Brief Communications

Tokushima An autopsy case of amyotrophic lateral sclerosis

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Received 25 February 2016; received in received from 29 February 2016; accepted 4 March 2016

Key words amyotrophic lateral sclerosis, ALS, autopsy

Introduction

Amyotrophic lateral sclerosis (ALS) is a rare neurological degenerative condition of the motor neurons leading to paralysis of skeletal muscles, characterized by rapid irreversible progression in most cases [1]. ALS is a fatal neurodegenerative disorder characterized by a progressive degeneration of upper and lower motor neurons leading to limb paralysis, dysphagia, dysarthria, and respiratory failure. The cause of the disease is unknown and there is no effective cure. Although it is generally reported that the mean survival of patients from symptom onset is 3–5 years [2], ALS has a considerable variability in outcome and its prognostic factors are not satisfactorily defined. The defining feature of ALS is the death of both upper and lower motor neurons in the motor cortex of the brain, the brain stem, and the spinal cord. Prior to their destruction, motor neurons develop protein-rich inclusions in their cell bodies and axons. This may be partly due to defects in protein degradation.[3] These inclusions often contain ubiquitin, and generally incorporate one of the ALS-associated proteins: SOD1, TAR DNA binding protein (TDP-43, or TARDBP), and/or FUS.[4] We report an autopsy case of ALS, showing the involvement of synucleinopathy and TAR DNA-binding protein 43 (TDP-43).

Case report

Patient was time 62 years old (at death) man. There is no important notice for a family history and medical history. Anarthria developed in 2007. He had a diagnosis of ALS, and was an outpatient until 2011. In February, 2012, we insert a transdermal esophagus gastric tube because of dysphagia. We tracheotomized it in August. He was placed under respirator management. In July, 2013, he was hospitalized in Tokushima National Hospital. Clinical course after the hospitalization He was given total parenteral nutrition. In February, 2015, pneumonia occurred. Antibiotics improved pneumonia temporarily. A platelet decreased from the end of February. DIC was diagnosed. In spite of several treatments, he was gradually in a condition of the multiple organ failure and died on March 20. Mycotic sepsis became clear posthumously. An autopsy was performed in (posthumously five hours) on March 21. Pathological anatomical diagnosis was shown in Table 1. All course of the ALS was eight years. Table 2 shows the anatomical findings. A motor system, a non-motor system showed TDP43-positive pathology. Nerve cells dropout was remarkable in the lower motor neuron region. The TDP43-positive findings appeared in glia cells. This was thought to reflect long-term course. Pyelonephritis was severe. We showed the lump of tubular necrosis and fungus. The evidence of pneumonia was not outstanding. Bleeding was found in the right lung. Severe edema was found in a whole

body.

Discussion

TDP-43 is a conserved ribonucleoprotein with diverse functions as exemplified by the ability to regulate gene transcription, mRNA splicing, and RNA stability [5-10]. While its physiological functions remain to be elucidated, TDP-43 translocates to the cytoplasm and forms ubiquitinated aggregates in neurodegenerative diseases including amyotrophic lateral sclerosis (ALS) and frontotemporal lobe degeneration (FTLD) [11-14]. TDP-43 proteinopathy, a hallmark of sporadic ALS and FTLD, is also observed in the other neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease [15-17]. Neurodegenerative diseases share some features in the pathogenesis and pathology. Most cases of the diseases are sporadic and only a small proportion of them have a clear genetic cause. A neurodegenerative disease is characterized by a selected group of neurons preferably affected at early disease stages, but it often affects a wide range of different neurons at advanced disease stages. For example, heterogeneous neuropathology is observed in sporadic ALS at advanced disease stages [18-20], although motor neurons are preferably affected in the disease at early disease stages. TDP-43 proteinopathy is direct evidence supporting that neurodegenerative diseases may be pathogenically interrelated.

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Table 1. Pathological anatomical diagnosis

1.	Amyotrophic lateral sclerosis
2.	Incidental Lewy body disease
3.	Pyelonephritis (bilateral)
4.	Pulmonary hemorrhage (right)
5.	Anasarca
6.	Bleeding tendency

7.	Emphysema (right upper lobe)
8.	Atelectasis (left lower lobe)
9.	Pleural effusion (left 600 ml, right 1100ml)
10.	Ascites(600 ml)
11.	Congestion (bilateral kidney and spleen)
12.	Atherosclerosis (aorta and coronary artery)
13.	Post cholecystectomy, suspected

Table 2. Pathological findings

Cause of death	Multiple organ failure
General findings	Height, 162cm; weight 62 kg; brain weight, 1,310 g; heart weight, 320 g; left lung weight, 245 g; right lung weight, 370 g; liver weight, 1,080 g; splenic weight 180 g; left kidney weight, 185 g; right kidney weight, 155 g; pericardial fluids, 20 ml, left pleural fluid, 600 ml; right pleural fluid, 1,100 ml; ascitic fluid, 600 ml (all yellow transparence)
Lower motor neurons	We recognize a myelin sheath stain-related difference by a root in the cauda equina. In the spinal cord, there was a myelin sheath stain-related decrease in an anterior root in comparison with the dorsal root with lumbar cord and the cervical cord. In the anterior roots, dorsal roots accepted medullary sheath hypochromasia with the dorsal together. The Onuf nucleus and the Clarke pillar were preserved. We showed the dropout of anterior horn cells and the increase of glia cells by spinal cord full length. There was spheroid/globule. There was no clear Bunina corpusculum. We accept antiphosphorylation TDP43 (Ps409/410) -positive granular structure / glialcytoplasmic inclusion (GCI) in ventral horn cells. Lumbar cord ventral horn showed the invasion of the CD68-positive active form microglia / macrophage、and GFAP-positive reactive astrocytic invasion.
Nucleus of hypoglossal nerve	We show a neuronal dropout and the increase of glia cells. The local invasion of the CD68, Iba1 immunostaining-positive active form macrophage / microglia was not clear. GFAP staining shows type much astrocyte manure. We show a few granular Ps409/410-positive GCI. There were no Bunina bodies.
Facial nerve nuclei	We showed a neuronal mild dropout and the increase of glia cells around the nerve cells. We observed a few granular Ps409/410-positive neuronal cytoplasmic inclusion（NCI）and GCI. CD68-positive active form microglia / macrophage and the GFAP-positive astrocytic local accumulation were not clear. There were no Bunina bodies.
Motor nuclei of	We showed a neuronal dropout. There were no Bunina bodies. We

the trigeminal nerve.	showed a few granular Ps409/410-positive NCI and GCI. The CD68-positive active form microglia / macrophage and the GFAP-positive astrocytic local accumulation were not clear. There were no Bunina bodies.
Oculomotor main nucleus	The maximal sectioned surface of the main nucleus was not included. Neighboring glial cytosis was not clear. Upper motor neuron limbic cortex. A portion of the amygdaloid nucleus showed very few pSyn-positive NCI and dots. Piriform lobe cortex showed many pSyn-positive neurites and dots. There were no pSyn-positive findings from the Meynert basal ganglia, transition entorhinal field and previous cingulate gyrus.
Cortex	There were no pSyn-positive findings in F1/2, T1/2 and the superior parietal lobule. The astrocytic cells had changed. There were no bush-like astrocytes and thorn-shaped astrocytes in the amygdaloid nucleus.