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CASE REPORT

Development of diabetes in a familial amyotrophic lateral sclerosis patient carrying the I113T *SOD1* mutation

Hidetaka Hamasaki [1], Yu Takeuchi [1], Yoshinori Masui [1], Yasuyuki Ohta [2], Koji Abe [2], Hiide Yoshino [3], Hidekatsu Yanai [1]

1 Department of Internal Medicine, National Center for Global Health and Medicine Kohnodai Hospital, 1-7-1 Kohnodai, Ichikawa, Chiba, Japan
2 Department of Neurology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, 2-5-1 Shikatacho, Okayama, Japan
3 Yoshino Neurology Clinic, 3-3-16 Kohnodai, Ichikawa, Chiba, Japan

Correspondence to: Hidetaka Hamasaki, MD.
Department of Internal Medicine,
National Center for Global Health and Medicine Kohnodai Hospital
1-7-1 Kohnodai, Chiba 272-8516, Japan.
TEL: +81 47 372 3501; FAX: +81 47 372 1858; E-MAIL: hhamasaki78@gmail.com

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Abstract

Familial amyotrophic lateral sclerosis (ALS) are caused by the mutations in the copper (Cu) / zinc (Zn) superoxide dismutase 1 (SOD1) gene. SOD1 has been reported to play a critical role in glucose metabolism in yeast and cell models, and mice. However, effects of SOD1 for glucose metabolism in humans remain unknown. A 72-year-old woman was admitted to our hospital due to hyperglycemia. She showed severe muscle atrophy and visceral fat accumulation due to ALS. Her serum free fatty acids levels elevated and serum Cu and Zn levels decreased. Her two younger brothers and aunt were also diagnosed as having ALS, and DNA sequence analysis revealed the presence of the I113T SOD1 mutation. She may have developed diabetes due to SOD1 dysfunction by the I113T SOD1 mutation, and severe insulin resistance induced by ALS. The I113T SOD1 mutation may be the causative factor for diabetes as well as familial ALS.

Abbreviations:
ALS - amyotrophic lateral sclerosis
Cu - copper
SOD1 - the copper/zinc superoxide dismutase 1
Zn - zinc

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by degeneration and death of upper and lower motor neurons. Most cases of ALS are sporadic but about 10% of them are familial (Rosen *et al.* 1993). Approximately 20% of familial ALS cases are caused by the mutations in the copper (Cu)/zinc (Zn) superoxide dismutase 1 (SOD1) gene (Rosen *et al.* 1993). SOD1 is widely expressed and its main function is thought to be as a cytosolic and mitochondrial antioxidant enzyme, converting superoxide to molecular oxygen and hydrogen peroxide (Bun-

ton-Stasyshyn *et al.* 2014). Raddi and Culotta reported that SOD1 integrates signals from oxygen and glucose to repress respiration (Raddi & Culotta 2013), suggesting that SOD1 plays a critical role in cellular aerobic glucose utilization. However, the relationship between familial ALS with *SOD1* mutation and the development of diabetes is unknown. Here, we report a familial ALS patient carrying *SOD1* mutation who developed diabetes.

CASE REPORT

A 72-year-old bedridden woman was admitted to our hospital because she has showed hyperglycemia. Her height was 153 cm and weight was 58.7 kg. She was diagnosed as having ALS seventeen years ago. She could not breathe without using the artificial respirator three years ago, and enteral nutrition (Racol-NFR) of 800 kcal/day was provided. Her plasma levels of glucose and hemoglobin A1c (HbA1c) were elevated to 420 mg/dL and 9.2%, respectively. She was complicated with fatty liver, however, was not complicated with dehydration, infection and malignancy which deteriorate glucose metabolism. Her endogenous insulin secretion was not impaired: serum and urinary C-peptide levels were 2.70 ng/mL (normal range: 0.61–2.09 ng/mL) and 104 μg/day (normal range: 29.2–167 μg/day), respectively. Serum levels of free fatty acids elevated to 1,184 μEq/L (normal range: 140–850 μEq/L). Serum levels of Cu and Zn decreased to 14 μg/dL (normal range: 68–128 μg/dL) and 49 μg/dL (normal range: 65–110 μg/dL), respectively. Computed tomography revealed remarkable muscle atrophy, increase in visceral fat area (342.2 cm^2) and subcutaneous fat area (200.1 cm^2). Body composition analysis by bioelectrical impedance analysis device (InBody S10, Biospace Co., Ltd, Tokyo, Japan) also showed decrease in skeletal muscle mass (12.5 kg) and increase in body fat percentage (56.6%). She was treated with intensive insulin therapy and her glycemic control was ameliorated. Her blood glucose levels were 90–170 mg/dL by using 26 units of insulin glulisine, taking daily 20 mg/day of teneligliptin and daily 1.25 mg/day of repaglinide, and then she was discharged. Her two younger brothers and aunt were also diagnosed as having ALS, and we diagnosed as her having familial ALS (Figure 1A). DNA sequence analysis of SOD1 gene revealed the presence of the I113T *SOD1* mutation (Figure 1B).

We report the development of diabetes in a familial ALS patient carrying I113T *SOD1* mutation, to our knowledge, which has not been previously reported in the literature. Reyes *et al.* showed mitochondrial dysfunction in skeletal muscle and insulin resistance in patients with ALS (Reyes *et al.* 1984), and insulin resistance was related to the inactivity associated with disease progression (Harris *et al.*1986). Shimizu *et al.* also reported five cases of hyperosmolar hyperglycemic syndrome in advanced ALS (Shimizu *et al.* 2011). They concluded that insulin resistance due to a marked loss of skeletal muscle might have been causative factor for hyperosmolar hyperglycemic syndrome in advanced ALS (Shimizu *et al.* 2011). In our case, we also observed insulin resistance due to muscle atrophy, visceral fat accumulation and increased free fatty

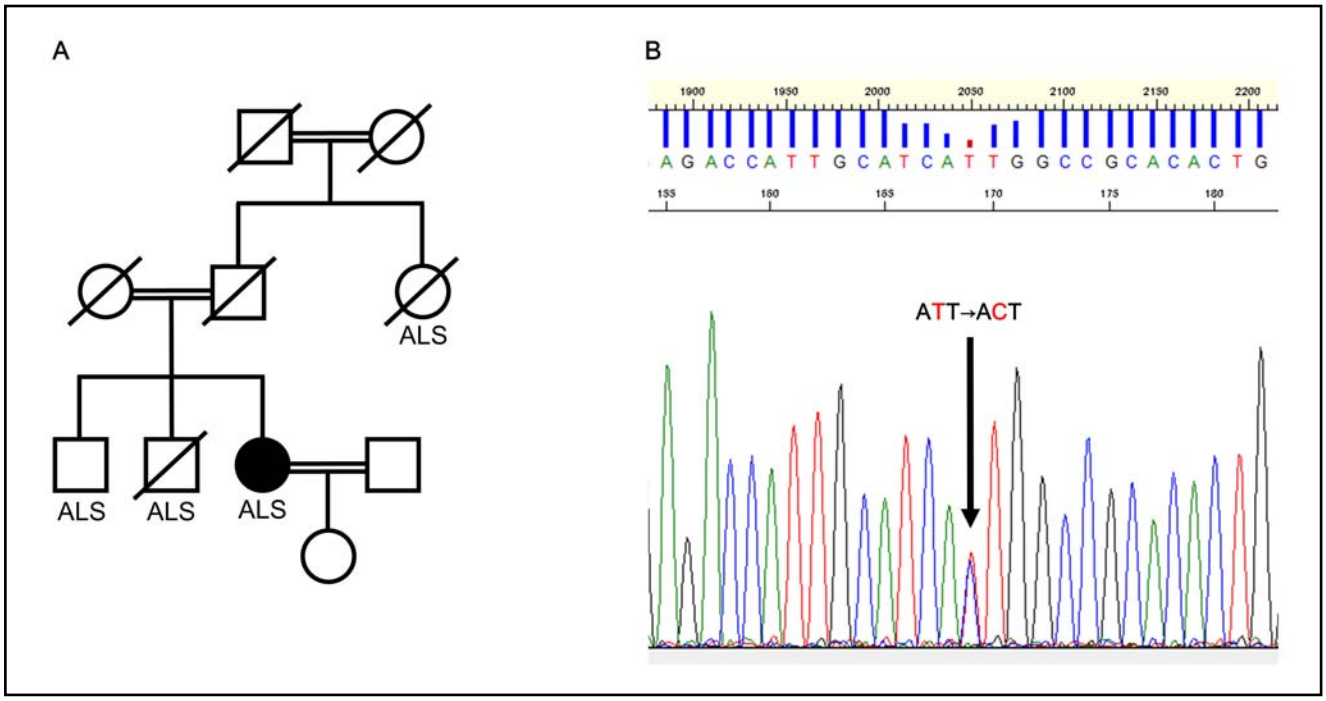

Fig. 1. (A) Pedigree chart. (B) A *SOD1* heterozygous point mutation in exon 4, resulting in a single amino acid substitution of isoleucine to threonine at codon 113.

acids, which may induce diabetes. Furthermore, *SOD1* mutation may have influenced on the development of diabetes. SOD1 is a mitochondrial antioxidant enzyme protecting the cell from reactive oxygen species toxicity (Bunton-Stasyshyn *et al.* 2014). Allen *et al.* reported that fibroblasts with the I113T *SOD1* mutation had significantly diminished spare respiratory capacity (by approximately 32%) compared with controls (Allen *et al.* 2013). They also showed that fatty acid oxidation and ATP production via oxidative phosphorylation were reduced in fibroblasts with the I113T SOD1 mutation (Allen *et al.* 2013). Oxidative stress is increased by SOD1 dysfunction due to the I113T *SOD1* mutation, which may induce insulin resistance. In Zn and Cu deficiency which were observed in our case, the normal SOD1 activity is lowered (Prohaska *et al.* 2003) and the mutant SOD1 also activates the endoplasmic reticulum stress (Bunton-Stasyshyn *et al.* 2014), which will further deteriorate insulin resistance. Our patient may have developed diabetes by these cumulative factors inducing insulin resistance.

Recently, the knockout of *SOD1* has been reported to impair pancreatic islet function and glucose homeostasis in mice (Wang *et al.* 2011), indicating that *SOD1* mutation is associated with insulin secretion as well as insulin resistance. Carrying the *SOD1* mutation may be a risk factor for the development of diabetes, by inducing insulin resistance and decreasing insulin secretion. Although we could not ascertain the family history of diabetes in this case, the pathogenic association between the I113T *SOD1* mutation and diabetes may exist. A recent study showed that metformin increased expression levels of SOD1 in mice (Forouzandeh *et al.* 2014), which suggests that glucose metabolism is partially regulated by SOD1. However, to elucidate the relationship between *SOD1* mutation and the development of diabetes, further studies should be needed in the future.

This case provides a new perspective for development of diabetes in a familial ALS patient carrying the I113T *SOD1* mutation. Oxidative stress due to SOD1 dysfunction by the mutation and Zn/Cu deficiency, and muscle atrophy and visceral fat obesity due to inactivity by ALS may have induced severe insulin resistance. The I113T *SOD1* mutation may be the causative factor for diabetes as well as familial ALS.

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