INTERNAL MEDICINE

□ CASE REPORT □

An Autopsy Case of Amyotrophic Lateral Sclerosis with Diaphragm Pacing

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Abstract

Respiratory insufficiency is a critical problem in amyotrophic lateral sclerosis (ALS) patients. We herein present the case of an autopsied patient with sporadic ALS who underwent diaphragm pacing (DP). The pathology showed several localized adhesions with a markedly atrophied diaphragm. A marked loss of motor neurons with Bunina bodies and phosphorylated TDP-43 positive inclusions was found in the spinal cord and primary motor cortex. Mild hyalinization and a few multinucleated giant cells were present around the electrode tracks in the diaphragm. However, no infiltration of inflammatory cells was detected. Our findings suggest that full-time DP might not cause severe damage to adjacent diaphragm tissue.

Key words: amyotrophic lateral sclerosis, respiratory insufficiency, diaphragm pacing

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Introduction

Amyotrophic lateral sclerosis (ALS) is a slowly progressive neurodegenerative disorder with no known curative treatments. Respiratory insufficiency is a critical problem, and earlier administration of non-invasive ventilation (NIV) prolongs the survival of ALS patients (1). Diaphragm pacing (DP), which was initially developed for patients with spinal cord injury (2), was considered to be useful and safe as NIV for ALS patients (3). Pre-clinical studies suggested an acceptable tissue response with full-time stimulation that would present a minimal risk to patients (4). We herein present a 63-year-old Japanese autopsy-proven ALS patient who underwent electrical DP.

Case Report

The patient, who had no remarkable past or family history, was a 60-year-old man. He noticed mild weakness in his left arm followed by a weakness in his right arm and atrophy of the right hypothenar muscle. At 62 years of age, he developed left leg weakness and was diagnosed with definite ALS according to the World Federation of Neurology El Escorial criteria. The patient presented neither behavioral nor cognitive impairment. We administered riluzole and implanted the NeuRx RA/4 Diaphragm Pacing System® (NeuRx, Synapse Biomedical, Oberlin, OH, USA) laparoscopically under general anesthesia according to previous reports (5, 6). Namely, the diaphragm was exposed, the phrenic nerve motor point was mapped, pacing electrodes were implanted, and finally the wires were routed to the external pulse generator. Two pacing electrodes were placed on the motor points of the diaphragm on each side and intraperitoneal electrodes had sufficient length to prevent them from being accidentally removed. Spontaneous breathing and diaphragm contraction with pacing were independent because NeuRx does not trigger spontaneous breathing. The implantation of NeuRx was approved by the Review Board of Tokushukai Medical Alliance, and the patient provided written informed consent in accordance with the Declaration of Helsinki before implantation.

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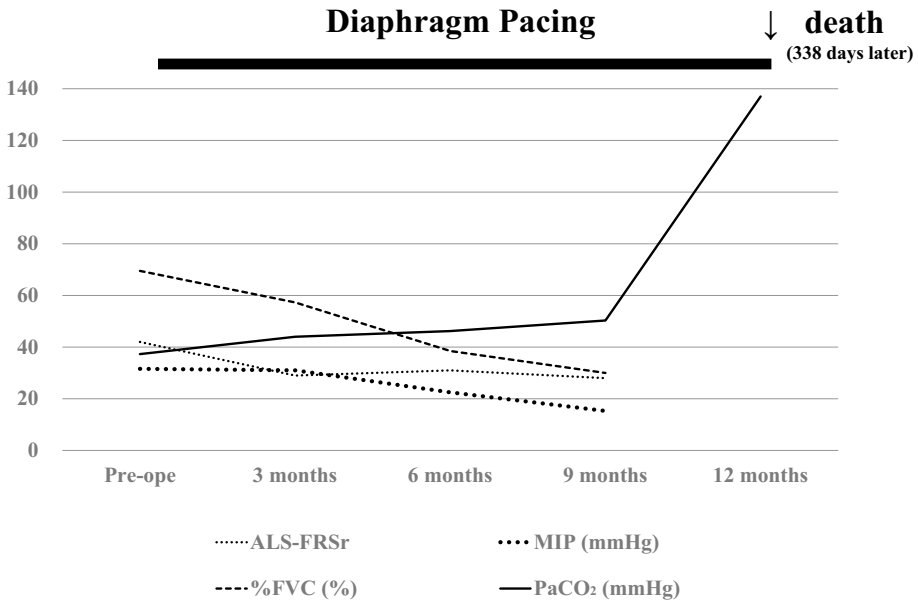

Figure 1. **The clinical course. The patient's respiratory function deteriorated with CO_2 accumulation despite DP (MIP: maximal inspiratory pressure).**

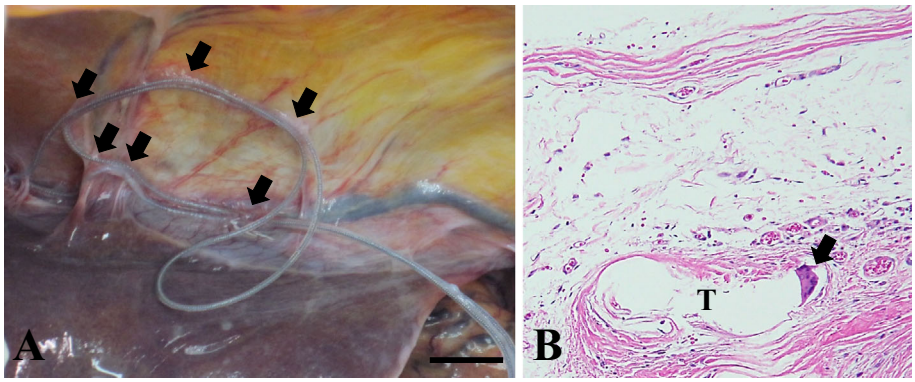

Figure 2. **Pathology of the diaphragm. A: Severely atrophied diaphragm with 2 DP electrodes on each side. Several localized adhesions of electrodes are indicated (arrows; bar=10 mm), B: Hematoxylin and Eosin staining of the diaphragm (magnification 100×). Mild hyalinization was observed around the DP electrode track (T). A multinucleated giant cell was detected (arrow), however, the infiltration of mononuclear cells around the track was not observed.**

DP was continued for 24 hours a day and did not show any complications. We did not observe dyssynchrony between spontaneous breathing and diaphragm contraction with pacing. The patient did not desire other NIV or feeding through gastrostomy throughout the course. Despite DP, he died at 63 years of age, 43 months from the onset and 338 days (11.1 months) after DP implantation, due to respiratory failure. Stimulation parameters were set at: frequency, 12 Hz; pulse width, 150 μsec; and intensity, 17 mA (Fig. 1).

Autopsy findings

The prefixed brain weighed 1,510 g, while the spine weighed 55 g without any apparent abnormal appearance except for moderate atherosclerotic changes in the basilar artery. There were no marked abnormalities in the trachea or lungs, however, the diaphragm showed severe atrophy. Several adhesions between the DP electrodes and diaphragm were observed adjacent to the tip of the DP electrodes (Fig. 2A). A microscopic examination revealed a marked loss of motor neurons in the anterior horn, particularly in the upper cervical cord, and primary motor cortex with glial proliferation. Bunina bodies were observed in the lumbar cord. Cytoplasmic inclusions of phosphorylated TAR DNA-binding protein of 43 kDa (TDP-43) were observed in the primary motor cortex, medulla oblongata, cervical cord, and lumbar cord. Mild hyalinization and a few multinucleated giant cells were present around the electrode tracks in the diaphragm. However, the infiltration of mononuclear cells around the tracks was not observed (Fig. 2B).

Table. The Comparison between the Results of Previous Trials and the Course of Our Patient.

Periods (months-median)	US study (8)	UK study (9)	Our patient
From initial onset to DP (all DP)	37.0	17.0	32.0
Survival from DP (all DP)	19.0	11.0	11.3
Survival from DP (DP only)	/	7.7	
Survival from initial onset (all DP)	56.0	28.0	43.3

Discussion

According to the results of a multicenter study (7), the US Food and Drug Administration approved NeuRx for humanitarian device exemption in 2011 (8). The pilot study in the US concluded that DP with NeuRx for ALS patients did not show any safety issues and positively influenced the movement of the diaphragm and the survival (3). Contrary to previous reports in the US (3, 7), a randomized, -controlled trial in the UK concluded that the combination of NIV and DP with NeuRx was less effective than NIV alone for the survival (9). The period from DP to death of our patient was longer than the DP alone group in the UK study and similar with that of the NIV plus DP group (Table). However, as our patient did not use other NIV, the concomitant use of NIV, such as BiPaP, could prevent CO_2 accumulation to extend the period from DP to death. On the other hand, the heterogeneity of clinical features and course of ALS might influence the different results observed in these clinical trials. The strong need for new international guidelines for clinical trials of ALS was recently proposed (10).

A post-mortem pathological study in ALS patients with NeuRx has not yet been reported. To the best of our knowledge, this is the first autopsied case of an ALS patient who underwent DP with NeuRx. Our pathological findings suggested that DP with NeuRx might have no safety issues regarding the adjacent diaphragm tissue. As adhesions in the diaphragm were limited, they would not likely cause significant respiratory failure. However, we might have to use absorbable adhesion barriers to reduce the incidence and severity of postoperative adhesions because they could restrict the movement of the diaphragm (11).

The clinical efficacy of DP with NeuRx for ALS patients has not yet been elucidated. Further pathological evaluations in more patients are warranted to verify the safety and efficacy of DP with NeuRx for ALS patients.

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

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