Editors:
Antony D. Kidman & John K. Tomkins

MUSCLE, NERVE AND BRAIN DEGENERATION

SYMPOSIUM OF THE FOUNDATION FOR LIFE SCIENCES

Muscle, nerve and brain degeneration

Proceedings of a Symposium of the Foundation for Life Sciences, Sydney, February 12-16, 1979

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Preface

These proceedings are the outcome of the first Foundation for Life Sciences Symposium held February 12th-16th, 1979 at Newport Inn Conference Centre, Sydney, Australia.

The Foundation for Life Sciences has been in existence officially since late 1977. It was set up to promote and support research in Australia by way of grants and symposia in areas such as the one covered in this book — 'Muscle, Nerve & Brain Degeneration'. This international symposium was the inaugural project sponsored by the Foundation for Life Sciences and it is planned to have a series of similar symposia over the next several years.

A group of prominent researchers and clinicians were invited to the Symposium to cover the broader aspects of nervous system and muscle degenerative disorders. The papers from other participants supported these contributions with research data appropriate to these areas of interest. The result is a cohesive collection of original data, results and ideas that represent current interest in these fields. It is from such exchanges as took place at this Symposium that productive research and therapeutic strategies can be planned.

We are most grateful to the invited speakers for the outstanding contributions in their formal papers and in their participation in the discussions.

We would like to thank the members of the Foundation for their generous support of the Symposium and the work they did in the organisation and fund raising. Thanks are also due to our colleagues in the Neurobiology Unit laboratory and especially to Miss O'Neill and Mrs. Hay for their contributions to typing and preparing materials for the Symposium.

MAY, 1979

A.D. KIDMAN
J.K. TOMKINS

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MUSCLE PATHOLOGY IN GENETIC MUSCLE DISORDERS: SOME PROBLEMS IN CLINICO-PATHOLOGICAL CORRELATION

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The pathological changes in neuromuscular disorders have traditionally been divided into 'myopathies' and 'neuropathies' on the basis of their distinctive pathological changes but in recent times even this distinction has been clouded by description of 'myopathic changes' in longstanding denervation and diagnosis of apparent 'denervation' in otherwise typical chronic muscular dystrophies.

The diagnostic features of myopathies are the random variability in fibre size, with the presence of abnormally large as well as abnormally small fibres diffusely scattered either throughout the whole muscle or through focally affected areas, together with the presence of internal nuclei, evidence of degeneration and phagocytosis of muscle fibres, evidence of regeneration and replacement of muscle tissue by proliferating connective tissue and adipose tissue. The term muscular dystrophy has been applied on clinical grounds to the genetically determined progressive degenerative myopathies and on pathological grounds to the picture of myopathy with evidence of degeneration and loss of muscle tissue and replacement by adipose tissue or connective tissue.

Neuropathic or neurogenic changes are recognised on the basis of groups of uniformly atrophic fibres (group atrophy) which may be either focal and limited or more extensive and affect whole bundles of fibres. In addition, evidence of reinnervation on the basis of clusters of normal-sized and enlarged fibres with uniformity of histochemical fibre type has also been used as a presumptive feature of a denervation process (1).

Most of the confusion in designation of pathological change and overlap between the neurogenic and myogenic lesions has arisen from the presence of apparent degenerative or myopathic change in individual fibres in an otherwise neurogenic pattern and the presence of clusters of atrophic fibres in an otherwise overall myopathic picture. Although it can at times be difficult to decide whether an advanced pathological picture is primarily myopathic or neuropathic in origin, I think the confusion that has arisen in interpretation is often an artificial one and based on attempts to interpret subsidiary changes rather than the overall pattern of the change within the biopsy as a whole and consequently missing the wood for the trees. In addition, it is imperative to always correlate the pathological picture with the clinical and electrodiagnostic features, so that a comprehensive and realistic diagnosis can be made.

In the Muscle Clinic at the Hammersmith Hospital it has been my policy after reviewing the pathological changes on muscle biopsy to see the patient again in order to make a final decision on the diagnosis in the context of both the pathological changes and the clinical picture. Under these circumstances one has frequently been struck by the apparent discrepancy between the degree of pathological change and the severity of the clinical condition, even in the face of apparently classical genetically determined clinical syndromes. This highlights the importance of not trying to either make a definitive diagnosis of a particular syndrome or to prognosticate on the basis of the pathology in isolation but to always co-ordinate the pathology with the clinical picture. In this review I would like to illustrate the problem of clinico-pathological correlation, both in relation to some of the genetically determined muscular dystrophies and also the so-called congenital myopathies and some of the neurogenic syndromes.

DUCHENNE MUSCULAR DYSTROPHY

In Duchenne muscular dystrophy the clinical features usually only become apparent after the child beings to walk, although there may already be earlier evidence of involvement such as delay in the motor milestones. However, the pathological changes are already present in the preclinical stages of the disease, and indeed evidence of involvement of the muscle is already reflected as well by raised serum enzyme levels at birth and probably even in the prenatal period.

In the early stages of the preclinical phase (up to the age of a few months) the muscle at biopsy already looks overtly abnormal but the changes are relatively mild and take the form of variability in fibre size, focal degenerative fibres, some evidence of focal regenerative activity, and possibly some early proliferation of connective tissue or adipose tissue (2). As the disease progresses the variability in fibre size becomes more striking, there is evidence of focal necrosis of fibres, either singly or in clusters, with associated phagocytosis, the regenerative efforts become less marked and less frequent, and there is progressive replacement either by proliferation of endomysial and perimysial connective tissue or by foci of proliferative adipose tissue, initially in the perimysium and subsequently also extending into the bundles themselves. In the later stages of the disease much of the muscle has disappeared and been replaced by adipose tissue.

In the potentially affected fetus with Duchenne muscular dystrophy the only changes that have been recognised that may be of potential significance are variability in fibre size and the presence of eosinophilic staining fibres, the so-called opaque or 'hyaline' fibres, which are also noted in the overtly pathological muscle in the later affected child.

The degree of pathological change in the affected child varies from one muscle to another and in order to compare degree of involvement it is thus important to consistently look at the same muscle. In addition, however, one frequently also sees a marked difference in the degree of pathological change in the same muscle

taken from children of comparable age with an apparently similar degree of clinical severity. It is thus not possible on the basis of the biopsy itself in isolation to try to prognosticate, and this needs to be correlated with the degree of clinical severity which again must be related to the age of the child. At times one may even note that a younger brother with Duchenne dystrophy who is at an earlier stage of the disease may have an apparently more extensive pathological change on the biopsy sample than the older brother.

CARRIERS OF X-LINKED DUCHENNE MUSCULAR DYSTROPHY

Approximately two-thirds of genetically obligatory carriers of Duchenne muscular dystrophy have elevated levels of creatine phosphokinase (CPK). A small proportion of carriers also have clinical suggestion of muscle involvement, usually in the form of an enlarged calf, which is often unilateral, occasionally some evidence of actual focal weakness of muscles, or the presence of muscle cramps on exercise. At biopsy a proportion of carriers show overt pathological change in the muscle which is usually focal, but occasionally may be fairly extensive throughout the biopsy. While carriers with high CPKs do tend to have more frequent evidence of pathological change, the correlation with elevated CPK is not absolute and some carriers with normal CPK do have unequivocal pathological change whereas others do not. The pathological changes at light microscopy level consist of variability in fibre size and evidence of focal degeneration of fibres. There may also be some proliferation of adipose or connective tissue. On histochemical examination there may be evidence of core fibres with absence of oxidative enzyme activity in isolated fibres. At electron microscopic level there may be evidence of focal degenerative changes and loss of myofibrils within individual fibres. Once again, this may be either focal or fairly extensive and does not correlate directly with the degree of change seen at light microscopy level.

BECKER TYPE X-LINKED MUSCULAR DYSTROPHY

The Becker type of muscular dystrophy has a similar distribution of weakness and pattern of inheritance to the Duchenne type but is much milder. Many of the affected cases remain ambulant into adult life and may have a relatively static course. Preclinical cases can be recognised even in early infancy by the presence of high CPK levels and electrodiagnostic changes as well as changes on muscle biopsy. The degree of clinical severity varies considerably from the most mild at one end of the spectrum to cases who are almost as severe as the Duchenne type and may have a lot of difficulty with ambulation by the time they are 14-16 years of age. It can, at times, be difficult on clinical or even pathological grounds to distinguish the Becker from the Duchenne type in individual presenting cases.

The degree of pathological change in Becker dystrophy may also show variability in severity and once again the clinical prognosis

has to be based on the degree of clinical weakness as well as the extent of pathological change.

LIMB GIRDLE MUSCULAR DYSTROPHY

The term limb girdle dystrophy has been used for the autosomal recessively inherited muscular dystrophy which has a similar distribution to the Duchenne type, affecting the pelvic girdle prior to the shoulder girdle and associated with degenerative change in the muscle on biopsy and an elevation of CPK in the blood. The clinical picture is a very variable one, ranging at the one extreme from a picture as severe as Duchenne in type (but also affecting females as well as males) to a very mild form with a very slowly progressive course. The pathological picture in the milder cases often shows a very striking pathological pattern with marked variability in fibre size, the presence of many grossly enlarged fibres and also striking structural changes within fibres such as whorling, splitting, ring fibres and also 'moth-eaten' fibres on the oxidative enzyme reactions. (Similar changes may also, however, be seen in biopsies from cases of Duchenne dystrophy so that this distinction pathologically is not absolute.) Some cases may show a pathological picture equal in severity to that of Duchenne dystrophy at an equivalent age yet the child may show very much less clinical weakness and may be actively ambulant.

Some cases show an unduly severe clinical rate of progression which is well within the Duchenne pattern or even more rapidly progressive than Duchenne, with loss of ability to walk within 3-4 years of the actual onset of weakness. The pathological picture in these cases may initially be very mild and on subsequent re-biopsy some of them show a very marked degree of progression of the change. It is difficult to be sure that these are all genetically determined autosomal recessive cases, although this has been implied on occasion by the parents being first cousins. Possibly some of these cases may be secondary to an acute inflammatory condition such as polymyositis, although there has not been evidence of this pathologically or on detailed viral and associated studies.

Occasionally one sees an unusual family in whom the degree of severity may vary considerably from one child to another. In one such family I have investigated the oldest affected boy was diagnosed initially as Duchenne dystrophy on the basis of a clinical picture indistinguishable from the Duchenne type and he subsequently lost the ability to walk at the age of 12 years and followed a very typical Duchenne course. However, he also has a younger sister with a fairly severe form of disease as well as (non-identical) twin brothers, one of whom has fairly severe involvement but the other twin has a subclinical picture with no obvious clinical disability but a very high CPK.

CONGENITAL MUSCULAR DYSTROPHY

In so-called congenital muscular dystrophy the position is even more complex since the pathological change is usually much more

extensive than the clinical severity and, in spite of this extreme degree of pathological change and an apparently dystrophic pattern, the condition tends to be static and non-progressive. The condition is probably a genetically determined one with an autosomal recessive pattern of inheritance which is supported by the fact that male and female siblings in the same family can be affected and there is also a high incidence of cousin marriages in isolated cases.

In some instances of children presenting with hypotonia from birth and usually some associated contractures and deformities a diagnosis of 'minimal change myopathy' has been made on the basis of very minimal pathological changes in the muscle not being quite compatible with normality and on the other hand not being distinctive enough to diagnose a muscular dystrophy (2). In two such cases subsequent biopsy at the time of orthopaedic procedures showed a marked change in the picture of the muscle and a pattern much more distinctive of congenital muscular dystrophy. It is thus possible that some of the cases with a very mild change early on, characterised mainly by variability in fibre size and possibly some internal nuclei, may later progress to a change in pathological picture with more extensive replacement of muscle by adipose tissue, as one tends to see in the more characteristic cases of congenital muscular dystrophy.

It is particularly in cases with so-called 'arthrogryposis' that one should be on the lookout for congenital muscular dystrophy as an aetiological basis as this is a common presentation of the condition.

SPINAL MUSCULAR ATROPHY

The autosomal recessive spinal muscular atrophies, which are characterised by involvement of proximal girdle muscles more than distal and the pelvic girdle before the shoulder girdle, can be divided on clinical grounds into three grades of severity depending on whether the affected infant is so severely affected that he is unable to maintain a sitting posture (severe); is able to sit unsupported but is unable to stand or walk (intermediate severity); or is able to walk unaided (mild). In all these grades of severity the degree of pathological change can be very similar and it is not possible to prognosticate at all on the basis of the pathological change. Particularly in the severe and intermediate forms, there is frequently large group atrophy with large numbers of even whole bundles of atrophic fibres and at times practically universal atrophy of the whole biopsy sample. The denervation pattern is recognised by the presence of isolated or groups of normal-sized or enlarged fibres, which histochemically usually show a uniformity of enzyme type and are thus presumably reinnervated fibres.

In addition to the apparent lack of correlation between clinical and histological severity in many instances, one can at times see variability within the biopsy taken from the same child. Since the pathological change is a relatively focal one, one may find areas within the muscle biopsy where there is universal atrophy of whole bundles of fibres, whereas contiguous areas may show a completely normal-looking bundle with perhaps only a few isolated

atrophic fibres in it. These apparently normal bundles usually have uniformity of enzyme pattern and are presumptively reinnervated fibres rather than unaffected bundles. In addition to the two extremes one also finds evidence of mixed pattern with groups of atrophic fibres alongside groups of reinnervated normal-sized fibres.

THE CONGENITAL MYOPATHIES

The term congenital myopathies has been applied as a generic term to a series of clinical syndromes in which the presenting pattern is very similar, with either a hypotonia and delayed motor milestones or presenting with either proximal or more generalised weakness often of a non-progressive pattern. Some of these syndromes are inherited through a dominant mechanism and others through an autosomal recessive. The descriptive names given to individual syndromes have been based on structural changes observed in the muscle. In recent times the specificity of some of these structural changes has been questioned because similar changes may be observed in muscle from other conditions and also, at times, more than one pathological change may be observed in the same muscle. However, within some of these families the changes have been distinctive and there has also been some consistent correlation between some of the clinical patterns and distribution of weakness and involvement, such as swallowing muscles or external ocular muscles, and particular pathological changes. I would like to illustrate the clinical and pathological aspects of some of these congenital myopathies with a few selected conditions.

Central Core Disease

The usual clinical picture in central core disease is one of mild weakness which may be either confined to proximal muscles or may be more generalised, and the course tends to be relatively non-progressive and the outlook thus very good. Inheritance is usually dominant but there are also sporadic cases with no apparent family history. The pathological picture shows two main features, marked predominance of type 1 fibres in most cases and the involvement of a variable proportion of fibres by central cores. The cores may be single and truly central or at times may be multiple and also eccentric.

In one family which I studied the mother had central core disease and had had a mild non-progressive proximal weakness from the age of 16 with little change in disability over the ensuing 14 years. Her son was followed from birth and showed no obvious initial disability but his mother thought that his general agility was less than that of her older son. At the age of 4 years he showed minimal difficulty in getting up from the floor but no other delay in motor milestones or deficit. Muscle biopsy at that stage showed the mother to have completely undifferentiated muscle with 99% type 1 fibres and total involvement of all the type 1 fibres by a single central core. The child's biopsy showed a normal distribution of type 1 and type 2 fibres, and only about 3% of the type 1 fibres had single eccentric cores in them. At subsequent follow-up the child continued to follow a mild course with no increase in disability, and

when recently reviewed at the age of 14 years he was still able to get up from the floor with minimal difficulty, was able to go up and down steps and to hop on one leg. A repeat of his muscle biopsy obtained by needle biopsy from the quadriceps showed a picture almost identical to that of his mother's muscle, with striking predominance of type 1 fibres and almost universal involvement of all the type 1 fibres by single central cores. The pathological picture thus evolved from a state of normal differentiation of muscle in early infancy with a small proportion of fibres involved to a pattern of predominance of type 1 fibres with almost universal involvement, without any apparent clinical change in his disability.

Minicore Disease

This is probably a distinct entity from central core disease and the cores, instead of being single long tubular structures running the length of the fibre, are small rounded or oval-shaped structures which are localised and multiple throughout the fibre. The condition is also a non-progressive one with mild weakness as a rule, but the inheritance is probably autosomal recessive rather than dominant. There is also a predominance of type 1 fibres in this condition and on routine stain there may be variation in fibre size and the presence of multiple internal nuclei. There is usually no evidence of active degeneration. At electron microscope level the cores tend to be unstructured with loss of normal pattern within the cores, in contrast to the central cores which are usually well structured. There have, as yet, been too few case reports to know whether there may be more severe variants of this particular condition.

Nemaline Myopathy (Rod Body Myopathy)

This is another of the mild non-progressive myopathies which may either occur as sporadic cases or with a dominant pattern of inheritance.

The proportion of muscle fibres affected by rods in the biopsy is very variable and does not seem to correlate at all with the clinical severity. In one recent mild case we have had, with almost no clinical disability at all, there was extensive and overt involvement of the muscle whereas other cases with more severe clinical weakness have only had isolated focal fibres affected which were difficult to identify on initial inspection of the biopsy.

The rods are most readily seen with the Gomori trichrome stain. In addition the muscle frequently shows a two fibre size pattern with large numbers of atrophic fibres and others which are normal-sized or hypertrophied. The atrophic fibres tend to be type 1 fibres and it is particularly in these that the rods occur.

There is a high incidence of associated respiratory problems in nemaline myopathy and the question arises whether there is some failure in the reflex control mechanism of breathing as a result of the involvement of the muscle, or possibly the spindle fibres, by the rods. The condition occasionally is fatal in early infancy owing to the severe respiratory involvement and some of these children seem to die suddenly, presumably as a result of acute respiratory failure, even in the absence of overt clinical