The spinal muscular atrophies are inherited neurodegenerative disorders characterized by progressive weakness secondary to degeneration of lower motor neurons.

**Clinical Features**

Clinical manifestations of the spinal muscular atrophies are secondary to progressive weakness and atrophy of skeletal muscle. Specific symptoms, physical findings, and clinical presentations vary with the severity of weakness, rate of progression, and age of onset.

The 10 affected children originally described by Werdnig and Hoffmann were well at birth, progressed normally for several months, developed weakness between 5 and 9 months of age, and lived until age 3 to 7. However, subsequent reports of cases with severe weakness at birth and death before age 18 months, onset in infancy with survival to adulthood, first symptoms in childhood or adolescence, or onset in adulthood called attention to the extraordinary clinical variability of SMA and promoted the classic vigorous debate between the “lumpers” and “splitters.”
of genetic diseases. This has led to numerous classifications, none of which are ideal.

The classification used here is adapted from the Warsaw University Classification and divides the spinal muscular atrophies encountered in the pediatric age group into four types: acute infantile, chronic infantile, juvenile, and intermediate. Based on clinical criteria, this schema emphasizes the intensity of symptoms and rate of progression (Table).

### Acute Infantile Spinal Muscular Atrophy

Acute infantile spinal muscular atrophy is a malignant disorder leading to death from respiratory complications before 2 years of age. Familiar to pediatricians as "Werdnig-Hoffmann disease," distinguishing features are severe weakness with rapid progression.

Affected children usually present at birth with profound hypotonia and severe generalized weakness. About one third of mothers will have noticed a change in strength and vigor of fetal movements during the last three months of gestation. This information is seldom volunteered and must be sought through careful questioning. Often, movement of the extremities is limited to the hands and feet. Muscles are thin, poorly developed, and "flabby" to palpation. Breathing is diaphragmatic with paradoxical flattening of the chest during inspirations. "Bell-shaped" deformity of the chest (a narrow, flattened upper thorax with outward, flaring lower ribs) is common. The cry is weak. Weakness of bulbar muscles interferes with feeding. Extraocular movements are normal. Since facial muscles are spared, affected infants appear alert and exhibit a normal range of facial expressions. Deep tendon reflexes are absent.

Close inspection of the tongue may reveal atrophy at the labial and gingival margins. Fasciculations of the tongue are sometimes seen. Unequivocal fasciculations of the tongue in the context of an alert newborn with profound weakness and hypotonia strongly suggests the diagnosis of SMA. Unfortunately, the normal quivering tongue movements seen in all infants are easily mistaken for "fasciculations," even by the most experienced clinician.

Although nearly all infants with acute infantile SMA are clinically affected from birth, some may escape detection for several months. The moment of recognition depends upon the intensity of the symptoms and the experience of the observer. Initial manifestations may be subtle, making it difficult to determine with certainty exactly when the problem began; or symptoms may seem to appear with surprising suddenness, prompting erroneous attribution to injury, infection, or immunization.

Affected infants not detected as neonates may come to attention because of hypotonia, feeding problems, poor head control, paucity of movement, or developmentally delayed milestones...
Infants with chronic infantile SMA most often come to attention because of delay or failure in attaining a major motor milestone.

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delay. Examination discloses weakness, hypotonia, and absent deep tendon reflexes. Weakness is most marked in proximal muscles. The legs assume a position of flexion, abduction, and external rotation at the hips ("frog-leg" posture) and cannot be lifted up off the plane of the crib. Movement of the lower extremities is limited to the feet and toes. The arms are similarly affected with better preservation of movement distally. Head control and trunk support are deficient. Weak cry, impaired gag reflex, and paradoxical respiratory movements complete the clinical picture. There may be atrophy and fasciculations of the tongue. Facial muscles and extra-ocular muscles are not affected.

In spite of significant motor impairment, nearly all affected infants are strikingly alert, bright-eyed, visually attentive, and socially responsive. Even if unable to lift or turn their heads, they readily follow with their eyes. Their faces are unusually expressive, and they are typically precocious in social interaction.

All infants with acute infantile SMA are overtly symptomatic by age 6 months, with 95% diagnosed in the first three months of life. Fewer than 25% are ever able to lift the head off the bed and less than 2% are ever able to maintain a sitting posture without support. The most severely affected infants, those profoundly weak at birth, have a median life expectancy of 7 months, with a few reaching their first birthday. Those who appear normal at birth may fare somewhat better, but even they rarely survive their second year.

The acute infantile form accounts for 23% of all cases of spinal muscular atrophy.10

Chronic Infantile Spinal Muscular Atrophy

The chronic infantile form of spinal muscular atrophy accounts for 24% of pediatric cases.10 It is distinguished from the acute infantile form by the intensity of symptoms and rate of progression. Age of onset is not an adequate differential criterion. Although chronic infantile SMA typically presents after 6 months of age, earlier appearance of symptoms is not uncommon. Frequently, chronic infantile SMA, a disorder consistent with prolonged survival, cannot be distinguished from the acute, malignant infantile form without a period of observation sufficient to determine rate of progression. Since children with chronic infantile SMA, even those symptomatic from birth, can live for many years, experienced clinicians know it is prudent to avoid premature prognostic declarations.

Infants with chronic infantile SMA most often come to attention because of delay or failure in attaining a major motor milestone. Most can move their limbs and lift their heads. Many progress to sitting or standing, and some will even take their first steps before showing progressive deterioration in strength and motor ability. The distribution of weakness is usually similar to that noted in the acute infantile form of the disorder, with trunk and proximal limbs more severely affected than hands and feet. Usually the legs are more severely affected than the arms, but there are exceptions. Fasciculations of the tongue are seen in many. Deep tendon reflexes may be preserved initially but are eventually lost. A fine tremor of the hands is sufficiently common that its presence supports the diagnosis.11 In time, weakness and impaired muscle development in the face of ongoing linear growth lead to progressive contractures and skeletal deformities. Severe kyphoscoliosis becomes particularly prominent in nearly all cases.

Chronic infantile SMA is invariably progressive. However, the clinical course of a given individual is difficult to predict. Weakness may follow a pattern of slow, steady progression over many years, or remain static for a long period. Periods of slow progression or apparent stability may be interrupted by sudden episodes of rapid deterioration. Before the advent of mechanical ventilation, even the most severely affected children sometimes survived to adulthood. Home ventilator care programs extend new choices by offering opportunities for enhanced longevity.

As Brooke suggests, "Perhaps the wisest course is not to try and predict the time at which death may occur but to plan for possible survival into adult life."12

Juvenile Progressive Spinal Muscular Atrophy

This disorder, described independently by Wohlfart6 and Kugelberg and Welander,7 is the mildest form of SMA encountered in the pediatric age group. Thirty-two percent of pediatric cases fall into this category.10

Typically these children present between 3 and 15 years of age because of slowly progressive difficulties in running, climbing stairs, or arising from the floor. In 80%, subtle symptoms unnoticed by parents were present much earlier.13 Common early manifestations include mild delay in motor milestones, clumsiness, and the inability to run as well as other children. There is muscle weakness and atrophy in a limb-girdle distribution. Mild pseudohypertrophy of the calf muscles is common. In affected males, this can lead to an erroneous impression of pseudohypertrophic muscular dystrophy of the Duchenne or Becker types. Weakness of muscles innervated by cranial nerves occurs in only 20% of cases14 and is mild when present. Deep tendon reflexes are variably normal, diminished, or absent.

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The most valuable diagnostic investigations include nerve conduction studies, electromyography, and muscle biopsy.

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Fixed skeletal deformities are uncommon, although weakness of hip muscles frequently promotes a compensatory lordotic posture. Weakness progresses so slowly that those affected may remain ambulatory 20 or even 30 years after the onset of symptoms. Life expectancy is nearly normal.

Intermediate Spinal Muscular Atrophy
The remaining 21% of cases of childhood spinal muscular atrophy are of intermediate severity and follow a clinical course milder than chronic infantile SMA, but more malignant than the juvenile (Kugelberg-Welander syndrome) form. Children with the intermediate form learn to walk but develop progressive weakness and atrophy, mainly of proximal muscles, between the ages of 2 and 6 years. Although weakness progresses, leading to immobilization after one to 10 years of illness, the survival period of these children is long. Deep tendon reflexes are absent, and fasciculations are often prominently visible. Progressive skeletal deformities are common.

DIAGNOSIS
The clinical manifestations of spinal muscular atrophy are usually sufficient to suggest the diagnosis. Depending on the patient's age, other causes of infantile hypotonia or progressive proximal weakness enter the differential diagnosis. The most valuable diagnostic investigations include nerve conduction studies, electromyography (EMG), and muscle biopsy.

Nerve Conduction Studies
Sensory nerve conduction velocities and sensory potential amplitudes are normal. Motor nerve conduction velocities are usually normal, although mild slowing of motor conduction sometimes occurs in acute infantile SMA or in cases of advanced disease. These findings distinguish SMA from the peripheral neuropathies, which are usually accompanied by abnormal sensory nerve conduction studies or significant slowing of motor nerve conduction velocities.

Electromyography
EMG needle examination shows increased insertional activity, abnormal spontaneous activity (fibrillation and fasciculation potentials), impaired recruitment of motor units, and increased amplitude and duration of voluntary motor unit potentials. This constellation of abnormalities differentiates SMA from the primary myopathies, muscular dystrophies, and disorders of neuromuscular transmission (e.g., myasthenia gravis).

Creatine Kinase Determinations
Plasma creatine kinase (CK) determinations are usually normal. Increased plasma levels of CK are more common in acute infantile SMA than in the more protracted forms. Elevations, when present, are usually modest although occasional levels over 10 times the upper limit of normal have been reported.

Muscle Biopsy
In acute infantile SMA, routine histologic stains typically show large sheets of atrophic fibers adjacent to clumps of hypertrophied fibers (cover). The myosin ATPase reaction after incubation at pH 7.4 shows nearly all of the hypertrophied fibers to be histochemical type I fibers. Some biopsies contain only sheets of small fibers. In such cases, interpretation is difficult. Muscle biopsy changes in the chronic forms of SMA are more variable. In the large series of biopsies reviewed by Namba and associates, 17 "neuropathic" changes were seen in 68% and "myopathic" changes in 5%. Mixed neuropathic and myopathic findings were present in 19%. The remaining 8% were either normal or showed nonspecific abnormalities.

GENETICS
Acute Infantile Spinal Muscular Atrophy
This form of SMA appears to be a distinct genetic entity in its own right. Inheritance is autosomal recessive with a risk of recurrence in siblings of 25%. Siblings of a child with the disease whose onset was before the age of 6 months and who died before 18 months of age are likely to have a similar malignant course if they develop the disease. Carrier frequency is estimated to be 1 in 90.

Chronic Childhood Spinal Muscular Atrophy
Over 90% of all cases of spinal muscular atrophy with onset in childhood and a protracted course, including the chronic infantile, juvenile, and intermediate varieties, are probably due to a single autosomal recessive gene. Favoring the single gene hypothesis is the remarkable discordance in age of onset, rate of progression, and age at death among affected members of some sets of siblings. The occurrence of isolated cases due to spontaneous dominant mutations and unusual pedigree patterns can complicate genetic counseling.

MANAGEMENT
Acute Infantile Spinal Muscular Atrophy
Treatment is supportive and does not alter the ulti-
mate outcome. Maintenance of nutrition requires care and patience, and tube feeding is sometimes appropriate. Infants surviving the first few months of life benefit from using a modified infant seat to permit sitting, encouraging age-appropriate cognitive activities. A small tray facilitates hand and finger play. Respiratory infections are treated with antibiotics, postural drainage, and gentle chest physical therapy. Prolongation of the course by use of mechanical ventilation is not recommended.

**Chronic Infantile Spinal Muscular Atrophy**

During the first year of life, emphasis is placed on range of motion, prevention of contractures, facilitated sitting, age-appropriate play, and cognitive development. Between 12 and 18 months of age a scooter board and standing frame can promote dramatic functional gains. Lightweight long leg braces and a walker allow some patients to walk. Motorized wheelchairs, introduced as early as 2 years of age, provide a safe and effective method of independent movement during formative years. Adaptive seating and spinal orthosis enhance sitting comfort, but do not retard the progression of scoliosis. Spinal fusion surgery using Luque instrumentation ameliorates severe spinal curvature. Mainstream educational opportunities are encouraged, which requires special transportation, elimination of architectural barriers, and sometimes an aide to assist at school. Electronic environmental control devices, personal computers, and voice amplification devices facilitate independence. Bathing, dressing, and eating are made easier through adaptive equipment. In many cases, long-term outpatient ventilator care enhances both length and quality of life. Children may require ventilatory assistance only at night. Others can use battery-operated respirators adapted to their electrically powered wheelchairs so that mobility is maintained.

**Juvenile and Intermediate Spinal Muscular Atrophy**

Treatment considerations are similar to those of chronic infantile SMA. However, treatment of scoliosis in ambulatory children with SMA presents special problems. The child still walking may be unable to do so with a back brace. Surgical correction of scoliosis in a younger whose ambulation is tenuous alters postural mechanics and may hasten wheelchair confinement.

**SUMMARY**

The spinal muscular atrophies are inherited neurodegenerative disorders characterized by progressive weakness secondary to degeneration of lower motor neurons. The disorders present in infancy with hypotonia and developmental delay, or later in childhood with progressive weakness of proximal muscles. Severity of weakness and rate of progression vary. Inheritance pattern is usually autosomal recessive. The most valuable diagnostic investigations are nerve conduction studies, electromyography, and muscle biopsy. Treatment promotes independent function and enhances quality of life, but does not alter the underlying disease process.

**ACKNOWLEDGMENTS**

The Table is modified from Hausmanowa-Petrusewicz and Fidzińska-Dolot.10

**REFERENCES**

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