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THE CARRIER IN DUCHENNE MUSCULAR DYSTROPHY

The muscular dystrophies are defined as a group of inherited disorders in which primary degeneration occurs in the muscle fibre.[1] There are probably three clinically distinct forms of muscular dystrophy which are inherited as X-linked recessive traits: that described by Duchenne,[2] a much rarer and less severe form recently defined by Becker[3] and a possible third variety, that reported by Dreifuss and Hagan.[4]

Of the several names which have been appended to the type of dystrophy which affects young boys, 'pseudohypertrophic muscular dystrophy' is perhaps the best known. This term is entirely descriptive, however, and can apply to other forms of dystrophy equally well. In accord with the suggestion of Walton,[5,6] therefore, the variety affecting young boys should be designated Duchenne muscular dystrophy. The latter is the commonest form of muscular dystrophy in the United States, affecting 279 out of every 1 million male births.[7] The evidence for X-linkage is three-fold:

(*a*) Affected children have been born of the same mother but of different fathers.

(*b*) In the few cases where affected males have survived long enough to reproduce, all their male offspring have been normal.

(*c*) Affected females have been noted to be examples of Turner's syndrome with an XO karyotype[6,8]—the XO status being equivalent to the hemizygous male (XY), where in both cases the abnormal gene is 'unopposed' on the single X.

Typically, the clinical picture is of onset in infancy or early childhood. There is weakness of the lower limbs and pelvic girdle associated with swollen calves. The condition progresses to involve the shoulder girdle, the patient is later unable to walk and is confined to a wheel chair by the age of 10. Later there is considerable muscle atrophy with contracture deformities, and death occurs at about the age of 20 from cardio-respiratory failure. The pedigree characteristically resembles that of classical haemophilia, with apparently normal females transmitting the peccant gene to half of their sons (who will be affected) and to half of their daughters (who like their mothers will be heterozygote carriers).

A formidable list of X-linked disorders in man has been compiled.[9] Further, the genes for the Xg^a blood group, glucose-6-phosphate dehydrogenase, deutan colour blindness and haemophilia have been spatially mapped along the X-chromosome in that order.[9] By contrast, nothing is known of the location of genes on the remaining 22 pairs of autosomes. The female receives one of her X-chromosomes from her mother (the matridinous-X or X^m) and one from her father (the patridinous-X or X^p). In terms of the Lyon hypothesis,[10,11] about 50% of the female's X-chromosomes become genetically inactivated somewhere before the 16th day of embryogenesis (this process being termed 'lyonization'). Lyonization appears to be random: in some cells the X^p is inactivated, in others the X^m. The proportion of functional patridinous and matridinous X-chromosomes thus varies from female to female and a state of X-chromosome mosaicism in fact exists.

It is immediately apparent that the hypothesis serves to explain both dosage compensation in the female (i.e. why the products of genes situated on the X-chromosome are not present in twice the quantity in the female with her 2 X-chromosomes as compared to the male with only a single X), and why certain X-linked traits may be minimally apparent in the heterozygous female. Other aspects growing out of the hypothesis with particular emphasis on the cytogenetic implications, are dealt with elsewhere in this issue of the *Journal* (see Triplo-X syndrome).

The importance from the point of genetic counselling in being able to delineate the carrier accurately is obvious. It should be remembered that since one-third of the cases are new mutations, the chances that the mother of an affected child is a carrier (assuming there are no other affected males in her family) is only 66%. The daughter of a known heterozygote mother has a 50% chance of herself being a carrier. Against this background of the implications of the Lyon hypothesis, the great significance of X-linked traits in man and the desirability of defining the carrier, workers in the Division of Medical Genetics at the Johns Hopkins Hospital[12] have employed several approaches to characterize the heterozygote female.

A careful history and examination are important consistent with the Lyon hypothesis; some weakness and pseudohypertrophy were found in a few carriers for Duchenne dystrophy (2 out of 24). The female then, is not always completely physically normal and the clinician should be alert to this possibility.

Linkage studies (using glucose-6-phosphate dehydrogenase, the Xg^a blood group and colour blindness as 'markers') have not so far proved to be helpful.

Serum enzymes, on the other hand, have been of considerable value. The levels are well elevated in actual dystrophies. On the average, phosphohexoisomerase shows a 2·4-fold, SGOT a 3·3-fold, LDH a 3·8-fold, SGPT a 5·2-fold, aldolase a 9-fold and creatine phosphotinase (CPK) a 50-fold rise above normal levels.[13] CPK is thus by far the most sensitive serum index. Lesser but nonetheless significant elevations of CPK have been noted in 55% of carriers. The test is now performed as an initial procedure on suspected carriers seen at Johns Hopkins.

Electrocardiographic changes in Duchenne dystrophy are fairly characteristic. Abnormally large R waves in the right

precordial leads result in alteration of the algebraic sum of R and S waves in V1. Certain female carriers evince similar changes in later life, but the significance of this is not clear.

Of the muscle tests, electromyograms are overtly abnormal in dystrophies but are probably of little value in the evaluation of carriers. Muscle histology is far more rewarding, and in 7 out of 9 carriers abnormalities of varying severity (in accord with the Lyon hypothesis) were demonstrated. Finally, muscle extract may be submitted to starch-gel electrophoresis, when 5 distinct bands, representing the 5 lactic dehydrogenase isoenzymes, will be apparent. The quantities of these isoenzymes vary in different tissues and provides an example of differential gene action.[14] LDH_1 occurs predominantly in cardiac muscle (but also elsewhere) whereas LDH_5 is the form mainly present in skeletal muscle. In cases with dystrophy, LDH_5 is entirely absent from muscle. In all carriers so far tested there has been a reduction in LDH_5 with some increase in the fast-moving bands LDH_{1-4}, as compared to normals.

In essence then, the heterozygous female can be pinpointed with a considerable degree of certainty on the basis of serum CPK levels, muscle histology and muscle LDH isoenzyme pattern. The benefits accruing on the side of more accurate genetic prognosis are clear. Furthermore, because the actual dystrophic with his massive muscle necrosis may well represent a clouded biochemical picture, it seems likely that 'abnormalities' detected in apparently healthy female carriers may be considered to be more closely related to the primary lesion. Investigation of such females, therefore, may well increase our understanding of the aetio-pathogenesis of the disease.

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GEELSUG AS GEVOLG VAN GENEESMIDDELS

Lewerbeskadiging word in toenemende mate aan die gebruik van geneesmiddels toegeskryf.[1] Die mikroskopiese beeld en funksiestoornisse is in hierdie gevalle uiteenlopend van geaardheid. Ook die prognose en immunologiese agtergrond verskil van geval tot geval.[2]

Popper *et al.*[3] het nagegaan of die verskillende histologiese beelde van die lewerbiopsies van hul pasiënte 'n verband toon met die aard van die middel wat die lewerbeskadiging veroorsaak het, of met die kliniese simptome wat dit meebring. By byna die helfte van die gevalle deur hulle ondersoek (64 uit 137 geelsuglyers) was die lewerbeskadiging toe te skryf aan die gebruik van kalmeermiddels (mono-amien-oksidaseremmers of fenotiasienderivate).

Op grond van hul bevindings het die skrywers hul pasiënte in ses groepe ingedeel. Die mikroskopiese beeld het binne sekere grense spesifiek geblyk vir bepaalde giftstowwe. 'n Sentrale vetneerslag en nekrose van die lewerlobules is uitsluitlik waargeneem by 8 pasiënte wat tetrachloorstof, ortodichloorbensol of 6-merkaptopurien ingeneem het. By 16 pasiënte wat noretandrolon, metieltestosteroon en fenielbutasoon geneem het, was die bevinding uitsluitend cholestase, sonder nekrose van die lewerselle of die aanwesigheid van ontstekeningsinfiltraat. Hepatosellulêre beskadiging sonder cholestase, wat mikroskopies nie onderskei kan word van die bee'd van virushepatitis, is by 19 pasiënte waargeneem wat chloorpromasien, perfenasien, oksiefenbutasoon, para-amino-salisielsuur en difeniel-hidantoïne ingeneem het. 'n Groot groep is gevorm deur 50 persone met 'n ooreenstemmende biopsiebeeld en by wie cholestase wél opgemerk is. Die geneesmiddels wat hier betrokke was, was chloorpromasien, chloorpropanied, tolbutamied, metiemazal, uretaan, isoniasied, eritromisienestolaat, etionamied, arsfenamien en polietiasied.

In 61 biopsies kon die mikroskopiese beeld nie onderskei word van dié van virushepatitis nie; 39 van hierdie gevalle het ernstige nekrose van die lewerselle in alle stadiums vanaf akute atrofie tot postnekrotiese sirrose getoon. Die geneesmiddels wat hiervoor verantwoordelik was, was die mondelinge antidiabetikum metaheksamied en die mono-amien-oksidaseremmer iproniasied—wat sedertdien uit die handel onttrek is—en die narkosemiddel halotaan. By die 10 pasiënte waarby halotaan betrokke was, het die siekte binne enkele dae 'n dodelike verloop gehad.

Lewerbeskadiging in 'n ligte graad is by enkele pasiënte waargeneem waar geneesmiddels hoofsaaklik ander organe aangetas het. By een geval is 'n noodlottige vorm van lewerskade waargeneem, bestaande uit groot vetvakuoles in die middel van die lewer-lobules; dit was vantevore beskryf uitsluitend by swanger vroue wat binne-aarse en binnespierse toedienings van tetrasiklien in hoë dosisse ontvang het.

Schalm, sowel as Popper en ander navorsers, het tot die gevolgtrekking gekom dat cholestatiese ikterus as gevolg van geneesmiddels relatief dikwels voorkom, dog dat die prognose meestal gunstig is. Gevalle van geneesmiddels wat beskadiging van die lewerselle veroorsaak kom meer selde voor, maar is oor die algemeen meer noodlottig. Daarom word aanbeveel dat hierdie middels, waar moontlik, deur ander vervang moet word.

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