Sensory Neuron Degeneration in Familial Kugelberg-Welander Disease

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ABSTRACT: A 53 year old man developed symptoms of motor neuron disease in childhood. There was a family history of a similar disorder and it was felt to represent a form of Kugelberg-Welander disease. In addition to the motor deficits, sensory abnormalities in his legs were documented during life. Autopsy revealed anterior horn cell loss throughout the length of the spinal cord, with preservation of the phrenic nucleus. The lumbar dorsal root ganglia showed active degeneration of sensory neurons, with nuclear changes exceeding cytoplasmic ones. The fasciculus gracilis showed Wallerian degeneration. The findings provide direct evidence that sensory neurons can degenerate in some forms of motor neuron disease, and that the "demyelination" or "degeneration" of posterior columns sometimes seen in the various forms of motor neuron disease may actually be secondary to cell body disease in the dorsal root ganglia.

CASE REPORT

The patient was 53 years old at the time of death. Although he was not considered to be a floppy infant, he did not begin to walk until 2 years of age, and then in an awkward manner. At age 3-4 years an orthopedic procedure was carried out to correct suspected club feet. During adolescence, there was a slow but progressive deterioration in his motor function. He recalled that he had to be carried up stairs or on long walks as he could not keep up. By age 15, he was confined to a wheelchair because of leg weakness. His arms were affected to a lesser degree. Bulbar symptoms were absent. Progression of his disease was characterized by episodes of deterioration and plateaus when the disease seemed stable.

He first saw a neurologist at age 22 years and was told he had Charcot-Marie-Tooth disease (CMTD). He married and had two neurologically normal children now aged 17 and 20 years. They were seen by a neurologist at age 7 and 10 respectively. EMG and nerve conduction studies done because of the father's diagnosis of CMTD were normal.

He was the youngest of four siblings (Figure 1). An older brother died at age 45 of a progressive, wasting neurologic disorder. He had been able to walk since his early teens, and had been confined to a wheelchair for most of his life. A sister and brother aged 73 and 68 respectively are alive and well with no neurologic disease. The father died of cardiac causes at 92 years of age, and also had a wasting neurologic condition of some years duration, but no autopsy was performed. The mother died at age 92 of a stroke, without other neurologic disease.

He was admitted to hospital 8 months prior to death with pneumonia. He required intubation and mechanical ventilation. A tracheostomy was performed. The neurologic diagnosis at that time was familial progressive spinal muscular atrophy, autosomal recessive (Kugelberg-Welander). In addition to the motor deficits, neurologic examination revealed a marked decrease in vibratory sensation in his legs, with a sensory deficit below the T6 level. Motor and sensory nerve conduction studies were normal. With some difficulty he was weaned from the ventilator and eventually was discharged after a 3 month hospital stay.

One month after admission, while being moved from his chair into bed, hemorrhage occurred around his tracheostomy site and from his oropharynx. Despite resuscitative attempts, he exsanguinated and died.
AUTOPSY FINDINGS

At autopsy, the cause of death was a ruptured fistula between the brachiocephalic artery and trachea, with massive pulmonary hemorrhage. The remainder of the general autopsy was normal except for the marked wasting and contracture of his legs, arms and axial skeleton. The brain, spinal cord (including dorsal root ganglia), and skeletal musculature were sampled.

Microscopy of the cerebral cortex, the basal ganglia and diencephalon were normal. Sections through the brainstem revealed only mild gliosis of the hypoglossal nuclei, with minimal neuronal loss.

Multiple levels of spinal cord revealed normal cortico-spinal tracts (Figure 2), but loss of anterior horn cells throughout the spinal cord, sparing the phrenic nucleus (Figure 3). There was pre-necrotic shrinkage of remaining motor neurons. The neurons of Clarke's column were normal.

Prominent degeneration was seen in the fasciculus gracilis (Figure 2). Examination of the lumbo-sacral sensory ganglia revealed that this was related to perikaryal disease. Neuronal cell bodies in the dorsal root ganglia were seen in all stages of degeneration, with nuclear pyknosis preceding cytoplasmic shrinkage. Chromatolysis was not seen. Most cells exhibited at least some degree of nuclear pyknosis, although some normal neurons were found (Figure 4). Extremely shrunken and pyknotic cells, apparently in the final stages of necrosis were also seen. Nodules of Nageotte marked the locations of former cell bodies which had disappeared (Figure 4). Histologic comparison with age-matched dorsal root ganglia taken from the same spinal levels at autopsy, from individuals who had died without neurologic disease, revealed that the frequency and density of these degenerative changes in the dorsal root ganglia of the present case was approximately five times control.

The previous presumptive diagnosis of Charcot-Marie-Tooth disease was not known at the time of autopsy, and peripheral nerve was not specifically taken, but intramuscular nerves and spinal roots were available for examination.

The dorsal and ventral nerve roots both showed axonal loss (Figure 5). The skeletal musculature showed individual muscle fiber atrophy and grouped fiber atrophy. Intramuscular nerves showed some depletion of axons and occasional axonal swellings (Figure 6).

Figure 1 — Family tree demonstrating pattern of affected family members, compatible with either autosomal or sex-linked recessive inheritance.
DISCUSSION

The onset of disease in childhood and the indolent clinical course place the present case in the spectrum between Werdnig-Hoffmann disease of infancy, and the classic adult form of motor neuron disease — amyotrophic lateral sclerosis, (ALS) and it is most appropriately considered as a form of Kugelberg-Welander disease. The case demonstrated the hallmark findings of motor neuron disease; severe anterior horn cell loss and gliosis. Sparing of the phrenic nucleus was seen, as reported in amyotrophic lateral sclerosis and Werdnig-Hoffmann disease.

A clinical diagnosis of Charcot-Marie-Tooth disease (CMTD) was made when the patient was in his early twenties, but subsequent nerve conduction studies later in the disease process were normal, weighing heavily against that diagnosis. The diagnosis of the rarer "neuronal form" of Charcot-Marie-Tooth disease could be applied in this case, in view of the motor and sensory neuron degeneration which can be seen in that disorder, as well as axonal spheroids in intramuscular nerves. However, patients with the neuronal form of CMTD have shown a relatively benign clinical course, without progressing to respiratory insufficiency requiring intubation. The nosologic distinction between "neuronal forms" of CMTD and forms of motor neuron disease involving sensory neurons is tenuous at best.

A familial form of motor neuron disease — amyotrophic lateral sclerosis has been described by Engel et al. The disease progressed over 2-3 years in several members of two families. At autopsy, there was degeneration of the fasciculus gracilis but the dorsal root ganglia were not examined.

Sensory abnormalities have been reported in ALS, noted in slightly over 10% of cases. However, this figure may be low. A report of four cases described sensory symptoms in the feet and legs. At autopsy, 2 had posterior column degeneration (fasciculus gracilis) and one had dorsal root ganglia involvement. Sensory neuron degeneration in motor neuron disease was strongly suggested by a morphometric study of dorsal and ventral roots.

Familial ALS has been suggested to have more common involvement of sensory tracts than sporadic ALS, perhaps as high as 70%. Recently Radtke et al have shown sensory evoked potential abnormalities in 7 of 16 patients with ALS, corroborating previous observations. There is evidence in classical motor neuron disease for involvement of the neurons of Clarke’s column in addition to sensory neurons — see Tandan and Bradley for review.

In Werdnig-Hoffmann disease, chromatolysis and neuronal degeneration have been reported in the dorsal root ganglia as well as the thalamus, dentate nucleus, optic nerve, Clarke’s column, and lateral geniculate body, suggesting that Werdnig-Hoffmann disease might best be classified as a neuronal system degeneration rather than a pure motor neuron disorder. Although sensory neuron involvement is possibly a con-
stant feature of Werdnig-Hoffmann disease, clinical sensory abnormalities are not a regular feature.\textsuperscript{13}

Familial cases have been more common than sporadic cases in previous reports of Kugelberg-Welander motor neuron disease.\textsuperscript{14,15} Although sensory changes are not usually reported, demyelination in the dorsal columns has been seen.

The present case is the first report of Kugelberg-Welander disease with documented sensory changes during life, long tract changes in the posterior columns, and autopsy-proven active degeneration of dorsal root ganglia neurons. The importance of neuropathologic examination of dorsal root ganglia in motor neuron disease is underscored. Degeneration of the posterior columns in motor neuron disease may not be a primary process in the spinal cord, but rather represent secondary Wallerian degeneration due to cell death in the dorsal root ganglia.

ACKNOWLEDGEMENT

The authors wish to thank Ms. E. Tingle for typing the manuscript.

REFERENCES