INTERNAL MEDICINE

An Autopsy Case of Respiratory Failure Induced by Repetitive Cervical Spinal Cord Damage due to Abnormal Movement of the Neck in Athetoid Cerebral Palsy

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Abstract

We herein report the clinical and autopsy findings of a 48-year-old right-handed man with athetoid cerebral palsy who suffered from cervical myelopathy due to abnormal neck movement, and who died of respiratory failure. Pathologically, the external appearance of the ventral surface of the cervical spinal cord revealed a linear indentation running obliquely at the level between the C4 and C5 segments. In the most severely compressed lesion, the gray matter was predominantly affected and severely atrophic. Microscopically, clusters of oligodendrocytes associated with thinly myelinated axons were also observed in the lateral funiculus. The latter findings are unique, and could be interpreted as regenerative and/or restorative phenomena of the central nervous system following chronic repetitive spinal cord compression.

Key words: athetoid cerebral palsy, myelopathy, respiratory failure, neuropathological finding, cervical spondylosis, oligodendrocyte

Introduction

Cerebral palsy (CP), one of the most common neurological disorders in childhood, is defined as a group of disorders affecting the development of movement and posture, which are attributed to non-progressive disturbances occurring in the developing fetal or infant brain (1). Among the several forms of CP, the athetoid form is well known for its tendency to lead to cervical myeloradiculopathy, which develops in association with abnormal neck movements, and which is associated with progressive disability, even in early adult life (2, 3).

To date, there have been few reports regarding respiratory failure as a late complication of athetoid CP or of the histopathological findings related to athetoid CP-associated myelopathy (4). We herein describe an autopsy case of athetoid CP that was associated with progressive respiratory failure and quadriplegia, which developed in adult life, and report on the histopathological findings of the cervical spinal cord.

Case Report

A 48-year-old right-handed Japanese man was admitted to our hospital due to respiratory failure. He had been diagnosed with athetoid CP and had experienced a moderate hearing disturbance since childhood. He had been independent in his activities of daily living and was able to walk and ride a bicycle until he was 40 years of age. At 41 years of age, he began experiencing episodes of weakness and sensory disturbance affecting all four limbs, but recovered spontaneously several times over the following 5 years. He had also repeatedly burned his fingers without noticing while smoking, due the apparently diminished temperature perception of his fingers.

At 45 years of age, he underwent emergency abdominal surgery due to paralytic ileus; however, the cause was unclear. He then gradually became unable to walk by himself, and at 47 years he became almost wheelchair-bound, leading
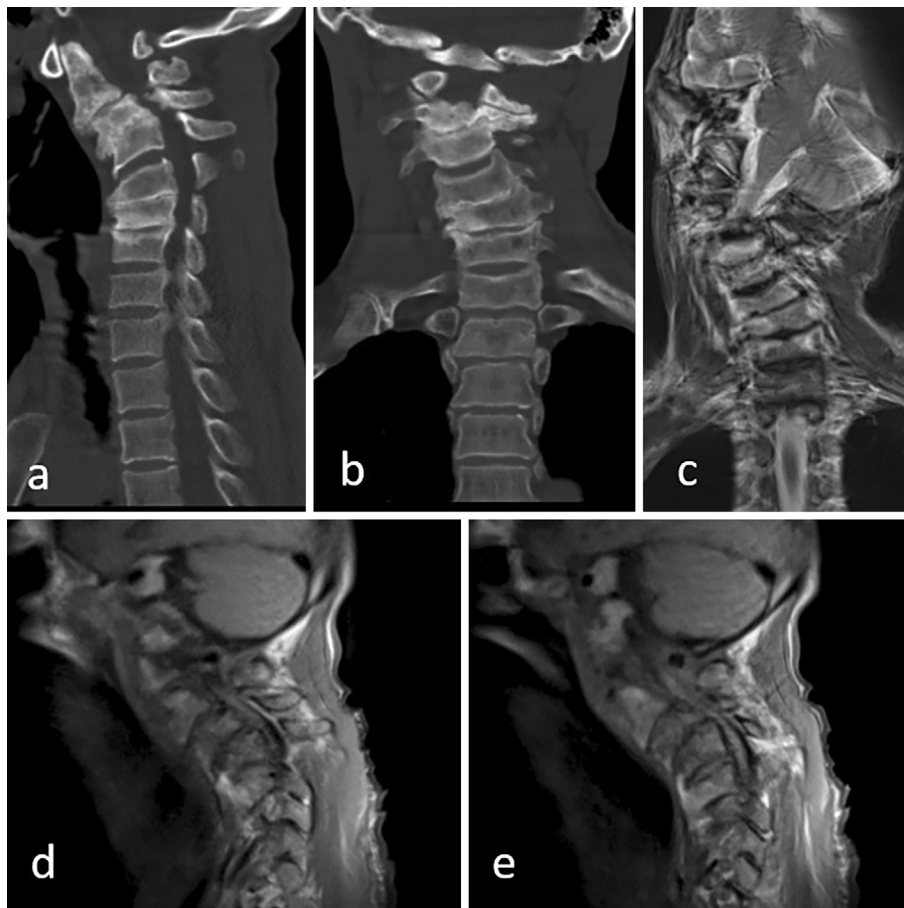
Figure 1. Cervical CT reconstruction images (lateral view [a] and anterior view [b]). The cervical vertebrae were twisted, and scoliosis, kyphosis, and disc-space narrowing of the C2/3, C3/4, C5/6, and C6/7 were evident. A coronal cervical MRI T2-weighted image (c) and sagittal cervical T1-weighted images (d, e). The cervical spine was rotated, and the spinal cord was compressed at the level of C3-C4.

to institutionalization at a care facility. He continued to be able to use his hands and eat by himself. At 48 years of age, he developed a consciousness disturbance with weakness of both upper extremities, and was transferred to a local hospital, where respiratory insufficiency was observed secondary to alveolar hypoventilation. Non-invasive positive pressure ventilation (NPPV) was therefore initiated. He regained consciousness, but the weakness of both upper extremities showed no improvement. Four months later, he was transferred to our hospital for further evaluation.

On general examination, he was mildly dyspneic at rest, showing shallow breathing with a respiratory rate of 25 breaths per minute. Neurologically, he was fully alert and oriented. His speech was dysphonic and unintelligible, but he was able to communicate using a board with written words and sentences. He showed continuous facial grimacing and orofacial-lingual dyskinesia. He exhibited irregular rotatory head movements with his head turning to the left for most of the time when he was awake. Marked muscle atrophy was observed in the distal parts of the upper and lower extremities. With the exception of the fingers of his right hand, which he could move voluntarily, he was quadriplegic.

Superficial sensations including pain and temperature were severely impaired below the level of the C4 dermatome, but his proprioceptive sensation was relatively well preserved. His biceps and triceps tendon reflexes were hypoactive, and his patellar tendon reflexes were hyperactive. Babinski signs were positive bilaterally. He had been catheterized due to urinary retention, and he also suffered from severe constipation.

An arterial blood gas analysis showed marked hypercapnia (pH 7.340, pCO_2 75.9 Torr, pO_2 53.3 Torr, HCO_3 39.9 mmol/L). The laboratory data on admission showed no other major abnormalities. Cervical spine radiographs indicated marked spondylotic changes from the C2 to C6 vertebral levels with kyphotic deformity. Coronal and sagittal computed tomography (CT) reconstruction images of the cervical spine showed cervical scoliosis, kyphosis, and disc space narrowing at the C2/3, C3/4, C5/6, and C6/7 intervertebral levels (Fig. 1a and b). Magnetic resonance imaging (MRI) performed under sedation revealed cervical scoliosis with severe focal compression of the cord at the C3-4 vertebral level (Fig. 1c, d and e).

The patient and his family opted not to undergo conventional tracheostomy positive pressure ventilation (TPPV) or
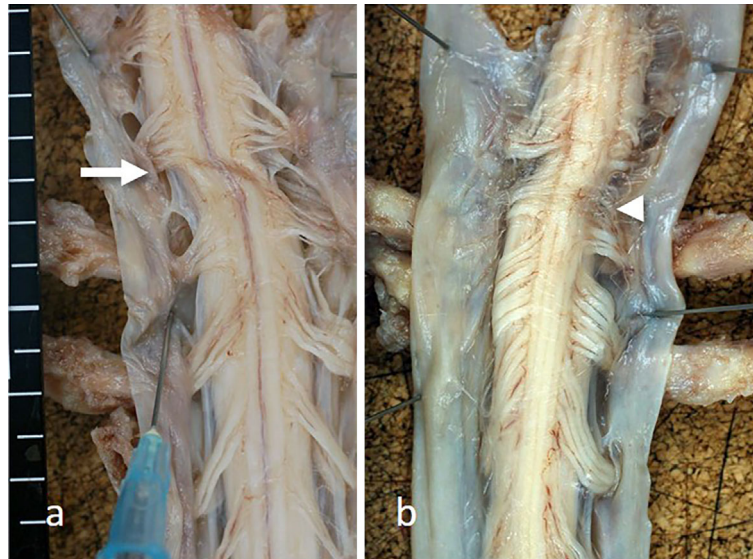
Figure 2.   The external appearance of the cervical spinal cord (ventral view [a] and dorsal view [b]). Oblique indentation was observed on the ventral surface of the cord at the lower C4 segment (arrow), and a dent was also observed on the right dorsolateral side (arrowhead). The ventral roots of the right C4, bilateral C5 and the dorsal roots of the right C4 appeared atrophic and brownish in color.

orthopedic surgical intervention. Despite conservative treatment, the patient's respiratory failure gradually worsened and he died six months later.

A general postmortem examination revealed pulmonary emphysema and fibrosis, massive pleural effusion, and ascites. Neuropathologically, the brain weighed 1,355 g after fixation with 10% formalin. The cerebrum and cerebellum were grossly unremarkable. On transverse sections of the midbrain, both the zona compacta and zona reticulata of the substantia nigra appeared to be slightly narrower on the right side than the left. Microscopically, the striate body showed mild status marmoratus, but the striatal neurons were well preserved. There was mild degeneration of the globus pallidus, thalamus, and subthalamic nucleus with an increased population of reactive astrocytes. Small necrotic foci were present in the lateral geniculate body. Mild increases in the reactive astrocytes of the hippocampus were also observed. The loss of pigmented neurons was observed in the right substantia nigra. Mild neuronal depopulation was found in the cerebellar dentate nucleus.

After the removal of the cervical vertebrae, the external appearance of the ventral surface of the cervical cord revealed a linear indentation, running obliquely at the level between the C4 and C5 segments (Fig. 2). The ventral roots of the right C4, bilateral C5 and the dorsal roots of the right C4 appeared atrophic and brownish in color (Fig. 2). Transverse sections were cut at the level of the indentation and the middle of each spinal segment.

The sections were embedded in paraffin, and thin sections were cut and subjected to Hematoxylin and Eosin and Klüver-Barrera staining. Epon-embedded sections (1-μm-thick) were prepared and stained with toluidine blue. Deparaffinized sections were also processed for immunohisto-

chemistry with mouse monoclonal antibodies against phosphorylated neurofilaments and oligodendrocytes as the primary antibodies. Morphometry of the whole cross-sectional and gray matter areas of the spinal cord was performed using the WinROOF software program (Mitani, Tokyo).

At the C4 segment, which showed severe indentation, the spinal cord was deformed and atrophic, and was surrounded by dense fibrous tissue (Fig. 3). Prominent atrophy of the gray matter was observed at the segment, and the anterior horn cells were almost absent. Even in the severely affected C4 segment, the dorsal funiculus was relatively well preserved. In contrast, mild degeneration of the ventrolateral funiculus, (where the spinothalamic tract is located) was observed.

The whole cross-sectional area at the C4 segment was 14.46 mm^2, while that of the gray matter was 1.36 mm^2. At the C5 segment, one segment below the indentation, the whole cross-sectional and the gray matter areas were 26.33 mm^2 and 5.81 mm^2, respectively. The anterior horn cells were relatively well preserved at the C5 segment. Wallerian degeneration of the lateral corticospinal tract was observed below the C4 segment and was traced to the lumbar segments; it was more evident on the right side than on the left. At the upper C4 segment, above the most severely affected segment, the bilateral cuneate fasciculi showed pallor, which was considered to represent secondary ascending degeneration due to the primary lesions of the dorsal horn and dorsal roots at the lower segments (Fig. 3). The lateral funiculi of the white matter at the C4 segment, were severely damaged; the damage on the right side was greater than that on the left. Numerous clusters of oligodendrocytes were demonstrated immunohistochemically by Olig-2 in the affected lateral funiculus (Fig. 4a). The epon-embedded semi-thin sec-
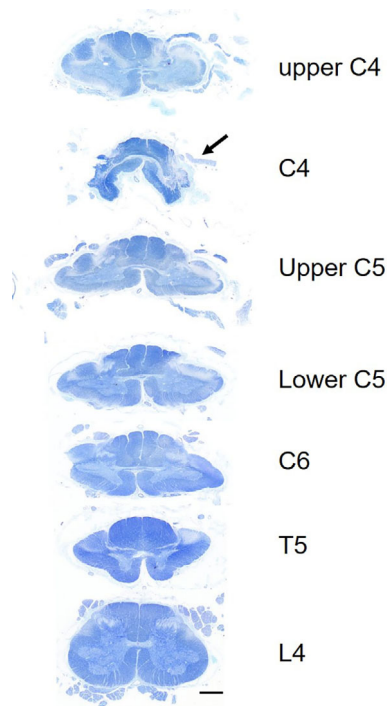
Figure 3. **A cross-section of the spinal cord at the upper C4, C4, upper C5, lower C5, C6, T5 and L4 segments. The C4 segment showed marked ventral indentation and a decrease in both the sagittal and transverse diameters. In this section, the atrophy of the gray matter was more prominent than the atrophy of the white matter, and anterior horn cells were almost completely absent. The lateral funiculi were severely damaged; the degree of damage was greater on the right side than on the left. The bilateral corticospinal tracts showed more marked secondary descending degeneration down to the lumbar segments on the right side than on the left. The right dorsal root showed pallor at the level of the indentation (arrow). At the upper C4 segment, above the most severely affected segment, the bilateral cuneate fasciculi showed pallor, which was considered to be secondary ascending degeneration caused by the primary lesions of the dorsal horn and dorsal roots at the lower segments (Klüver-Barrera staining, scale bar=1 mm).**

tions showed markedly decreased numbers of myelinated fibers and thinly myelinated axons around the damaged region (Fig. 4b). The proliferation of the capillaries was observed, but neither obstructed nor recanalized vessels were found within the cord.

Discussion

Athetoid CP, which accounts for approximately 10% of all cases of CP, is clinically characterized by abnormal involuntary movements (5). Kernicterus and neonatal anoxic encephalopathy are the two leading causes of athetoid CP, and they are often associated with the characteristic neuropathology (6, 7). The present case showed status marmoratus in the striate body, and slight but definite degenerative changes in the globus pallidus, subthalamic nucleus, and dentate nucleus. Neuronal loss was observed in the right substantia nigra. These findings may be considered to be the morphological sequelae of a neurological insult in the neonatal period, and were consistent with those of kernicterus (6).

Degenerative changes in the cervical spine are well-known late complications of athetoid CP and are often associated with the gradual or stepwise progression of myelopathy and/or radiculopathy (8). The degenerative changes have been ascribed to excessive neck movements, including the sudden turning of the head and neck, leading to cervical spondylosis at a much younger age than is observed in healthy individuals. It is assumed that children are more vulnerable to the development of this condition because of the increased laxity of the spinal ligament during childhood. Harada et al. reported that disc degeneration was observed before 34 years of age in 97% of 180 athetoid CP patients, and that the C5/6 disc was the most frequently affected level; however, the degeneration was noted to progress to other levels with increasing severity (9). The sites of the onset of disc degeneration were usually at the C4/5, C5/6 and C6/7 disc levels. However, they also reported that disc degeneration started at the C3/4 disc level in some athetoid CP patients. In our patient, cervical spondylotic changes were prominent and were associated with marked kyphosis and the narrowing of the spinal canal at the C3/4, C4/5, and C5/6 disc levels, forming a macroscopic indentation on the ventral surface of the C4 segment.

The cervical spondylosis around the C4 segment in our patient may have caused phrenic nerve dysfunction and diaphragmatic weakness. In addition, respiratory muscle weakness and decreased pulmonary capacity, which are frequently observed in CP (10), may have contributed to the respiratory failure in our patient.

Conservative therapy is not appropriate for preventing the worsening of cervical spondylosis and myelopathy, and spinal cord decompression and spinal fusion are generally performed (11, 12). The intramuscular injection of botulinum toxin has recently been used to treat cervical dystonia in patients with athetoid CP (13). In our patient, the respiratory insufficiency had already progressed, and there was no chance of performing surgical treatment.

In a Japanese-language report, Nokura et al. (4) described their clinical and pathological study of the myelopathy of an elderly athetoid CP patient with tetraplegia. The pathological investigation showed a decreased anteroposterior diameter and degeneration in the gray matter, with severe degenerative changes in the spinal segments. Ito et al. (14) reported seven autopsy cases of non-CP adults with spondylotic myelopathy of varying severity and duration. They concluded that the anterior horn and intermediate zone of the gray matter were most vulnerable to chronic compression, followed by the lateral and dorsal funiculi. The findings in the present case were consistent with their report, in that the spinal gray matter was more severely damaged than the white matter in the compressed segment. Despite the severe
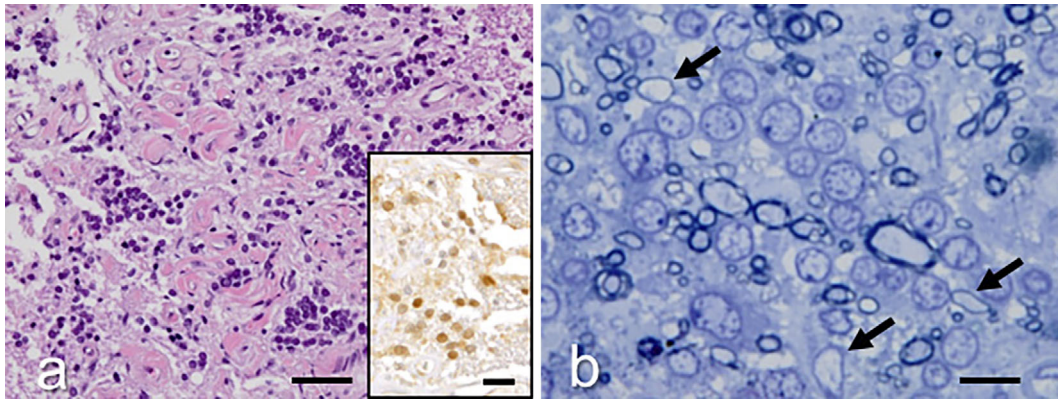
Figure 4. **The histological findings of the right lateral funiculus at the C4 segment. The right lateral funiculus was severely damaged with reactive gliosis and capillary proliferation (a). Clusters of oligodendrocytes were conspicuous, as demonstrated by immunohistochemical staining (a, inset). An epon-embedded semi-thin section stained with toluidine blue (the area corresponds to panel a) revealed a marked decrease in the population of myelinated fibers and clusters of oligodendrocytes were often associated with small myelinated axons. Thinly myelinated fibers were also observed (arrows). a: Hematoxylin and Eosin staining, scale bar=100 μm, inset; Olig-2 immunohistochemical staining, scale bar=20 μm. b: An epon-embedded semi-thin section stained with toluidine blue, scale bar=10 μm.**

degeneration of the gray matter of the compressed cervical segments, including the posterior horn, the dorsal funiculus was relatively well preserved in the present case. This may have been responsible for the dissociated sensory loss that was observed in this patient.

Previous histopathological studies have reported the appearance of aberrant peripheral nerve bundles and remyelination by peripheral myelin within the chronic compressive cord lesions. These pathological findings are considered to present the regenerative response of Schwann cells, although their significance in functional recovery remains questionable (4, 15). The occurrence of central remyelination by newly proliferated oligodendrocytes has been described in acute spinal cord injury, both experimentally and clinically in animals (16, 17). In general, a spinal cord injury results in a continued loss of neurons and glia, including oligodendrocytes. In an experimental setting, it has been shown that oligodendrocyte numbers decrease within 24 h after acute spinal cord injury, and thereafter steadily decline in the lesion from 3-7 days after injury. Within 4 weeks after injury, the oligodendrocyte progenitor cells proliferate and become oligodendrocytes (18). These central regenerative and/or restorative phenomena can occur after acute spinal cord injury, and may contribute to some functional recovery. Ito et al. (14) reported the presence of thinly myelinated axons within the compressed spinal cord in autopsy cases of cervical spondylotic myelopathy and suggested that central remyelination might occur after chronic spinal cord compression. However, they did not detect a marked increase in the number of oligodendrocytes.

The pathological findings in the present case suggest that the neogenesis of oligodendrocytes and central remyelination can occur and then continue for a long period of time after chronic repetitive cord compression. These central regenerative and/or restorative processes within the compressed cord may therefore have important implications regarding the functional recovery of such patients.

The authors state that they have no Conflict of Interest (COI).

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