CHAPTER 30

Childhood Spinal Muscular Atrophy

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HISTORY

Werndig and Hoffmann were working in the tradition of German neurology of the late 19th century when they conducted autopsies on their patients who had a new form of infantile paralysis. They described a striking atrophy of the ventral nerve roots of the spinal cord on gross examination and correlated this finding with the histologic appearance of the anterior horns that showed a decreased number of motor neurons. Moreover, a pattern of atrophy in muscle fibers was consistent with loss of innervation (1). In the 1890s, Guido Werndig was a retired battalion physician working at the Institute of Anatomy and Physiology of the Central Nervous System at the University of Vienna. His lecture, entitled “On a case of muscular dystrophy with positive spinal cord findings” (2), was probably the first full description of spinal muscular atrophy (SMA). In 1891, he published a paper describing two infantile hereditary cases of progressive muscular atrophy. The following year, Professor Johann Hoffmann of Heidelberg University used the term, in German, “spinale muskelatrophie,” in English, “spinal muscular atrophy” (3). Together, their papers presented the clinical and pathologic aspects of infantile SMA: onset during the first year of life, occurrence in siblings with normal parents, progressive hypotonia and weakness, hand tremor, and death from pneumonia in early childhood. Moreover, Hoffmann talked about progressive and chronic types of SMA (4,5).

CLASSIFICATION

The classification of SMA has always been controversial. The work of Hoffmann and Werndig immediately suggested some biologic difference between those infants with a severe fatal form of the disease and those with the chronic form. Beginning with Byers and Banker (6), a classification of SMA according to severity was thought to facilitate prognostication. The relationship between age at onset and severity was supported by the observations of Dubowitz (7). Based on the work of an international collaboration (8,9), most pediatric neurologists now use the following nomenclature: SMA type 1 (or I) for onset of symptoms before age 6 months, SMA type 2 (II) for onset between 6 and 18 months, and SMA type 3 (III) for onset after age 18 months (Table 1). The three types may be subdivided on the basis of mortality or highest motor milestone achieved. For example, SMA1 patients almost never sit without support when placed (10). In fact, most SMA patients of all types can never pull themselves to sitting position or roll over at any age. SMA1 patients with onset before 3 months of age have the highest mortality rate (90%), whereas those with onset after age 3 months may survive to adulthood, albeit with severe motor handicap. SMA3 patients often are independently ambulatory at least for part of their life and may have a normal life expectancy (11). Most SMA patients have type 1, with decreasing incidence for types 2 and 3, respectively. In other words, the incidence is highest for type 1, then 2, and type 3 has the lowest incidence. Considering the relative mortality rates, it is not surprising that the highest prevalence is for SMA types 2 and 3.

Spinal Muscular Atrophy Type 1

One of the difficulties with previous classification systems has been the inconsistent use of eponyms. Synonyms for SMA type 1 are “infantile onset SMA” and “Werndig-Hoffmann disease.” SMA1 is the most severe form of the disease beginning at birth or in the first few months of life and frequently resulting in death from respiratory failure before 2 years of age. On physical exam-
TABLE 1. Classification of SMA

<table>
<thead>
<tr>
<th>Onset of weakness (mo)</th>
<th>Highest function</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMA1 &lt;6</td>
<td>Most nonsitters; few sitters</td>
<td>90%; a few survive to 2nd decade</td>
</tr>
<tr>
<td>SMA2 6–18</td>
<td>Most sitters; few walkers</td>
<td>Variable; most survive to 2nd or 3rd decade</td>
</tr>
<tr>
<td>SMA3 &gt;18</td>
<td>Many walkers</td>
<td>Many with normal life expectancy</td>
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SMA, spinal muscular atrophy.

Ination, these infants have severe weakness and profound hypotonia. There is a striking discrepancy between the infant’s level of social interaction and lack of motor skills. There may be no spontaneous movement except in the hands and feet. The infant lies in the frog-leg position. There is often a fine tremor in the fingers called polymyoklonus. Deep tendon reflexes are usually absent, whereas sphincter tone and sensation remain intact. Tongue fasciculations are common. Atrophy of the tongue may be manifest as scalloping of the border. Weak intercostal muscles countered by diaphragmatic breathing result in inefficient respiration, the pectus excavatum deformity, and flaring of the lower ribs (bell-shaped deformity) (Fig. 1). Bilateral eventration or paralysis of the diaphragm may be a presenting manifestation (12).

The most common cause of death is respiratory failure, although it may be preceded by several months of subtle changes due to complications of weakness. SMA1 babies tire quickly during feeding and, if breast fed, may begin to lose weight before it is evident that they are not taking in appropriate calories. Malnutrition and respiratory insufficiency exacerbate fatigue and cause susceptibility to aspiration. Any minor upper respiratory infection may quickly become a life-threatening crisis.

Spinal Muscular Atrophy Type 2

Synonyms for SMA2 include “juvenile SMA,” “intermediate SMA,” or “chronic SMA” (13,14). Patients usually achieve normal milestones up to 6 to 8 months of age, although they are hypotonic. The legs tend to be more involved than the arms so that failure to walk is a typical chief complaint (Fig. 2). Patients may be thought to have a paraparesis and occasionally are born with club foot deformity. The pattern of deep tendon reflexes may be variable with preservation in muscle groups that are fairly strong. Minipolymyoklonus may be prominent in these infants. The pathophysiologic origin of these movements is not known, although fasciculations of the intrinsic hand muscles may contribute.

Many patients with type 2 are able to sit without support if placed in position during all or some of their life; rarely, some are able to stand or walk with aid. The age for sitting or walking is nearly always delayed, and walking, whether with or without assist, is usually temporary. The age at death is quite variable, from 7 months to 7 years (6). Many survive to the third or the fourth decade; the eldest patient in one prospective study died at age 72 years (15). The difference between survivors and nonsurvivors seems to be good pulmonary function.

Spinal Muscular Atrophy Type 3

“Wohlfart-Kugelberg-Welander syndrome” is the eponym for mild SMA or SMA type 3 (16,17) when onset may be any time after age 18 months. SMA3 usually presents in late childhood or adolescence as a proximal neurogenic muscular atrophy that may be confused with limb girdle muscular dystrophy (18–21). Patients frequently have elevated serum creatine kinase levels (22), although the mechanism is poorly under-

FIG. 1. A 3-month-old infant with spinal muscular atrophy type 1 who has a bell-shaped chest. She died of respiratory failure soon afterward.
progression of weakness over several years in patients with type 2 or 3 (11). The authors suggested that SMA may not be a neurodegenerative disease.

The classification of SMA into three types is an artificial representation of a biologic spectrum of disease. However, understanding the underlying mechanisms that result in mild or severe disease may contribute toward finding effective treatment.

LABORATORY EVALUATION

The diagnostic workup for SMA has changed since the discovery of the SMN gene. The diagnosis now can begin with blood DNA for direct mutation analysis of the gene (24,25). For infants with deletions of exons 7 and 8, no further workup is necessary. Although most patients have deletions in SMN, rare patients with duplication have been described. If DNA analysis is normal, then a more traditional approach may be necessary for diagnosis.

This traditional approach includes measurement of serum creatine kinase; electrodiagnostic studies, including nerve conduction velocities (NCV) and needle electromyography; and muscle biopsy. As already stated, the creatine kinase may or may not be elevated, although it usually is normal in SMA types 1 and 2.

Measurement of motor NCV in infants may be difficult because of the small-sized limbs and short distance between stimulus and recording electrodes. Examination usually documents either normal NCV or, occasionally, faster conduction velocities than expected. If there is profound muscle atrophy, it may be difficult to interpret responses to nerve stimulus (26). International diagnostic criteria mandate that motor and sensory NCV be normal. The occasional case of typical SMA in which NCV or amplitudes are abnormal may be explained as a technical artifact, but not always. Axonal dysfunction can theoretically result in abnormal electrodiagnostic studies. Needle electromyography usually shows evidence of acute denervation including fibrillation potentials and reinnervation in the form of large polyphasic motor units and reduced recruitment. In infants, electromyography may be normal or suggestive of a myopathic process because of small amplitude, short duration, polyphasic motor units.

Muscle biopsy should show neurogenic atrophy and/or evidence of reinnervation. Preservation of large round fibers in the denervated fasciculi is common (6). This is frequently called the "infantile pattern of neurogenic atrophy." From mid-childhood, one may see angular fibers indicating acute denervation and type grouping indicating reinnervation. Nonspecific changes such as fiber size disproportion may occur, possibly as a result of sampling error (12) or developmental variations. In such a case, repeat biopsy of another muscle or at a later age may show more typical evidence of neurogenic atrophy.
GENETICS

Epidemiologic studies indicate an autosomal recessive mode of inheritance (27) and nearly equal sex distribution with a slight predominance in males (28), but autosomal dominant transmission is a rare occurrence (29). Several families have been described in which the co-occurrence of SMA and amyotrophic lateral sclerosis was documented (30,31). Molecular testing is required to determine whether such occurrences are merely coincidental.

A rare form of severe SMA with arthrogryposis occurs in an X-linked inheritance pattern. Symptoms are apparent at birth or shortly after birth (32,33). Death usually occurs from respiratory failure within the first few months of life. Male infants are exclusively affected, whereas carriers are asymptomatic. Only a few families with this entity have been identified worldwide, but linkage analysis has shown that all map to the same locus.

Linkage of autosomal recessive SMA to chromosome 5q11.2-13.3 was reported by Gilliam et al. in 1990 (34). An international consortium studied families with evidence of recessive transmission only, although they were able to document phenotypic heterogeneity within families (35–37). In 1994, Melki et al. (38) reported the occurrence of major deletions at 5q11.2-13.3 in patients with severe SMA (Werndig-Hoffmann phenotype) as compared with patients with mild SMA (Kugelberg-Welander phenotype) who had none or smaller deletions. Clinical evidence suggests that early-onset SMA represents a spectrum of disease, a finding that would be consistent with a single gene locus (39,40).

Two genes were found at the 5q locus. The gene for neuronal apoptosis inhibitory protein (NAIP) maps to the 5q13 region and 67% of SMA patients were shown to have deletions in this gene, whereas only 2% of control subjects had deletions (41). A novel gene, whose function remains unknown, called the survival motor neuron gene (SMN), also at 5q13, was found to contain deletions in 229 (>98%) SMA patients (42,43). Furthermore, at least two patients with duplications of SMN have now been reported, providing more evidence that SMN is the correct gene. The presence of multiple copies of SMN (telomeric, SMNc, and centromeric, SMNc) and of heterogeneity in deletions of various exons has been a challenge for investigators (44). A role for gene dosage in clinical severity is under investigation (45). Normal individuals have two alleles each of SMN1 and SMN2. The disease appears to be caused by mutations in both alleles of SMN1, whereas there may be some or none of SMN2 present. Recent work has shown that in some cases of SMA2 or 3, SMN1 is converted to SMN2. It appears that SMA disease is caused by mutation of both telomeric alleles of SMN, whereas increasing the number of SMNc copies may ameliorate the severity of the phenotype. (46) The addition of mutations in NAIP may increase the severity of the clinical phenotype.

The protein product of SMN is known to interact with RNA-binding proteins and may actually be a spliceosome. Immunohistochemistry of tissues from control individuals has shown normal SMN activity in both nuclei and cytoplasm of motor neurons (47). Nuclear activity occurs in structures called gems that are closely related to chromosome activity during mitosis. Reaction product was absent from neurons of SMA1 patients and reduced in neurons of SMA2 and SMA3 patients compared with motor neurons from control subjects. Thus, it seems that the amount of gene product may be inversely proportional to the severity of the clinical phenotype. Loss of spliceosomes could theoretically affect the production of mRNA, but there is no clear indication as to why only motor neurons are affected. A knockout mouse model was nonviable past the blastocyst stage of embryo development.

MANAGEMENT

Because there is no effective therapy for SMA, management consists of preventing or treating the complications (48). Complications of severe weakness include restrictive lung disease, poor nutrition, orthopedic deformities, immobility, and psychosocial problems (Table 2). Restrictive lung disease results from weakness of intercostal muscles and diaphragm, causing hypoventilation and weak cough (Fig. 3). Aggressive prophylaxis against pneumonia and atelectasis may include assisted cough, chest percussion therapy, and intermittent positive pressure breathing. Some clinics recommend ambu-bagging, in/exsufflation, and night-time mask ventilation to prevent or reverse microatelectasis. Patients require assistance to maintain good pulmonary toilet even when not experiencing an acute infection and may require intervention to prevent progressive atelectasis (49–52).

Risk for pneumonia increases as forced vital capacity (FVC) decreases, which may occur even without significant change in limb or trunk strength. Some clinicians begin prophylaxis before the FVC reaches 50% of expected. A few clinics monitor maximum inspiratory pressure, which has been shown to be an early indicator of restrictive disease. Oxygen therapy should be contraindicated except with the use of assisted ventilation. Patients with restrictive lung disease develop retention of CO2 before hypoxia, and administration of oxygen may cause death from apnea secondary to suppression of the respiratory drive. It is helpful to monitor blood gases on a regular basis along with the FVC. When CO2 retention occurs, then noninvasive ventilation, either positive or negative pressure, during acute infection or at night as prophylaxis may be helpful and restorative.

Poor nutrition with failure to thrive often occurs as a result of a weak suck, unprotected airway, or easy fatiga-