Assessment and Investigation of Neonatal Hypotonia (the 'Floppy Infant')

University Hospitals of Leicester NHS Trust

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1. Introduction and Who Guideline applies to

This guideline is aimed at all Health care professionals involved in the care of infants within the Neonatal Service.

Key Points

- Neonatal hypotonia (the 'floppy infant') is an important clinical presentation in the newborn period with a wide differential diagnosis
- Investigations need to be guided by the history and examination findings
- The Neonatal Hypotonia Investigations Checklist (Appendix 1) should be used to keep a record of the samples sent and the results obtained.

Aim

This guideline offers a stepwise approach to the assessment and investigation of newborn infants with hypotonia to aid diagnosis without unnecessary investigations.

Contents

2. Guideline Standards and Procedures

Background

The floppy infant represents a diagnostic challenge. This is firstly because there are a wide range of differential diagnoses – including central or peripheral nervous system abnormalities, muscle disorders, genetic disorders, endocrinopathies and metabolic diseases. Hypotonia may also be a transient phenomenon seen in acute illness or prematurity. Secondly, when a decision is made to investigate these babies further, the tests required may be extensive, which means following up results and keeping track of what has been requested can be difficult. Therefore, a systematic approach to assessment and investigation is required.

Aetiology of Neonatal Hypotonia and Definitions:

The causes of Neonatal Hypotonia can be subdivided into Central causes (80% of cases - brain, spinal cord, but excluding the motor neurone) and Peripheral causes (lower motor neuron including motor neurone, axon, neuromuscular junction and muscle).

Hypotonia: A reduced resistance to passive movements, which may be accompanied by an increased range of movements around the joints. Hypotonia is often identified by an abnormal posture (e.g. frog-leg posture), and there can be associated weakness.

Weakness: A reduction in the muscle power that can be generated (e.g. lack of muscle movement against gravity).

Hypotonia (floppy) without weakness: Where there is hypotonia but strength is relatively preserved (e.g. anti-gravity limb movements are present), a **CENTRAL** cause of hypotonia is more likely.

Hypotonia with weakness: Hypotonia accompanied by weakness is more suggestive of a **PERIPHERAL**, neuromuscular cause. In such cases, reflexes are often reduced or absent. (Table 1)

Table 1 Causes of Hypotonia by Anatomical Site

	Site	Causes	Floppy - preserved strength	Floppy and Weak
Central causes (80% of all cases)	**Brain**	**Acute** • Hypoxic-ischaemic encephalopathy • Acquired and congenital infections causing encephalopathy • Intracranial haemorrhage • Drug effects	☑	
		Chronic • Chromosomal abnormalities (e.g. Down syndrome and Prader-Willi syndrome) • Cerebral structural malformations	☑	
		• Inborn errors of metabolism (e.g. Zellweger syndrome)	☑	☑
	Spinal cord	• Birth trauma to spinal cord		☑
Peripheral neuromuscular causes	**Anterior horn cell**	• Spinal muscular atrophy		☑
	Neuromuscular junction	• Transient acquired myasthenia gravis • Congenital myasthenia • Infantile botulism		☑
	Peripheral nerves	• Congenital demyelinating neuropathy • Hypomyelinating neuropathy • Hypomyelinating neuropathy • Axonal neuropathy • Guillain-Barré syndrome		☑
	Muscle	• Muscular dystrophies • Congenital myopathies • Myotonic dystrophy and congenital myotonias • Endocrine myopathy e.g. hypothyroidism • Metabolic myopathies (e.g. Glycogen storage diseases) • Energy depletion - muscle mitochondria e.g. fatty acid oxidation and carnitine disorders, respiratory chain disorders		☑
Connective tissue disorders		• Ehler Danlos syndrome • Marfan syndrome • Osteogenesis imperfecta	☑	

History taking

Important aspects to consider during history taking are:

Antenatal

- Maternal disease:
  - Diabetes, epilepsy, myotonic dystrophy, myasthenia
- Previous pregnancies:
  - Stillbirths, childhood deaths
- This pregnancy:
  - Maternal drug use (prescribed or recreational)
  - Antenatal infection
  - Screening risk for Trisomies
  - Decreased fetal movements, abnormal presentation and oligo/ polyhydramnios

Perinatal

- Apgar scores
- Resuscitation required
- Cord gases
- Risk factors for sepsis

Postnatal

- Character of cry – a weak cry may be seen in infants with neuromuscular weakness
- Respiratory effort
- Ability to feed
- Level of alertness
- Level of spontaneous activity
- Seizures

Clinical Examination

A thorough systems based clinical examination with recording of baseline observations is required. Neurological examination should include the features detailed in Table 2, including assessment for any dysmorphic features. While clinical examination can be helpful in indicating whether a central or peripheral cause is more likely, there can be overlap between the findings in some conditions.

	Central	Peripheral
General Examination	Dysmorphic features Microcephaly Decreased alertness Seizures	Muscle atrophy Joint contractures Tongue fasciculations (SMA)
Strength	Some preserved strength	Hypotonic and weak
Antigravity Movements	Present	Absent
Tendon reflexes	Normal or brisk, clonus	Hypo/areflexia

Table 2: Examination findings associated with Central and Peripheral Hypotonia (SMA – spinal muscular atrophy)

The following table summarises the likely examination findings depending on the area or anatomical site of the nervous system affected:

Site	Facial involvement	Oculomotor	Deep tendon Reflexes	Pattern of Weakness
Central	Normal		Normal or brisk	Relatively preserved strength
Anterior horn cell	Normal but can occur	-		Prominent limb weakness
Peripheral nerve	Normal	-	Decreased	Prominent: Distal > Proximal
Neuromuscular junction	Prominent - ptosis	Yes	Normal	Prominent limb weakness
Muscle - muscular dystrophy	Not usually	Not usually	Decreased	Proximal > Distal
Muscle - myopathy	Myopathic facies*	Unusual- can be seen in myotubular myopathy	Decreased	Proximal > Distal

*also seen in myotonic dystrophy

Table 3: Clinical findings by anatomical site

Investigations

(see Fig. 1)

Blood Count and Routine Biochemistry

Baseline blood tests including FBC, U&Es,CRP,LFT and bone profile (including calcium and magnesium) are important in excluding infection and electrolyte disturbances as causes for hypotonia. Thyroxine (T4) and TSH should be checked, looking for evidence of congenital hypothyroidism. Creatine Kinase (CK) is an enzyme found in muscles. Increased amounts of CK are released into the blood when there is muscle damage. Levels are therefore raised in Congenital Muscular Dystrophy (5 to 10 times normal). However, it is important to be aware that CK levels can be raised in the first hours of life and also increase with acidosis - for example following Hypoxic Ischaemic Encephalopathy (HIE). Therefore, if CK is raised in an early sample, it is worth repeating it after a few days. CK levels should also be taken prior to Electromyography (EMG) studies or muscle biopsies as these can cause raised levels. In cases of multisystemic involvement, screening for inborn errors of metabolism is recommended.

Genetic Testing

Should be chosen according to clinical presentation and presence of any dysmorphic features. A Rapid FISH Screen can be requested for trisomies - these results are usually available within 48 hours. Microarray results take 2 weeks for a neonate (less than 28 days of age) and 4-6 weeks for a baby over 28 days old. Molecular genetics: these samples are sent to Nottingham. If requested, the molecular genetics team can conduct a ‘Floppy Infant Screen.’ This includes testing for three conditions - Prader Willi Syndrome, Myotonic Dystrophy and Spinal Muscular Atrophy. Please ensure you specify this on the form. It is useful to send a separate EDTA bottle for DNA storage in case further testing is required in the future.

Lumbar puncture

Cerebrospinal fluid (CSF) can be examined for evidence of infection. Raised protein levels may also be suggestive of peripheral neuropathy or neurodegenerative disease.

Imaging

Chest x-ray may show cardiomegaly which is suggestive of possible cardiomyopathy. Thin ribs at birth may be seen in neuromuscular conditions. In terms of neuroimaging, floppy babies should undergo a cranial ultrasound scan on the neonatal unit. This may initially be performed by a neonatologist to rule out acute changes, although a scan by a radiologist is also needed.

Cranial ultrasound can identify gross abnormalities of brain structure. It is likely that in such infants, further imaging (usually MRI head and spine) will be needed. These scans are helpful in the identification of structural malformations, neuronal migration defects, brain stem and cerebellar abnormalities, and can identify features suggestive of mitochondrial abnormalities and metabolic diseases. Requests for such scans should be discussed with the radiology team.

Electrophysiological studies

Seizures and encephalopathy may be identified by EEG. On the neonatal unit, CFM (aEEG) can be used to classify the background cerebral activity and to detect seizures over longer periods of time. Electromyograms (EMGs) and nerve conduction studies are useful in diagnosing disorders of the lower motor neurone unit (disorders of either the muscle, neuromuscular junction or peripheral nerves.) Nerve conduction studies produce consistent and reliable results after 32 weeks of gestation. These investigations can be booked on the ICE system although it is best to also discuss them with the neurophysiology team by telephone.

Muscle biopsies

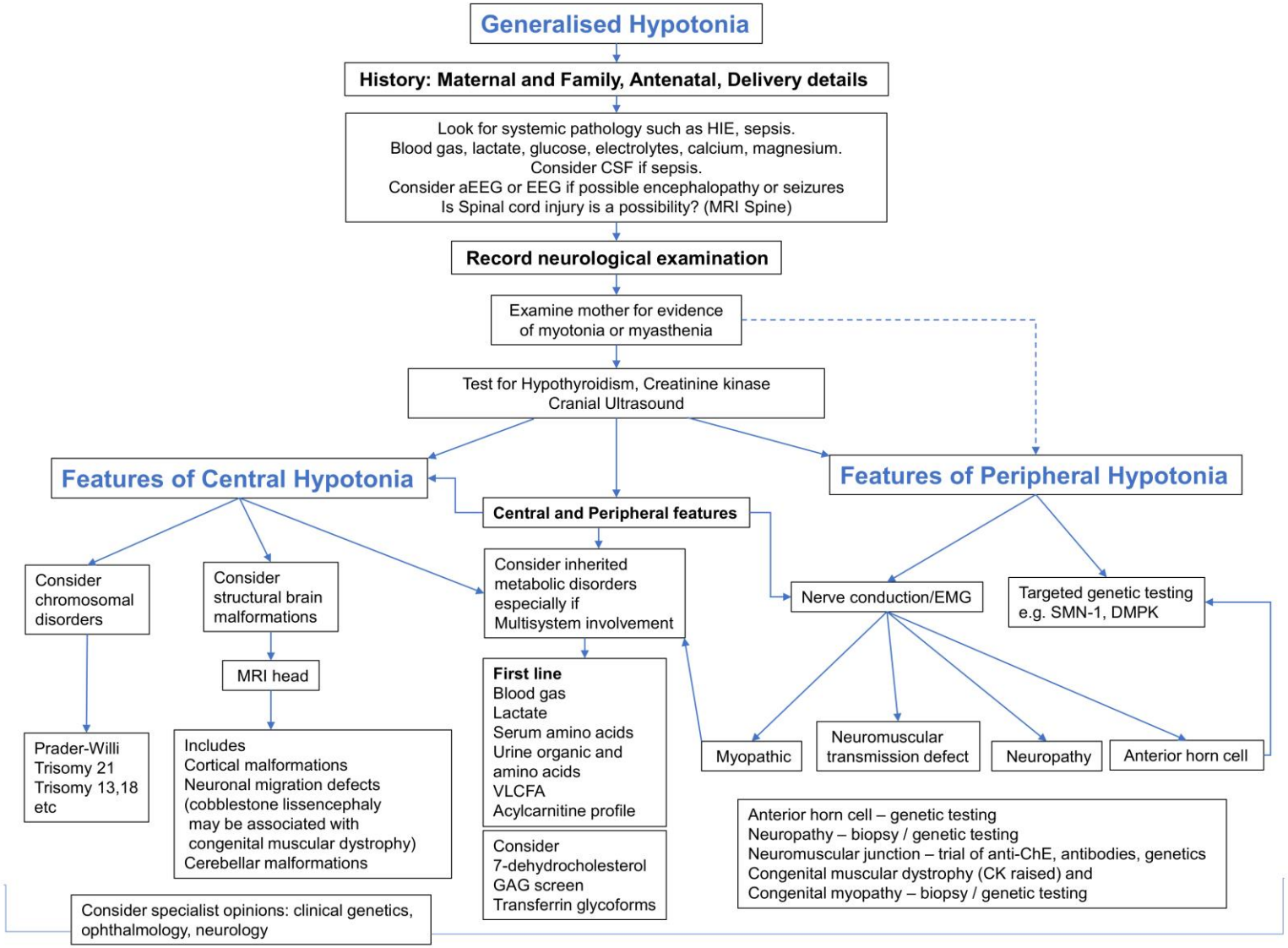
Neonatal muscle biopsy results are difficult to interpret and therefore biopsies may be delayed until babies are around 6 months of age, depending upon the clinical picture.

Multidisciplinary team assessment

Involvement of other clinical teams may be sought - these may include neurology, respiratory, cardiology, ENT, renal, ophthalmology and metabolic. In cases where there are dysmorphic features but no clear unifying diagnosis, it is useful to refer to the clinical genetics team for a ward review. Referral to the above specialities is a consultant-led decision.

Fig 1. History, Examination and Investigations flowchart

Please see Appendix 1: Neonatal Hypotonia Checklist for sample details.



3. Education & training

None

4. Audit Criteria

1. Neurological Examination should be recorded in the notes (100%)
2. Investigations checklist used to record investigations sent and results received (100%)

5. Supporting References

1. Newborn Services Clinical Guideline: Neonatal Hypotonia, Auckland District Health Board
2. Ahmed MI, Iqbal M, Hussain N. A structured approach to the assessment of a floppy neonate. *J Pediatr Neurosci* 2016;11:2-6
3. Miralles R, Panjwani D. Neonatal Hypotonia. In *Emerging Topics and Controversies in Neonatology*. Boyle EM, Cusack J (eds.). Springer Nature Switzerland AG 2020

6. Key Words

Central hypotonia, Generalised hypotonia, Neurological, Peripheral hypotonia

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The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

Contact and review details			
Guideline Lead (Name and Title) Sumit Mittal - Consultant		**Executive Lead** Chief Nurse	
Original Author Jennifer Mann, Robin Miralles			
Details of Changes made during review:			
Date	**Issue Number**	**Reviewed By**	**Description Of Changes (If Any)**
Feb 2020	**1**		
June 2020	**1**	Neonatal Guideline and Governance Group	
Jan 2022	**2**	Neonatal Guideline and Governance Group	**No changes**

Appendix 1: Neonatal Hypotonia Investigations Checklist

Investigation	Tick if required	Sample requirements	Date sent/req	Turn around	Result	Date of result
Baseline bloods						
Full blood count		0.5ml EDTA bottle		Hours		
U&Es and CRP		0.5ml lithium heparin bottle for all		Hours		
LFTs				Hours		
Bone profile				Hours		
T4 and TSH		0.5ml white bottle		Hours		
Creatine Kinase		0.5ml lithium heparin bottle		Hours		
Infection screen						
Blood culture		1ml in blood culture bottle		2 days		
CSF MCS		3 white top bottles with 5 drops CSF in each. 1 yellow bottle. Consider discussing with neurology prior to LP in case further samples are required		2 days		
CSF protein and glucose				Hours		
Genetics: Please note the genetics lab is only open 9am-5pm therefore send during daytime hours						
Rapid FISH		1.2 lithium heparin bottle and 1.2ml EDTA bottle		2 days		
Microarray				14 days		

Investigation	Tick if required	Sample requirements	Date sent/req	Turn around	Result	Date of result
Molecular genetics		1.2 ml EDTA bottle: Floppy baby screen -Prader Willi, Myotonic Dystrophy and SMA		2 weeks		
DNA for storage		1.2ml EDTA bottle		n/a		
Metabolic screen: Please note special chemistry lab is only open 9am-5pm therefore collect and send during daytime hours						
Blood gas with glucose and lactate		1 cap gas tube test on unit		Minutes		
Ammonia		1.2ml lithium heparin-to lab on ice within 30 minutes		Hours		
Ketones		Ketone meter or urine dipstick		Bedside		
Amino acids		1.2ml lithium heparin bottle		2 weeks		
Organic acids		Urine plain white top 5ml		2 weeks		
Acylcarnitine profile		1.2ml lithium heparin bottle		2 weeks		
Free fatty acids		1.2ml yellow top bottle		2 weeks		
Very Long Chain FA		1.2ml lithium heparin bottle		2 weeks		
Glycosaminoglycans		Urine plain white top 5ml		2 weeks		
Imaging						
Chest x-ray		Request on ICE and discuss as required with the Radiology team		n/a		
Cranial US				n/a		
MRI /CT head				n/a		

Investigation	Tick if required	Sample requirements	Date sent/req	Turn around	Result	Date of result
Neurophysiology tests						
EEG		Request on ICE and discuss with the Neurophysiology team		n/a		
EMG				n/a		
Nerve conduction study				n/a		
Other tests						