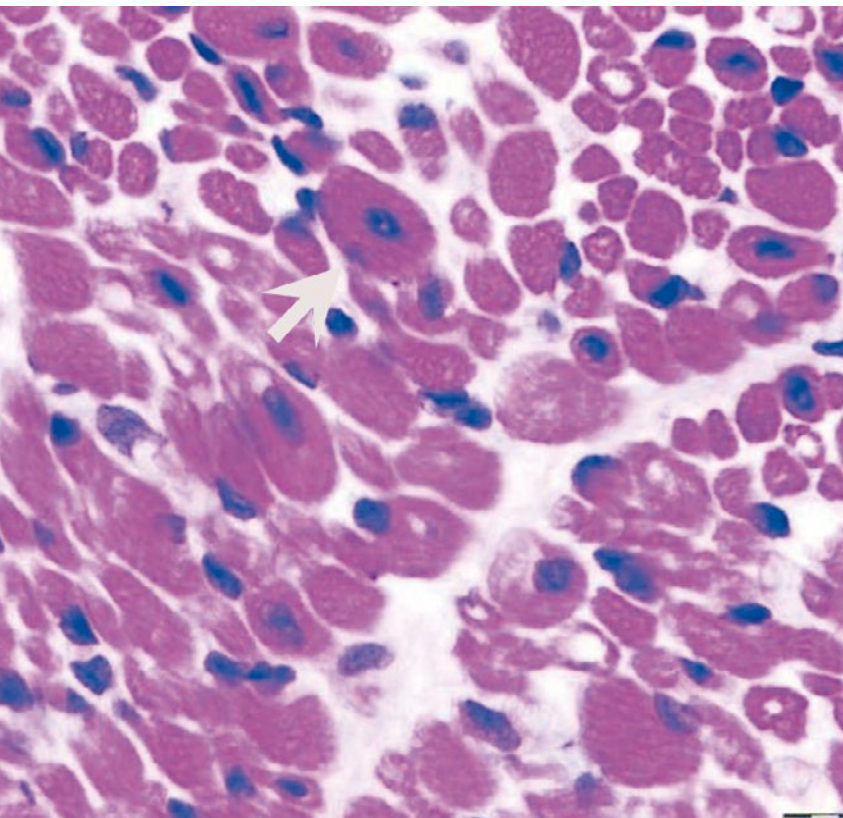


Floppy neonate

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The “floppy neonate” is a well known and recognized entity for neonatologists. It is used to describe a neonate with poor muscle tone. This clinical diagnosis has numerous etiologies and a specific diagnosis is not always obvious or easy to establish. As some etiologies have a very poor prognosis and the results of the diagnostic tests often take weeks to be confirmed, the neonatologist must be able to rely mainly on clinical features to begin counselling the families at an early stage. This is partly possible, as Paro-Panjan et al. managed to diagnose 50% of their cases based on clinical data and the results of clinical examinations alone (1). Because of the numerous etiologies, Paro-Panjan et al. (1) and Prasad et al. (2) each recently published an algorithm as an aid to approaching the floppy neonate.

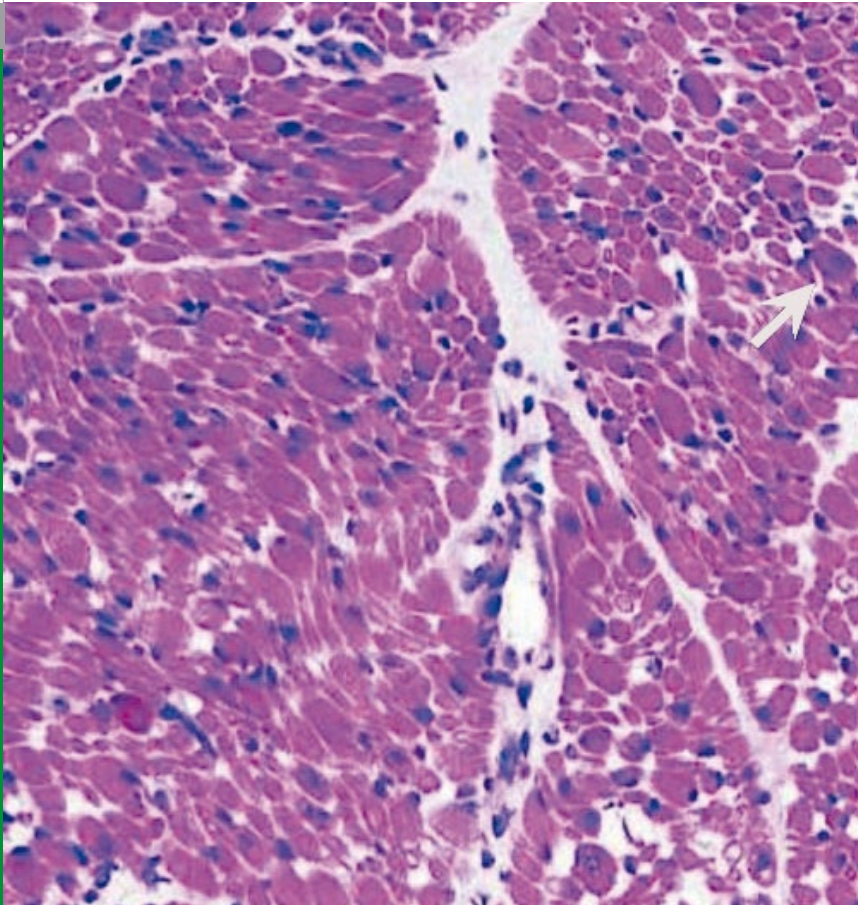
We would like to present three cases to illustrate the importance of a diagnostic algorithm to help neonatologists arrive at a rapid clinical diagnosis, thus allowing better management of such infants.

CASE REPORT 1

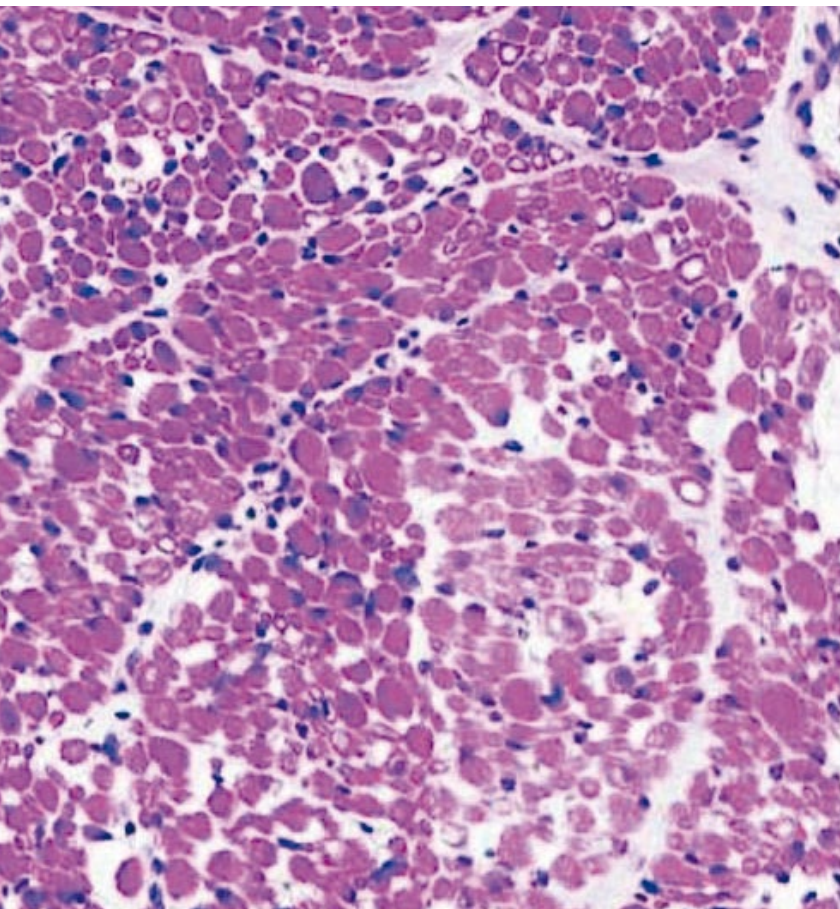
The mother, a 28-year-old, G2/P1 with Stein-Leventhal syndrome and adipositas per magna, had had a first pregnancy that ended in a spontaneous abortion in the 25th week of gestation. The current pregnancy was complicated by cystitis in the 13th week and because of pregnancy induced hypertension lung maturation was induced in the 27th week of gestation.

Muscle biopsy showing centrally placed nuclei in the muscle fibres (arrow).

Fig. 1



She delivered a premature male infant by forceps-assisted vaginal delivery due to birth arrest following premature contractions in the 33rd week of gestation. The infant's birth weight was 1710 g (P 10-50), the length 45 cm (P 50-90) and the head circumference 31.5 cm (p 50-90). The Apgar score was 1, 2, 2 after 1, 5, and 10 minutes, respectively and the arterial cord blood pH was 7.23. The newborn was intubated at 5 minutes due to lack of spontaneous

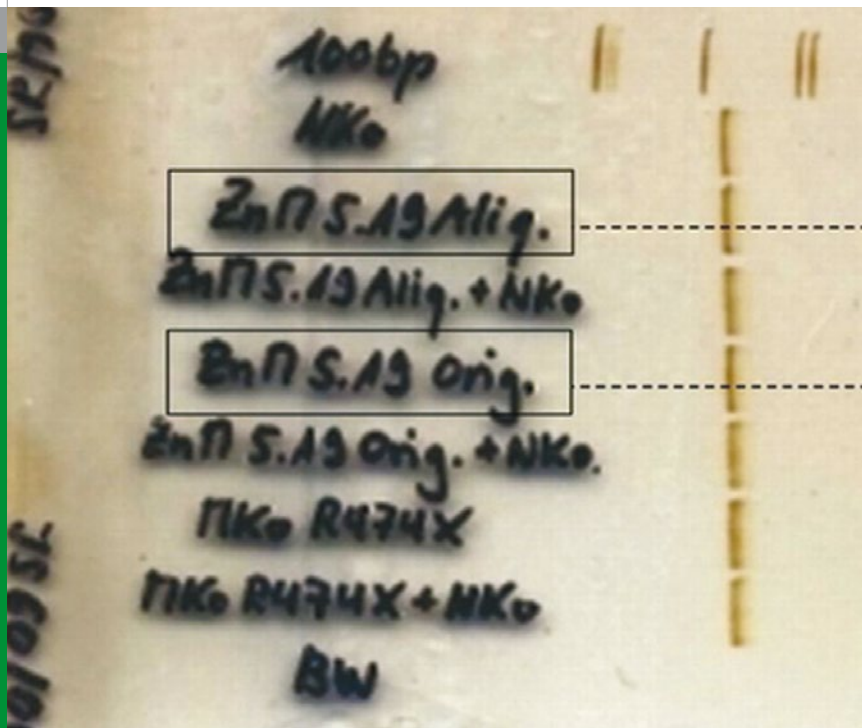


breathing and difficult bag-mask ventilation. In the following days, extreme muscular hypotonia with respiratory insufficiency requiring continuous mechanical ventilation, lack of swallowing, cough and tendon reflexes, uncoordinated spontaneous movements of the extremities and only partially opened eyes were noted. No malformations were found.

Electrophoresis gel after PCR amplification of the MTM1-gene on the X-chromosome: note the missing band in ZnM5.19 Aliq. and in ZnM5.19 Orig.

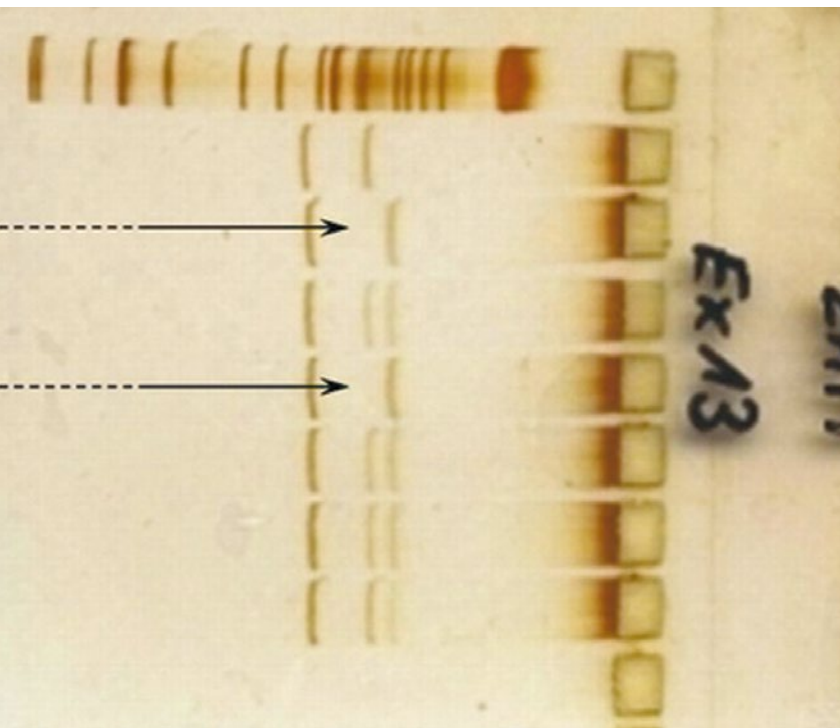
These missing bands are due to the nonsense-mutation p.Arg474X in exon 13 of the MTM1-gene on the X-chromosome.

Fig. 2



A neuromuscular illness was therefore suspected and myotonic dystrophy (Steinert's disease), spinal muscular atrophy and Prader-Willi syndrome were excluded. Nerve conduction velocity, brain ultrasound, as well as echocardiography, amino acid and organic acids screen showed normal results. A muscle biopsy was performed at the age of one and a half months that showed a myotubular myopathy (Fig. 1) and a mutation was subsequently detected in the MTM1-gene on the X chromosome (Fig. 2).

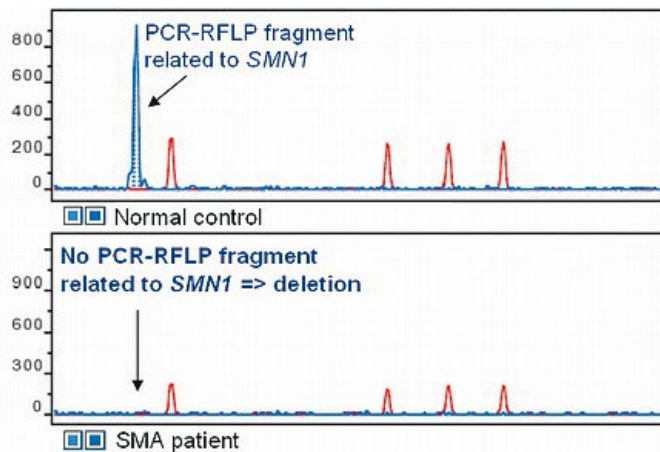
After extensive ethical and parental discussions and at the explicit wish of the mother, a tracheostomy was carried out at the age of three months and the boy was discharged with a home ventilation device at the age of six months.



He is now five years old and depends on constant mechanical ventilation. He has no expressive speech and severe cognitive impairment, as well as chronic pneumopathy due to repetitive aspiration episodes. Because of swallowing difficulties, feeding was initially administered by a jejunal tube, and subsequently a fundoplication followed by a gastrostomy was performed. He has progressive joint contractures, ptosis, myopia and external ophthalmoplegia. In addition, he has middle ear deafness, atopic dermatitis and progressive osteopenia, as well as accelerated growth and bone age with premature adrenarche. He has had generalized seizures since the age of two.

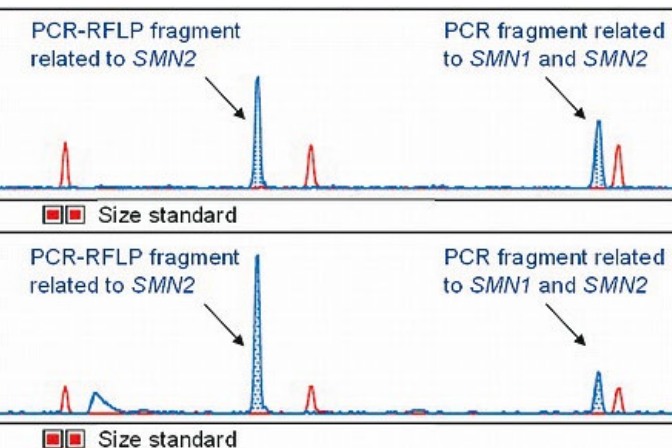
Spinal muscular atrophy mutation: PCR-RFLP-analysis of exon 7 on both SMN-genes on the chromosome 5 (upper tracing: normal control, lower tracing: patient 2.

Fig. 3



This boy is the second child of fourth-grade consanguineous parents with no family history of genetic diseases. The 28-year-old mother, a G2/P2 with an uneventful pregnancy except for slightly decreased fetal movements, delivered the term infant by cesarean section because of transverse presentation at 39 1/7 weeks of gestation. The infant's birth weight was 3980 g (P 75-90), his length 50 cm (P 10-25) and his head circumference 35 cm (P 50). The Apgar score was 8, 8, 9, after 1, 5, and 10 minutes, respectively. He required oxygen supplementation using a face mask for two hours after delivery. Although he was slightly hypotonic he was discharged home after a few days in good condition.

His parents consulted the pediatrician at the age of 11 days because of muscular hypotonia. The boy was then transferred to the intensive care unit because of generalized muscular hypotonia, decreased spontaneous movements, areflexia and irregular spontaneous



breathing efforts. Breastfeeding was not a problem. Amino acid and organic acid screens, abdominal and brain ultrasound were normal. Prader-Willi syndrome was excluded. A homozygote deletion in the SMN1-gene on exon 7 of chromosome 5 confirmed the clinical suspicion of spinal muscular atrophy (Type 1, Werdnig-Hoffman) (Fig. 3).

Before the diagnosis was confirmed genetically, the child had been discharged back home because of his good developmental condition and follow-up is now being carried out by neurologists in his home country.

CASE REPORT 3

A 22-year-old G1/P1 with a pregnancy complicated by slightly reduced fetal movements and polyhydramnios had a secondary cesarean section at 41 3/7 weeks because of fetal bradycardia for over a period of 8 minutes. Postnatally, the male infant was weak, hypotonic, bradycardic with no spontaneous breathing and was therefore intubated. His birth weight was 3430 g (P 10-50), his length 54 cm (P 90) and his head circumference 36.5 cm (P 90). No Apgar score was recorded; the arterial cord blood pH was 7.29.

In the family history (remembered after the delivery) there had been numerous boys that had died of "weakness and no strength to breathe, a few days after birth" (Fig. 4). A mutation analysis of most women in the family undertaken 20 years earlier had shown a mutation in the MTM1-gene on the X-chromosome,

thus confirming the diagnosis of myotubular myopathy (for histology see case report 1, Fig. 1). The mother had not been aware of the results of the mutation analyses.

The boy had extreme muscular hypotonia, respiratory insufficiency requiring continuous mechanical ventilation, lack of swallowing, cough and tendon reflexes, uncoordinated spontaneous movements of the extremities and only partially opened eyes.

After ethical discussions with the family and the intensive care team, he was extubated on the 9th day of life and died of respiratory failure three hours later. The MTM1-gene mutation of the mother diagnosed 10 years earlier was confirmed post mortem in the boy.

Pedigree of case 3 with myotubular myopathy

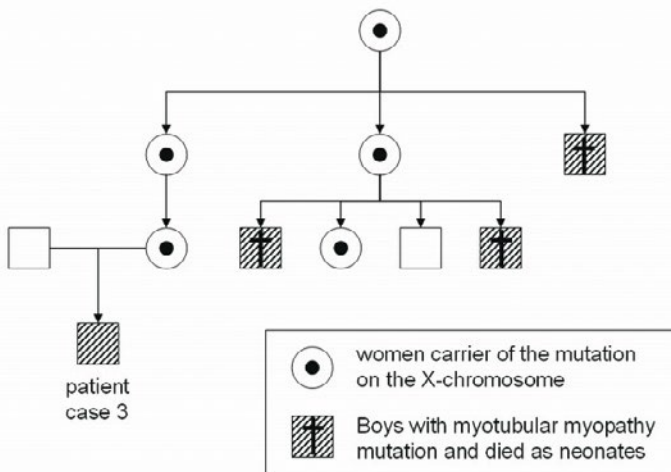


Fig. 4

DISCUSSION

The floppy infant is a recognised entity characterized by generalized hypotonia presenting at birth or in early life (2, 1). Hypotonia presenting in the neonatal period should always alert the neonatologist because of the potentially serious underlying condition.

In this report, we discuss a few important points to be considered when confronted with a floppy neonate and present a diagnostic algorithm in order to facilitate clinical decision making and to guide the neonatologist in the subsequent treatment options (2) (Table, see page 15).

The first clinical step when presented with a floppy neonate should always be to obtain a detailed history of the family, social environment, pregnancy, birth and neonatal period, as thereafter most pathologies can either be suspected or excluded (2). The second clinical step is evidently the physical examination (Table, see page 16). Hypotonia presents in the neonate with full abduction and external rotation of the legs as well as flaccid extension of the arms. When traction is delivered to the arms, there is a prominent head lag. A myopathic facies with paucity of facial expression as well as a high-arched palate are often noted in infants with neuromuscular disorders.

Algorithms to help physicians when confronted with a floppy infant are very useful tools, and several have been published in the past few years (1-3). A recent

publication in the journal of the Swiss Society of Paediatrics also addressed this interesting topic (4). An efficient and clinically relevant way to approach the floppy neonate is to distinguish two main groups: infants with isolated hypotonia and those with hypotonia coupled with multisystem involvement.

Isolated hypotonia can be subdivided into lesions of the upper motor neuron, which make up 66% of all floppy infants; or lesions of the lower motor neuron which consequently make up 33% (5). Upper motor neuron lesions present with hypotonia, depressed levels of consciousness, feeding difficulties, seizures, apnea, hyperactive deep tendon reflexes, abnormal body position, abnormal eye movements and abnormal brainstem reflexes. Weakness (except for axial weakness) is uncommon except in the acute stages. Lower motor neuron lesions present with profound weakness as well as hypotonia, paucity of antigravity movements, hypo/areflexia, weak suck, low-pitched cry/progressively weaker cry, arthrogryposis, external ophthalmoplegia, and fasciculations but with an alert look (6).

If hypotonia presents at birth with respiratory insufficiency severe enough to require tracheal intubation, the prognosis is often very poor. Examples include severe birth trauma, neonatal sepsis, myotubular myopathies, and Steinert's disease.

If the onset is in the first days or weeks, with progressive feeding and breathing difficulties, hypotonia and poor spontaneous movements, the prognosis is still poor, but the infants can survive for months or years. Examples include spinal muscular atrophy, Prader-Willi syndrome, spinal muscular atrophy with respiratory distress (SMARD), Pompe's disease, and congenital myopathy.

A floppy neonate with multisystem involvement needs a structured, multidisciplinary diagnostic approach, coordinated by the neonatologist. A rough distinction should be made between toxic and metabolic lesions. For more details, please see the article by Prasad et al. (2).

CONCLUSIONS

Neonatologists are often confronted with floppy neonates as hypotonia is a relatively common presentation at birth or in the first few days of life. It is therefore important to be aware of the different degrees and presentations of hypotonia and to have knowledge of diagnostic and prognostic implications. An algorithm is an easy way of categorising symptoms and helps the clinician to establish a rapid diagnosis and initiate treatment measures.

As described in the case reports, if the classical symptoms of peripheral motor neuron lesions are present at birth (with respiratory insufficiency, lack of swallowing, cough and tendon reflexes) the prognosis is very

poor, independent of the exact diagnosis. Such a presentation should lead to timely ethical discussions as well as parental counselling and to the consideration of early extubation.

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ACKNOWLEDGMENTS

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FLOPPY NEONATE: ISOLATED HYPOTONIA

Step 1: History

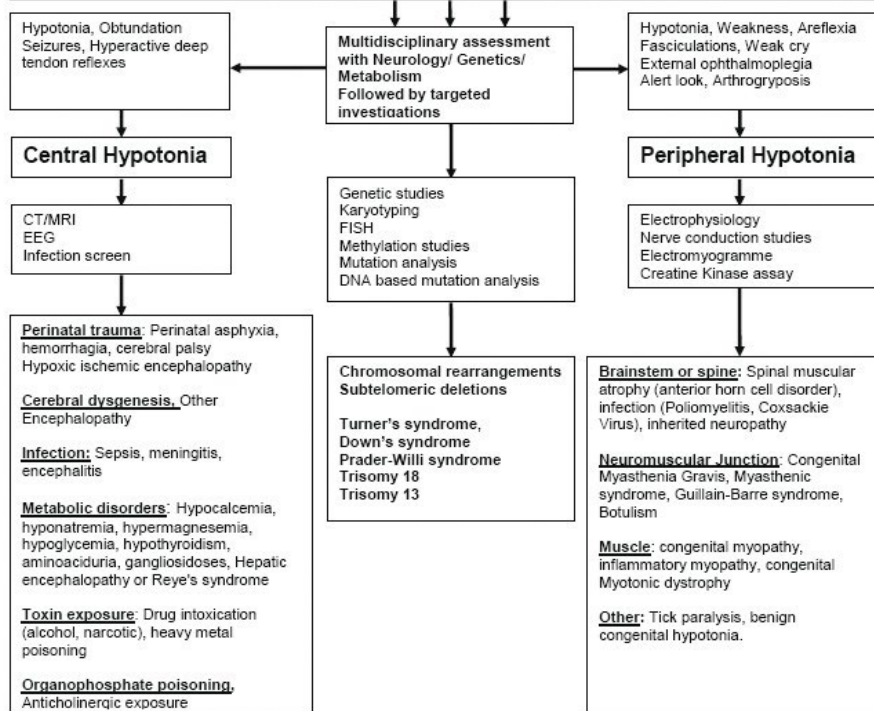
- **Family history:** Parent consanguinity (SMA), parental age, history of neuromuscular diseases (myotubular myopathies), clinically slightly affected mothers (X-linked).
- **Social history:** Drug and teratogen exposure (heavy metal intoxication).
- **Pregnancy history:** Reduced fetal movements, polyhydramnios (swallowing pathologies), breach presentation, short umbilical cord (poor fetal movements), arthrogyposis or contractures at birth (they may regress in the first weeks), electrolyte pathologies, maternal infections or diseases (diabetes, epilepsy).
- **Birth history:** Perinatal birth trauma, anoxia, delivery complications, low APGAR scores (especially tone, reflexes and respiratory effort) and onset of hypotonia.

Step 2: Physical Examination

Specific clinical signs should be searched actively:

- Dysmorphic features of genetic diseases such as
 - Cryptorchism in Prader-Willi syndrome
 - Hydrops in Turner's syndrome
 - Upslanted palpebral fissures, Brushfield's spots, macroglossia, single simian crease in Down's syndrome

- Large tongue in Pompe's disease
- Tongue fasciculation in anterior horn cell involvement and denervation
- Ptosis, external ophthalmoplegia in myasthenic syndromes
- Cataracts, pigmentary retinopathy, kidney cysts in peroxisomal disorders (Zellweger syndrome)
- Organomegaly in storage diseases.



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