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Werdnig-Hoffmann Disease: Proposal of a Pathogenetic Mechanism

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Summary. Light and electron microscopic study and morphometric analysis were performed on the spinal cords and roots from six cases of acute Werdnig-Hoffmann disease and four control cases, in search of the pathogenesis of the selective motor neuron changes considered primarily responsible for Werdnig-Hoffmann disease. This investigation posits a centrifugal traction mechanism based upon the discovery of cylindrical outgrowths of glial bundles, selective loss of large myelinated fibers, and axonal degeneration in the proximal portion of anterior spinal roots (and to a lesser extent in posterior spinal roots) in all six disease cases. This traction mechanism exerts principally upon anterior spinal nerve roots and can account for morphologic and morphometric data characteristically ascribed to Werdnig-Hoffmann disease.

Key words: Werdnig-Hoffmann disease – Infantile spinal muscular atrophy – Anterior spinal nerve roots – Posterior spinal nerve roots – Glial bundles – Displaced motor neurons.

Werdnig-Hoffmann disease – infantile spinal muscular atrophy – is a well-known clinical entity; transmitted by an autosomal recessive trait and characterized by early onset of muscle weakness, floppiness, and absent tendon reflexes. It is progressively fatal, although exceptional cases with benign clinical courses have been reported. Described pathologic findings include loss of large motor neurons which leave "empty-cell beds" and chromatolytic neurons in the anterior horn of the spinal cord. These neuronal changes are considered to be primarily responsible for this disease, but their pathogenesis remains unexplained.

In addition to classical histopathology findings, Chou and Fakadej (1971) reported prominent glial proliferation in the proximal portion of otherwise atrophic anterior spinal roots in a case of Werdnig-Hoffmann disease. In order to explore the susceptive pathogenesis, we undertook this investigation. Six autopsied cases with Werdnig-Hoffmann disease and four control subjects were subjected to morphometric analysis of their anterior and posterior spinal roots – to correlate neuronal loss with the newly discovered glial proliferation. Electron microscopy and nerve teasing technique was also applied to root fibers.

Materials and Methods

Six autopsy cases with a history of progressive muscle weakness since early infantile stage were selected. All infants were clinically diagnosed as having acute Werdnig-Hoffmann disease (Pearn and Wilson, 1973), or Type I spinal muscular atrophy (Emery, 1971), and died before the age of 9 months from respiratory problems (Table 1).

Four cases without involvement of nervous system or skeletal muscles, who died at 2 days, $5^1/_2$ months, $6^1/_2$ months and 7 months

Table 1. Clinical summary of 6 autopsied cases with Werdnig-Hoffmann disease

Case No.	Sex	Age of death	Family history	Pregnancy	Onset of disease
1	M	9 M	–	N	neonate
2	M	$4^1/_2$ M	sibling	N	3 weeks
3	M	3 M	–	N	neonate
4	M	9 M	–	↓fetal movement	few weeks
5	M	3 M	–	N	7 weeks
6	F	7 M	?	?	neonate

N = unremarkable pregnancy

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respectively, were studied as controls. Autopsies were done within 12 h after death; entire spinal cords and roots were fixed in 4% buffered glutaraldehyde solution for 1–2 days. Since the third lumbar cord and root segments were well preserved and easily recognizable in most cases, those were selected for this investigation[1]. To compare severity and extent of pathological findings at different levels of spinal roots and cords, equivalent studies were performed at levels T3, T9, L3 and L5 in case No. 6.

Both diseased and control spinal roots and posterior ganglia were post-fixed in buffered osmium tetroxide for 5 h and embedded in epoxyresin. Small parts of the osmicated roots were studied with the nerve teasing technique. The resin-embedded proximal and distal segments of the spinal roots were transversely cut, stained with paragon, and photographed at a final magnification of ×1000 to count the number and measure the diameter of glial bundles and myelinated fibers as well as their axons. Diameter averages were obtained in 3 groups of nerve fibers: a small (up to 5 μ) fiber group; a medium (between 5–10 μ) group; and a large (larger than 10 μ) group.

To determine the ratio of the diameter of the axons to the diameter of the myelinated fibers, 200 fibers of the L3 anterior roots from each case of 3 controls and 6 cases with Werdnig-Hoffmann disease, were measured and plotted on section papers. A regression line was obtained by the method of least squares. Data was applied to the following equation: $y = ax + b$; where y = diameter of axon, x = diameter of myelinated fiber, $a = 200\,\Sigma xy - \Sigma x \cdot \Sigma y / 200\,\Sigma x^2 - (\Sigma x)^2$ and $b = \Sigma x^2 \cdot \Sigma y - \Sigma x \cdot \Sigma xy / 200\,\Sigma x^2 - (\Sigma x)^2$. The standard deviation was accordingly calculated.

Results

I. Histopathology and Electron Microscopy

Although histopathological findings in representative sections from the central nervous system differed from case to case in distribution and severity of altered neurons, the characteristic abnormalities described in previous studies were seen in the motor neurons of the spinal cord and brainstem. There was a remarkable loss of large motor neurons in the anterior horns with an appearance of "empty-cell beds". The remainder of the motor neurons occasionally showed central chromatolysis.

Clusters of motor neurons were located at the periphery of the spinal cord or were entrapped in the glial bundles at the exits of the anterior spinal roots; often bilaterally; at various levels; and in all cases (Fig. 1 A). At high magnification, these "heterotopic" neurons frequently displayed central chromatolysis (Fig. 1 B, C). In one micron section of resin-embedded spinal roots stained with paragon, many glial bundles were observed among scattered small myelinated fibers, in all the proximal portions (at the exit) of anterior spinal roots examined in cases with Werdnig-Hoffmann disease (Figs. 1 D, 2 A). No glial bundles were seen in the control roots (Fig. 2 B). Cells with a round nucleus, a prominent nucleolus, and a basophilic cytoplasm resembling neurons were often entrapped within glial bundles (Fig. 1 D, inset). The glial bundles had tapered off and were no longer discernible at a level approximately 1.5 cm distal to the exit.

Electron microscopy of anterior spinal roots revealed glial bundles consisting of numerous glial filaments closely packed in fibrils; arranged in a longitudinal fashion, and with occasional fibrocytic astrocyte nuclei, but without any collagen fibrils (Fig. 2 C). The glial fibrils within each bundle appeared tightly adherent to each other through punctate adhesions (Fig. 2 C, inset). Cells resembling neurons were readily distinguishable from astrocytes because of an absence of glial filaments and abundant rough endoplasmic reticulum in the cytoplasm. In the distal portion of the anterior spinal roots, no glial bundles were recognizable and degenerating myelinated fibers were occasionally encountered.

Compared to anterior spinal roots, the posterior spinal roots and spinal ganglia were relatively well-preserved; apart from a mild selective loss of thick myelinated fibers (Fig. 3 A). Glial bundles were also present in two of five examined cases below the level of L3 in posterior proximal segments (Fig. 3 A, asterisk). These glial bundles were far smaller in size and less in number than those in anterior spinal roots at corresponding levels.

On nerve teasing, axonal degeneration – characterized by sporadic "linear rows of myelin ovoids" (Dyck et al., 1975) – was occasionally demonstrated in anterior and posterior spinal roots in all cases (Fig. 4 B). Myelin ovoids were also confirmed on electron microscopy (Fig. 4 A) especially at distal segments where glial bundles were tapering off (Fig. 4 B, arrowheads) and collagen fibrils proliferated.

II. Morphometric Analysis

a) Myelinated Fibers in Anterior Spinal Roots (Table 2)

In controls, anterior spinal roots were well myelinated at level L3. The total numbers of myelinated fibers varied from 4194 to 5848 in bimodal distribution and peaked at 2–3 μ and at 7–8 μ. Average diameter of the small fiber group was 3.04 μ; the medium fiber group, 7.65 μ. In cases with Werdnig-Hoffmann disease, the majority of thick fibers had disappeared and the total numbers of small myelinated fibers ranged from 1652 to 2077, at the proximal portion of L3. Average fiber diameters ranged from 2.87–4.42 μ and showed a unimodal distribution with a complete disappearance of large fibers. Both the total number and size of myelinated fibers in patients with Werdnig-Hoffmann disease were less than $^1/_2$ those of controls in given roots. A set of histograms (Fig. 5) represents frequency distributions of diameters of myelinated fibers per L3 anterior spinal roots, from 4 controls and 5 cases with Werdnig-Hoffmann disease. The selective loss of thick myelinated fibers in Werdnig-Hoffmann disease is clearly demonstrated.

b) Myelinated Fibers in Posterior Spinal Roots (Table 3)

The total numbers of myelinated fibers in posterior spinal roots at the level of L3 in controls, ranged from 12261 to 20911, with a frequency distribution peak at 2–3 μ (Fig. 6). Average diameters ranged from 3.87–4.46 μ. In the 5 Werdnig-Hoffmann disease cases, total numbers of myelinated fibers in the L3 posterior spinal roots varied from 10550 to 17518, with peak frequency distribution at 2–3 μ. Average diameters ranged from 3.30–4.11 μ (Fig. 6). Total numbers of myelinated fibers in L3 posterior roots differed considerably among cases with Werdnig-Hoffmann disease. Average total numbers of myelinated fibers between the 5 Werdnig-Hoffmann cases and 4 controls were approximately the same, despite the loss of large fibers in Werdnig-Hoffmann disease. Unlike the bimodal anterior spinal root fibers, diameter frequency distribution of myelinated fibers in L3 posterior roots was unimodal. The distribution peak was at a 2.0–3.0 μ range in both control and Werdnig-Hoffmann cases. Although average diameters in Werdnig-Hoffmann patients appeared to have shifted slightly to smaller fiber sizes, this was deemed secondary to a preferential loss of the large fiber group (as occurred in anterior spinal roots).

c) Glial Bundles in Spinal Roots (Table 4)

No single glial bundle was found in either the L3 anterior or L3 posterior roots in 4 controls. In Werdnig-Hoffmann disease, glial

[1] In case 5, the lumbar cord had been previously removed for other studies, leaving only the lower thoracic cord and roots available for study

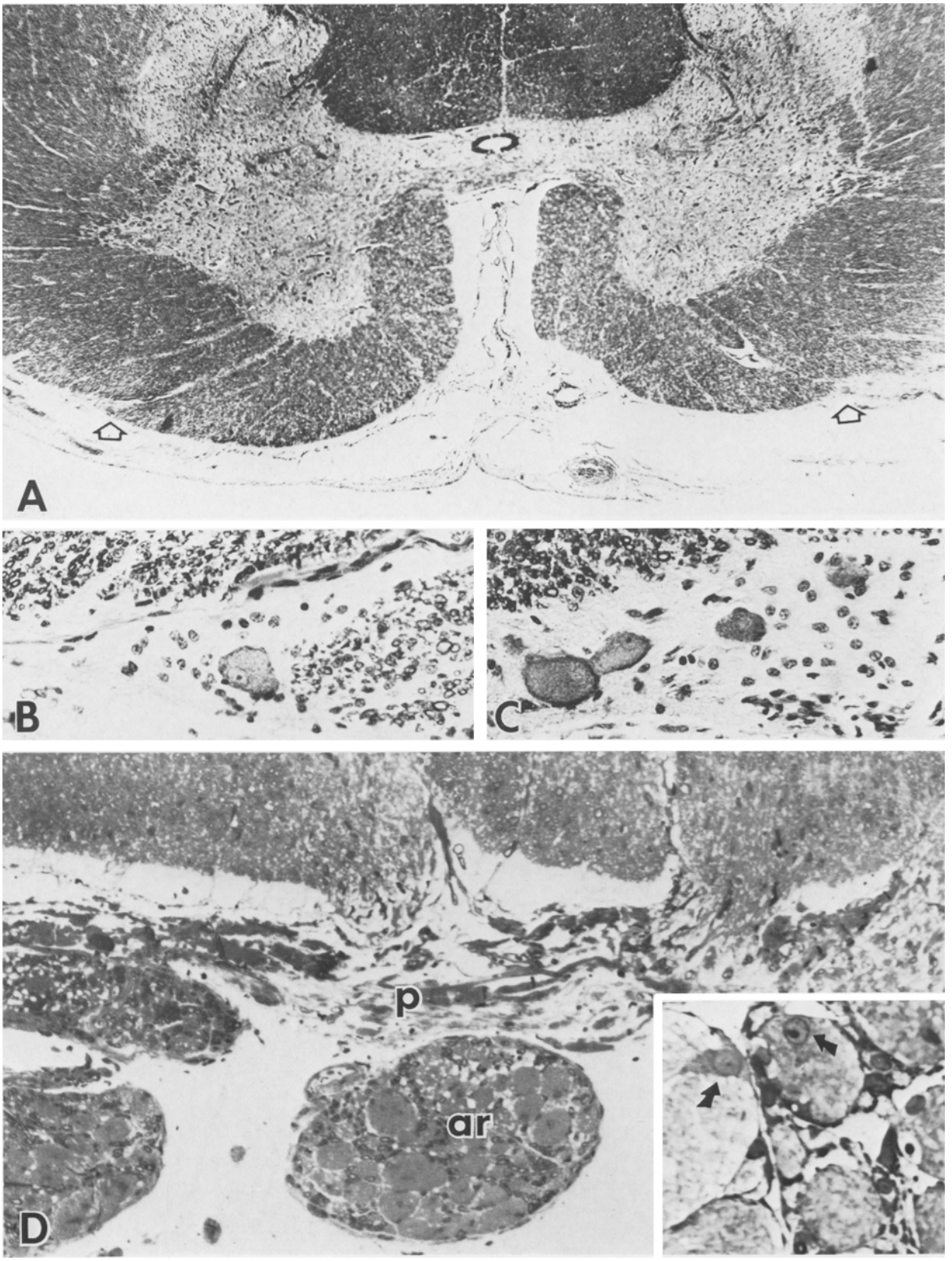

Fig. 1. **A** Loss of large motoneurons in the anterior horns of the cervical spinal cord. Distally displaced neurons (arrow) are entrapped in glial bundles at the exit of each anterior spinal root. Kluver strain; × 40. **B** Higher magnification showing displaced neurons with central chromatolysis in the left root. × 160. **C** Clusters of chromatolytic neurons in the right root. × 160. **D** Numerous glial bundles in the proximal portion of anterior spinal root (ar) at the exit through the fibrotic pia matter (p). Resin-embedded section, Paragon stain; × 180. Inset: at high magnification, entrapped neurons (arrow) are occasionally recognizable. × 900

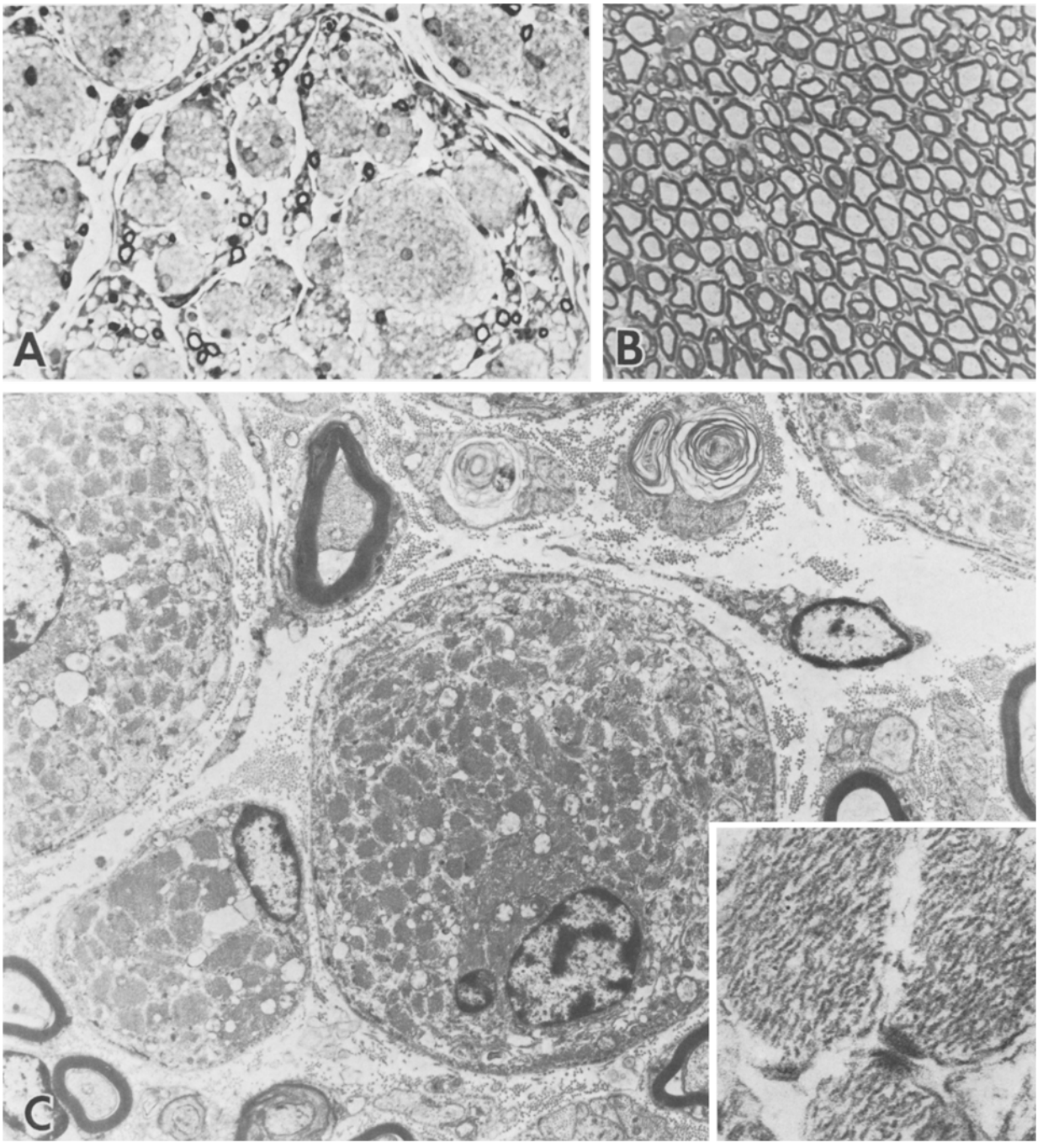

Fig. 2. A Glial bundles in the proximal portion of anterior spinal root at L3. Note marked loss of thick myelinated fibers; relatively well preserved thin myelinated fibers. Resin-embedded section, Paragon stain; ×500. **B** Absence of glial fibers in the L3 anterior root from a control – $5^1/_2$ month-old child. ×500. **C** Electron micrograph of anterior spinal root from case no. 6 demonstrating transversely sectioned glial bundles consisting of numerous glial fibrils. ×6000. Inset: Glial fibrils – containing glial filaments measuring 70 – 80 μ in diameter – adherent to each other with punctate adhesions. ×68000

bundles were consistently found. The numbers of glial bundles varied from case to case, ranging from 18 – 325. Diameters varied from 5 – 70 μ, with an averaged median diameter of 15.9 μ. In posterior spinal roots, glial bundles were less in number and diameter in comparison to corresponding anterior roots: up to 125 (at L5 in case No. 3); diameters ranged from 5 – 50 μ, with an averaged median diameter of 7.2 μ.

d) Relationship of Diameter of Axon to Diameter of Myelinated Fiber in Anterior Spinal Roots (Fig. 7)

In order to assess the process of either axonal degeneration or demyelination which might exist in Werdnig-Hoffmann disease, the ratio (g) of the diameter of the axons to the diameter of the myelinated fibers in the L3 anterior spinal roots was compared

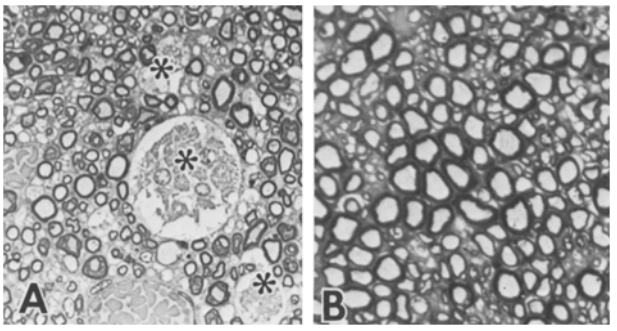

Fig. 3. A Proximal portion of posterior spinal root (L3) from case no. 6, showing a mild selective loss of thick myelinated fibers and scattered glial bundles (asterisk). Resin-embedded section, Paragon stain: ×365. **B** Posterior spinal root (L3) from $6^1/_2$ month-old control child. ×365

with the ratio in controls. As illustrated in Figure 8, no significant difference of the regression line, (as well as 2 standard deviations about the line), was noted between those of controls and cases with Werdnig-Hoffmann disease. This suggested that the small myelinated fibers in Werdnig-Hoffmann disease were not the result of axonal degeneration or atrophy of large neurons, but represented preserved nerve fiber populations, corresponding to the small fiber group in the controls.

Discussion

In addition to classic findings of degeneration and loss of anterior motor neurons in the spinal cord and brainstem, this investigation evidenced significant new findings in all 6 Werdnig-Hoffmann cases studied. These findings consisted of marked glial outgrowth and a selective loss of thick myelinated fibers, with active axonal degeneration in both anterior and posterior spinal roots.

Werdnig (1891, 1894) and Hoffmann (1893) originally reported—in patients with Werdnig-Hoffmann disease—an abnormality of anterior spinal roots; describing them as being grossly thinned from degeneration and containing decreased numbers of myelinated nerve fibers. Hoffmann briefly described a profound proliferation of the neuroglia at the exit of anterior spinal roots which extended into the white matter along the intramedullary portion of anterior spinal roots. But Chou and Fakadej (1971) first described the presence of glial outgrowth within the proximal anterior spinal roots using histopathological techniques and electron microscopy. They concluded that this glial outgrowth reflected the basic defect in Werdnig-Hoffmann disease. The presence of glial bundles was subsequently confirmed by Chou (1973) in two additional cases and by Carpenter et al. (1975), Ohama et al. (1976), and Goebel et al. (1976).

The cylindrical glial bundles in the present and previously reported cases measured up to 70 μ in diameter and were predominantly seen in the lower

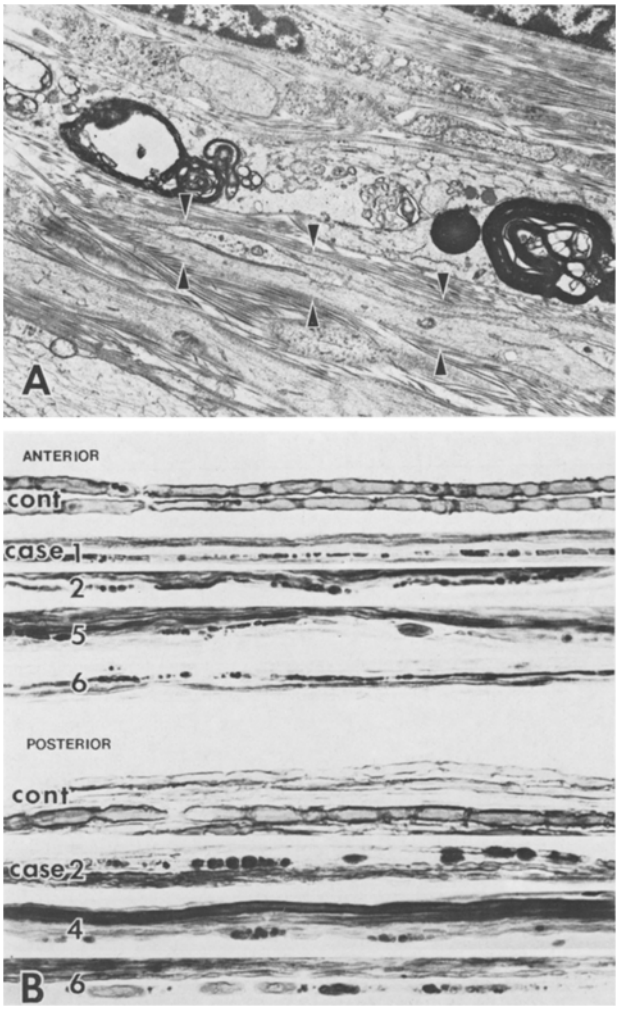

Fig. 4. A Degenerated myelin breakdown products (myelin ovoids) in neurilemma tube. Glial bundles are tapering off (arrow heads) and replaced by collagen fibrils. ×3765. **B** Teased nerve fibers of both anterior (from a control and cases no. 1, no. 2, no. 5, and no. 6) and posterior (from a control and cases no. 2, no. 4, and no. 6) spinal roots. Note numerous myelin ovoids or balls in cases with Werdnig-Hoffmann disease, suggesting active axonal degeneration

lumbar and upper sacral anterior spinal roots. They were longitudinally arranged and tapered off along the roots' distal pathways. On electron microscopy, they were composed of fibrils which contained glial filaments measuring 70–80 Å in diameter and occasionally, astrocytic or neuronal nuclei and cytoplasm.

The morphogenesis of glial bundles is unknown. It seems probable that injury to spinal roots may trigger and promote glial proliferation in Werdnig-Hoffmann disease, because glial bundles are seen in both anterior and posterior spinal roots without microscopic evidence of degeneration in posterior spinal ganglia. Additionally, the ultrastructural characteristic of

Table 2. Numbers and average diameters of myelinated fibers in anterior spinal roots at exit of spinal cord

Case number	Sex/Age	Level	Total numbers	$\leqq 5\mu$	$\leqq 10\ \mu$	$>10\ \mu$
Controls						
1	F/2 d	L3	5583 (5.99)	1904 (3.40)	3635 (7.27)	44
2	M/5 M	L3	5848 (4.45)	3995 (2.95)	1806 (7.60)	47
3	F/6½ M	L3	4194 (6.15)	1506 (3.09)	2664 (7.80)	24
4	M/7 M	L3	5150 (5.26)	2861 (2.89)	2212 (8.12)	77
(Average numbers at L3)			5194 (5.29)	2567 (3.04)	2579 (7.65)	
Werdnig-Hoffmann cases						
1	M/9 M	L3	1978 (2.87)	1973 (2.80)	5 (6.00)	0
2	M/4½ M	L3	1761 (3.12)	1699 (2.99)	62 (6.50)	0
3	M/3 M	L3	2077 (3.53)	1776 (3.07)	301 (6.20)	0
4	M/9 M	L3	1975 (3.04)	1925 (2.95)	50 (6.00)	0
5	M/3 M	low thoracic	847 (3.19)	830 (3.12)	17 (6.23)	0
6	F/7 M	L3	1652 (4.42)	1483 (2.93)	169 (6.27)	0
		T3	1201 (2.63)	1177 (2.55)	24 (6.20)	0
		T9	999 (3.47)	904 (3.19)	95 (6.11)	0
		L5	1420 (4.42)	1089 (3.87)	331 (6.23)	0
(Average numbers at L3)			1889 (3.37)	1771 (2.94)	118 (6.23)	0

( ): average diameters in micra

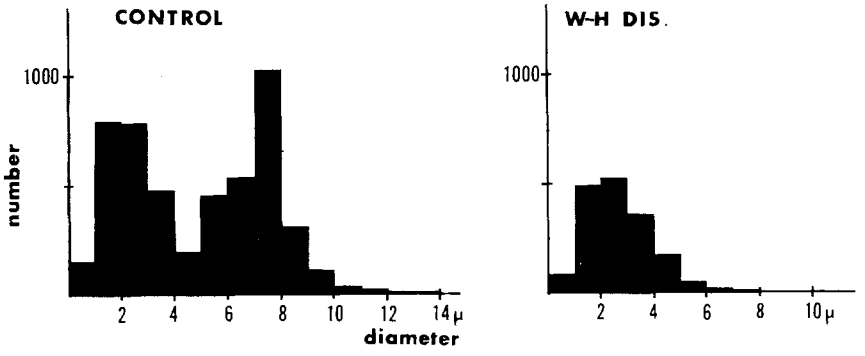

Fig. 5
Comparison of anterior spinal nerve fibers size in five patients with Werdnig-Hoffmann diesease and four control cases at L3

central chromatolysis in the anterior motor neurons (Chou and Fakadej, 1971) were considered consistent with those seen after a distal nerve section or injury (Engh and Schofield, 1972).

Proliferation of collagenous elements in spinal roots occurs after a local injury. If glial proliferation is a repair process, it may be a unique reaction to an unusual injury. Strands of collagenous tissue in anterior spinal roots were reported in a case with familial arthrogryposis multiplex congenita (Bargeton et al., 1961) and in two similar cases by Peña et al. (1968). Muscle lesions in these three cases were similar to those of Werdnig-Hoffmann disease. Additionally, three cases with chronic progressive polyradiculopathy with elevated cerebro-spinal fluid protein (Kasman and Bernstein, 1974) exhibited clinical courses and neurologic findings indistinguishable from Werdnig-Hoffmann disease. Two of them, examined neuropathologically, showed a significant fibrous proliferation in anterior spinal roots with marked loss of myelinated fibers, but with only minor changes of anterior horn cells. A case reported by Bargeton et al. (1961) and case I of Peña et al. (1968) displayed changes consistent with central chromatolysis in their anterior horn cells. All these investigators believed the fibrosis in anterior spinal roots to be the primary lesion, rather than the changes in the anterior horn cells. It is possible that these fibrotic strands were glial bundles, since attempts were not made to distinguish between fibrous and glial strands in their studies.

In amyotrophic lateral sclerosis (Brownell et al., 1970) and hypertrophic neuropathy, diffuse fibrosis and "onion bulb" fibrosis (Dyck and Lambert, 1968) have been (respectively) described in anterior spinal roots.

In Werdnig-Hoffmann disease, glial proliferation appears to be a pathognomonic feature and to have started early in fetal life with insidious progression. What makes these Werdnig-Hoffmann disease glial bundles singularly unique and distinctively different from banal astrogliosis of the CNS is: 1. cylindrical

Table 3. Numbers and average diameters of myelinated fibers in posterior spinal roots at entrance of spinal cord

Case number	Level	Total numbers	≦5 μ	≦10 μ	>10 μ
Controls					
1	L3	12261 (4.46)	9248 (3.76)	3004 (6.60)	9
2	L3	20911 (3.87)	16935 (3.10)	3860 (7.08)	116
3	L3	13393 (4.40)	9513 (3.11)	3742 (7.42)	138
4	L3	14855 (4.28)	11480 (3.15)	2936 (7.60)	439
Average numbers at L3		15355 (4.20)	11794 (3.24)	3385 (7.18)	176
Werdnig-Hoffmann cases					
1	L3	15849 (3.45)	13326 (2.77)	2510 (7.02)	13
2	L3	17518 (4.11)	13518 (3.45)	3965 (6.89)	35
3	L3	16136 (3.81)	12804 (3.03)	3327 (6.83)	5
4	L3	15646 (3.30)	13724 (2.82)	1922 (6.69)	0
5	low thoracic	6667 (3.48)	5814 (3.01)	853 (6.69)	0
6	L3	10550 (4.06)	8064 (3.23)	2485 (6.75)	1
Average numbers at L3		15140 (3.73)	12287 (3.04)	2842 (6.84)	11

( ): average diameters in micra

Table 4. Numbers and median diameters of glial bundles in anterior and posterior spinal roots of Werdnig-Hoffmann disease

Case number	Level	Total numbers	Median diameters (μ)	Range (μ)
Anterior spinal roots				
1	L3	18	28.33	5–70
2	L3	325	14.30	5–64
3	L3	310	13.66	5–60
4	L3	82	14.65	5–30
5	low thoracic	2	12.50	10–15
6	L3	100	15.90	5–60
	T3	2	15.00	10–20
	T9	3	15.00	5–30
	L5	180	13.47	5–38
Posterior spinal roots				
3	L3	1	7.0	7.0
	L5	125	8.33	5–50
6	L3	2	6.00	5– 7
	L5	77	7.12	5–28
	S2	3	7.50	5–10

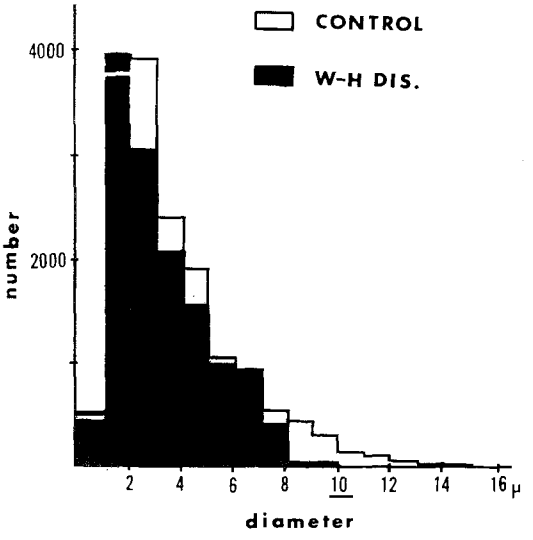

Fig. 6. Comparison of posterior spinal nerve fibers size in five patients with Werdnig-Hoffmann disease and four control cases at L3

elongation; 2. basement membrane ensheathment; 3. averaged median diameters of 15.9 μ in anterior and 7.2 μ in posterior roots; 4. tapering off and disappearance 1.5 cm distal to exits; 5. astrocytic, neuronal soma and nuclei enclosed within; 6. complete absence of collagen fibers inside.

Before discussing the histogenesis of these peculiar, glial bundle structures, other histopathologic characteristics – central chromatolysis, selective loss of large motor neurons, "empty-cell beds", displaced neurons – and data from morphometric analysis must be conjunctively evaluated. "Empty-cell beds" may represent sites previously occupied by large motor neuron somas; a plausible supposition since both morphometric studies on cytons (Robertson et al., 1977) and anterior spinal root fibers in this study indicate a selective loss of large motor neuron soma and their axons and since Ramón y Cajal's (1909) classic study confirmed large axons are derived from large neurons. Hence, in Werdnig-Hoffmann disease, large motor neurons probably once developed and somehow progressively disappeared. The relatively well preserved small nerve fibers are consequently not part of a sequel of either atrophy or hypoplasia of large motor neurons; according to this investigation's data determining the ratio (g) between the axon and total fiber diameters. How have large motor neurons selectively vanished, leaving "empty-cell beds" in the anterior horns? The central chromatolysis or ballooning of motor neurons must have preceeded the process of disappearance, leaving these "beds". If this assumption is correct, the pathogenic process must initially reside at the axons in the anterior roots; a fact previously suspected by Batten (1910). What kind of injury would induce selective damage to large fibers; leaving small fibers, including γ fibers

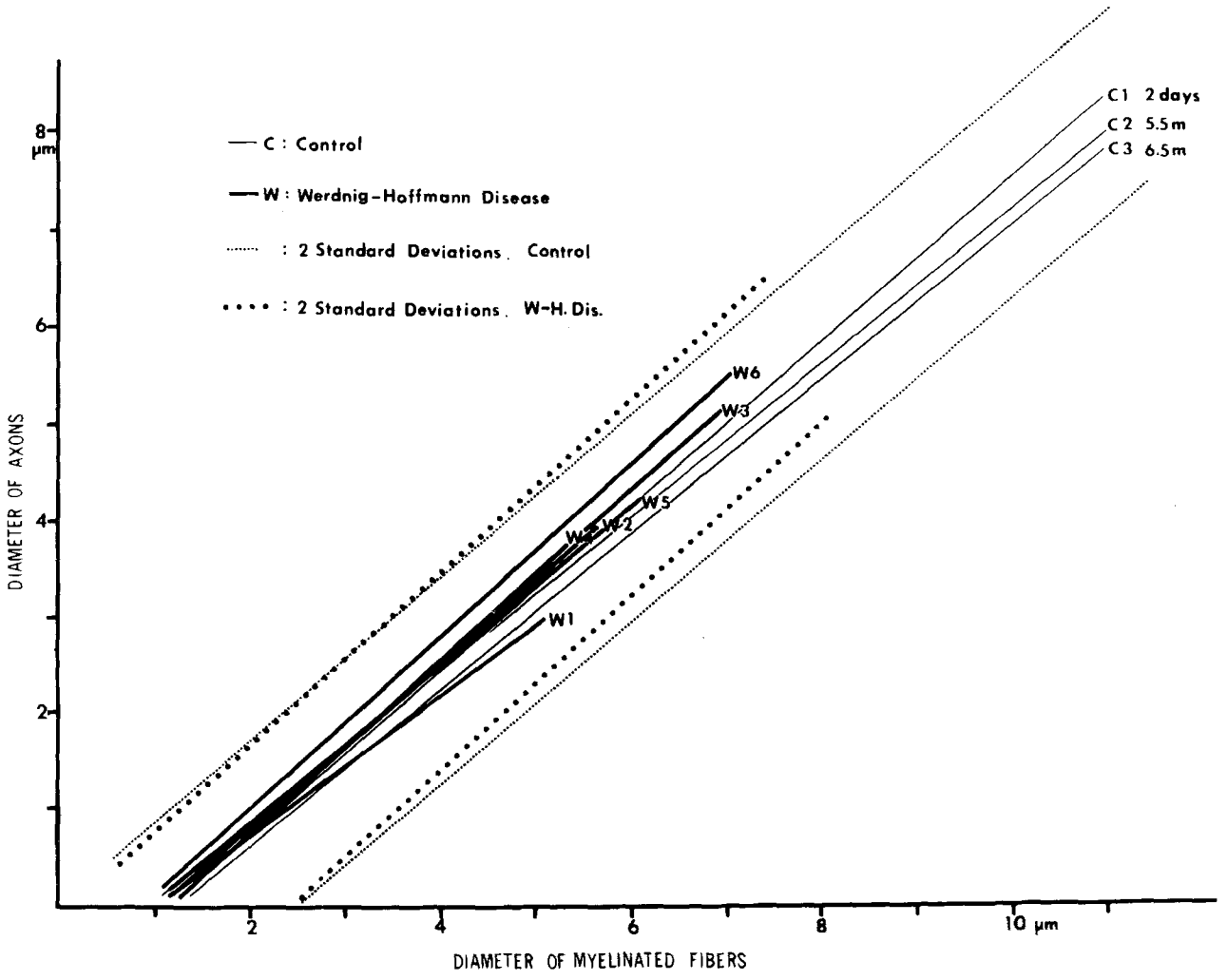

Fig. 7. No significant difference of the regression line – as well as 2 standard deviations about the line – was noted between controls and Werdnig-Hoffmann cases

intact? Preservation of thin myelinated fibers was described by Greenfield and Stern (1927) in peripheral nerves and would explain why muscle spindles were not affected in Werdnig-Hoffmann (Nonaka et al., 1974). Various prenatal injuries by metabolic, nutritional, infectious, circulatory and hereditary factors have been presumed in the etiology of Werdnig-Hoffmann disease (Brandt, 1950). The development of peculiar glial bundles, distal displacement of motor neurons, central chromatolysis, "empty-cell beds", and especially, the selective loss of large motor fibers can be best (collectively) explained by mechanical injury to spinal roots. Such a mechanical injury is probably predetermined by a hereditary factor; transmitted specifically by an autosomal recessive trait.

The pathomechanism causing selective loss of thick myelinated fibers can be explained by a pressure vessel model or Laplace's law, i.e., "the tension (t) in the wall of a cylinder is proportional to the difference between internal and external pressures (p) and to radius (r) of the cylinder ($t = p \times r$)" (Strain and Olson, 1975; MacGregor et al., 1975). In other words, when an external pressure or stress is applied to a nerve, the larger the diameters of nerve fibers, the greater the stress and damages inflicted. This phenomenon has been well documented in animals following experimental compression of various nerves (Aguayo et al., 1971; Ochoa et al., 1972; Strain and Olson, 1975) and in entrapped nerves as a result of aging in guinea-pigs (Marotte, 1974).

In Werdnig-Hoffmann disease, a pressure effect may be exerted on the anterior and posterior spinal roots. This investigation confirmed a recent report (Goebel et al., 1976) that active degeneration – with diminished numbers of thick myelinated fibers – and glial outgrowth occurs in the posterior spinal roots of lower lumbar and sacral segments. However, posterior root changes were less severe than those seen in anterior spinal roots. This active pathological process in posterior spinal roots may subsequently

produce a secondary degeneration in posterior spinal ganglia and in ascending pathways in the spinal cord (Beevor, 1902; Conel, 1940; Ajuriaguerra et al., 1950; Nieves and Castello, 1970; Marshal and Duchen, 1975; Carpenter et al., 1975; and Goebel et al., 1976). These spinal cord findings must be the result of a degeneration secondary to lesions at the posterior roots, since none of our six cases – all of whom died before nine months of age – demonstrated any significant alterations in posterior spinal ganglion cells. Although sensory deficit is often not clinically detectable, a sensory involvement concurrent to muscle weakness does not preclude a diagnosis of Werdnig-Hoffmann disease. Therefore, should Werdnig-Hoffmann disease be classified as a motor neuron disease or as a hereditary radiculopathy?

Distally displaced neurons with occasional central chromatolysis entrapped in glial bundles at the exits or within anterior spinal roots were observed in all examined cases with Werdnig-Hoffmann disease. A similar finding was described by Goebel et al. (1976) as a probable egression of central nervous system elements from the cord. The presence of neurons in anterior spinal roots initially led us to assume they were being slowly pulled out from the anterior horns by a centrifugal traction (Nonaka and Chou, 1976) and imposing a simultaneous "tethering" effect upon spinal roots. As was stated by de Lange (1938), a few scattered heterotropic neurons may be encountered at the marginal white matter near the anterior horns in normal infants under one year of age. We have examined eight cases of infants without neurological symptoms and found a few neurons in all at or below S2 – S3 levels; none of them displayed central chromatolysis. These distally displaced neurons may be more common and numerous in Werdnig-Hoffmann disease than in normal subjects. As cited by de Lange (1938) "heterotopic" neurons have also been described by Werdnig (1891 and 1894), Dunken and Weingartner (1921), Bielschowsky (1929), and Geddes et al. (1936) in Werdnig-Hoffmann disease. Furthermore, Brandt (1950) – in his extensive study on Werdnig-Hoffmann disease – noted . . . "the best preserved anterior horn cells to be situated near the margin of the anterior horns". He attempted to explain this on the basis of blood circulation and absorption of nutrient. The preservation of peripheral neurons may be simply due to displacement.

Our conjectured centrifugal traction theory effectively explains established morphometric data. The "tethering" effect upon spinal roots would induce incessant centrifugal displacement of motor neurons – preferentially the larger neurons – followed by a cylindrical out-growth of glial bundles after filling the "empty-cell beds" and projecting into the myelinated axons in anterior spinal roots. The egressed glial bundles would eventually occupy space inside the neurilemmal tube, destroying myelin sheath, but leaving the basement membrane intact. Such a "tethering" process in anterior spinal roots would preferentially disrupt larger myelinated fibers, bringing about central chromatolysis of the perikarya in anterior horns and selective loss of large peripheral nerve fibers. In posterior spinal roots, this "tethering" process would also disrupt large intramedullary nerve fibers, inducing similar glial outgrowth, and (rarely) ascending tract degeneration in the posterior column as well as secondary changes in posterior spinal ganglia. Additionally, this "tethering" or traction mechanism would provide an explanation as to why the loss of large myelinated fibers is greater distally in anterior but greater proximally in posterior spinal roots (Nonaka and Chou, 1976).

The fundamental pathogenic process responsible for this traction effect remains speculative. But the traction theory proposed as responsible for the genesis of hydrocephalus in Arnold-Chiari malformation (Lichtenstein, 1942), may be applicable in Werdnig-Hoffmann diesease; i.e., the longitudinal growth of vertebral bodies in patients with Werdnig-Hoffmann diesease may be greater than the growth of their spinal cord or roots. The fetal curvature of a spine and the timing of its extension may account for the fact that anterior spinal roots are more severely involved than posterior roots. If this supposition is tenable, maintaining patients with Werdnig-Hoffmann disease in a fetal posture could ameliorate the usual grave prognosis.

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