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Review article

The floppy infant: contribution of genetic and metabolic disorders

Asuri N. Prasad[a,*], Chitra Prasad[b]

[a]Section of Pediatric Neurosciences, Department of Pediatrics and Child Health, Faculty of Medicine, University of Manitoba, Manitoba, Canada
[b]Section of Genetics and Metabolism, Department of Pediatrics and Child Health, Faculty of Medicine, University of Manitoba, Manitoba, Canada

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Abstract

The floppy infant syndrome is a well-recognized entity for pediatricians and neonatologists. The condition refers to an infant with generalized hypotonia presenting at birth or in early life. The diagnostic work up in many instances is often complex, and requires multidisciplinary assessment. Advances in genetics and neurosciences have lead to recognition of newer diagnostic entities (several congenital myopathies), and rapid molecular diagnosis is now possible for several conditions such as spinal muscular atrophy (SMA), congenital muscular dystrophies (CMD), several forms of congenital myopathies and congenital myotonic dystrophy. The focus of the present review is to describe the advances in our understanding in the genetic, metabolic basis of neurological disorders, as well as the investigative work up of the floppy infant. An algorithm for the systematic evaluation of infants with hypotonia is suggested for the practicing pediatrician/neonatologist.

Keywords: Floppy infant; Investigation; Diagnosis; Genetics; Metabolic

1. Introduction

The term ‘floppy baby or infant’ is used to denote an infant with poor muscle tone affecting the limbs, trunk and the cranial–facial musculature. The condition is usually evident at birth or is identified during early life as poor muscle tone results in an inability to maintain normal posture during movement and rest. There are numerous etiologies and establishing a specific diagnosis in the individual case can be labor intensive. The rapid expansion in the knowledge of genetic disorders, underlying gene mutations and availability of DNA based diagnostic tests has made non-invasive and rapid diagnosis possible for several disorders (Prader–Willi syndrome (PWS), congenital myotonic dystrophy, spinal muscular atrophy (SMA)). On the other hand, the list of disorders that can be presently considered in the differential diagnosis of the floppy infant grows longer and more complex. The focus of the present review is the process of clinical evaluation and investigation of generalized hypotonia in the neonatal period and infancy. We examine the advances in our understanding of these disorders and propose a systematic approach to the evaluation of the floppy infant.

The concept of central vs. peripheral disorders causing hypotonia is clinically useful. The myotactic reflex is the basis of normal tone in a muscle. Muscle tone is maintained at the peripheral level by the participation of the fusimotor system: pathways involving the muscle spindles that promote muscle contraction in response to stretch and the inverse myotactic reflex involving the golgi tendon organ that provides a braking mechanism to the contraction of muscle. A lesion interrupting the stretch reflexes at any level in the lower motor neuron (LMN) will result in a loss of muscle tone and stretch reflexes i.e. flaccidity [1]. The output of gamma motor neurons to the muscle spindle is influenced by supraspinal influences. These influences are predominantly inhibitory, thus lesions affecting the upper motor neuron result in the reduction of these inhibitory influences, in turn causing an increase in excitatory output of the gamma motor neurons to the muscle spindle [2]. However, in early infancy, contrary to expected increase in muscle tone, the response to an upper motor neuron lesion in the early stages is flaccidity and loss of muscle tone [3]. This pattern of hypotonia is usually associated with preserved or hyperactive reflexes, and later evolves into spasticity. The

* Corresponding author. Pediatrics and Neurology, AE 108, HMH Childrens Hospital, 820-840 Sherbrook St. Winnipeg MB, Canada R3A 1S2. Fax: +1-204-7871922.
E-mail address: aprasad@hsc.mb.ca (A.N. Prasad).

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clinical distinction between an upper motor neuron and LMN lesion provides a rationale for investigations based on the localization of lesion in the pathway of motor control (central vs. peripheral hypotonia).

2. Clinical evaluation of the floppy infant

2.1. Prenatal, neonatal and perinatal assessment

The assessment should include a detailed pedigree and documentation of prenatal risk factors: a history of drug or teratogen exposure, breech presentation, reduced fetal movements and presence of polyhydramnios, maternal diseases (diabetes, epilepsy). The importance of parental age, consanguinity, a family history of neuromuscular disease and the identification of other affected siblings cannot be overemphasized. Details of perinatal birth trauma, birth anoxia, delivery complications, low APGAR scores (lower scores for tone, reflexes and respiratory effort) and onset of the hypotonia should be carefully recorded. A shortened umbilical cord and abnormal fetal presentation reflects poor fetal movement or immobility. Infants requiring ventilator assistance soon after birth to maintain respiration in addition to hypotonia suggest the presence of significant muscle weakness. In a majority of infants, hypotonia is often noticed at or soon after birth. Infants with severe CNS abnormalities develop signs of impairment in level of consciousness, feeding difficulties, seizures, apneas, abnormal posturing, abnormalities of ocular movements and of brain stem reflexes, in addition to hypotonia. The presence of congenital malformations in other organ systems, deformations, craniofacial dysmorphic features can help the geneticist establish a syndromic diagnosis.

2.2. Clinical characteristics of muscle hypotonia and weakness

Most hypotonic infants demonstrate a characteristic posture of full abduction and external rotation of the legs as well as a flaccid extension of the arms (Fig. 1a). When traction is delivered to the arms, there is a prominent head lag (Fig. 1b). The neurological examination directs the clinician in localizing the site of the lesion to the central (upper motor neuron) or peripheral motor unit (LMN). The presence of profound weakness as well as hypotonia suggests a disorder of LMN. Weakness can be easily detected in the presence of a low-pitched cry/progressively weaker cry, readily distinguished from the vigorous cry of a normal infant. There is a paucity of antigravity movements in the weak and hypotonic infant. In addition, infants with neuromuscular disease are visually quite alert in comparison to those with central nervous system involvement where obtundation and depressed level of consciousness is often present. Weakness is uncommon in central hypotonia except in the acute stages. The presence of characteristic patterns of regional weakness may favor certain etiologies (Table 1). In central hypotonia, axial weakness is a significant feature. The relative preservation of muscle power with hypotonia and hyperreflexia favors a central origin to the hypotonia, while the combination of weakness in the antigravity limb muscles and hypo/areflexia together favor a neuromuscular disorder. Such a clear distinction, however, may not always be possible and the features may overlap in conditions where the pathology affects both the CNS and peripheral nerve (Pelizaeus–Merzbacher disease, leukodystrophies) [4].

2.3. Additional clinical clues to differential diagnosis

A systematic examination can provide additional clues to specific etiology. The presence of a typical ‘myopathic’ facies and paucity of facial expression are common in

Table 1
Pattern of weakness and localization in the floppy infant

Anatomical region of hypotonia	Corresponding disorders	Pattern of weakness and involvement
Central nervous system	Chromosomal disorders Inborn errors of metabolism Cerebral dysgenesis Cerebral, spinal cord trauma	Central hypotonia Axial hypotonia more prominent Hyperactive reflexes
Motor neuron	SMA	Generalized weakness, often spares the diaphragm, facial muscles, pelvis and sphincters
Nerve	Peripheral neuropathies	Distal muscle groups involved Weakness with wasting
Neuromuscular junction	Myasthenia syndromes Infantile botulism	Bulbar, oculomotor muscles exhibit greater degree of involvement
Muscle	Congenital myopathies Metabolic myopathies CMD Congenital myotonic dystrophy	Weakness is prominent Proximal musculature Hypoactive reflexes Joint contractures

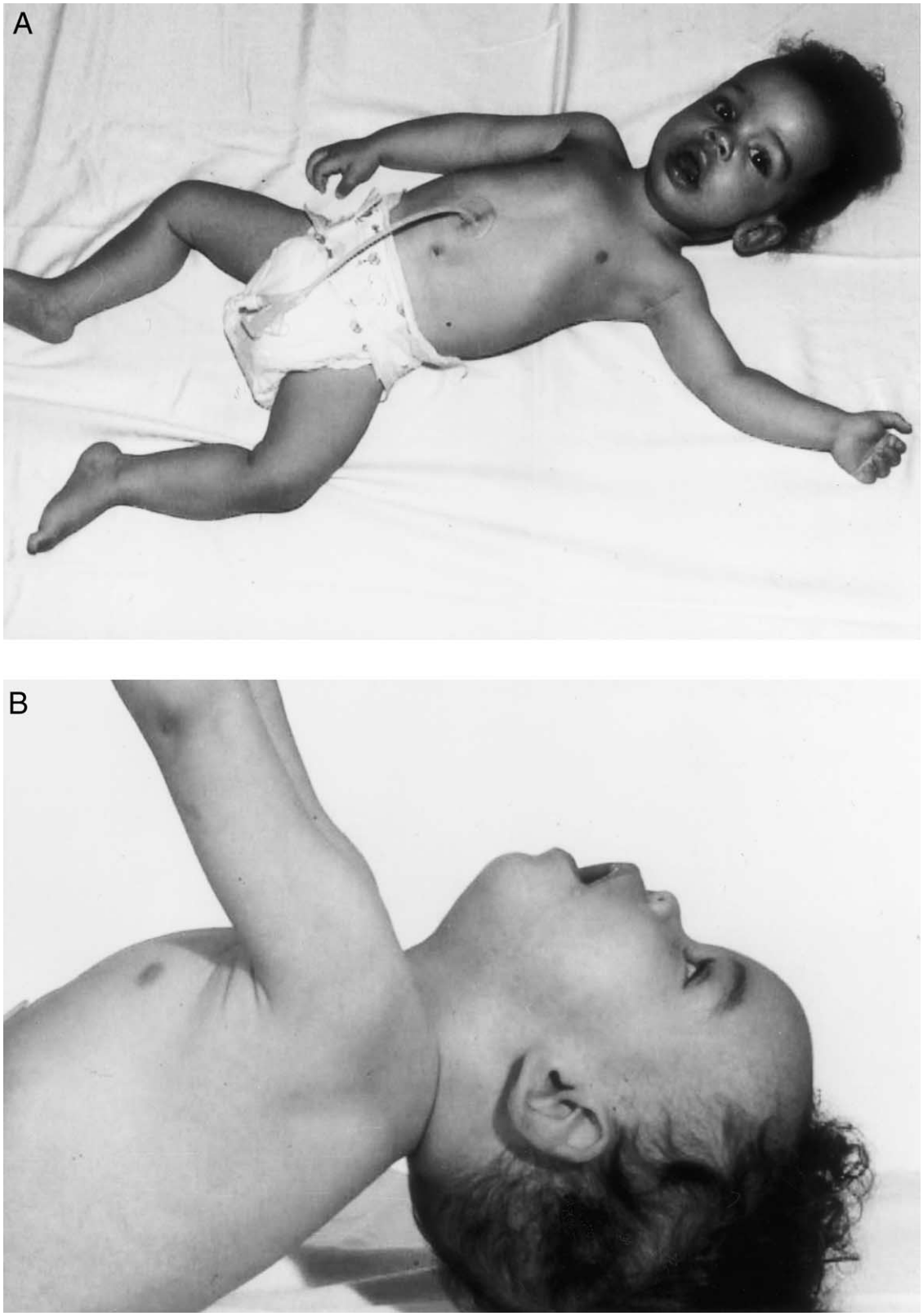

Fig. 1. (a) Typical posture of limbs and trunk of a infant with generalized hypotonia (acid maltase deficiency). (b) Prominent head lag on pull to sit, with a traction force being delivered through the arms.

hypotonic infants. A high arched palate is often noted in infants with neuromuscular disorders, while the tongue may be large in storage disorders (acid maltase/Pompe disease), the presence of tongue fasciculation suggests anterior horn cell involvement and denervation. Examination of eye movements may provide clues to the presence of ptosis, external ophthalmoplegia (myasthenic syndromes), cataracts (peroxisomal disorders), pigmentary retinopathy (peroxisomal disorders), and lens dislocation (sulfite oxidase/molybdenum cofactor deficiency). Other features to look for include findings such as lipodystrophy and inverted nipples (congenital disorders of glycosylation).

The examination of the limbs and joints may show the presence of arthrogryposis. Arthrogryposis refers to the fixed position and limitation of joint mobility affecting both proximal and distal joints. The main feature shared by these disorders appears to be the presence of severe weakness in early fetal development, which immobilizes joints, resulting in contractures. This can be a feature encountered in both neurogenic and myopathic disorders. Neurogenic disorders are associated with a higher incidence of other congenital anomalies, while the infants with myopathic features are less likely to be associated with other defects [5,6]. Visceral enlargement (hepatomegaly + splenomegaly), which suggests storage disorders, the presence of renal cysts (peroxisomal disorders) are additional abnormalities to look for in the hypotonic infant [7–9 (158 pp.), 10–14].

3. Laboratory investigations

The disorders leading to the floppy infant syndrome will be considered under two categories for the purpose of our discussion: to the first group belong infants with pure hypotonia of central or peripheral origin, while the second group includes infants with hypotonia and multisystem features (hypotonia plus). Appropriate and cost effective use of laboratory investigations to establish a specific etiologic diagnosis is always desirable. The history and physical assessment will provide clear indications of birth related trauma, perinatal asphyxia, sepsis early in the evaluating process. We suggest a systematic approach based on the tests currently utilized in the evaluation of infants with hypotonia (Fig. 2a), clinical details and relevant diagnostic tests are discussed in conjunction with specific disorders. For infants with central hypotonia, the initial investigations recommended include: karyotype and a neuroimaging study (computed tomography (CT)/magnetic resonance imaging (MRI)).

3.1. Cytogenetic and molecular biological tests

The karyotype will disclose any obvious cytogenetic defects such as chromosomal duplications, deletions and trisomies such as Down syndrome (DS, trisomy 21) at a standard 500 band level. The use of multiple telomeric fluorescent in-situ hybridization (FISH) probes as well as newer techniques of automated fluorescent genotyping will make it easier to pick up microdeletions and disomies [15,16] that cannot be detected by conventional cytogenetics, once these techniques become available for clinical use. Molecular diagnosis provides the advantage of speed and diagnostic specificity without being invasive. DNA based diagnostic tests (using methylation studies, polymerase chain reaction (PCR)/Southern blot assay) establish the diagnosis of PWS, SMA. Direct mutation analysis for survival motor neuron (SMN) deletion and myotonic dystrophy (detection of triplet repeat expansion) should be carried out, the choice of the tests being dictated by the clinical presentation.

3.2. Electrophysiological studies

In the case of hypotonia arising from a lesion in the lower motor unit, invasive tests become necessary. Nerve conduction and electromyogram (EMG) studies are useful in assessment of disorders affecting the lower motor unit. These tests are particularly helpful in making a rapid electrophysiological diagnosis, in localizing the site of involvement in the motor unit, as well as in instances where a genetic analysis has failed to make a specific diagnosis. It must be pointed out that the performance of nerve conduction and EMG in the newborn and young infant is fraught with difficulties in technique and interpretation. Therefore, these tests are only of value in experienced hands. EMG is very accurate in spinomuscular atrophy [17] and is often used as supportive evidence in establishing the diagnosis of SMA. Myopathic findings include low amplitude compound muscle action potentials (CMAPs) and small polyphasic motor unit potentials that are rapidly recruited. Fibrillation potentials are also described with a variety of myopathic disorders, a finding that may lead to diagnostic errors especially if interpreted as a neuropathic sign. It is the duration, amplitude and configuration of the motor unit potential per se that aids the distinction between myopathies and neuropathies [18]. Slow nerve conduction velocity (NCV) and conduction block favor peripheral nerve involvement. Nerve conduction and EMG studies are also useful in the investigation of hereditary motor sensory neuropathies and in distinguishing axonal disorders from demyelinating conditions. Molecular DNA diagnostic testing can then be used to further test for specific demyelinating disorders. Commercial testing is not yet available for most axonal forms of hereditary neuropathies. The EMG can also be useful when the diagnosis of a disorder of the neuromuscular junction is under consideration (botulism, congenital forms of myasthenia gravis). The presence of a decremental response at 2–3 Hz rates of stimulation in at least one muscle (the testing should include at least two distal and two proximal muscles) is very suggestive of defective neuromuscular transmission in congenital myasthenic syndromes. Low amplitude of CMAPs associated

with at least a 25–100% post-tetanic potentiation is very suggestive of botulism. To distinguish between the various forms of myasthenia gravis, advanced studies with microelectrode recordings, patch clamp recordings, along with molecular genetic analysis are required [19,20], and these facilities are available only at few centers.

3.3. Studies of muscle pathology

Muscle biopsy should be considered in the diagnosis of suspected myopathies and muscular dystrophies, even if the electrophysiological studies are normal [4]. Immunohistochemistry techniques that utilize antibodies against muscle proteins are especially helpful in the diagnosis of congenital muscular dystrophies (CMD) and congenital myopathies. Electron microscopy can provide useful information on abnormal organelles, inclusions and storage material.

3.4. Biochemical studies

Muscle enzymes (creatine kinase assay) are rarely helpful in the floppy infant, with the exception of muscle disorders where creatine kinase values are elevated (CMD and in some forms of the congenital myopathies). If the clinical evaluation suggests complex multisystem involvement (hypotonia plus, Fig. 2b.), the work up should also include screening for inborn errors of metabolism. These biochemical defects belong to one of three categories: toxic encephalopathies (accumulation of toxic metabolites), energy deficient encephalopathies (inborn errors affecting energy production or utilization) and disorders affecting the intracellular processing of complex molecules [21]. The laboratory evaluation for metabolic disorders includes: assays for ammonia (urea cycle defects, organic acidemias, fatty acid oxidation disorders) and lactate (disorders of carbohydrate metabolism, mitochondrial disease) in blood and other body fluids (urine and CSF), quantitative analysis of amino acids in blood and urine (aminoacidopathies), organic acid and acylcarnitine profiles in the blood using tandem mass spectrometry (MS–MS) (organic acidemias, fatty acid oxidation defects), assays of very long chain fatty acids (VLCFA) in the plasma (peroxisomal disorders), uric acid (normal in sulfite oxidase deficiency and low in molybdenum co factor deficiency), isoimmune electrophoresis for transferrin (low in disorders of glycosylation) and 7-dehydrocholesterol (elevated in Smith–Lemli–Opitz syndrome (SLOS)). These tests permit the detection of abnormal metabolites that are biochemical markers for known metabolic disorders. Cranial imaging, complimented by biochemical screening tests can often be helpful in pointing towards a specific organelle dysfunction. Consultation with a clinical biochemical geneticist is often very helpful in prioritizing the investigations. The list of neurometabolic disorders causing hypotonia is exhaustive and it is beyond the scope of this review to comprehensively cover every single disorder in all aspects. We, therefore, discuss selected disorders with the key clinical features in aiding a diagnosis, the gene loci (if known), laboratory tests and characteristic abnormalities in specific categories.

3.5. Neuroimaging studies

Cranial CT/MRI studies of the brain are helpful in the identification of structural malformations, neuronal migration defects (e.g. lissencephaly), altered signal characteristics of white matter (e.g. laminin deficiency). Signal abnormalities in the basal ganglia (e.g. mitochondrial cytopathies), as well as the detection of brain stem and cerebellar abnormalities (e.g. Joubert syndrome, pontocerebellar hypoplasia) are findings that may be pathognomonic for specific disorders.

4. Etiological considerations

4.1. Chromosomal disorders

These syndromes are often associated with distinctive craniofacial and physical dysmorphisms that suggest a diagnosis to the clinical geneticist (Table 3). Aneuploidy, microdeletions and subtelomeric cryptic deletions can present with hypotonia as a prominent feature in early life. A karyotype study is essential in the work up of a hypotonic infant, as extensive and expensive investigations are rendered unnecessary, if a cytogenetic abnormality is picked up early in the course of investigations. The most commonly encountered conditions that are easily screened for include: (1) DS with a population frequency of 1 in 600–700 births is one of the most frequently encountered causes of neonatal hypotonia. The aneuploid state (trisomy 21) is easily confirmed by conventional karyotype, and prenatal screening is routinely offered to women at risk. (2) PWS with an incidence of 1 in 25000 births is characterized by the presence of neonatal hypotonia, feeding problems and failure to thrive. Hyperphagia and obesity develop much later [22]. PWS may arise from a paternal deletion (70%), maternal uniparental disomy (~15–20%) or other rare imprinting mutations. DNA methylation of certain loci in the region of 15q11–q13 results in different expression of maternal and paternal alleles in PWS [23]. Methylation analysis using PCR with parent specific PCR primers is currently used as a first line investigation. Methylation patterns permit us to determine the presence of PWS, while FISH and mutation analysis helps to identify the class of mutation.

Subtelomeric deletions (a relatively new category of disorders that account for unexplained mental retardation) are easily detected with in-situ hybridization using chromosomal telomeric probes [24,25]. Together, these subtelomeric deletions account for about 5–7% of unexplained

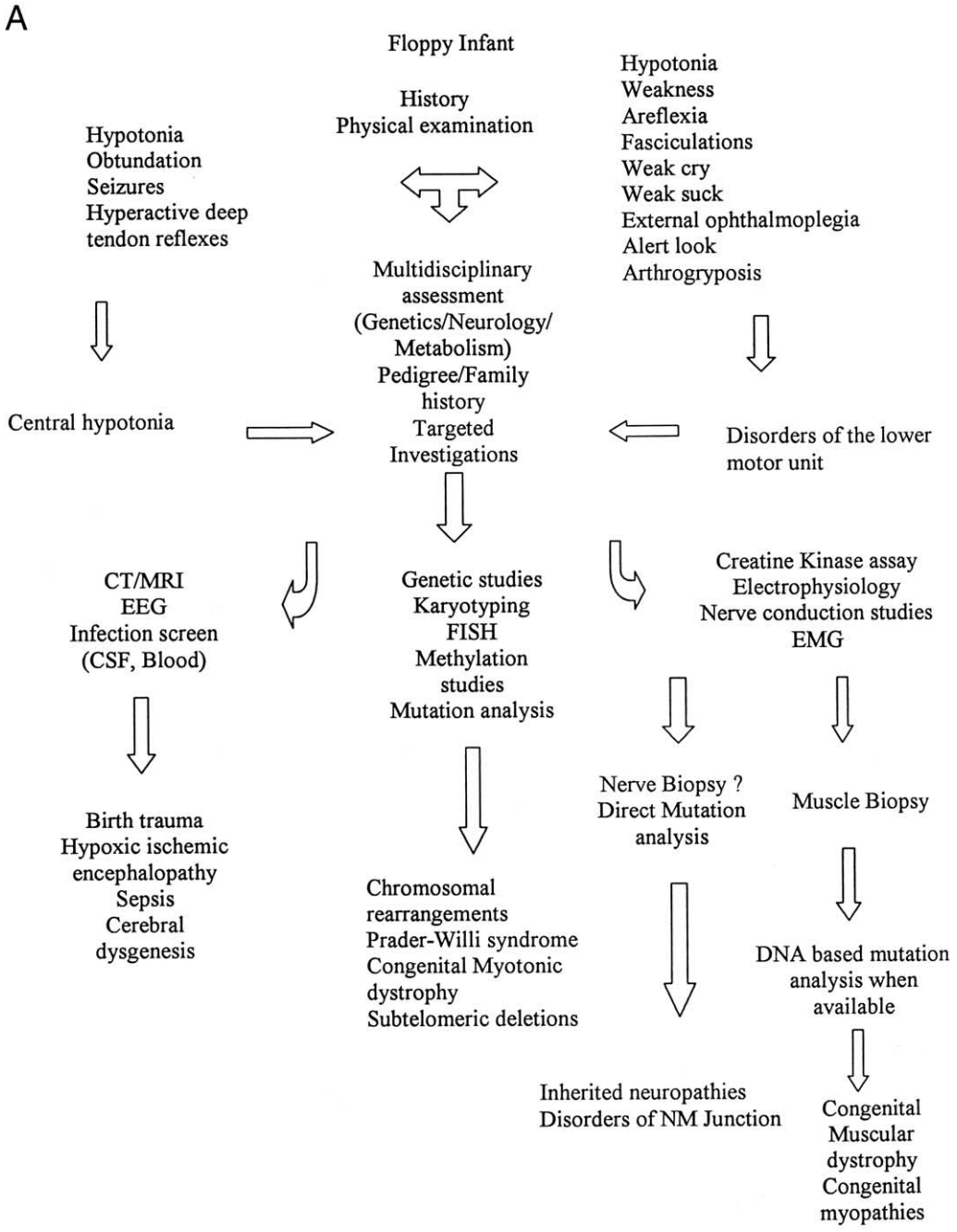

Fig. 2. (a) Initial work up of the floppy infant based on clinical presentation, localization and diagnostic yield. (b) Suggested investigation scheme in the floppy infant with multisystem involvement.

cases of mental retardation, where hypotonia in the neonatal period can be a prominent feature e.g. in the terminal 22q13.3 deletion syndrome [26].

4.2. Structural CNS malformations/encephalopathies

This category includes: congenital malformations of the nervous system (lissencephaly, holoprosencephaly) and acquired disorders (birth trauma, hypoxic ischemic encephalopathy) that are associated with profound hypotonia in the neonatal period. In the majority of instances in this group of disorders, hypotonia is rarely the sole feature at presentation. The presence of other features such as seizures, craniofacial dysmorphisms (e.g. holoprosencephaly, agenesis of the corpus callosum) and the findings on neuroimaging lead the clinician to the diagnosis. In this group of infants, muscle tone may improve or progress to spasticity during follow-up.

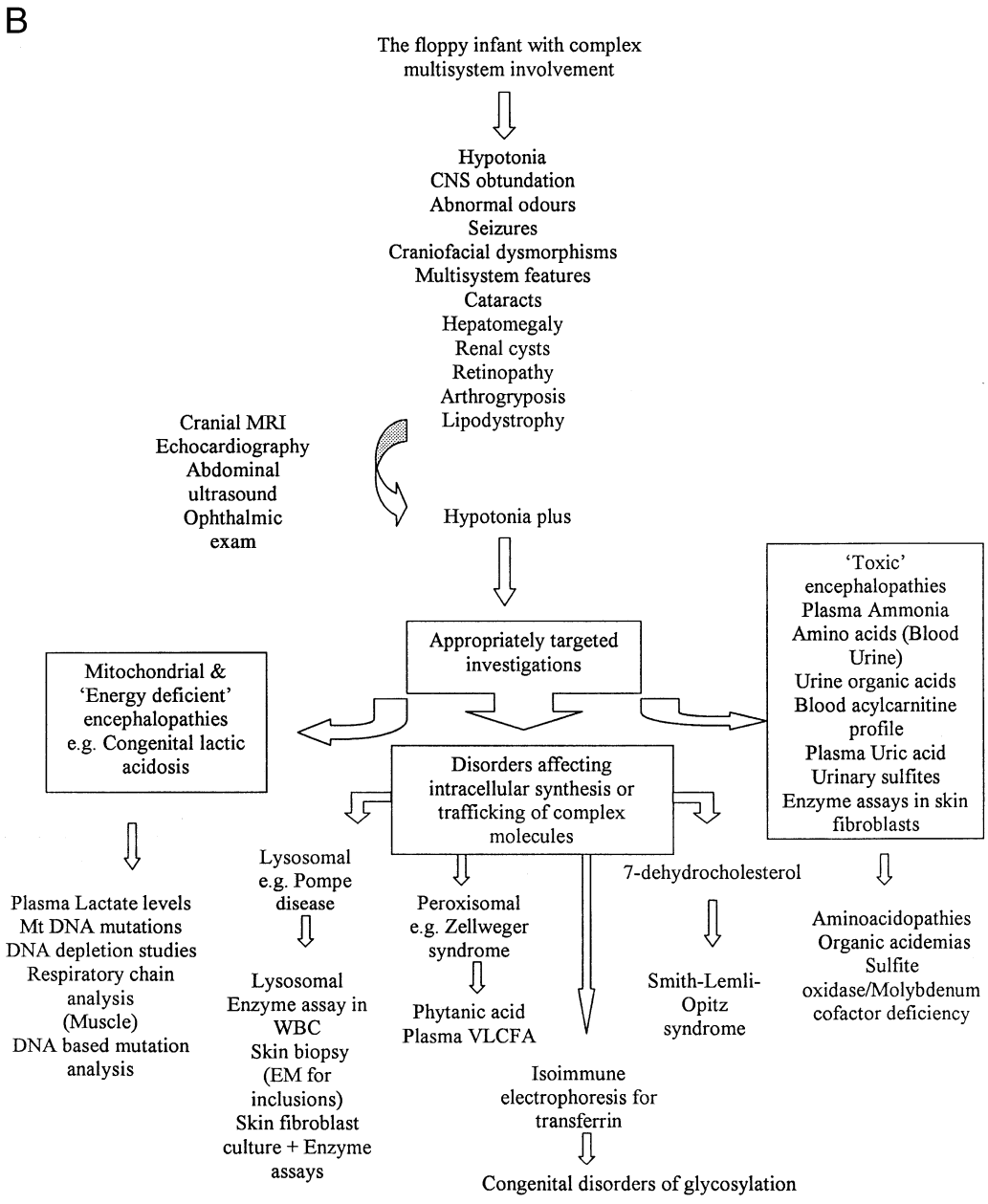

Fig. 2 (*continued*)

5. Motor neuron disorders

5.1. Spinal muscular atrophy (Werdnig–Hoffman disease)

(Table 2) SMA is an autosomal recessive disorder involving the degeneration of the anterior horn cells. Infants with SMA are hypotonic and weak, at birth or soon after. The combination results in poverty of spontaneous movements and an abnormal posture typical for a floppy infant. The presence of tongue fasciculation and absent deep tendon reflexes, mild contractures and decreased fetal movements before birth complete the clinical picture. The weakness usually involves the bulbar and respiratory muscles, causing significant respiratory distress and infants develop pneumonia and respiratory failure [27]. The diagnosis is often clinical, while laboratory investigations are helpful in confirming the diagnosis. EMG usually shows spontaneous fibrillation potentials at rest. The muscle biopsy shows grouped neurogenic atrophy and evidence of presence of hypertrophic type I myofibres (rennervation), though this test has been largely replaced by the DNA based molecular diagnostic tests.

There are two nearly identical genes located on chromosome 5q13, termed SMN^{T} (SMN-telomeric) and SMN^{C}, at the telomeric and centromeric ends, respectively. SMA is caused by a gene deletion affecting the telomeric

Table 2
Chromosomal abnormalities presenting as a floppy infant

Chromosomal Disorder	Genetic defect/gene loci/common mutations	Selected Clinical features	Laboratory/ diagnostic tests
Down syndrome MIM #190685, *605298	Trisomy 21 contiguous gene syndrome	Short stature, characteristic facies (micro-brachycephaly, epicanthal folds, upslanted palpebral fissures, flat nasal bridge) Cardiac anomaly Hypotonia (100%) Mental retardation	Karyotyping FISH
Prader–Willi syndrome MIM #176270, *601491	Deletion of 15q11–13 (70%) Maternal uniparental disomy (UPD) Methylation defect Imprinting mutation	Neonatal hypotonia (profound) Hyporeflexia Feeding difficulty Hypogonadism Almond shaped eyes Characteristic facies	Methylation patterns for SNRPN FISH

SMN gene (SMN^1 or SMN^T). Individuals with milder disease phenotype exhibit a higher number of copies of the SMN^C gene [28]. A rapid DNA diagnostic test is now available to test for the deletions of exon 7 affecting SMN gene [28,29]. Ninety-five percent of affected patients are homozygous for this deletion, about 5% are heterozygotes for the exon 7 mutation and $<1\%$ carry a subtle intragenic mutation in either a heterozygous or a homozygous state [30]. The molecular defects in this disorder may be associated with secondary defects in fatty acid oxidation [31,32].

In addition to the classic 5q linked form of SMA, there exist clinical presentations where the typical electroclinical features of SMA are associated with other phenotypic features suggesting a heterogeneous group of disorders. These include: diaphragmatic involvement [33], arthrogryposis and bone fractures [34], pontocerebellar hypoplasia [35]. Some of the patients with arthrogryposis and a lethal neonatal phenotype have turned out to have the deletion of the SMN gene [36], while others have an X linked disorder with linkage to Xp11.2–11.3 [37,38]. There is also a benign variant of congenital SMA described with a similar phenotype [39].

5.2. Disorders of peripheral nerves

(Table 3) Although acquired conditions such as the Guillain–Barre syndrome (demyelinating and axonal forms) [40,41] and Asian paralysis (motor neuropathy) [42] are reported in the floppy infant, they are distinctly rare. Inherited neuropathies are also uncommon and complex in terms of inheritance and molecular genetics [43], but definitely merit consideration in the discussion of the floppy infant with areflexia. These disorders can be screened for by the nerve conduction studies as NCV are dramatically reduced in comparison to norms. Reduced NCV interferes with proper impulse transmission to the neuromuscular junction, giving rise to hypotonia and weakness. Nerve biopsy reveals thinning or near complete absence of myelin sheaths. Inherited neuropathies that can be considered in the floppy infant include the Dejerine Sottas syndrome (DSS) and congenital hypomyelination (CH) syndrome (CMT4E). The terminology can be confusing as molecular studies have revealed overlapping phenotypes caused by mutations in the same gene, therefore, clinical criteria have been developed to help in the distinction. DSS is characterized by variable patterns of inheritance, very low NCV (<6 m/s), congenital or early childhood, virtual absence of myelin on nerve biopsy [44]. CH is of a greater severity than DSS, with affected infants manifesting severe hypotonia, weakness and respiratory and feeding difficulties. Nerve biopsy findings in CH syndrome are similar to the DSS picture of complete absence of myelin, with onion bulb formation [45].

At a molecular level, there are four gene products whose defects are known to be associated with the spectrum of inherited neuropathies. It is well recognized that phenotypic similarity can be produced through defects at different loci affecting different proteins. Gene dosage and degree of under or over expression of these proteins contribute to the degree of phenotypic variability. The gene products are: peripheral myelin protein (PMP22), myelin protein zero P_0 glycoprotein (MPZ), early growth response 2 (EGR) and connexin 32. Mutations in the genes for P_0, PMP22 and EGR2 can result in the DSS phenotype, while mutations in the P_0 protein and the EGR2 genes are reported with the severe phenotype of CH neuropathy [46,47]. Since the genes underlying these specific proteins are known, several techniques (single stranded conformation polymorphism, heteroduplex analysis and DNA sequencing) are being used to detect disease causing mutations [48,49].

Table 3
Disorders affecting anterior horn cells, peripheral nerves

Neurological/ Neuromuscular disorder	Gene defect/Locus	Selected Clinical features	Laboratory/ Diagnostic tests
Spinomuscular atrophy MIM #253300	5q11–q13 95% are homozygous for a deletion of exon 7 of the SMN^T gene ($\Delta 7SMN^T$) ~5% are compound heterozygotes for the deletion or carry an intragenic mutation of exon 7	Three variants can present in early life (prenatal–6 months) Congenital axonal neuropathy Arthrogryposis multiplex congenital-SMA^2 SMA^1	Direct DNA analysis to detect a homozygous deletion of exon 7 of the SMN^T Dosage test to determine the number of copies of SMN^T carrying the exon 7 Several limitations to interpretation of this test
CMT1A MIM #118220	AD 17p11 PMP22 (homozygotes with four copies) AR forms Point mutations in PMP22	Neonatal hypotonia Severe weakness	Abnormal NCV (slow) Mutation analysis
Dejerine Sottas MIM #145900	AD Mutations in PMP22, P_0 and EGR2 mutations 17p11.2	Neonatal onset Hypotonia Slow progression	Abnormal NCV (very slow) Onion bulb formation in nerve biopsy Elevated CSF protein Mutation analysis
CMT4E (CH neuropathy) MIM #605253	AR 1q22 P_0 protein mutations AD or AR 10q21.1–q22.1 Early growth factor protein (zinc finger protein)	Neonatal onset Hypotonia Arthrogryposis	Abnormal NCV (slow) Absence of myelin Occasional onion bulb Mild to moderate axonal loss Mutation analysis

AD (Autosomal dominant), AR (Autosomal recessive).

5.3. Disorders of the neuromuscular junction

(Table 4) Infants presenting with the myasthenia syndrome share several features including: hypotonia, facial diplegia, ptosis, feeding difficulties, apnea, respiratory difficulties and generalized weakness and a progressively weakening cry [20]. The following disorders affecting the neuromuscular junction can be considered in the differential diagnoses of the floppy infant.

5.4. Transient myasthenic syndrome

The disorder occurs in infants born to mothers with myasthenia gravis. The acetylcholine receptor (AchR) antibody that causes MG crosses the placenta and exerts a blocking effect that is responsible for the interference with neuromuscular transmission. The symptoms caused are temporary and recovers in about 6 weeks [50].

5.5. Hypermagnesemia of the newborn

Elevated magnesium levels can be encountered in the newborn following treatment of maternal eclampsia with magnesium sulfate or following the use of magnesium antacids in the newborn, resulting in an encephalopathic infant with hypotonia, depressed deep tendon reflexes, abdominal distension due to ileus and irregularities of cardiac rhythm [51,52]. Elevated magnesium levels result in impaired neuromuscular transmission.

5.6. Infantile botulism

Infantile botulism usually occurs within 6 weeks to 1 year after birth, usually in situations where the infant has been fed honey contaminated with spores of the *C. botulinum*. The first symptom is usually constipation. Later, listlessness, ptosis, facial weakness, decreased eye movements and feeding difficulties, and progression to respiratory failure occur [12]. If the diagnosis is suspected, a presynaptic block of neuromuscular transmission demonstrated by electrophysiological studies is often the quickest method to diagnosis [12,53]. The presence of small amplitude motor potentials and an incremental response noted to rapid repetitive stimulation is pathognomonic [53]. Stool cultures may also be helpful in confirmation, but the results are usually delayed.

5.7. Congenital myasthenic syndromes

These disorders are only rarely encountered in the

Table 4
Disorders of neuromuscular junction – congenital myasthenic syndromes

Neurological/ Neuromuscular disorder	Genetic/Biochemical defect	Common Clinical features	Laboratory/ Diagnostic tests
Congenital myasthenia with episodic apnea MIM *254210	17p13 10q11.2 mutations affect choline acetyltranseferase (CHAT) gene	Neonatal hypotonia Easy fatigability Recurrent aspiration Feeding difficulty Cyanosis and apnea	EMG repetitive motor nerve stimulation shows repetitive CMAPs linked to a single stimulus Motor point muscle biopsy Staining for AchE and AchR
Slow channel and fast channel syndrome MIM #601462	2q24–q32, 17p12–p11, 17p13 Mutations affect α, β and ε subunits of AchR (CHRN) α and ε subunit mutations also result in fast channel syndrome		Quantitative EM studies of the end plate Micorelectrode recordings Patch clamp recordings Mutation analysis
Endplate cholinesterase deficiency MIM #603034	3p24.2 Mutations affect COLQ gene coding for the collagen tail of endplate acetylcholinesterase		

neonatal period as they often present in later infancy [20]. There have been extensive and rapid developments in our understanding of congenital myasthenic syndromes both at the molecular level as well as in the electrophysiology and kinetics of neuromuscular transmission. Many disease associated mutations have been identified in the AchR subunits [20]. A diagnosis of congenital myasthenia can be considered on the basis of fatigable weakness affecting ocular, bulbar and limb musculature, a family history of affected individuals, an abnormal EMG response and a negative test for AchR antibody.

The presence of stimulus linked repetitive CMAPs with a single motor stimulus suggests a post-synaptic defect in neurotransmission is encountered in endplate AchE deficiency and the slow channel syndromes. In the familial infantile form of myasthenia gravis, an electrodecremental response is often seen only in the weak muscles at 2–3 Hz rates of stimulation [54]. Morphological changes in the post-synaptic membrane can also be demonstrated in the form of smaller endplates in the slow channel syndrome and absence of AchE staining in the endplate AchE deficiency syndromes [55]. A detailed overview of the spectrum of these syndromes, and an algorithm to investigate congenital myasthenic syndromes is covered in a workshop report of the 73rd ENMC International Workshop held in Naarden, The Netherlands [19].

5.8. CMD and congenital myopathies

(Tables 5 and 6) The congenital myopathies and CMD represent a complex and genetically heterogeneous group of disorders. The muscular dystrophies comprise a group of disorders that are characterized by weakness and wasting that is progressive i.e. CMD [56]. The congenital myopathies represent a group of neuromuscular disorders that present in infancy or early childhood, they are non-progressive or slowly progressive with recognizable morphological alterations at the structural level. The muscle pathology in the former show a mixture of changes attributable to muscle degeneration, necrosis, extensive fibrosis and regeneration. Muscle enzyme (CK) levels are significantly elevated in the dystrophies, but are normal or slightly elevated in congenital myopathies. We discuss selected forms of CMD and congenital myopathies that are likely to present in early infancy with significant hypotonia.

5.9. Congenital muscular dystrophies

These disorders as a group are recessively inherited. These disorders appear to be related to gene defects that lead to absence or deficiency of key structural proteins in muscle. Two broad categories are recognized based on the partial or complete primary deficiency of a protein (laminin α2) chain also known as merosin whose absence in the muscle can be demonstrated by immunostaining in affected patients. Laminins provide the backbone for basement membranes. Laminin (merosin) deficiency is seen with the classic form of CMD and the FCMD. The merosin positive group tend to show wide variation in severity, progression and associated features now include conditions such as CMD associated

Table 5
Disorders with prominent muscle involvement (muscular dystrophies and myopathies)

Neurological/ Neuromuscular disorder	Gene Locus/common mutations	Common Clinical features	Laboratory/ Diagnostic tests
Congential Muscular Dystrophies (CMD)		Severe hypotonia in early infancy Multiple joint contractures Variable CNS involvement (neuronal migration defects, white matter changes) Variable severity of ocular involvement Mental retardation variable	Immunohistochemistry for laminin α2 chain deficiency in the muscle biopsy MRI brain may show neuronal migration defects, white matter changes
(Merosin negative) CMD MIM *156225	Laminin α (merosin) deficiency (6q22–23)		
Fukuyama CMD MIM #253800	Fukutin deficiency 9q31		
Muscle Eye Brain disease #253280	1p34–p33 *O*-mannose β-1,2-*N*-acetylglucosaminyltransferase (POMGnT1)		
Walker–Warburg syndrome *236670 Heterogeneous	(9q31) ?2 other loci Mutation in *O*-mannosyltransferase (POMT1)		
Rigid-spine CMD MIM #602771	(1p35–36) SEPN1 (Selenoprotein deficiency)	Prominent neck weakness Rigidity of the spine (late) Scoliosis (late)	
Ullrich scleroatonic dystrophy MIM #254090	AR 21q22.3 (COL6A2) 2q37 (COL6A3) Recessive mutations of collagen VI α subunits	Proximal joint contractures Distal hypermobility Muscle wasting and weakness	
Bethlem Myopathy MIM #158810	AD Locus heterogeneity 21q22.3, 2q.37 Mutations affect Collagen Type VI subunits (α1, α2, α3)	Neonatal hypotonia Torticollis Proximal weakness Contractures of elbow and interphalangeal joints of the last four fingers	Muscle biopsy findings are non-specific Mutation analysis
Congenital Myotonic dystrophy (DM) MIM #160900	Triplet repeat CTG expansion of the DMPK (DM protein kinase) and SIX5 genes at the 19q13 locus Abnormal splicing of chloride channels mRNA leads to the myotonia	Infantile hypotonia Mental retardation Respiratory difficulties	DNA based diagnostic test detects CTG expansion >37 repeats in 100% of affected individuals In congenital DM repeat expansion are usually >750 repeats in size

AD (Autosomal dominant), AR (Autosomal recessive).

Table 6
Congenital myopathies

Neurological/ Neuromuscular disorder	Gene locus/Biochemical defect	Selected Clinical features	Diagnostic features on muscle biopsy
Central Core Myopathy MIM #117000	AD Gene locus 19q13.1 Mutation affects the ryanodine receptor-1 (RYR1)	Neonatal hypotonia Delayed milestones 'Flabby muscle'	Loss of oxidative enzyme activity in the 'central cores' throughout the length of the muscle
Nemaline Myopathy MIM #161800	AD TPM3 (1q22–q23) (tropomyosin-3) AD or AR ACTA1 (2q22, 1q42.1) α-actin AR (2q22) Nebulin AR 19q13.4 Sarcomeric thin filament protein (TNNT1)	Neonatal hypotonia Craniofacial weakness Respiratory and feeding difficulties	Nemaline rods derived from Z disc and thin filament
Myotubular myopathy MIM #310400	X linked disorder Xq28 Mutations affect a dual specificity phosphatase, Myotubularin	Severe neonatal phenotype Hypotonia Weakness of suck and swallow Respiratory failure	Muscle cells with large centrally located nuclei
Multicore myopathy MIM #255320	AD AR Unknown locus	Axial weakness Severe scoliosis Pharyngolaryngeal weakness Arthrogryposis Amyotrophy of hand muscles	Disorganized sarcomeres Mini cores exhibiting lack of oxidative enzyme activity Mini cores do not extend throughout the fibre
Congenital myopathy with fibre type disproportion MIM 255310	AR Likely locus heterogeneity	Severe neonatal phenotype Weakness Hypotonia Joint contractures Respiratory difficulties	

AD (Autosomal dominant), AR (Autosomal recessive).

with a rigid spine [57] and Ullrich's scleroatonic dystrophy [58].

5.10. Classical CMD

Affected infants usually present at birth, because of poor muscle tone, weakness and contractures. The muscle enzyme CK is elevated, the muscle biopsy shows a dystrophic pattern without fatty replacement, abnormal immunostaining patterns for merosin (laminin α2), while the MRI scan of the brain shows white matter signal abnormalities [59]. Mutation of the α2 laminin gene on the 6q22–23 is associated with manifestations of laminin deficiency [60]. The severity of protein deficiency is

reflected in the clinical severity of the muscle weakness and complications. White matter changes on MRI scans are always seen in primary laminin deficiency, irrespective of the degree of the protein deficiency [62]. The disorder needs to be distinguished from other subtypes of CMD [62] and Bethlem myopathy, a slowly progressive myopathy that rarely presents with hypotonia and contractures in the neonate [63].

5.11. Fukuyama muscular dystrophy

Fukuyama muscular dystrophy (FCMD) presents with generalized weakness, hypotonia, joint contractures, decreased deep tendon reflexes, microcephaly, myopia, global delay and seizures [64]. FCMD typically presents at birth, affected infants become progressively weaker through childhood, and are usually rendered non-ambulatory by 10 years of age. The majority die by the second decade. Neuroimaging often reveals various neuronal migration defects: heterotopias, polymicrogyria, diffuse cerebral pachygyria in the cerebrum and cerebellum. In the Fukuyama type of CMD, the laminin deficiency is likely a secondary phenomenon, the primary gene defect responsible for the disease is caused by a retrotransposal insertion of tandemly repeated sequences on chromosome 9q31 locus [65]. The protein named Fukutin may be located in the extracellular matrix and may function by modifying cell surface glycoproteins [66].

5.12. Walker–Warburg syndrome (WWS)

The typical features of this autosomal recessive disorder include generalized weakness, hypotonia, severe neuronal migration defects in the brain and eye abnormalities. Ocular abnormalities are described earlier and are severe [67]. Death typically occurs a few months after birth. Neuroimaging studies are helpful in confirming the presence of type II lissencephaly with or without polymicrogyria, cerebellar hypoplasia, Dandy–Walker malformation and an absent corpus callosum which are malformations well described in association with this syndrome [68a]. A specific gene mutation in the locus coding for the enzyme *O*-mannosyltransferase POMT1 has now been identified in several patients with this disorder [68b].

5.13. Muscle–eye–brain disease

Muscle–eye–brain disease (MEB) was first described by Santavuori, the majority of the patients are of Finnish descent [69]. MEB presents with severe neonatal hypotonia, mental retardation and visual failure. Retinal degeneration, with optic atrophy and a pale retina, delayed and giant flash VEPS are typical. MEB and FCMD show a cobblestone type of nodular cortical defect in migration. The clinical course is less severe in comparison to Walker–Warburg syndrome (WWS). It is argued that MEB disease is genetically a distinct disorder based on linkage studies that have identified a separate locus on 1p32–34 [70]. Defective *O*-mannosylglycosylation may underlie some forms of muscular dystrophy associated with neuronal migration defects. MEB patients have been shown to carry mutations in the gene for the enzyme protein *O*-mannose β-1,2-*N*-acetylglucosaminyltransferase (POMGnT1) [71]. A mouse model carrying a deletion of brain specific dystroglycan manifests with many of the structural and functional CNS anomalies encountered in CMD [72].

5.14. Ullrich CMD

A subgroup of the patients with CMD, present with a peculiar and striking combination of distal joint hypermobility and contractures affecting proximal joints, muscle weakness and wasting since birth was described by Ullrich [58]. The disorder is now considered a subtype of the merosin positive forms of CMD. Homozygous and compound heterozygous mutations affecting gene loci on 21q22 and 2q37 affecting the α2 and α3 chain of collagen VI [73] result in this phenotype. On the other hand, dominant negative or haploinsufficiency of genes encoding the α1, α2 and α3 chains of collagen VI cause the autosomal dominant Bethlem myopathy.

5.15. Bethlem myopathy

This disorder presents with slowly progressive muscle weakness with contractures in early infancy and the neonatal period. The condition is dominantly inherited and has been described in Dutch families [63]. In the neonatal period torticollis and multiple contractures affecting hips, knees, ankles and elbows are noted. Moderate elevation in CK levels is observed while the muscle biopsy reveals nonspecific findings of myopathy; a secondary deficiency of laminin has also been reported. Contractures of the interphalangeal joints are considered very characteristic for the disorder that has a relatively benign course in the infancy and childhood years. The condition tends to be progressive in later life leading to the loss of ambulation and respiratory insufficiency [74]. Mutations affecting the genes coding for collagen type VI subunits (α1, α2 and α3) on chromosome 21q 22.3 and 2q37 underlie this disorder [75–78]. Collagen type VI plays a role in anchoring cells to basement membranes, and may also act as a bridge between cells.

5.16. Rigid spine-muscular dystrophy (RSMD1)

This form of merosin positive CMD presents with a wide variation in phenotype. In early infancy, the presentation is one of hypotonia with prominent neck weakness. With age, there is stabilization of muscle strength, scoliosis and spinal rigidity make their appearance [57,79]. There is genetic heterogeneity in this disorder [80] with one locus mapped to 1p36–p35. Mutations in the gene SEPN1 coding for a

selenoprotein N have been identified in families with this disorder [81]. Selenium appears to have a role in the function of striated muscles, as its deficiency is associated with a form of muscle disease in cattle [82].

5.17. Congenital myotonic dystrophy

Congenital myotonic dystrophy often presents in the neonatal period with hypotonia, global delay, respiratory problems and failure to thrive. Distinctive features seen in the affected infants include: facial weakness, high arched palate, triple furrowed tongue, 'tent mouth', an inability to close their eyes tightly [83] and patulous anus. The affected child usually has an affected mother with myotonic dystrophy, even if she does not manifest with overt symptoms and signs. In approximately 25% of infants with congenital myotonic dystrophy, respiratory problems result in death. Children who do survive, often show improvement in muscle function, but in later life develop myotonic dystrophy and progressive myopathy [84]. The muscle biopsy usually shows small fibres with poor differentiation, suggesting poor maturation of muscle. The diagnosis can now be established by demonstrating triplet repeat expansion on mutation analysis [85]. This disorder demonstrates the phenomenon of anticipation, which is the occurrence of increasing disease severity and an earlier age of onset in successive generations. Triplet expansions are unstable and demonstrate expansion during meiosis, in the case of congenital DM, the expansion occurs in the maternal line [86,87].

Congenital myotonic dystrophy is caused by a mutation in the myotonin or myotonic dystrophy protein kinase (DMPK gene at 19q13.3). The mutation involves a repeat expansion of the triplet CTG nucleotide repeat in the 3′ untranslated region of the myotonin gene [88]. The majority of affected children have repeat expansions in the range of 1000 to >2000 repeats. The gene is thought to cause abnormal transcripts, or may affect the function of neighboring genes such as SIX5/formerlyDMAHP (DM locus associated homeodomain protein) [88,89] resulting in reduced proteins, while abnormal splicing of muscle chloride channel RNA is thought to underlie the myotonia [90].

5.18. Congenital myopathies

(Table 6) The traditional description of congenital myopathies is based on morphological abnormalities, variation in size and number of fibre types and/or the presence of inclusions on electron microscopy. Infants present with a combination of flabby muscles and weakness, hyporeflexia, along with somatic abnormalities such as facial amimia, micrognathia, open bite and a high arched palate. In the absence of other systemic disorders, serum CK evaluations are usually normal: the EMG often shows small amplitude of polyphasic motor potentials. Muscle biopsy along with histochemical and electron microscopic analysis is often most helpful in establishing a diagnosis [91]. Fibre type disproportion, nemaline myopathy, central core disease, multicore, centronuclear and myotubular myopathies are a few of the myopathies distinguishable by the morphological characteristics (Table 2, Table 6) [91]. The demonstration of protein accumulation within inclusions (sarcoplasmic bodies, cytoplasmic bodies, granulofilamentous material) has given rise to the concept of 'surplus protein myopathies'. Mutations in the protein related genes are beginning to be identified. Mutations identified in the desmin and α-crystallin genes have given rise to newer labels to disorders characterized by excess accumulation of specific proteins such as 'desminopathies' [92,93]. The precise mechanisms by which these mutations give rise to formation of protein aggregates are not well understood. The following disorders that have been the subject of an extensive recent review [94] will be touched upon briefly.

5.19. Central core disease

The disorder is characterized by the identification of well-defined cores in type I fibres in infants who are hypotonic since birth. Proximal muscle weakness, skeletal deformities including: hip dislocation, kyphoscolisosis and finger flexion contractures are described. The diagnosis is made on muscle biopsy. Both autosomal dominant, as well as sporadic forms of inheritance are noted [94]. The majority carry mutations in the genes encoding for the ryanodine receptor gene (RYR1) [95], which is responsible for the mediation of Ca release in the process of muscle contraction [96,97]. The condition is closely associated with the susceptibility to malignant hyperthermia [98], which is often triggered by the exposure to volatile anaesthetics and skeletal muscle relaxants.

5.20. Nemaline myopathy

The presence of 'thread like' nemaline rods identifiable on muscle histology gives the disorder its name. There is considerable variability in the phenotype and the severe forms present in the neonatal period with hypotonia, proximal weakness, paucity of facial movement and feeding difficulties [99]. Craniofacial dysmorphic features and cardiac involvement is also reported. There is locus heterogeneity as this disorder is caused by mutations affecting several genes coding for proteins involved in skeletal muscle filaments [100]. Compound heterozygous and homozygous mutations affecting the α tropomyosin (TPM3) gene 1q21 [101], nebulin on 2q21[102], α actin gene on 1q42 [103,104] and skeletal muscle troponin (TNNT1) on 19q13.4 have so far been identified [105]. The mutations cause truncation of the affected protein with loss of function. The TNNT1 mutation is associated with a recessive form of myopathy noted in the Amish. The disorder presents with hypotonia, multiple contractures

affecting proximal joints (hip and shoulders) and the affected infants often die of respiratory failure in the second year of life [105].

5.21. Myotubular (centronuclear) myopathy

Although the disorder is known to occur in autosomal dominant and recessive forms, the X linked form of the disorder is probably the best defined. It is characterized by generalized hypotonia with onset in the perinatal period and a uniformly poor outcome [106]. The gene is localized to the Xq28 locus and mutations have been identified in the MTM1 gene which codes for myotubularin, a protein tyrosine phosphatase [107]. Patients with MTM1 mutations display impairment in the ability of muscle cells to dephosphorylate phosphotidyl inositol 3 phosphate [108]. The appearance of the muscle fibres on pathology typically resembles myotubes with central nuclei. A large number of mutations (more than 133) have been described [109]. Several types of mutations have been described, with the missense mutations affecting the phosphatase site or the SET (Suvar3-9, Enhancer of zeste, trithorax) interacting domain have been associated with a severe phenotype [110].

5.22. Congenital fibre type disproportion

At present, the small size of the type I fibres is not considered to be a characteristic feature of this disorder [111], as similar features have been identified in the time course of many myopathies [112]. The clinical features vary from mild hypotonia in the lower limbs to profoundly affected infants with non-progressive muscle weakness, joint contractures and skeletal deformities [113]. The pure form of this disorder has been linked to mutations in the insulin receptor genes [114]. The prognosis even in severe instances is relatively good [115], therefore, establishing a diagnosis is very important for treatment considerations.

5.23. Congenital hypotonia with a favorable outcome (benign congenital hypotonia)

A discussion of the floppy infant would not be complete without consideration of this controversial entity. When it was first introduced by Walton [116], our understanding of neuromuscular disorders could have been considered as primitive. This designation is no longer considered to be a specific diagnostic entity as many patients carrying this label initially on careful investigation, have been diagnosed with specific neuromuscular disorders with a well-defined structural or biochemical basis in later years [117]. Nevertheless, there remains a group of patients in whom a specific diagnosis cannot be established despite best efforts [118,119]. These patients share in common generalized hypotonia since birth, active movement with preserved tendon reflexes, mild motor retardation or normal development (in some), normal investigations (normal muscle enzymes, EMG and nerve conduction studies and muscle biopsy). This group of infants demonstrate a high familial incidence for this condition. Significant joint laxity or hypermobility is a clinical feature in this group. A favorable outcome is common particularly if the muscle shortening that appears later in some can be prevented by the use of appropriate exercises [119].

5.24. Metabolic disorders

(Table 7) These disorders rarely present with hypotonia as the sole feature. The subject has been covered in excellent reviews and the reader is referred to these for greater details [21,120]. Usually these conditions affect multiple organ systems and are associated with dysmorphic features and multiple malformations. The presentation varies reflecting 'energy deficiency' or toxic states of acute or chronic encephalopathy, hypotonia and seizures, associated with biochemical abnormalities. Selected conditions reflecting different organelle involvement presenting with prominent hypotonia in the neonatal period are listed in Table 7. The clinical features, genetic basis and underlying molecular defects are summarized and appropriate diagnostic tests are listed. Toxic accumulations of metabolites resulting in acute encephalopathies (aminoacidopathies, organic acidemias, congenital lactic acidoses, sulfite oxidase deficiency) and chronic encephalopathies related to disorders of glycogen metabolism (acid maltase deficiency), defects of energy production (mitochondrial encephalopathies), defects in the intracellular synthesis of molecules such as cholesterol (SLOS), defective trafficking of complex molecules in Zellweger syndrome (peroxisomal processing of VLCFA) and disorders of sialotransferrin related glycoprotein metabolism (congenital disorders of glycosylation) should be considered in the differential diagnosis. The key to the recognition of many of these disorders is familiarity with the clinical presentation and a high index of suspicion in the clinical context. Screening tests and targeted assays are likely to be more helpful in establishing a diagnosis. The help of an experienced specialist in metabolic disorders is invaluable.

6. Conclusions

Our understanding of genetic, neurological and metabolic considerations in the floppy infant is reaching a far greater degree of complexity, in comparison to earlier descriptions of this condition [121]. In a majority of disorders, the hypotonia is due to consequences of genetic and/or metabolic deficits at a molecular level. These genetic alterations affect key structural proteins, ion channels, receptors or metabolic pathways within the nervous system, in the nerve, neuromuscular junction and muscle. The mechanisms by which these disorders affect muscle tone are varied and depend upon the underlying gene defect and its

Table 7
Metabolic disorders presenting with severe hypotonia in infancy

Neurological/ Neurometabolic disorder	Gene locus/Biochemical defect	Selected Clinical features	Laboratory/ Diagnostic tests
Acid Maltase deficiency (Pompe) MIM #232300	AR 17q25.2–q25.3	Infantile onset hepatic dysfunction, hepatomegaly, hypoglycemia seizures, hypotonia Respiratory insufficiency Cardiac involvement seen in prominently in Acid Maltase deficiency	Elevated muscle enzymes Hepatic dysfunction Hypoglycemia Muscle biopsy Vacuolar myopathy and excess glycogen storage on EM Abnormalities on specific histochemical staining
Pyruvate dehydrogenase (PDH) complex deficiency MIM *312170	PDH is X linked (Xp22.1–p22.2) E1-α polypeptide1 subunit	Infantile presentations can be fatal with severe metabolic acidosis	Enzyme assay in fibroblast cultures
Pyruvate carboxylase (PC) MIM *266150	AR PC 11q13.4–q13.5	Congenital Lactic acidosis	Enzyme assay in fibroblast cultures
Mitochondrial disorders Respiratory Chain defects	Defects can involve mutations of nuclear DNA or mt. DNA, as well as mitochondrial DNA depletion syndromes	Slowly progressive myopathic presentation also known	Lactate levels in blood CSF Muscle biopsy (presence of ragged red fibres) Mt DNA mutation analysis Activity of respiratory chain complexes assayed in fresh muscle
Zellweger syndrome MIM #214100	AR Genes affect peroxisome biogenesis 2p15, Chr.1, 1q22, 12p13.3, 7q21-q22, 6q23-q24 Absence of peroxisomes and all enzymes	Neonatal hypotonia Facial dysmorphism Ocular abnormalities Pigmentary retinopathy Cataracts Renal cysts Patellar calcifications	Elevated levels of Plasma VLCFA
Smith Lemli–Opitz syndrome MIM #270400	AR Deficiency of 7-dehydrocholesterol reductase	Dysmorphic facies Midline defects Hypotonia 2-3 toe Syndactyly CNS malformation Behavioral phenotype	Assay of 7 dehydrocholesterol Levels in plasma
Congenital disorders of Glycosylation (CDG)	AR Defect in *N*-glyosylation in the Endoplasmic reticulum		Isoelectric focusing of transferrin
CDG Ia MIM #212065	Deficiency of Phosphomannomutase-2(PMM-2)	Failure to thrive Axial hypotonia Psychomotor retardation Seizures Ataxia Stroke like episodes	MRI shows cerebellar hypoplasia in CDG Ia Low levels of LDL-cholesterol and Factor XI Enzyme assay for PMM-2
CDG Ic MIM #603147	Deficiency of dolichyl-P-Glc:Man9GlcNAc2-PP-dolichyl glucosyltransferase	Failure to thrive Axial hypotonia Psychomotor retardation Seizures	Enzyme assay for dolichyl-P-Glc:Man9GlcNAc2-PP-dolichyl glucosyltransferase

AD (Autosomal dominant), AR (Autosomal recessive).

consequences for cell function. In some instances such as the congenital myasthenic syndromes, the dysfunction affects a specific region (pre- or post-synaptic defect of neuromuscular junction), whereas in metabolic disorders, the molecular defect may even carry widespread multi-system consequences e.g. peroxisomal disorders (Zellweger syndrome). The practicing clinician faced with the challenge of making a diagnosis in a floppy infant needs to be

aware of the various etiologies, availability of specific diagnostic tests and the role of supportive investigations in order to facilitate this process in a speedy and cost effective way. A detailed history and physical examination can help sort the issue of isolated hypotonia, from the hypotonic/dysmorphic infant with multisystem manifestations. Acute neurological conditions such as sepsis, hypoxic ischemic encephalopathy are easily excluded. To the experienced clinical geneticist, the constellation of dysmorphic and multisystem features may suggest an identifiable syndrome. A karyotype is a must in the dysmorphic/hypotonic infant and this can be combined with a search for cryptic deletions using in-situ hybridization with specific telomeric probes in selected cases. DNA based tests using methylation studies (PWS), as well as direct mutation analysis are useful in identifying common mutations (congenital myotonic dystrophy). Use of cranial MRI will help pick up the cases with structural CNS malformations, neuronal migration defects. A family pedigree is essential to carry out linkage studies where a specific gene locus is yet unidentified. This process is more labor intensive than direct mutation analysis.

If a disorder of the lower motor unit is suspected, then electrophysiological studies in a laboratory with experience in pediatric neuromuscular disorders are helpful. The findings are helpful in localizing the site of the lesion to the anterior horn cell, nerve or the neuromuscular junction. Identification of anterior horn cell involvement can be followed by a direct mutation analysis for SMA. Eventually, the wider availability of direct mutation analysis may make it easier for more specific diagnoses to be established in the inherited neuropathies and congenital myasthenic syndromes. A muscle biopsy, interpreted by an experienced neuromuscular pathologist utilizing immunohistochemistry and electron microscopy is often helpful in narrowing the diagnosis to the various forms of CMD and myopathies. Eventually, direct mutational analysis may become commercially available for these disorders too. Establishing a specific diagnosis in each case is important in order to give the parents an idea of the anticipated outcome for the condition, and for purposes of genetic counselling (parents and family members). With the availability of excellent online databases such as OMIM and the Neuromuscular Home Page, the task of keeping abreast of the numerous advances in the field of neuromuscular disease is made easier. The algorithms outlined in this paper will help the pediatrician/neurologist to take a more systematic and informed approach to the diagnostic process involved. The focus of this paper has been primarily on the diagnostic aspects, although we have not mentioned therapeutic aspects, these remain at the forefront. Advances in neonatal care, nutrition and home ventilation are leading to longer lives for many infants born with severe hypotonia. The floppy infant poses a chronic neurological problem demanding multidisciplinary skills and support for both diagnosis and management.

7. Electronic database sources accessed in the preparation of this manuscript

Gene clinics: Clinical Genetic Information Resource [Database online]. Copyright, University of Washington, Seattle, 1995. Available at http://www.geneclinics.org.

Online Mendelian Inheritance in Man, OMIM (™) [62][database online]: McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD), 2000. Available at http://www.ncbi.nlm.nih.gov/omim/ Online mendelian inheritance in Man.

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Neuromuscular Home Page: Washington University School of Medicine, St. Louis, MO. Alan Pestronk MD.1996–2002 Revisions. Available at http://www.neuro.wustl.edu/neuromuscular/.

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