

ABSTRACT

Infantile and childhood neuromuscular disorders are a significant cause of motor delays in childhood. Neuromuscular disorders may present either with hypotonia and weakness in early infancy or falls and difficulties in walking later in childhood. The first goal in approaching a patient with suspected muscle disease is to ascertain the correct site of the lesion, followed by the cause of the lesion. Extraordinary breakthroughs in the area of genetic testing have resulted in a decrease in reliance on muscle biopsies and neurophysiological testing.

The importance of recognising such disorders is because viable treatment options are now available for the treatment of affected children. Early recognition allows patients to receive therapy at a stage of the disease that will give the best long-term outcomes. Even in the absence of definitive treatment, supportive management and preventive care have revolutionized the care of neuromuscular disorders with longer quality life spans in a good majority of patients.

Keywords: Neuromuscular disorders, infantile hypotonia, weakness, motor delay

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INTRODUCTION

Neuromuscular disorders are a significant group of conditions in paediatric neurology and prevalence rates globally range from 1 in 2700 to 1 in 1600.^{1,2} In addition, with increased survival rates of both adults and children, international trends have shown increased disease prevalence of ten percent a year in children.³ Increased survival has resulted in the need for a multidisciplinary approach in managing these patients to maintain a good quality of life.

Neuromuscular disorders in children may be recognised when there is low muscle tone, motor delays, abnormal gait, or muscle weakness. Muscle weakness is a relatively common sign in infants and young children and may result from different conditions, including disorders of the brain, spinal cord, peripheral nerve, neuromuscular junction, and muscle. There

are specific symptoms and signs that will enable the clinician to recognise disease patterns that will narrow down the differential diagnoses. Most neuromuscular conditions are either congenital (present at birth) or genetic, and genetic testing is key not only to shortening the diagnostic odyssey but is also the basis for patient access to international clinical trials or commercially available gene therapies.⁴

Infantile hypotonia

Hypotonia in infants poses a diagnostic challenge as it may be due to either a systemic illness or an underlying neurological disorder of the central or peripheral nervous system. Early diagnosis is imperative as many of these infants present with a need for ventilatory support and therefore, a clear diagnosis and understanding of prognosis are important for parents to guide in decision making. A broad algorithm is shown in figure 1.

A good history is the key to the workup; this should include a detailed three-generation family pedigree for any history of muscle weakness, detailed pregnancy history, especially regards fetal movements, previous fetal losses and or intrauterine infections, drug or teratogen exposure as well as any suggestive post-natal insults. Early developmental milestones would also be critical, such as the developmental progress and trajectory (especially any stagnation or regression of milestones). Involvement of non-motor domains such as language or social skills, presence of visual or hearing abnormalities may point to central nervous system disorders.⁵ Early respiratory symptoms are a serious clinical feature and require early referral to a tertiary institution with neurology or neuromuscular services for evaluation.

Clinical examination is important in narrowing down the differential diagnoses. The diagnostic approach includes ascertaining the signs consistent with upper motor neuron versus lower motor neuron lesions. Additional distinctives such as dysmorphism, vision and hearing problems, delay in non-motor domains of development, abnormalities of head size and abnormal persistence of primitive reflexes or unusual hand fisting are also suggestive of central nervous system disorders. Patients with peripheral nervous system disorders are rarely dysmorphic but may have profound facial weakness in some infants, recognisable as a myopathic facies (eyelid ptosis, narrow face, tent-shaped mouth).

Establishment of weakness is usually conducted with what is known as the “180-degree examination” (Figure. 2) where the infant is placed first in the supine position and observed for dysmorphism, typical frog-leg posture and any spontaneous anti-gravity movements. The infant is then pulled into a sitting balance and observed for head lag as well as curvature of the trunk, then put into sitting position and assessed for sitting balance and strength. The infant is then carried up with the

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examiner's hands under the armpits and assessed for any arm slip sign, and an attempt should be made to see if the infant can bear weight on both legs. The infant is then put into ventral suspension – a child with early spasticity may at this point arch the back, but the infant with peripheral nervous system weakness would have head, trunk and limbs drooping with little anti-gravity movements. The final position of the infant should be in a prone position, to see if there is any ability to lift the head and trunk, or if the patient is profoundly weak, if there is any ability to clear the face off the bed. In patients with signs of peripheral nervous system disorder, careful evaluation of the distribution of weakness such as involvement of the face, trunk, proximal or distal limb muscles should be conducted. Neurological examination for range of movement, tone, deep tendon reflexes and power is essential. The presence of key distinctives such as tongue fasciculations (spinal muscular atrophy), dilated pupils (infantile botulism), contractures (arthrogryposis multiplex congenita) or a bell-shaped chest and paradoxical respiration (spinal muscular atrophy) should be noted. It may also be useful to do a developmental assessment to ascertain if the infant has an isolated or global developmental delay.

It should be noted that the distinctive separation of central versus peripheral nervous system involvement is not always clear; patients with neuromuscular disorders may suffer from a hypoxic injury at birth because of poor respiratory effort and some specific conditions such as congenital muscular dystrophy, disorders of muscle glycosylation as well as mitochondrial disorders which have both brain and muscle involvement and therefore may have overlapping phenotypes.

The weak child

The typical presentation of a child with neuromuscular weakness is that of falls, difficulties in climbing stairs or getting up from the floor or a chair, or exercise intolerance. This is because the majority of muscle disorders appear to show up in large anti-gravity muscle groups such as that seen in the lower limbs. However, specific muscle conditions may demonstrate upper limb weakness as well, which usually manifests in complaints of lifting objects overhead, or washing or combing the hair. Similar to the infantile presentation, there needs to be careful history taking that encompasses a detailed family history of muscle weakness or developmental difficulties, onset, and progression of weakness, as well as symptoms of fluctuating muscle strength in the day or fatigability. Presence of pain, in particular, must be considered as this may lead to abnormal gait and falls, and may be misinterpreted as weakness. Other symptoms such as exercise intolerance, e.g. myalgia, cramps, myotonia and myoglobinuria should be elucidated as these may be suggestive of a metabolic myopathy or an inflammatory myositis. Previous drug exposure, other systemic conditions and anaesthetic complications, e.g. malignant hyperthermia is important.

The temporal evolution of symptoms is also important. It should include the age of onset, the presence of constant versus episodic weakness (suggestive of metabolic myopathy or

periodic paralysis) and the rate of progression. An acute or subacute onset of symptoms may be suggestive of an endocrine or inflammatory myositis, the chronic onset of symptoms may be more suggestive of muscle dystrophies or genetic neuropathies, and non-progressive symptoms may be suggestive of chronic myopathies.

Finally, history taking should also include an evaluation of the impact on other systems such as nocturnal hypoventilation with daytime sleepiness and headaches in the morning and any change in functional ability, e.g. school attendance and performance (e.g. handwriting speed, ability to keep up with physical exercise lessons or tests), self-care or activities of daily living (e.g. dressing, climbing stairs, feeding and swallowing difficulties).

A physical examination would centre on gait characteristics (e.g. tiptoe walking, hyperlordosis, waddling gait) as well as a careful neurological examination for the presence of wasting, contractures, range of movement, tone, power, and reflexes. As it is easier to ascertain the signs of peripheral nervous system disorder in a child or teenager, the focus of examination is to carefully identify the specific area of weakness as this may help narrow down the differential diagnoses. Weakness in the pelvic girdle muscles is ascertained with a Gower test and that of the shoulder girdle with testing for scapular winging or arm slip sign. Table 1 lists special manoeuvres to identify weakness in specific muscle groups. Specific features may be extremely useful in narrowing the differential diagnoses. For example, presence of ptosis or extraocular weakness may be suggestive of ocular myasthenia gravis, myotonic dystrophy, Chronic Progressive External Ophthalmoplegia (CPEO) or Kearns Sayre Syndrome or congenital myopathies. Fatigability would be the next logical step for examining a patient with ptosis or extraocular weakness as this may further narrow down the differentials to ocular myasthenia gravis.

Again, similar to the infant examination, other features such as dysmorphism, tongue fasciculations, myotonia, calf or deltoid pseudohypertrophy, waddling gait, hyperlordosis and skin rash should be looked for. These clinical clues can be integrated into a form of pattern recognition of the likely anatomical category of disorder (Table 2).

A complete examination would also include a systematic evaluation for extra-neurological comorbidities such as cardiac examination for any obvious cardiomyopathy, respiratory examination as well as evaluation for scoliosis, hip dislocation, and contractures.

Investigations

As seen from above, a careful history and physical examination may narrow down the choice of investigations, and an astute clinician would be able to sequentially conduct a series of investigations in a workup that is both quick and cost-efficient. Several general principles can be considered:

1. If the child is suspected of having a central cause of motor

- delay/hypotonia, neuroimaging with MRI brain and appropriate chromosomal/genetic testing can be considered.
- If the child has evidence of lower limb involvement and preservation of upper limb function, then the spinal cord MRI would be the choice investigation.
 - If the child is suspected of having a peripheral cause of motor delay/hypotonia, the choice of investigation hinges on the category of condition suspected. For example, fatigability is suspicious of myasthenia gravis and therefore, a Tensilon (edrophonium) test should be conducted with obtaining anti-AChR antibody levels. Presence of calf pseudohypertrophy and proximal muscle weakness should prompt testing of creatine kinase levels that would be high in cases of muscle dystrophy.

Below is a list of investigations that can be considered in the neuromuscular workup of a hypotonic infant or a weak child.

- Creatine kinase level – this is usually done preferentially over other muscle enzymes such as aldolase in patients with suspected muscle dystrophy. Creatine kinase levels may be 50-100 times above normal in patients with early Duchenne and Becker muscular dystrophy. More modest elevations in the creatine kinase levels may be seen in limb girdle muscle dystrophies and congenital muscle dystrophy.⁶ The presence of normal muscle enzymes does not preclude a neuromuscular disorder. Additionally, it should be noted that alanine transaminase and aspartate transaminase levels that are routinely done in most liver function tests may also be high in children with muscle dystrophies as these are both muscle enzymes and are not specific to the liver alone.^{7,8} Finally, caution needs to be exercised in the interpretation of raised creatine kinase levels, especially if the child has had recent trauma or an intramuscular injection.
- Metabolic workup comprising ammonia, lactate, plasma amino acids and urine organic acids may be considered if there is a strong suspicion of a metabolic disorder of energy production, e.g. mitochondrial disorder. Other quick diagnostic tests include dried blood spot for acid alpha glucosidase (GAA) for any child with weakness and hypotonia with abnormal cardiac function. Early diagnosis of infantile Pompe Disease is imperative in view of the availability of enzyme replacement therapy and the need to initiate treatment before six months of age.
- Endocrine testing including thyroid function testing and electrolytes may be considered if there is episodic weakness and suspected periodic paralysis.
- Neurophysiology: Electromyogram or Nerve Conduction Testing has lost its prominence in the wake of genetic tests as these are generally considered invasive and are generally poorly tolerated by young children. Repetitive nerve stimulation is, however, a rapid diagnostic test for ocular myasthenia gravis.
- Genetic testing is often the cornerstone of the workup of neuromuscular disorders. Specific tests are available, e.g. SMN testing for suspected Spinal Muscular Atrophy (complete testing with SMN2 copy number evaluation is recommended), Prader Willi Syndrome MS-PCR testing. However, in less clinically obvious cases, clinicians may offer

affordable gene panels targeting neuromuscular disorders which are faster and less costly than whole exome or whole genome sequencing. The choice of whole exome or whole genome sequencing may be considered if the clinical features are not specific, and if the parents prefer a comprehensive option. Appropriate choice of test and counselling of families should be conducted only by an experienced neurologist, neurogeneticist or geneticist as there are important economic and social consequences of testing.

- Muscle biopsy or nerve biopsy has also been somewhat superseded by genetic testing. However, muscle biopsies are often performed in the context of inflammatory myopathies and if genetic testing has been uninformative.
- Tensilon (Edrophonium) test is a quick and efficient test for recovery from the fatigable weakness seen in myasthenia gravis.
- MRI brain can be considered in central causes of motor delay or in cases where there is suspected concomitant involvement of brain and muscle, e.g. congenital disorders of muscle glycosylation such as Walker Warburg syndrome or Muscle-Eye-Brain disease.

Management

Over the past three years, there have been rapid advancements of targeted treatments for neuromuscular disorders such as Duchenne Muscular Dystrophy (DMD) and Spinal Muscular Atrophy (SMA). In particular, the therapeutics for SMA have been particularly impactful, with evidence of preserved motor function and decrease in mortality in the most severe forms of the disease. Results for DMD such as ribosomal read through and exon skipping, unfortunately, have been less impactful. Below is a brief summary of available treatments:

Spinal Muscular Atrophy (SMA)

SMA has unique genetics, which may have resulted in it being one of the first neuromuscular disorders with viable targeted treatments. SMA is a recessive disorder caused by loss of both copies of the *SMN1* gene (in more than 95 percent a deletion of exon 7). There is also a homologous gene *SMN2* (that differs from *SMN1* by having a mutation in exon 7 resulting in unstable protein product), and the number of copies of *SMN2* influences the severity of the disease. For example, patients with SMA type 1 is usually associated with two copies of *SMN2*, SMA type 2 with three copies of *SMN2*, and SMA type 3 with three or more copies of *SMN2*. Therefore, treatment has been targeted either by increasing the stability of *SMN2* protein product or by modifying the *SMN1* gene.⁹

Nusinersen (Spinraza) is an antisense oligonucleotide medication that was FDA approved in 2016. Nusinersen binds to specific sequences of ribonucleic acid and alters the expression of the encoded gene product, incorporating exon 7 into the mRNA transcript and increasing SMN protein production. Quarterly administration of intrathecal Nusinersen has resulted in significant improvements in motor response of patients with SMA type 1, with longer event-free survival and decreased use of permanent assisted ventilation.¹⁰ In particular, early pre-symptomatic administration of Nusinersen has been

promising, with near-normal motor development in some infants. This has resulted in new recommendations for neonatal newborn screening of SMA as well as a treatment algorithm for the treatment of such patients.¹¹ Results for SMA type 2 have also shown improved motor scores.¹² There remain concerns however, about the high cost of Nusinersen treatment as this would require continued treatment for life, as well as the need for repeated lumbar punctures for drug administration.

Risdiplam is an oral small molecule that is an *SMN2* pre-mRNA splicing modifier.¹³ Single doses of risdiplam have been shown to produce increased amounts of full-length *SMN2* mRNA, and clinical trials are ongoing, for which interim reports suggest improved survival and attainment of motor milestones.

Omnasemnogene abeparvovec-xioi (Zolgensma) is a gene therapy that was FDA approved in 2019. This utilizes an adeno-associated virus 9 (AAV9) vector and is a single dose treatment that is currently licenced for children below 24 months and is administered intravenously. The use of this gene therapy has been shown to have lasting improvements in motor abilities, improved permanent ventilator-free survival as well as improved motor milestones over time.^{14,15} Trials are also underway for intrathecal delivery of the gene therapy for older patients with SMA types 2 and 3. The cost, like nusinersen, remains prohibitive.

In the absence of accessibility to the above targeted therapies for SMA, consensus management remains for such patients, including diagnostic evaluation, genetic counselling, pulmonary management, and peri-operative care.¹⁶

Duchenne Muscular Dystrophy (DMD)

DMD is a progressive X-linked muscular dystrophy resulting from the mutation of dystrophin gene, the largest gene in the body. Dystrophin is an essential link between the cell membrane and the cytoskeleton of the muscle cell. Lack of dystrophin protein results in increased injury to the muscle with muscle contractions, resulting in loss of muscle mass and progressive weakness.

Standard of care consensus guidelines exist for DMD, and this includes the use of steroids for disease management to slow down the rate of decline in muscle function, specialised care from different subspecialties as well as the transition of care across different age groups.¹⁷⁻¹⁹ These standards of care are usually upheld by specialised multi-disciplinary clinics and have resulted in improved quality of life as well as prolonged lifespans for the affected. Steroids remain the backbone of DMD management, and there is abundant evidence for the benefits of steroids such as the prolonged ability to walk, preservation of upper limb and respiratory function as well as reduced need for major surgeries such as scoliosis surgery. There are various steroids being used, such as prednisolone and deflazacort, with several regimens such as daily, intermittent, and high dose weekend doses. Vamorolone is a novel dissociative steroid that has anti-inflammatory effects through the glucocorticoid

receptor but reduced transcriptional activation and therefore has less side effects of other steroids. Clinical trials are still underway for head-to-head comparison of Vamorolone and prednisolone.²⁰

Genetically targeted therapies for DMD include exon skipping and ribosomal read through treatments. Drisapersen and Eteplirsen are antisense oligonucleotides that target exon 51 and would be relevant to 13 percent of DMD patients who have mutations in that region of the dystrophin gene. The initial phase 1 and 2 clinical trials for drisapersen appeared to show some promise but a larger phase 3 placebo-controlled trial unfortunately did not show any statistically significant improvement in the six-minute walk test compared to a control group. Eteplirsen did show some functional improvement and small increases in dystrophin production on muscle biopsies and received accelerated FDA approval pending results for an ongoing larger confirmatory clinical trial.

Ataluren (Translarna) is an orally administered small molecule that encourages read-through of nonsense mutations. Ataluren is approved for use in Europe, South Korea, and Israel, but not in the USA. Recent updates have shown the delayed loss of ambulation of patients on Ataluren (median age group 14.5 years) compared with natural history study group (median age group 11 years).²¹

Other strategies for targeted treatment are ongoing, such as gene replacement with mini- and microdystrophin constructs, as well as genome editing. It remains to be seen if these potential treatments are safe and effective.

Other Neuromuscular Disorders

Enzyme replacement therapy is available for Pompe disease and Fabry disease. Gene therapies are also under investigation for sarcoglycanopathies, Charcot-Marie-Tooth disease, myotonic dystrophy, X-linked myotubular myopathy and congenital myasthenic syndromes.

General management

While such treatments are pending, there remains a need to have a rational approach to managing neuromuscular disorders and these are summarised below:

1. Mobility Management

Appropriate use of walkers, standers, manual and motorised wheelchairs is necessary for ambulant and non-ambulant patients. These are often customised to prevent worsening of deformity, improve weight-bearing where appropriate and allow independence of movement as much as possible.

2. Pulmonary Care

Assessment of pulmonary status is done primarily through regular lung function tests (spirometry, peak cough flow and polysomnography). Nocturnal hypoventilation is essential to identify and would be a strong indicator for the need for non-invasive ventilation at night.

3. Orthopaedic Care

Prevention of contractures may be affected with appropriate resting splints of the ankles. Proper seating is also key to preventing progression of scoliosis. Hip surveillance is essential in the prevention of hip dislocations which may also cause secondary scoliosis.

4. Cardiac Care

Yearly 2D echocardiogram and ECG would be necessary in specific muscle conditions associated with cardiomyopathy (DMD, BMD, LGMD, Emery-Dreifuss muscular dystrophy) as well as arrhythmias and AV block (LGMD, Emery-Dreifuss muscular dystrophy, fascioscapulohumeral dystrophy and myotonic dystrophy).

5. Neurological Care

Specific conditions like congenital muscular dystrophy may have associated epilepsy and require appropriate anti-epileptic drug treatment. Long-term use of these drugs is expected.

6. Bone Health

Weight-bearing and adequate vitamin D supplementation are essential in bone health. Bisphosphonates may be considered in patients who are wheelchair-bound and who have experienced spontaneous fractures, or who are also on steroids and are at high risk of fractures.

7. Nutrition

Swallowing difficulties may result in weight loss in late non-ambulatory patients, while decreased mobility may result in weight gain in early non-ambulatory patients. It is critical to continue regular monitoring of weight to avoid rapid fluctuations in weight and loss of muscle mass. The role of the dietitian and speech therapist is key in preventing weight loss from poor swallowing or poor nutrition.

8. Perioperative care

If the patient requires anaesthesia and has not had a diagnostic workup completed, the anaesthetist needs to be informed about the suspected muscle disorder so that volatile anaesthetic agents and depolarizing muscle relaxants can be avoided.

9. Palliative care

Recent advances in care have not yet constituted a cure for the large majority of neuromuscular patients. Medical management includes sensitive end-of-life discussions, exploring the aspirations and values of the affected patients and their families and offering respite where it is needed. Involvement of palliative care specialists is essential in this process.

CONCLUSIONS

Ten years ago, there were few viable treatment options for patients with neuromuscular disorders. Diagnosis was cumbersome, costly, and invasive. Fortunately, with the advent of next-generation sequencing, genetic testing for

neuromuscular diseases has resulted in faster and more accurate diagnosis. Furthermore, new treatments are in the pipeline or are already available for certain neuromuscular disorders, and these give hope for these children to live better and longer.

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LEARNING POINTS

- **Neuromuscular weakness may be found in infants with hypotonia and delayed motor milestones or in older children with frequent falls, difficulty walking or climbing stairs. A careful history and physical examination are essential in the diagnostic workup in this complex group of disorders, and a rational approach to diagnosis is possible.**
 - **Genetic testing is now the mainstay of the evaluation of neuromuscular disorders and can range from single gene testing, a panel of genes known to cause neuromuscular disorders as well as whole exome and whole genome sequencing.**
 - **Management of neuromuscular disorders is multidisciplinary and requires comprehensive coverage of mobility management, pulmonary, orthopaedic, cardiac, neurology and bone health care, nutrition management, perioperative and palliative care. Consensus guidelines exist for various conditions. New gene targeted therapies are becoming available, and patients need to have their gene testing done to identify eligibility for treatment.**
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Figure 1. Diagnostic approach algorithm for floppy infant

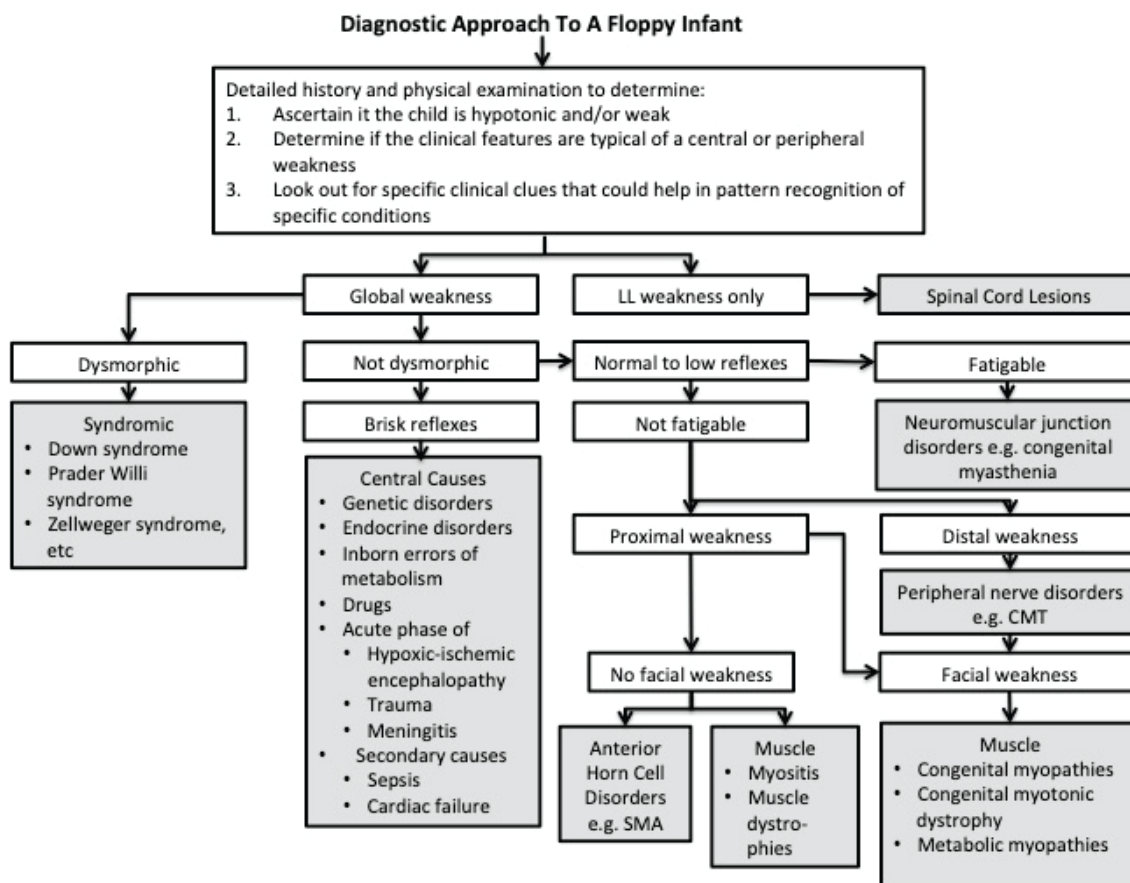


Figure 2. 180-degree examination of the different positions an infant is put in to evaluate for presence and severity of weakness

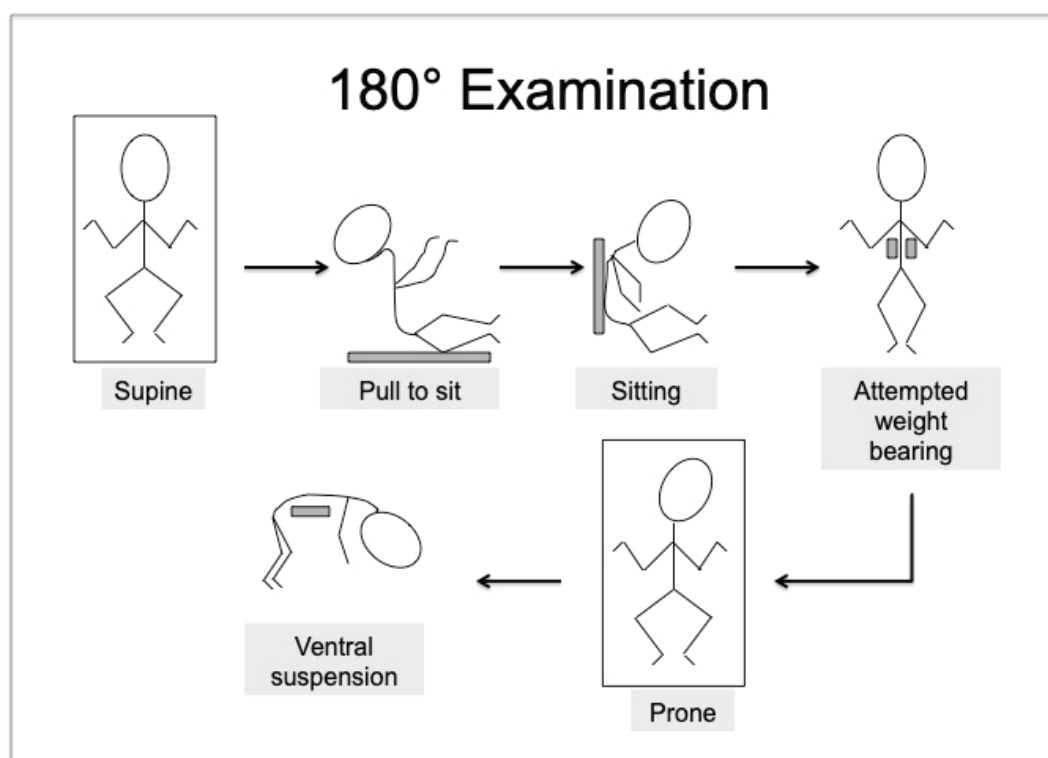


Table 1. Features of specific muscle weakness that can be ascertained by history and physical examination

Muscle Group	Features
Facial	Inability to bury eyelashes, “horizontal” smile, inability to whistle
Ocular	Double vision, ptosis, dysconjugate eye movements
Bulbar	Nasal speech, weak cry, nasal regurgitation of fluids, poor suck, difficulty swallowing, recurrent aspiration pneumonia
Neck	Poor head control
Trunk	Scoliosis, lumbar lordosis, protruberant abdomen, difficulty sitting up
Shoulder Girdle	Difficulty lifting objects overhead, scapular winging
Forearm/Hand	Inability to make a tight fist, finger or wrist drop
Pelvic Girdle	Difficulty climbing stairs, waddling gait, Gower’s sign
Leg/Foot	Foot drop, inability to walk on heels or toes
Respiratory	Use of accessory muscles of respiration

Table 2. Specific patterns of weakness and clinical clues according to the anatomical location of the lesion

Anatomical locus of lesion	Weakness				Muscle stretch reflexes	Distinctive Clinical Features
	Face	Arms	Legs	Proximal versus distal		
Central	0	+	+	>/=	Normal or ↑	Seizures, delayed development, vision, or hearing impairment
Spinal Cord	0	0 (depends on level)	+++	=	↓ in LL (depends on level)	Sensory, motor level evident; bladder and bowel symptoms
Anterior horn cell	Late	++++	++++	>/=	0	Tongue
Peripheral nerve	0	+++	+++	<	↓	Sensory deficit, ↑ CSF protein, ↓ NCV, abnormal nerve biopsy
Neuro-muscular junction	+++	+++	+++	=	Normal	Response to edrophonium (MG); constipation and fixed pupils (botulism)
Muscle	variable	++	+	>	↓	Elevated muscle enzyme levels (muscle dystrophies)

CSF – cerebrospinal fluid; NCV – nerve conduction velocities