassured.

Screening of newborn infants. One sure way that this tragedy could have been prevented would have been by the screening of newborn male infants using Antonik's method of serum CK determination on a drop of blood. This method has been shown to be easy and reliable, and although false-positive results are common because of the presence of high levels of CK in the serum of newborn infants, these can be easily distinguished from true-positive results when Duchenne's dystrophy is sought. Four such screening projects have resulted in the identification of confirmed cases of Duchenne's dystrophy, the incidence in male infants being 1/1700 in Germany and 1/6000 in France. Unfortunately, this technique was not available at the time that the first son was born; had it been available the presence of Duchenne's dystrophy could have been identified in the first son and, theoretically, the birth of other affected siblings prevented. However, as Gardner-Medwin has pointed out, there is no guarantee that parents will heed the genetic advice given. I recall an intelligent, educated professional woman whose son had Duchenne's dystrophy and who was shown to be a carrier; she opted to take the 1-in-2 risk of having another affected son and refused fetal sexing. She gave birth to another son who, fortunately, was unaffected. She took this chance because she was quite convinced that if she did not produce a normal son her husband would remarry.

The whole question of routine neonatal screening is still debatable, especially as there is no treatment available for the disease. In an editorial in 1975, the British Medical Journal discussed the controversy and stated that it doubted the value of screening for an untreatable disease. Gardner-Medwin also argued against neonatal screening on the grounds that theoretically it would prevent only 10-15 cases of Duchenne's muscular dystrophy in the UK each year, but more especially on the grounds of the possible adverse psychological effects of early diagnosis on the families. He suggests that all male infants who are not walking by the age of 18 months be screened by means of estimation of the serum CK level — this would identify about 50% of the cases of Duchenne's muscular dystrophy. On the other hand, Zellweger argued for screening because: (i) about 70-90% of parents interviewed wanted to know at birth or soon afterwards whether their sons had Duchenne's muscular dystrophy so that they could make the necessary social, recreational and educational adjustments and prevent the birth of other affected sons; (ii) it is poor medical practice to withhold information from individuals at risk of certain diseases; and (iii) it may allow recognition of a sizeable number of female carriers of the Duchenne's muscular dystrophy gene — however, this is questionable because as Gardner-Medwin points out, we do not know enough about the significance of CK levels in carriers at birth or later in childhood.

There can be no doubt that the most important preventive measures are early diagnosis, detection of carriers and genetic counselling. All male children should be screened soon after birth. Where this is not possible, all male children who are not walking by 18 months, have a clumsy gait or frequent falls should undergo estimation of the CK level. All female relatives of patients with confirmed Duchenne's dystrophy should be investigated for carrier status by means of CK blood tests, and these should preferably be done at an early age. Appropriate genetic advice should then be given by experienced persons.

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REFERENCES