Familial Amyotrophic Lateral Sclerosis with a Novel G85S Mutation of Superoxide Dismutase 1 Gene: Clinical Features of Lower Motor Neuron Disease

Takanori Takazawa¹, Ken Ikeda¹, Takehisa Hirayama¹, Kiyokazu Kawabe¹,
Yoshikazu Nakamura¹, Hirono Ito¹, Osamu Kano¹, Yasuhiro Yoshii¹, Fumiaki Tanaka²,
Gen Sobue² and Yasuo Iwasaki¹

Abstract

Amyotrophic lateral sclerosis (ALS) is a devastating disease characterized by upper and lower motor neuron damage. Mutations of Cu/Zn superoxide dismutase gene (SOD1) account for 20% of familial ALS (FALS). We report a unique clinicogenotype of a Japanese family with a novel SOD1 mutation. A 37-year-old woman (the proband) noticed muscle weakness in the left lower limb. Her mother had developed progressive lower motor neuron signs in four extremities at 38 years of age. Subsequently she was diagnosed as ALS and died of respiratory failure at 15 months after clinical onset. Neurological examination of the proband showed absent muscle stretch reflexes in the left knee and the left ankle without Babinski signs. Mild to moderate degree of muscle weakness existed in the left lower extremity. Muscle atrophy was presented in the left thigh. Initial pulmonary function revealed forced vital capacity of 91.1%. Electromyography disclosed ongoing denervation muscle potentials in the left lower extremity. SOD1 analysis demonstrated amino acid substitution of glycine by serine at codon 85 (G85S) in exon 4. Six months later, marked muscle weakness and atrophy expanded to four extremities. All muscle stretch reflexes were absent. Three months later, ventilator support with a tracheostomy was needed. The patient died at 18 months after clinical onset. Clinical hallmarks of this FALS family indicate that G85S mutation of SOD1 may cause rapidly progressive form of pure lower motor neuron signs.

Key words: amyotrophic lateral sclerosis, Cu/Zn superoxide dismutase, G85S mutation, lower motor neuron disease

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Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal disease characterized by motor neuron degeneration, leading to progressive paralysis and death from respiratory failure. Familial ALS (FALS) accounts for 5-10% of all patients and various genes are identified in FALS (1). Mutations of Cu/Zn superoxide dismutase gene (SOD1) are discovered as the first causative gene of FALS in 1993 (2). SOD1 mutations are linked with 20% of FALS patients. Over 100 kinds of SOD1 mutations are listed currently in FALS patients (http://alsod.iop.kcl.ac.uk/). Several kinds of SOD1 mutations are reported in Japanese ALS families. The clinicogenetic expression or new subtypes of FALS are addressed (3-8). We encountered a Japanese family with a novel SOD1 mutation that has young onset and rapid progression of lower motor neuron disease. Here, we report such a unique family of SOD1-mutated FALS.

¹Department of Neurology, Toho University Omori Medical Center, Tokyo and ²Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya

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Correspondence to Dr. Ken Ikeda, keni@med.toho-u.ac.jp
Case Report

A 37-year-old healthy woman (II-1, the proband) noticed muscle weakness in the left lower extremity during running for exercise. Two months later, she was admitted to our department. She had played professional volleyball until 28 years of age. A family history showed her mother (I-1) developed muscle weakness and atrophy in the lower extremities at 38 years of age and subsequently motor deficits progressed to four limbs and the diagnosis of ALS was made (Fig. 1). The maternal medical record exhibited flaccid motor paralysis and absent muscle stretch reflexes in four extremities. Her mother died of respiratory failure at 39 years of age. The total disease course was 15 months. Physical examination of patient II-1 (the proband) showed body mass index (BMI) of 17.3 kg/m$^2$. On neurological examination, muscle stretch reflexes were absent in the left knee and the left ankle, and other reflexes were normal. There were no pathological reflexes, including Babinski signs. Medical Resource Council revealed 3/5 in the left iliopsoas, hamstring and gastrocnemius muscles, and 2/5 in the left anterior tibial muscle. Muscle atrophy was presented in the left thigh. Cognitive function and cranial nerves, sensation, cerebellar function and autonomic function were normal. On laboratory blood analyses, serum creatine kinase levels were increased slightly to 165 IU/L (normal range, 49-159). Arterial blood gas revealed pH 7.40, Pco$_2$ 41.2 Torr and Po$_2$ 99.4 Torr. The first pulmonary function test showed forced vital capacity of 91.1% (Table 1). Electromyography disclosed ongoing denervation muscle potentials in the quadriceps, the hamstring, the gastrocnemius and the anterior tibial muscles of the left lower limb. Electromyographic findings were normal in the upper and the right lower extremities. Informed consent of gene study was obtained from the patient and her family. Genomic DNA was extracted from peripheral lymphocytes obtained from the patient II-1 (the proband) and 60 normal Japanese subjects. Five exons of SOD1 were amplified by polymerase chain reaction (PCR) using five sets of oligonucleotide primers. A novel missense mutation G to A at codon 85 in exon 4 and amino acid substitution of glycine by serine (G85S) was identified only in our patient II-1 (Fig. 2). For further analysis of SOD1, PCR restriction fragment length polymorphism method was performed. All normal subjects showed the homozygous pattern of the wild type. The proband (patient II-1) had the heterozygous pattern of the mutated and the wild type.

At 6 months after clinical onset, muscle weakness expanded from the left lower limb to all extremities. Marked atrophy was presented in both thenar muscles. Fasciculations appeared in the body and four extremities. She was unable to walk and became bedridden. Gag reflexes were absent, but there was no dysarthria or dysphagia. Three months

![Figure 1](image1.png)  
**Figure 1.** Family pedigree of FALS. Members affected with ALS are shown by solid symbols. Squares and circles represent male and female members, respectively. Arrow indicates the proband. The ages below symbols exhibit each patient’s age at clinical onset.

![Figure 2](image2.png)  
**Figure 2.** SOD1 analysis shows a point mutation G to A at codon 85 in exon 4, resulting in amino acid substitution of glycine by serine (G85S). Arrows indicate a G to A substitution.

### Table 1. Serial Changes of Body Mass Index, Respiratory Function and Serum Creatinine Levels

<table>
<thead>
<tr>
<th></th>
<th>After clinical onset</th>
<th>2 months</th>
<th>4 months</th>
<th>6 months</th>
<th>9 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index kg/m$^2$</td>
<td>17.3</td>
<td>16.7</td>
<td>16.0</td>
<td>14.5</td>
<td></td>
</tr>
<tr>
<td>Forced vital capacity %</td>
<td>91.1</td>
<td>69.2</td>
<td>44.2</td>
<td>32.5</td>
<td></td>
</tr>
<tr>
<td>Arterial blood gas*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.40</td>
<td>7.42</td>
<td>7.40</td>
<td>7.38</td>
<td></td>
</tr>
<tr>
<td>Pco$_2$ Torr</td>
<td>41.2</td>
<td>48.2</td>
<td>50.0</td>
<td>65.6</td>
<td></td>
</tr>
<tr>
<td>Po$_2$ Torr</td>
<td>99.4</td>
<td>89.3</td>
<td>88.8</td>
<td>62.6</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine mg/dL</td>
<td>0.62</td>
<td>0.59</td>
<td>0.42</td>
<td>0.26</td>
<td></td>
</tr>
</tbody>
</table>

* Arterial blood gas was measured under room air condition.
later, BMI was decreased to 14.5 kg/m² with a weight loss of 8 kg. Serum creatinine levels were decreased to 0.26 mg/dL (normal ranges, 0.30-0.70) in comparison with 0.62 at admission. Forced vital capacity also declined to 32.5%. Arterial blood gas suggested obstructive patterns of pH 73.8, PaO₂ 65.6 Torr and PaCO₂ 62.6 Torr (Table 1). A tracheostomy was performed and ventilator was attached. She died of pneumonia at 18 months after clinical onset. Autopsy was performed and ventilator was attached. She died of respiratory failure approximately 9 months after clinical onset. Likewise with the present family, no upper motor neuron signs existed in those two patients throughout the disease courses (8).

In a United Kingdom family with a mutation of histidine to glutamine at codon 48 (H48Q) in exon 2, one patient had short survival and predominantly lower motor neurons signs (12). Scandinavian FALS patients with SOD1 mutations also have heterogeneous clinico-genotypes, including rapidly progressive lower motor neuron disease (10). Furthermore, the phenotype similar to the present family was described in FALS patients with a mutation of alanine to valine mutation at codon 4 (A4V) of SOD1; the proband had A4V mutation originated from the Farr family in Vermont, USA (13, 14). This is the most common mutation in North America and accounts for 50% of SOD1-related FALS (13). Those patients suggest rapidly progressive form of pure lower motor neuron disease. The median survival (SD) from clinical onset is 1.0 (0.4) year (13). Pathological examination also demonstrates severe involvement of lower motor neurons without upper motor neuron abnormalities in A4V-mutated patients (14). Those clinical hallmarks of A4V-mutated patients mimic the clinical signs and courses of our Japanese family with G85S mutation.

Although a novel SOD1 mutation was found in our patient II-1, the present patient did not fulfill the revised El Escorial diagnostic criteria required for both upper and lower motor neuron signs (15). This diagnostic problem suggests that current criteria need to be modified in some of SOD1-mutated FALS patients. In addition to A4V-mutated North American families and the S134N-mutated Japanese family, the present family with G85S mutation indicates the clinical phenotype of rapidly progressing lower motor neuron disease, leading to lethal respiratory failure and bedridden state within one year from onset. Physicians should pay more attention to such distinct SOD1-mutated ALS patients with rapid progression of only lower motor neuron signs.

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