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Diagnostic approach to neonatal hypotonia: retrospective study on 144 neonates

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Abstract The objectives of our study were to determine the actual frequency of the different disorders causing neonatal hypotonia and to assess the reliability of the first physical examination as well as the contribution of the main standard diagnostic tests. One hundred and forty-four infants diagnosed with neonatal hypotonia between January 1st 1999 and June 30th 2005 in our tertiary care facility were retrospectively included in the study. Perinatal history, clinical type of hypotonia, results of standard diagnostic tests, final diagnosis and outcome were abstracted from the original charts. A final diagnosis was reached in 120 cases. Central (cerebral) causes represented 82% of the elucidated cases, mostly hypoxic and hemorrhagic lesions of the brain (34%), chromosomal aberrations and syndromic disorders (26%) and brain malformations (12%). Peripheral (neuromuscular) causes were mainly represented by spinal muscular atrophy (6%) and myotonic dystrophy (4%). Positive predictive value of the initial clinical examination was higher in central type hypotonia. Neuroimaging, karyotype analysis and DNA-based tests were the most helpful diagnostic tools. These recent clinical data can be used to improve our strategy in investigating neonatal hypotonia and a diagnostic algorithm is proposed based on our findings.

Keywords Neonatal hypotonia · Diagnostic algorithm · Central hypotonia · Peripheral hypotonia

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Introduction

Neonatal hypotonia is frequently and easily recognized by the first pediatric examination of the newborn. Finding the real cause of this hypotonia often requires a much more complex diagnostic process, since numerous disorders can underlie this condition. The list of available investigations is also particularly long and is even growing longer with the recent advances in molecular genetics. Accurate diagnosis is essential to guide the interventional approach, and to inform the parents on prognosis and genetic counseling.

Some valuable reviews have been published addressing the clinical evaluation and investigation of neonatal hypotonia, but their authors have mostly considered this diagnostic approach from a theoretical and didactical point of view [4, 11, 13, 16]. Assuming that the knowledge of the actual diagnostic profile of neonatal hypotonia will help to improve our diagnostic strategy, our primary objective was to determine in a large retrospective study the relative frequency of the different disorders that can possibly cause neonatal hypotonia. Our secondary objectives were to evaluate the relevance in everyday practice of the classical distinction between central and peripheral hypotonia, and to

assess the diagnostic value of the first clinical examination and the contribution of standard diagnostic tests. The diagnostic approach to neonatal hypotonia is discussed on the basis of our results.

Patients and methods

Patients were identified through a systematic search of two databases: the global database of the Strasbourg-Hautepierre University Hospital and the specific database of the Department of Neonatalogy. Results were cross-checked to ensure the most accurate and exhaustive recruitment of patients. The item hypotonia was used to retrieve all patients referred to our hospital between January 1st 1999 and June 30th 2005 for diagnostic investigation and/or clinical management of neonatal hypotonia, either in conventional or intensive care units. Patients were only eligible for inclusion if hypotonia had been first noticed before the 28th day of life and had lasted for at least two weeks. To allow inclusion in the study, neonatal hypotonia and its consequences also had to be the main reason for referral or to contribute significantly to the clinical picture. Exclusion criteria were gestational age less than 35 weeks (as pathological hypotonia may not be reliably assessed for more premature children) and obvious extra-neurological diagnosis (mainly neonatal infection and congenital heart failure). Relevant data were collected from the original clinical records, using a standard form.

The initial clinical presentation of the hypotonia was classified as apparently central or apparently peripheral, according to the following criteria derived from Dubowitz [7]. Presence of antigravity limb movements, normal or increased peripheral tone, poor visual contact, seizures, brisk tendon reflexes were considered as indicative of apparently central hypotonia, whereas muscular weakness, absence of antigravity movements, decreased reflexes, global hypotonia and preserved social interaction were the hallmarks of apparently peripheral hypotonia. The existence of contradictory items in the same patient prompted classification in a third "undetermined" group. This retrospective classification was performed blindly, without knowledge of the final diagnosis, on the only basis of the initial physical examination made by a senior neonatologist or pediatric neurologist, as stated in the original medical record. Whenever obtained, the final diagnosis was then also classified as either central or peripheral as follows: the central group included all cerebral lesions or malformations, neurometabolic diseases and chromosomal disorders, whereas the peripheral group included all disorders affecting the motor unit, namely anterior horn cell, peripheral nerve, neuromuscular junction and muscle. Among the central group, the diagnosis of hypoxic-ischemic encephalopathy required evidence of clinical encephalopathy, history of perinatal asphyxia as defined by the combination of late decelerations on fetal monitoring, low Apgar score (< 7 at 5 minutes) and acidosis (arterial cord blood pH < 7.1), and absence of other identified causes of neonatal hypotonia. The diagnostic contribution of laboratory tests and imaging techniques used in the investigation of neonatal hypotonia was retrospectively evaluated and characterized as follows: (1) contributive, (2) normal or non-specific, (3) contradictory to the final diagnosis.

Statistical analysis was performed using the chi-square test whenever applicable. Test results were considered significant when P-value was lower than 0.05.

Results

One hundred and forty-four neonates met the inclusion criteria and were included in the study. This cohort represents 4.2% of the 3455 neonates of 35 weeks' gestation or above admitted to our Department during the study period. The characteristics of the study population are detailed in Table 1. Seventy-seven patients were male (53% of the cohort). Mean age at the time of referral was 11.8 days (SD=7.2 days) and 52 patients were less than 3-days old. Seventy-eight patients (54%) were inborn and 66 were referred from another facility. One hundred and one neonates (70%) had swallowing difficulties, justifying either tube feeding and/or parenteral nutrition, and 79 (55%) had respiratory distress symptoms.

On the basis of the first neurological examination reported in each patient's chart, the initial presentation of neonatal hypotonia could be classified as apparently central in 87 cases (60%), according to the clinical criteria detailed above. Forty cases (28%) were classified as apparently peripheral and in 17 cases, the clinical items were contradictory or imprecise. A final diagnosis was reached in 120 cases (83%). Among these elucidated cases, the final cause for neonatal hypotonia was classified as central in 98 cases (82%), peripheral in 22 cases (18%). The mean age at final diagnosis was 1.5 months (range 0–20 months). Among the 87 infants who displayed an apparently central type of hypotonia, the final diagnosis was eventually proved to be central in 75 cases (positive predictive value of the first clinical examination was 86% in this case). When the initial examination indicated an apparently peripheral type of hypotonia (40 cases), the final diagnosis revealed 21 cases of proven peripheral origin (positive predictive value was 52%). Among the 17 undetermined cases for which the first clinical evaluation was inconclusive, 14 cases were finally proved to be of central origin.

Identified disorders fell into five separate clusters. Hypoxic-ischemic and/or hemorrhagic lesions of the brain

Table 1 Characteristics of the patient population

	Total population (n=144)	Central disorders (n=98)	Peripheral disorders (n=22)	Undetermined cases (n=24)
Sex distribution				
Male	77	47	13	17
Female	67	51	9	7
Gestational age (mean), wk	38.1	37.9	38.7	38.5
Birth weight (mean), g	3057	3028.8	3112.1	3129.2
Birth weight (SD), g	420	464	302	345
Prenatal history				
Decreased fetal movements	12	3	6	3
Polyhydramnios	15	5	6	4
Intrauterine growth retardation	11	9	1	1
Mode of delivery				
Vaginal	75	46	13	16
Cesarean section	69	52	9	8
Perinatal asphyxia	77	60	8	9
Respiratory distress	79	56	13	10
Feeding difficulties	101	67	19	15
Deaths	40	22	11	7

constituted the major group in our cohort as these lesions appeared to be the primary cause of neonatal hypotonia in 41 cases (34% of elucidated cases). Chromosomal abnormalities and syndromic disorders (including Prader-Willi syndrome) were found in 31 cases (26%), neuromuscular disorders in 22 cases (18%), central nervous system malformations in 15 cases (13%), metabolic or endocrinal diseases in 11 cases (9%). The detailed diagnoses for each group are listed in Table 2.

Decreased fetal movements and/or polyhydramnios were reported in 19 pregnancies (13% of the cohort) and the presence of one of these signs was predictive of a prenatal cause of neonatal hypotonia in 15 cases ($p<0.05$). Perinatal asphyxia was reported in 77 cases but was finally considered to be the only and direct cause of persistent neonatal hypotonia in only 39 cases. Conversely, 28 of the 79 infants whose hypotonia was finally proven to be of prenatal origin had suffered from perinatal asphyxia (35%).

Outcome data (at least at one year) were available for 137 patients (95%): forty patients (29%) had died at the time of the study, whereas eight patients showed a completely normal outcome. The mean age of death was 5.2 months (range 0.5–60 months) and 22/40 newborns died in the first two months. A peripheral cause was present in 14/40 cases, a central cause in 20/40 and no diagnosis could be identified in the remaining six cases. Initial respiratory distress, prolonged feeding difficulties and neuromuscular causes could be considered as poor prognostic factors, as they were significantly associated with a higher mortality in our cohort ($p<0.05$). All patients with a completely normal outcome had been initially described as mildly hypotonic and had not shown any other specific clinical finding (4/8 were first classified as apparently central, 3/8 as apparently peripheral and 1/8 could not be classified).

The use of the different diagnostic tests and their contribution to the final diagnosis are presented in Table 3. Neuroimaging was performed for 124 patients, using different techniques (sometimes in combination): cranial ultrasound was performed in 118 cases, usually as a first-line investigation, in the first three days of life or immediately after referral; computed tomography (CT-scan) was used in 46 cases, mostly between 3 and 14 days of life; magnetic resonance imaging (MRI) was used in 38 cases, mostly after the first week of life. These neuroimaging techniques altogether contributed to the final diagnosis in 50 cases. This contribution was decisive for the diagnosis of brain malformations (especially MRI) and intracranial hemorrhage (especially CT-scan). Neuroimaging also contributed to confirm the clinically suspected diagnosis of hypoxic-ischemic encephalopathy in 23 cases, mainly through the identification of diffuse cerebral edema on early cranial ultrasounds or CT-scans, areas of reduced density on CT-scans or focal signal abnormalities on MRI. In five other cases, these techniques showed secondary hypoxic-ischemic lesions in neonates with other primary disorders. EEG was performed in 92 patients and contributed to the final diagnosis in 35, mainly in cases of hypoxic and/or hemorrhagic brain lesions and in some rare cases of metabolic disorders or gyration abnormalities.

Table 2 Summary of diagnoses

Diagnosis	Number of cases
Central hypotonia	***98***
Ischemic/hemorrhagic lesions of the brain	41
Hypoxic-ischemic encephalopathy	29
Intracranial hemorrhage	12
Chromosomal abnormalities/syndromic disorders	31
Down syndrome	18
Other chromosomal abnormalities	6
Prader-Willi syndrome	4
Noonan syndrome	1
Other syndromic disorders	2
Brain malformations	15
Agenesis of corpus callosum	5
Dandy-Walker malformation	2
Joubert syndrome	2
Lissencephaly	2
Other malformations	4
Metabolic/endocrinal disorders	11
Respiratory chain defect disorders	4
Peroxisomal disorders	2
Nonketotic hyperglycinemia	2
Methemoglobinemia	1
Hypothyroïdism	2
Peripheral hypotonia	***22***
Motoneuron/nerve disorders	
Spinal muscular atrophy type I	7
Congenital neuropathy	1
Muscle disorders	14
Myotonic dystrophy	5
Congenital muscular dystrophies	2
Congenital myopathies	2
Metabolic myopathies	2
Unspecified myopathies	3
Undetermined	***24***
Total	**144**

DNA-based diagnostic tests were performed in 43 cases and were decisive in 18 cases. Molecular tests for Prader-Willi syndrome, myotonic dystrophy or spinal muscular atrophy were used for 34 patients. In 17 cases, the clinical features were clear enough to ask for only one of the three tests, which then confirmed the diagnosis in 11 cases (spinal muscular atrophy, n=5; myotonic dystrophy, n=5; Prader-Willi syndrome, n=1). In another 17 cases these three tests were performed simultaneously, in the absence of sufficient clinical indication and to avoid any additional diagnostic delay, and still yielded the final diagnosis in 4 cases (Prader-Willi syndrome, n=3). Karyotype analyses were performed in 59 neonates and contributed to the diagnosis in 24 cases: all these 24 neonates had facial dysmorphic features that had been noticed in the first physical examination. Retrospectively, the final diagnosis could have been reached with a combination of neuroimaging, DNA-based tests for Prader-Willi syndrome, spinal muscular atrophy and myotonic dystrophy, and karyotype analyses in 82% of the eventually elucidated cases.

Various metabolic tests were performed in 45 cases (mainly assays for ammonia, lactate, very long chain fatty acids, 7-dehydrocholesterol and isoimmune electrophoresis for transferrin in blood, quantitative analysis of aminoacids in blood and urine, organic acid and acylcarnitine profiles in blood). These tests contributed to the final diagnosis in 9 cases. General metabolic screening always showed normal results in cases with isolated hypotonia. Electrophysiological tests including electromyography (EMG) and nerve conduction studies (NCS) were performed in 23 neonates. These tests contributed to the final diagnosis in 10 cases but also yielded the highest rate of erroneous results (3/23): one case of spinal muscular atrophy mistaken for demyelinating neuropathy, and two false negative results in two muscular disorders (one case of myotonic dystrophy and one case of congenital muscle dystrophy). Muscle biopsy was performed in 14 cases and helped to reach the final diagnosis in 6 cases, but failed to detect any significant changes in one congenital neuropathy and in one mitochondrial disease. Neostigmine test was performed in ten patients but never induced any clinical improvement and no congenital myasthenia has been evidenced in our series.

Discussion

The investigation of neonatal hypotonia is often addressed from a theoretical standpoint. Only few clinical studies

Table 3 Contribution of standard diagnostic tests

Test	Total	Contributive	Normal or non-specific	Misleading or contradictory
Neuroimaging	124	50 (40%)	69 (56%)	5 (4%)
EEG	92	35 (38%)	53 (58%)	4 (4%)
Molecular biology	43	18 (42%)	25 (58%)	0
Karyotype analysis	59	24 (41%)	35 (59%)	0
NCS/EMG	23	10 (43.5%)	10 (43.5%)	3 (13%)
Muscle biopsy	14	6 (43%)	6 (43%)	2 (14%)
Neostigmine test	10	0	10 (100%)	0
Metabolic investigations	45	9 (20%)	36 (80%)	0

have published accurate data on large series of patients, and they partly refer to years before most DNA-based diagnostic tests became routinely available [1, 10, 14, 17]. Several studies are biased by a specific recruitment, for example limited to intensive care units [15], or focus on particular subgroups such as neuromuscular diseases [5, 6, 9, 18, 23], genetic and metabolic disorders [16] or benign congenital hypotonia [3, 19, 21]. The retrospective design of these studies and ours is a significant limitation, but several conclusions can still be drawn from the study of our large cohort which reflects the diagnostic profile of neonatal hypotonia in a tertiary care hospital in the era of modern molecular genetics.

In our study, the percentage of elucidated cases (83%) was similar to the percentage reported by other studies (from 67 to 85%) [1, 6, 23]. Our results confirm the large predominance of central causes of neonatal hypotonia over peripheral causes, in a nearly 5:1 ratio close to the proportion of 80 to 88% of central causes found in two other recent studies [1, 15]. Hypoxic and/or hemorrhagic brain lesions represent one quarter to one third of all cases in almost all published studies and this proportion does not seem to have been significantly modified in over 40 years [1, 14, 15, 17]. The proportion of peripheral causes has only been found significantly higher (34%) in the more severely affected population of intensive care units, in accordance with the poorer prognosis of neuromuscular causes, also demonstrated in our study [17, 23]. Among the peripheral group, spinal muscular atrophy and myotonic dystrophy represent together half of the neuromuscular causes of neonatal hypotonia in our study and others [1, 15, 17]. Neuromuscular junction disorders were remarkably absent from our study and from many others [6, 17, 23], and should probably be more specifically searched for when hypotonia is associated with ptosis, facial diplegia and apneas [11, 16].

Most reviews emphasize the prominent role of physical examination in the evaluation of congenital hypotonia [4, 7, 11, 13, 24], but few studies have attempted to really demonstrate this common statement. Our results indicate that the initial physical examination, based on the clinical profiles defined by Dubowitz [7], could correctly identify the type of hypotonia in eight out of ten eventually elucidated cases. The positive predictive value of the initial examination was higher for the clinically central type of neonatal hypotonia. This may be explained by the fact that the criteria for central hypotonia are positive signs (presence of seizures, presence of brisk tendon reflexes, presence of antigravity movements), which may be easier to identify with certainty than the mainly negative signs of peripheral hypotonia (absence of antigravity movements, absent or decreased deep tendon reflexes). True muscular weakness should be considered as a key element to improve the positive predictive value of the clinical examination for peripheral disorders [23]. Cases of Prader-Willi syndrome have often been misclassified in our study as mentioned by others [22, 24] and it has been recommended to look for this diagnosis by molecular testing before any muscle biopsy [17].

The good diagnostic yield of neuroimaging and EEG is in accordance with the predominance of ischemic-hemorrhagic brain lesions and the reliability of the first clinical examination in the group of apparently central hypotonia. Ischemic-hemorrhagic lesions and perinatal asphyxia should however

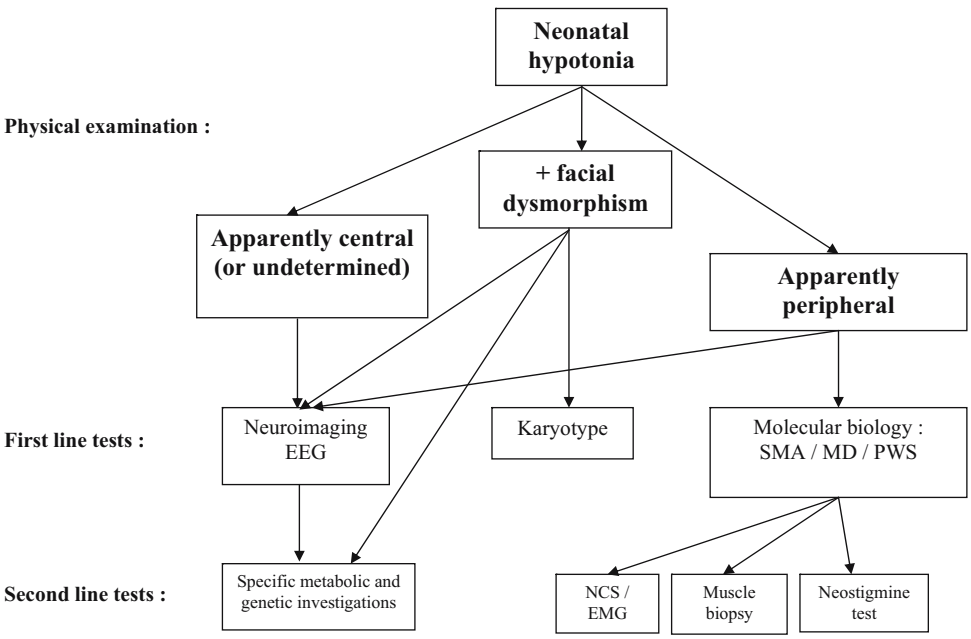

Fig. 1 Proposed diagnostic algorithm. Apparently central hypotonia is well predictive of cerebral disorders and should be investigated by neuroimaging and EEG first. Presence of dysmorphic features should prompt karyotype analysis or other specific metabolic or genetic tests. Apparently peripheral hypotonia should be investigated by DNA-based tests for the most common genetic disorders (SMA, spinal muscular atrophy; MD, myotonic dystrophy; PWS, Prader-Willi syndrome), before any electrophysiological study or muscle biopsy

be considered cautiously, as they may either be the cause or the consequence of neonatal hypotonia [17, 23]. History of polyhydramnios or reduced fetal movements in this case can draw attention to a possibly preexisting peripheral disorder. Within the peripheral group, the concordance between nerve conduction studies, EMG and muscle biopsy is often unsatisfactory in the newborn period, in our study and others [1, 12, 17]. DNA-based diagnostic tests have been successfully used as time- and money-saving shortcuts to reach a specific diagnosis in many cases of apparently peripheral hypotonia [1]. Karyotype analyses have only revealed chromosomal abnormalities in cases when the initial clinical examination had found evidence of dysmorphic features. The diagnostic yield of metabolic screening tests has been disappointing in most studies including ours, in relation with the fact that inborn errors of metabolism rarely present with isolated neonatal hypotonia [1, 17]. These tests should probably be saved for selected indications of "hypotonia plus" when there is evidence of multisystem involvement or acute neurological deterioration [1, 16]. Other specific tests can be useful in the diagnosis of undetermined cases but have not been performed in our cohort (abnormal ratio of urinary pyridinoline crosslinks in Ehlers-Danlos syndrome type VI [20] or elevated serum triiodothyronine levels in Allan-Herndon-Dudley syndrome [8]).

Existing diagnostic algorithms propose either a tree-structured approach based on the distinction between central and peripheral hypotonia [4, 13, 16, 23] or a sequential method considering successively the available tests according to their diagnostic yield [15]. A combination of these two complementary approaches can be proposed based on our findings (Fig. 1). Our results confirm the validity of the clinical distinction between central and peripheral hypotonia, but underline that central disorders are nearly five times more frequent and that the initial physical examination has a higher positive predictive value for central type hypotonia. In the group of central type hypotonia, neuroimaging and EEG should be used as first line tests, unless there is evidence of facial dysmorphism which would directly point to a particular diagnosis. In the group of peripheral type hypotonia, DNA-based tests for spinal muscular atrophy, myotonic dystrophy and Prader-Willi syndrome should be performed as first line tests [1, 2, 12]: there is usually sufficient clinical evidence to select only one of these tests as a priority, and the examination of the mother can be very helpful in diagnosing myotonic dystrophy. Muscle biopsy and NCS/EMG should be performed as second line tests. Neuroimaging should also be considered in the group of apparently peripheral hypotonia when true muscular weakness has not been identified with certainty. For the remaining undetermined cases, a longer follow-up can reveal specific clinical signs and eventually lead to the final diagnosis. These indications based on recent clinical data may provide helpful guidelines to the clinicians faced with the diagnostic challenge of neonatal hypotonia.

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