Chapter 13 – Common Problems in Pediatric Neurology

Section 2

Juvenile Myoclonic Epilepsy (impulsive petit-mal)
This syndrome usually appears at puberty with equal sex distribution. It is a familial disorder with the gene localized to the short arm of chromosome 6. Early morning myoclonic seizures are characteristic with single or repetitive, irregular myoclonic jerks, predominantly in the arms, associated with sudden falls and no noticeable disturbance of consciousness. GTCS and absence seizures are less frequent. The seizures frequently occur on awakening and may be exacerbated by sleep deprivation. Patients often do not recognize the seizures but readily give history of morning jitteriness, clumsiness, and propensity to drop objects. EEG shows brief paroxysms of generalized rapid, irregular spike and polyspike and wave discharges that are provoked by photic stimulation. Valproic acid is the drug of choice and is often effective even at low doses. Patients who are refractory to valproic acid should be referred to a neurologist. These seizures tend to relapse on discontinuation of medication and therefore patients require life-long treatment.

Single Seizure
Approximately 20,000 children in the United States are seen annually for a first unprovoked seizure. The therapeutic approach in these children remains controversial. Estimates of the risk of recurrence have varied widely. In one prospective study of 237 patients of all ages with first unprovoked seizure, the recurrence rate at follow up was estimated at 14 percent, 28 percent and 36 percent at one, three and five years respectively. The risk is highest within the first year following the seizure. The risk of recurrence is low if the patient has a normal neurological examination, a single GTCS with negative family history of epilepsy, a normal neuroimaging study and a normal EEG. Indications for treatment include clear-cut abnormalities on EEG and MRI, abnormal neurological examination suggesting prior CNS dysfunction, ongoing active CNS infection, the first seizure presenting as status-epilepticus, certain seizure types including infantile spasms, Lennox-Gastaut syndrome, focal seizures and unprovoked or asymptomatic seizure with history suggesting a prior occurrence.
Hypoxic-ischemic encephalopathy

Table 13.2-1: Most frequently identified etiologies of neonatal seizures

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial hemorrhage</td>
<td>Intraventricular, intracerebral, subdural, subarachnoid</td>
</tr>
<tr>
<td>Infection</td>
<td>Meningitis, encephalitis, TORCH (toxoplasmosis, other such as HIV, rubella, cytomegalovirus, herpes)</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>Arterial, venous, polycythemia</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Hypoglycemia, hypocalcemia, hypomagnesemia</td>
</tr>
<tr>
<td>Neurocutaneous syndromes</td>
<td>Tuberous sclerosis</td>
</tr>
<tr>
<td>Congenital abnormalities</td>
<td>Lissencephaly, holoprosencephaly and other malformations.</td>
</tr>
<tr>
<td>Inborn errors of metabolism</td>
<td>Aminoacidurias, urea cycle defects, organic acidurias, pyridoxine deficiency and dependency</td>
</tr>
<tr>
<td>Genetic</td>
<td>Benign familial neonatal convulsions, chromosomal anomalies</td>
</tr>
<tr>
<td>Maternal drug dependency</td>
<td>Cocaine, narcotics, barbiturates</td>
</tr>
</tbody>
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Selected Readings


Floppy Infant

Introduction

A floppy infant is an infant with decreased muscle tone. Muscle tone may be assessed as active or passive. Tone is often defined as resistance to passive movement at a joint. The resistance offered by the muscles may be normal, increased or decreased. Increased muscle tone is either spastic (clasp knife) or rigid (lead pipe) in type. A common example of spastic tone is a child with spastic hemiplegia. A typical example of decreased muscle tone is a child with Down syndrome. Muscle tone alterations may also be inferred from a child’s posture. Thus, a child with hemiplegia may keep his arm flexed against his chest and a child with spastic diplegia may keep his knees flexed when standing. A neonate with decreased muscle tone is likely to assume a “frog leg” posture with his legs abducted and at least partially extended at the hips in contrast to a “normal” posture of hip adduction and flexion in a neonate. As a result of decreased muscle tone, floppy infants not only have decreased resistance to passive movements, they also display an increased range of joint mobility and unusual and bizarre postures.

An organized approach is essential when evaluating an infant with decreased...
muscle tone or hypotonia. Hypotonia may be due to a disease affecting: 1) the motor unit (consisting of the anterior horn cell in the spinal cord, its axon in the peripheral nerve, the neuromuscular junction, and the muscle fibers it supplies); 2) the suprasegmental structures or the “upper motor neuron” (the spinal cord, brainstem, cerebellum, and the cerebral hemispheres); or 3) systemic, generalized disease. In general, presence of decreased muscle strength and diminished deep tendon reflexes distinguishes diseases of the motor unit from the other two categories. It is not always easy to detect muscle weakness in an infant. However the character of cry, withdrawal of limbs to painful stimulus and ability to sustain them against gravity may be useful indicators. It is important to remember that neuromuscular disease may be present in the absence of these characteristics as seen in some myopathies (e.g., congenital myotonic dystrophy) symptomatic in the neonatal period with respiratory and swallowing dysfunction and hypotonia but with ability to hold limbs against gravity. On the other hand, an infant with Prader-Willi syndrome may be nearly immobile. Some of the common conditions from each category are discussed below.

Neuromuscular Diseases
Neuromuscular diseases are characterized by hypotonia, weakness, and decreased deep tendon reflexes and may involve the anterior horn cells, peripheral nerve, neuromuscular junction, or the muscle itself. An organized anatomical approach is the best aid to diagnosis.

Anterior Horn Cell Diseases
Childhood degenerative anterior horn cell diseases are broadly called the spinal muscular atrophies; three types, type I, II, and III are distinguished. Werdnig-Hoffmann disease is the same as type I spinal muscular atrophy (SMA), or the severe infantile variety. SMA type III is the mild variety and is also called the Wolfhart-Kugelberg-Welander disease. SMA type II is the intermediate variety with variable clinical picture and outcome.

SMA Type I, Werdnig-Hoffmann disease
Patients may be weak at birth or even preterm. However, the most common presentation is with normal early development for several weeks or months followed by progressive weakness. Characteristically these infants never learn to sit. Patients are weak and lose milestones, with eventual swallowing and respiratory difficulty because of bulbar and respiratory muscle weakness. Examination reveals hypotonia and absent deep tendon reflexes in addition to weakness. Fasciculations of the tongue may be present and are best seen with the tongue at rest in sleep. Characteristically patients are alert with spared facial muscles. Clinical course is one of relentless progression with death generally within the first year or two.

SMA Types II and III
SMA II usually becomes symptomatic by 18 months of age. Most commonly children learn to sit but are too weak to walk. Intelligence is spared and children learn to speak without difficulty. Parents may complain about finger tremors; fasciculations of the tongue and fingers, and “minipolymyoclonus” may be seen. Severity of the disease is quite variable. The most severely affected children develop respiratory difficulties early, with poor prognosis. Mildly affected patients survive into adolescence and young adulthood.
Patients with SMA III have normal development for the first year or two and learn to walk. These patients usually present with hip weakness. Intelligence is not affected. Patients have a relatively static course with preserved strength and survival into adulthood. There may be deterioration late in life.

Investigations reveal neurogenic abnormalities on electromyogram (EMG) with fibrillations at rest and reduced interference pattern. In chronic cases (types II and III) polyphasic potentials may also be present. Nerve conduction velocity (NCV) is normal. Muscle biopsy shows neurogenic atrophy but rarely is necessary. Most cases of SMA are caused by mutation of the survival motor neuron gene 1 (SMN1) on chromosome 5. Molecular testing on blood confirms the clinical diagnosis of SMA1 nearly 100 percent of the time. In ninety-five percent of cases this testing shows homozygous deletion of SMN1 exon 7. Additional gene testing is needed rarely.

*Spinal muscular atrophies have autosomal recessive inheritance.* Consultation with a neurologist and geneticist is advisable.

**Peripheral Neuropathies**

Peripheral neuropathies are uncommon in infants. Presence of sensory symptoms and signs in addition to motor abnormalities are characteristic but often difficult to detect in infants. *Hereditary motor sensory neuropathy* (HMSN) type I and II (Charcot-Marie-Tooth disease, demyelinating and axonal type respectively), type III (Dejerine-Sottas disease), and Refsum’s disease (previously HMSN IV) are seen in children. Type III is the most severe and presents at an earlier age than types I and II; NCV are slowed. Type I and II are autosomal dominant; type III is probably recessive though other patterns of inheritance have been described. Hypomyelinating neuropathy may present in infancy with hypotonia and weakness. Molecular diagnosis is possible. There is duplication of *PMP22* in CMT 1A (classic Charcot-Marie-Tooth disease); others have either mutation in *PMP22* or others such as *MPZ* (P0), Connexin 32 etc. There is considerable genetic heterogeneity and consultation with a neurologist and geneticist is advisable.

**Diseases of the Neuromuscular Junction**

*Myasthenia gravis* the prototype disease. Infants usually have the transient form because of transplacental transfer of maternal antibodies. *The condition should be considered in all infants born to mothers with myasthenia gravis.* Infants may appear normal at birth only to develop weakness with feeble cry, and swallowing and respiratory difficulties at several hours of age. Recognition and prompt treatment with neostigmine or similar drugs is necessary. Patients recover completely as maternal antibodies are cleared over several weeks.

*Botulism* may occur in early infancy. Characteristic findings are acute onset of hypotonia, weakness, ptosis, dysphagia, unreactive pupils and constipation. Patients may have respiratory difficulties and require ventilatory support. Electromyographic study shows facilitation of motor potential following repetitive nerve stimulation at high rates. Prompt treatment with antitoxin toxin may be helpful in addition to supportive treatment.

Several congenital myasthenic syndromes (CMS) have been described, some of which are symptomatic in infancy. CMS are genetically determined and result from presynaptic or postsynaptic defects. Some syndromes remain poorly characterized. Investigation of these patients is complex and referral to a specialist is recommended.
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Muscle Diseases

Myopathy is a disease of muscle; myositis is an inflammatory myopathy and muscular dystrophy is a genetic, progressive myopathy. Congenital myopathy is a relatively nonprogressive myopathy that may be genetic; however symptoms may not appear until adulthood. Children usually present with hypotonia and clumsiness rather than prominent weakness as a symptom. Table 13.2-2 lists common congenital myopathies. EMG may be normal or may reveal myopathic features. Diagnosis is by muscle biopsy.

There are a host of congenital myopathies that may present in infancy or childhood. Most muscular dystrophies such as Duchenne or Becker muscular dystrophy (X-linked) usually present in childhood rather than infancy. CK levels are elevated in the active disease phase and decline in late stages of the disease. Most common presentation of Duchenne muscular dystrophy is progressive weakness of proximal lower extremity muscles in boys who may also have history of delayed walking. Early in the course of the disease there is pseudohypertrophy of the gastrocnemius muscles (and sometimes of the deltoids). With progressive weakness and atrophy of muscles children are wheelchair bound by teenage with death in the third decade with cardiac involvement. Cognition is impaired in some boys. Becker muscular dystrophy is similar but with a slower progression of the disease and much longer lifespan. There is a defect in dystrophin, a major muscle protein, in both of these muscle diseases and hence the term dystrophinopathies is used sometimes. Muscle biopsy stained for dystrophin shows nearly complete absence in Duchenne and spotty staining in Becker muscular dystrophy. Dystrophin is encoded by the DMD gene on the X-chromosome and hence X-linked recessive inheritance. Approximately two-thirds of mothers of affected boys are carriers so genetic counseling is important. Molecular diagnosis is possible with demonstration of a deletion or mutation in the affected gene. Most commonly there is absence of dystrophin protein in Duchenne muscular dystrophy (due to “out of frame” mutation) while in the Becker muscular dystrophy there is a decreased amount of abnormal molecular weight dystrophin (“in frame” deletion). Consultation with a geneticist is advisable for counseling families and for carrier detection.

Other muscular dystrophies, such as the several limb girdle muscular dystrophies, vary in clinical onset of symptoms from early childhood to middle age and have mild to severe clinical course. Many have defects in dystrophin related proteins such as sarcoglycans.

Myotonic dystrophy is of two types (type 1? DM1 and type 2? DM2). Only DM1 presents in the neonate with respiratory and swallowing difficulties. Although inheritance is autosomal dominant, the mother is most often the affected parent in this type of presentation, and her examination often aids in the diagnosis. DM1 is caused by a CTG trinucleotide repeat expansion in the DM1 gene. Age of onset varies with size of this expansion; congenital cases are associated with large expansions. DM2 is caused by a CCTG repeat expansion in the DM2 gene. Myotonic dystrophy and Emery-Dreifuss dystrophy (X-linked recessive inheritance with emerin deficiency) have associated cardiac dysfunction (usually in late childhood or young adulthood) that may be clinically important. Consultation with a neurologist and a cardiologist is advisable.
Table 13.2-2: Selected congenital myopathies

- Central core disease
- Nemaline myopathy
- Centronuclear (myotubular) myopathy
- Severe congenital X-linked myotubular myopathy
- Congenital fiber-type disproportion
- Minicore (multicore) myopathy
- Minimal change myopathy

Systemic Diseases

Hypotonia may be seen in a variety of systemic diseases and syndromes. In these conditions weakness is usually not associated with hypotonia. Chromosomal disorders such as Down syndrome are associated with hypotonia. Severely decreased muscle tone is also a central feature of several genetic disorders such as Prader-Willi syndrome, and Zellweger’s syndrome. In many connective tissue disorders such as Ehlers-Danlos syndrome joint laxity and joint hypermobility and hyperextensibility is hard to distinguish from decreased muscle tone. Infants with metabolic and endocrine conditions such as hypoglycemia, hypercalcemia, and hypothyroidism may also have hypotonia. Neonates with sepsis and meningoencephalitis often present with decreased tone among other signs and symptoms. Aminoacidurias, organic acidurias, lipidoses, and sometimes mitochondrial cytopathies may be associated with decreased muscle tone. Cerebral palsy may be hypotonic. Children destined to develop kernicterus pass through a hypotonic phase.

Management of these children depends upon accurate identification of the underlying disease process.

Selected Reading