We report two sibling cases of Addison’s disease without any evidence of sexual precocity, adrenal hyperplasia, or autoimmune disease. The diagnosis of primary adrenocortical insufficiency was made at the age of 5 in the younger brother and at the age of 18 in the elder brother. The younger brother had been inactive during infancy and had diffuse skin pigmentation without abnormal external genitalia, while the elder brother had been healthy until the age of 17 when he noticed skin pigmentation and small testes. Both boys had delayed puberty due to hypogonadotropichypogonadism. The diagnosis of adrenal hypoplasia congenita (AHC) was established by genetic analysis of DAX-1 gene (dosage-sensitive sex reversal-adrenal hypoplasia gene on the X chromosome, gene 1) with the same single frameshift mutation (305delG). However, yet-uncharacterized epigenetic, nongenetic and/or genetic factors other than the DAX-1 gene may be responsible for the differential onset of AHC in these sibling cases.

Key words: Addison’s disease, adrenal hypoplasia congenita, sibling cases, DAX-1 gene

(DOI: 10.2169/internalmedicine.46.6082)
Figure 1. ACTH and LH-RH stimulation tests. (Left) plasma cortisol levels after intravenous injection of ACTH (250 μg) in Cases 1 and 2, (Right) plasma LH and FSH levels after intravenous injection of LH-RH (100 μg) in Cases 1 and 2.

(17α-OHP).

Standard image tests revealed no adrenal mass or calcification and 131I-adosterol scintigram showed decreased radioactive uptake in bilateral adrenal glands. Based on these clinical and endocrine data, the diagnosis of early onset primary adrenal insufficiency was made. Soon after replacement of hydrocortisone (35 mg) and fludrocortisone (0.03 mg) with sodium chloride (4.0 g) was started, the ACTH
level became normal and pigmentation disappeared. Thereafter, he was well on the maintenance doses of steroid replacement therapy.

He was 176 cm tall and weighed 66 kg. He had delayed secondary sexual development with a small penis (P3~4) and testes (8 ml/12 ml) and scanty pubic hair (P-3). The laboratory data were normal, and the endocrine data (Table 1) showed decreased plasma levels of testosterone, DHEA-S and aldosterone, increased FSH and normal LH, ACTH and PRA levels. LH-RH stimulation test showed low responses of LH and FSH consistent with secondary hypogonadism (Fig. 1). Treatment with weekly injections of HCG (6000 IU) was started at the age of 20, and plasma testosterone level became normal. He married at the age of 26. He is currently 30 years old with normal testosterone levels and no children; the number of sperm is null.

Case 2 (Elder brother)

The elder brother noticed gradual development of skin pigmentation at the age of 17. He was admitted to our hospital for endocrine evaluation at the age of 18. Physical examination revealed a mild skin pigmentation and small testes. His blood pressure was 106/68 mmHg. Endocrine data revealed a markedly elevated plasma ACTH level and PRA, decreased cortisol, DHEA and 17-OHP levels, and decreased urinary excretion of steroids (Table 1). ACTH stimulation test did not increase cortisol or aldosterone levels (Fig.1). Computed tomographic (CT) scan of the abdomen revealed atrophy of the adrenal glands. Based on these clinical and endocrine data along with the findings of his younger brother’s disease, the diagnosis of AHC was made. After replacement with hydrocortisone (30 mg), his plasma ACTH level became normal and skin pigmentation gradually disappeared. However, the plasma testosterone level was low and LH-RH stimulation test showed low responses of LH and FSH consistent with secondary hypogonadism (Fig. 1). Treatment with weekly injections of HCG (6000 IU) was started at the age of 20, and plasma testosterone level became normal. He married at the age of 26. He is currently 30 years old with normal testosterone levels and no children; the number of sperm is null.

Discussion

Here, we describe two sibling cases of Addison’s disease caused by AHC. AHC is a rare familial disease characterized by an undeveloped adrenal gland. AHC has been classified into 4 types according to its clinical manifestations (2); type 1 is sporadic form associated with pituitary hypoplasia; type 2 is autosomal recessive form; type 3 is X-linked cytomegalic form associated with hypogonadotropic hypogonadism (4); type 4 is X-linked form associated with glyceral kinase deficiency (GKD), psychomotor retardation, Duchenne’s muscular dystrophy in most patients, and a characteristic facies. The present sibling cases associated with Addison’s disease and hypogonadotropic hypogonadism appear to be compatible with the most common type 3 AHC.
Recently, it has been suggested that interplay among DAX-1, steroidogenic factor-1 (SF-1), and their downstream genes plays an important pathophysiological role in the process of adrenal cortex differentiation and the age of onset in AHC (5).

Twenty-nine mutations of the DAX-1 gene in type 3 AHC have been reported to date (6); 15 frameshifts, 9 nonsenses, 4 missenses, and 1 deletion in frame. Among these cases, nine siblings with AHC by the same DAX-1 gene mutation have been shown to consist of 4 frameshift, 3 nonsense, and 2 missense mutations (3, 4, 7-9). Their clinical manifestations and the ages of onset (usually in early infancy and childhood) appear to be almost the same in each family, but different among the families. Therefore, the age of onset of type 3 AHC may be related to the type of each mutation.

The ages of onset in our sibling cases differed considerably from 3 years old in the younger to 18 years old in the elder brother, in spite of the same single frameshift mutation without any other mutations, of the DAX-1 gene. As summarized in Table 2, there have been three families reported to date with siblings of considerably different ages of onset (3, 5). The first set of sibling cases, diagnosed at 3 years old and one month old, had both AHC and GKD caused by the same deletion of approximately 650 kb, including the DAX-1-GKD gene locus. The second set of sibling cases, diagnosed at 10 years old and 3 weeks old, had AHC with the same frameshift (796 ins CAGG) in the DAX-1 gene. The third set of sibling cases, diagnosed at 3 years old and 3 days old, had AHC with the same frameshift (507 CG-T) in the DAX-1 gene. Moreover, two adult-onset sibling cases diagnosed as AHC at the age of 28 have been reported (10, 11). They had different sites of missense mutation (I439S and Y380D) in DAX-1 gene. In the present sibling cases, the elder brother was early adult onset, while the younger one was infant onset. Thus, there seems to be no apparent relationship between the onset of disease and the site of mutation.

Taken together, it seems that there is no apparent correlation between the type of mutation and the age of onset in AHC. Thus, the onset of adrenal insufficiency and hypogonadotropic hypogonadism in type 3 AHC could be affected by some other genetic, epigenetic and/or nongenetic factors rather than DAX-1 gene mutation.

This study was supported in part by Grants-in-Aid from the Ministry of Health, Labor and Welfare, and the Ministry of Education, Science, Sport and Technology, Japan.

References


