The female carrier of Duchenne muscular dystrophy

Duchenne muscular dystrophy is an X-linked recessive disorder, affecting only males and transmitted by females, who have a 50% risk of an affected son or a carrier daughter. The incidence has been estimated at between one in 3000 and one in 5000 male births, but not all the mothers of affected infants are carriers; a substantial proportion of cases will represent new mutations. According to Haldane, the mutation rate for a potentially lethal X-linked condition in which the biological fitness (fertility) of affected males is practically zero would be one-third. Estimates based on population studies have produced a similarly high figure.

If, then, one-third of the mothers of affected infants are not carriers the investigation of the carrier state and genetic counselling are vitally important for the families concerned. The first essential step in genetic counselling must always be to verify the diagnosis in the index case. Next, a detailed family tree should be constructed before investigation of the possible carrier is begun. A genetically definite or obligate carrier is a woman with an affected son and an additional affected male relative; all other female relatives are possible carriers.

The creatine kinase test is the most reliable for detecting carriers. The serum activity of the enzyme is grossly raised in patients with Duchenne dystrophy, and raised to a mild-to-moderate extent in some but not all female carriers of the gene. Several studies have shown the proportion of genetically obligate carriers with definitely raised creatine kinase activities to be about two-thirds. Since creatine kinase activity is normal in about a third of definite carriers it clearly does not exclude the carrier state. An accurate estimate of the statistical risk that a woman with a normal creatine kinase activity is a carrier can be made from the actual activity of the creatine kinase, on the basis of the distribution curves in normal controls and in obligate carriers and the application of Bayesian theory, which takes account both of the antecedent family history and of the creatine kinase activity of the person at risk and of other female relatives. Follow-up studies of families counselled in this way have verified the validity of this approach. The creatine kinase activity can be spuriously high after vigorous exercise and it drops during pregnancy. Genetic counselling requires the combined skills of the physician and the laboratory and is best undertaken in specialised centres; random counselling based on isolated results of estimation of creatine kinase can have disastrous consequences.

Other biochemical tests have been tried in the detection of carriers. Some, such as that based on raised serum activity of pyruvate kinase, are at least potentially practicable, though having little or no advantage over creatine kinase. Others, such as the tests based on abnormal polyribosomal protein synthesis of muscle in vitro, changes in phosphorylation of erythrocyte membrane spectrin II, increased lactate dehydrogenase isoenzyme 5, and reduction in lymphocyte capping, are much more complex and still need validation. Electrocardiographic abnormalities, changes on quantitative electromyography, and pathological changes in the muscle under light or electron microscopy have also been used as supplementary tests for detecting carriers; and some authors have favoured combined tests.

All these methods detect only some carriers; but an abnormality on one test, such as abnormal histological appearances of muscle, may occur with normal activities of creatine kinase and vice versa. Careful quantification of histochemical and histological features on needle biopsy in obligate carriers and volunteer controls has helped to standardise the methods and to identify significant deviation in fibre size, fibre type, and internal nuclei. On clinical examination several features may be found in carriers, ranging from prominence of the calves (often unilateral) through muscle cramps or minimal weakness to overt muscle wasting and weakness. Moser and Emery estimated that about 8% of female carriers have symptoms. Roses et al detected muscle weakness in a very high proportion of female relatives but as their findings were based on subjective manual testing more objective quantitative estimates of muscle force in definite carriers and normal controls are needed to validate (or refute) this claim.

The striking variability of all abnormalities in carriers can be explained on the Lyon hypothesis of random inactivation in each cell of one X chromosome, which can be either the paternal (normal) or maternal (abnormal) X chromosome. This would also explain the discordance of creatine kinase
activity and histological features\(^1\) or of clinical weakness\(^4\) in monogenic twin carriers.

The overtly weak heterozygote with the Duchenne gene may on rare occasions manifest the actual disease owing to a concomitant chromosomal abnormality such as (presumptive) Turner’s syndrome (45, 46), XO/XX mosaicism\(^4\) or a translocation with partial deletion of the X chromosome.\(^4\) Such women must also be distinguished from those with autosomal recessive limb girdle dystrophy.\(^4\) A further three carriers of Duchenne muscular dystrophy with overt clinical weakness, high creatine kinase activities, electrophysiographic abnormalities, and histological changes have recently been reported from Japan.\(^4\) Only one was a genetically definite carrier (with two affected sons and an affected brother); the other two were mothers of isolated cases.

Accurate diagnosis of the non-carrier state in the female at risk, such as the sister of an affected boy, continues to present a difficult clinical problem. At present the best that can be offered is a statistical estimate based on accurate laboratory and associated data. Further tests based on secondary manifestations of the gene are unlikely to help to identify all carriers more accurately. For this we may have to await discovery of the basic biochemical abnormality, unless the application of recent advances in recombinant DNA technology\(^4\) provides a reliable marker for Duchenne dystrophy.

Hopefully, diagnosis on the basis of the defect in DNA would accurately diagnose all cases, both prenatally and post-natally, as well as all carriers of the gene, even before the fundamental abnormality became clinically apparent.

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