ELSEVIER

Original Articles

Diagnostic Profile of Neonatal Hypotonia: An 11-Year Study

Lawrence P. Richer, MD*, Michael I. Shevell, MD*†, and Steven P. Miller, MD*

The profile of disorders presenting with neonatal hypotonia to the neonatal intensive care unit has not been studied previously. An 11-year retrospective cohort study of neonates, who were identified through computer database records and were admitted to the Neonatal Intensive Care Unit from January 1989 to December 1999 at the Montreal Children's Hospital (Montreal, Québec), is presented. The final diagnoses, tests obtained, and outcome were determined from a structured review of the subject's hospital record. The database search generated 95 records, of which 50 neonates met the inclusion criteria. The hypotonia was classified as central in 33 patients (66%) and peripheral in 17 (34%). Hypoxic-ischemic encephalopathy (n = 13), Prader-Willi syndrome (n = 6), myotonic dystrophy (n = 6), other muscle disorders (n = 6), chromosomal disorders (n = 4), and peripheral nerve disorders (n = 3) were the most common diagnoses. The genetic tests of highest yield were fluorescent in situ hybridization for Prader-Willi syndrome, DNA methylation studies for Prader-Willi syndrome, trinucleotide repeat testing for myotonic dystrophy, and karyotype analysis. A diagnostic approach is proposed based on the results.

Richer LP, Shevell MI, Miller SP. Diagnostic profile of neonatal hypotonia: an 11-year study. Pediatr Neurol 2001;25:32-37.

Introduction

The list of disorders that may present with neonatal hypotonia is long, and the diagnostic process often is complex. Knowledge of the relative frequency of disorders that present with significant neonatal hypotonia will help in the selection of appropriate investigations. Previous reviews on the differential diagnosis of neonatal hypotonia were performed before the availability of current molecular and genetic tests [1-3]. Furthermore, no studies have looked specifically at neonates admitted to the intensive care unit for the evaluation of hypotonia [4,5].

Our primary objective was to determine the diagnostic profile of neonates with significant hypotonia who were admitted to the neonatal intensive care unit. The utility of certain clinical markers was evaluated as a secondary objective, in addition to the diagnostic yield of electrophysiologic, neuroimaging, biochemical, and genetic testing. The developmental outcome was also reviewed. To address these objectives, neonatal hypotonia patients presenting to the neonatal intensive care unit over the last 11 years were reviewed retrospectively. An approach to neonatal hypotonia is proposed based on our results.

Materials and Methods

The subjects were identified through a database search of hospital discharge records. The diagnostic code for hypotonia was used to search for patients admitted to the neonatal intensive care unit at the Montreal Children's Hospital (Montreal, Québec, Canada) from January 1989 to December 1999 (inclusive 11 years). This Level III neonatal intensive care unit functions as a tertiary referral center for outborn children throughout southwest Québec. Neonates included in the study were referred because they had a predominant problem of hypotonia. Exclusion criteria were as follows: neonates with a non-neurologic primary diagnosis that became evident early in the investigation and management of the infant.

One investigator (L.P.R.), using a structured format, reviewed all the hospital charts of the identified patients. The final diagnosis of each patient was obtained from a review of the entire inpatient and outpatient chart and classified as either central or peripheral. Central disorders were those in which the central nervous system, including the spinal cord, was predominantly affected, and included the following: hypoxic-ischemic encephalopathy; myelodysplasia; chromosomal disorders; neurometabolic disorders; and congenital syndromes, such as Prader-Willi syndrome (PWS). Peripheral disorders were those with a predominant effect

From the Departments of *Neurology/Neurosurgery and †Pediatrics; McGill University; Division of Pediatric Neurology; Montreal Children's Hospital; Montreal, Québec, Canada.

Communications should be addressed to:
Dr. Shevell; Room A-514; Montreal Children's Hospital; 2300 Tupper Street; Montreal, Québec H3H 1P3, Canada.
Received November 13, 2000; accepted March 5, 2001.

PII S0887-8994(01)00277-6 • 0887-8994/01/$—see front matter

on the motor unit, which included the following: anterior horn cell, peripheral nerve, neuromuscular junction, and muscle disorders.

Demographic data and relevant historical information for each patient were obtained. Recorded clinical events were as follows: the presence of an affected family member; consanguinity; intra-uterine growth restriction; decreased prenatal movements; polyhydramnios; fetal heart rate abnormalities; breech presentation; delivery by cesarean section; birth weight; gestation; Apgars at 1 and 5 minutes; meconium staining or thick meconium; respiratory distress requiring resuscitation; intubation and the duration of intubation; the occurrence of neonatal seizures; the duration of hospitalization; and death. Features from the physical examination that were recorded included facial dysmorphism, degree of spontaneous movement observed, and reflexes obtained.

All investigations relevant to the diagnosis were recorded, including Tensilon tests, electrophysiologic studies, neuroimaging studies, muscle and nerve biopsies, and selected laboratory tests. Electrophysiologic tests included electromyography (EMG), nerve conduction studies (NCS), repetitive stimulation studies, electroencephalography, somatosensory-evoked responses, and auditory brainstem responses. The selected laboratory tests included creatine kinase, lactate, pyruvate, ammonia, serum amino acids, urine organic acids, and very long chain fatty acids. All genetic and molecular studies were recorded. Each patient was classified according to the following: (1) *normal*; (2) *diagnostic* if the result was pivotal in the final diagnosis; (3) *contributive* if the result contributed to the final diagnosis by suggesting a pathophysiologic mechanism (e.g., fiber type of grouping on muscle biopsy); or (4) *nonspecific* if abnormalities were noted but did not contribute to the final diagnosis.

The hospital chart was also reviewed for measures of motor development, which included the following: ambulation; formal standardized developmental assessments; and physical examinations by pediatric neurologists, physical therapists, and occupational therapists. Motor outcome was classified as follows: (1) *normal* if the outcome was normal (based on follow-up neurologic evaluation and recorded standardized developmental assessments) or (2) *delay* when delays in meeting major motor milestones were documented but eventually were achieved and developmental progress was documented. Persistent motor deficits were stratified according to the following criteria: (1) *mild* if persistent motor deficits were documented (e.g., mild hemiparesis or spastic diplegia), but ambulation was achieved without aids; (2) *moderate* if persistent motor deficits were documented and ambulation achieved but only with the help of aids; and (3) *severe* if ambulation was not achieved and significant motor impairments persisted without significant developmental progress. When there was insufficient evidence, the motor outcome was classified as *unknown.*

Results

The database search generated 95 records, and of these 50 neonates met the inclusion criteria. The diagnoses of infants that were excluded included diaphragmatic hernia (n = 3), sepsis (n = 8), congenital heart disease (n = 4), other primary pulmonary disorders (n = 12), and no hypotonia objectively documented (n = 18). Neonates with mild or transient hypotonia were included in the central group because mild hypoxia is likely the most common cause of the transient symptoms. The included patients were composed of 21 females and 29 males. Three neonates were between 32 and 33 weeks gestation, seven were 34-35 weeks, and 11 were near term (36-37 weeks). Thirty-nine neonates survived the neonatal period with a mean duration of stay of 49.4 days (S.D. ± 60 days) with a range of 4-270 days. Eleven neonates died in the intensive care unit at a mean age of 67.5 days (S.D. ± 56.5) with a range of 1-167 days. Seven of these 11 children had a peripheral disorder. Three more children died approximately 1, 1.5, and 3 years after discharge, and all three manifested a central disorder. All the patients died from causes related to the underlying disease process.

Table 1. Summary of diagnoses

Primary Diagnosis	Number
Central	
HIE	13
Syndromic disorders	
Prader-Willi syndrome	6
Pena-Shokeir syndrome	1
Kabuki syndrome	1
Syndrome NYD	1
Chromosomal disorders	
4p-syndrome	1
Trisomy 18	1
Trisomy 13	1
4q+ partial duplication	1
Dysmyelinating disorders	
Pelizaeus-Merzbacher disease	1
Myelination disorder	1
Migration disorders	
Lissencephaly	1
Myelodysplasia	1
Transient hypotonia	3
	33
Peripheral motor neuron disorders	
SMA type I	1
Peripheral nerve disorders	
Axonal neuropathy	2
HMSN type III	1
Muscle disorders	
Myotonic dystrophy	6
Centronuclear myopathy	1
Nemaline myopathy	1
Fiber type of disproportion	1
Unspecified myopathy	4
	17
TOTAL	50

Abbreviations
HIE = Hypoxic-ischemic encephalopathy
HMSN = Hereditary motor-sensory neuropathy
NYD = Not yet diagnosed
SMA = Spinal muscular atrophy

Table 1 summarizes the diagnostic findings. The hypotonia was classified as central in 33/50 patients (66%) and peripheral in 17/50 (34%). The mean duration of stay was longer in the peripheral group (73.4 days [S.D. ± 82.1] vs 38 days [S.D. ± 46]), but the range was similar 4-248 days vs 16-270 days, respectively.

Table 2 summarizes the characteristics of the central and peripheral groups. Patients suffering from a peripheral disorder most commonly had an affected sibling or parent, but the observation is biased, with six of nine patients having myotonic dystrophy. No consanguinity was documented. Neonatal seizures often are considered indicative of a central disorder, such as asphyxia, but the proportion with seizures in the central group (18% [6/33]) was similar to that observed in the peripheral group (12% [2/17]).

Table 2. Summary of characteristics in the central and peripheral groups

	Central (n = 33)	Peripheral (n = 17)
Family history		
Affected family member(s)	1	9
Prenatal history		
Decreased fetal movements	5	3
Polyhydramnios	4	5
Intra-uterine growth restriction	4	4
Perinatal history		
Fetal heart rate abnormalities	15	8
Breech presentation	3	2
C-section	13	9
Postnatal history		
Birthweight (gm)	3068 (S.D. ± 792)	2701 (S.D. ± 709)
Apgar between 1 and 3 at 1 min	9	9
Apgar between 1 and 3 at 5 min	1	4
Meconium	6	6
Respiratory distress	18	13
Resuscitation	18	11

Notably, 39% of neonates (13/33) in the central group and 53% (9/17) in the peripheral group required a cesarean-section delivery (44% [22/50] of the entire cohort). The reason for cesarean-section delivery was a breech presentation in five neonates (central = 3; peripheral = 2). Finally, facial dysmorphism was observed frequently in both groups (central = 14/33 [42%] vs peripheral 5/17 [29%]).

However, a positive trend for two clinical markers generally considered in peripheral disorders were decreased or absent: deep tendon reflexes and decreased antigravity limb movement. Decreased antigravity movement was observed in 88% (15/17) of the peripheral group and in 39% (13/33) of the central group. Decreased or absent reflexes were also observed in 88% (15/17) of the peripheral group and in 36% (12/33) of the central group. If the five patients with Prader-Willi syndrome and the one patient with Pelizaeus-Merzbacher disease (in addition to a demyelinating neuropathy) are excluded, only 18% (6/33) of the central group had decreased or absent reflexes. In 22 of 27 neonates with decreased or absent deep tendon reflexes an EMG/NCS was performed and was abnormal in 11/22 or 50% (myopathic or neuropathic). All neonates with an abnormal EMG/NCS were diagnosed with a peripheral disorder. Of the remaining 11 normal studies, the final diagnosis in the majority was myotonic dystrophy (n = 3) or Prader-Willi syndrome (n = 4), whereas the remainder included nemaline myopathy (n = 1), unspecified myopathy (n = 1), Kabuki syndrome (n = 1), and lissencephaly (n = 1).

Neonates in the peripheral group (71% or 12/17) required intubation more often, compared with 33% (11/33) in the central group. The mean duration of intubation was longer (62.7 days vs 7.6 days) in the peripheral group, and all intubated patients in the peripheral group (12/12 or 100%) required assisted ventilation for greater than 5 days compared with only 36% (3/11) of intubated neonates in the central group.

The diagnostic yield of standard diagnostic tests, including Tensilon test, NCS, repetitive stimulation studies, electromyography, electroencephalography, somatosensory-evoked responses, auditory brainstem responses, muscle and nerve biopsy, and neuroimaging (computed to-

Table 3. Summary of results from standard tests

Test	Total	Central (n = 33)	Peripheral (n = 17)	Diagnostic	Contributive	Nonspecific	Normal
Tensilon test	4	1	3	—	—	1	3
Muscle biopsy	16	6	10	3	4	5	4
Nerve biopsy	16	6	10	—	4	2	10
MRI	16	13	3	2	2*	2	10
CT	43	28	15	1 (5)†	14*	3	18
EMG/NCS	34	18	16	N/A	14	—	20
RSS	22	14	8	—	—	—	22
EEG	39	28	11	N/A	15†	—	16
SER	34	25	9	N/A	N/A	20§	14
ABR	35	26	9	N/A	N/A	15¶	20

* CT or MRI, which demonstrated evidence for ischemia.
† Secondary diagnosis: intraventricular hemorrhage (n = 3), hydrocephalus (n = 2).
‡ Burst-suppression (n = 3), epileptiform (n = 4), mild disturbance (n = 8), moderate disturbance (n = 4), severe disturbance (n = 4) of cerebral activity.
§ Bilateral loss of N20 waveform (n = 17), decreased peripheral conduction (n = 3).
¶ Decreased central conduction (n = 4), decreased hearing (n = 11).

Abbreviations:
ABR = Auditory brainstem response
CT = Computed tomography of the head
EEG = Electroencephalography
EMG/NCS = Electromyography and nerve conduction studies
MRI = Magnetic resonance imaging of the head
N/A = Not applicable
RSS = Repetitive stimulation studies
SER = Somatosensory-evoked response

mography [CT] and magnetic resonance imaging [MRI] scans) are summarized in Table 3. A cranial CT scan demonstrated ischemic changes in 5 of 17 patients (28%) with a peripheral disorder. Four of five patients with a peripheral disorder and ischemic changes on CT scan (80%) also demonstrated a clinical pattern consistent with a neonatal encephalopathy.

The concordance between EMG and muscle biopsy abnormalities was high. Thirty-four EMG/NCS were performed, and seven (21%) demonstrated myopathic changes, although six revealed neuropathic changes (demyelinating, n = 3; axonal, n = 3; and brachial plexopathy, n = 1). Two of seven with myopathic changes on EMG had myotonic dystrophy, and a muscle biopsy was not performed. The other five underwent muscle biopsy, and four (80%) had an abnormal result (congenital myopathy, n = 2; nonspecific myopathy, n = 2). The biopsy was diagnostic for a congenital myopathy in three of 16 procedures (19%). Two of three congenital myopathies (66%) had myopathic changes demonstrated on EMG. Similarly, an EMG/NCS in five of six patients with myotonic dystrophy revealed myopathic abnormalities in two (40%).

Specific molecular and genetic diagnostic tests helped determine diagnoses. Analysis for expansion of the CTG trinucleotide repeat on chromosome 19 was ordered in seven neonates and diagnostic for myotonic dystrophy in six. The clinical diagnostic suspicion for myotonic dystrophy was high in all confirmed patients with either an existing maternal diagnosis of myotonic dystrophy or maternal clinical manifestations. Fluorescent in situ hybridization for Prader-Willi syndrome was ordered in nine neonates, and the diagnosis was made based on the test in three. Another three neonates were diagnosed with Prader-Willi syndrome based on the analysis of DNA methylation. Karyotype analyses were performed in 35 neonates, and four patients were diagnosed with a primary chromosomal disorder. All patients with a chromosomal disorder also had facial dysmorphism. Pelizaeus-Merzbacher disease was diagnosed in one neonate based on proteolipid protein gene testing that was suggested by white matter abnormalities observed on the MRI.

Numerous tests (molecular and genetic) were performed, including arylsulfatase A (n = 1), ATPase 6 (n = 1), carnitine (n = 4), cytochrome oxidase (n = 1), Fragile X testing (n = 1), hexosaminidase (n = 1), purines/pyrimidines (n = 2), and succinate cytochrome C reductase (n = 1), but did not contribute to the diagnosis. Similarly, no metabolic screening tests, including lactate (n = 26), mucopolysaccharides (n = 2), ammonia (n = 15), oligosaccharides (n = 2), pyruvate (n = 12), serum or urine amino acids (n = 22), urine organic acids (n = 21), and very long chain fatty acids (n = 13), contributed to the diagnosis in our series.

None of the children in the peripheral group were considered to have a normal outcome, whereas eight in the central group were classified as normal. In the peripheral group the outcome was classified *severe* in two patients, *mild* in four, *delayed* motor development in two, and *unknown* in nine. In the central group the outcome was considered *severe* in eight patients, *moderate* in one, *mild* in two, *delayed* motor development in seven, and *unknown* in seven.

Discussion

The classification of neonatal hypotonia has been approached in many different ways. Central hypotonia includes disorders of the central nervous system that cause decreased tone by interrupting pathways involved in its modulation. Others have referred to this category as *suprasegmental factors* [1] or *supranuclear hypotonia* [6]. Peripheral hypotonia represents disorders of the motor unit-anterior horn cell, peripheral nerve, neuromuscular junction, or muscle. Dubowitz [3] proposed that hypotonia be divided into those with weakness and those without. A third category for metabolic disorders has been suggested [7].

Our results demonstrate that the proportion of central and peripheral causes of neonatal hypotonia has not changed despite technologic improvements in diagnostic tests. The largest series by Eng [8], originally published in 1975, included all infants between 0 and 3 years of age examined for problems in tone—either hypotonic or hypertonic. The cohort included 332 patients; 85% were central and 15% peripheral using the classification scheme described herein. The predominant diagnosis in the central group was cerebal palsy (88%), whereas the peripheral group was composed of anterior horn cell disorders (51%) and muscle disorders (31%). Jebsen et al. [7] described brain damage in 18 of 31 patients (58%), although the peripheral group included Werdnig-Hoffman disease (n = 4), undefined lower motor neuron disease (n = 4), benign congenital hypotonia (n = 3), polyneuritis (n = 1), and metabolic myopathy (n = 1). These results were published at a time when EMG was just beginning to be used clinically. Paine [2] followed 112 infants with slow motor development and hypotonia, of which 105 had a neurologic diagnosis on follow-up. According to Paine's report, 80% were central in origin, consisting predominantly of cerebral palsy and mental retardation. In the peripheral group (n = 21) a specific diagnosis was made in 38% of patients (Werdnig-Hoffman syndrome [n = 4], muscular dystrophy [n = 3], and a probable congenital myopathy [n = 1]). The remainder (n = 13) formed a group he referred to as *congenital muscular hypotonia.*

The relative frequency of disorders in our cohort may be helpful in the approach to a neonate with hypotonia. Although there is no specific test for hypoxic-ischemic encephalopathy, the disorder diagnosed on the basis of clinical manifestations, birth history, and neuroimaging evidence remains an important cause of neonatal hypotonia. However, it must be emphasized that peripheral disorders may also present with asphyxia—an observation

made in 28% of the patients. Peripheral problems consisted predominantly of muscle disorders and, less frequently, peripheral nerve disorders. Prader-Willi syndrome and chromosomal disorders comprised the remainder of the most common central problems. Myotonic dystrophy is common in Québec [9], and the prevalence of the disorder is reflected in the number observed in this study.

Neuromuscular junction disorders were notably absent. Neonatal botulism may manifest later and thus patients may not be admitted to the neonatal intensive care unit, and no mothers in our group had myasthenia gravis. However, it may also be speculated that the screening was inadequate, and the group of four with nonspecific myopathies may have a congenital myasthenic syndrome. Anterior horn cell disorders were also underrepresented in this cohort of patients. Children with spinal muscular atrophy have been treated at the Montreal Children's Hospital during the time period of this study, but they presented later and were not admitted to the neonatal intensive care unit.

A stepwise approach to the evaluation of a neonate with hypotonia can be suggested based on our findings. A detailed history of the prenatal, natal, and postnatal course is essential. Although neonatal seizures, clinical or neuroimaging evidence for hypoxia-ischemia, and a neonatal encephalopathy are suggestive of a central disorder, the results demonstrate that peripheral disorders may also present this way. However, diminished reflexes and decreased antigravity limb movements are suggestive of a peripheral disorder, an observation that others have described [10]. Notably, intubation for longer than 5 days was observed in 100% of the peripheral group and only 36% of the central group. This clinical observation may serve as another indicator of an underlying peripheral disorder associated with weakness.

Electrophysiologic studies are recommended next if a peripheral disorder is clinically suspected [11]. Despite the availability of molecular testing for many neuromuscular disorders, EMG/NCS continues to play an important role in the acute setting of the intensive care unit to expedite the generation of a differential diagnosis. The one exception may be myotonic dystrophy. All patients with this autosomal-dominant disorder had an affected mother, and the disorder was readily diagnosed clinically. Specific testing for the expanded CTG trinucleotide repeat sequence on chromosome 19q13.2-q13.3 was used only to confirm the diagnosis.

Although not observed in our cohort, congenital myasthenic syndromes, botulism, and transient autoimmune myasthenia may also present with hypotonia associated with ocular, bulbar, or respiratory muscle weakness in the neonatal period [12]. These disorders of the neuromuscular junction require specialized repetitive nerve conduction studies and the intravenous edrophonium test to support the diagnosis and should be performed in the appropriate clinical setting [12]. Stimulated single-fiber EMG is a sensitive alternative test for neuromuscular junction disorders that can be performed on uncooperative patients [13].

Areflexia, decreased limb movements, and the demonstration of denervation on EMG should prompt investigation for anterior horn cell disorders. Homozygous deletion of exon 7 in the telomeric survival motor neuron gene is found in approximately 95% of type I SMA patients [14,15] and is commercially available. Decreased conduction velocities on NCS would suggest a demyelinating neuropathy. Charcot-Marie-Tooth (CMT) type 3 (also named Dejerine-Sottas disease), congenital hypomyelinating neuropathy (CMT 4E), and possibly other subtypes of CMT 4 are known to present in the neonatal period with prominent peripheral demyelination, but molecular testing for these disorders is presently available on a research basis only. Guillain-Barré syndrome presenting in the neonatal period has been reported rarely [16,17]. The demonstration of cerebral myelin abnormalities and peripheral demyelination would suggest Pelizaeus-Merzbacher disease with a mutation in the proteolipid protein [18], the recently described SOX10 mutation [19], or other known leukodystrophies, such as Krabbe's disease. Mutation analysis is available commercially for Pelizaeus-Merzbacher disease, and mutations in the proteolipid protein gene are identified in 65-95% of patients [20].

Failure to identify electrophysiologic abnormalities in a neonate with profound hypotonia should next prompt testing for Prader-Willi syndrome. A DNA methylation study for Prader-Willi syndrome detects 99% of patients, including deletion of the Prader-Willi syndrome region, uniparental disomy of chromosome 15, or an imprinting defect [21]. Our results support the use of the DNA methylation study as the primary screening test because only 50% were identified with the fluorescent in situ hybridization study alone. A karyotype for other chromosomal disturbances is also warranted in this clinical setting and is of reasonable yield.

Biopsy of muscle and nerve often is regarded as the next most important diagnostic procedure especially when EMG abnormalities suggest a myopathy [22]. Unfortunately the concordance between findings on EMG and muscle biopsy is variable and ranges between 40 and 76% (reviewed in [11]). Most congenital myopathies present with a normal serum CK and EMG/NCS [23], which is in agreement with our observations. Performing a muscle biopsy is recommended in neonates with weakness without electrophysiologic evidence of an anterior horn cell, nerve, or neuromuscular junction disorder even if the needle EMG examination is normal. It is reasonable to await the results of studies for Prader-Willi syndrome before pursuing a biopsy when the EMG/NCS is normal.

Finally, neuroimaging tests, including CT scan or MRI of the brain, are important to determine whether there is evidence for a cerebral lesion contributing to the presentation. Abnormalities, such as a leukodystrophy, may suggest a diagnosis especially when combined with peripheral nerve demyelination. Moreover, we have ob-

served that hypoxic ischemic encephalopathy remains a frequent cause of neonatal hypotonia without other overt manifestations. Further evaluation with metabolic screening tests, although of low yield, should be pursued if the former tests have not suggested a diagnosis. Appropriate screening procedures should include very long chain fatty acids to screen for peroxisomal disorders even if the presentation is atypical [24].

In summary, the diagnostic profile of neonates presenting with hypotonia to the neonatal intensive care unit is diverse, and careful clinical observation is vital to the proper evaluation of these critically ill children. The more common disorders include hypoxic ischemic encephalopathy, Prader-Willi syndrome, chromosomal disorders, peripheral nerve disorders, and congenital myotonic dystrophy. An approach to diagnosis has been proposed based on 11 years of experience. The selective use of specific molecular and genetic tests based on the clinical evaluation, as well as the relative frequency of disorders presenting with neonatal hypotonia, is likely to be more time and cost efficient.

References

[1] **Brooke** MH, Carroll JE, Ringel SP. Congenital hypotonia revisited. Muscle Nerve 1979;2:84-100.

[2] **Paine** RS. The future of the "floppy infant": A follow-up study of 133 patients. Dev Med Child Neurol 1963;5:115-24.

[3] **Dubowitz** V. The floppy infant. Philadelphia: J.B. Lippincott Company, 1980.

[4] **Stiefel** L. Hypotonia in infants. Pediatr Rev 1996;17:104-5.

[5] **Vannucci** RC. Differential diagnosis of diseases producing hypotonia. Pediatr Ann 1989;18:404-10.

[6] **Gay** CT, Bodensteiner JB. The floppy infant: Recent advances in the understanding of disorders affecting the neuromuscular junction. Neurol Clin 1990;8:715-25.

[7] **Jebsen** RH, Johnson EW, Knobloch H, Grant DK. Differential diagnosis of neonatal hypotonia. Am J Dis Child 1961;101:34-43.

[8] **Eng** GD. Neuromuscular disease. In: Avery GB, Fletcher MA, Macdonald MG, eds. Neonatology: Pathophysiology and management, 4th ed. Philadelphia: J.B. Lippincott Company, 1994:1174-6.

[9] **Mathieu** J, De Braekeleer M, Prevost C. Genealogical reconstruction of myotonic dystrophy in the Saguenay-Lac-Saint-Jean area (Quebec, Canada). Neurology 1990;40:839-42.

[10] **Dubowitz** V. The floppy infant syndrome. In: Dubowitz V, ed. Muscle disorders in childhood, 2nd ed. London: Saunders, 1995:457-72.

[11] **Jones** HR Jr. Electromyographic evaluation of the floppy infant. In: Jones HR, Bolton CF, Harper CM, eds. Pediatric clinical electromyography. Philadelphia: Lippincott-Raven Publishers, 1996:37-104.

[12] **Engel** AG, Ohno K, Sine SM. Congenital myasthenic syndromes. In: Engel, AG, ed. Myasthenia gravis and myasthenic disorders. New York: Oxford University Press, 1999:251-97.

[13] **Stälberg** E, Trontelj JV. Recording procedures with different types of activation. In: Stälberg E, Trontelj JV, eds.. Single-fiber electromyography: studies in healthy and diseased muscle, 2nd ed. New York: Raven Press, 1994:29-40.

[14] **Parsons** DW, McAndrew PE, Monani UR, Mendell JR, Burghes AH, Prior TW. An 11 base pair duplication in exon 6 of the SMN gene produces a type I spinal muscular atrophy (SMA) phenotype: Further evidence for SMN as the primary SMA-determining gene. Hum Mol Genet 1996;5:1727-32.

[15] **Simard** LR, Rochette C, Semionov A, Morgan K, Vanasse M. SMN(T) and NAIP mutations in Canadian families with spinal muscular atrophy (SMA): Genotype/phenotype correlations with disease severity. Am J Med Genet 1997;72:51-8.

[16] **Buchwald** B, de Baets M, Luijckx GJ, Toyka KV. Neonatal Guillain-Barré syndrome: Blocking antibodies transmitted from mother to child. Neurology 1999;53:1246-53.

[17] **al-Qudah** AA, Shahar E, Logan WJ, Murphy EG. Neonatal Guillain-Barré syndrome. Pediatr Neurol 1988;4:255-6.

[18] **Garbern** JY, Cambi F, Lewis R, et al. Peripheral neuropathy caused by proteolipid protein gene mutations. Ann NY Acad Sci 1999;883:351-65.

[19] **Inoue** K, Tanabe Y, Lupski JR. Myelin deficiencies in both the central and the peripheral nervous systems associated with a SOX10 mutation. Ann Neurol 1999;46:313-8.

[20] **Garbern,** James. Pelizaeus-Merzbacher disease/spastic paraplegia 2. In: GeneClinics: Clinical genetic information resource [online database]. © University of Washington, Seattle, WA. Updated Jun/4/99. Available at http://www.geneclinics.org/profiles/pmd/. Accessed Feb/12/2001.

[21] **Cassidy** SB, Schwartz S. Prader-Willi syndrome. In. GeneClinics: Clinical genetic information resource [online database]. © University of Washington, Seattle, WA. Updated Jun/26/2000. Available at http://www.geneclinics.org/profiles/pws/. Accessed Feb/12/2001.

[22] **Miller** S, Shevell M, Silver K, Kramer M, The Montreal Children's Hospital Neuromuscular Group. The diagnostic yield of the nerve-muscle skin biopsy in paediatric neurology practice. Pediatr Rehabil 1998;2:95-100.

[23] **Fardeau** M, Tomé FMS. Congenital myopathies. In: Engel A, Franzini-Armstrong C, eds. Myology: Basic and clinical, 2nd ed, Vol. 2. New York: McGraw-Hill, 1994:1487-532.

[24] **Baumgartner** MR, Poll-The BT, Verhoeven NM, et al. Clinical approach to inherited peroxisomal disorders: A series of 27 patients. Ann Neurol 1998;44:720-30.