STUDY PROTOCOL

Australian Paediatric Surveillance Unit

Neuromuscular disorders of childhood

COMMENCING January 2007

BACKGROUND

Neuromuscular disorders have very variable signs and symptoms, severity and impact on quality of life and life span. Diagnosis of these conditions is based on clinical, neurophysiologic, pathologic and genetic criteria (Table). Recent advances in these areas have resulted in a marked increase in the complexity of classification of many of these conditions.

Worldwide incidence and prevalence data for neuromuscular conditions in children are often outdated and incomplete. There are no such Australian data. International studies have shown considerable variability in the incidence of specific conditions in different populations and ethnic groups,[19-21, 23-26] and the effect of antenatal diagnosis on disease incidence is generally unknown. While these disorders are individually rare, the impact of a single child with a neuromuscular disorder upon the family and community can be enormous. Affected children require extensive community and hospital services for diagnosis, management and therapy, hospitalisations, access to and assistance with school, adaptive equipment and home modification, respite care, and social and financial support. Support services are largely dependent on state or federal funding, which is contingent upon perceived need. In the absence of accurate epidemiologic data, such services may be inadequately funded.

Better epidemiologic data is required to secure adequate provision and funding of clinical, diagnostic and research services in order to maintain the current high standard of care for paediatric neuromuscular disorders in Australasia.

STUDY OBJECTIVES

1. To describe the epidemiology of inherited and chronic auto-immune neuromuscular disorders diagnosed in Australian children, including:
   a. Type and frequency b. Family history c. Clinical presentation
2. To determine methods of diagnosis of these disorders in Australia.

CASE DEFINITION

Please report any child seen in the last month, aged 15 years or less, with a **newly <u>diagnosed</u> inherited or chronic auto-immune neuromuscular disorder as described in the table below.**

Inherited neuromuscular disorder refers to any genetic disorder of the lower motor neuron i.e. disorders of anterior horn cell, motor and/or sensory peripheral nerve, neuromuscular junction or muscle.

Chronic auto-immune neuromuscular *disorders* are acquired immune-mediated disorders of peripheral nerve, neuromuscular junction or muscle causing permanent or persistent (>3 months duration) symptoms. These disorders include chronic inflammatory demyelinating polyneuropathy (CIDP), myasthenia gravis and dermatomyositis.

Table: Case definitions

Disorder	***Clinical characteristics***	***Method of diagnosis***
Spinal muscular atrophy[1]	• A motor neuronopathy causing progressive weakness in childhood, with facial sparing and tongue fasciculations. • Classification into types I - III based on clinical severity: o Type I – does not achieve sitting o Type II – achieves sitting but not standing o Type III – achieves standing and walking.	• Diagnostic: Recessive mutations in *SMN1.* • Diagnostic: Typical neurogenic abnormalities on muscle biopsy. • Supportive: EMG: chronic neuropathic abnormalities, normal sensory studies.
Charcot-Marie -Tooth disease (hereditary motor and sensory neuropathy)[2]	• A group of chronic progressive nerve disorders. • Presentation with abnormal gait, progressive distal weakness and orthopaedic abnormalities. • Classification based on neurophysiology and genetic testing	• Diagnostic: Confirmatory genetic testing. • Diagnostic: NCS: axonal or demyelinating neuropathy. • Supportive: Exclusion of other causes of neuropathy.
Myasthenia gravis	• Auto-immune disorder caused by acquired antibodies to nicotinic post-synaptic acetylcholine receptors (AChR). • Associated with acquired fluctuating ophthalmoplegia +/- ptosis, +/- weakness of the proximal limb musculature.	• Diagnostic: Positive anti-AChR antibody test. • Diagnostic: EMG: decremental response on repetitive nerve stimulation. • Supportive: exclusion of hypothyroidism.
Congenital myasthenic syndromes[3]	• Congenital myopathies affecting the extraocular, bulbar, and proximal limb muscles. • Onset in infancy or early childhood.	• Diagnostic: EMG: decremental response on repetitive nerve stimulation. • Supportive: Negative anti-AChR antibody test.
Chronic inflammatory demyelinating polyneuropathy[4]	• Acquired chronic inflammatory neuropathy with proximal or distal weakness and variable sensory loss.	• Diagnostic: NCS: Acquired demyelinating neuropathy (variable slowing of nerve conduction +/- conduction block). Supportive: elevated CSF protein, abnormal nerve biopsy.

Congenital myopathies		
Nemaline myopathy[5]	• Congenital myopathy: proximal weakness, hypotonia. • Classification into severe, intermediate and typical congenital, childhood-onset and adult-onset forms.	• Diagnostic: Muscle biopsy: rod-shaped bodies on LM. • Diagnostic: Genetic testing for *ACTA1, TPM3,* or other causative mutations. • Exclusions of other conditions causing development of nemaline bodies.
Central core disease[6]	• Congenital myopathy with weakness, hypotonia and motor delay.	• Diagnostic: Muscle biopsy: central cores in type 1 fibres, type 1 fibre predominance. • Diagnostic: Genetic testing for *RYR1* mutations.
Myotubular (centronuclear) myopathy[6]	• Congenital myopathy affecting the extraocular, facial, neck & limb muscles. • Classification: severe X-linked neonatal, later-onset milder forms (autosomal recessive and dominant).	• Diagnostic: Muscle biopsy: central nuclei in extrafusal muscle fibres. • Diagnostic: Genetic testing for *MTM1, DNM2* or other causative mutations.
Congenital fibre-type disproportion[7]	• Congenital myopathy with weakness, hypotonia +/- multiple joint contractures. • Multiple aetiologies.	• Diagnostic: Muscle biopsy: discrepancy in size between type 1 and type 2 muscle fibres. • Diagnostic: Genetic testing for *TPM2, ACTA1, SEPN1* or other causative mutations.
Minicore myopathy[6]	• Congenital myopathy often associated with contractures and scoliosis. • Variable association with ophthalmoplegia and respiratory insufficiency.	• Diagnostic: Muscle biopsy: multiple small cores (minicores) within muscle fibres. • Diagnostic: Genetic testing for *SEPN1, RYR1* or other causative mutations.
Muscular dystrophies		
Duchenne muscular dystrophy[8]	• Muscular dystrophy presenting with delayed motor milestones <5y of age. • Progressive weakness with loss of ambulation by age 12-15y.	• Diagnostic: Dystrophin gene analysis: out of frame OR frameshifting point mutation • Diagnostic: Muscle biopsy: absent/ <3% dystrophin. • Supportive: Dystrophic muscle biopsy. • Supportive: Markedly elevated CK.
Becker muscular dystrophy[9]	• Milder phenotype of Duchenne muscular dystrophy • Ambulation preserved >15 yrs	• Diagnostic: Muscle biopsy: decreased expression (3-20%) of quantitatively/ qualitatively abnormal dystrophin. • Diagnostic: Dystrophin gene analysis: in-frame deletion.
Congenital muscular dystrophies[10]	• Genetic myopathies presenting at <2 years of age with weakness and hypotonia. • Variable elevation of serum CK.	• Diagnostic: Genetic testing: where available • Diagnostic: Muscle biopsy: dystrophic pattern, no specific EM changes, variable abnormalities on ICC.
Facioscapulohumeral muscular dystrophy[11]	• Slowly progressive form of muscular dystrophy with onset <30 yrs. • Weakness in the facial, scapular and humeral muscles. • Autosomal dominant inheritance.	• Diagnostic: Genetic testing: decrease in the number of repeats of a 3.3 kb tandem repeat sequence *(D4Z4*) on chromosome 4q35.
Limb-girdle muscular dystrophy[12]	• Slowly progressive form of muscular dystrophy. • Weakness preferentially affecting the shoulder or pelvic girdle muscles and generally sparing the face. • Dominant or recessive inheritance.	• Diagnostic: Diagnostic Western blot or genetic testing by a reference laboratory. • Supportive: Dystrophic changes on muscle biopsy. • Supportive: Muscle ICC: characteristic changes in some forms of LGMD.
Myotonic dystrophy (DM)[13]	• Onset from infancy to adulthood • Generalised weakness • Classification based on age at presentation: o Congenital DM1 - Hypotonia, weakness or respiratory insufficiency in the first 4 wks of life. o DM1 - Presentation after the first 4 wks of life.	• Diagnostic: Genetic testing: abnormal CTG repeat expansion in the *DM1* protein kinase gene on chromosome 19.
Dermatomyositis	• An idiopathic inflammatory myopathy with characteristic cutaneous findings, causing myalgia, proximal weakness and variable involvement of the viscera.	• Diagnosis based on clinical presentation. • Supportive: EMG or pathologic evidence of an inflammatory/ necrotizing myopathy.

CK: creatine kinase ICC: immunocytochemistry LM: light microscopy NCS: nerve conduction studies EM: electron microscopy EMG: electromyography

FOLLOW-UP OF REPORTED CASES

A brief questionnaire requesting further details will be forwarded to responders reporting a newly diagnosed case.

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