

Management of a Floppy Neonate

Key Points

- 'Floppy' infant is used to describe hypotonia (rather than weakness)
- Tone is resistance to passive stretching or movement
- Secondary causes of hypotonia are common (please see other relevant guidelines)
- Primary causes of hypotonia can be categorised as **central** (60-80% of cases) or **peripheral**.

Version: 1.0
Date Issued: 26 June 2024
Review Date: June 2027
Key words: Floppy neonate, floppy baby, hypotonia

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Abbreviations

AA	Amino Acids (test)
aEEG / EEG	(amplitude integrated) electroencephalogram
AN	Antenatal
Ca, Mg	Calcium, Magnesium (blood test)
CK	Creatinine Kinase (blood test)
CMD	Congenital Muscular Dystrophy
CrUS	Cranial Ultrasound
EMG	Electromyography
FBC	Full Blood Count (blood test)
HIE	Hypoxic Ischaemic Encephalopathy
IM	Intramuscular
IVH	Intraventricular Haemorrhage
LFT	Liver Function Tests (blood test)
MRI	Magnetic Resonance Scan
OA	Organic acids (test)
PWS	Prada Willi Syndrome
SC	Subcutaneous
SMA	Spinal Muscular Atrophy
SMARD	Spinal Muscular Atrophy with Respiratory Distress
TORCH	Toxoplasmosis, Rubella, Cytomegalovirus, Herpes Simplex and HIV
U&E	Urea and electrolytes (blood test)

1. Definition

The term ‘floppy’ should be used to describe hypotonia¹. Tone is resistance of a muscle to passive stretching² or passive motion³. Hypotonia in a newborn is a common presenting feature and a diagnostic challenge, with a range of possible diagnoses.

It is important to stabilise the baby first – secondary causes of hypotonia are common³ and include: HIE, sepsis, meningitis, hypoglycaemia congenital heart disease and significant jaundice. Please use alternative appropriate guidelines for the management of these conditions.

Most babies with hypotonia have a **central cause (60-80%)**¹.

Most babies with hypotonia do not have a persistent neuromuscular disorder.

2. Aetiology

Clues from the History

- **Family history:** including consanguinity, previous miscarriages, developmental delay/delayed motor milestones, premature death, metabolic or muscle disease².
- **Antenatal history:** including reduced² or abnormal foetal movements (seizure activity), polyhydramnios/oligohdramnios, breech², in-utero infections (TORCH)², maternal exposures (medications, drugs, alcohol) and AN scans.
- **Consequences of fetal immobility:** hip dislocation, talipes, arthrogryposis¹.
- **Perinatal / birth history:** HIE is a common cause of hypotonia.
- **Neonatal Clinical features:** onset of floppiness, respiratory efforts, feeding difficulties, abnormal cry, encephalopathy, seizures.

There is a wide range of possible diagnosis and are usually categorised into:

- **central hypotonia** (brain, brainstem, spine) or
- **peripheral hypotonia** (anterior horn cells, peripheral nerves, neuromuscular junction, muscles)
- See table 2.

Most common causes

	Cause	Frequency
Central	HIE	19%
	Genetic/chromosomal	31% (T21: 13% Prader Willi: 5%)
	Metabolic	3%
Peripheral	Congenital myopathies	5%
	Congenital myotonic dystrophy	4%
	SMA	2%
	Congenital muscular dystrophy	2%
	Neuropathy	1.4%
	Neuromuscular junction disorders	0.4%

Table 1 (adapted from Neonatal Neurology course handbook⁶)

Central Hypotonia	Peripheral Hypotonia
Acute Encephalopathy • Birth trauma, IVH, Stroke • HIE • Hypoglycaemia • Infection – sepsis, meningitis	Anterior horn cell • SMA Type 1 – Werdnig-Hoffmann disease • Chronic SMA – Type 2&3 • SMARD 1
Chronic Encephalopathy • Cerebral malformations • Hypotonic cerebral palsies • Inborn errors of metabolism (Mucopolysaccharidoses, Aminoacidurias, Organic acidurias, Lipidoses, Mitochondrial diseases, Glycogen storage diseases and Menkes syndrome) • Peroxisomal Disorders (Neonatal adrenoleukodystrophy, Zellweger syndrome)	Neuropathies • Hereditary motor-sensory neuropathy • Congenital hypomyelinating neuropathy • Acute demyelinating polyneuropathy • Inflammatory neuropathies (maternal Guillain Barre) • Paralytic poliomyelitis Neuromuscular junction problems • Transient neonatal myasthenia • Autoimmune myasthenia • Congenital myasthenic syndromes • Infantile Botulism (usually after 2 weeks of age after exposure e.g., honey, corn syrup, dust, soil. Initially presents with constipation)⁴ • Aminoglycoside toxicity (aminoglycosides have the potential to cause neuromuscular blockage and can also worsen myasthenia-like syndromes)⁴. • Magnesium toxicity (Mg inactivates acetylcholine at neuromuscular junction, consider if mum gives MgSO₄ or Mg antacids given to neonate)⁴

Table 2 (adapted from Jain et al¹ and Smrithi et al⁵)

Central Hypotonia	Peripheral Hypotonia
Chromosomal disorders • Prader-Willi Syndrome • Trisomy 21	Muscular disorders • Congenital myopathies (Nemaline rod myopathy, Myotubular myopathies, Central cord disease, Minicore disease, Bethlem and Ullrich myopathies) • Congenital muscular dystrophies (Walker-Warburg, Fukuyama, Muscle-eye-brain disease, Merosin-positive CMD etc) • Congenital myotonic dystrophy • Metabolic myopathies (Acid maltase deficiency, Phosphorylase deficiency, Mitochondrial myopathy) • Endocrine myopathies (hypothyroidism)
Genetic disorders • Familial dysautonomia • Lowe syndrome	
Endocrine/Nutrition disorders • Hypothyroidism • Rickets • Renal tubular acidosis	
Connective tissue disorder • Ehlers-Danlos • Osteogenesis imperfecta • Congenital ligamentous laxity • Benign congenital hypotonia	
Spinal cord: • Spinal cord injury • Spinal lesion (abscess, neuroblastoma) • Craniocervical junction lesions (e.g., Chiari malformation)³	
Conditions where central and peripheral hypotonia may coexist • Familial dysautonomia (rare genetic condition affecting autonomic nervous system)¹. • HIE • Infantile Neuroaxonal degeneration (rare genetic neurodegenerative disease) • Lipid storage diseases • Lysosomal disorders • Mitochondrial disorders • Perinatal asphyxia secondary to motor unit disease	

3. Examination

- Clinical examination is key in narrowing the differential diagnosis.
- Determine if the hypotonia is of central or peripheral origin to guide investigations.
- There may be specific features that provide clues to specific diagnosis.

Signs of hypotonia¹ (hypotonia = reduced resistance to passive movement)

- Frog-legged posture – full abduction and external rotation of legs
- Flaccid extension of arms
- Marked head lag on pull-to-sit
- Excessively rounded back when held sitting (>33 weeks gestation)
- “Slip through” at the shoulders on vertical suspension
- Draping on ventral suspension / “rag doll” posture⁷

Central vs peripheral hypotonia

- **Babies with central hypotonia often have other central features**, including:
 - Signs of abnormal consciousness / encephalopathy²
 - Seizures¹ or apnoeas
 - Micro/macrocephaly, Dysmorphic / syndromic²
 - Abnormal posturing
 - Feeding difficulties²
 - Features of spasticity: tight fisting of hands, scissoring of legs^{1,2}, brisk tendon reflexes¹
 - Muscle power is relatively preserved
- **Babies with peripheral hypotonia have marked weakness but are more alert than those with central hypotonia**
 - May have myopathic faces (open mouth with tented upper lip, poor seal when sucking, lack facial expressions, ptosis, restricted eye movements^{1,7}) - not in SMA⁷.
 - May involve respiratory muscles
 - May have contractures³
 - May have muscle atrophy or hypertrophy¹
 - (May have reactions to anaesthetic agents including malignant hypertension and rhabdomyolysis)¹

Table 3 (adapted from Smrithi et al⁹)

	Central Hypotonia	Peripheral Hypotonia
Antigravity Movements	Present	Absent
Tendon Reflexes	Normal/Exaggerated	Diminished/Absent
Postural Reflexes	Present	Absent
Brain Dysfunction	Seizures/Encephalopathy	Variable
Fisting	Present	Absent
Fasciculations	Absent	Variable (rare but diagnostically important) ¹
Facial Weakness	Absent	Variable (may be present) ⁷
Limb Weakness	Variable	Present +++
Arthrogryposis	Absent	May be present ⁷

Specific features on examination

- Hypogonadism / cryptorchidism – Prada Willi syndrome
- Sparing of extra-ocular muscles (anterior horn disease), Ptosis and extra-ocular muscle weakness (NMJ disorders)
- Examination of parents:
 - Unable to release grip immediately after shaking hands (congenital myotonic dystrophy)
 - Fatiguability of eyelids on upward gazing and arms on sustained forward extension (neonatal myasthenia)
- Cardiomyopathy (carnitine deficiency, fatty acid oxidation disorders, acid maltase deficiency, Pompe's disease)¹
- Hepatosplenomegaly (storage disorders or congenital infections)¹

4. Investigations

Baseline

1. Bloods
 - FBC, Clotting
 - Sepsis screen +/- LP
 - Gas / lactate, Ammonia, glucose
 - LFT, U&Es including Ca, Mg, bone profile
 - CK (can be high at birth and increase in first 24 hours)
 - Thyroid function, Vitamin D +/- Parathyroid hormone
2. Cranial Ultrasound
3. Urine toxicology
4. Chest X-ray (enlarged heart in Pompe or cardiomyopathy, thin ribs if reduced fetal breathing movements)²

Central Hypotonia

(See **Appendix 1** – use presence / absence of encephalopathy and dysmorphism to guide choice of investigations)

1. Neuroimaging
 - Cranial ultrasound
 - MRI (structural malformations, neuronal migration defects, brain stem and cerebellar abnormalities, features of mitochondrial and metabolic disease)
2. aEEG/EEG
 - if seizures present
3. Genetics
 - Consider if dysmorphic features
 - Karyotype/FISH (lithium heparin bottle) / Rapid microarray³
 - Ideally use rapid genome or exome sequencing as first line for Neonatal Intensive care patients with significant unexplained hypotonia³ (in these patients the diagnostic yield is >50%)³
 - use GeNotes website⁸ for further information, consider R48 (critical region methylation testing) for PWS, or R69 panel, or R14 if acutely unwell. (EDTA bottle)
4. Congenital infection screen
5. Metabolic tests (urine OA, plasma and urine AA, acylcarnitine, **see Appendix 3** for further metabolic tests)
6. Ophthalmology opinion

Peripheral

(See **Appendix 2** – use CK to guide choice of investigations)

1. Consider if baby has SMA phenotype (see below): genetics
2. CK: if elevated, repeat after few days (can be high at birth and increase in first 24 hours)
3. Genetics (use GeNotes website⁸ for further information, consider R70 panel or R14 if acutely unwell). (EDTA bottle)⁸
4. Ophthalmology review
5. Nerve conduction studies
6. EMG and muscle biopsy
7. Maternal antibodies and Neostigmine test (tensilon test)
8. Nerve Biopsy (rarely done)

Other specialised tests (may be suggested after dw tertiary specialist) – **see Appendix 3.**

5. Specific Conditions

a. Prader-Wili syndrome⁹

- CTG trinucleotide repeat (chromosome 19q13.2-q13.3)¹
- Profound hypotonia, characteristic faces (narrow nasal bridge and forehead, almond shaped eyes, thin upper lip, down turned corners of mouth)³, hypogonadism / cryptorchidism, feeding difficulties, weak cry, hypopigmentation (skin, eyes, hair) relative to family background
- Diagnosis: genetics

b. Spinal Muscular Atrophy (SMA) type 1

- Cognitively bright, normal facial features, sparing of extra-ocular muscles
- Tongue fasciculations, diaphragmatic breathing and bell-shaped chest⁴, areflexic, weakness
- Diagnosis: genetics, normal CK¹

c. (transient) Neonatal Myasthenia Gravis

- Affects 10-15% of babies born to mother with Myasthenia Gravis (but 75% risk of recurrence in subsequent pregnancies if has occurred)⁹
- Transient condition due to placental transfer of maternal anti-acetylcholine antibodies (Not related to severity of maternal illness), generally lasts 2-4 weeks⁴
- Typically presents within few hours (within 3 days)⁹, feeding difficulties, respiratory difficulties, facial diplegia, weak suck and cry, polyhydramnios, arthrogryposis, generalized weakness but deep tendon reflexes are present⁹.
- Diagnosis: neostigmine IM or SC improvement of symptoms in 15-30 mins
- (NB different to Congenital Myasthenic Syndromes: group of genetic disorders also affecting the neuromuscular junction, may present later in life, fatigable weakness, often ptosis)^{9,4}

d. Congenital Myotonic Dystrophy

- Autosomal dominant, inherited from mother (CTG trinucleotide repeat, showing anticipation)⁹
- Examine mum: facial weakness and grip myotonia⁹
- Family history: learning difficulties, cataracts
- Weakness, facial diplegia, tent-shaped mouth, respiratory impairment, arthrogryposis, talipes, polyhydramnios and reduced fetal movements
- Diagnosis: genetics (NB EMG and CK may be normal, usually high)

e. Congenital Muscular Dystrophies

- A group of conditions with muscle degeneration
- Autosomal dominant
- Profound weakness (proximal >distal), contractures³, feeding difficulties, facial weakness
- Some have other features: seizures, cardiac involvement⁹
- Diagnosis: raised CK, abnormal EMG, muscle biopsy (abnormal with fibrosis, degeneration/regeneration)⁹

f. Congenital Myopathies

- A group of conditions with abnormal muscle biopsy but not degeneration
- Mostly recessive / X linked
- Weakness (proximal >distal)⁹, areflexic, prominent facial weakness and ptosis⁹, can be dysmorphic, respiratory and bulbar weakness in severe cases⁹
- Diagnosis: muscle biopsy

g. Metabolic myopathies

- A group of conditions
- Clues: hypoglycaemia, high lactate, high ammonia, hepatomegaly

6. Prognosis

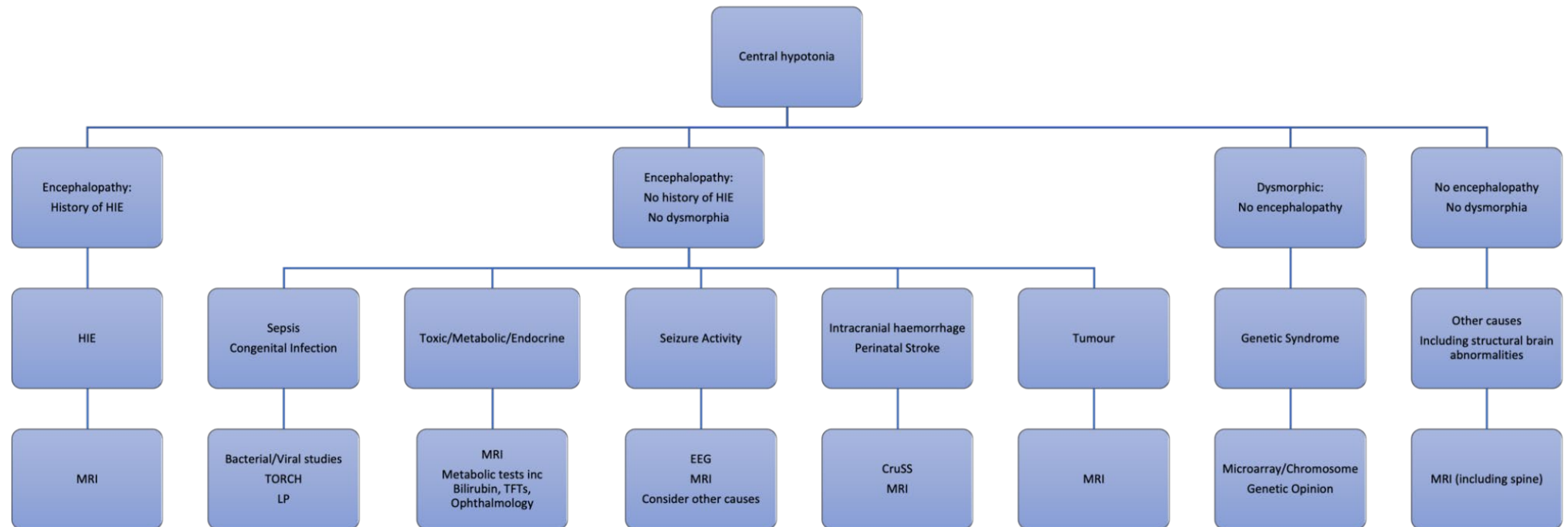
Prognosis is variable and depends on the underlying cause. Involvement of bulbar and chest muscles will often determine survival¹. Many babies have an improvement in tone with time but may remain developmentally delayed¹, on-going multi-disciplinary input is often needed.

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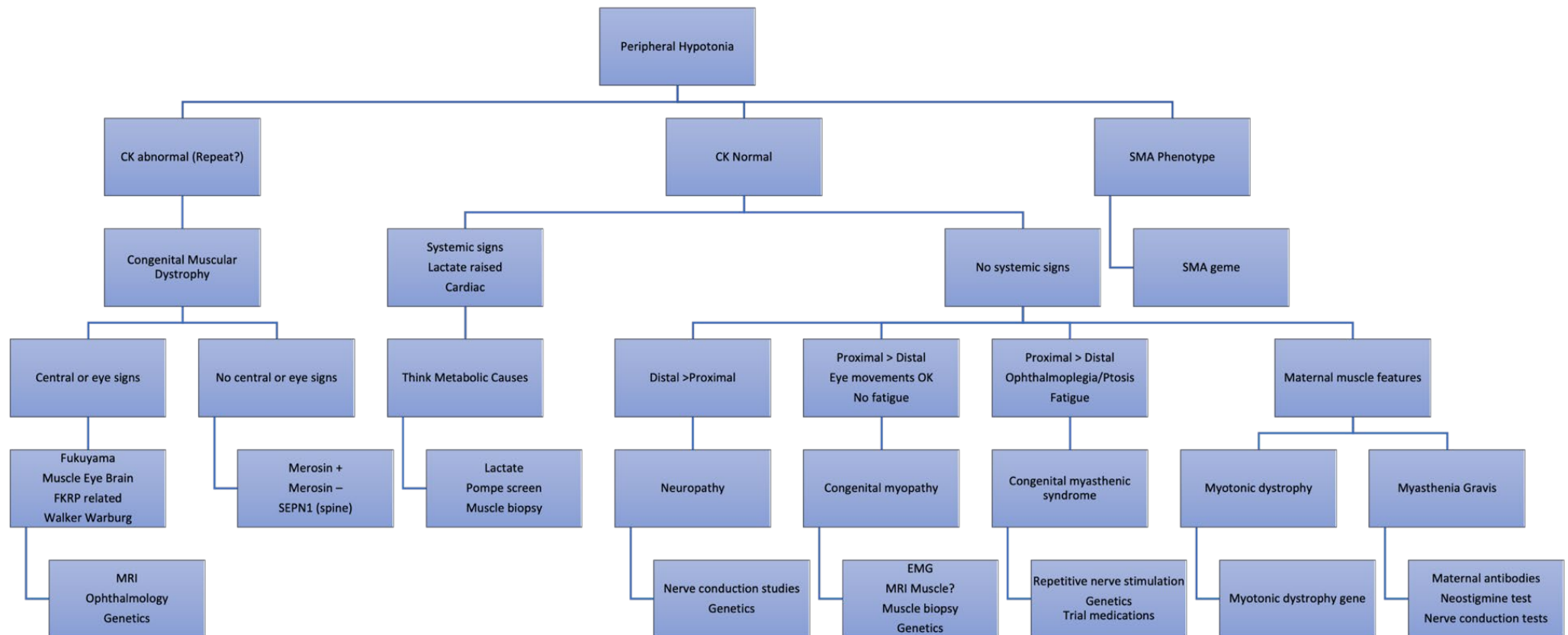
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Appendix 1: Differentials and investigations for central hypotonia in a neonate

adapted from Neonatal Neurology course handbook6



Appendix 2: Differentials and investigations for peripheral hypotonia in a neonate



adapted from Neonatal Neurology course handbook6

Appendix 3: Metabolic investigations and further specialist investigations to consider

- Urine organic acids
- Urine and plasma amino acids
- Acyl carnitine (organic acidaemias, fatty acids oxidation disorders)

Hypotonia with seizures:

- VLCFAs = Very Long Chain Fatty Acids (Peroxisomal disorders)
- Biotinidase (biotinidase deficiency)
- Pivalic acid (pyridoxine deficiency, peroxisomal disorders)
- CSF lactate, glycine, amino acids and biotinidase (oxidation defects, non ketotic hyperglycinaemia, congenital lactic acidosis)
- Urine AASA =alpha aminoadipic semialdehyde (pyridoxine deficiency)
- Plasma uric acid and urine sulphite (Xanthine/sulphite Oxidase deficiencies, molybdenum cofactor deficiency, purine and pyrimidine deficiency)
- Copper and ceruloplasmin (Menkes disease)

Other blood tests:

- Lactate with pyruvate (congenital lactic acidosis)
- White cell enzymes (Lysosomal storage disorders)
- Transferrin isoforms (congenital disorders of glycosylation)
- Gal1Put (Galactosemia)

Other urine tests:

- Urine GAGs (Mucopolysaccharidoses)
- Urine Orotic acid (homocystinuria)
- Urine oligosaccharides (lysosomal storage disorders)
- Urine Sialic acid (lysosomal storage disorders)

Full version control record

Version:	1.0
Guidelines Lead(s):	Dr Claire Oclee-Brown, Consultant Paediatrician
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Lead Director / Chief of Service:	Dr Rekha Sanghavi, CoS for Paediatrics and Neonates
Library check completed:	03/05/2024
Ratified at:	Paediatrics Clinical Governance, 19 June 2024
Date Issued:	26 June 2024
Review Date:	June 2027
Pharmaceutical dosing advice and formulary compliance checked by:	N/A
Key words:	Floppy neonate, floppy baby, hypotonia

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Version History

Version	Date	Guideline Lead(s)	Status	Comment
0.1	Jan 2024	Dr C Oclee-Brown, Consultant Paediatrician	Draft	Derived from: Floppy Neonate (FPH), Author - L Wright; and Management of Unexplained Neurological impairment (WPH), Author - D. Alexopoulou.
1.0	June 2024	Dr C Oclee-Brown, Consultant Paediatrician	Final	

Related Documents

None