Cause of Death in Japanese Patients with Amyotrophic Lateral Sclerosis on Tracheostomy-Positive Pressure Ventilation

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Dear Sirs,

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by loss of upper and lower motor neurons, leading to weakness and wasting of the affected muscles [1]. Previous reports have shown that the most common cause of death in patients with ALS is respiratory failure followed by other causes, including cardiac problems (myocardial infarction, arrhythmia), sepsis and malignancies [2–5]; however, knowledge about the causes of death in patients treated with tracheostomy-positive pressure ventilation (TPPV) is very limited. In this study, we investigated the causes of death of ALS patients on TPPV.

We retrospectively reviewed the medical records of 112 consecutive patients with ALS referred to our hospital between April 2006 and September 2011. Diagnosis of ALS was made according to El Escorial diagnostic criteria [6] and clinically probable or definite patients were evaluated in this study. We identified 51 patients who died in this period and divided them into two groups: 13 patients who had been assisted with TPPV at the time of death and 38 patients who had not (9 patients had been assisted with noninvasive positive pressure ventilation, and 29 patients had not received any mechanically assisted ventilation). The causes of death were eval-

uated from the medical records and autopsy findings if available. Differences between the two groups were assessed by nonparametric analysis.

The characteristics of the patients are shown in table 1. There were no significant differences in gender, age at onset and age at death between the two groups; however, disease duration was significantly longer in patients with TPPV than without TPPV (Wilcoxon's test, $p < 0.05$). The hospitalization period until death was also significantly longer in patients with TPPV (Wilcoxon's test, $p < 0.05$). All patients with TPPV died in hospital, whereas a few patients without TPPV died at home. Twenty-two patients underwent autopsy and the diagnosis of ALS was confirmed in all patients by pathologic study.

The causes of death in this study are shown in table 2. The most frequent cause of death in patients with TPPV was respiratory failure (46.2%), as well as in patients without TPPV (89.6%). It was previously reported that 81.3% of ALS patients without TPPV died of respiratory failure [4]. Taken together with a previous report [4] and our study, the frequency of respiratory failure as a cause of death in patients with TPPV seems to be lower than in patients without TPPV. In addition, it is notable that all patients with TPPV developed re-

spiratory failure from pneumonia/bronchopneumonia, whereas most patients without TPPV developed respiratory failure from terminal respiratory insufficiency due to respiratory muscle weakness.

Problems other than respiratory failure, especially sepsis, arise as a cause of death in patients with TPPV. In patients with sepsis, two of three patients with urinary tract infection had urinary tract stones and the patients with biliary tract infection had gall bladder stones. It is conceivable that these stones may partly affect urinary or biliary tract infection, leading to sepsis. In addition to the existence of stones, the presence of antibiotic-resistant bacteria should be considered. In patients with TPPV, as the disease duration lengthens, the opportunities for developing infectious disease increase. By repeated use of antibacterial drugs, antibiotic-resistant bacteria may increase and it gradually becomes difficult to control infectious diseases such as pneumonia/bronchopneumonia, and urinary or biliary tract infections. In our study, 8 of 13 patients with TPPV were found to have methicillin-resistant *Staphylococcus aureus* (MRSA) by sputum or urine culture performed within 3 months before death. It is uncertain whether MRSA directly affected the condition of our patients; however, it is con-

Table 1. Clinical characteristics of the patients according to the respiratory support

	Respiratory support	
	with TPPV (n = 13)	without TPPV (n = 38) (NIPPV n = 9, no assistance n = 29)
Gender, male/female	10/3	21/17
Age at onset, years (mean $\pm$ SD)	59.7 $\pm$ 13.8	65.4 $\pm$ 10.9
Range	39 – 83	34 – 83
Age at death, years (mean $\pm$ SD)	68.5 $\pm$ 11.9	68.6 $\pm$ 9.6
Range	46 – 87	46 – 84
Disease duration, months* (mean $\pm$ SD)	103.5 $\pm$ 61.8	41.6 $\pm$ 35.4
Range	24 – 246	8 – 159
Site of onset, n (%)		
Bulbar	5 (38.4)	14 (36.9)
Respiratory failure	2 (15.4)	0
Upper extremities	4 (30.8)	17 (44.7)
Lower extremities	2 (15.4)	7 (18.4)
Nutrition support, n (%)		
Oral intake	0	9 (23.7)
Nasogastric tube	2 (15.4)	3 (7.9)
Gastrostomy	11 (84.6)	25 (65.8)
Intravenous hyperalimentation	0	1 (2.6)
Place of death, n (%)		
Home	0	4 (10.5)
Hospital	13 (100)	34 (89.5)
Hospitalization period until death month, range* (mean $\pm$ SD)	73.0 $\pm$ 57.8 14.5 – 230	7.9 $\pm$ 12.7 0.1 – 67**
Autopsied patients, n (%)	9 (69.2)	13 (34.2)

TPPV = Tracheostomy-positive pressure ventilation; NIPPV = noninvasive positive pressure ventilation.

* $p < 0.05$; ** except four patients who died at home.

Table 2. Cause of death of ALS patients according to the respiratory support

	Respiratory support	
	with TPPV (n = 13)	without TPPV (n = 38) (NIPPV n = 9, no assis- tance n = 29)
Respiratory failure, n (%)	6 (46.2)	34 (89.6)
Pneumonia/bronchopneumonia	6	6
Terminal respiratory insufficiency	0	26
Asphyxia	0	2
Sepsis, n (%)	4 (30.8)	1 (2.6)
Urinary tract infection	3	0
Biliary tract infection	1	0
Unknown infectious origin	0	1
Heart failure, n (%)	1 (7.7)	1 (2.6)
Ventricular fibrillation	1	0
Congestive heart failure	0	1
Malignancy, n (%)	1 (7.7)	1 (2.6)
Carcinoma of the oral floor	1	0
Hepatocellular carcinoma	0	1
Intestinal problem, n (%)	1 (7.7)	1 (2.6)
Ileus	1	0
Intestinal hemorrhage	0	1

TPPV = Tracheostomy-positive pressure ventilation; NIPPV = noninvasive positive pressure ventilation.

ceivable that there is a background for developing antibiotic-resistant bacteria in patients with TPPV, leading to difficult to control infectious diseases. Generally, it should be noted that infectious diseases were the major cause of death in patients with TPPV.

A recent report, based on the nationwide registration system of the Ministry of Health, Labor and Welfare of Japan, showed that 29.3% of Japanese ALS patients are treated with TPPV [7]. Conversely, it is reported that the frequency of TPPV-assisted ALS patients is 1.5–3.2% in western countries [2, 8, 9]; therefore, Japa-

nese patients are more likely to undergo invasive ventilation. A better understanding of the cause of death of ALS patients on TPPV is required for patients and their caregivers to improve the decision-making process for TPPV induction and palliative care at the end of life.

Our study is limited by its small number of patients at a single center. In addition, not all patients underwent autopsy and the causes of death were based on a clinical diagnosis in some patients. Further larger studies are required for better understanding of the cause of death of ALS patients on TPPV.

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Disclosure Statement

The authors declare that they have no conflicts of interest.

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