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NOTE

Unilateral adrenalectomy can be an alternative therapy for infantile onset Cushing's syndrome caused by ACTH-independent macronodular adrenal hyperplasia with McCune-Albright syndrome

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Abstract. We report herein the case of a 1-year-old boy with McCune-Albright syndrome (MAS) who presented with infantile-onset Cushing's syndrome caused by ACTH independent macronodular adrenal hyperplasia (AIMAH). Abdominal CT, MRI, and adrenal scintigraphy with ^{131}I-adosterol identified bilateral adrenal involvement with the left adrenal gland being larger and functionally more active. Unilateral adrenalectomy of the left gland was performed and ameliorated many clinical symptoms, such as Cushingoid appearance and height restriction, and it also normalized many endocrinological data, such as diurnal rhythms of ACTH and cortisol, ACTH and cortisol responses to CRH, and urinary 24 hr free cortisol. Glucocorticoid was replaced for the first 1 year and 6 months after the operation. One adrenal crisis episode occurred at 3 weeks after the operation, but none have occurred since. These results suggest that unilateral adrenalectomy of the larger gland can be an alternative therapy for infantile onset Cushing's syndrome caused by AIMAH with MAS, when asymmetric involvement is evident and the smaller gland is not markedly enlarged.

Key words: ACTH-independent macronodular adrenal hyperplasia (AIMAH), Unilateral adrenalectomy, McCune-Albright syndrome (MAS), Cushing's syndrome, Childhood

MCCUNE-ALBRIGHT syndrome (MAS) is characterized by the triad of polyostotic fibrous dysplasia, café-au-lait skin lesions, and GnRH independent sexual precocity [1, 2]. Various other endocrinopathies, such as hyperthyroidism, Cushing's syndrome, growth hormone excess, hyperprolactinemia, and hyperparathyroidism have been also observed [3]. Somatic gain-of-function mutations in the *GNAS1* gene, which encodes for the $G_s\alpha$ protein, have been identified in each affected tissue [4]. In the adrenal glands these mutations can cause ACTH-independent macronodular adrenal hyperplasia (AIMAH), which can lead to ACTH-independent Cushing's syndrome [5].

Cushing's syndrome caused by AIMAH in patients with MAS usually occurs in infancy, and historically has been treated by bilateral adrenalectomy [6]. This can effectively ameliorate Cushingoid appearance and hypercortisolism; however, lifetime steroid replacement therapy is required after this operation. Recently, there have been several reports of unilateral adrenalectomy for AIMAH in adult patients successfully improving clinical symptoms and endocrinological status in Cushing's syndrome, particularly in cases with definite asymmetric involvement [7-9]. However, to our knowledge, there have been no reports of unilateral adrenalectomy for children with AIMAH resulting from MAS. We report herein a case of infantile onset

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Cushing's syndrome caused by AIMAH with MAS. The patient underwent unilateral adrenalectomy at 2 years of age, and growth and endocrinological data have improved in the 2 years since operation.

Case report

The patient was born as the first son of nonconsanguineous Japanese parents at 39 weeks' gestation after an uncomplicated pregnancy and delivery. His birth weight was 3,074 g and his length was 51.0 cm. His mental and motor development was normal. At 1 year and 2 months of age, he was referred to our hospital due to growth failure, café-au-lait skin lesions on his torso and legs, and liver dysfunction. His length was 66.1 cm (−4.19 SD) and weight was 7.68 kg (−2.12 SD). Café-au-lait skin lesions with irregular margins were seen on his left chest, right abdomen, back, and both legs. He had some Cushingoid features, such as moon face (Fig. 1A), acne, and hirsutism (written informed consent to publish his photographs was obtained from his parents). His laboratory data were as follows: AST 40 IU/L, ALT 32 IU/L, ALP 2913 IU/L, ACTH 5.5 pg/mL, cortisol 18.5 μg/dL, and DHEA-S 2360 ng/mL (reference range: 28-223 ng/mL). Although abnormal data were evident, and the parents were contacted, they did not return to our hospital with the child for about 8 months.

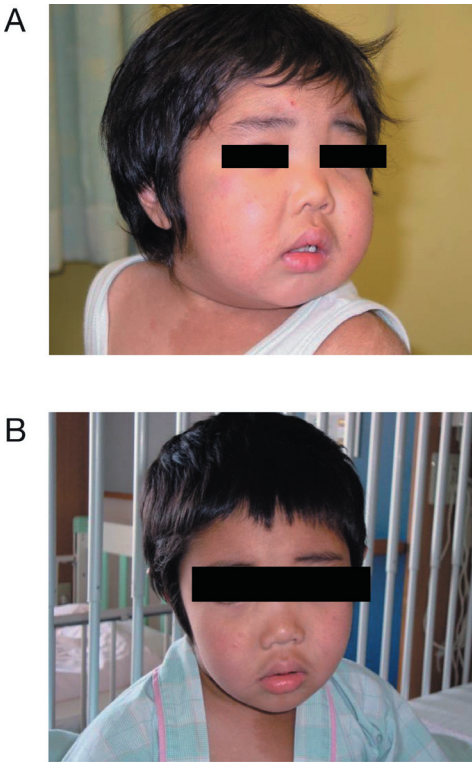

Fig. 1 Photographs of the patient
Moon face was seen before the operation (A); however, it was not evident 2 years after the operation (B). A café-au-lait skin lesion can be seen on the left chest.

At 1 year and 10 months of age, his length was 70.4 cm (−4.66 SD), weight 10.4 kg (−0.75 SD), and blood pressure 98/50 mmHg. Cushingoid features were unchanged from those seen at the first physical examination. The testes each had a volume of 1-2 mL. No pubic hair, axillary hair, or skin pigmentation were seen. X-ray showed ground-glass appearance of the craniofacial bone, with a bone age of 1 year and 3 months (Greulich-Pyle method). Bone scintigraphy showed abnormal accumulation in the ribs, femurs, left radius, and craniofacial bone. Urinary free cortisol was 186 μg/m^2/day (reference range: 25-75 μg/m^2/day). Urinary steroid profile by gas chromatography/mass spectrometry in selected ion monitoring mode showed elevation of almost all the metabolites of steroids except DOC, corticosterone, and aldosterone (data not shown). Early morning ACTH was <5.0 pg/mL, cortisol 20.1 μg/dL, DHEA-S 3390 ng/mL, 17-OH progesterone 0.4 ng/mL, and testosterone 35 ng/dL. Cortisol at 2300h was 18.5 μg/dL. ACTH and cortisol response to CRH (1.5 μg/kg) were 5.9→10.7 pg/mL (30 minutes) and 21.7→34.4 μg/dL (60 minutes), respectively. The serum cortisol was not suppressed (24.3→20.1 μg/dL) by high-dose overnight dexamethasone test in which a single 8-mg/m^2 dose of dexamethasone was administered orally at 2300h. These data strongly suggested ACTH independent Cushing's syndrome. Imaging studies showed bilateral asymmetrical adrenal involvement. Abdominal CT (Fig. 2A) and MRI (Fig. 2B) showed bilaterally enlarged adrenal glands with greater enlargement on the left side, and adrenal scintigraphy with ^{131}I-adosterol confirmed left-side dominant radioisotope uptake (Fig. 2C).

We diagnosed McCune-Albright syndrome accompanied by Cushing's syndrome caused by AIMAH. At 2 years and 1 month, we performed left adrenalectomy by laparoscopy without any steroid replacement. Pathological examination of the left adrenal gland showed multinodular hyperplastic adrenal enlargement, and the nodules were separated by thin connective bands and composed of large, clear, cortical cells

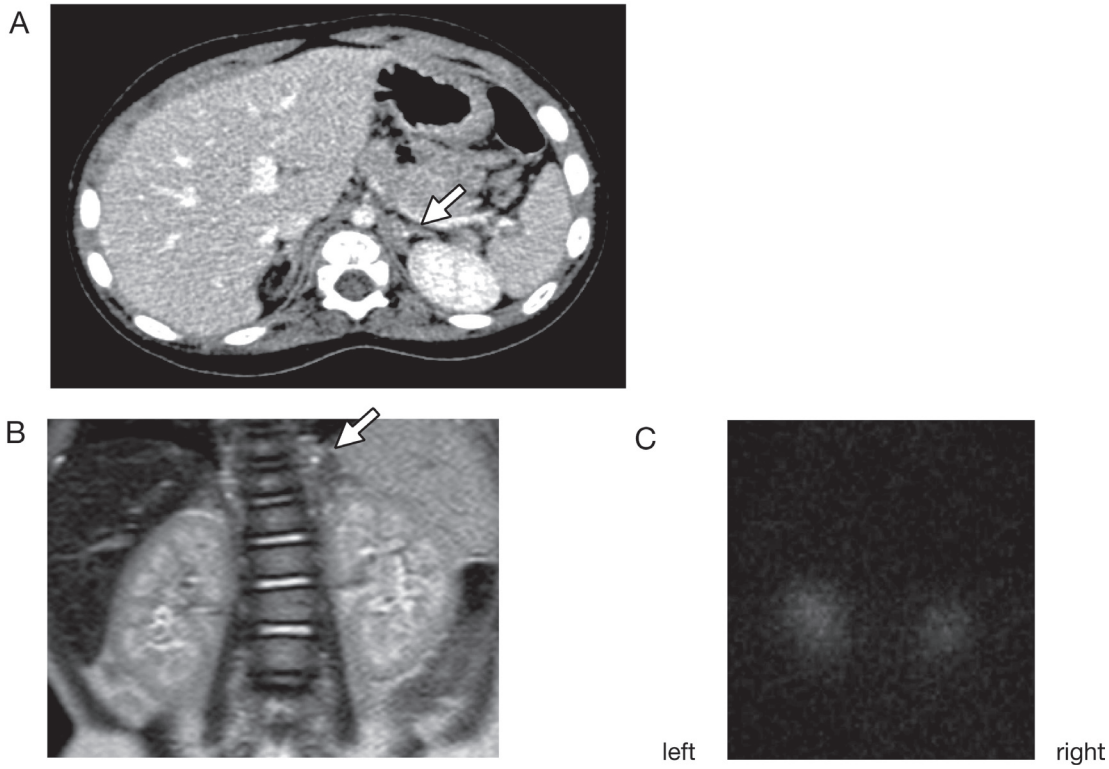

Fig. 2 Imaging findings of the adrenal glands
CT (A) and MRI (B) showed asymmetrical bilateral enlargement of the adrenal glands. The left gland (arrows in A and B) was larger than right. Radioisotope uptakes on adrenal scintigraphy with ^{131}I-adosterol showed asymmetrical bilateral uptake with predominance on the left side (C).

and small compact cells (data not shown). *GNAS-1* gene analysis was performed by the previously reported peptide nucleic acid (PNA)-clamping method [10]. We identified a R201H mutation, which has been previously reported as common in MAS, in both the left adrenal gland and peripheral blood leukocytes (data not shown) [11]. These pathological and genetic findings confirmed the diagnosis of AIMAH and MAS.

Postoperative early morning cortisol levels on postoperative days 1, 4, and 5 were 14.9, 8.4, and 7.7 μg/dL, respectively. We observed him carefully without steroid replacement therapy, considering that steroid production would likely be adequate from the right adrenal gland. Three weeks after the operation, he was brought to our hospital because of high fever and nausea. His activity was poor and his face was pale. Serum sodium was 133 mEq/L, blood glucose 100 mg/dL, HCO_3^- 19.5 mmol/L, and cortisol 21.6 μg/dL, and plasma ACTH was 9.2 pg/mL. We suspected acute adrenal failure and administered 100 mg/m^2 hydrocortisone sodium succinate intravenously. His general condition recovered within 3 hr of the injection. This prompt improvement and relatively low cortisol level despite the stress verified acute adrenal failure. He was therefore started on hydrocortisone 10 mg/m^2 every morning, and no episode suggesting adrenal failure have been seen since. Hydrocortisone was discontinued at the age of 1 year and 6 months because of the recovery of morning ACTH and cortisol, and ACTH and cortisol responses to CRH (data not shown).

His clinical findings have improved dramatically since the operation. Physical findings at 4 years of age (2 years after the operation) were as follows: height was 93.8 cm (−1.64 SD), weight 16.95 kg (+0.68 SD), testicular volume 2 mL, and no Cushingoid appearance (Fig. 1B) or secondary sex characteristics were seen.

Many of the initial endocrinological data have also improved or normalized at 2 years after the operation.

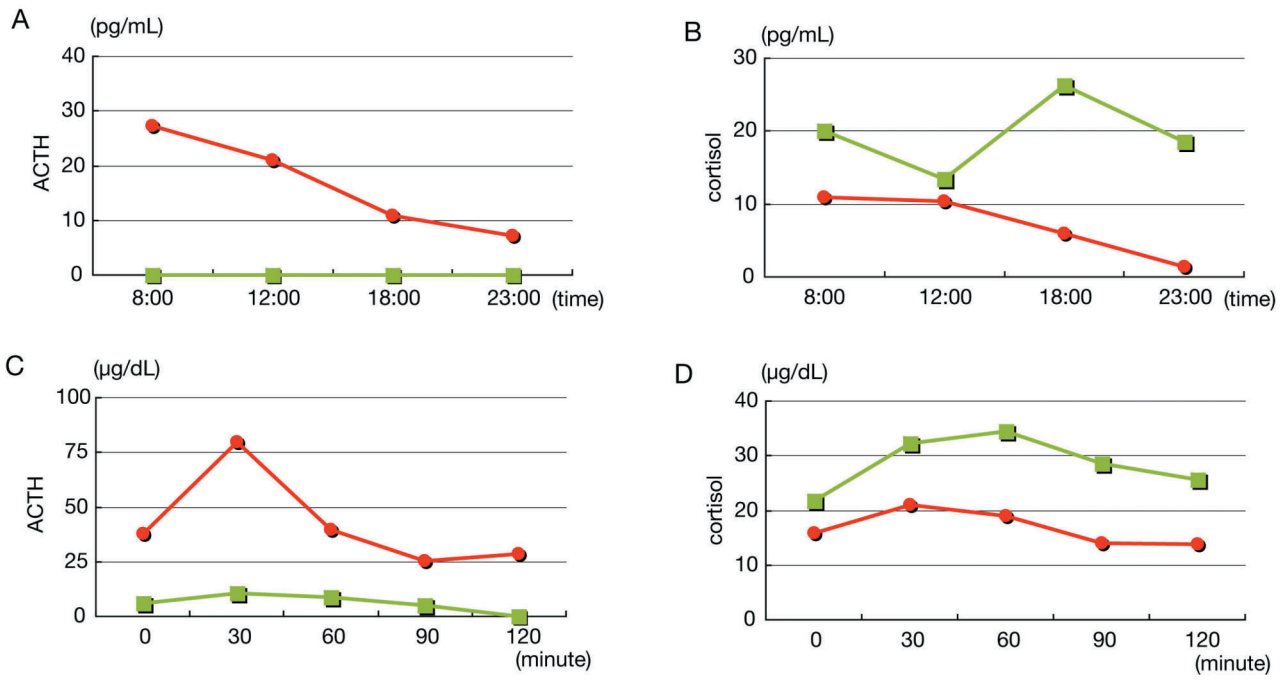

Fig. 3 Changes in diurnal rhythm of ACTH (A) and cortisol (B), ACTH response to CRH (C), and cortisol response to CRH (D) before and at 2 years after the operation

Morning ACTH and cortisol levels at 2 years after operation were 27.2 pg/mL and 10.9 μg/dL, respectively (A, B). Midnight ACTH and cortisol levels at 2 years after operation were 7.1 pg/mL and 1.4 μg/dL, respectively (A, B). ACTH and cortisol response to CRH had normalized at 2 years after the operation (C, D).

■: before the operation ●: 2 years after the operation

Diurnal rhythms and responses to CRH of ACTH and cortisol are normal (Fig. 3). Urinary free cortisol is 74 μg/m^2/day (reference range: 25-75 μg/m^2/day). The right adrenal gland has remained the same size as determined by CT. Some data have improved but have not yet normalized, such as morning cortisol after high-dose dexamethasone suppression test (7.9 μg/dL), DHEA-S (694 ng/mL), and testosterone (27.9 ng/dL). His gonadotropin levels (LH <0.1 mIU/mL, FSH 0.4 mIU/mL) are not elevated, and his bone age (Tanner-Whitehouse 2 method for Japanese children) is 3 years and 11 months at 4 years of chronological age.

Discussion

Unilateral adrenalectomy of the larger gland resulted in remarkable improvement in clinical symptoms and endocrinological data in the present case. First, the patient's height has improved dramatically from −4.66 to −1.64 SD without development of any secondary sex characteristics or acceleration of bone age. Next, his Cushingoid appearance disappeared. Then, his diurnal rhythms of ACTH and cortisol, and ACTH and cortisol responses to CRH, normalized. Finally, hydrocortisone replacement therapy could be discontinued.

In adults, unilateral adrenalectomy of the larger gland can be considered as an alternative therapy for AIMAH, when the other gland is not markedly enlarged [7-9]. Iacobone *et al.* reviewed seven adult patients with AIMAH who underwent unilateral adrenalectomy of the larger gland. At a median follow-up of 53 months, serum and urinary free cortisol levels were significantly decreased in six patients, blood pressure was significantly reduced in all patients, diabetes (seen in 40% of patients) was well controlled, and health-related quality of life, as evaluated by SF-36, improved significantly. The adrenal involvement was markedly asymmetrical in their successfully treated patients; the mean size of the largest excised adrenal, which was evaluated as the largest measurable diameter of the gland at CT or MRI, was 59 mm, whereas the remain-

ing gland was always <30 mm, suggesting that the size of the other gland might be critical [7]. Lamas *et al.* reported four adult patients with AIMAH who underwent unilateral adrenalectomy of the larger gland. Two patients developed transient post-surgical adrenal insufficiency and required steroid replacement therapy for 60 and 14 months, respectively. After a mean follow-up of 78.8 months, all patients remained free from any evidence of Cushing's syndrome. Urinary free cortisol and serum cortisol, after the adrenal insufficiency stage, remained within the normal range. No further enlargement of the contralateral gland has been documented in three of the four patients [8].

As far as we know, this is the first report of unilateral adrenalectomy performed for a child with AIMAH secondary to MAS. Bilateral adrenalectomy is usually performed, because, typically, both adrenal glands are affected. On the other hand, spontaneous resolution and prolonged remission after the therapy with metyrapone and aminoglutethimide have been reported in children [12, 13]. Considering that MAS is caused by somatic mutation of the *GNAS1* gene, non-affected adrenal tissue is possible, particularly in smaller gland. In this regard, Boston *et al.* reported that the *GNAS1* mutation was detected in nodular adrenal tissue, but was essentially absent in normal adrenal tissue [5]. This suggests that the slightly enlarged adrenal gland may have only small nodules and sufficient normal adrenal tissue. One unresolved issue is the indication of unilateral adrenalectomy in children. By analogy from the adult cases described above, the size of the other gland, i.e. the degree of asymmetry, may be critical. Obviously, further cases in children are needed to resolve this issue.

The ultimate goal of treatment for AIMAH is to ameliorate hypercortisolism and preserve sufficient cortisol production without any replacement therapy. Although bilateral adrenalectomy can ameliorate hypercortisolism completely, lifetime glucocorticoid replacement therapy is then necessary. In the present case, hypercortisolism normalized, glucocorticoid replacement therapy could be discontinued, and no adrenal crisis has occurred other than one episode at 3 weeks after the operation. The patient appears to have been in remission since the operation.

Close clinical and endocrinological observations are indispensable when unilateral adrenalectomy is performed in children with AIMAH. We consider that there are two major concerns for our patient: residual *GNAS1* mutation in the contralateral adrenal gland may cause hypercortisolism, and excess adrenal androgen production may lead to GnRH-independent precocious puberty. Although high-dose dexamethasone suppression test suggested the existence of some autonomous cortisol production from the preserved adrenal gland, we have observed the patient carefully without excising the gland for the following reasons: first, other normal data, such as 24 hr urinary cortisol, diurnal rhythm of ACTH and cortisol, and ACTH and cortisol responses to CRH, indicated that autonomous cortisol production was not abundant. Secondly, spontaneous resolution of Cushing's syndrome has been reported in children [12]. Finally, his clinical symptoms, such as the Cushingoid appearance and height restriction, have improved. Concerning hyperandrogenism, the serum levels of DHEA-S and testosterone, have fallen somewhat but have been above their age related normal ranges since the operation. Although progressive catch-up growth has been seen since the operation, there have been no secondary sex characteristics, such as testicular enlargement, pubic hair, or acceleration of bone age. Additionally, his catch-up growth began after levels of DHEA-S and testosterone decreased after the operation, and no elevation of gonadotropins has been seen. We therefore believe that the elevated DHEA-S and testosterone have not affected his postoperative catch-up growth. The above findings suggest that unilateral adrenalectomy could be an alternative therapy in children as well as adults.

In conclusion, we have reported a patient who underwent unilateral adrenalectomy of the larger gland for infantile-onset AIMAH with MAS. Unilateral adrenalectomy ameliorated the clinical features of Cushing's syndrome and several abnormal endocrinological data. Although further study and long term follow-up are necessary, unilateral adrenalectomy might be an alternative therapy for some children who have AIMAH with MAS, when asymmetric involvement is evident and the smaller gland is not markedly enlarged.

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