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MR Findings of Werdnig-Hoffmann Disease in Two Infants

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Summary: We report two infants with Werdnig-Hoffmann disease diagnosed by means of spinal MR imaging, histopathologic examination of muscle biopsy specimens, cloned DNA analysis, electrophysiological examination, and clinical history. The MR findings were consistent with previous histopathologic reports.

Werdnig-Hoffmann disease (WHD), or progressive infantile spinal muscular atrophy, is a genetically determined degenerative condition that manifests during the first 2 years of life and involves the anterior horn cells in the spinal cord and the cranial nerve motor nuclei in the brain stem. It is considered the second most common fatal recessively inherited disease of childhood (1). Magnetic resonance (MR) has proved useful in the diagnosis of spinal cord disease (2, 3).

Case Reports

Case 1

A 14-month-old boy, born after an uneventful prenatal course, was well until 2 months of age, when decreasing limb movements were noted by his mother. By 3 months of age he showed generalized hypotonia of the limbs and poor head control. A survey of disorders of amino acids and organic acids was normal. At 4 months of age, an MR examination of the brain showed findings suggesting atrophy, although electromyography (EMG) showed no signs of denervation. At 6 months of age, the patient was admitted for severe bronchopneumonia and hypotonia. He was noted to have a bell-shaped chest wall, diffuse rhonchi and rales over both lung fields, marked weakness of the muscles in all limbs, absence of deep tendon reflexes, fasciculation of the tongue, absence of Babinski's sign, and head lag; although function of the cranial nerves was intact. A repeat EMG revealed prominent signs of denervation with poor recruitment. An MR study of the whole spine showed a pair of high-signal-intensity dots in the anterior horns of the cervical cord on axial T2-weighted images (Fig 1A). The cervical cord appeared atrophic on both long- and short-repetition-time images. A nerve conduction velocity test revealed marked reduction of amplitude and delayed response of F waves. Examination of the muscle biopsy specimen disclosed fat infiltration, increased interfascicular fibrosis, group atrophic fibers on hematoxylin-eosin stain (Fig 1B), and fiber grouping on Nicotinamide adenine dinucleotide hydrogenase (NADH) stain (Fig 1C). Linkage analysis with a cloned DNA probe showed that the patient was symptomatic homozygous for deletion of the telomeric survival motor neuron gene and that both his parents were asymptomatic carriers.

Case 2

A 13-month-old girl was born by vaginal delivery at term after an uneventful pregnancy, although she was small for gestational age (birth weight, 2400 g). She was well until 3 months of age, when progressive "floppiness" developed. At age 8 months, she experienced an episode of apnea, cyanosis, and loss of consciousness while being fed. No vital signs were detected on admission to a hospital 15 minutes later. Her vital signs returned after a 30-minute resuscitation effort, and she was transferred to our unit for intensive care. Examination at this time revealed floppiness with a frog-leg posture, drooling, a bell-shaped chest wall, rhonchi and rales over both lung fields, tongue fasciculation, decreased muscle power in the limbs, and absence of deep tendon reflexes. Cerebral sonography and MR imaging were performed 9 days later. The former showed mild brain atrophy and increased echogenicity of the basal ganglia. The later demonstrated findings of mild atrophy of the cerebral cortex with increased signal in the globi pallidus on T2-weighted images (Fig 2A). An MR study of the whole spine showed a high-signal-intensity lesion in the central gray matter of the cervical and thoracic portions of the cord on axial T2-weighted images (Fig 2B). The cord was slightly atrophic. EMG disclosed signs of denervation, poor recruitment, and fibrillation potentials. A nerve conduction velocity test showed prominent reduction in amplitude. Histopathologic examination of the muscle biopsy specimen produced findings similar to the descriptions in case 1. Life was maintained by nasogastric feeding and tracheal intubation with machine ventilation.

Discussion

WHD was described by Werdnig in 1891 (4). The disease is characterized by profound weakness of the proximal muscles of the limbs and of the intercostal muscles, and occasionally by marked bulbar dysfunction. Affected infants often assume a frog-leg position. The narrowed thorax usually has a pectus excavatum deformity, and there is flaring of the lower ribs (bell-shaped deformity). Weakness of the tongue and accompanying fasciculations are common, and there may be marked weakness or absence of deep tendon reflexes. The infant's cry is of low volume and unsustained. A small percentage of patients have associated congenital anomalies, mainly orthopedic abnormalities. Pain, temperature, and superficial sensation remain normal. The heart is not involved. Patients are usually within the normal intel-

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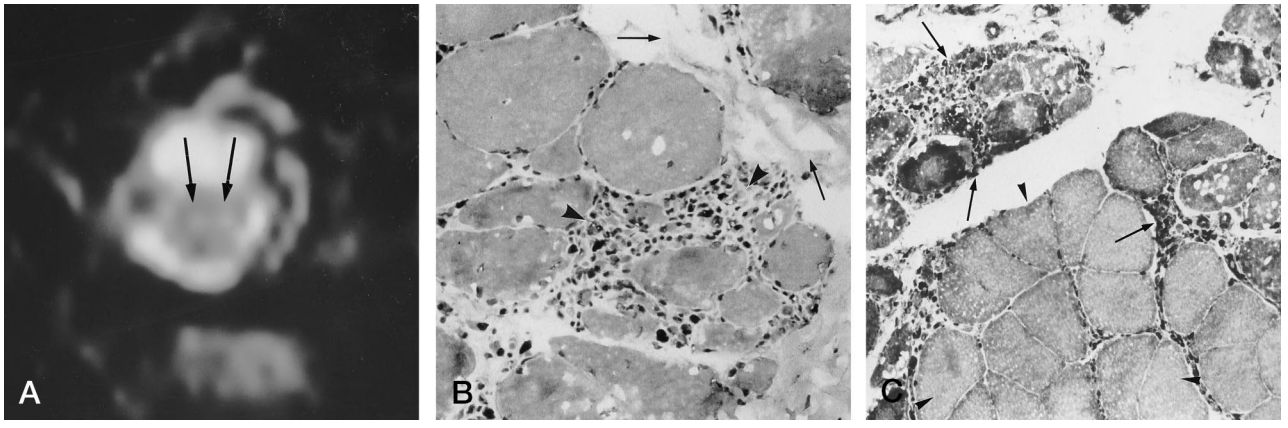

FIG 1. Case 1: 14-month-old boy.

A, Axial T2-weighted MR image (2000/90/2 [repetition time/echo time/excitations]) of cervical spine at C-5 shows a pair of high-signal-intensity dots (*arrows*) in the anterior horn regions of the atrophic cord.

Photomicrographs from histopathologic examination of biopsy specimen from the left quadriceps femoris. *B* shows fat infiltration (*arrows*) and group atrophic fibers (arrowheads) (hemotoxylin-eosin, ×200), while *C* shows fiber grouping (atrophy of group I fibers [*arrows*] and hypertrophy of group II fibers [arrowheads]) (NADH, ×200).

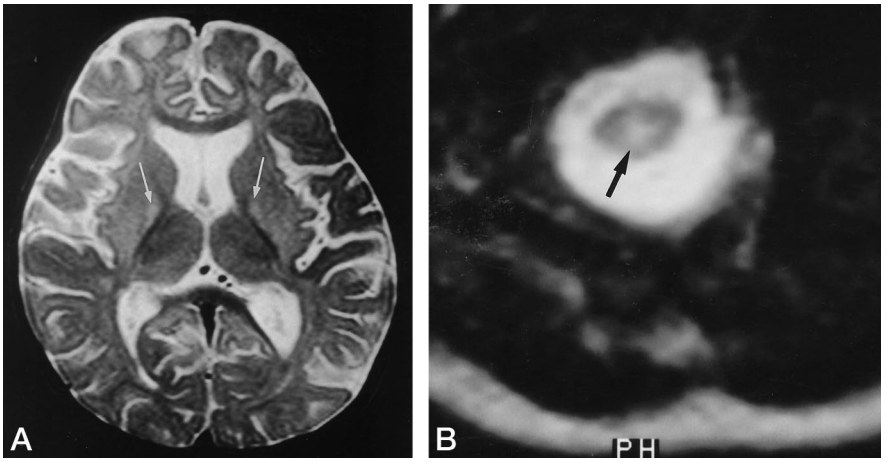

FIG 2. Case 2: 13-month-old girl.

A, MR image of the brain and spine show increased signal in bilateral globi pallidus (*arrows*) and generalized cortical atrophy and mild ventricular dilatation.

B, Axial T2-weighted image (3000/90/1) shows high signal in the central gray matter of the cervical cord (*arrow*).

lectual range. These infants are rarely, if ever, able to sit without aid, roll over, or stand. Clinical progression consists of progressive weakness and increasing inability to manage oropharyngeal secretions, with resultant pneumonitis. Nasogastric or gastrostomy tubes may be required for feeding. With relatively few exceptions, these patients do not survive beyond 3 years of age. The disease is transmitted as an autosomal recessive trait. Linkage analysis with cloned DNA probes has shown that the mutation causing WHD is located on chromosome 5 (5q12–q14) (5, 6). Genetic analysis for the prenatal diagnosis of spinal muscular atrophy is now feasible (5, 6).

EMG shows fibrillation potentials and other signs of muscle denervation (7). Latencies of fibromuscular response and motor nerve conduction velocity along the entire course of the median and ulnar nerves from the spinal cord to the muscle are decreased significantly (8). Microscopic studies of muscle tissue removed during biopsy reveal group lesions of affected fibers interspersed with normal fiber bundles. The affected fibers are smaller in diameter than those in normal tissue, and fat tissue is more abundant between the fiber bundles. Disproportionate preservation of large, rounded fiber in the denervated fasciculi has been found (9). There is no medical treatment to delay the progression of disease. Supportive therapy includes orthopedic care with particular attention to scoliosis and joint contraction, physiotherapy with particular attention to pulmonary drainage, and mechanical aids for assisting the patient to eat and to be as functionally independent as possible.

MR imaging has proved to be useful in the diagnosis of congenital or acquired spinal cord disease in infants and adults (2, 3). In our patient in case 1, the T2 high-signal-intensity lesions in the anterior horn regions of the cervical cord appear to correspond to the motor neuron loss and the pale swollen cells described in a previous histopathologic study (10). It is not known why the disease involves the cervical portion of the cord more obviously than the thoracic or lumbosacral region, as evidenced by T2-weighted MR images. Perhaps a decline in disease progression is one of the causes. This phenomenon was also observed in patient 2, who had abnormal, high T2 signal intensity in the cervical and thoracic cord, although her history of hypoxic-ischemic insult might have contributed to the preexisting brain and spinal cord abnormality stemming from WHD. Moreover, the young spinal cord is particularly vulnerable to hypoxic-ischemic injury in the lumbosacral region owing to the anatomic watershed distribution (11). The high-signal abnormalities in the anterior horn of the spinal cord on T2-weighted images have been described as "owls' eyes"

in adult patients who have sustained spinal cord ischemia during aortic clamping (12). Other diseases, including poliomyelitis, amyotrophic lateral sclerosis, multiple sclerosis, and acute disseminated encephalomyelitis, may produce similar MR findings (13, 14). Thus, in conjunction with clinical history, physical examination, and findings at muscle biopsy, MR imaging may be helpful in the diagnosis and follow-up of this rare lower motor neuron disease.

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