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Case Report

Autopsy findings in the early stage of amyotrophic lateral sclerosis with "dropped head" syndrome

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Dropped head syndrome (DHS) has been rarely observed in amyotrophic lateral sclerosis (ALS), and the neuropathological findings of this condition have almost never been described. The identification of transactivation response DNA-binding protein 43 kDa (TDP-43), which binds to RNA/DNA has provided a new method for studying ALS and frontotemporal lobar degeneration (FTLD). Postmortem examination of an adult sudden death case of a 71-year-old patient who complained of DHS exhibited severe loss of anterior motor neurons in the cervical cord (C4-6). Loss of nerve fibers of the anterior roots was striking compared with posterior roots, together with marked neurogenic atrophy of posterior muscles semispinalis cervicis. Bunina bodies were found in large neurons of Betz giant cells, but not in the motor neurons of spinal cords, or neurons of bulbar regions. Phosphorylated TDP-43 (p-TDP-43)-positive structures were detected in the residual neurons of the cervical, thoracic and lumber cords, hypoglossal nucleus, cerebellar dentate nucleus and parahippocampal cortex, together with ubiquitin-positive inclusions. Phosphorylated Tau positive structures in neuronal cytoplasm were found in the amygdala, entorhinal cortex and parahippocampal cortex, some of which co-expressed p-TDP-43. The medial zone of cervical cords may be the first onset site, and that is the cause of head drop in the early stage of ALS. In spite of detailed examination, the direct cause of sudden death was not verified. This autopsy report revealed the relation of DHS which is a rare clinical manifestation of ALS, and neuropathological findings.

Key words: ALS, autopsy report, dropped head syndrome, sudden death, TDP-43.

INTRODUCTION

Dropped head syndrome (DHS) is characterized by severe weakness of the cervical paraspinal muscles that results in the chin-on-chest deformity.[1] This deformity has a significant impact on the quality of life of patients, resulting in considerable restrictions to ambulation, activities of daily living, for example having a meal, and social interactions. DHS contains a heterogenous condition, and it can be categorized into neurological, neuromuscular, muscular, and other causes.[2] With reference to etiologies, some neurodegenerative diseases were reported as a cause of dropped head, including multisystem atrophy,[3] Parkinson's disease,[4] and amyotrophic lateral sclerosis (ALS). In ALS, neck and trunk muscle weakness is observed as the first symptom in 2% of patients,[5] and neck flexion is typically affected.[6] The neck extensor muscle weakness with head drop has been reported in a few patients, and there are only two case series in India[7] and Niigata.[8] Furthermore, the neuropathological findings of this condition have been rarely described.

Transactivation response DNA-binding protein 43 kDa (TDP-43) molecule has provided a new approach to the

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discovery of etiological factors in ALS. Neuropathologically, abnormal TDP-43 proteins which were positively stained using immunohistochemical methods are detected and ubiquitinated inclusion bodies were found in neurons of the degenerated spinal cord. Bunina bodies found in the residual neurons were negative for TDP-43. It can be said that the genetic mutations of TDP-43 are one of the causative factors of ALS, and the presence of abnormal protein TDP-43 is the diagnostic hallmark of ALS.[9,10]

We experienced the autopsy case of a patient who developed in DHS in the early phase of ALS. In this paper, we present the neuropathological findings from the cervical cord, which relate specifically to DHS, together with the immunohistochemical demonstration of phosphorylated TDP-43 (p-TDP-43).

CASE REPORT

A 71-year-old man had noticed discomfort associated with his neck region for the past 3 years and had developed emaciation affecting the arms. He exhibited the difficulty in holding up his head due to neck weakness, suggestive of DHS, but a clinical and neurological examination was not performed. Six months previously, he had difficulty in buttoning of clothes and using chopsticks. Neck weakness gradually increased and ultimately he was unable to lift his chin. The presence of mild fatigue became gradually worse over 3 days, and he was treated with infusion therapy containing vitamins. After 3 days hospitalization, the patient was discharged and the following day was found dead in his dormitory room.

Several months before his death, some abnormal behaviors had been detected, suggestive of visual hallucination. Neither ALS nor frontotemporal lobar degeneration (FTLD) was evident in the patient family.

PATHOLOGICAL FINDINGS

Macroscopically, the spinal cord did not show any abnormality except for the atrophic ventral roots. Microscopically, loss of anterior horn neurons and large fibers from anterior roots were observed on the cervical cord, in which neuronal loss was replaced by glial cells (Fig. 1A). Dividing the anterior horn into the medial, intermediate and lateral zones, loss of neurons was most prominent in the medial zone, which was seen as pallor of the neuropil (Fig. 1B, C). Atrophic neurons were loaded with lipofuscin, but Bunina bodies were not observed. Although thoracic and lumber cords were also affected, neurons were relatively preserved in lumber cords. The sacral cords including Onuf's nucleus were well preserved. The myelin pallor was found in the posterior spinocerebellar tracts by Klüver–Barrera (KB) stain.

Subsequently, we investigated the erector muscle of the spine. Among the posterior cervical muscles, semispinalis cervicis muscles, which were innerved by neurons in the medial zone of cervical cords, showed severe neurogenic grouped atrophy by hematoxylin-eosin (HE) stain (Fig. 1D).

The brain weighing 1360 g, was externally unremarkable. Microscopically, neither cortical atrophy nor neuronal loss was found, but Bunina bodies were found in the Betz giant neurons (Fig. 1E, F). On coronal section, an old linear infarction 1.5 cm in size was found on the right putamen.

Immunohistochemically, anterior horn neurons in cervical, thoracic and lumbar spinal cords contained ubiquitin and p-TDP-43-positive structures in the neuronal cytoplasm (Fig. 1G, H). The structures were identical to so-called thread-like or skein-like and necklace-like inclusions. p-TDP-43-positive structures were also found in the hypoglossal nucleus, cerebellar dentate nucleus and parahippocampal gyrus, but not in the cerebral cortex, including the motor cortex. In this case, phosphorylated Tau (p-Tau)-positive structures were found in the amygdala, entorhinal cortex and parahippocampal gyrus. The serial sections revealed that a few neurons in the parahippocampal gyrus expressed both p-TDP-43 and p-Tau in neuronal cytoplasm (Fig. 1I, J). The arrow and arrowheads indicate the neurons p-TDP-43 and p-Tau co-expressed (the arrow indicates the inset neuron). Senile plaques were found only in the parahippocampal gyrus. The α-synuclein deposition was not detected.

DISCUSSION

The present patient had been working as a pathologist. When he attended a party in the year before his death, we noticed abnormalities of the cervical spine with anterior translation of his head which was reversible by holding his head with his arms, but which was irreversible without holding. However, he had no problems with other functions such as swallowing, speaking and cognitive functions.

Previous reports have divided ALS into eight phenotypes: classic, bulbar, flail arm, flail leg, pyramidal, respiratory, pure lower motor neuron and pure upper motor neuron.[11] In this case, head drop was the initial early clinical manifestation. This doesn't apply to any phenotypes; however, the Indian study also reported neck weakness tended to occur as a relatively early feature,[7] which may be a new phenotype of ALS.

Pathologically, it was revealed there was more severe neural loss in the medial zone of cervical cords than the other regions and there was neurogenic atrophy of cervical erector spinae muscle in the early stage of ALS. Regarding the mechanism, recent biological studies demonstrated that ALS originates from a single (or multifocal) onset site

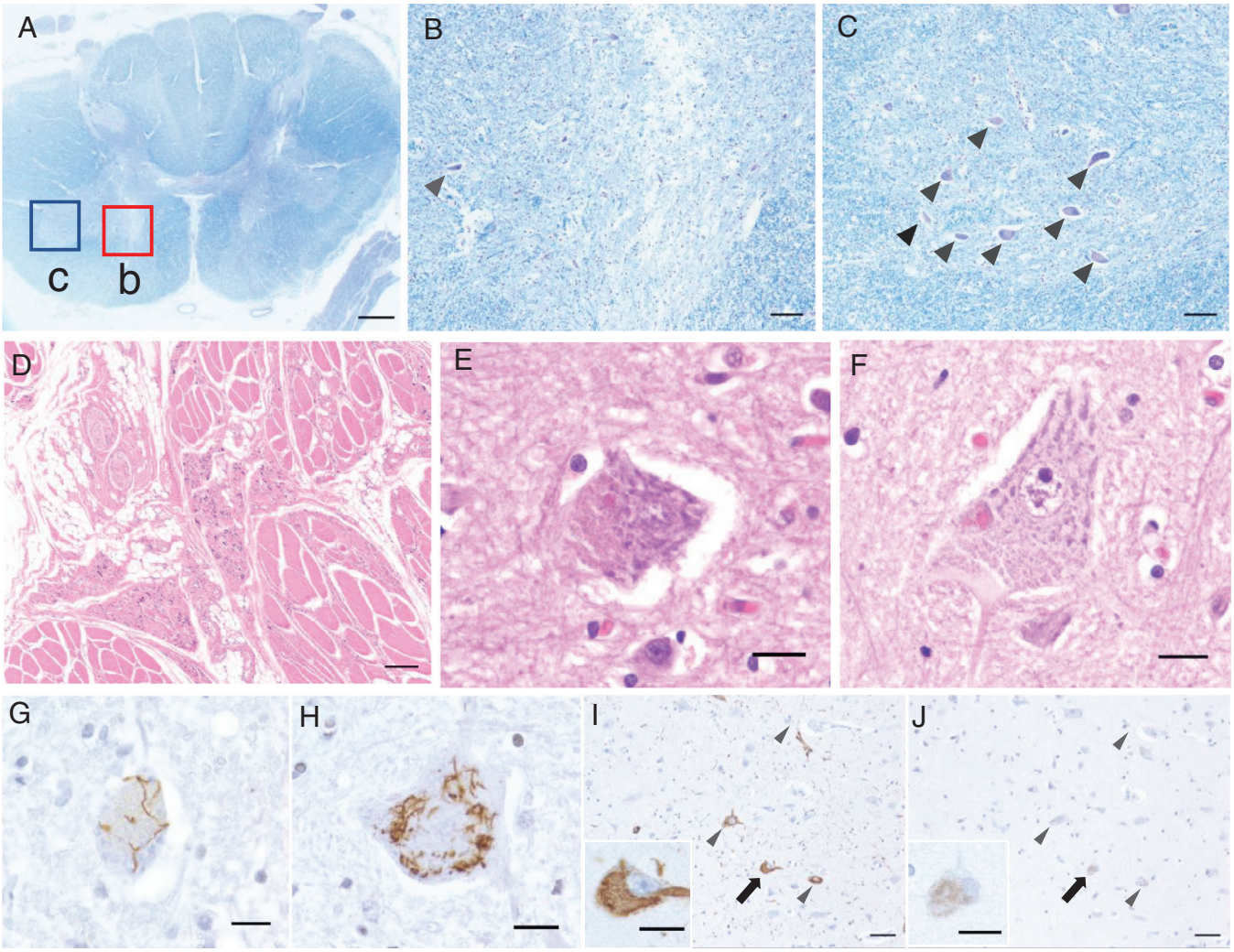

Fig. 1 Histological (A-F) and immunohistochemical (G-J) observations. A semimacroscopic image of the cervical spinal cord C5 level shows atrophy of the anterior horns (A). At a higher magnification of panel A (b), neurons in the medial side of the anterior are almost completely depleted (B, arrowhead: residual neuron). At a higher magnification of panel A (c), neurons in the lateral side are relatively preserved (C, arrowheads: residual neurons). Paraspinal muscle of the neck shows group atrophy (D). Bunina bodies are seen in a Betz cell in the left (E) and right (F) motor cortices. p-TDP-43-positive skein-like inclusions are seen in C5 level (G), and p-TDP-43-positive necklace-like inclusions are seen in L3 level (H). In serial sections of the cortex of parahippocampal gyrus, p-Tau (I, arrow) and p-TDP-43 (J, arrow) are coexpressed in neuronal cytoplasm. KB staining (A-C), HE staining (D-F), immunohistochemical staining (G-J). Scale bars: 1 mm (A), 100 μm (B, C), 200 μm (D), 20 μm (E-J), 50 μm (I, J: insets).

and contiguously spreads.[12,13] In this case, the medial zone of cervical cords may be the first onset site, and that is the cause of head drop. It is unknown why the onset site started in that region.

TDP-43 is the diagnostic hallmark of ALS and FTLD; however, recent reports also revealed that TDP-43 positive structures also appear with aging[14] or neurodegenerative diseases such as Alzheimer's disease,[15] Lewy body disease,[14] argyrophilic grain disease,[14] corticobasal degeneration[16] and progressive supranuclear palsy.[17] These reports suggest TDP-43 deposition will start from the amygdala and entorhinal cortex. In this case, there was no TDP-43 deposition in those regions. Unusual p-TDP-43 deposition in ALS and FTLD will have different mechanisms from aging or when accompanying other neurodegenerative diseases.

We detected TDP-43 and Tau co-expressed structures in the parahippocampal gyrus. A recent study described normal TDP-43 in the nucleus suppresses Tau expression via promotion of Tau messenger RNA instability; on the other hand, cytoplasmic unusual TDP-43 accumulation promoted Tau expression and aggregation because of loss essential function of TDP-43.[18] In this case, the expression of p-TDP-43 and p-Tau were also detected in the cytoplasm. We may observe the part of Tau expression via

cytoplasmic TDP-43. The clinical implication is unknown, but it may be a preclinical pathological feature of the cognitive disorder associated with TDP-43.

In spite of detailed examination, the direct cause of death was not verified, but the medial group of the cervical cord contains neurons of respiratory function and a few references of respiratory failure in patients with DHS have been described, and this condition is rare accounting for 1–3%,[7,8] so further examination was required for this possibility.

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DISCLOSURE

There is no conflict of interests for this article.

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