Wellcome Film Project

Muscle Disorders in Children

The Scientific Basis of Medicine

Presented by Professor Victor Dubowitz, Professor of Paediatrics, Institute of Child Health.

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Black-and-white
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<Opening titles>

< Dubowitz to camera>

I think it appropriate for any discussion of muscle disorders, particularly in childhood to start with our patron saint of muscle diseases, Duchenne.

<Dubowitz narrates over painting of Duchenne examining a patient>

This somewhat eccentric physician came from a fishing family in Boulogne and spent most of his years there. And it was only in the latter part of his career that he moved to Paris where he did all his pioneering work in relation to muscular and various other neurological problems.

<Dubowitz to camera>

Although he was unable to get an appointment at any of the Paris hospitals, they allowed him to visit various outpatient clinics where he applied electrical methods for the first time to patients with various problems, and was the father of the introduction of electricity into medicine both from a diagnostic as well as a therapeutic point of view.

In the second edition of his famous book on this application of electricity in medicine, he first recorded the case of muscular dystrophy which he had observed.

<Dubowitz narrates over moving scan of text in French and illustration from Duchenne's book>

At that time he thought that the condition might possibly be of cerebral origin in view of the associated intellectual impairment in that particular child. We see illustrated the very fine drawings which Duchenne made of that particular patient. In the third edition of his book in 1872 and also a few years earlier in the medical press of the time, he described a further series of patients with the same problem and coined the word 'pseudohypertrophic' to account for the unusual enlargement of the muscles in this condition in spite of the fact that there was associated weakness.

<Dubowitz to camera>

This term 'pseudohypertrophy' has remained firmly entrenched in the medical literature until fairly recently, but we now no longer use the term because we know that it is a relatively non-specific feature and may occur in many other forms of muscle disease as well. As a result, we now colloquially use the term Duchenne dystrophy for the common and severe childhood form of the disease.

I think one can take it that it is absolutely inevitable in medicine that if anybody's name gets attached to any particular disorder, you can be quite certain that he is going to turn out to be the second person who described the particular condition, and Duchenne dystrophy happens to be no exception. If one scratches a little bit further back in the literature, not surprisingly one comes across an article […]

<Dubowitz narrates over image of page from an article from 1851 on 'Granular And Fatty Degeneration Of The Voluntary Muscles'>

[…] some ten years or so before Duchenne's initial paper, by a physician in London in fact who described in very clear detail the exact same condition of muscle wasting and weakness in a family where three boys were in fact affected. And he also described an autopsy in one of the cases and pointed out the apparent normality of the nervous system in this particular condition.

<Dubowitz to camera>

A few years later the famous British neurologist, Gowers, gave a series of five lectures at Queen's Square on pseudohypertrophic paralysis, as he called it, and these were published in The Lancet and also separately as a monograph in 1879; and it bears rereading because of some of the absolutely superb word pictures that Gowers painted in describing the progressive nature and the mysterious character of this particular disorder.

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Over the years very little was, in fact, added to our understanding of muscular dystrophy and it is only in comparatively recent times that there has been renewed interest in this and many other forms of muscle disease, and various advances have now been made as a result. I would like, first of all, to review some of the clinical aspects of muscular dystrophy and in the short time available today, I think most of our comments are going to be confined to Duchenne muscular dystrophy itself, and we shall only be saying a few words at the end on some of the other types of muscle problems in childhood.

<Dubowitz narrates over a three photographs of children of increasing ages>

This illustration shows the progression of the disease. What we see here are three brothers affected with the disorder. The little boy on the left is only about eighteen months of age at the time the picture was taken and was at that stage showing very early features of the disease with a slightly waddling gait, a bit of difficulty going up steps and also some difficulty getting up from the floor when lying down. His brother, in the middle, who was about ten years of age at the time, had just lost the ability to walk and was confined to a wheelchair. As you will notice, his back is still quite straight and there are no obvious deformities which is such a striking feature of the later phases of the disease.

On the right hand side, we see the third brother who was sixteen years old at the time and he already showed various severe deformities in the way of a scoliosis as well as marked equinovarus deformity of the feet. There were also contractures of various muscles of the hips and the knees and the elbows which are an invariable feature of the later phases of the disease.

<Dubowitz to camera>

Many of these severe deformities such as scoliosis as well as talipes equinovarus are potentially preventable and I think this is an important aspect of management of these children which I shall come back to presently. One of the major advances that has come these recent years is our ability now to diagnose Duchenne muscular dystrophy with absolute confidence even before it is clinically apparent.

< Dubowitz narrates over diagrammatic slide>

This particular slide illustrates the one particular enzyme which we now routinely use as a diagnostic criterion. Over the past ten or fifteen years, it has become apparent that quite a number of enzymes are elevated in the serum in Duchenne muscular dystrophy as well as other forms of muscle disorder, but the CPK, or creatine phosphokinase, is the one which shows the highest elevation and is thus the most useful one to use in clinical practice.

The other thing of particular interest is that the enzyme is at its highest levels at the earlier stages of the disease in Duchenne dystrophy and gradually declines with time. It is assumed that this is due to the fact the enzyme leaks out of the muscle fibre as a result of some abnormality in the muscle membrane, and as the abnormal fibres perhaps disappear with progression of the disease, less enzyme is present to leak out. The other point to make is that if one is using this as a diagnostic sign early on that one has to see a gross elevation of the enzyme in order to confirm the diagnosis of Duchenne dystrophy in a suspected case.

As you see illustrated, the normal range, by the one particular method which is now used, is up to about 70 international units per litre. In early cases of muscular dystrophy, the level may be somewhere in the region of 2000 units or even more. If one gets a result of somewhere around 100 or 200 units, this should, in a sense, serve to exclude the diagnosis rather than to support it, and one may well be dealing with some other muscle disorder under those circumstances. In the later stages of the disease, the enzyme level is still up though, as we said, it tends to approach to the normal range.

<Dubowitz to camera>

Things have moved a little further than this in comparatively recent times since there is now a technique available which will pick up the raised CPK on a single drop of blood which can be dried on to a filter paper.

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<Dubowitz narrates over image of CK-Screening-Test >

This immediately raises the possibility of doing a screening of large populations of newborn infants much in the same way as one screens for things like phenylketonuria.

<Dubowitz to camera>

The single drop of blood on the filter paper is allowed to dry and can then be sent through the mail to a referral laboratory where the appropriate test can be done. This test was originally described about a year or two ago in America where a pilot study was undertaken, and more recently a large population study has been started in Germany.

<Dubowitz narrates over diagrammatic slide>

The test is based on a completely different method for the assessment of creatine kinase dependent on the release of light by the breakdown of luciferin by luciferase. This luciferase, in fact, is obtained from the firefly and it is a particular firefly that has to be used, namely the American firefly as no other fireflies apparently seem to be satisfactory for the particular test. As a result, there is a comparative expense involved in this and the method itself is not generally available for routine laboratory use. The main problem, however, that arises at the present time is an ethical one as to whether it is justified to screen large normal populations with the purpose in mind of early detection of Duchenne dystrophy which as one now appreciates can be diagnosed at birth in this particular way.

<Dubowitz to camera>

Where one has no particular therapeutic agent to offer these children and when one makes an early diagnosis, it is doubtful whether there is much to be gained from this approach. Apart from the fact that one might be able to give genetic counselling to the mother and avoid a second affected child which might have occurred if diagnosis were delayed in the first place. For the moment the method has not been widely applied but, of course, if some therapeutic potential becomes available then it would be mandatory for all children to be screened for possible Duchenne dystrophy disorder for early diagnosis to be made.

<Dubowitz narrates over two photomicrographs in turn>

Looking at the histological change within the muscle in Duchenne dystrophy, one sees early on a so-called myopathic pattern of change where there is variation in the size of fibres, some of them being much larger than normal – and may be two or three times normal even in diameter – and others again are fairly atrophic and small. The pathological change is uniformly present throughout the muscle and is not a focal one. In addition, one also sees some rather opaque looking fibres as illustrated by the two fibres – one in the centre and one to the left of the centre in this particular biopsy. There is also a tendency for the nuclei, which normally lie at the periphery of individual muscle fibres, to be centrally placed and often to be multiple within the fibre.

There is also a proliferation of connective tissue, both the endomysium around the fibres and the perimysium connective tissue between bundles of fibres, and at an early stage one may even see some adipose tissue proliferation, but this is a much more striking feature in the later phases of the disease <*next slide*> where, in fact, it may replace much of the available muscle bulk as shown in this particular biopsy which came from came from a child of about 16 years of age.

<Dubowitz narrates over two photographs of same child>

I mentioned that we can now diagnose muscular dystrophy with confidence before it is clinically obvious and this picture illustrates a completely normal child at the age of 6 months with completely normal milestones, both of a motor and an intellectual character, but yet we do know that this child does have Duchenne muscular dystrophy because a previous sibling was affected and this child had a CPK test done which was grossly elevated.

00:14:42:12

<Dubowitz narrates over two photomicrographs in turn>

If one looks at the muscle biopsy in children in the early stages – and this one came, in fact, from a child of just under 3 months with Duchenne dystrophy – one sees that

there are already pathological changes present. Illustrated here is some variation in the size of the fibres beyond the range that one would normally see in a normal muscle of this age, and also a focus of abnormal looking fibres in the upper central part of the biopsy.

<*Next slide*> These fibres which are smaller and clustered together are usually regenerating fibres as shown in this particular section which was stained for RNA. You will see there is one dark staining cluster around about 12 o'clock on the biopsy and another one around about 7 o'clock in this particular illustration. One also sees areas of degenerating fibres which one can show up by using acid phosphatase reaction in the biopsy slides.

<Dubowitz to camera>

I think that it is quite likely that one will find pathological change in the affected foetus with Duchenne dystrophy. To date there is as yet no convincing documented case of a definitely affected foetus. And I do not think that the so-called hyaline fibres which some authors have described as specific to Duchenne dystrophy in some of the foetuses looked at – who were potentially affected because they came from carrier mothers – I do not think that these particular fibres are in themselves specific to Duchenne dystrophy, but merely reflect hypercontracted fibres often in formalin-fixed rather than frozen material.

I would now like to make a few comments about the various aspects of management of children with Duchenne muscular dystrophy. As things stand at present, we do not yet have any specific therapeutic agent for Duchenne dystrophy and most of the aspects of management that one can offer are supportive. However these are important and may maintain ambulation in these children as well as prevent some of the complications of the disease.

The first important principle I think I would like to stress that applies particularly to Duchenne dystrophy and does not apply to the same extent to other types of

neuromuscular disorders or other forms of neurological disorder is that if one immobilises […]

<Dubowitz narrates over slide>

[…] these children for any reason, be it surgical or be it some minor illness, they tend to get rapidly weaker and may lose the ability to walk as a result of this immobilisation. It is thus imperative that these children are kept ambulant and encouraged to remain ambulant for as long as they are able to do so.

<Dubowitz to camera>

One other development that has occurred in recent years is that efforts have been made to prolong the period of ambulation beyond the usual deadline of about 12 years, which is the maximum to which most of these children remain ambulant, […]

<Dubowitz narrates over photographs of a child wearing callipers>

[…] by the fitting of callipers to give support to the legs and very often to the hip muscles as well. These callipers have to be fitted at the stage at which the child is still able to stand and usually to walk on the level but having great difficulty in doing so.

<Dubowitz to camera>

As a result of the fitting of callipers in this way and associating this with an intense programme of physiotherapy, and in a sense rehabilitation of the child because he now needs to get used to carrying the weight of the callipers and to try and re-mobilise with them, some authors, particularly Vinios[?] in Cleveland and people in a few other centres who they have developed this particular approach, have claimed that they can keep these children going on average up to about 3 years longer beyond the stage that they would normally be going off their feet. This certainly is a useful gain of ambulation and the whole management of the child is very much

easier from the parents' point of view, and probably from the child's own psyche as well if he is ambulant rather than chair-bound.

Once the child goes off his feet, the important thing is to prevent the severe scoliosis and the other deformities such as equinovarus deformity of the feet.

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I think that the scoliosis is largely preventable by adequate care and attention of the posturing of the spine […]

<Dubowitz narrates over photographs of child in a wheelchair>

[…] in the sitting position. I've long felt that the scoliosis is the result of simple mechanical factors and that once the child is off his feet, he has difficulty maintaining an upright position and is thus likely to slouch to one or other side as a result of the weakness of his muscles. Once he does this a scoliosis becomes incipient and this will gradually progress with time. It is thus important to make sure that the back rest of the wheelchair is not in an absolutely vertical position but slightly inclined backwards, and that also it has a soft canvas type material which will support the spine. I think that this is all that is needed and efforts, which at one time I thought might be useful, of getting some type of moulding into the wheelchair conforming to the exact shape of the spine of the child and the contours of the back of the child is probably not entirely necessary.

Other approaches include the fitting of particular jackets and braces […]

<Dubowitz to camera>

[…] to support the spine and various materials are now available which can be used in this way. The posture of the feet in the wheelchair is also important and the ankles should be kept at a right angle to prevent them hanging down and resulting in talipes deformity.

One or two other aspects of importance in relation to Duchenne dystrophy are worth mentioning. The usual prognosis of these children for life expectancy is somewhere in the region of say 16 to 20 years or a little bit beyond that, and the usual cause of death is respiratory infection. A relatively mild respiratory infection, which would be no problem to a normal person, is life-threatening to these children because it often results in a subsequent pneumonia because of the associated weakness of the intercostal and diaphragmatic muscles and their inability to cough up sputum that is formed. In addition there is also an element of cardiac involvement which is probably an invariable accompanying feature of this disorder.

<Dubowitz narrates over a slide showing a series of ECG readouts>

One can find changes in the electrocardiogram even in early cases of Duchenne dystrophy in a fair proportion; and in the later stages the majority will show cardiac ECG anomalies and at autopsy there is often extensive fibrosis in the muscle. The cardiac involvement is thus probably also an important factor in the prognosis, although these children don't usually show any evidence of cardiac decompensation and overt evidence of cardiac failure.

<Dubowitz to camera>

One other aspect of interest is that a proportion of these children, perhaps about 40% or so, will show an equivocal intellectual impairment in addition to their muscle weakness. The various series that have been investigated over the past few years have […]

<Dubowitz narrates over diagrammatic slide>

[…] shown that the average IQ in cases of Duchenne dystrophy lies somewhere around 80 as compared with a normal average of about 105. There is a normal distribution curve of the a gaussian type that one gets in cases of Duchenne

dystrophy much as in the normal population but the shift is to the left as you see illustrated in this particular picture.

<Dubowitz to camera>

The other thing of interest is that the intellectual impairment is not associated with […]

<Dubowitz narrates over two of slides in turn>

[…] the severity of the disease. It is not related to the progression of the muscle weakness and there does not appear to be any progression of the intellectual impairment itself, and it is not related to socio-economic factors or various other factors that in the past have been implicated. <*Next slide*> The average IQ of siblings of Duchenne dystrophy falls within the normal range, and the IQ of other types of muscle disorders, such as spinal muscular atrophy with equal weakness, also falls within the normal range.

<Dubowitz to camera>

This associated intellectual impairment raises interesting questions in connection with the pathogenesis of the disease and the actual nature of the disease itself and whether, in fact, one is dealing with purely a muscle disorder or whether the muscle involvement is, perhaps, but one manifestation of a more widely dispersed disorder of affecting other systems as well.

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Now let us move to one other aspect of management that is of particular importance in clinical practice. This is the question of genetic counselling, carrier detection and as a result the prevention of further cases of Duchenne dystrophy in females at risk.

<Dubowitz narrates over two diagrammatic slides in turn>

As you will see from this particular family tree, the condition is an x-linked one carried by females and manifesting in males. The mother of the index case on the left hand end of the illustration is a definite carrier because she has a number of affected male cousins via female aunts of her family and there is also one uncle who died of Duchenne dystrophy. It is the investigation of definite carriers like this that has helped to delineate some of the advances in recent years of carrier detection.

The case that is likely to come up for counselling is the sister of this child with Duchenne dystrophy who will want to know whether she is a carrier or not at the time that she is going to have children herself. From a genetic point of view there would obviously be an implication of a 50% risk of this girl being a carrier where her mother is a known carrier of the disease.

<*Next slide***>** The use of CPK we have already referred to in connection with the actual diagnosis of the disease; it has also proved very useful in carrier detection. As you will note there is one essential difference in its use in carrier detection as compared to early diagnosis of the early detection of cases of Duchenne dystrophy themselves. This is in the actual degree of elevation of the enzyme. Very often the amount of elevation in definite carriers is only slightly above the normal range although occasionally it may be 1 or 200 units or a bit more than that. It is thus imperative that the method used is reliable and also that one assesses it on more than one occasion to make sure that one has proper control of the actual levels.

The thing of importance in addition to the actual degree of elevation is the fact that in known carriers only about 70% are, in fact, showing elevated CPK. This means that the CPK can still be normal in about 30% of definite carriers. Recent advances in the interpretation of the CPK data has led to a statistical approach where one can actually calculate an at risk estimate based on the actual level of the CPK itself. This is helpful in cases where the CPK is within the normal range and implies that for example somebody with a CPK of 65 units would have a higher risk than somebody whose level was about 10 units. And by comparing the normal range, by the particular method in the laboratory that is doing the tests, with the particular

abnormal or higher than normal carrier or potential carrier being investigated, one can work out this at risk figure.

<Dubowitz to camera>

The other thing of interest is that if one were to look at potential female carriers early in infancy, perhaps one might find that the level is higher at that stage than at the later age when they usually come up for assessment and counselling. I might mention in passing that we have recently seen a female infant who was, in fact, referred for investigation of her hypotonia, who turned out to have a CPK in the region of about 1000 international units and on further investigation we found that a male sibling with intellectual retardation was in fact suffering from Duchenne dystrophy. It is likely that the level of enzyme may be higher early on in known carriers and gradually decline with time much in the same way as cases of actual Duchenne dystrophy itself do.

In addition to the actual use of CPK, there are one or two other approaches that can be used and one of these is the actual investigation of the muscle itself by muscle biopsy.

<Dubowitz over photograph>

This picture shows in a sense a historic calf. This is the calf of a known carrier of Duchenne muscular dystrophy who had an affected boy as well as an affected brother, and we observed that her one calf was in fact larger than the other. In view of the possible implications in the context of so called pseudohypertrophy of muscle in Duchenne dystrophy, she was agreeable to having a biopsy done. This was way back in 1962 and the biopsy […]

<Dubowitz narrates over photomicrograph>

[…] in fact showed unequivocal evidence of myopathic change with, as you see illustrated, a marked variation in fibre size, internal nuclei and evidence of degeneration of individual fibres.

<00:30:39:00>

That particular lady's CPK was also elevated, but we now know that one might find pathological change in the muscle even in cases with a normal CPK. It is thus a useful additional test to do in cases with normal CPK if one wants to try and delineate more specifically a definite carrier status. Unfortunately, not enough data is yet available to quantitate muscle biopsy and its pathological state in the same way as has already been done for giving a statistical approach to the CPK level itself.

There is one other useful technique that may be helpful in addition and that is to do an EMG on cases who are potentially carriers, and in some of them the EMG may be overtly abnormal showing a myopathic pattern of change, whereas in others the abnormality may be picked up if one quantitates the EMG and assesses it in this way.

All these additional tests are of some value if one is going to try and improve on the current method of using CPK alone of detecting carriers of the disease. At present the CPK is the most widely used method and is certainly the single most effective way of detecting carriers, but I must stress again that it is essential that genetic counselling and carrier detection is done in laboratories where they are doing CPKs routinely, and where the interpretation of results can be undertaken in a careful and objective way.

I would finally like to say something about the procedure of muscle biopsy itself and what sort of information one can obtain from muscle biopsy in the context of not only Duchenne dystrophy but perhaps also one or two other disorders of muscle.

<Dubowitz narrates over photographs of surgical procedure>

We usually go for the quadriceps muscle and in children we routinely tend to do open biopsies, but in recent times we have done a comparative study <*next photograph*> of needle biopsy at the same time as open biopsies and found a good correlation from a diagnostic point of view with the needle biopsy material.

<Dubowitz to camera>

Needle biopsy has been very widely used in adult muscle investigation and has the advantage of being a rapid procedure that can be done at an ordinary outpatient clinic and that the incision required is simply a small nick in the skin which will heal rapidly without any suture and simply a butterfly tape applied.

The advantage of the open biopsy technique is that we can obtain 3 or 4 samples from the same biopsy site and this gives us a wider range of biopsy material to assess. In addition, if we are doing any additional procedures or special investigations of the muscle, the open biopsy has the advantage of making this available. For example we have recently been particularly interested in tissue culture of muscle, both normal and diseased, and have undertaken an extensive range of studies of the behaviour of muscle under these circumstances and this is routinely done on the biopsy samples that we obtain.

The muscle biopsy, once it is taken, is rapidly frozen after being mounted on a slice of cork with some appropriate gum to maintain it in an upright position. The cork is then submerged in isopentane cooled in liquid nitrogen in order to obtain rapid freezing. This preserves the morphology of the muscle as well as the enzymes.

I think that one can reasonably say that the time has now come where it is probably unjustified and unethical to take a muscle biopsy after subjecting a child to such a procedure and then destroying the muscle essentially by throwing it into formalin and fixing it in the usual pathological way. All muscle should be appropriately processed with modern histochemical techniques in order to get the maximum information from it.

00:35:27:19

I would like to comment on some of the advances in knowledge that have come as a result of application of histochemical techniques to muscle biopsy. With the sections obtained in a cryostat from this frozen material, we can do various histological stains that would routinely be done in a histological laboratory and in addition the histochemical enzyme techniques on the muscle. Let us first of all look at a section […]

<Dubowitz narrates over two photomicrographs in turn>

[…] stained by routine H&E in this frozen material. As you see the muscle looks fairly uniform and one muscle fibre looks very much like its neighbour. <*Next slide*> Once one applies a histochemical enzyme technique, one immediately sees that there is a checkerboard pattern with some fibres being dark and some being light. This is the basis of the subdivision of muscle into fibre types and as a result of this fibre typing, we have learned a lot more, not only about the structural abnormalities and pattern of muscle but also correlative aspects of its function.

<Dubowitz to camera>

As a result of more widely used histochemical techniques on muscle biopsy, a completely new family of disorders has arisen which in the past would probably all have been dismissed as simply being cases of muscular dystrophy. We thus think it is essential for any muscle to be adequately investigated in order to recognise some of these disorders which can present clinically in a very similar way to muscular dystrophy. To illustrate this […]

<Dubowitz narrates over two photomicrographs in turn>

[…] here is an example of a particular biopsy obtained from a patient who was thought to have muscular dystrophy. The routine staining with H&E of this frozen section shows a fairly normal looking muscle with no obvious dystrophic pattern apart

from one or two rather small fibres. <*Next slide*> On the other hand, once we did the histochemical stains, and the one showing here is an oxidative enzyme, there was this very striking pattern of central cores through the individual fibres which are devoid of any enzyme activity. This is quite characteristic of the condition known as central core disease.

<Dubowitz to camera, glancing at his wristwatch>

Goodness! We seem to have run out of time. Well, I think we will probably have to stop at that point and perhaps if I get invited back on a future occasion, I could tell you about some of the many other exciting new muscle disorders that I still had in store for you. Good Day.

<End credits>