The Royal New Zealand College of General Practitioners

Volume 28
Number 02

April 2001

Focus

Neuromuscular disorders (I)

Michelle Smith is the neuromuscular educator for the Muscular Dystrophy Association of NZ Inc. Te Ropu Mate Horokiwa o Aotearoa

This article describes the features of a range of neuromuscular conditions (NMCs). A second article will focus on management of neuromuscular disorders.

Introduction

There are over 60 different types of NMCs covered by the Muscular Dystrophy Association, and of these, 13 are classified as muscular dystrophy (MD). These conditions are characterised by loss of muscle strength as progressive muscle wasting or nerve deterioration occurs. Almost all the conditions are genetic. Some cause shortened life expectancy, and there is variability in severity between and within the conditions.
The NMCs are indiscriminate, affecting individuals regardless of age, race or gender. They are all rare and have no cure. However, many drugs are being trialled, and research in gene therapy is making progress. Some types of NMCs are obvious at birth or early childhood, while others do not manifest until early or late adulthood. Most allow for a normal life span but there are a few disorders that are fatal early in life.
It is important to understand the progressive and unpredictable nature of these conditions because this makes them different to other physical disabilities. The outcome of most cannot be predicted at diagnosis. Comparisons cannot be made regarding progression between individuals. Even if there is a family history, family members will not be affected in the same way – there can be dramatic variations as to how each person is affected by the changes and at what stage changes occur in their lives.The NMCs are surrounded by many issues for those who live with the effects. This complexity that calls for a multi-professional approach for their management.1

Distinguishing different conditions

Muscular deterioration differs between disorders and is used to distinguish types. In some conditions muscle weakness is localised. In others, major muscles are involved first, with others becoming involved later. Opposing muscle groups often deteriorate at different rates. There are no remissions. Often after a rapid

KEY POINTS

- There are over 60 different types of neuromuscular conditions, characterised by progressive muscle wasting and weakness
- These conditions are progressive and unpredictable in outcome, in how each person is affected, and at what stage changes occur in their lives
- Muscular deterioration differs between disorders and is used to distinguish types. Spinal and limb girdle musculature is involved most frequently, usually early and profoundly
- Diagnosis is usually through blood testing, muscle biopsy, nerve conduction studies and electromyography
- Almost all the conditions are genetic in origin and

progression there is a period where the deterioration apparently slows down. Once the muscles are damaged, they do not recover. The essential feature of each condition is muscle wasting and weakness. Although any of the voluntary muscles can be affected, spinal musculature and the limb girdles are involved most frequently, and usually are affected earliest and most profoundly.

research in gene therapy is making progress

Origin and diagnosis

Almost all the conditions are genetic in origin (except myasthenia gravis and metabolic disorders), often the result of a damaged or absent gene. Diagnosis is usually through blood testing, muscle biopsy, nerve conduction studies and electromyography. Often more than one test is necessary to confirm diagnosis. Some conditions have no genetic tests available, and must be diagnosed by way of clinical features. NMCs can be sometimes difficult to diagnose as symptoms are vague or seemingly unrelated to neuromuscular problems.
These disorders fall into three genetic categories: X-linked, autosomal recessive and autosomal dominant. Genetic mutations can also be responsible for the occurrence of an X-linked or a dominant condition.
Clinical signs are:

- difficulty running
- difficulty climbing stairs
- difficulty rising from the floor without assistance
- difficulty getting from lying to sitting
- difficulty standing on one leg
- difficulty with fine motor movement (for some).

Clinical Criteria

The following are examples of criteria used to distinguish some of the common types of NMCs.

Duchenne muscular dystrophy[2]

- Symptoms present in boys before age five, initially in lower limbs.
- Progressive, symmetrical muscular weakness.
- Proximal limb muscles affected more than distal.
- Patient walks on toes, abdomen pushed forward, with a waddling gait.
- Use of Gowers sign.
- Calf hypertrophy often present.
- Wheelchair dependency before 13 years of age.
- Respiratory problems are the main cause of death (due to weakness, the boys are more prone to chest infections).
- Cardiomyopathy may be present.
- May present with learning difficulties.

Becker muscular dystrophy[2]

- Weakness is similar to that of Duchenne.
- Weakness of quadriceps femoris may be the only manifestation for a long time.
- Contractures of elbow flexors may occur late in the course of the disease.
- May present with cardiomyopathy.
- If there is wheelchair dependency, it is after 16 years of age.

- Death may occur in 20s or 30s, but often survival is into middle-age and beyond.

Facio-scapulo-humeral dystrophy2

- Onset in facial/shoulder girdle muscles.
- 50 per cent have varying degrees of facial weakness, particularly an inability to close the eyes properly and to whistle.
- Onset in the second decade of life.
- Scapular fixators are prominently affected.
- Possible early involvement of abdominal and foot extensor muscles.
- Pelvic girdle and upper arm weakness may occur (50 per cent never have any pelvic girdle weakness).
- Stepping/waddling gait. Running becomes impossible.
- Lordosis is common.
- Progression rate and severity are highly variable.
- Possibility of contractures and pseudohypertrophy.
- Possibility of progressive hearing loss.
- Normal life expectancy.

Limb girdle muscular dystrophy2

- Group of genetically determined progressive disorders.
- Pelvic or shoulder girdle musculature primarily involved.
- Calf hypertrophy common.
- Onset at any age.
- Progression varies from very fast to very slow.
- Possibility of some asymmetry.
- Can be cardiac involvement.
- Six different dominant types have been described and genes identified.
- Eight different recessive types have been described and genes located.
- Diagnosis needs to be made with care and qualification.

Myotonic dystrophy2

- A generalised multi-system disorder.
- Congenital: before 10 years of age. Can result in stillbirth or severe muscular weakness and hypotonia. There is often sucking, swallowing and respiratory insufficiency. Symptoms present in mother.
- Early childhood: intellectual impairment, and generalised weakness especially of face and distal limbs. Myotonia usually starts between ages five and 10. Symptoms are present in one parent.
- Juvenile/adult 10 to 50 years: myotonia of grip, weakness in distal limb muscles. Weakness in one or more of pharyngeal muscles. Cortical cataract. Positive family history.
- Lethargy and general apathy are common traits.
- Life-span usually to middle-age and beyond if not congenital, or if no significant heart problems.

Friedreich's ataxia2

- Most common of all hereditary ataxias.
- Degenerative atrophy of posterior columns of spinal cord leading to progressive ataxia, sensory loss and muscle weakness.
- Often associated with scoliosis, foot deformity and heart disease.
- Onset is before 25 years of age.

- Progressive limb and gait ataxia.
- Dysarthria.
- No reflexes.
- Affects both central and peripheral nervous systems.

Congenital muscular dystrophy[2]

- Term widely used for infants presenting with muscle weakness at birth, or within first few months of life, in association with a dystrophic pattern on muscle biopsy.
- Hypotonia or arthrogryposis and associated contractures.
- Slow progression/appears to be static.
- Variable respiratory and swallowing problems – can lead to respiratory failure later in childhood/adolescence.

Spinal muscular atrophy[2]

- Type 1 (infantile) onset at birth to six months, with death resulting before two years. No signs of muscle wasting. There is an arrest of development of motor milestones, and most children are never able to sit without support.
- Type 2 (intermediate) onset before 18 months; if death occurs it is after two years of age. Tremor in the hands often observed. Also an arrest of development of motor milestones.
- Type 3 (mild) onset after 18 months with death in adulthood. Tremor in the hands often observed. Children do develop the ability to stand and walk.
- Criteria are arbitrary and subject to overlap.
- Symmetrical muscle weakness.
- Proximal limb muscles with lower limbs being weaker.
- Can be sensory disturbances, CNS dysfunction and involvement of other neurological systems.

Charcot Marie Tooth type 1a (are 6 to 7 types)[2]

- Symmetrical muscle wasting and weakness.
- Distal part of lower limbs.
- Later wasting and weakness of intrinsic hand and quadriceps muscles.
- Possible impaired sensation.
- Possible scoliosis, nerve hypertrophy and CNS involvement.
- Sometimes other major organs are involved, affecting vision, hearing and cardiac function.
- Slowly progressive condition.
- Inherited as autosomal dominant.

The cutting edge: current research

Research is constantly changing information. For some NMCs the location of the affected gene is yet to be found. With inroads at least in gene therapy and drug use, positive findings will have an impact on the management and treatment of NMCs and will change the focus of these conditions. Some of the most recent and most exciting research is given below:

1. Gene therapy: new genes are inserted into cells, whereby a modified virus is used to help transport new genes.
In limb girdle MD clinical trials have started whereby the protein utrophin is being injected into muscle, with the hope that it will rebuild muscle that has already deteriorated. The results are still to be

published.
In Duchenne MD there are mouse trials of gene therapy, again with the protein utrophin being injected, and with the use of viral vectors. Because larger amounts of muscle are involved, clinical trials will not begin until it is determined safe and effective. Mice with a form of Duchenne MD did show improvement when the utrophin gene therapy was used.3,4

2. Stem cells: these are being trialled in Duchenne MD. This is the newest and most exciting approach to Duchenne MD therapy: stem cells from a healthy donor are injected into the bloodstream of a mouse that lacks dystrophin. In response to injury signals from the muscle, the dystrophin-containing stem cells gradually migrate into all muscles.3,4

3. Getting the cells to "ignore" the mutation in the Duchenne MD gene: a promising new drug therapy that may be suitable for a range of genetic disorders.
Gentamycin has been found to act on the protein-producing machinery in the cell. The drug can help the cell to "read through" mutations, resulting in the production of full-length protein.
Due to the powerful side effects, US trials are aimed at finding a dosage regimen which will give the greatest benefit while minimising the side effects.
In Australia antisense RNA is used to trick the muscle cells into skipping out the part of the Duchenne MD gene containing the mutation, thereby converting a potentially severe case of Duchenne MD into a milder case of Becker MD.3,4

4. Energy production and muscle building: creatinine is being tested to see if it can increase muscle energy production and storage, thus preserving muscle cells and increasing strength in Duchenne MD. Only shortterm trials have been done with further research needed to determine correct dosage and potential long term side effects.3,4
Albuterol (salbutamol) has shown anabolic effects in facio-scapulo-humeral dystrophy, with an increase in muscle mass of 10 per cent. Trial results showed that it had no effect on muscle strength, but did improve grip strength and skeletal muscle mass, suggesting that it may preserve or develop muscle to a limited extent in this disorder.5

References

1. Carter, GT. Rehabilitation management in neuromuscular disease. *J Neuro Rehab* 1997;11:69-80.
2. Emery, AE. Diagnostic criteria for neuromuscular disorders. *ENMC, The Netherlands*, 1994.
3. Wahl, M. MDA research at year 2000: moving from lab to clinic. *Quest Magazine* 2000;1:16-20.
4. Barton, Dr. Update on recent research in muscle disorders: gene therapy. *MDI Magazine* 2000;14.

5. Research updates. Albuterol study in FSHD negative, but 'provocative'. *Quest Magazine* 2000;4:42-43.

Other resources not cited

Emery, AE. Muscular dystrophy: the facts. Second edition. Oxford: OUP, 2000.
Lane, RJM (ed). Handbook of muscle disease. New York: Marcel Dekker Inc., 1996.
MD Group – United Kingdom, Fact Sheets.
MDA USA Fact Sheets and various articles.
MDA NZ Fact Sheets, produced and updated 1995-2000.

• *Michelle has had a lot of involvement with the Muscular Dystrophy Association over the past few years in both employment and voluntary capacities. She has a degree in Education and History from the university of Auckland. Michelle has facio-scapulo-humeral muscular dystrophy, and has wide and varied interests liking to challenge herself to keep her mind and body as active as possible.*