Investigation of Neuromuscular Disorders

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The investigation of neuromuscular disorders falls into three broad areas, namely serum enzymes, electrodiagnostic procedures and muscle biopsy[1, 2]. The first two are essentially screening procedures whereas the latter may be looked upon as the definitive diagnostic arbiter. There is, of course, no substitute for an accurate and careful history and a detailed clinical examination, to which any investigations are supplementary. Moreover, if the results of special investigations are incompatible with one's clinical diagnosis the special investigations are likely to be wrong. It is important to be aware that, in neuromuscular diseases, investigative results may be discordant with the clinical picture.

Serum Enzymes

Although the blood concentration of various enzymes may be raised in relation to several of the neuromuscular disorders, the one commonly used is creatine kinase (CK) and this is generally the most sensitive, reliable and useful enzyme to study. In muscular dystrophy (MD), particularly of the Duchenne type, CK is grossly elevated early in the disease. Similar levels of elevation, however, are also found in milder forms of MD such as the Becker and limb girdle varieties; thus the actual level of the elevation is no index of the severity of the disease. On the other hand, a relatively mild elevation of only a few hundred rather than several thousand units should alert one to an alternative diagnosis, as it is essentially incompatible with dystrophy of the Duchenne or Becker types.

In the spinal atrophies, particularly the severe Werdnig-Hoffmann form, the enzymes tend to be normal but moderate elevation may occur in some of the milder varieties. Dermatomyositis in childhood can also be associated with perfectly normal enzyme levels, in spite of severe weakness. In most of the floppy infant syndromes[3], with the exception of congenital muscular dystrophy in which a proportion of cases have elevated enzyme levels, CK tends to be normal and is thus of little help in diagnosis. The CK levels in a consecutive series of our cases are illustrated in Fig. 1 and the changes in various disorders are summarised in Table 1.

Recent advances in automation and computerisation have led to the occasional and somewhat unexpected diagnosis of a case of dystrophy, as illustrated by a 4-month-old apparently normal boy referred to our clinic. He had seen his local paediatrician for a relatively mild gastrointestinal illness and, because of associated vomiting, a request for blood electrolytes had gone to the laboratory. The result was a computer print-out with 101 or so unrequested additional biochemical parameters, including a creatine kinase which was raised to several thousand units. Unfortunately the child does have Duchenne muscular dystrophy, as confirmed by the consistently raised CK as well as by an overly abnormal needle biopsy of his muscle.

Table 1. Serum CK levels in neuromuscular disorders.

| Disorder                  | Gross elevation | Moderate elevation | No elevation |
|---------------------------|-----------------|--------------------|-------------|
| Duchenne MD               | +               |                    |             |
| Becker MD                 | +               |                    |             |
| Limb girdle MD            | +               | +                  |             |
| Congenital MD             | +               | +                  |             |
| Dermatomyositis           | +               |                    |             |
| Spinal muscular atrophy   | +               |                    |             |
| (Werdnig-Hoffmann)        |                 |                    |             |
| Spinal muscular atrophy,  | +               | +                  |             |
| intermediate; mild        |                 |                    |             |
| Floppy infant             |                 |                    |             |
| (except congenital MD)    |                 |                    |             |

Fig. 1. CK levels in a consecutive series of children attending our muscle unit. DMD—Duchenne muscular dystrophy; B&LGD—Becker and limb girdle dystrophy; CMD—congenital muscular dystrophy; DM—dermatomyositis; SMA—spinal muscular atrophy, severe (S), intermediate (I) or mild (M).
As CK is grossly elevated early in the disease it is now possible to screen a normal population for Duchenne muscular dystrophy. The recent development of a technique which is sensitive and reliable on a single drop of dried blood has made it feasible to screen for Duchenne muscular dystrophy and phenylketonuria on the same sample. The only reason for this screening not yet being universally applied is our inability to provide any therapy (other than supportive) for the disease. However, one advantage of early screening is that, with genetic counselling, the family at risk may be prevented from having other affected children.

The possibility of antenatal diagnosis based on a potentially elevated CK during the first trimester has also become a feasible diagnostic approach now that pure samples of fetal blood can be obtained by fetoscopy. However, this approach has not proved successful and there have been false negative results in the USA, with normal CK in fetal blood but the presence of Duchenne dystrophy at birth. Prenatal diagnosis will have to await a more sensitive marker in early pregnancy than CK (or possible other secondary enzyme changes). Present research in recombinant DNA work and the attempt to find a marker near the p 21 locus on the short arm of the X chromosome, where the Duchenne gene is thought to reside, may provide both a solution to this problem and a more reliable means of carrier detection or exclusion in females at risk for the X-linked Duchenne dystrophy.

Electrodiagnostic Procedures

Nerve conduction velocity and electromyography (EMG) are useful screening procedures in all cases of neuromuscular disorder. The following extract from the case notes of a child I saw some years ago, while examining at a university, illustrates the need for a paediatric approach to infants and children: 'Electromyography in young children is a distressing procedure for both patient and operator and unless it is essential in relation to the clinical examination I would much prefer to delay it until she is 10 years old or even later.'

Adult neurologists do tend to treat children as miniature adults, and they should not be surprised if, having stripped the child, laid it supine on a couch and carried out an EMG procedure of needling multiple muscles, the child turns round and bites them. Electrodiagnostic procedures can be part of the ordinary clinical diagnostic work-up at a clinic, provided the child is adequately distracted and is left on the mother’s lap. As much information as possible should be extracted from a single needling of a muscle (we usually use the quadriceps) and from the muscle both at rest and on volitional activity. Nerve conduction velocity, which we usually do before the EMG, can be done with surface electrodes and is usually well accepted by the patients. A slow motor nerve conduction velocity may be found in the dominantly inherited form of peroneal muscular atrophy (hereditary motor and sensory neuropathy type I, as the modern classification has it) and a similarly low result is frequently found in one or other parent, who may be totally free of any clinical symptoms. This is useful from a genetic counselling point of view. The condition tends to be relatively mild and slowly or non-progressive. Slow nerve conductions may also reflect a more generalised disorder such as a leucodystrophy, which may be suspected from the clinical history.

Electromyography helps one to decide whether the muscle response is normal or abnormal and, if abnormal, whether the pattern is a denervation or a myopathic one. In the normal EMG there is silence at rest, the potentials produced on volition tend to be bi- or tri-phasic and there is a full interference pattern which essentially means loss of the baseline with continuity of the responses. In denervation one may find spontaneous activity at rest with sharp positive waves and on volition there are giant polyphasic potentials due to large motor units produced by reinnervation and there is also reduction in the

![Fig. 2.](image-url) (a) A transverse plane ultrasound of the thigh of an 8-year-old child, showing the echoes from the skin (S), the fascia lata below the skin (FL), the strong echo from the bone (B), the echo from the interfascial plane between the bone and the skin and the relative absence of echo from the muscle. (b) In contrast an ultrasound result from a child of the same age with Duchenne dystrophy shows a remarkable increase in muscle echo and complete loss of any echo from the bone owing to deflection of all the ultrasonic waves prior to reaching the bone.
interference pattern so that areas of baseline show up with no potentials. In myopathy there is silence at rest and a full interference pattern but the potentials tend to be small and polyphasic. In addition to the visual write-out of the responses, these results can be interpreted by the acoustic amplification of the response. In conditions such as myotonia, the spontaneous myotonic bursts (100/sec) with the characteristic 'dive-bomber' or 'motor-bike ton-up' sound can occasionally give a conclusive diagnosis. A word of caution in relation to diagnosis; in the congenital form of myotonic dystrophy, which presents at birth as a severely floppy infant with the associated characteristic features of facial weakness and respiratory and swallowing problems, it may not be possible to confirm the diagnosis, as there is usually no myotonia and even the muscle biopsy may be relatively normal in appearance. Confirmation comes from examination of the mother, who invariably carries the gene and shows some evidence of the disorder, either clinically in the form of facial weakness and inability to close the eyes tightly or electromyographically with evidence of myotonia.

**Muscle Biopsy**

Muscle biopsy is a relatively minor procedure which can be done under local anaesthetic; there is no justification for giving general anaesthesia to children with neuromuscular disorders whose respiratory function may already be compromised. The recent advent of needle biopsy has made the procedure much quicker and it entails only a small nick in the skin under local anaesthetic. The nick requires no stitch and heals almost without a visible scar following application of a butterfly dressing. Multiple samples can be obtained through the same hole, even without removing and reinserting the needle. During the past four years we have used needle biopsy exclusively.

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**Fig. 3.** Real-time ultrasound scan of thigh of (a) Duchenne dystrophy in a 4-year-old-boy, showing remarkable increase in echo both in the transverse and longitudinal plane, compared with (b) normal control.
and are now approaching almost 1,000 biopsies by this method. The samples obtained are perfectly satisfactory for diagnostic as well as additional research and investigative purposes. The technical handling of the samples has been well standardised and perfected. Proper orientation of the sample under a dissecting microscope prior to freezing will give perfectly oriented transverse sections. A full range of histochemical reactions, in addition to the standard histological stains, is essential for the recognition of many of the congenital myopathies with specific structural changes which may not be apparent with routine stains. The histochemical techniques also enable the specific fibre types within human muscle to be recognised and to identify disorders that may reflect a particular pathological process, even in the presence of apparently normal muscle on routine histological staining. Thus, for example, grouping of fibres of the same type may suggest a denervation/reinnervation process even in the absence of any other change on the biopsy.

I will not go into the details of all the exciting and picturesque disorders that muscle biopsy may reveal but I want to make a few general comments on some of the common disorders such as muscular dystrophy and spinal muscular atrophy. In both these conditions no pathologist can look down his microscope at a biopsy and tell you what the type of muscular dystrophy is; and the classical picture of spinal muscular atrophy with large groups of atrophic fibres is consistent with a severe Werdnig-Hoffmann disease in a severely paralysed child who may not survive the first year of life or with an intermediate spinal muscular atrophy of much less severity in a child who is likely to survive into adolescence. The pathologist can only describe the type of pathological change; the clinical syndrome has to be confirmed by correlation of the pathological change with the actual clinical severity. This is also well reflected in congenital muscular dystrophy; some children may achieve ambulation (with appropriate encouragement and supportive help) in spite of the fact that the biopsy looks like a very advanced type of dystrophy with hardly any residual muscle in a sea of fat and connective tissue. By contrast, other patients with congenital muscular dystrophy may show relatively less change on the biopsy and yet have quite severe clinical disability.

This discordance between clinical and pathological severity, and the need to decide whether or not they are mutually compatible, are the main reasons why we have always followed the policy of bringing the child back with the parents for review of the biopsy.

Ultrasoundography

A new field of investigation has mushroomed in the last year or two, which seems to have remarkable potential in the diagnostic screening of neuromuscular disorders. A few years ago, Dr John Heckmatt in our Muscle Unit, fired mainly by the tremendous output of new information from the application of ultrasound to the investigation of the intracranial contents of pre-term newborn infants, decided to jump on the ultrasound bandwagon and, in a moment of remarkable serendipity, asked:

Fig. 4. (a) Congenital muscular dystrophy with initial hypotonia and weakness but gradual improvement in a 4-year-old girl who now has very little physical disability. Ultrasound scan of the thigh shows a remarkable increase in the echo from the muscle and complete loss of the bone echo. (b) Ultrasound scan of control.

‘Why not muscle?’ In an initial study using a static B scanner belonging to the oncology unit conveniently near to our paediatric out-patient clinic, he showed[4] that there was a remarkable increase in the echoes in dystrophic muscle compared with controls of the same age (Fig.
After a pilot study on Duchenne dystrophy he demonstrated similar changes in other disorders, including the spinal atrophies, congenital dystrophies and some of the congenital myopathies with structural changes such as central core disease, even in the absence of marked clinical weakness. With the subsequent financial support of the MRC we have been able to obtain a real-time linear array ultrasound machine for use in our out-patient clinic and Dr Heckmatt is currently undertaking a 'blind' prospective study comparing the ultrasound picture with electromyography in every new patient coming to the clinic. We shall need to have the data on several hundred patients before drawing general conclusions on the practical use of ultrasound but, as things stand at present, it seems as though it is as good a diagnostic screen as electromyography, and may perhaps have the edge on electromyography, particularly in relation to floppy infants and in the first weeks of life. In addition, of course, it is non-invasive and perfectly acceptable to the child and, as far as we know, completely safe. Figures 3-5 show the ultrasound scans of three children with Duchenne dystrophy, congenital dystrophy and mild spinal atrophy and the scans of a normal control of similar age.

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