

Summary

- NF1 is the most common single gene disorder affecting the human nervous system, with an incidence of 1 in 3 000 - 4 000 individuals of all ethnic backgrounds.
- Despite many patients manifesting few phenotypic signs, 40% of all affected individuals will develop medical complications in their lifetime, making long-term follow-up mandatory.
- The diagnosis is made on clinical features based on the NIH Consensus Development Conference of 1988.
- The most common complication of NF1 worldwide is academic learning disability, affecting up to 50% of affected individuals (most have an IQ in the normal range).
- Early surveillance allows for early intervention with regard to learning difficulties and minimises long-term morbidity.
- Controversy exists surrounding how far to investigate individual patients, especially with regard to neuro-imaging.
- Whatever the policy, consensus exists that all patients require long-term follow-up, preferably in a multidisciplinary setting.
- Plexiform neurofibromas occur in about 30% of affected patients and remain a huge management dilemma because of their extensive penetration, often encasing vital internal structures and therefore making surgical resection difficult.
- Malignant, peripheral nerve sheath tumours (MPNSTs) develop in up to 10% of NF1-affected individuals within plexiform neurofibromas, usually in adolescence or adulthood. Malignant transformation is difficult to diagnose and has a poor prognosis.
- Research studies are currently looking at medical therapy using antifibrotic and alternate chemotherapeutic agents to manage plexiform neurofibromas.

Further reading available at www.cmej.org.za

A medical approach to the care of children with Duchenne muscular dystrophy

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Duchenne muscular dystrophy (DMD) is an X-linked condition with an incidence of 1:3 600 - 6 000 live male births. Aspects of the internationally accepted management guidelines^{1,2} are challenging in the South African setting, but attempts should be made to incorporate them.

Diagnosis

Diagnostic clues. Consider DMD in any child (especially a boy) with proximal weakness, calf hypertrophy and language delay, and who frequently falls. Boys typically present between 3 and 5 years of age. Creatine kinase (CK) levels are usually >10 000 mmol/l.

Confirming the diagnosis. This is essential, as the management and inheritance differ from other muscular dystrophies. DNA analysis, with written consent from the parents, results in diagnostic confirmation in about 50% of patients. The remainder require a muscle biopsy, performed at a centre where the full range of immunohistochemistry stains are available (Figs 1 and 2).

Chronic care

Ideally the patient should be managed by a multidisciplinary neuromuscular team (Table I).

Corticosteroids prolong ambulation by 2 - 3 years. The ideal regimen has not been established. Our policy is 0.75 mg/kg/day prednisone daily. Children should be

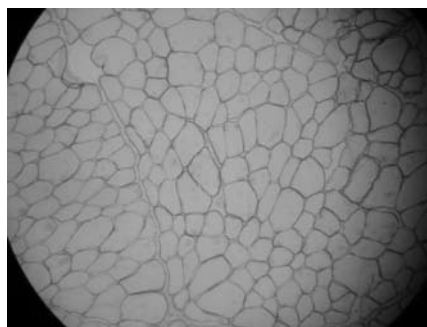


Fig. 1. Normal muscle light microscopy section demonstrating normal architecture and immunohistochemical staining for dystrophin.



Fig. 2. Abnormal muscle biopsy from a child with Duchenne muscular dystrophy, showing complete absence of dystrophin staining; muscle fibres are hypertrophied with connective tissue infiltration.

assessed every 3 months for progress and side-effects (weight, blood pressure, height, muscle power score and glycosuria). They should be vaccinated against varicella before starting treatment, and tuberculosis should be excluded. Routine influenza and pneumococcal vaccinations should be given. Annual ophthalmological assessments and bone density screening are recommended. Our policy is to discontinue steroids once ambulation is lost. The optimal starting time is unknown, but is accepted to be once the child is clinically affected (i.e. difficulty in getting up, falling more often). This usually occurs by 5 years of age.

Vitamin D. Replacement therapy with vitamin D is recommended at 600 IU/day to limit osteoporosis.

Physiotherapy. Daily stretching of the tendo-achilles and hamstring regions should be reinforced. Contractures de-stabilise the child and may result in premature loss of ambulation. Appropriate footwear with light-weight shoes, no wedge and good ankle support is ideal. Children with proximal weakness may be more unstable with ankle-foot-orthoses; these should rather be used as night splints.

Cardiac care. Ambulant children require functional cardiac assessments (including echocardiograms) every 2 years; once non-ambulant they should be assessed yearly, but more often if symptomatic. Start prophylactic treatment with ACE inhibitors from about 5 years of age. At our hospital 2.5 mg enalapril is administered, which stabilises progressive left ventricular dysfunction.

Backs/seating. Prolonged ambulation into puberty, aided by steroid treatment, reduces the degree of scoliosis formation. Appropriate seating with adequate back support is essential once a wheelchair becomes necessary. Development of scoliosis should be determined by an orthopaedic spinal specialist to assess the need for spinal rod intervention.

Dietician. Non-ambulant children gain weight rapidly; therefore early intervention to avoid weight gain is essential.

Nocturnal BIPAP. FEV₁ and FVC should be recorded at each clinic visit. If the FEV₁ (<40%) or FVC starts to decrease, or the child complains of features consistent

Table I. Neuromuscular multidisciplinary team

Neurologist
Pulmonologist (home care ventilation support)
Physiotherapist/occupational therapist
Speech therapist
Dietician
Orthopaedic specialist (interest in orthotic devices and scoliosis care)
Cardiologist
Counsellor (genetic and social)

with nocturnal hypoventilation (daytime drowsiness, headache, poor sleep pattern), then overnight respiratory monitoring is required and BIPAP (bi-level positive airway pressure) intervention should be considered.

Schooling and independence. It is hard for a child to lose ambulation and to see his peers/siblings outpace him. All attempts must be made to respect the individual through appropriate school placement, an electric wheelchair and access to computer skills. Children with DMD are often in mainstream education and may have to transfer to a special school once they are no longer ambulant.

Ethics and counselling. Older children may have better insight into their condition than parents realise. However, their concerns tend to focus more on how the disability limits their activities of daily living. Thoughts of their longevity are not an immediate priority, while this dominates for many parents. Open-ended questions enable the child to respond if they have issues, but a child should not be confronted with a list of health concerns. Routine screening of unaffected/possibly pre-symptomatic male siblings is not recommended. Refer the family for formal genetic counselling to ensure they fully understand the implications of testing and the reliability of such screening. If maternal aunts or the mother requests screening and if there is DNA confirmation, then linkage analysis may enable carrier status to be established. Otherwise CK levels sometimes, but not reliably, indicate whether they are carriers.

Parents and carers. Their needs are often forgotten or there is no adequate support network. Encouraging them to contact the Muscular Dystrophy Foundation (<http://www.mdsa.org.za/index.htm>) may help them to cope with the emotional and physical burdens.

The future

There is currently no cure for DMD. Gene therapy may be one intervention, but to date it is not available. Other possible therapies include the role of PTC124, an agent which allows 'read through' of a premature stop codon and the production of dystrophin. Such treatments are targeted at specific genetic mutations. It is important to ensure that the DNA from all affected children is stored. The expanding capacity of genetic screens is resulting in further mutations being identified in children previously reported deletion negative. Some 20 years ago children with DMD died a difficult death – often by 14 years of age. Currently, with a multidisciplinary approach, children can survive with a good quality of life to over 30 years of age. Management is not directed at prolongation of life, but more at the rights of the individual to reach their full potential.

Summary

- DMD affects mainly boys.
- The clinical onset is typically by 3 - 5 years of age.
- The creatine kinase is usually >10 000 mmol/l.
- Confirming the diagnosis is essential, as the management and inheritance differ from other muscular dystrophies.
- Prophylactic corticosteroids and ACE inhibitors are known to improve survival and quality of life.
- Multidisciplinary care results in better quality of life and longevity into the second or third decade.

References available at www.cmej.org.za

Post-streptococcal neuropsychiatric movement disorders or Sydenham's chorea spectrum disorder: an update on management

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Sydenham's chorea (SC) was first described in 1686 by Thomas Sydenham.¹ It is a major criterion for the diagnosis of acute rheumatic fever and its presence alone is sufficient to make this diagnosis.² Up to 60% of people who present with SC will later develop rheumatic heart disease.³

SC is an anti-neuronal, antibody mediated neuropsychiatric disorder.⁴ Antibodies that arise in response to group A beta-haemolytic streptococcus (GABAS) infection cross-react with epitopes on neurons within the basal ganglia, frontal cortex and other regions.⁴ A cerebral arteritis with cellular degeneration occurs.⁵ This results in dopaminergic dysfunction, which has an effect on movements, attention and emotion.⁶

Clinical presentation

The clinical features of SC include both neurological abnormalities and psychiatric disorders. The former comprise involuntary choreatic movements, voluntary movement incoordination, muscular weakness and hypotonia.⁷ Psychiatric disorders

include emotional lability, hyperactivity, distractibility, obsessions and compulsions.² Difficulty in the execution of activities of daily living results, such that the condition impacts negatively on the quality of life of affected children.

Choreatic movements are involuntary, irregular, purposeless, non-rhythmic, abrupt, rapid and unsustained.⁸ Movements disappear with sleep and rest. Voluntary movements make the chorea worse.⁹ Hypotonia and weakness range from mild to severe. The severe form is termed chorea mollis or chorea paralytica and may be confused with the clinical appearance of a stroke.¹ Obsessions may include harm to loved ones, separation anxiety and fear of contamination, resulting in compulsive washing.¹⁰ Children may have severe chorea (ballistic movements) and/or hypotonia with few psychiatric symptoms or mild chorea with pronounced psychiatric symptoms.² A change in behaviour may precede the chorea.

Classic descriptions of SC indicate that it is benign and self-limiting.¹¹ At best the condition lasts for 6 months, but more usually it has a relapsing course for up to 2 years.¹² It may evolve into a chronic movement disorder.¹² It is important to quantify the severity of symptoms as a therapeutic index. Aron's clinical classification refers to 'mild' in the presence of minimal movements, 'moderate' in the presence of movements of obvious inconvenience to the patient but which do not interfere with self-care, and 'severe' if there are movements sufficiently incapacitating for the patient to require assistance for the activities of daily living.⁵

Therapeutic interventions

Treatment has four main tenets: elimination of the streptococcus, symptomatic treatment of the involuntary movements, incoordination and psychiatric symptoms, treatment of the immune and inflammatory response and supportive measures.

Primary treatment: elimination of streptococcus

Treatment with penicillin is mandatory to eliminate the streptococcus. When SC is diagnosed penicillin 500 mg twice daily for 10 days should be given, and rest is advised.¹³ Adverse outcomes and a chronic relapsing course of SC are more common in children who do not receive 10 days of penicillin and bed rest.¹²

Prophylaxis with long-term penicillin is primarily given to protect the heart. Intramuscular benzylpenicillin every 28 days or oral penicillin VK 250 mg twice daily is advocated as secondary prevention of rheumatic heart disease.¹³ Patients must also be advised to seek primary treatment for future streptococcal sore throats.