A 29-year-old patient with adrenoleukodystrophy presenting with Addison’s disease

Hajime Tanaka1)*, Naoko Amano2)*, Kumiko Tanaka1), Takeshi Katsuki1), Tomohide Adachi1), Nobuyuki Shimozawa3) and Toshihide Kawai1)

1) Department of Internal Medicine, Tokyo Saiseikai Central Hospital, Minato-ku, Tokyo 108-0073, Japan
2) Department of Pediatrics, Tokyo Saiseikai Central Hospital, Tokyo 108-0073, Japan
3) Division of Genomics Research, Life Science Research Center, Gifu University, Gifu 501-1193, Japan

Abstract. Adrenoleukodystrophy (ALD) is an X-linked disorder caused by a hemizygous mutation of the ABCD1 gene. Patients with ALD show progressive central nervous system demyelination and primary adrenal insufficiency. In Japan, most reported ALD cases were childhood-onset, and only one case of an adult patient with Addison’s disease form of ALD has ever been reported. Herein, we present a case of a 29-year-old man with Addison’s disease form of ALD. The patient had anorexia, weight loss, and skin pigmentation from 18 years of age. At first visit, his weight had decreased by 12 kg from 57 kg when he was 15 years old. Endocrinological examination showed low serum cortisol (1.2 μg/dL) with high plasma ACTH (4,750 pg/mL), and abdominal computed tomography showed normal adrenal glands. Very-long-chain fatty acid (VLCFA) levels were elevated, and the ABCD1 mutation, p.Gly116Arg, was identified in hemizygous state. He had no significant neurological findings on physical examination and no white matter lesions on brain magnetic resonance imaging (MRI). He was diagnosed with ALD presenting as Addison’s disease, and glucocorticoid replacement therapy was initiated. Four years after the diagnosis, he still did not show any neurological findings and any white matter lesions on brain MRI. Evaluating VLCFA levels for ALD diagnosis is important in young adult men with idiopathic primary adrenal insufficiency as well as in children. Early diagnosis enables more rational approaches including the early detection of neurological complications and might improve the prognosis of patients.

Key words: Adrenoleukodystrophy, Primary adrenal insufficiency, Very-long-chain fatty acid (VLCFA)
disease of ALD and highlight the importance of evaluating VLCFA for the early diagnosis of ALD in young adult males with idiopathic PAI.

**Case Report**

A 29-year-old man was referred to our hospital for morning nausea and anorexia. He had experienced the morning nausea and anorexia and had noticed progressive pigmentation of the skin and tongue from around the age of 18 years. At first visit, his weight had decreased by 12 kg from 57 kg when he was 15 years old. His growth and development were normal, and he did not have any significant past medical history or any family history including neurological disorders, adrenal insufficiency and unexplained death. On physical examination, his height, weight and body mass index were 174 cm, 45 kg, and 14.9 kg/m$^2$, respectively. His blood pressure was 89/65 mmHg. He had pigmentation at the lips, gingiva, tongue, and nipples. His mental status and neurological evaluation were normal.

On laboratory examination, the serum electrolytes and plasma glucose were normal. Endocrinological examination showed low serum cortisol (1.2 μg/dL, normal range 4.0–18.3 μg/dL) with high plasma ACTH (4,750 pg/mL, normal range 7.2–63.3 pg/mL) and low urinary free cortisol (5.9 μg/day, normal range 11.2–80.3 μg/day). Plasma renin activity and serum aldosterone levels were normal (Table 1). Abdominal computed tomography showed normal adrenal glands without any hemorrhagic lesions and masses (Fig. 1). We diagnosed him with PAI and introduced glucocorticoid replacement therapy.

We measured the levels of autoantibody against the adrenal cortex of adrenal glands and the levels of VLCFA for investigating the cause of his PAI. The levels of autoantibody were negative, and the levels of VLCFA were elevated, suggesting adrenoleukodystrophy (Table 2). We obtained written informed consent from the patient for molecular studies, which were approved by the Institutional Review Board of Gifu University Graduate School of Medicine. We extracted genomic DNA from the peripheral lymphocytes and analyzed ABCD1 (NM_000033.4) with PCR-based Sanger sequencing. The primer sequences and PCR conditions are available upon request. We identified a hemizygous mutation, p.Gly116Arg, which was already reported [5, 6]. After genetic counseling, we performed the genetic analyses of his family members. His mother carried the mutation, while his sister and her son did not. To investigate the presence of neurological complication associated with ALD, we performed neurological examination and brain magnetic resonance imaging (MRI) on the patient. He did not show any obvious abnormal neurological findings including progressive spastic paraparesis and peripheral neuropathy and did not have any white matter lesions on MRI (Fig. 2). Finally, we diagnosed him with ALD presenting as Addison’s disease.

After the introduction of glucocorticoid replacement therapy, his pigmentation disappeared, and his weight increased. At the age of 33 years, he continues glucocorticoid replacement therapy with hydrocortisone (19.0 mg/m²), and his body weight is 62 kg. He still does not show any significant neurological abnormalities or any white matter lesions on brain MRI.

| Table 1 | Laboratory data of the patient |
|---------|-------------------------------|
| WBC     | 5.4 × 10³ /μL |
| Eo      | 7 % |
| Na      | 142 mEq/L |
| K       | 4 mEq/L |
| Cl      | 107 mEq/L |
| Ca      | 9.3 mg/dL |
| iP      | 3.4 mg/dL |
| BUN     | 12 mg/dL |
| Cr      | 0.72 mg/dL |
| eGFR    | 105.7 mL/min/1.73 m² |
| FPG     | 92 mg/dL |
| TSH     | 5.18 μU/mL |
| FT3     | 3.07 pg/dL |
| FT4     | 1.05 ng/dL |
| GH      | 0.67 mg/mL |
| IGF-1   | 1.32 ng/mL |
| LH      | 9.94 mIU/mL |
| FSH     | 2.27 mIU/mL |
| Testosterone | 9.49 ng/mL |
| ACTH    | 4,750 pg/mL |
| Cortisol | 1.2 μg/dL |
| Urinary free cortisol | 5.9 μg/day |
| PRA     | 1.9 ng/mL/hr |
| PAC     | 72.3 pg/mL |
| DHEA-S  | 30 μg/dL |
| Anti-TG antibody | (−) |
| Anti-adrenal antibodies | (−) |

IGF-1, insulin-like growth factor; PRA, plasma renin activity; PAC, plasma aldosterone concentration; DHEA-S, dehydroepiandrosterone sulfate
We report a case of a young adult male with ALD presenting Addison’s disease phenotype. In Japan, most reported ALD cases presenting with PAI are children, and there is only one adult ALD case report of Addison’s disease form [4]. Conversely, in Western countries, the percentage of ALD in childhood-onset PAI (1–16 years) and adolescent to adulthood-onset PAI (14–58 years) is 31% [7] and 15% [8], respectively. Moreover, according to the recent Western international multicenter retrospective study of 159 patients with ALD, 37.7% of the patients had PAI as the initial symptom, and the incidence of PAI increases with age (47% at 10 years of age, 75% at 40 years of age, and 80% at 56 years of age). Totally, PAI was observed in 71.1% of adult patients [9]. These observations suggest that PAI would be a major symptom in adults with ALD as well as in children. Therefore, some adult Japanese patients with ALD might be diagnosed with idiopathic PAI, namely Addison’s disease, and be treated with hydrocortisone replacement therapy alone.

Our patient has undergone the neurologist’s check-up and brain MRI once a year to access the presence of neurological complications including white matter lesions for 4 years after the diagnosis of ALD. Fortunately, he has not shown any significant abnormal findings. The recent international multicenter retrospective study reported that neurological symptoms due to demyelination most often appeared after the diagnosis of PAI, and spinal cord and cerebral symptoms appeared at the mean ages of 27 and 35 years [9]. In children with cerebral ALD, hematopoietic stem cell transplantation is the most promising therapy [10]. Currently, hematopoietic stem cell transplantation is also tried in young adult patients with cerebral ALD [11]. However, this therapy is applicable only in patients with early-phase cerebral ALD complications. Therefore, early diagnosis would be critical for young adults and children with ALD to improve their life prognosis. We should evaluate serum VLCFA levels routinely in young adult male patients diagnosed with idiopathic PAI, i.e., Addison’s disease for the diagnosis of ALD.

We identified a hemizygous mutation, p.Gly116Arg. More than 700 ABCD1 mutations have been reported [12] in ALD. The mutation, p.Gly116Arg, was already reported in two cases from other countries. One patient had cerebral ALD, and the other patient had AMN phe-

### Table 2  Peroxisomal fatty acid profile

| Results | Average ± SD |
|---------|--------------|
| C24:0/C22:0 | 1.56 ± 0.16 |
| C25:0/C22:0 | 0.051 ± 0.006 |
| C26:0/C22:0 | 0.076 ± 0.005 |

C22:0, docosanoic acid; C24:0, tetracosanoic acid; C25:0, pentacosanoic acid; C26:0 hexacosanoic acid

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**Fig. 1** Image of abdominal computed tomography

Abdominal computed tomography showed normal adrenal glands without any hemorrhagic lesions and masses.

**Fig. 2** Image of brain MRI (T2)

Brain MRI showed no white matter lesions.
notype [5, 6]. Patients with ALD show no genotype-phenotype correlation [13], and the genetic, epigenetic, and environmental factors contribute to the development of cerebral ALD [14]. Therefore, predicting his final phenotype is difficult, and close monitoring of neurological complication would be required.

In conclusion, we should evaluate VLCFA levels in young adult males with idiopathic PAI as well as in children for the diagnosis of ALD. Early diagnosis enables more rational approaches including the early detection of neurological complications and might improve the prognosis of the patients. Further cumulative data are necessary to understand the pathological conditions young adult patients presenting with Addison’s disease ALD.

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Disclosure

None of the authors have any potential conflicts of interest associated with research.

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