Anterior Horn Changes of Motor Neuron Disease Associated with Demyelinating Radiculopathy

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Abstract. Morphologic study of the spinal cord of a patient with generalized motor deficits revealed changes in the anterior horns characterized by the selective loss of large motor neurons, gliosis and the abnormal accumulation of 10 nm filaments which appeared as argyrophilic spheroids in the perikarya and axons of motor neurons. The ventral roots were predominantly affected and showed a variable loss of axons. The remaining axons displayed prominent onion-bulb formations, frequent axonal sprouting and occasionally evidence of active demyelination. The coexistence of a demyelinating motor radiculopathy and anterior horn changes simulating those of amyotrophic lateral sclerosis (ALS) may contribute to our understanding of the unresolved question of whether the neuronal perikaryon or its axon is the primary target in the pathogenesis of ALS. These observations also indicate that a rigid separation of pathogenetic mechanisms into neuronopathy, axonopathy and myelinopathy may not be always possible.

Key Words: Amyotrophic lateral sclerosis; Hypertrophic neuropathy; Motor neuron disease; Onion-bulb formations; Radiculoneuropathy, demyelinating; Regeneration, axonal; Spheroids.

INTRODUCTION

We describe a patient in whom the morphologic changes in the ventral roots were suggestive of a chronic demyelinating neuropathy while the changes in the anterior horns closely simulated those seen in amyotrophic lateral sclerosis (ALS). These observations raise a basic question about the site of the primary abnormality in this patient, i.e. neuronal perikaryon, or their axons. This question also appears to be relevant to the pathogenesis of ALS (1, 2).

CLINICAL HISTORY

This 64-year-old man was admitted for evaluation of large bowel polyps which had been detected by a barium enema. The patient's major complaint was progressive weakness which began insidiously about three to four months before admission. Because of increasing leg weakness which significantly interfered with walking and climbing steps he had to retire from his job as a plumber. There was no family history of neuromuscular disorder. There was no known heavy exposure to lead or other toxic materials.

On the second hospital day, he underwent a fiberoptic colonoscopy which was complicated by perforation. A laparotomy was done for repair of the perforated colon. A neurologic consultation was requested because of persistent hypoventilation and the inability to wean him from the respirator.

A detailed neuromuscular evaluation disclosed moderate to severe weakness of various muscles of the arms and legs. There was atrophy of the anterior tibial and interosseus muscles bilaterally. Sparse fasciculations were observed in the right bi-
Fig. 1. Lower lumbar spinal cord. A. This section shows demyelinated ventral roots (V), normal dorsal roots (D) and a paucity of large neurons. LFB-PAS. ×12. B. This section shows diffuse gliosis of the anterior horn. Holzer. ×12.

ceps. The knee and ankle reflexes were absent; biceps and brachioradialis reflexes were present. The plantar reflexes were flexor. Except for some weakness of the facial and jaw muscles, and questionable fasciculations of the tongue, the cranial nerves were unremarkable. No sensory deficits were detected.

Electrodiagnostic evaluation on the seventh hospital day revealed severe slowing of motor nerve conduction velocity in the left peroneal (21 m/second (s)), left posterior tibial (26 m/s), and left median nerves (25 m/s) with low amplitude, prolonged dispersed compound muscle action potentials and prolonged distal motor latencies. Left median F-response was markedly delayed. No sensory nerve action potentials were obtained. Electromyography revealed single unit interference pattern and moderate fibrillation and sharp wave activity.

Laboratory tests included: normal blood levels of Vitamin B₁₂, folate, lead, creatine kinase, antinuclear antibodies and serum proteins. The electrophoretic patterns of serum proteins and thyroid function tests were normal. Urinary heavy metal screening including coproporphyrin and uroporphyrin showed no abnormality. The cerebrospinal fluid (CSF) was acellular with normal glucose and a protein of 16 mg/dl. A sural nerve biopsy showed no pathologic changes. No morphometric study or teasing preparation was done on the biopsy.

A tentative diagnosis of chronic inflammatory polyradiculoneuropathy was made and the patient was treated with high doses of prednisone with mild temporary improvement. On the 50th hospital day another sample of CSF showed a protein of 28 mg/dl with an IgG/albumin ratio of 0.28, normal myelin basic protein and
absent oligoclonal bands. Electrodiagnostic studies repeated on the 60th hospital day showed continued slowing of motor nerve conduction velocities and evidence of denervation. The patient suffered irreversible hypoxic brain damage after he became accidentally disconnected from the respirator and died several weeks later.

MATERIALS AND METHODS

The autopsy was done four hours after death. A large number of tissue blocks from the brain and various segments of the spinal cord were processed for paraffin embedding and the sections were stained with hematoxylin and eosin (H&E), luxol fast blue (LFB)-PAS, silver (Bodian), Nissl and Holzer's stains. For electron microscopy, samples were obtained from the anterior horns as well as from both ventral and dorsal roots at different levels after the spinal cord had been fixed in formalin for several weeks.

RESULTS

The pathologic changes in the spinal cord were limited to the anterior horn and the roots, predominantly the ventral. The large motor neurons of the anterior horns were reduced in number at all levels and there was a diffuse astrocytic gliosis (Fig. 1). The most severe loss was seen in the lumbosacral segments. In some segments, the neuronal loss appeared asymmetrical and patchy in distribution. There was no discernible loss of neurons in the intermediolateral and Clarke's columns. The Onufrowicz nucleus of the sacral segments also appeared to be intact. Central chromatolysis was seen in an occasional remaining large motor neuron. No Bunina bodies were identified. There were several accumulations of microglia-like cells suggestive of neuronophagia (Fig. 2). There was no evidence of long tract degeneration. The most remarkable features were frequent argyrophilic spheroids of variable size in the anterior horns at all levels, most abundantly in the lumbosacral segments (Fig. 3). The spheroids were composed of densely packed 10 nm filaments sometimes associated with remnants of cytoplasmic organelles (Fig. 4). They were seen in the axons as well as within neuronal perikarya (Figs. 3, 4).

The ventral roots displayed a severe loss of axons compared to the relatively normal-appearing dorsal roots at the same levels (Fig. 5). A large number of the remaining axons in the ventral roots showed prominent onion-bulb formation (Fig.
5A). In addition, an occasional glial bundle and frequent clusters of regenerating axons were seen in the affected roots (Fig. 6). Most of the dorsal roots appeared remarkably normal with no appreciable reduction of axon (Figs. 1, 5B). A small number of regenerating axons were seen in some of the dorsal roots (Fig. 5B). No inflammatory cells were present.

Electron microscopic study of the ventral roots demonstrated typical onion-bulb formation both around myelinated and demyelinated axons (Fig. 7). In addition, an occasional fiber displayed a vesicular degeneration of myelin with preservation of the axons (Fig. 8) similar to that seen in the active phase of a variety of demyelinating conditions (3). Occasional phagocytes containing myelin debris were seen. The fine structure of the regenerating axons appeared similar to that described under experimental conditions (4) and was characterized by collections of axonal sprouts of varying diameter accompanied by Schwann cell processes, all within the confines of a continuous basal lamina (Fig. 9). The glial bundles were composed of a large number of parallel cylindrical astrocytic processes as described previously (5).

The brain showed widespread hypoxic changes in the cortex, basal ganglia and thalamus. There was questionable neuronal loss in the nucleus ambiguus of the medulla accompanied by axonal loss in an occasional lower cranial nerve root. The spinal ganglia, peripheral nerves and skeletal muscles were not available for study. The general autopsy findings were unremarkable.

DISCUSSION

The pathologic changes in the anterior horns of this patient were a selective loss of large motor neurons, argyrophilic spheroid formation and gliosis and are virtually
Fig. 4. A. A spheroid in an axon is composed of interwoven 10 nm filaments with remnants of other organelles. ×12,000. B. An accumulation of 10 nm filaments displacing Nissl substance (arrows). ×4,200; inset ×12,000.

identical to the changes in ALS. The clinical manifestations also indicated lower motor neuron degeneration. However, the presence of demyelination with onion-bulb formation in the ventral roots seems inconsistent with the diagnosis of motor neuron disease and raises the question of whether the neuronal perikarya or their
axons were primarily affected. Onion-bulb formation is generally regarded as the result of the repeated demyelination and repair seen in several acquired or genetically determined conditions (6). Although segmental demyelination and remyelination have been seen in occasional ventral root axons in ALS (7), onion-bulb formation has not, to our knowledge, been reported in ALS or Werdnig-Hoffmann disease, in both disorders degeneration of lower motor neurons is generally considered as the primary event. Therefore, it seems reasonable to assume that the anterior horn changes in this patient were most likely secondary to a ventral radiculopathy.

Coexistence of onion-bulb formation in the ventral roots and neuronal loss in the anterior horns in the same patient as described here appears to be exceedingly rare. We are aware of only one other similar example, a 75-year-old man with advanced Charcot-Marie-Tooth disease (CMTD) since childhood (8). Unlike our patient, onion-bulb formation and axonal loss were also described in the dorsal roots with degeneration of the posterior column. The mechanism of segmental demyelination and remyelination in CMTD with hypertrophic neuropathy is not clear. In keeping with the assumption that the basic abnormality in CMTD is in the neurons and axons (9), it has been postulated that degeneration of myelin may be the result of failure of the axonal mechanism involved in the maintenance of myelin (10). However the possibility remains that there may be a concomitant abnormality of Schwann cells as well (9, 11). Despite a remarkably similar combination of neuronal loss and onion-bulb formation in these two patients, our case is clearly different from CMTD in many respects, both clinical and pathological.
Fig. 6. A. Ventral root with regenerating axons (arrows) and glial bundle (gb). Resin-embedded section. Toluidine blue. ×300. B. Higher magnification of a tangle of regenerating axons sectioned at different planes. Resin-embedded. Toluidine blue. ×650.

Fig. 7. Onion-bulb formation around demyelinated axon (Ax). ×9,000.
The precise nature of the radiculopathy in this case remains obscure. Based on the morphologic changes, this might be classified as a chronic demyelinating polyradiculoneuropathy (12, 13) which usually involves both motor and sensory nerves. Although the peripheral nerves were not studied at autopsy, the abnormal conduction velocities in selected nerves were compatible with a demyelinating neuropathy. Furthermore, a normal sural nerve biopsy and a paucity of sensory deficits were in keeping with the pathologic finding that the ventral roots were predominantly affected. Pure motor neuropathy clinically resembling motor neuron disease appears to be quite uncommon and little information is available on the pathologic aspects of this condition. Autopsy study of one such case with underlying plasma cell dyscrasia demonstrated a demyelinating neuropathy involving the motor nerves; however, no neuronal loss was seen in the anterior horns (14). Detailed studies of the spinal cord in chronic demyelinating radiculoneuropathy are surprisingly few and reveal no consistent changes in the anterior horns. The changes, when present, usually include a variable degree of central chromatolysis and loss of motor neurons which is attributed to retrograde degeneration following axonal loss (12, 13). Indeed the loss of motor neurons has been demonstrated in patients with limb amputation (15). Therefore the neuronal loss in the patient we report seems likely to be the consequence of axonal loss which, in turn, was related to a primary demyelinating neuropathy.

Although small argyrophilic spheroids composed of 10 nm filaments are occa-
sionally seen in the anterior horns in otherwise normal spinal cords (16, 17) their number, size and distribution in this case were clearly abnormal and appeared similar to those described in ALS (18–20). Spheroid formation has been seen in the anterior horns in various unrelated disorders (18–20) as well as in certain experimental animals (21–23). We are not aware of their occurrence following axonal damage which might be the possible explanation for their presence in the case we report. These spheroidal structures have received particular attention in recent years in connection with the pathology of ALS. They are seen in a large proportion of ALS cases apparently in greater number in the early stage of the disease. Furthermore, an abnormal accumulation of filaments in the lower motor neurons is a conspicuous feature in accelerated hereditary canine spinal muscular atrophy, an animal model that closely resembles human motor neuron disease (23). Although impaired slow axonal transport has been implicated in some conditions (24), the pathogenesis and significance of this apparent cytoskeletal abnormality are not clear in most instances. The site of filamentous accumulations whether in the cell body, dendrite or in the axon appears to reflect the underlying cause. For example, such filamentous accumulations in chronic β-β’-iminodipropionitrile (IDPN) toxicity tends to occur in the proximal part of the axons while it is seen in the perikarya and dendrites in chronic aluminum toxicity (25). The findings in our case suggest the possibility that an abnormality of axons outside the central nervous system might be capable of inducing accumulation of neurofilaments in the perikarya and their processes. This might be added to the other underlying conditions that are known to be associated with spheroid formation in the anterior horns.

Another interesting finding in this case is the occurrence of frequent regenerating axonal sprouts. Although a variable degree of axonal damage is known to accompany demyelinating neuropathy (26, 27), little is known about the subsequent morphologic changes especially regeneration in such axons in humans. Axonal sprouting in this case was quite extensive and appeared similar to that described in experimental allergic neuritis (28). This provides further evidence that the primary abnormality in this case affected the axons and not the neuronal perikarya since normally functioning neuronal bodies would seem to be essential for initiating and supporting such exuberant axonal sprouts (29). Occasional regenerating axons have been described in the ventral roots of ALS patients (2, 7, 30) and wobbler mice with inherited spinal motor neuron disease (31). This implies that axonal regeneration, although to a much lesser extent, is possible despite a primary defect of the perikarya (31, 32).

Since the nature of the neurologic illness in this patient is not known, it is difficult to be certain about the pathogenesis and significance of our findings. From the strictly morphologic standpoint, three possibilities might be considered to account for the changes affecting the neurons and myelin in this case, changes that are seldom seen together in the lower motor neurons. First, the most likely possibility is that a demyelinating radiculoneuropathy was the basic lesion and the anterior horn changes were secondary. This seems particularly relevant to the ongoing discussion about whether the perikaryon or its axon is the primary site of motor neuron involvement in ALS (2). Second, an abnormality of the perikaryon or axon might have been the initial event which subsequently induced segmental demyelination. Induction of demyelination and onion-bulb formation by axonal disease has previously been hypothesized (21). This suggests that axon and myelin are interdependent in the maintenance of their structural integrity. Third, it is conceivable that the otherwise normal large motor neurons and the myelin around their axons in the ventral roots were affected independently by a common etiologic factor. If so, then this case may be regarded as unique. Whichever of these possibilities is correct, our observations suggest that the classification of neuropathy into distinct categories namely, neuronopathy, axonopathy and myelinopathy as suggested by Spencer and Schaumburg (33), should not obscure the close interaction of pathogenetic events in the perikaryon, the axon and its myelin sheath.

REFERENCES


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