

Floppy Infant Syndrome: new approach to the study of neonatal hypotonia through the analysis of a rare case of X-Linked Myotubular Myopathy

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Abstract

The Floppy Infant Syndrome includes a variety of signs and symptoms: decrease in muscle tone (hypotonia), in muscle power (weakness) and ligamentous laxity and increased range of joint mobility. Strictly speaking, the term "floppy" should be used to describe a form of hypotonia. In our case the clinical and molecular study of a rare form (1:50.000) of X-Linked Myotubular Myopathy (X-Linked MM), with an early onset of peripheral hypotonia, led us to develop a general protocol for the differential diagnosis of neonatal hypotonia.

Keywords

Floppy infant, weakness, neonatal hypotonia, myotubular myopathy, newborn onset, central and peripheral hypotonia.

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Introduction

The term “Floppy Infant” is used to describe a newborn with poor muscle tone and power (weakness) with increased joint mobility [1]. This clinical diagnosis has numerous etiologies and a specific diagnosis is not always easy to establish except in more common and widely recognized conditions, such as chromosomal disorders [2]. The underlying pathology of infantile hypotonia can be divided into four broad categories: the central nervous system, the peripheral nerves, the muscle and the neuromuscular junction [3, 4]. Based on clinical criteria hypotonia can be classified in two major groups: central hypotonia and peripheral hypotonia. Central origin accounts for about 66% to 88% of cases, with peripheral origins or unknown causes accounting for the balance. In addition several congenital disorders that are characterized by hypotonia have both central and peripheral symptoms, such as metabolic and genetic disorders [2]. A detailed family, pregnancy and birth history should be conducted first [5, 6]. Family history should include any other family member with hypotonia, muscle diseases or genetic disorders. Prenatal history should include the mother’s description of fetal movements, polyhydramnios or oligohydramnios, any maternal illness, maternal exposure to infectious agents and maternal drugs and alcohol use [7, 8]. Moreover perinatal history should include abnormal fetal presentation, Apgar scores, feeding difficulties, abnormal postures and seizures [5, 8]. The initial clinical approach to the hypotonic neonate is to determine if the problem is central or peripheral. This is of crucial importance when planning diagnostic investigations [9], that must include neurological assessment and an evaluation of weakness [9, 10]. In fact paralytic hypotonia with significant weakness and without cognitive delay suggests a peripheral neuromuscular problem, whereas non-paralytic hypotonia without significant weakness points can be attributed to a central cause which may be neurological, genetic or metabolic [9]. The prevalence of specific signs or symptoms can help to perform a differential diagnosis between central and peripheral hypotonia. The presence of mixed clinical features can help to orient towards a mixed and more complex hypotonia due to syndromic conditions [2]. We describe a newborn with a rapid and severe onset of peripheral hypotonia since the first hours of life, with a rare form of X-Linked Myotubular Myopathy (X-Linked MM), diagnosed via a diagnostic work-

up oriented toward the early identification of clinical symptoms. This underlines the importance of a correctly conducted differential diagnosis, in order to allow a rapid clinical assessment, thus allowing better management of such infants.

Case report

A 1-day old newborn, male sex, was admitted to our hospital for respiratory failure and hypotonia. He was born at term (37.4 weeks of gestational age) by elective cesarean delivery and he was adequate for gestational age (AGA, weight 2.850 kg). Apgar score was 7/8. Pregnancy history was normal. The mother, was 35-years-old, G2P0, had a first pregnancy that ended in a cesarean delivery at the 38th week of gestation for dystocic presentation. The maternal clinical phenotype was normal and familiar history was unremarkable. At the birth the neonate revealed an early onset of severe hypotonia with necessity of early intubation and mechanical ventilation. The clinical examination, at a few hours of life, detected the presence of marked hypotonia with an absence of active movements, severe respiratory failure, reducing glare and bilateral cryptorchidism. Laboratory evaluations were performed, including: markers of infections, blood culture, asphyxia indices (CK-MB, troponine), muscle enzymes (CK, LDH) and ammonia. All tests were negative and also the brain ultrasound, performed in the first day of life, was normal. The clinical picture and results of laboratory tests confirmed an early-onset form of peripheral neonatal hypotonia. Therefore, we started a differential diagnosis among the most frequent forms of neonatal hypotonia: Steinert’s syndrome, Prader-Willi’s syndrome and Spinal Muscle Atrophy type I (SMA I). Specifically, in our case, Steinert’s syndrome was excluded for the absence of familiarity, myotonia and other typical changes, such as cataract and hypothyroidism. Prader-Willi’s syndrome, initially evaluated for the presence of hypotonia and cryptorchidism, was later excluded for the absence of typical clinical signs (such as high prominent forehead, narrow bifrontal diameter, downturned corners of the mouth, micrognathia, dysplastic ears and small hands and feet) and for the presence of severe form of hypotonia with rapid appearance of respiratory failure. The SMA I was also excluded, being characterized by later onset of symptoms and by the absence of cryptorchidism. Conversely the combination of hypotonia, muscle weakness, male gender, bilateral cryptorchidism and severe respiratory failure was compatible with

a form of Myotubular Myopathy (MM). Therefore, a muscle biopsy was performed, considering the extreme severity of the general conditions of the infant and the rapid progression of clinical symptoms. The muscle microscopic examination showed centronuclear myopathy with numerous central nuclei compatible with a form of MM. The negative family history and the severity of the clinical picture excluded the presence of an autosomal MM; therefore, a molecular analysis of the *MTM1* gene was performed. *MTM1* gene is located on chromosome Xq28 and is involved in the pathogenesis of X-Linked MM. The molecular analysis, performed by direct sequencing, confirmed the presence of the mutation c.85 C>T (p.R29X) on the exon 3 of the *MTM1* gene in the mother and in the newborn (Fig. 1).

Discussion

The X-Linked MM is a rare form of peripheral hypotonia (1:50.000), which affects only male infants, characterized by congenital hypotonia with weakness, severe respiratory failure at birth, difficulty in nutrition, specific dysmorphisms (ptosis eyelid, head and body elongated, slender hands and

feet), cryptorchidism and other signs which are less frequent and include anemia, hepatic cysts, cardiac problems and cognitive delay. The disease is caused by mutations of the myotubularin gene (*MTM1*), located on chromosome Xq28. The molecular analysis in affected patients and in female carriers confirms the presence of a mutation in the *MTM1* gene. The prognosis is unfortunately unfavorable [11, 12]. The critical analysis of this case study allowed us to revise our constructive approach to differential diagnosis of neonatal hypotonia, through the development of a shared internal protocol for diagnosis and clinical management. The diagnostic protocol classifies neonatal hypotonia into three different forms (central, peripheral and mixed) according to the onset of the symptoms. These symptoms must be assessed by a careful maternal and familiar history and a proper neurological and clinical examination, such as the evaluation of the active and passive tone, the presence of sensory impairment, weakness, archaic and tendon reflex and stability of respiratory function. In fact, the peripheral forms are characterized by hypotonia in the presence of weakness, hypo- or areflexia, respiratory failure, crying faint and weak suck. Instead, the central forms are characterized by

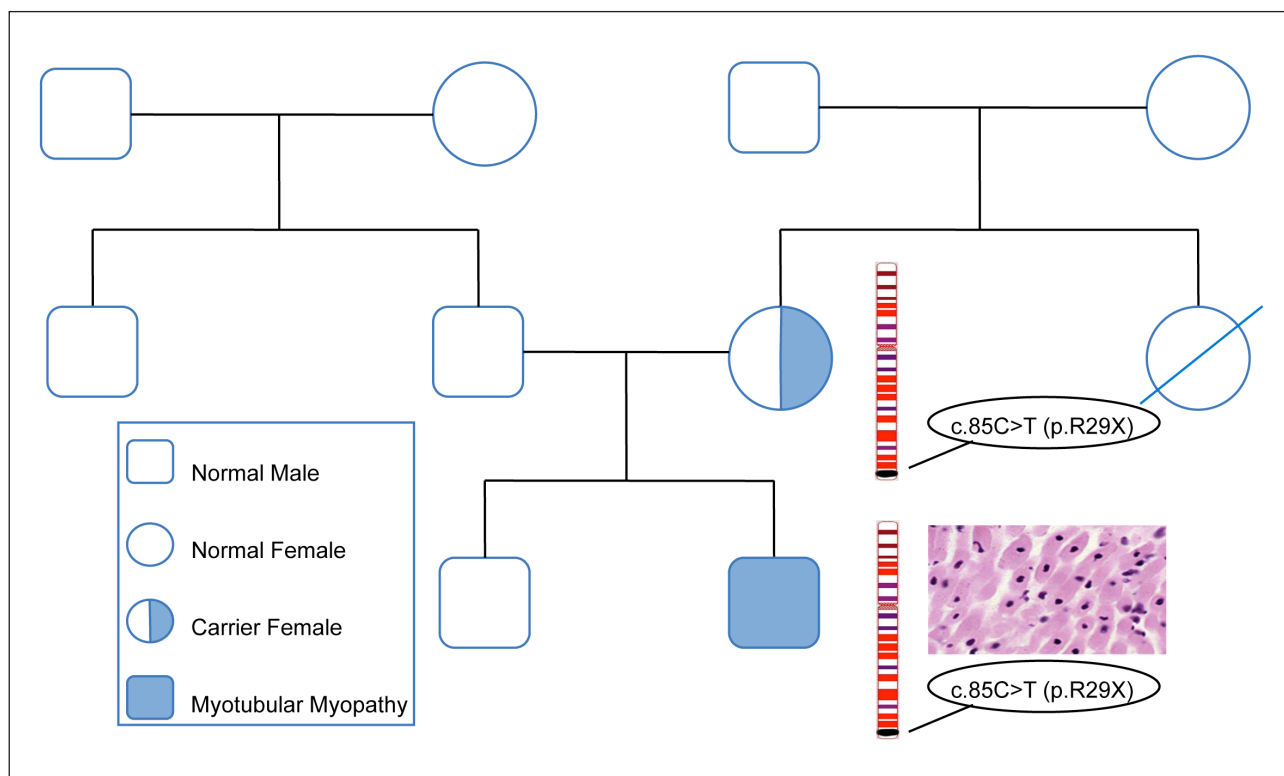


Figure 1. Family tree. No family history of muscular disorders. In the newborn the muscle biopsy shows a centronuclear myopathy. The *MTM1* gene mutation on Xq28 region (c.85C>T) is present in mother (Carrier Female) and newborn (Myotubular Myopathy).

hypotonia with sensory impairment, seizures and hypo- or hyperreflexia; finally, in mixed forms there is an overlap of symptoms between peripheral and central forms. This initial clinical assessment helps to plan a specific diagnostic approach that allows a more rapid and less laborious diagnosis using targeted laboratory and instrumental examinations, either of first or second level. For diagnosing central hypotonia the first level (I level) examinations require the tests for the infections (blood culture, infection markers) and metabolic diseases (ammonia in the first) and the evaluation of cerebral function (EEG and/or aEEG); subsequently the second level (II level) analysis requires neuroimaging (Cerebral Ultrasonography, head CT and/or MRI). In peripheral forms the I level investigations are the muscle enzymes (CK, LDH) and the II level analysis includes the neuromuscular functionality tests (EMG, muscle biopsy), with molecular biology if indicated for confirmation. Lastly, in mixed forms, only a multidisciplinary approach (genetic, neurological, metabolic) may facilitate a rapid and direct diagnosis (**Tab. 1**). In conclusion, diagnosis of congenital hypotonia remains elusive in many cases, despite the advent of sophisticated laboratory and neuroimaging tests. However, our case highlights the importance of first clinical

approach for its crucial role in contribution of an early diagnosis and in differentiating disorders of central versus peripheral origin by performing a careful history of the infant, mother and family and conducting non-invasive clinical and developmental assessments. The primary objective of the diagnosis is to enable, where possible, an early identification of the problem to start an effective supportive therapy. A precise etiological diagnosis also allows formulating a more accurate prognosis. Last but not least, the identification of forms of neonatal hypotonia with familial transmission is crucial for the formulation of a genetic counseling for future pregnancies. Ideally, these assessment and diagnostic strategies are best accomplished by an interdisciplinary team of developmental specialists (pediatricians, obstetrics, medical geneticists and child neurologists). However, a linear protocol is an easy way to help the clinician to establish a rapid diagnosis and initiate an early treatment.

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Table 1. Protocol for differential diagnosis of Congenital Hypotonia. This protocol puts neonatal hypotonia into three different forms (central, peripheral and mixed) according to the onset of the symptoms, maternal and familiar history and neurological and clinical examination. The laboratoristic and instrumental investigations are established according to the initial orientation.

Signs and symptoms	Type	I Level	II Level	Diagnosis
Hypotonia, weakness, hypo-areflexia, respiratory failure, crying faint, weak suck, maternal and familiar history suggestive	Peripheral Hypotonia	Muscle enzyme (CK, LDH)	EMG, muscular biopsy	If suggestive, search for mutations = Ereditary neuropathies (SMA I), congenital muscular dystrophies (Steinert), congenital myopathies (myotubular, nemaline...)
Hypotonia, sensory impairment, seizures, hypo-hyperreflexia, personal and pregnancy history suggestive	Central Hypotonia	Screening for sepsis (blood culture, infection's indices), ammonia, EEG and/or aEEG	Neuroimaging (cerebral ultrasonography, head CT and/or MRI)	= Congenital trauma, HIE, HIC, infections, brain malformations
Mixed symptoms	Mixed Hypotonia	Multidisciplinary approach (Geneticists, Neurologists, experts on metabolism)	Karyotype, molecular analysis, FISH	= Chromosomal rearrangements, trisomy: 13, 18, 21 = Subtelomeric deletions (+ tests of methylations) = Prader-Willi's syndrome (+ dysmorphism, abnormal odors, multiorgan disorders: cataracts, hepatomegaly, etc.) = metabolic and storage diseases

CK: serum Creatine Kinase; LDH: Lactate Dehydrogenase; EMG: Electromyography; EEG: Electroencephalography; aEEG: amplitude-integrated Electroencephalography; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; FISH: Fluorescence In Situ Hybridization; SMA: Spinal Muscular Atrophy; HIE: Hypoxic Ischemic Encephalopathy; HIC: Intracranial Hemorrhage.

Declaration of interest

The Authors have no conflicts of interest to declare.

References

1. Rochat M, Boltshauser E, Klein A, Frey B, Bänziger O. Floppy neonate. Swiss Society of Neonatology, 2007. Available at: <http://neonet.ch/assets/cotm/index.php?book=2007-06>, last access: February 2014.
2. Harris SR. Congenital hypotonia: clinical and developmental assessment. *Dev Med Child Neurol*. 2008;50(12):889-92.
3. Brown RH Jr, Grant PE, Pierson CR. Case records of the Massachusetts General Hospital. Case 35-2006: a newborn boy with hypotonia. *N Engl J Med*. 2006;355(20):2132-42.
4. Prasad AN, Prasad C. Genetic evaluation of the floppy infant. *Semin Fetal Neonatal Med*. 2011;16(2):99-108.
5. Vasta I, Kinali M, Messina S, Guzzetta A, Kapellou O, Manzur A, Cowan F, Muntoni F, Mercuri E. Can clinical signs identify newborns with neuromuscular disorders? *J Pediatr*. 2005;146(1):73-9.
6. Kim CT, Strommen JA, Johns JS, Weiss JM, Weiss LD, Williams FH, Rashbaum IG. Neuromuscular rehabilitation and electrodiagnosis. 4. Pediatric issues. *Arch Phys Med Rehabil*. 2005;86(3 Suppl 1):S28-32.
7. Crawford TO. Clinical evaluation of the floppy infant. *Pediatr Ann*. 1992;21:348-54.
8. Prasad AN, Prasad C. The floppy infant: contribution of genetic and metabolic disorders. *Brain Dev*. 2003;25:457-76.
9. Gowda V, Parr J, Jayawant S. Evaluation of the floppy infant. *Paediatr Child Health*. 2007;18(1):17-21.
10. Dubowitz LMS, Dubowitz V, Mercuri E. *The Neurological Assessment of the Preterm and Full-term Newborn Infant*. 2nd ed. Clinics in Developmental Medicine No. 148. London: Mac Keith Press, 1999.
11. Lee EH, Yum MS, Park SJ, Lee BH, Kim GH, Yoo HW, Kob TS. Two Cases of X-Linked Myotubular Myopathy with Novel MTM1 Mutations. *J Clin Neurol*. 2013;9:57-60.
12. Jungbluth H, Wallgren-Pettersson C, Laporte JF; Centronuclear (Myotubular) myopathy Consortium. 198th ENMC International Workshop: 7th Workshop on Centronuclear (Myotubular) myopathies, 31st May – 2nd June 2013, Naarden, The Netherlands. *Neuromuscul Disord*. 2013;23(12):1033-43.