THE FLOPPY CHILD

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.

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.
- 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.
• 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 he hands’ during vertical suspension testing and inverted U position on ventral suspension are further indicators (Fig. 2.1 and 2.2).³

Floppy strong
Increased tendon reflexes
Extensor plantar response
Sustained ankle clonus
Global developmental delay
Microcephaly or suboptimal head growth
Obtundation convulsions
Axial weakness a significant feature

Floppy weak
Hypo- to areflexia
Selective motor delay
Normal head circumference and growth
Preserved social interaction
Weakness of antigravitational limb muscles
Low pitched weak cry
Tongue fasciculations
Paradoxical chest wall movement

Upper motor neuron disorder
Central hypotonia

Lower motor neuron disorder
Peripheral hypotonia

Creatine kinase assay
EMG
Nerve conduction studies

Muscle or nerve biopsy

Congenital structural myopathies

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)
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.

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.

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 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).
Nerve fibre: neuropathies
(Demyelinating or axonal)
Acquired: Guillain-Barré syndrome
Infectious: diphtheria, syphilis, coxsackie, HIV
Toxic: drugs, heavy metals
Nutritional: Vit B1, B6, B12, E, folate
Endocrine: Diabetes, uraemia
Metabolic neurodegenerative causes
Hereditary: Charcot-Marie-Tooth disease

Neuromuscular junction
Myasthenia gravis
Botulism

Muscle
Dystrophinopathies (lack of specific muscle protein):
Duchenne, Becker’s fascioscapular humeral, limb girdle and congenital muscular dystrophies
Congenital myopathies (abnormal muscle structure)
Muscle membrane disorders: congenital myotonias, congenital myotonic dystrophies
Inflammatory myopathies: dermatomyositis, polymyositis
Metabolic myopathies: lipid glycogen storage diseases
Endocrine myopathies: hypothyroidism
Energy depletion within muscle: mitochondrial, free fatty acid oxidation and carnitine disorders

Anterior horn cell:
Spinal muscular atrophy
Poliomyelitis

Fig. 3. LMN compartments and disease associations.
Table I. Clinical clues and investigations of the more common phenotypes of the floppy weak infant

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<tr>
<th>Condition</th>
<th>Clinical clues</th>
<th>Investigations</th>
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<tr>
<td>Spinal cord transection or disease</td>
<td>Haemangioma or tuft of hair in midline</td>
<td>MRI spinal cord</td>
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<td>Syringomyelia or other forms of spinal dysraphism</td>
<td>Evidence of bladder or bowel dysfunction</td>
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<td></td>
<td>Mixed deep tendon reflexes with absent abdominal and anal reflexes</td>
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<tr>
<td>Spinal muscular atrophy</td>
<td>Tongue atrophy and fasciculations</td>
<td>ECG: Baseline fasciculations</td>
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<td>Paradoxic breathing pattern</td>
<td>Deletion of the survival motor neuron (SMN) gene by PCR testing</td>
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<td>Severe proximal muscle weakness with absent tendon reflexes</td>
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<td></td>
<td>Preserved social interaction</td>
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<td></td>
<td>Weakness predominantly distal</td>
<td>Motor nerve conduction studies</td>
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<td></td>
<td>In most cases absent deep tendon reflexes</td>
<td>Sural nerve biopsy</td>
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<td></td>
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<td>Molecular DNA testing is available for specific demyelinating disorders</td>
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<td>Response to acetylcholine esterase inhibitors</td>
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<td>Serum antibodies to acetylcholine receptors</td>
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<td>Electrodiagnostic studies not universally positive in young patients</td>
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<td>Peripheral neuropathy</td>
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<td>Myasthenia gravis</td>
<td>Greater involvement of oculomotor and bulbar muscles</td>
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<td></td>
<td>True congenital myasthenia due to receptor defects is rare</td>
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<td>Exclude transient neonatal form from maternal history</td>
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<td>Infantile botulism</td>
<td>Acute onset descending weakness, cranial neuropathies, ptosis, unreactive pupils, dysphagia, constipation</td>
<td>Isolation of organism from stool culture</td>
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<td>Congenital muscular dystrophy</td>
<td>Hypotonia, weakness and contractures at birth</td>
<td>Presence of toxin in the stool</td>
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<td>Associated brain and eye problems</td>
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<td>Congenital myotonic dystrophy</td>
<td>Polyhydramnios with reduced fetal movements</td>
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<td>Inverted V-appearance of the mouth</td>
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<td>Examination of mother’s face shows inability to bury her eyelashes and grip myotonia</td>
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<td>Premature cataract surgery in the mother</td>
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<td>Congenital structural myopathy</td>
<td>Slender stature</td>
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<td></td>
<td>Hypotonia with feeding problems at birth</td>
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<td></td>
<td>Weakness that is often non-progressive</td>
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<tr>
<td></td>
<td>Nemaline myopathy: often associated with feeding problems</td>
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<td>Central core: most often associated with malignant hyperthermia</td>
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<td></td>
<td>Myotubular myopathy: Ptosis and extraocular palsies consistent clinical features</td>
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<td>Glycogen storage disease</td>
<td>Enlarged heart in a very floppy weak newborn</td>
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<td>Pompe’s disease</td>
<td>Unexplained cardiac failure</td>
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<td></td>
<td>Tongue may appear large</td>
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lic 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.

**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 (VLFA) 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 (creatinine 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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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.
The onset of the hypotonia is also important as it may distinguish between congenital and acquired aetiologies.

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.

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

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

**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 hyperthermia (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.