Later presentation
Any unexplained neurological syndrome; static, intermittent or progressive with
- seizures/encephalopathy
- coma
- stroke
- spasticity
- dystonia/rigidity/choreoathetosis
- ataxia
- myopathy/ptosis
- neuropathy
- deafness.

Other organ involvement is common. The central nervous system (CNS) may be secondarily involved, as in galactosaemia.

Investigations
Emergency or baseline investigations usually include:
- full blood count (FBC)
- acid base
- electrolytes
- urea, creatinine
- glucose – if low, ketones, insulin, free fatty acids
- liver functions
- calcium, magnesium
- clotting profile
- urine-reducing substances.

Ammonia and lactate tests are not readily available but are important – contact the nearest tertiary centre if an infant remains acidotic.

Lactate may be falsely elevated in a struggling child or after using a tourniquet. It will be elevated if there is respiratory or hepatic compromise or circulatory disturbance.

Further investigations are best done in consultation with the laboratory or relevant specialist and may include:
- amino and organic acids on blood and urine
- acylcarnitine profiles
- enzyme analyses
- genetic studies
- histology
- imaging.

If advice is not readily available, or the patient is critically ill, heel-prick blood spots on filter paper can be dried, stored frozen (-20°C) and used for future genetic and biochemical testing. Frozen urine, heparinised plasma and EDTA blood samples are useful for analysis. A small sterile skin biopsy in culture medium for fibroblast culture would complete the samples required for further testing.

Treatment
There are potentially treatable disorders where *early* intervention, as for galactosaemia and hypothyroidism, is imperative. Broad neonatal screening is the only way to effectively diagnose these disorders prior to clinical presentation. It is performed routinely in many countries, excluding South Africa. Research is required to delineate which conditions would be most cost effective to screen for in South Africa.

Treatment principles include:
- Treat correctable factors immediately: hypoglycaemia, acidosis, seizures, cardiac failure, hyperammonaemia.
- Start a galactose-free formula if galactose is present in the urine.
- Supplementation with pyridoxine, folinic acid or biotin may be effective for early-onset drug-resistant seizures if there is an underlying defect in any of these pathways.
- Severe hyperammonaemia may require dialysis.

Specific treatment requires the establishment of a diagnosis and a personalised management plan devised by the neurometabolic team, including therapists and a dietician.

Role of the family practitioner
- Recognition of the at-risk infant and appropriate referral.
- Baseline screening.
- Chronic care assistance in liaison with the paediatrician and tertiary care centre or subspecialist.

Role of the paediatrician
- Will vary depending on special interests/area of practice.
- Recognition of the at-risk infant, baseline +/- specific investigations and imaging.
- Stabilisation, management of acute crises in liaison with subspecialist/tertiary centre.
- Referral as necessary for dialysis, intensive care monitoring and subspecialist investigation.
- Chronic care in liaison with subspecialist.

In summary
- If an infant or child's presentation is atypical or unexplained, think of metabolic causes.
- Acute presentation often resembles sepsis, with refractory acidosis, recurrent vomiting, seizures, or altered level of consciousness.
- Chronic presentation is easy to miss and includes failure to thrive, developmental delay, epilepsy, 'cerebral palsy' (especially dystonic), and unexplained intellectual disability.
- Thoroughly check the family history.
- Investigate if there is no clear cause for severe disability.
- The clinical findings are the key to guiding investigations.

Acknowledgement
Dr George van der Watt, Head of Chemical Pathology, Red Cross Children's Hospital and executive member of the Southern African Metabolic Disease Group.

References and further reading available at www.cmej.org.za
Websites for further reading
Acute management protocols for known IEM (UK): http://www.bimdg.org.uk/
Human metabolome database: http://www.hmdb.ca.
IEM protocols (USA): http://newenglandconsortium.org/
Newborn screening: North West University: http://www.newbornscreening.co.za
North West University: http://www.pliem.co.za
SSIEM: http://www.ssiem.org/webresources_inborn.asp
University of Cape Town Chemical Pathology and Metabolic laboratory: http://www.madlab.uct.ac.za

Neurofibromatosis

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The neurocutaneous syndromes are unique for their neurological and cutaneous manifestations.

Neurofibromatosis type 1 (NF1)
Neurofibromatosis type 1 (NF1) is the most common neurocutaneous disorder, with a prevalence of 1 in 3 000 - 4 000 individuals. It is inherited as an autosomal dominant condition and about 50% of cases are new mutations. The gene is located on chromosome 17q11.2 and is a tumour-suppressor gene. This large gene has many different mutations, making routine genetic testing difficult. Prenatal diagnosis is possible but of little prognostic value. There is poor correlation between specific mutations and clinical phenotype, except for deletions of the entire gene where a more severe phenotype and higher numbers of neurofibromas occur. NF1 has variable expressivity and does not run true within a family. NF1 affects all ethnic groups. After the National Institutes of Health (NIH) Consensus Development Conference in 1988, the diagnosis of NF1 has been based on the presence of two or more of the following criteria:
- six or more café au lait spots >5 mm (prepubertal) and >15 mm (post-pubertal) in diameter
- axillary or inguinal freckling

- optic glioma
- two or more iris hamartomas (Lisch nodules)
- a typical osseous lesion such as sphenoid dysplasia or tibial pseudoarthrosis
- one or more first-degree relative with NF1.

Clinical manifestations

Up to 50% of affected individuals manifest few phenotypic signs. However, medical complications occur in up to 40% of affected individuals. As such, NF1 carries significant morbidity and mortality, and life-long follow-up is mandatory.

- Café au lait spots (Fig. 1) and axillary and inguinal freckling are the most common and earliest clinical features, and usually form the basis of the diagnosis.
- Lisch nodules are innocuous iris hamartomas evident in patients older than 2 years (Fig. 2).
- Affected individuals have an increased risk of developing benign and malignant tumours.
- Neurofibromas are most common, manifesting as heterogeneous, benign, peripheral nerve sheath tumours after the second decade.

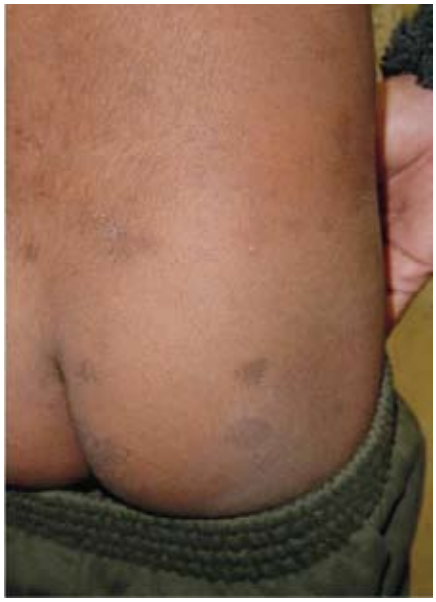

Fig. 1. Café au lait spots.

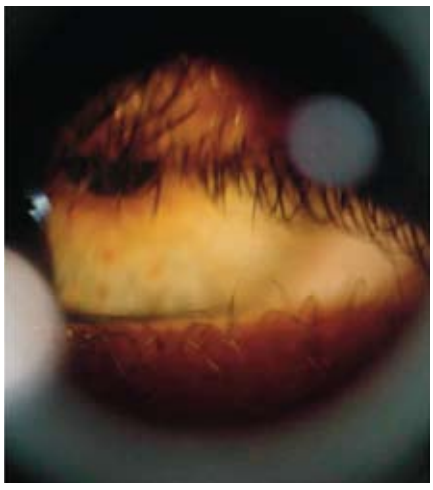

Fig. 2. Lisch nodules – iris hamartomas.

- Plexiform neurofibromas occur in up to 30% of all NF1 patients; these are diffuse lesions, composed of the same cell types as dermal neurofibromas and are present from birth (Fig. 3). Their size may be underestimated as they may be subcutaneous or deep and track along the routes of major nerves with a rich vascular supply. They are associated with regional hypertrophy and overlying pigmentation. MRI allows the true extent of the lesions to be demarcated. In addition to location-specific complications, malignant transformation may occur.

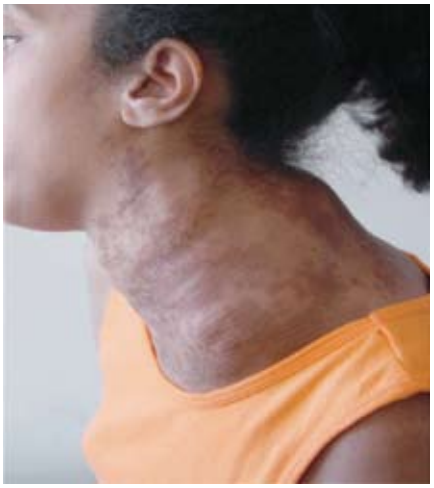

Fig. 3. Plexiform neurofibroma.

- Optic gliomas (Fig. 4) are the most common CNS tumours in NF1, with a prevalence of 11 - 19%. Tumours may be unilateral or bilateral, affecting the optic nerves, optic tracts and/or chiasm. Growth is insidious, and children with symptomatic tumours usually present with visual disturbance between 4 and 6 years of age. Children with NF1 and optic gliomas have a better prognosis than unaffected individuals with optic gliomas. An optic glioma in an NF1-affected individual may increase the risk for other CNS malignancies. Management is often conservative.
- Typical osseus lesions include tibial pseudoarthrosis (Fig. 5), sphenoid wing defects and vertebral scalloping. Many lesions are asymptomatic.

Associated features of NF1

Academic learning disability

Learning disabilities occur in about 50% of affected individuals. There is no consistent profile of learning problems – specific deficits in visuospatial ability, executive function, expressive and receptive language and attentional difficulties have been described. Academic learning disability can lead to significant morbidity, resulting in major lifestyle impact for parents and affected children.

MRI T_2-signal abnormalities

MRI signal abnormalities include focal areas of high signal intensity on T_2-weighted images. These are pathognomonic of NF1,

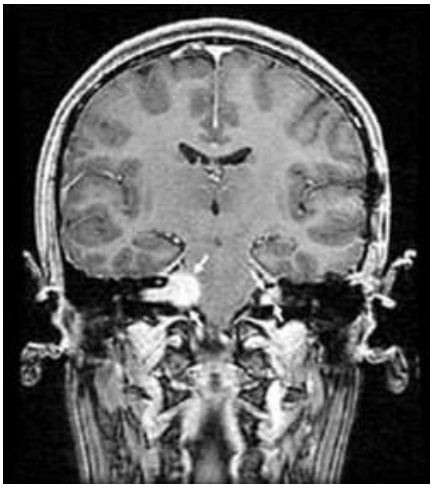

Fig. 4. Optic glioma.

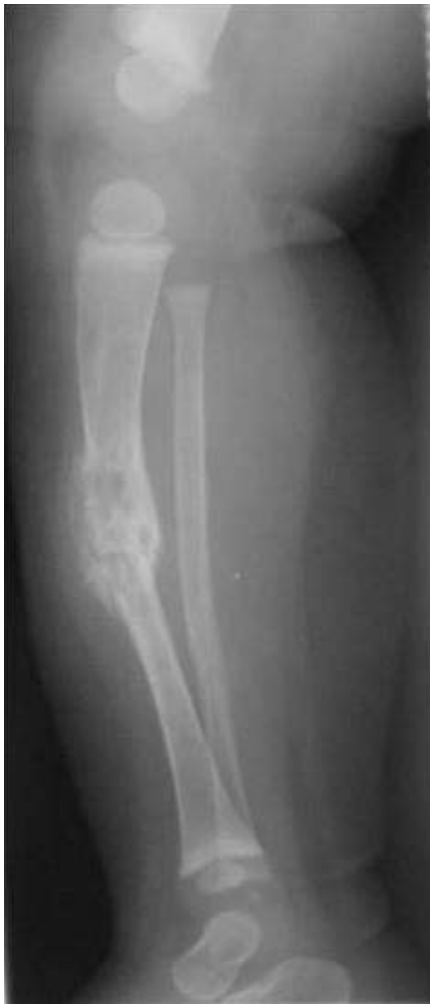

Fig. 5. Tibial pseudoarthrosis.

and most prevalent in children under 10 years of age. The basal ganglia, cerebellum, brainstem and subcortical white matter are most commonly affected. Lesions thought to be due to myelin vacuolisation either remain static or decrease with time and are not clinically associated with disease severity.

Neoplasms

The incidence of CNS malignancies other than optic gliomas is less than 5%. Malignant peripheral nerve sheath tumours (MPNSTs) are the most frequent malignant

Table I. Management of neurofibromatosis (based on guidelines from the multidisciplinary Neurocutaneous Clinic at Red Cross War Memorial Children's Hospital – in operation since 2001)

Multidisciplinary team	In the clinic: paediatric neurologist, neuro-developmental paediatrician, genetic counsellor, neurosurgeon	Affiliated to the clinic: ophthalmology, plastic surgery, orthopaedic surgery and dermatology
	All affected family members attend together	
Assessment: First visit	Personal and family history is taken at initial visit, including neuro-developmental history and school progress report	Ophthalmology review at first visit
	Parents and caregivers receive genetic counselling at initial visit and are given an information pamphlet about NF1	Diagnosis confirmed according to inclusion criteria
Follow-up assessments	Younger patients are seen 6-monthly. Older, more stable children are seen annually	
Neuro-imaging (brain)	An MRI scan of the brain and orbit is performed in all affected children at about 8 years of age if they are asymptomatic, or earlier – at presentation of clinical symptoms. Eight years is the optimal age when most children can tolerate an MRI without sedation, and optic glioma typically manifests before 6 years of age	MRI screening for all patients allows for appropriate counselling and follow-up of patients with optic pathway lesions. In a setting where many patients travel long distances to attend clinics, a single detailed scan once in a child's lifetime proves to be beneficial, allowing better surveillance of patients who need more vigilant follow-up
Neuro-imaging (other)	Other neuro-imaging, usually an MRI scan of specific lesions, is performed according to clinical suspicion such as for plexiform neurofibromas where the extent of the lesion needs to be defined	Spinal MRI scans are performed if there is a plexiform neurofibroma close to the spine, or to evaluate the presence of scoliosis
School performance	Preschool-age children are referred for a detailed neurodevelopmental assessment. Referrals to allied health professionals facilitate early intervention	School-going children with learning difficulties are referred for detailed evaluation to the relevant school health service, with provision of detailed information about the child and NF1 in general
Interim care	Patients are followed up at their local clinic, by their GP or private paediatrician, with access to the multidisciplinary service readily available	

neoplasms, occurring in up to 10% of affected individuals. The International Consensus Statement on MPNSTs in NF1 states that management is challenging as MPNSTs are rarely completely resectable and respond poorly to radiotherapy and chemotherapy.

Growth parameters

Patients tend to be below average height and have an above average head circumference for age.

Hypertension and vascular complications

Hypertension occurs commonly in affected patients, especially in adulthood. This is due to an NF1 vasculopathy causing renal artery stenosis, coarctation of the aorta or other vascular lesions associated with hypertension. There is also a higher frequency of essential hypertension. Moyamoya syndrome may occur, where the small collateral vessels appear as a 'puff of smoke' around the stenotic area on cerebral angiography.

Noonan's phenotype

This has been described in up to 12% of affected individuals. Features include hypertelorism, downslanting palpebral fissures, low-set ears, a webbed neck and pulmonary artery stenosis.

Approach to management of the NF1-affected child

There is universal consensus regarding the diagnostic criteria for NF1 and lifelong follow-up. Controversy surrounds extensive baseline investigations in affected individuals. The NIH Consensus Development Conference 1988 guidelines recommend that beyond regular medical and ophthalmological assessments, other investigations should only be performed if there is a clinical indication. The rationale is that treatment is only administered for symptomatic complications, thereby avoiding unnecessary anxiety and cost. Several international centres oppose these guidelines, emphasising the value of early detection and intervention. Consensus exists regarding multidisciplinary clinics where patients receive more centralised and uniform quality of care (Table I).

Neurofibromatosis type 2 (NF2)

This is a completely separate autosomal dominant condition, with the gene located on chromosome 22q. NF2 is far less common than NF1, with a prevalence of less than 1 in 100 000. Most patients present in the second decade of life or later, the hallmark being the development of bilateral acoustic neuromas, i.e. Schwann cell tumours of the 8th cranial nerve. Patients may have skin stigmata, usually café au lait spots, but these may be subtle. The diagnostic criteria are given below:

- CT or MRI evidence of bilateral internal auditory canal masses consistent with acoustic neuromas
  OR
- A first-degree relative with bilateral acoustic neurofibromatosis and one of the following:
  - CT or MRI evidence of unilateral internal auditory canal mass consistent with acoustic neuroma

  OR
- Two of the following:
  - plexiform neurofibromata
  - eningioma
  - glioma (including astrocytoma or ependymoma)
  - schwannoma (including spinal root schwannoma)
  - juvenile, posterior, subcapsular lenticular cataract
- Other clinical features such as seizures, skin nodules, dermal neurofibromas, café au lait spots (much less common than in NF1).

Segmental neurofibromatosis

Segmental or regional neurofibroma occurs where features of NF1 are restricted to one part of the body and relatives are unaffected.

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 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.

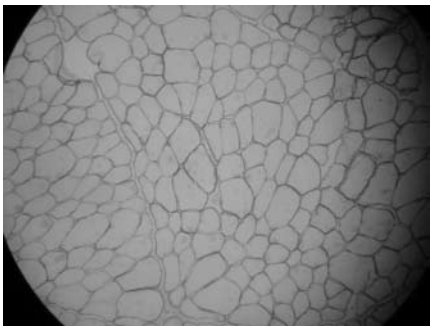

Fig. 1. Normal muscle light microscopy section demonstrating normal architecture and immunohistochemical staining for dystrophin.

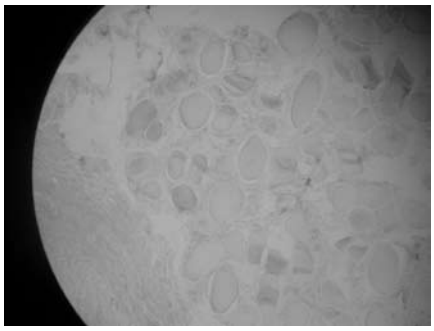

Fig. 2. Abnormal muscle biopsy from a child with Duchenne muscular dystrophy, showing complete absence of dystrophin staining; muscle fibres are hypertrophied with connective tissue infiltration.

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. FEV_1 and FVC should be recorded at each clinic visit. If the FEV_1 (<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)