
MATERIALS AND METHODS

Within 6 to 72 hours of death, 50 human cadavers without obvious neurological or neuromuscular diseases underwent removal of their cervical spinal cords with attached roots, dorsal root ganglion, and meninges. The cords were perfused and fixed with a mixture of formalin, alcohol, phenol, glycerin, and water in proportions of 4:20:3:4:29, respectively, using approximately 400 ml per kilogram of body weight.

RESULTS OF POSTMORTEM CERVICAL X-RAY EXAMINATION AND MACROSCOPIC OBSERVATION REVEALED THAT SIX CADAVERS HAD A C5–6 DISC SPACE OF HALF OR LESS THAN THE NORMAL NEIGHBORING INTERVERTEBRAL SPACES AND MARKED OSTEOPHYTES ON ONE C5–6 LUSHKA JOINT. THESE SIX CASES ALSO DEMONSTRATED POSTERIOR INDENTATION IN BOTH THE VENTRAL AND DORSAL ROOTS PROXIMAL TO THE C-6 DORSAL ROOT GANGLION, DUE TO A DISC PROTRUDING POSTERIORLY OR OSTEOPHYTES ON THE INDENTED SIDE; BOTH THE VENTRAL AND DORSAL ROOTS ON THE OTHER SIDE APPEARED NORMAL (FIG. 1). THESE SIX CASES WERE DESIGNATED THE RADICULOPATHY GROUP. X-RAY FINDINGS IN SEVEN CADAVERS SHOWED A NORMAL APPEARANCE OF THE VENTRAL AND DORSAL ROOTS ON BOTH THE RIGHT AND LEFT SIDES; THESE CADAVERS WERE DESIGNATED THE CONTROL GROUP. THE MEAN AGES AT DEATH ± STANDARD DEVIATION (YEARS) IN THE RADICULOPATHY GROUP AND CONTROL GROUP WERE 77 ± 9 AND 77 ± 10, RESPECTIVELY.

SPECIMEN PREPARATION

From the C-6 nerve roots on both the right and left sides in the radiculopathy and control groups, specimens 5 mm in length of all fascicles of each ventral and dorsal root were taken from the site in which both ventral and dorsal roots were indented, 5 mm from the proximal end of the C-6 dorsal root ganglion. The specimens were fixed with 1% osmium tetroxide for 6 hours, dehydrated, and embedded into epoxy. Transverse epoxy sections (1-μm thick) of each fascicle were stained with toluidine blue. Photographic enlargements (× 40) were used to obtain the total transverse fascicular area (TTFA) (mm²/root) for each transverse section of ventral and dorsal roots from each side of each cadaver. Another set of photographic enlargements (× 1000) of every 12th field of the endoneurial area of the transverse section of each root

LOWER NUMBER AND THINNER MYELIN OF LARGE MYELINATED FIBERS IN HUMAN CERVICAL COMPRESSION RADICULOPATHY

YOSUKE OISHI, M.D., AKIO OHNISHI, M.D., KATSUMI SUZUKI, M.D., AND TERUYUKI HOJO, M.D.

DEPARTMENTS OF ORTHOPAEDIC SURGERY, NEUROLOGY, AND ANATOMY AND ANTHROPOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF OCCUPATIONAL AND ENVIRONMENTAL HEALTH, KITAKYUSHU, JAPAN

THE AUTHORS CONDUCTED A MORPHOMETRIC INVESTIGATION OF THE HISTOPATHOLOGICAL ALTERATIONS IN MYELINATED FIBERS (MFs) OF THE NERVE ROOTS OF C-6, WHICH SHOWED MACROSCOPIC INDENTATION, PRESUMABLY DUE TO CERVICAL SPONDYLOTIC RADICULOPATHY. IN SIX CADAVERS, DESIGNATED AS THE RADICULOPATHY GROUP, IN WHICH THE NERVE ROOTS OF C-6 SHOWED INDENTATION DUE TO COMPRESSION ON ONE SIDE (INDENTED SIDE) AND THE REMAINING NERVE ROOTS (NORMAL SIDE) SHOWED A NORMAL APPEARANCE MACROSCOPICALLY, MORPHOMETRIC FINDINGS OF THE NERVE ROOTS AND THE MFs ON BOTH THE INDENTED AND NORMAL SIDES WERE EVALUATED AND SUBJECTED TO BLIND COMPARISON. SEVEN CADAVERS WITH NORMAL-APPEARING C-6 NERVE ROOTS SERVED AS CONTROLS. IN THE CONTROL GROUP, THERE WERE NO DIFFERENCES IN THE MORPHOMETRIC PARAMETERS: THAT IS, TOTAL TRANSVERSE FASCICULAR AREA, TOTAL NUMBER OF SMALL AND LARGE MFs, AND RELATIONSHIP BETWEEN MYELIN THICKNESS AND THE RADIUS OF THE AXON BETWEEN THE RIGHT AND LEFT SIDES IN EITHER THE VENTRAL OR DORSAL ROOTS. THERE WAS NO EVIDENCE FOUND OF AXONAL DEGENERATION, ONGOING DEMYELINATION, OR LOSS OF MFs IN EITHER THE VENTRAL OR DORSAL ROOTS IN THE RADICULOPATHY GROUP ON THE INDENTED SIDE. HOWEVER, THERE WERE SIGNIFICANTLY LOWER NUMBERS OF LARGE MFs PER ROOT AND SIGNIFICANTLY THINNER MYELIN SHEATHS RELATIVE TO AXON SIZE ON THE INDENTED SIDE COMPARED WITH THOSE ON THE NORMAL SIDE IN BOTH THE VENTRAL AND DORSAL ROOTS. THESE FINDINGS ARE CHARACTERISTIC ALTERATIONS OF THE MFs PRODUCED BY CHRONIC LOW-GRADE COMPRESSION.

KEY WORDS • MYELINATED FIBER • COMPRESSION • CERVICAL RADICULOPATHY • MORPHOLOGICAL STUDY • PATHOLOGY
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was used to obtain the MF density (number/mm²), which was care-
fully distinguished from the Schwann cell nuclei, and a histogram of the size–frequency distribution of the diameter of MF from the MF area was determined mathematically. The transverse profiles were assumed to be circular; an image analyzer (IBAS Interaktives Bild-Analyzen System, Kontron Bilanlyse, Eching, Germany) was used.

The total MF number (number/root) of each root was calculated based on the TTF/A (mm²/root) and the MF density (number/mm²). The demarcation value of the diameter difference between the large and small MFs was obtained based on the diameter–distribution histo-
gram in the controls. Subsequently, the total number of MFs in the ventral root was divided into the numbers of large (diameter ≥ 7 µm) and small (diameter < 7 µm) MFs. Similarly, the total number of MFs in the dorsal root was divided into the numbers of large (diameter > 7 µm) and small (diameter ≤ 5 µm) MFs.

From this information, the morphometric parameters, such as TTF/A (mm²/root), MF density (number/mm²), total MF number (number/root), number of large MFs (number/root), number of small MFs (number/root), ratio of the number of large MFs to total number of MFs and ratio of the number of small MFs to total number of MFs were obtained for each ventral and dorsal root. Furthermore, in each ventral and dorsal root on both the right and left sides in each case assigned to the control and radiculopathy groups, light microscopic images, with a final magnification × 4000 of 100 MFs sampled at random, were used to obtain the MF area (µm²), including both the myelin sheath and axon areas and the axon area (µm²) surrounded by the innermost layer of the myelin sheath, in each MF. These calculation were mathematically con-
verted to fiber radius and axon radius, respectively, using an image analyzer (Cosmozone 1S, Nikon, Japan).

In 100 MFs from each root, the size–frequency distribution of the radii of axons was obtained and the total number of axons (as in total number of MFs) in the ventral root was divided into the num-
ber of large (radius > 3 µm) and small (radius ≤ 3 µm) axons and the total number of axons (as in total number of MFs) in the dorsal root was divided into the number of large (radius > 3 µm) and small (radius ≤ 2 µm) axons. Furthermore, axon diameter (the shortest diameter in micrometers), axon/myelin ratio (axon area/myelin area) and axon/fiber ratio (axon area/MF area) were calculated. Each of the above morphometric analyses was per-
formed without knowing whether it was on the right or left side in the controls, and whether it was on the indented or normal side in the radiculopathy group.

Statistical Analysis

The Wilcoxon signed-ranks test was used for statistical analysis of the differences in the data for each of the ventral and dorsal roots between the right and left side in the control group and between the indented and normal side in the radiculopathy group.

Results

Macroscopic and Light Microscopic Findings

An obvious unilateral posterior indentation of C-6 ven-
tral and dorsal roots, approximately 10 mm in length, not-
ed especially at the subarachnoid angle was macroscopi-
cally identified in the radiculopathy group (Fig. 1). On light microscopy, it was found that small MFs were dis-
tributed more frequently and diffusely in both the ventral and dorsal roots on the indented side than on the normal side in the radiculopathy group. On the indented side, nar-owing of the lumen of the endoneurial vessels and peri-
nervial fibrosis were evident compared with findings on the normal side.

Representative transverse sections with high-power magnification of the ventral and dorsal roots on both the indented and normal sides in the radiculopathy group are shown in Fig. 2. Myelin ovoids indicating active axonal degeneration, demyelinated axons, onion-bulb formation, clusters of small MFs, and infiltration of phagocytic macrophages were not found in any section of the roots from the control group or in either normal or indented roots from the radiculopathy group.

Morphometric Study of the Control Group

There were no significant differences in any morpho-
metric parameters of the ventral or dorsal roots between the right and left sides in the control group. The his-
tograms of the size distribution of the diameters and radii of axons of the MFs on the right and left sides of each ven-
tral and dorsal root showed very similar patterns, which were characteristic for ventral and dorsal roots, respec-
tively.

Morphometric Study of the Radiculopathy Group

The morphometric data are summarized in Tables 1 and 2. On the indented side, TTF/A, large MF number, large MF number/total MF number, and number of large axons were decreased (p < 0.05), and MF density, small MF number/total MF number, axon/myelin ratio and axon/fiber ratio were increased (p < 0.05) compared to those in the normal side in both ventral and dorsal roots. On the indented side, the numbers of small MFs and small-radius axons were greater than those on the normal side only in the ventral root (p < 0.05). However, the normal and indented side showed no significant difference in total MF number and axon diameter.

Histograms of the size–frequency distribution of the di-
ameters of the MFs in the ventral root (Fig. 3 upper left and right) revealed that the number of MFs larger than 10
μm in diameter was less on the indented side than on the normal side. The peak in the size–frequency distribution of large MFs 10 to 12 μm in diameter in the normal side was not found in the indented side. Similarly, in the dorsal root (Fig. 3 lower left and right), there were fewer MFs larger than 5 μm in diameter on the indented side than on the normal side. The peak in size distribution of large MFs 6 to 8 μm in diameter in the normal side was not found in the indented side. In histograms of the size–frequency distribution of the radii of the axons of the MFs of the ven-

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
\textbf{C-6 Root} & \textbf{TTFA} (mm\(^2\)) & \textbf{MF Density} (no. mm\(^{-2}\)) & \textbf{Total No. of MFs} (no./root) & \textbf{No. of Large MFs} (no./root) & \textbf{Ratio of Large MFs to Total MFs} \\
\hline
ventral indented side & 1.081 & 6.452 & 6,738 & 3,355 & 3,383 & 0.481 & 0.319 \\
SD & 0.668 & 1,222 & 1,385 & 1,656 & 1,011 & 0.179 & 0.180 \\
normal side & 1.596 & 4.776 & 6,942 & 4,874 & 2,068 & 0.696 & 0.304 \\
SD & 0.680 & 1,384 & 1,255 & 1,235 & 496 & 0.076 & 0.076 \\
significance & p < 0.05 & p < 0.05 & NS & p < 0.05 & p < 0.05 & p < 0.05 & p < 0.05 \\
dorsal root & & & & & & & \\
indented side & 2.540 & 12,071 & 25,664 & 8,634 & 17,201 & 0.327 & 0.673 \\
mean & 1.184 & 6,153 & 6,422 & 4,464 & 6,375 & 0.166 & 0.166 \\
SD & 3.307 & 8,896 & 27,954 & 13,692 & 14,260 & 0.496 & 0.505 \\
significance & p < 0.05 & p < 0.05 & NS & p < 0.05 & NS & 0.061 & 0.061 \\
normal side & 1.021 & 2,228 & 4,951 & 1,781 & 3,862 & 0.061 & 0.061 \\
mean & 1.021 & 2,228 & 4,951 & 1,781 & 3,862 & 0.061 & 0.061 \\
significance & p < 0.05 & p < 0.05 & NS & p < 0.05 & NS & 0.061 & 0.061 \\
\hline
\caption{Morphometric analysis of the parameters of myelinated fibers in C-6 ventral and dorsal roots, comparing indented and normal sides in six cadaveric specimens in the radiculopathy group*}
\end{tabular}
\end{table}

* Abbreviations: TTFA = total transverse fascicular area; MFs = myelinated fibers; SD = standard deviation; NS = not significant.
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![Composite histograms of the size–frequency distribution of the diameters of myelinated fibers (MFs) in the ventral (upper left and right) and dorsal (lower left and right) C-6 roots from six cadaveric specimens in the radiculopathy group.](image)

**TABLE 2**

Comparison of the number of large and small axons, axon diameter, axon/myelin ratio, and axon/fiber ratio in the ventral and dorsal roots between the indented and normal side in six cadaveric specimens in the radiculopathy group.

<table>
<thead>
<tr>
<th>C-6 Root</th>
<th>No. of Large Axons (no./root)</th>
<th>No. of Small Axons (no./root)</th>
<th>Axon Diameter (μm)</th>
<th>Axon/Myelin Ratio</th>
<th>Axon/Fiber Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>ventral indented side</td>
<td>4,931</td>
<td>1,807</td>
<td>0.97</td>
<td>3.70</td>
<td>0.77</td>
</tr>
<tr>
<td>mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>919</td>
<td>1,166</td>
<td>0.10</td>
<td>1.54</td>
<td>0.07</td>
</tr>
<tr>
<td>normal side</td>
<td>3,991</td>
<td>2,951</td>
<td>1.13</td>
<td>1.66</td>
<td>0.62</td>
</tr>
<tr>
<td>mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>700</td>
<td>830</td>
<td>0.31</td>
<td>0.17</td>
<td>0.03</td>
</tr>
<tr>
<td>significance</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
<td>NS</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>dorsal indented side</td>
<td>20,227</td>
<td>5,437</td>
<td>0.78</td>
<td>3.46</td>
<td>0.76</td>
</tr>
<tr>
<td>mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>6,059</td>
<td>3,549</td>
<td>0.90</td>
<td>1.18</td>
<td>0.06</td>
</tr>
<tr>
<td>normal side</td>
<td>18,339</td>
<td>9,613</td>
<td>0.86</td>
<td>1.41</td>
<td>0.58</td>
</tr>
<tr>
<td>mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>4,235</td>
<td>1,937</td>
<td>0.07</td>
<td>0.39</td>
<td>0.07</td>
</tr>
<tr>
<td>significance</td>
<td>NS</td>
<td>p &lt; 0.05</td>
<td>NS</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

* SD = standard deviation, NS = not significant.

**Discussion**

Many patients with cervical spondylotic radiculopathy show mild sensorimotor symptoms and signs, compared with those suffering acute compression of the spinal roots. Typical symptoms, such as pain, paresthesia, and discomfort in the shoulder or upper extremity, are predisposed to relief with conservative therapy. Therefore, to improve understanding of the pathological process underlying such symptoms, spinal roots were examined histologically that were presumed to have been chronically compressed in the cervical spondylotic radiculopathy shown on post-mortem X-ray examination. Unfortunately, there was no information about the symptoms and signs in the subjects prior to death. However, this study is unique in comparing MFs in indented spinal roots with contralateral roots without indentation, especially using systematic morphometric methods.

**Fig. 3.** Bar charts showing composite histograms of the size–frequency distribution of the diameters of myelinated fibers (MFs) (mean ± standard error) in the ventral (upper left and right) and dorsal (lower left and right) C-6 roots from six cadaveric specimens in the radiculopathy group. In the ventral root, there were fewer MFs larger than 10 μm in diameter on the indented side (upper right) than on the normal side (upper left). In the dorsal root, there were fewer MFs larger than 5 μm in diameter on the indented side (lower right) than on the normal side (lower left). See text for further explanation.
Morphometric Study

Based on the morphometric data we concluded the following: 1) the nature and degree of the pathological change in both ventral and dorsal roots were very similar; 2) active axonal degeneration, ongoing demyelination, and loss of MFs were absent; 3) the number of large MFs was significantly decreased without significant decrease in the total number of MFs; 4) the thickness of the myelin sheath relative to axon size on the indented side. In the ventral root, in which the greater percentage of TTFA is occupied by large MFs compared with that area in the dorsal root, the decrease in the large MFs may easily lead to a decrease in the TTFA.

Histopathological Study of the Chronically Compressed Root

In animal experiments, Delamarter, et al., analyzed the electrophysiological and histopathological effects of mechanical constriction of the cauda equina in beagles; the constriction was acutely applied and chronically maintained. Their histological results in the cauda equina that had been constricted 25% were comparable to our findings; in our data the mean TTFA in the ventral and dorsal roots on the intended side was 32% and 23% less, respectively, than on the normal side in the radiculopathy group. They found enlargement of axons in three, loss of fibers with axonal degeneration in two, and slight loss of myelin without loss of axon in one of three animals. There were no morphometric studies performed using epoxy-embedded sections; therefore, it is difficult to compare the data sets. However, their findings seem to reflect more severe compression of the nerve fibers producing a blockage of axoplasmic transport and axonal membrane damage leading to axonal degeneration than our findings.

Histopathological Studies of the Chronically Compressed Nerve Trunk

Other researchers’ histopathological findings of MFs in chronically compressed nerve trunks in humans were similar to our findings in the spinal roots. Thomas and Fullerton showed the reduction of MF size in the median nerve under the retinaculum in a patient with carpal tunnel syndrome; Dellon and Mackinnon demonstrated a decrease in the large MFs and marked thinning of the myelin sheath in an entrapped human ulnar nerve, although their morphometric data were limited. In the subclinical entrapment of the human ulnar nerve, the presence of bulbous swelling in the myelin and intercalated demyelinated segments in teased fiber preparations were described with a normal MF diameter spectrum.

In an experimental study, Aguayo, et al., showed a decrease in the number of large MFs in a chronically constricted sciatic nerve in rabbits and the presence of an internode of thin myelin sheath in teased fiber preparations at the compression site. However, there were no significant differences in the mean diameter or the density of the MFs between control nerves and compressed nerves distal to the site of constriction at the ankle level. Therefore, histopathological findings of chronically compressed MFs of peripheral nerves in humans and experimental animals were characterized by a decrease in the number of large MFs without significant loss, axonal degeneration, and thinning of the myelin sheath. Consequently, we conclude that our findings in the spinal roots are similar to those in MFs of the chronically compressed peripheral nerve trunk. Probably the nature and degree of such pathological changes are essentially the same between motor and sensory myelinated nerve fibers because our morpho-
metric findings were almost identical in ventral and dorsal roots.

Pathogenesis of the Alterations of Cervical Spondylotic Radiculopathy

The pathogenetic mechanisms of alterations in the MFs in chronic compression of the spinal roots and nerve trunks are not as well understood as those mechanisms in acute compression. However, it is known that in chronic compression, adverse effects, such as direct mechanical deformation of the myelin sheath and axon, ischemia of the compressed segment due to narrowing of epineurial and endoneurial arteries, endoneurial edema with increased endoneurial pressure and with biochemical alteration of the endoneurial fluid due to disruption of blood-nerve-barrier, and derangement of axoplasmic transport may affect the nerve over a long period, although the effects are much less severe than in acute compression. There were no MFs that showed axonal degeneration or ongoing demyelination; therefore, regeneration following axonal degeneration and remyelination following demyelination do not seem to be satisfactory explanations for the presence of MFs with thin myelin sheaths relative to axon size or the lower number of large MFs produced by both the thinner myelin sheaths and smaller axons. However, the thinner myelin sheaths and smaller axons may be independently produced directly and locally by the multiple adverse effects discussed above.

With regard to clinical implications, our finding is that the presence of the focal narrowing of axons in ventral roots is direct evidence supporting the double-crush syndrome. 16

Conclusions

We systematically performed morphometric studies on the C-6 nerve roots with an indentation presumably due to chronic compression, in cervical spondylotic radiculopathy subjects. The decrease in the number of large MFs and large axons without decrease in the total number of MFs, and the thinner myelin sheath relative to axon size and decrease in the TTFAs were concluded to be characteristic of chronically compressed MFs in human spinal roots. These findings are useful for understanding the signs and symptoms as well as the effect of surgical treatment in patients with cervical spondylotic radiculopathy.

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References


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Address reprint requests to: Yosuke Oishi, M.D., Department of Orthopaedic Surgery, University of Occupational and Environmental Health, School of Medicine, Iseigaoka 1–1, Yahatanishi-ku, Kitakyushu 807, Japan.