Spinal Muscular Atrophy, Type I

**Alternative Names**
- SMA I
- SMA, Infantile Acute Form
- Muscular Atrophy, Infantile
- Werdnig-Hoffmann Disease

**Record Category**
- Disease phenotype

**WHO-ICD**
Diseases of the nervous system > Systemic atrophies primarily affecting the central nervous system

**Incidence per 100,000 Live Births**
11-50

**OMIM Number**
253300

**Mode of Inheritance**
- Autosomal recessive

**Gene Map Locus**
- 5q12.2-q13.3

**Description**
The spinal muscular atrophies represent a heterogeneous group of neuromuscular disorders with predominantly autosomal recessive inheritance, characterized by degeneration of the anterior horn cells in the spinal cord and, in some cases, of the motor nuclei in the brain stem, resulting in symmetrical muscle weakness and atrophy. The spinal muscular atrophies are the second most common autosomal recessive disease among Caucasian populations, with a prevalence of between 1 in 6000 and 1 in 10,000 live births, and an estimated carrier frequency of about 1 in 50. The condition is clinically heterogeneous and has been divided into several subtypes according to age of onset and clinical severity.

Acute infantile spinal muscular atrophy (SMA1) forms 80% of all types of spinal muscular atrophies. It is a rare and severe form of spinal muscular atrophy with onset in utero with reduced fetal movements or within the first 6 months of life. SMA1 is characterized by degeneration of groups of nerve cells (motor nuclei) within the lowest region of the brain (lower brainstem) and certain motor neurons in the spinal cord (anterior horn cells). Affected children have normal intelligence, but are unable to sit without support and usually have feeding difficulties. The majority of children with spinal muscular atrophy type I die from aspiration or respiratory failure within the first 2 years. For infants who appear to have normal development for several months prior to the onset of muscle weakness, the disorder may tend to have a more slowly progressive course.

The male-to-female ratio is 2:1. Males show more severe courses than females. SMA1 is the most severe form of spinal muscular atrophies and it is the most common single genetic cause of death in infancy. Medical care and physical therapy may help prevent complications and ensure the best possible quality of life for those affected.

**Molecular Genetics**
Linkage studies in families of spinal muscular atrophy patients found that 95% of all cases of spinal muscular atrophy were linked to the 5q13 region of chromosome 5. Two candidate genes within this region were first described: the survival motor neuron (SMN) gene and neuronal apoptosis inhibitory protein gene. Each of these genes was found to be present in at least two copies. Later, the p44 gene (a subunit of the basal transcription factor) was identified as a third candidate gene.

Recently, two candidate genes, namely SMN (survival motor neuron) and NAIP (neuronal apoptosis inhibitory protein), have been suggested as SMA-determining and SMA-modifying genes,
respectively. The SMN gene has been found to be homozygously absent or interrupted in 98.6% of childhood SMAs and in at least some patients with the adult form. The frequency of homozygous deletion of the intact NAIP gene was found to be different in SMA type I and type II/III (45% versus 18%), thus leading to the suggestion that the severity of the disease may depend on the deletion of the NAIP gene.

Analysis of both the SMN and NAIP genes is significantly complicated by the existence of highly homologous genes that limit the ability of the currently used tests to detect only homozygous deletion of these genes. The SMN gene is present in two almost identical copies, one telomeric (SMN1) and one centromeric (SMN2 or cBCD541). Both the centromeric and telomeric copies contain 9 exons. They differ only in 8 nucleotides; 5 are intronic and 3 are exonic, located in exons 6, 7 and 8. The telomeric copy is the functional. Homozygous deletions of exons 7 and 8 of SMN1 were found to occur in >95% of patients with spinal muscular atrophy, but not in normal control populations. Phenotypic variability may result from more extensive deletions, de novo point mutations, variation in centromeric copy (SMN2) number and chimeric SMN gene. SMN2 may also be associated with disease phenotype in selected cases. In addition to deletion of SMN1, point mutations may also be present.

**Epidemiology in the Arab World**

**Bahrain**

[See also: Kuwait > Haider et al., 2001]

**Kuwait**

Samilchuk et al. (1996) carried out deletion analysis of the SMN and NAIP genes in 11 cases of type I SMA and 4 cases of type II SMA. The patients were of Kuwaiti origin and represented all of the patients diagnosed in years 1995-1996 in Kuwait. They also analyzed samples from 41 healthy relatives of these patients and 44 control individuals of Arab origin. They found homozygous deletions of exons 7 and 8 of the SMN gene in all SMA patients studied. Exon 5 of the NAIP gene was homozygously absent in all type I SMA patients, but was retained in the type II patients. Among relatives, they identified one mother with a homozygous deletion of NAIP. All of the control individuals had normal SMN and NAIP. Samilchuk et al. (1996) concluded that the incidence of NAIP deletion is much higher in the clinically more severe cases (type I SMA) than in the milder forms, and all of the type II SMA patients in their study had at least one copy of the intact NAIP gene. Furthermore, Samilchuk et al. (1996) suggested that SMA type-I chromosomes, with the dual deletion of the SMN and NAIP genes, are more common in Arabs than in patients of other ethnic origin.

Haider and Moosa (1997) investigated the presence of survival motor neuron gene and neuronal apoptosis inhibitory protein gene deletions in 17 Arab and 1 Indian families with spinal muscular atrophy (15 type I and 3 type II). Homologous deletions were detected in exons 7 and 8 of the survival motor neuron gene and exon 5 of the neuronal apoptosis inhibitory protein gene in all patients with type I spinal muscular atrophy. No deletion was detected in healthy siblings or the parents.

In 2001, Haider et al. assayed deletions in two candidate genes, the survival motor neuron (SMN) and neuronal apoptosis inhibitory protein (NAIP) genes, in 108 samples, of which 46 were from SMA patients, and 62 were from unaffected subjects. The SMA patients included 3 from Bahrain, 9 from South Africa, 2 from India, 5 from Oman, 1 from Saudi Arabia, and 26 from Kuwait. Type I SMA patients had onset before the age of 6 months, with symmetrical proximal muscle weakness in the absence of extraocular, diaphragmatic, or cardiac weakness, sensory disturbance, arthrogryposis or CNS dysfunction. SMN gene exons 7 and 8 were deleted in all type I SMA patients. None of the 62 unaffected subjects had deletions in either the SMN or NAIP gene. The incidence of biallelic polymorphism in SMN gene exon 7 (BsmAI) was found to be 97%. The incidence of a second polymorphism in SMN gene exon 8 (presence of the sequence ATGGCCT) was 97%.

**Libya**

Radhakrishnan et al. (1988) diagnosed 24 patients (18 index cases) with spinal muscular atrophy (hereditary motor neuropathy, HMN), 9 with myasthenia gravis (MG), 6 with progressive supranuclear palsy (PSP), and 5 with subacute sclerosing panencephalitis (SSPE) in Benghazi during a 4-year study period, January 1983 to December 1986. The HMN group comprised 6 acute infantile, 12 chronic childhood, and 3 each with adult-onset proximal, and distal forms of the disease. The crude average annual incidence of acute infantile HMN was 0.3/100,000 total population and 1/12,500 births in Benghazi. The crude prevalence rates of chronic childhood, adult-onset proximal, and distal types of HMN were 2.3, 0.6 and 0.6/100,000, respectively.
Oman
Aithala et al. (1995) reported the co-occurrence of spinal muscular atrophy (SMA) with arthrogryposis multiplex congenita in monozygotic male twins who were the product of a consanguineous marriage. They presented at the age of three and a half months with a history of generalized weakness and delayed gross motor milestones. There was no significant family history of still births, abortions, neurological disorders, or joint contractures. At birth, the twins had good apgar scores, but were noted to have contractures. The twins presented with weights below the 10th and 3rd centile, severe generalized hypotonia and wasting of the proximal and distal groups of limb muscles, along with symmetrical distal joint flexion contractures, obvious fasciculations of the tongue during sleep and activity, paradoxical respiratory movements, and mild spinal scoliosis. The other organ systems were normal. Blood investigations revealed normal creatinine phosphokinase and lactate dehydrogenase. EMG revealed denervation, increased insertional activity, and fibrillations with polyphasic potentials. Histopathology of muscle biopsy of one of the twins showed hypertrophied fibers intermingled with atrophic ones. ATP staining was consistent with neurogenic atrophy. The twins were then diagnosed to have infantile SMA and distal arthrogryposis. They died at the age of eight months from severe pneumonia. In the presence of consanguinity and the absence of family history, Aithala et al (1995) presumed autosomal recessive mode of inheritance of SMA in this case. They further surmised that these infants might form a separate sub group as the occurrence of SMA and arthrogryposis has not been seen in the same families as classic SMA disease.

[See also: Kuwait > Haider et al., 2001]

Saudi Arabia
Mahdi (1991) studied 98 Saudi children with genetic neurodegenerative disorders. Mahdi (1991) indicated that the four most encountered diagnoses were: spinal muscular atrophy, storage (lysosomal) disorders, neurocutaneous syndromes and aminoacidopathies. He noted consanguinity in about 50% of the families.

Yohannan et al. (1991) conducted CT scan imaging of the brain in eight children with Werdnig-Hoffmann Disease (SMA type I). Seven of the patients showed generalized cerebral cortical atrophy and one had low attenuated, non-enhancing areas in the white matter involving both frontal lobes. Yohannan et al. (1991) attributed these changes to repeated episodes of hypoxic injury.

Al Rajeh et al. (1993) reported the findings of a total population survey of Thugbah community in the Eastern Province of Saudi Arabia (SA) to determine its point prevalence of neurological diseases. During this two-phase door-to-door study, all Saudi nationals living in Thugbah were first screened by trained interviewers using a pretested questionnaire (sensitivity 98%, specificity 89%) administered at a face-to-face interview. A total of 23,227 Saudis (98% of the eligible subjects) were screened and those residing in Thugbah on the reference date (22,630) were used to calculate the point prevalence rates. Consanguineous marriages especially between first cousins were present in 54.6%. The overall crude prevalence ratio for all forms of neurological disease was 131/1,000 population. Headache syndromes were the most prevalent disorder (20.7/1,000). Central nervous system (CNS) malformations (0.49/1,000) such as hydrocephalus and meningomyelocele were more prevalent than spinal muscular atrophy (0.13/1,000), congenital brachial palsy (0.13/1,000) and narcolepsy (0.04/1,000).

Salih et al. (1996) studied the pattern of childhood neuromuscular disorders seen in a decade (1982-1992) at King Khalid University Hospital, Riyadh, Saudi Arabia. Eighty-four children (< or = 16 years) were assigned to an entity of neuromuscular disease following review of the clinical, biochemical and neuropsychological data, and after re-examination of the histological and histochemical features of the muscle biopsies. Of the 84 ascertained cases, 40 (48%) had different forms of muscular dystrophy (MD), 26 (31%) had one of the various types of spinal muscular atrophy (SMA) and two (2.4%) hereditary motor and sensory neuropathy type I. A history of consanguinity was present in 55%. Of the 26 cases of SMA, type I (Werdnig-Hoffman disease) was the most prevalent (69%). Consanguinity was ascertained in 65% of SMA families and histories revealed another 14 affected siblings.

[See also: Kuwait > Haider et al., 2001]

United Arab Emirates
Al Talabani et al. (1998) studied the pattern of major congenital malformations in 24,233 consecutive live and stillbirth at Corniche hospital, which is the only maternity hospital in Abu Dhabi, between January 1992 to January 1995. A total of 401 babies (16.6/1,000), including 289 Arabs, were seen with
major malformation. Single gene disorders accounted for 24% of the cases, 76% were due to autosomal recessive disorders. In their study, Al Talabani et al. (1998) observed three cases of type I spinal muscular atrophy born to first cousin couples from the United Arab Emirates. Recurrence was reported in the families. Al Talabani et al. (1998) concluded that their study was very close to representing the true incidence of congenital abnormalities in the whole United Arab Emirates, as they investigated over 98% of deliveries in Abu Dhabi, the capital of United Arab Emirates.

References
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