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PRACTICAL NEUROLOGY

Muscular Dystrophies and their Management

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The muscular dystrophies are a group of genetically determined disorders which give rise to progressive weakness and wasting of skeletal muscles; the nature of the pathological process responsible for these diseases is as yet unknown, but much has been learned in recent years concerning their classification, genetic characteristics, diagnosis, and management.

Classification

While rare ocular, distal, and congenital forms of muscular dystrophy exist, the most common varieties of the disease can be classified into three groups: the Duchenne, limb-girdle, and facioscapulohumeral forms.

The Duchenne type usually becomes apparent in young boys at about the age of 3 years with difficulty in walking, frequent falling, difficulty in climbing stairs, and a tendency to waddle. Such patients show characteristic difficulty in rising from the floor and often "climb up their legs" when doing so. Difficulty in walking generally increases progressively, so that by about the age of 10 years most children are unable to walk. Following confinement to a wheelchair at about this age, muscular weakness causes progressive skeletal deformity and multiple contractures. Cardiac muscle is almost invariably affected in the later stages, and most boys die from cardiac failure or respiratory infection before the end of the second decade. Hypertrophy of muscles (particularly calves, quadriceps, and deltoids) is a common feature in the early stages, but is later succeeded by progressive wasting. A disorder which is genetically and clinically similar, though of later onset and running a much more benign course, occurs in occasional families and is generally referred to as the benign X-linked *Becker type* of muscular dystrophy. The rare form of muscular dystrophy closely resembling the Duchenne type which occasionally afflicts young girls also tends to be less rapidly progressive than the classical Duchenne variety.

The limb-girdle type is seen equally in the two sexes and is generally manifest first in adolescence or early adult life, though occasionally such cases first develop in middle age. It is characterized by progressive and selective weakness and atrophy of proximal muscles, beginning either in the upper limbs (serratus anterior, pectorals, biceps, brachioradialis are usually affected) or in the lower (hip flexors, quadriceps, and anterior tibials are usually involved early). Sometimes muscular involvement is asymmetrical, and typically the first symptoms are difficulty in raising the arms above the head when the upper limbs are first affected, or difficulty in walking or in climbing stairs when the disease begins in the pelvic girdle. In general, the cases of scapulohumeral onset are somewhat more benign than those in which the pelvic girdle is first involved, but after 10 or 15 years it is almost invariable to find that the disease process spreads from the upper to the lower limbs or vice versa.

While much more benign than the Duchenne type, the condition is slowly progressive, and most patients become severely disabled in about 20 years from the onset and generally die before the normal age. Contractures and skeletal deformity occur late and cardiac involvement is uncommon in this group.

The facioscapulohumeral variety is the most benign of all. Facial involvement, with difficulty in closing the eyes, pouting of the lips (the tapir mouth), and inability to whistle or to retain air under pressure in the cheeks is soon apparent, and is accompanied by winging of the scapulae, difficulty in raising the arms above the head, and subsequently by involvement of biceps, brachioradialis, and of other arm and forearm muscles. In the legs the anterior tibial muscles are often first affected in these patients, but eventually a typical waddling gait with involvement of quadriceps, hamstrings, and hip flexors appears, and some patients with this form of the disease show a particularly striking accentuation of the lumbar lordosis. This variety also affects the sexes equally, and it is characteristic that within affected families some individuals suffer from the disease in a form so mild that they are virtually unaware that they have it. In these so-called abortive cases it is not uncommon to find that after progressive atrophy of certain selected muscles the disease fails to progress. While occasional cases are severely disabled in early adult life, many survive, though with increasing disability, to a normal life span.

Also classified at present with the muscular dystrophies is myotonic dystrophy or dystrophia myotonica. In this condition progressive weakness and wasting of facial muscles, of the sternomastoids, and of the distal muscles of the limbs is generally accompanied by the phenomenon of myotonia, seen particularly in the tongue, hand, and forearm muscles. Myotonia is the continued active contraction of a muscle persisting after the cessation of voluntary effort or stimulation. Patients with dystrophia myotonica commonly complain of stiffness of the muscles, of difficulty in relaxing the grip, and of other symptoms due to their myotonia rather than to their muscular weakness, at least in the early stages of the disease. Many patients also show frontal baldness in the male, cataracts, gonadal atrophy, and mental backwardness or dementia.

Diagnosis

When faced with a clinical picture suggesting a progressive and as yet incurable disease such as one of the muscular dystrophies, it is the doctor's first duty to confirm the diagnosis with reasonable confidence—for it is now clearly apparent that this is a condition which has many clinical imitators, some of which have a totally different prognosis, while others are amenable to treatment. Clinical examination alone, if painstakingly performed and combined with careful history-taking, is often invaluable in this regard, but of the modern investigative methods widely utilized in the diagnosis of neuromuscular disease the most important are serum enzyme studies, electromyography, and muscle biopsy.

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If more than one member of a family is affected it is then probable that the disease is genetically determined, an important point in favour of a diagnosis of a muscular dystrophy. On the other hand, recent experience has clearly demonstrated that *pseudomyopathic spinal muscular atrophy* (the Kugelberg-Welander syndrome) may present with proximal weakness and wasting in the upper and lower limbs in children; and in this disease, unlike other forms of neuropathic wasting, there may even be a modest rise in the serum creatine kinase. The pattern of muscular involvement is often different from that of muscular dystrophy (for instance, in the upper limbs the deltoid is commonly affected in spinal atrophy but is spared in the early stages of muscular dystrophy); the presence of fasciculation in the tongue or elsewhere is a valuable pointer to disease in the cranial nerves and in the anterior horn cells. The E.M.G. pattern of neuropathic, as distinct from myopathic, atrophy is usually distinctive, and muscle biopsy may be conclusive (despite increasing evidence to suggest that secondary myopathic change may commonly occur in chronically denervated muscle). While commonly affecting more than one member of a sibship—it is a disorder of autosomal recessive inheritance—benign spinal muscular atrophy of this type often carries a better prognosis than does muscular dystrophy of the Duchenne type. Not infrequently the disease becomes arrested for prolonged periods or even indefinitely, and it may vary in severity in more than one affected member of a family.

An increase in serum creatine kinase activity to 300 or more times the normal upper limit is found almost exclusively in the Duchenne type muscular dystrophy. However, less substantial but nevertheless striking increases can be observed in *polymyositis*. The electromyogram, as in muscular dystrophy, reveals short-duration or polyphasic (myopathic) motor unit action potentials on volition, though in *polymyositis* there may also be spontaneous fibrillation and positive sharp waves which are rarely seen in dystrophic subjects. While *polymyositis* is commonly associated with inflammatory changes in the skin, a Raynaud syndrome, or other evidence of collagen or connective tissue disease, there are many patients in whom the condition runs a subacute course and appears clinically to be limited to the voluntary muscles. The presence of dysphagia and of weakness of the anterior or posterior neck muscles is a valuable pointer to the diagnosis, as is the diffuse and relatively non-selective weakness, more severe than the degree of atrophy would suggest, which it commonly produces in proximal limb muscles. Sometimes, too, this condition runs a more acute or variable (relapsing and remitting) course than is ever observed in muscular dystrophy. It should also be noted that in muscular dystrophy the tendon reflexes tend to be lost early, particularly those subserved by the weakened muscles, while in *polymyositis* they are more often well preserved and even at times surprisingly brisk. Muscle biopsy is particularly valuable in differential diagnosis. Differential diagnosis between the two disorders must depend upon a combination of clinical, biochemical, electromyographic, and histological findings. It is of considerable importance, since most patients with *polymyositis* show substantial improvement or even eventually complete recovery on treatment with steroid drugs.

Apart from *polymyositis*, there are many other forms of myopathy affecting particularly proximal limb muscles which may on occasion resemble muscular dystrophy. These include a number of *endocrine and metabolic myopathies* associated with disorders as diverse as thyrotoxicosis, myxoedema, Addison's disease, Cushing's syndrome, and metabolic bone disease. Associated clinical evidence of such disorders must be assiduously sought in all patients presenting with a non-specific proximal myopathy. Elevation of the serum creatine kinase activity is usually slight if indeed it occurs at all in this group of diseases, and histological abnormalities are relatively non-specific, though evidence of myopathy can usually be recognized in the E.M.G. in each of them. Less common are a variety of forms of glycogen storage disease,

of which one—namely, acid maltase deficiency (Pompe's glycosidosis)—can occasionally give a clinical picture superficially resembling that of muscular dystrophy; in such cases, however, the histological finding of a gross vacuolar myopathy in muscle biopsy sections is virtually diagnostic, and histochemical and biochemical tests will then be confirmatory.

It is less common to find that confusion arises in the differentiation of benign and relatively *non-progressive congenital myopathies* on the one hand, including such rare diseases as central core disease, nemaline myopathy, and myotubular myopathy, and muscular dystrophy on the other; in this instance it is the histological findings on muscle biopsy which are again conclusive.

Treatment

Drugs.—It is generally agreed that no drug treatment is at present known which has any influence on the course of the disease in any form of muscular dystrophy. Among the many drugs given in the past which have proved unsuccessful have been glycine, vitamin E, corticosteroids, multiple amino-acid and vitamin therapy, isoniazid, adenosine triphosphate and other nucleotides and nucleosides, and high-energy anabolic steroids.

Myotonia can, however, be relieved by drugs. Quinine was the first remedy to be successfully employed, but more recently it has been shown that prednisone in a dosage of 20–30 mg. daily will also relieve or abolish this symptom, as will procainamide given orally in doses varying between 250 and 500 mg. three or four times daily. Even more effective, however, is diphenylhydantoin in a standard dosage of 100 mg. three times a day. While these drugs are therefore beneficial in relieving some of the muscular stiffness and the apparent impairment in muscular relaxation which are sometimes prominent in cases of dystrophia myotonica, they have no influence upon the progressive wasting and weakness of facial, neck, and distal limb muscles which are the major cause of disability in these patients.

Complications.—Respiratory infection is an ever-present risk in cases of muscular dystrophy and is the commonest cause of death. Thus a child with muscular dystrophy developing even an innocuous respiratory infection should always be given appropriate antibiotics, particularly in the late stages of the disease. In the later stages, however, there comes a time when vigorous treatment is no longer justified, and there is certainly no indication for tracheotomy or assisted respiration in advanced cases of the Duchenne type. Very rarely, however, in limb-girdle muscular dystrophy diaphragmatic and intercostal weakness may so impair respiratory efficiency at a time when limb muscles are relatively less severely affected that carbon dioxide retention occurs together with other evidence of hypoxia. In some such cases the use of peroral positive pressure respiration with a Bird respirator is helpful and fully justified. Similar respiratory insufficiency, accompanied by an intolerance of barbiturate-type intravenous anaesthetics and a relatively specific impairment of maximum expiratory pressure, occurs in cases of dystrophia myotonica.

Cardiac failure, which is an occasional cause of death and results from myocardial involvement in cases of the Duchenne type dystrophy and less often in dystrophia myotonica, usually develops acutely and is rapidly fatal. Though digoxin and diuretics should be given, as should atropine and its derivatives in patients who develop severe pulmonary oedema, these drugs are usually of little avail.

Fractures, another common complication, are treated along standard orthopaedic lines. Though limb bones become slender and extremely fragile in immobile patients, fractures generally heal satisfactorily—but further deterioration in muscle strength inevitably follows enforced immobilization.

Dental care, when required, is usually best carried out in hospital in severely disabled patients. In adults with the limb-girdle and facioscapulohumeral varieties of the disease pregnancy is often remarkably uneventful, but in dystrophia myotonica assistance in the second stage is usually required.

Physical Treatment.—Physical activity is beneficial in all forms of muscular dystrophy, and patients should be encouraged to use their limbs and to exercise regularly, though not to the stage of exhaustion. Inactivity, immobilization, and confinement to bed for any reason are detrimental. Hence children suffering exanthemata or febrile illnesses must be got up and encouraged to walk as soon as possible. Massage and electrical stimulation are generally contraindicated, but graduated exercises carried out initially under the supervision of a physiotherapist and subsequently with the encouragement of parents or relatives are to be commended; swimming is particularly valuable.

Contractures, a common complication, are usually preventable and reversible at least in the early stages. Passive stretching of muscles which have a tendency to shorten (especially the soleus and gastrocnemius, the hip flexors, the biceps brachii, and the hamstrings) is an important part of management. Parents and relatives should be taught to perform these movements, which should be carried out repetitively 10 or 12 times at least twice daily.

The use of mechanical supports in such patients is controversial, but there is now good evidence to suggest that when spinal muscle weakness begins to result in the development of scoliosis light spinal supports which do not constrict the chest and so interfere with respiration are valuable. For long it has been thought that surgical lengthening of tendons showing a tendency to contracture is contraindicated, but there is now good evidence to suggest that it is not the surgical operation itself but rather the enforced subsequent immobilization which has been harmful. There is now much support for the view that in selected cases, particularly of the Duchenne type, tenotomy of the Achilles tendons and of the iliotibial bands may enable the affected boys to walk for longer than they would otherwise have done, *provided* the operation is followed by the immediate mobilization of the patient either in walking plasters or full-length callipers utilized under the supervision of skilful physiotherapists. It is particularly important to look for progressive skeletal deformity and increasing contractures when the child eventually is confined to a wheelchair, since scoliosis and consequent deformity of the thoracic cage is an important factor in impairing respiratory efficiency.

Obesity is another important complication in some cases of muscular dystrophy; sometimes it results from overfeeding by overindulgent parents. Rigorous dieting is then necessary, as increasing weight results in difficulty in handling and consequent risk of fracture. Oedema of the limbs can generally be controlled by diuretics or elastic stockings. Bed-sores are fortunately uncommon, and the general health of these patients usually remains remarkably good.

Psychological Management

The emotional reaction of a patient to his disease varies from individual to individual and from family to family. In the severely disabled, overindulgence on the part of the family and friends may create a whining, petulant, and hypochondriacal invalid. Some children become frankly depressed, a phenomenon which can be mistaken for the apathy associated with the intellectual impairment which occasionally accompanies the Duchenne type of disease. Treatment with antidepressive drugs such as amitriptyline in appropriate dosage may then be helpful. Fortunately those who become frustrated, resentful, and aggressive are few, and most affected individuals adjust well to the severity of their disability with an attitude of combined acceptance and resignation. Management with an attitude of restrained optimism and of continual encouragement

is of great importance. Intelligent children must certainly be told that they have a condition which tends for a time to deteriorate, and it is reasonable to explain that though no effective treatment has yet been found research may yet lead to the discovery of an effective remedy.

Education must be directed to training the affected children for some form of sedentary occupation. Clerical and administrative work may be possible for some time, particularly with mechanical aids. Comparatively few children suffering from the Duchenne type dystrophy achieve useful employment, but many of those suffering from the limb-girdle and facioscapulohumeral varieties and from dystrophia myotonica are eventually employed, despite their disease, though some require accommodation and employment in suitable residential homes or hospitals with sheltered workshops. Occupational therapy has an increasingly important part to play in their management. Society has not yet answered all the problems and difficulties which beset the chronically disabled in their everyday lives, but if boredom and loneliness can be overcome sympathetic understanding and encouragement can pay great dividends.

Genetic Considerations

Dystrophia myotonica, like other disorders associated with myotonia, is inherited by an autosomal dominant mechanism, and there is good evidence to suggest that the gene responsible for the disease is completely penetrant. This means that it is transmitted only by an affected individual, though this is one condition in which there is some evidence to indicate that on occasion the condition shows increasing severity in successive generations. Thus a history of cataract in antecedents may be followed by the fully developed clinical syndrome in subsequent generations. When the disease presents in infancy with diffuse hypotonia the diagnosis can as a rule be made only by the discovery of an affected parent or by electromyography.

The Duchenne type muscular dystrophy and the less common benign Becker type are both inherited as X-linked (sex-linked) recessive disorders. This means that they are transmitted by clinically unaffected females and are manifest in males. Thus a female carrier of the gene is likely to transmit the disorder to 50% of her sons, and 50% of her daughters will themselves be carriers. This information is of particular value in counselling the sisters of affected boys. Recent work has clearly shown that most carriers show a slight elevation of serum creatine kinase activity, and some in whom serum enzyme activity is normal can be identified by quantitative electromyography; muscle biopsy is also of some value in this connexion. More than 90% of such carriers can now be identified, and the Muscular Dystrophy Group of Great Britain has sponsored centres throughout the United Kingdom at which tests for the carrier state can be performed. If such female carriers can be identified with confidence and decide (as most of them do) not to have children, then the number of affected boys being born in the future will undoubtedly diminish. At the present time carrier detection of carriers in families with the Becker type X-linked muscular dystrophy is less satisfactory, in that less than 50% of such carriers can at present be identified.

Limb-girdle muscular dystrophy, by contrast, and the rare type which resembles the Duchenne variety but may also affect girls, are both inherited as autosomal recessive factors; this means that they are likely to affect one in four members of a sibship and are the product of a marriage between clinically unaffected heterozygotes, who cannot be identified by any methods at present available. Thus there is rarely any history of the disease having occurred in previous generations of the family, and the chance that an affected individual will pass the condition on to his children can be estimated to be little more than 1 in 200—that is, the chance that he or she will marry a clinically unaffected heterozygote. As with all auto-

somal recessive disorders, the risk is greatly increased in marriages between blood relations.

Facioscapulohumeral muscular dystrophy, like dystrophia myotonica, is a disorder of autosomal dominant inheritance. Here again, penetrance appears to be complete, so that the disease can be transmitted only by affected individuals, who are likely to pass it on to half of their children of either sex.

FURTHER READING

Walton, J. N., and Gardner-Medwin, D., Progressive muscular dystrophy and the myotonic disorders, Chapter 14 in *Disorders of Voluntary Muscle*, 2nd ed., ed. J. N. Walton, 1969. London, Churchill.

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ANY QUESTIONS?

We publish below a selection of questions and answers of general interest.

Premature Ejaculation

Q.—What treatment is there for a healthy man who has had premature ejaculation during his 16 years of marriage and whose wife is nervously affected by it?

A.—Premature ejaculation is common early in marriage but usually responds to encouragement and reassurance. After 16 years, however, the man will undoubtedly have developed a host of secondary anxieties, reinforcing the tendency to premature ejaculation. These will include feelings of inadequacy and of letting his wife down, and both partners will be likely to consider sexual intercourse as something of a test and an ordeal. In other words, a lot of "situational anxiety" will have developed by this time, and this, like any other phobic condition, is best tackled by desensitization.

Friedman¹ has described six such patients treated by desensitization with methohexitone. Five of the six were cured at the end of treatment and three at least remained cured at follow-up a year later. Failing this, some patients are helped by giving a tricyclic antidepressant such as imipramine, which often delays ejaculation, though dosage is difficult, since too much may result in failure to get an erection and too little will be ineffective.

REFERENCE

¹ Friedman, D., *Behaviour Research and Therapy*, 1968, 6, 257.

Dog Bite

Q.—What is the immediate treatment for a dog bite?

A.—Most dog bites are more frightening than serious, and amount to little more than small abrasions surmounting bruises. Cleansing and perhaps a dressing is all the local treatment they require. The opportunity should be taken to start active immunization against tetanus, or to reinforce it if more than about three years have elapsed since the last injection of adsorbed toxoid.¹ An antibiotic such as penicillin, or a derivative, or erythromycin would further reduce the risk of tetanus.

Less often a dog bite causes a more or less complicated, almost incised wound that

probably results from a slash with the teeth. These injuries heal well when repaired carefully, and they may require no trimming. An antibiotic and tetanus toxoid should be given in these cases, as stated above.

Snapping bites can break bones in a hand as well as damaging the soft tissues. X-ray examination and careful exploration are therefore advisable before undertaking toilet and closure of the wound. Occasionally a bite will remove parts of the pursed lips of an unsuspecting child that wants to kiss a supposedly "nice doggie." These are best dealt with by a plastic surgeon, but if this is impossible split-skin grafts will probably cause less difficulty in later reconstruction than the simple and perhaps more reliable step of sewing the wounds up with as little distortion as possible. Any trimming should be as sparing as possible. An antibiotic and tetanus toxoid should be used as above.

REFERENCES

- White, W. G., Barnes, G. M., Griffith, A. H., Gall, D., Barker, E., and Smith, J. W. G., *Lancet*, 1969, 2, 95.
- Barclay, T. L., *British Journal of Plastic Surgery*, 1956, 9, 34.

Intra-articular Injection of Corticosteroids

Q.—Are there any contraindications to the intra-articular injection of crystalline preparations of corticosteroids?

A.—Intra-articular injection of micro-crystalline corticosteroids such as hydrocortisone acetate should be given only if there is clear evidence that the joint is not infected. Since injection is of greatest therapeutic value in monarticular involvement, this means that a preliminary aspiration or biopsy and culture (aerobic and anaerobic) as well as direct examination and, if indicated, guinea-pig inoculation for possible tubercle should be performed. It must also be remembered that increased symptoms in one joint in rheumatoid arthritis may be associated with super-added pyogenic infection. This should also be excluded by similar means.

Apart from infection, there is no contraindication to a single or a few intra-articular injections, but it must be borne in mind that the effect is purely palliative and lasts usually

only one to two weeks. Multiple and repeated intra-articular injections in weight-bearing joints may lead to aseptic necrosis due to unrestrained use of a damaged bone end. In addition the risk of infection, though small under usual conditions, is also increased.

No complications due to sensitivity to the suspending agent sodium carboxymethylcellulose have been reported in man, but cows develop hypersensitivity reactions to this substance.¹ The cost should also be borne in mind. It is much greater for preparations other than hydrocortisone acetate, without very obvious commensurate advantages. A 5 ml. vial of methyl prednisolone acetate 40 mg./ml., for example, costs the hospital service 56s. as against 1s. 8d. for a vial of hydrocortisone acetate 25 mg./ml.

REFERENCE

¹ Leeman, W., de Weck, A. L., and Schneider, C. H., *Nature*, 1969, 223, 621.

Bubble Baths

Q.—What are "aerotone" remedial baths, and in what conditions may they be beneficial?

A.—Aerotone remedial baths are not known to be in use in any orthodox department of physical medicine in Britain. It is understood that air bubbled through water produces light skin stimulation. There seems no reason to believe that this would do more than produce a pleasant sensation.

Chalones

Q.—What are chalones (colyones), and what function do they perform?

A.—The term "chalones" refers to a group of substances, presumably proteins, which act as intracellular regulators. Their mechanism of action is unknown, but is thought to be analogous to genetic repressors in micro-organisms, and they may be key factors in such diverse processes as differentiation, carcinogenesis, tissue homeostasis, and hormone action.

The questioner should consult the book by the inventor of the term "chalones."¹

REFERENCE

¹ Bullough, W. S., *The Evolution of Differentiation*, 1967. London, Academic Press.