

CLINICAL APPROACH TO THE FLOPPY CHILD

The floppy infant syndrome is a well-recognised entity for paediatricians and neonatologists and refers to an infant with generalised hypotonia presenting at birth or in early life. An organised approach is essential when evaluating a floppy infant, as the causes are numerous.



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A detailed history combined with a full systemic and neurological examination are critical to allow for accurate and precise diagnosis. Diagnosis at an early stage is without a doubt in the child's best interest.

HISTORY

The pre-, peri- and postnatal history is important. Enquire about the quality and quantity of fetal movements, breech presentation and the presence of either poly- or oligohydramnios. The incidence of breech presentation is higher in fetuses with neuromuscular disorders as turning requires adequate fetal mobility. Documentation of birth trauma, birth anoxia, delivery complications, low cord pH and Apgar scores are crucial as hypoxic-ischaemic encephalopathy remains an important cause of neonatal hypotonia. Neonatal seizures and an encephalopathic state offer further proof that the hypotonia is of central origin. The onset of the hypotonia is also important as it may distinguish between congenital and acquired aetiologies. Enquire about consanguinity and identify other affected family members in order to reach a definitive diagnosis, using a detailed family pedigree to assist future genetic counselling.

CLINICAL CLUES ON NEUROLOGICAL EXAMINATION

There are two approaches to the diagnostic problem. The first is based on identifying the neuro-anatomical site of the lesion or insult. The second is to determine whether or not the hypotonia is accompanied by weakness. Careful neurological examination should, in most cases, localise the site of the lesion to the upper motor neuron (UMN) or lower motor neuron (LMN) unit. Useful clues are listed in Fig. 1.

Next assess whether the hypotonia is accompanied by weakness. Weakness is uncommon in UMN hypotonia except in the acute stages. Hypotonia with profound weakness therefore suggests involvement of the LMN. Assessment of muscle power of infants is generally limited to inspection.

Useful indicators of weakness are:

- Ability to cough and clear airway secretions ('cough test'). Apply pressure to the trachea and wait for a single cough that clears secretions. If more than one cough is needed to clear secretions, this is indicative of weakness.²
- Poor swallowing ability as indicated by drooling and oropharyngeal pooling of secretions.
- The character of the cry — infants with consistent respiratory weakness have a weak cry.
- Paradoxical breathing pattern — intercostal muscles paralysed with intact diaphragm.

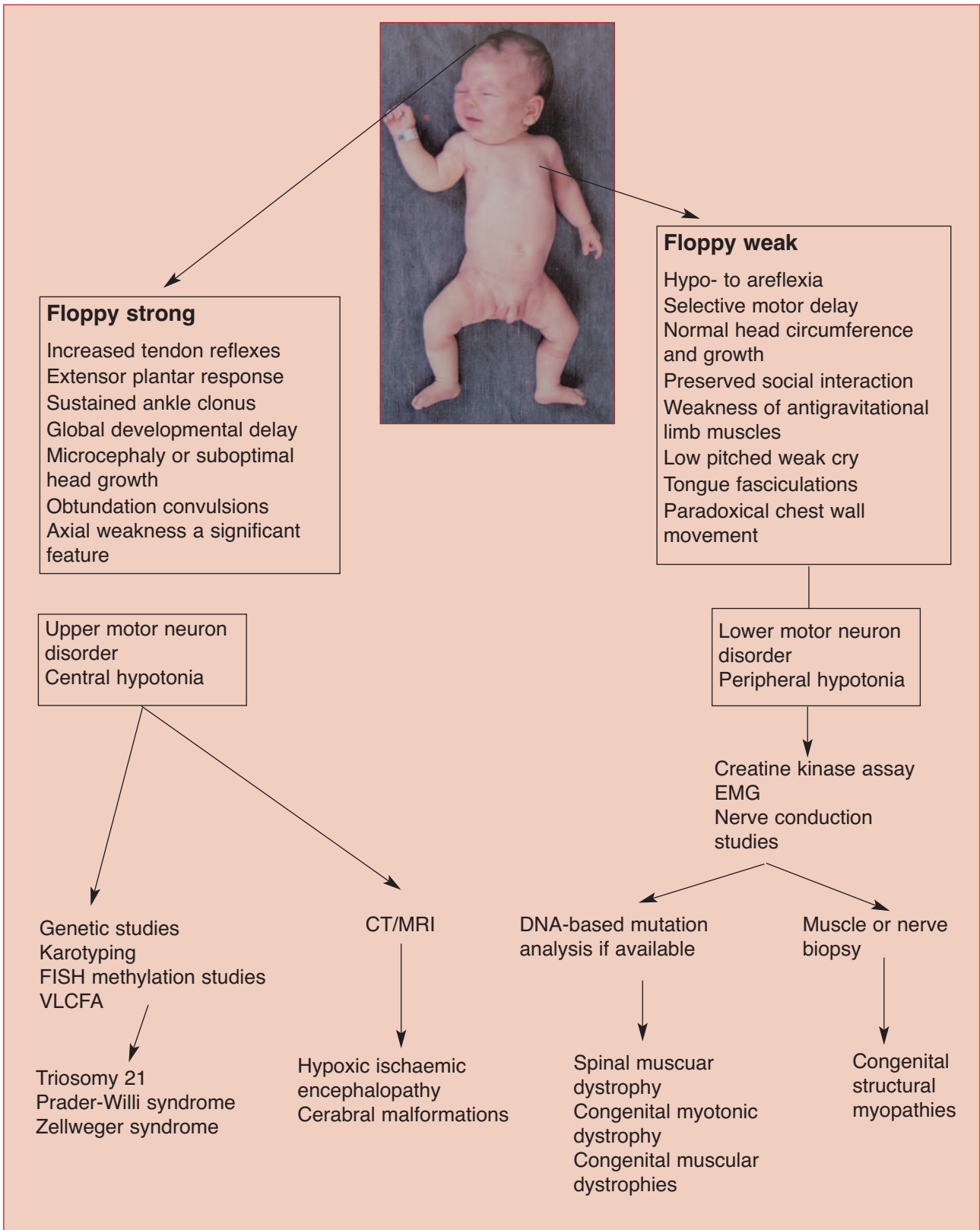


Fig. 1. Clinical clues on neurological examination (EMG = electromyogram; CT= computed tomograph; MRI = magnetic resonance imaging; VLCFA = very long-chain fatty acids; FISH = fluorescent in situ hybridisation)

- Frog-like posture and quality of spontaneous movements — poor spontaneous movements and the frog-like posture are characteristic of LMN conditions.

Further confirmation of the last indicator can be obtained by means of informal neurological examination in the test positions. Excessive head lag will be evident on 'pull to sit'. Minimal

support with a sensation of 'slipping through the hands' during vertical suspension testing and inverted U position on ventral suspension are further indicators (Fig. 2.1 and 2.2).³



Fig. 2.1. A 12-week-old male infant with excessive headlag evident on 'pull-to-sit'. Note the hypotonic posture of the legs with external rotation.



Fig. 2.2. The same infant in horizontal suspension. Note the inverted U posture.

A distinct pattern of weakness may favour certain aetiologies:

- Axial weakness is a significant feature in central hypotonia.
- Generalised weakness with sparing of the diaphragm, facial muscles, pelvis and sphincters suggests anterior horn cell involvement.
- With myasthenic syndromes, the bulbar and oculomotor muscles exhibit a greater degree of involvement.
- Progressive proximal symmetrical weakness suggests a dystrophinopathy. Signs of proximal weakness in the older infant include a lordotic posture, Trendelenburg gait and Gower sign.
- A striking distribution of weakness of the face, upper arms and shoulders suggests fascioscapulohumeral muscular dystrophy.
- Distal muscle groups are predominantly affected with peripheral neuropathies. Signs suggesting distal weakness in an older infant would include weakness of hand grip, foot drop and a high stepping, slapping gait.

THE FLOPPY WEAK INFANT

Table I gives a comprehensive approach to the clinical clues and investigations for the more common phenotypes of the weak floppy infant.

Once the lesion has been localised to the LMN proceed with further neuroanatomical localisation according to the compartments of the LMN. The compartments and disease associations are listed in Fig. 3.

Examine the tongue for size and fasciculations. Fasciculations, irregular twitching movements, generally indicate an abnormality of the anterior horn cells (Fig. 4). Do not examine the tongue while the infant is crying. The co-existence of atrophy would strongly favour a denervative aetiology. An ECG may be helpful in demonstrating baseline fasciculations of the intercostal muscles (Fig 5). Enlargement of the tongue may suggest a storage disorder such as Pompe's disease.



Fig. 4. Tongue fasciculations in a child with spinal muscular atrophy. The combination of fasciculations with atrophy is strongly indicative of muscle denervation.



Fig. 5. ECG of a floppy infant with spinal muscular atrophy demonstrating baseline fasciculations arising from the underlying intercostal muscles.

The presence of a facial diplegia (myopathic facies) suggests either a congenital structural myopathy or myasthenia gravis. Respiratory and bulbar weakness can accompany both conditions. Fluctuation in strength would favour myasthenic syndromes (Fig. 6).



Fig. 6. Ptosis and external ophthalmoplegia in a floppy weak child suggestive of myasthenia gravis.

Where clinical evaluation suggests complex multisystem involvement (i.e. hypotonia plus) inborn errors of metabolism should be excluded. Referral to a tertiary centre for metabolic investigations would then be indicated.

THE FLOPPY STRONG CHILD

The presence of facial dysmorphism should alert the doctor to the possibility of an underlying syndrome or genet-

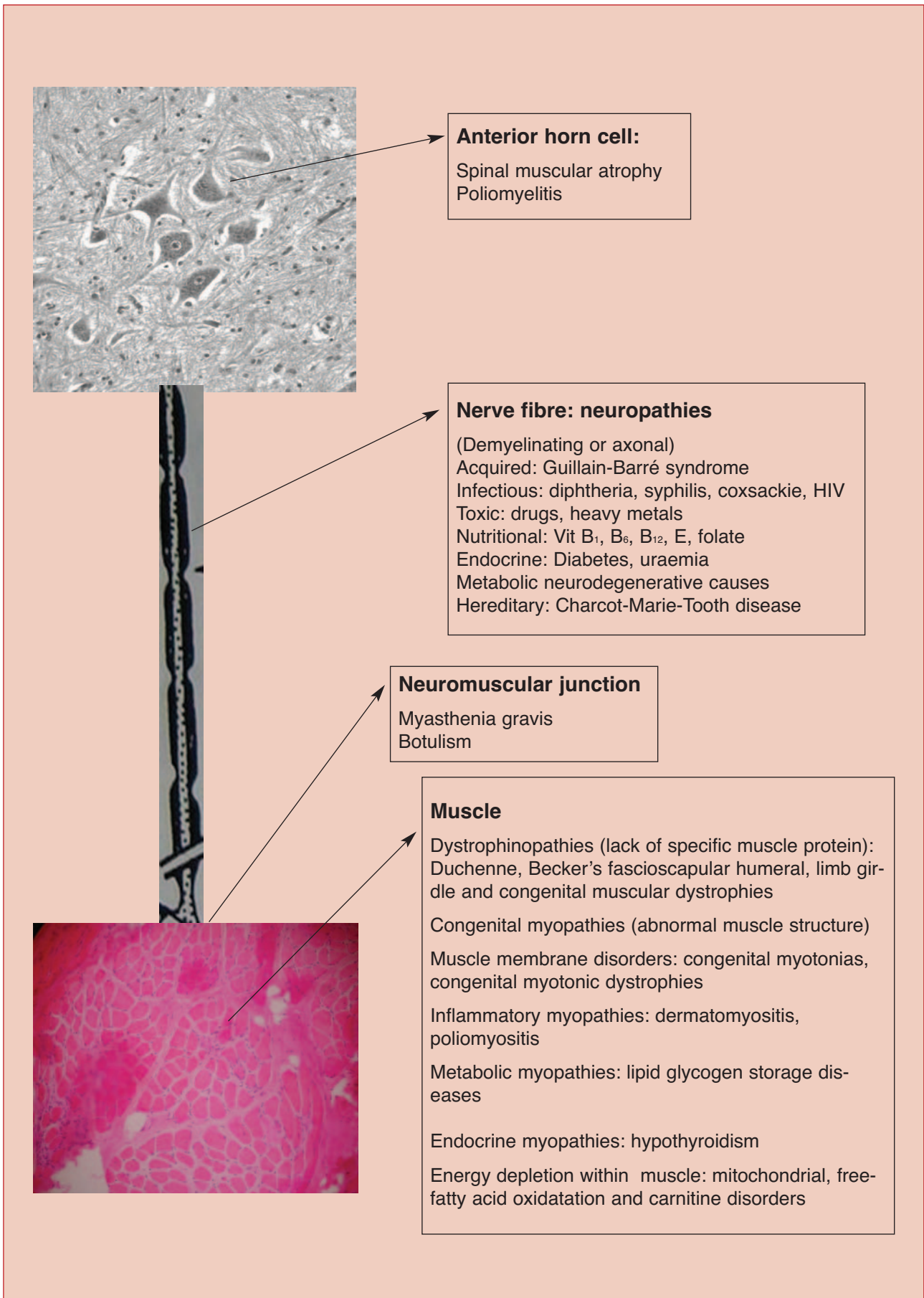


Fig. 3. LMN compartments and disease associations.

Table 1. **Clinical clues and investigations of the more common phenotypes of the floppy weak infant**

Condition	Clinical clues	Investigations
Spinal cord transection or disease Syringomyelia or other forms of spinal dysraphism	Haemangioma or tuft of hair in midline Scoliosis Evidence of bladder or bowel dysfunction Mixed deep tendon reflexes with absent abdominal and anal reflexes	MRI spinal cord
Spinal muscular atrophy	Tongue atrophy and fasciculations Paradoxical breathing pattern Severe proximal muscle weakness with absent tendon reflexes Preserved social interaction	ECG: Baseline fasciculations Deletion of the survival motor neuron (SMN) gene by PCR testing
Peripheral neuropathy	Weakness predominantly distal In most cases absent deep tendon reflexes Pes cavus	Motor nerve conduction studies Sural nerve biopsy Molecular DNA testing is available for specific demyelinating disorders
Myasthenia gravis	Greater involvement of oculomotor and bulbar muscles True congenital myasthenia due to receptor defects is rare Exclude transient neonatal form from maternal history	Response to acetylcholine esterase inhibitors Single-fibre EMG Serum antibodies to acetylcholine receptors Electrodiagnostic studies not universally positive in young patients
Infantile botulism	Acute onset descending weakness, cranial neuropathies, ptosis, unreactive pupils, dysphagia, constipation	Isolation of organism from stool culture Presence of toxin in the stool
Congenital muscular dystrophy	Hypotonia, weakness and contractures at birth Associated brain and eye problems	Creatine kinase usually elevated Brain MRI for structural and white matter abnormalities Muscle biopsy: merosin stain Molecular DNA testing by determining number of CTG repeats (normal range 5 - 39 repeats)
Congenital myotonic dystrophy	Polyhydramnios with reduced fetal movements Inverted V-appearance of the mouth Examination of mother's face shows inability to bury her eyelashes and grip myotonia Premature cataract surgery in the mother	EMG of the mother
Congenital structural myopathy	Slender stature Hypotonia with feeding problems at birth Weakness that is often non-progressive Nemaline myopathy: often associated with feeding problems Central core: most often associated with malignant hyperthermia Myotubular myopathy: Ptosis and extraocular palsies consistent clinical features	CK and EMG usually not helpful Muscle biopsy is critical for definitive diagnosis. ECG when nemaline and desmin myopathies are suspected The genetic basis for several of the congenital myopathies has now been determined
Glycogen storage disease Pompe's disease	Enlarged heart in a very floppy weak newborn Unexplained cardiac failure Tongue may appear large	Blood smear vacuolated lymphocytes Urine oligosaccharides Typical ECG and ECHO changes Acid maltase assay in cultured fibroblasts Muscle biopsy usually not necessary

ic disorder. Conditions that need to be excluded include trisomy 21, Prader-Willi and Zellweger syndrome. At birth the facial anomalies in Prader-Willi syndrome are often insignificant and the diagnosis is usually only established after onset of obesity. Useful early markers include the presence of feeding difficulties, small hands and feet, almond shaped eyes, narrow bifrontal diameter and hypogonadism (Fig. 7). Failure to identify electrophysiological abnormalities in a neonate with profound hypotonia should prompt testing for Prader-Willi syndrome. This can be done by a DNA methylation study which will detect 99% of cases.



Fig. 7. A 1-year-old girl with Prader-Willi syndrome. Marked hypotonia and feeding difficulties were evident during the first few months of her life.

Zellweger syndrome presents in the newborn with typical facial dysmorphism including high forehead, wide patent fontanelles and sutures, shallow orbital ridges, epicanthus and micrognathia. Neurological manifestations are dominated by severe hypotonia with depressed or absent tendon reflexes, and poor sucking and swallowing. Hepatomegaly and liver dysfunction are consistent findings.

VALUE AND CHOICE OF DIAGNOSTIC MODALITIES

Special investigations should be guided by clinical findings. Evaluation of tone and power should be delayed in the systemically unwell nutritionally compromised child. Infective and biochemical parameters should first be normalised before attempts are made to examine tone and power. Hypokalaemia and hypophosphataemia in particular will cause reversible weakness. Serum albumin, calcium, phosphorus, alkaline phosphatase and thyroxine levels will provide confirmation of clinical suspicion in malnutrition, rickets and hypothyroidism.

SUSPECTED CENTRAL CAUSE

For infants with central hypotonia, initial investigations include karyotype and neuroimaging (CT or MRI scan). A karyotype is a must in the dysmorphic hypotonic child. This can be combined with FISH testing if Prader-Willi syndrome is suspected. Cranial MRI will identify patients with structural CNS malformations, neuronal migration defects and those with white matter changes (congenital muscular dystrophies in particular). Hypotonia may also be prominent in connective tissue diseases such as Ehlers Danlos or Marfan's syndrome. An excessive range of joint mobility, unusual joint postures, the ability to do various contortions of the limbs and/or hyperelasticity of the skin are important diagnostic clues. Although metabolic disorders are well recognised as the cause for central hypotonia, because of the rarity of the conditions, the diagnostic yield is low. Very long-chain fatty acids (VLCFA) testing should be performed if a peroxisomal disorder such as Zellweger is suspected.

SUSPECTED PERIPHERAL CAUSE

Major discoveries have been made in the genetic analysis of the muscular dystrophies, spinal muscular atrophies and hereditary neuropathies. This

means that most neuromuscular conditions can now be diagnosed by molecular testing. Examples include spinal muscular atrophy which can now be confirmed by polymerase chain reaction (PCR) testing for a deletion of the survivor motor neuron (SMN) gene and congenital myotonic dystrophy which can be diagnosed by demonstrating an expansion of cytosine thymine guanine (CTG) triplet repeats.

DNA Xp21 deletion testing (PCR assays) can confirm the diagnosis in 65% of males with Duchenne muscular dystrophy and 80% of males with Becker's muscular dystrophy. Only in the remaining cases is muscle biopsy still advocated. Muscle enzymes levels (creatine kinase assay) are rarely helpful in the floppy infant, with the exception of muscle disorders where creatine kinase values are elevated, such as congenital muscular dystrophies and in some of the congenital structural myopathies.

Electromyography (EMG) should not be performed in isolation. It does not allow for a definitive diagnosis as there are virtually no waveforms that are pathognomonic for specific disease entities. In the floppy child, EMG is indispensable in deciding whether there is true weakness due to neuromuscular disease, or merely hypotonicity from causes in other systems or other parts of the nervous system. The abnormalities detected may then assist in localizing the disease process to the neuron, neuromuscular junction or muscle. EMG is also useful to confirm a clinical suspicion of myotonia in the older child.

Nerve conduction studies are useful in the investigation of hereditary motor sensory neuropathies and distinguishing axonal from demyelinating disorders. Molecular DNA testing can then be used for specific demyelinating disorders. Commercial testing is not yet available for most axonal forms of hereditary neuropathies.

Muscle biopsy remains the investigation of choice in an infant with a sus-

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Children with neuromuscular disorders deserve special attention when it comes to anaesthesia.

pected congenital structural myopathy, as none of the clinical features are truly pathognomonic. Even a CK within the reference range and normal EMG does not exclude the presence of a myopathy. Muscle biopsy is also indicated in infants with suspected limb-girdle muscular dystrophies (LGMD).

The term 'benign essential hypotonia' or 'hypotonia with favourable outcome' should be used with caution since newer investigative techniques have resulted in most previously labelled cases being classified into specific disorders. There are however many benign congenital hypotonia cases that remain unclassified, even with detailed examination of the muscles. Patients labelled as 'hypotonia with favourable outcome' should fulfil all of the following criteria':

- early hypotonia, usually since birth
- active movements of limbs and nor-

mal tendon reflexes

- normal or mild motor retardation that improves later on
- normal muscle enzymes, EMG, motor nerve conduction studies (MNCS) and histology.

PRINCIPLES OF MANAGEMENT

Regular physiotherapy will prevent contractures. Occupational therapy is important in facilitating activities of daily living. Vigorous treatment of respiratory infections is indicated. Annual flu vaccination is necessary. Annual orthopaedic review is required to monitor for scoliosis and to exclude hip dislocation/subluxation.

Feeding intervention by nasogastric tube or gastrostomy will benefit the undernourished child. Maintenance of ideal weight is important, as excessive weight gain will exacerbate existing weakness. Children with neuromuscular disorders deserve special attention when it comes to anaesthesia. The anaesthetist should be forewarned about the possibility of an underlying muscle disease even if the child has very mild or non-existing symptoms. A family history of muscle disease or mild hyper-CK-aemia may be of importance. Muscle relaxants should only be used if essential because of their more profound and prolonged effect in myopathic children. All children with neuromuscular disease should also be considered potentially susceptible to malignant hypothermia (the strongest correlation is with central core disease) and implicating agents should therefore be avoided.

Ethical considerations such as the appropriateness of cardiopulmonary resuscitation in the event of cardiac arrest or acute respiratory failure need to be addressed sensitively.

References available on request.

IN A NUTSHELL

When evaluating a floppy infant, the first goal should be to distinguish whether the disorder is central or peripheral in origin.

Hypotonia with weakness suggests a lower motor neuron lesion, whereas weakness is uncommon in disorders affecting the upper motor neuron except during the acute stage.

Evaluation of tone and power should be delayed in the unwell, nutritionally compromised child.

Muscle enzymes are rarely helpful in the floppy child, with the exception of the congenital muscular dystrophies and some of the structural congenital myopathies.

EMG does not allow a definitive diagnosis but is indispensable in deciding whether there is weakness due to neuromuscular disease, or merely hypotonia from causes in other systems or parts of the nervous system.

The most common of the neuromuscular disorders, spinal muscular atrophy (SMA), is now diagnosable by molecular genetic analysis (PCR).

Where clinical evaluation suggests complex multisystem involvement (i.e. hypotonia plus) inborn errors of metabolism should be excluded.

Children with neuromuscular disorders deserve special attention when it comes to anaesthesia.

The term 'benign essential hypotonia' or 'hypotonia with a favourable outcome' should be used with caution and only after compliance with strict diagnostic criteria.