Neonatal hypotonia: is it a diagnostic challenge?

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Introduction. Hypotonia is a frequent sign of disease in newborns. However, it's a nonspecific clinical finding: may be the presentation form of a systemic or neurological disease.

Aims. To study the main causes of neonatal hypotonia as well as to evaluate the diagnostic accuracy of the anamnesis and physical examination of the hypotonic newborn.

Patients and methods. A 22-year retrospective study of hypotonic neonates admitted to the Neonatal Intensive Care Unit was conducted. It was performed an initial blind classification of hypotonia's type (central-CH, peripheral-PH or undetermined hypotonia) based on the clinical history and the recorded data of physical examination.

Results. 91 infants were included. 42 (46.2%) had prenatal history abnormalities: polyhydramnios (28.6%), intrauterine growth restriction (21.4%) and pelvic presentation (19.0%). 53 (58.2%) required resuscitation at birth. The main associated symptoms were respiratory distress (65.9%), feeding difficulties (36.5%) and decreased spontaneous movements (22.4%). The final diagnosis was reached in 64 newborns (70.3%): 81.3% with CH, 18.7% with PH. The positive predictive value of the initial classification was 97.9% in CH and 66.7% in PH group. The mortality rate was 8.8% and it was higher in PH group (58.3% vs 1.3%).

Conclusions. Neonatal hypotonia can be associated to an extensive list of disorders. A detailed clinical history associated to a careful neurological evaluation present a high diagnostic predictive value that should guide the etiological investigation.

Key words. Diagnosis. Floppy infant. Hypotonia. Neonatal hypotonia. Newborn.

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Accepted:
23.04.18.

How to cite this paper:
Mesquita M, Ratola A, Tiago J, Basto L. Neonatal hypotonia: is it a diagnostic challenge? Rev Neurol 2018; 67: 287-92.

Versión española disponible en www.neurologia.com

Introduction

Hypotonia is one of the most frequent signs of disease in neonates and can be a diagnostic challenge for the neonatologists [1-3]. It's a nonspecific finding that may be the clinical presentation form of a central or peripheral nervous system abnormality, myopathies, genetic disorders, endocrinopathies, metabolic diseases and acute or chronic illness [2]. The differential diagnosis is extensive, requiring a methodical and systematic approach. Clinical history and physical examination are the first and main program in the diagnosis of neonatal hypotonia [4], helping the clinician to localize the problem in a specific region of the nervous system [1]. Despite recent substantial advances in neuroimaging and laboratory diagnostic technology, the clinicians' judgment about anatomical localization cannot be replaced [4].

There are frequent implications for future pregnancies and specific treatments may be available for a few disorders [1]. For this reason it's extremely important to know the etiology of neonatal hypotonia, as well as to recognize the distinctive features in the history and physical examination. This can help making the diagnosis, guiding the research and therapeutic approach.

The aim of the study was to determinate the frequency of the main causes of hypotonia in neonates admitted to the Neonatal Intensive Care Unit (NICU) as well as to evaluate the diagnostic accuracy of the anamnesis and physical examination of the hypotonic newborn.

Patients and methods

Study design and patients

This was a retrospective systematic review of the neonates diagnosed with hypotonia who were admitted to a NICU of a tertiary care centre during the last 22 years (1995-2016). Admitted infants were only eligible for inclusion if hypotonia had been first noticed before the 28th day of life and if gestational age was more than 30 weeks.

Based on clinical history and recorded physical examination data, a semiological evaluation of the newborn has been done according to the Dubowitz's neurological evaluation scale [5,6]. This is an

internationally recognized, scientifically approved and widely used method for the newborn's neurological evaluation that can be easily applicable to both preterm and full-term newborns. According to this data it was performed an initial blind retrospective classification of neonatal hypotonia's type: central hypotonia (CH), peripheral hypotonia (PH) and undetermined hypotonia (UH). The authors considered as central hypotonia when the newborn had signs of abnormal consciousness or seizures combined with preserved muscle power and normal or hyperactive deep tendon reflexes; whereas the presence of weakness along the antigravity limb muscles with decreased or absent reflexes as indicative of peripheral hypotonia; undetermined hypotonia was considered when the clinical history and the physical examination data were scarce, incongruent or didn't allow to follow the aforementioned classification. We also defined transient hypotonia as hypotonia lasting less than 24 hours; static hypotonia as the one that maintains the same intensity over time; unstable or fluctuant hypotonia as that with intensity variation over time; progressive hypotonia as the one that increases in intensity over time.

The final diagnosis, whenever obtained, was classified as either central or peripheral according to the main anatomic local affected. The authors included cerebral lesions or malformations, neurometabolic diseases and chromosomal disorders in the central group, whereas the peripheral group included disorders affecting the anterior horn cells, peripheral nerve, neuromuscular junction and muscle.

Data collected

Demographic data and relevant historical information were obtained for each infant. Recorded prenatal and perinatal clinical events were as follows: polyhydramnios, intrauterine growth restriction, breech presentation, decreased prenatal movements, threat of premature labor; type of delivery, gestational age, birth weight, neonatal resuscitation and requirement of intubation, five-minute Apgar score. Data collected about clinical presentation: age of onset, hypotonia's evolution, and associated symptoms (respiratory distress, apneas, abnormal consciousness, seizures, feeding difficulties, weakness and decreased spontaneous movements). Features from the physical examination recorded included facial dysmorphisms, inexpressive face, weak cry, deformities of bones or joints (arthrogryposis) and deep tendon reflexes obtained. The final diagnosis and mortality had also been recorded.

Statistic methods

The statistical analysis of the collected data was performed on SPSS v. 21.0, using absolute and relative frequencies for categorical variables, medians, means and standard deviation for continuous variables. Statistical analysis was performed using the chi-square test whenever applicable. Test results were considered significant when p-value < 0.05.

Results

The database search generated 132 records and out of these 91 neonates met the inclusion criteria. Forty-six (50.5%) were male, 47 (51.6%) were delivered by caesarean section, at the median gestational age of 37 weeks (range: 30-42), with a birth weight range between 1120-4100 g (median: 2920 g) (Table I). The hypotonia was first classified as CH in 48 neonates (52.7%), PH in 15 (16.5%) and UH in 28 (30.8%).

Forty-two (46.2%) neonates had at least one prenatal history abnormality: polyhydramnios (28.6%), intrauterine growth restriction (21.4%), pelvic presentation (19.0%), threat of premature labor (19.0%) and decreased prenatal movements (11.9%). The percentage of infants with prenatal abnormalities in the CH group was 39.2% in comparison to 91.7% in the PH group, and this difference was statistically significant (p = 0.02). Fifty-three (58.2%) newborns required resuscitation at birth: 53.2% of the CH neonates against 91.7% of the PH group (p < 0.001); out of which 26 (49.1%) demanded endotracheal intubation. Globally, the fifth minute Apgar score ranged between 3-10 (median: 8).

Data on the onset of clinical presentation of hypotonia were obtained in 65 newborns. The hypotonia started at the first 12 h of life in 80% of the neonates, 4.6% between 12-24 h, 4.6% between 24-48 h and 10.8% after 48 h of life. It wasn't found relation with statistical significance between the age of clinical presentation's onset and the hypotonia's type (p = 0.704). Concerning hypotonia's clinical course, it was considered static in 87.0% of the infants, unstable in 7.6% and progressive in 5.4%. Among neonates of CH group, 81.3% had a static clinical course and this was significantly associated with the CH (p < 0.001). Eighty-five infants (93.4%) presented other symptoms beyond hypotonia. These were respiratory distress (65.9%), feeding difficulties (36.5%), seizures (21.2%), abnormal consciousness (14.1%), weakness and decreased spontaneous movements (22.4%) and apnea (14.1%). Among the symptoms presented, only weakness with decreased

spontaneous movements was significantly more frequent in one of the hypotonia's group, in this case PH ($p < 0.001$).

The physical examination revealed other abnormalities in 39 infants (42.9%), which are detailed in table II. The presence of inexpressive facies, weak cry, arthrogryposis affecting multiple joints and decreased deep tendon reflexes were significantly associated to PH's type in our cohort.

Twenty-two cases (24.2%) presented transient hypotonia. The main causes were poor adaptation to extrauterine life (63.6%), toxics (maternal administration or anesthesia; 13.6%), hypoglycaemia (13.6%) and traumatic delivery (9.2%).

The final diagnostic classification included 79 infants in CH group (86.8%) and 12 in PH group (13.2%). However, the final diagnosis was only established in 64 neonates (70.3%) with a median age of 9 days-old (range: 0-50 days-old). Diagnosis belongs to the central diseases' group in 81.3% of the infants, 18.7% to the peripheral's group. Detailed diagnosis for each group are listed in table III.

Among the 48 infants who had initially been classified as CH, the final diagnosis was proved to be central in 47 cases, which corresponds to a positive predictive value of 97.9%. Comparatively, among the 15 infants classified as apparently peripheral hypotonia, the final diagnosis proved the peripheral etiology in 10 cases (positive predictive value: 66.7%). Finally, 28 infants were first classified as UH cases but the central origin was proved in 27 of them. The authors recognized the hypotonia's type in 62.6% ($n = 57$) of the cases.

Eight newborns (8.8%) died during the hospital stay, the median age of death was 19 days-old (range: 3-50 days-old). The mortality rate was 58.3% in the PH's group and 1.3% in CH ($p < 0.001$).

Discussion

Hypotonia, or low muscle tone, is defined by the decreased resistance to passive movement and might be associated with decreased muscle strength or weakness [3]. The tone's clinical evaluation can be difficult in newborns and infants [3]. The first aspect to assess is posture (flexed in a healthy newborn) followed by muscle tone proper, using specific manoeuvres of the neonatal neurological examination such as recoil of the limbs, scarf sign, adductors, popliteal and leg-foot angles, ventral and dorsal incurvation of the axis [7].

Anatomically, the neurologic inputs which control muscle tone are divided into two major catego-

Table I. Study population characterization. Results are presented for each hypotonia's group.

		Total ($n = 91$)	Central hypotonia ($n = 79$)	Peripheral hypotonia ($n = 12$)	p
Gender	Male	46 (50.5%)	40 (50.6%)	6 (50.0%)	
	Female	45 (49.5%)	39 (49.4%)	6 (50.0%)	
Gestational age (median and range)		37 weeks (30-42)	38 weeks (30-42)	35 weeks (32-40)	0.016
Mode of delivery	Vaginal route	44 (48.4%)	42 (53.2%)	2 (16.7%)	0.027
	Caesarean section	47 (51.6%)	37 (46.8%)	10 (83.3%)	
Birth weight (median and range)		2920 g (1120-4100)	3115 g (1120-4100)	2340 g (1550-3340)	0.016
Apgar score 5 min (median and range)		8 (3-10)	9 (3-10)	8 (5-10)	0.850
Prenatal history abnormality		42 (46.2%)	31 (39.2%)	11 (91.7%)	0.020
Perinatal history: resuscitation at birth		53 (58.2%)	42 (53.2%)	11 (91.7%)	< 0.001
Positive pressure ventilation		27 (50.9%)			
Endotracheal intubation		26 (49.1%)			

Table II. Clinical presentation and physical examination of the hypotonic neonates according to the type of hypotonia. The results are presented for each hypotonia's group.

	Total ($n = 91$)	Central hypotonia ($n = 79$)	Peripheral hypotonia ($n = 12$)	p
Symptoms	85 (93.4%)	73 (85.9%)	12 (14.1%)	0.297
Respiratory distress	56 (65.9%)	45 (61.6%)	11 (91.7%)	0.270
Feeding problems	31(36.5%)	25 (34.2%)	6 (50.0%)	0.333
Seizures	18 (21.2%)	16 (21.9%)	2 (16.7%)	0.533
Decreased spontaneous movements	19 (22.4%)	11 (15.1%)	8 (66.7%)	< 0.001
Abnormal consciousness	12 (14.1%)	11 (15.1%)	1 (8.3%)	0.550
Apnea	12 (14.1%)	8 (11.0%)	4 (33.3%)	0.120
Physical examination	39 (42.9%)	27 (69.2%)	12 (30.1%)	< 0.001
Dysmorphic features	13 (33.3%)	12 (44.4%)	1 (8.3%)	0.092
Inexpressive face	10 (25.6%)	6 (22.2%)	4 (33.3%)	0.021
Weak cry	14 (35.9%)	7 (25.9%)	7 (58.3%)	< 0.001
Absent or decreased tendon reflexes	12 (30.8%)	3 (11.1%)	9 (75.0%)	< 0.001
Arthrogryposis	7 (17.9%)	1 (3.7%)	6 (50.0%)	< 0.001

Table III. Summary of the established final diagnosis grouped by hypotonia type (*n* = 64).

Central hypotonia (*n* = 52; 81.3%)	Hipoxic encephalopathy	14 (26.9%)
	Toxics/medication	10 (19.2%)
	Endocrine/metabolic disease	8 (15.4%)
	Infection	7 (13.5%)
	Hydroelectrolytic disturb	6 (11.5%)
	Genetic/chromosomal disease	4 (7.7%)
	Cerebral haemorrhage	3 (5.8%)
Peripheral hypotonia (*n* = 12; 18.7%)	Muscular dystrophy	7 (58.3%)
	Anterior horn cells disease	3 (25.0%)
	Neuromuscular disease	2 (16.7%)

ries: supraspinal or suprasegmental structures and motor unit or segmental structures [8]. The conditions that affect the brain and brainstem, either diffusely or focally are called supraspinal conditions, although the term 'central hypotonia' is frequently used when the cause of the hypotonia is thought to be secondary to a CNS condition [8]. Peripheral hypotonia term is used when the involvement of the peripheral nervous system is suspected, specifically the motor unit which includes the anterior horn motor neurons of the spinal cord [8]. The association of hypotonia to central or peripheral causes is the priority when evaluating a floppy infant, which helps determine hypotonia's etiology [3,6].

Even though the list of differential diagnoses for neonatal hypotonia is extensive [2,3], most of these neonates have distinctive features in their familial, prenatal and perinatal histories, and physical examination. These can help differentiate into central and peripheral disorders, and sometimes can lead to specific diagnoses within these groups [1].

It is important to investigate the pregnancy and delivery history, noting any complications such as polyhydramnios, intrauterine growth restriction, breech presentation, threat of premature labor, abnormal prenatal movements and caesarian section; and neonatal ones (need for assisted ventilation, presence of neonatal asphyxia, hypoglycaemia, hyperbilirubinaemia, heart disease) [7]. In our study, although we did not have a control group, we were able to associate the presence of these prenatal abnormalities with PH disorders. Another study demonstrated that reduced fetal movements and polyhydramnios had a very high specificity (0.88 and 0.75, respectively) and a lower sensitivity [9]. More than a half of the newborns were delivered by caesarean-section and had required resuscitation at birth. The peripheral group required resuscitation at birth more often (91.7%), which reflects their profound weakness.

The published reviews describe that clinically the neonates with central causes of hypotonia appear lethargic, do not track visually, and may present a depressed level of consciousness, axial weakness, normal strength, and hyperactive or normal reflexes. These newborns who have cortical brain dysfunction may also have early seizures, abnormal eye movements, apnea or exaggerated irregular breathing patterns. Other clues to central hypotonia are dysmorphic features, fisting hands, scissoring on vertical suspension and malformations of other organs [2]. On the other hand, if a hypotonic neonate is alert or responds appropriately to surroundings and shows normal sleep-wake patterns, probably the hypotonia is secondary to peripheral nervous system's disease. These disorders are associated with profound weakness, hyporeflexia or areflexia in association to hypotonia [2]. Neonates with PH can also have muscle atrophy, respiratory and feeding problems and impairments on ocular or facial movement [2].

In our cohort most of the neonates presented other symptoms in addition to hypotonia – respiratory distress, feeding difficulties, seizures, abnormal consciousness, weakness with decreased spontaneous movements and apnea. Among these, weakness with decreased spontaneous movements was significantly associated with PH and should draw attention to an underlying peripheral disorder. Vasta et al [9] showed that absent or markedly reduced antigravity movements was the symptom with the highest sensitivity and specificity for neuromuscular disorders (0.97 and 0.75, respectively). According to what had been previously reported, we were able to demonstrate in our cohort that the presence of inexpressive face, weak cry, arthrogryposis and decreased deep tendon reflexes in the physical examination of these floppy neonates were clues for PH.

Concerning to the clinical presentation, the majority of the neonates started the hypotonia in their first 12 h of life but no statistically significance was found in relation to the type of hypotonia. In agreement with what is described in the literature [2], we demonstrate in our cohort that static evolution was more frequent in CH neonates.

The percentage of final diagnosis achieved (70.3%) in our study was similar to other studies (from 67% to 85%) [2,7,9-11]. The CH was substantially more frequent in neonates admitted in our NICU with a

ratio higher than 4:1 (CH: 81.3%; PH: 8.7%). This result is very similar to Paro-Panjan and and Neubauer [12] and accordant to other published records that CH accounts for 60%-80% of the cases, whereas PH is the cause in about 15% to 30% [2,4,7,9-11, 13]. The most common central cause of hypotonia in our cohort was hypoxic encephalopathy (26,9%), like the most published literature which reports a representation of one quarter to one third of all cases [10,12,14]. Although some studies have mentioned genetic and chromosomal disorders as the main cause of CH [2,12,13], in our cohort this percentage was lower than these reports, what we believe had been due to the some cases that remained without a final diagnosis. Among the PH group, the muscular dystrophies represented more than a half of the cases (58.3%), all of them were congenital myotonic dystrophy. Myopathies and neuromuscular disorders were markedly less present in our cohort but these data are comparable to other studies [9, 10,14]. Despite congenital myopathies might not be infrequent during the neonatal period [4,15], this is a complex diagnosis requiring specific genetic testing which many of them are only available recently. [15]. Presumably this is the reason for a lack of these diseases in our 22-year study.

Based on some research evidence, at least 50% of patients who have hypotonia are diagnosed by history and physical examination alone [4,11,12]. Despite several reviews emphasize this role, only few studies have been able to demonstrate it [4,11,12,14]. In our study the authors could recognized 62.6% of the neonatal hypotonia cases only based on the semiological evaluation of the newborn. The positive predictive value of the initial classification was almost 100% in the CH and higher than in the PH group (97.9% vs 66.7%). These results are accordant to reported by Laugel et al [11] and demonstrate the importance and accuracy of the clinical history and physical examination in the diagnosis and orientation of these neonates. Richer et al [14] and later Paro-Panjan and Neubauer [12] proposed a stepwise approach to evaluate the hypotonic newborn based on similar data.

The mortality rate during the NICU stay was 8.8% which was lower than the 30% reported by other studies [4,11]. The diseases with PH were associated with a significantly higher mortality in our sample which was also described by other authors [14] and result from complications of these diseases. The presence of severe neuromuscular involvement at birth (with respiratory insufficiency, lack of swallowing, cough, and tendon reflexes) is associated a very poor prognosis [1].

The retrospective design of our study, the inherent type of data collection, missing data, and the lack of a control group were limiting factors of our study. Despite these limitations, we have a relatively large sample size and several conclusions can be drawn based on our results about the diagnostic profile of neonatal hypotonia in a tertiary care centre.

In summary, neonatal hypotonia can be associated to an extensive list of differential diagnoses and the diagnostic process can be complex and challenging. However a proper and systematic approach can help to overcome this limitation. Firstly it's crucial to have the knowledge of the main disorders that can be presented with hypotonia in the neonates admitted at the NICU. Secondly, having in mind the high diagnostic predictive value of the clinical history and the physical examination of the floppy neonate, it's imperative to do a detailed clinical history, a careful neurological evaluation and to know the distinctive features of each hypotonia's type that should guide etiological investigation.

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Hipotonía neonatal: ¿entraña un diagnóstico difícil?

Introducción. La hipotonía constituye un signo habitual de enfermedad en el neonato. Ahora bien, se trata de un signo inespecífico: puede ser la manifestación inicial de una enfermedad neurológica o multisistémica.

Objetivos. Estudiar las principales causas de la hipotonía neonatal y evaluar la exactitud diagnóstica de la anamnesis y la exploración física en el neonato hipotónico.

Pacientes y métodos. Estudio retrospectivo de 22 años con recién nacidos afectados por hipotonía e ingresados en la unidad de cuidados intensivos neonatales. A partir de la anamnesis y de los datos recabados durante la exploración física, se hizo una clasificación inicial en condiciones de enmascaramiento del tipo de hipotonía: central, periférica o indeterminada.

Resultados. El número de pacientes estudiados ascendió a 91. De ellos, 42 (46,2%) presentaban antecedentes de alteraciones prenatales: polihidramnios (28,6%), retraso del crecimiento intrauterino (21,4%) y presentación de nalgas (19%). Cincuenta y tres (58,2%) habían precisado reanimación al nacer. Los principales síntomas asociados consistieron en disnea (65,9%), dificultades de alimentación (36,5%) y escasez de movimientos espontáneos (22,4%). El diagnóstico definitivo se obtuvo en 64 neonatos (70,3%): el 81,3% mostraba hipotonía central, y el 18,7%, hipotonía periférica. El valor predictivo positivo de la clasificación inicial alcanzó el 97,9% en la hipotonía central y el 66,7% en la hipotonía periférica. La tasa de mortalidad fue del 8,8%, y resultó superior en el grupo de hipotonía periférica (58,3% frente a 1,3%).

Conclusiones. La hipotonía neonatal aparece vinculada con una larga lista de trastornos. Una anamnesis minuciosa y una valoración neurológica cuidadosa brindan un alto valor predictivo diagnóstico que debe orientar el estudio etiológico.

Palabras clave. Diagnóstico. Hipotonía. Hipotonía neonatal. Lactante hipotónico. Neonato.