

- 101** A female case of classical  $3\beta$ -hydroxysteroid dehydrogenase deficiency with multicystic ovary and anovulatory menstruation: Evaluation of ovarian function after puberty

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**Introduction:** Some female patients with classical  $3\beta$ -hydroxysteroid dehydrogenase ( $3\beta$ -HSD) deficiency have been reported to develop secondary sexual development spontaneously, however, ovarian function after puberty remained obscure. We report here an 18-year-old girl with  $3\beta$ -HSD deficiency manifesting multicystic ovary and anovulatory menstruation after puberty. **Case:** The patient manifested severe salt-losing crises soon after birth. She was diagnosed as having  $3\beta$ -HSD deficiency based on the high ratio of serum  $\Delta 5$  to  $\Delta 4$ -steroids at 5 years of her age. Molecular analysis showed homozygous mutation for Arg249stop in the type II  $3\beta$ -HSD gene. She had been in good control with the replacement of glucocorticoids and mineralocorticoids. Pubic hair growth was noticed at the age of 10 4/12 years. Breast budding appeared at 10 8/12 years of age. At the age of 11 8/12 years, spontaneous menarche occurred. LHRH stimulation showed normal responses in puberty stage. Her menstruation cycle was irregular since 17 years of age and anovulatory at 18 years of age. Multicystic changes in the ovary were detected on ultra sonography. Histopathological findings of the ovary showed multiple cystic follicles with the wall composed of granulosa and theca cell layers. **Discussion:** The patient manifested appropriate secondary sexual maturation with an elevation in serum estradiol levels at pubertal age, which suggest that  $\Delta 5$ -steroid precursors would convert to  $\Delta 4$ -steroid by a few of gonadal type I  $3\beta$ -HSD expressed by gonadotropin stimulation at pubertal age as proposed previously on a male patient with identical mutation in the type II  $3\beta$ -HSD gene. The activity of gonadal type-I  $3\beta$ -HSD, however, would not be enough for ovulation. The multicystic change of the ovary might be a characteristic manifestation in female with classical  $3\beta$ -HSD deficiency, although the etiology remained unknown.

- 103** A BOY WITH LEYDIG CELL TUMOR AND TRUE PRECOCIOUS PUBERTY

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We report a case of true precocious puberty induced by Leydig cell tumor. [Case report] The patient was a 6-year-old boy. From the age of 3, rapid increase in height and penile hypertrophy were seen. He had some emotional problems. His height SD score was +3.4 at his first medical examination at the age of 5. Left hand X-ray showed that his skeletal maturation corresponded with standardized bone maturation of a 12-year-old Japanese boy. He already showed signs of pubertal development, and his testicular volumes were 8ml (left) and 3ml (right), respectively. Serum testosterone level was 383ng/dl. Serum LH and FSH levels were under least detectable values. Ultrasonography showed a low echoic mass lesion in the left testis. He received left orchidectomy and histological analysis led to a diagnosis of Leydig cell tumor. Postoperatively, serum testosterone level immediately decreased. However, two months later, both testosterone and gonadotropin levels revealed pubertal patterns, and his growth rate remained high. He then was diagnosed as true precocious puberty induced by Leydig cell tumor, and was treated with a LH-RH analog. This treatment regressed the clinical findings and hormonal determination. Although low grade fever had persisted before surgery, he became afebrile two months after the operation. [Discussion] It is suggested that true precocious puberty may occur if a child is exposed to superfluous testosterone over a long period. Either lymphocyte activation by the tumor or bone resorption promoted by its testosterone may have induced hypercytokinemia (Interleukin-6:351pg/ml), a probable cause for his low grade fever.

- 102** 2 cases of precocious puberty associated with hypothalamic hamartoma

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Hypothalamic hamartoma is a congenital malformation and isolated close to the interpeduncular cistern and mamillary bodies. It is often associated with precocious puberty, gelastic seizures, abnormal behavior and mental retardation.

We report 2 cases of precocious puberty associated with hypothalamic hamartoma. Case 1 is a 6 years and 10 months old boy with gelastic seizures since neonatal period, but his parent did not understand it. At the age of 3 years and 8 months old, he received EEG examination and was diagnosed as epilepsy. MRI (magnetic resonance imaging) demonstrated a hypothalamic mass. At the age of 5 years, he was treated with  $\gamma$ -knife and later, hormonal research showed a high concentration of testosterone, following administration of LH-RH, his LH and FSH response showed a pubertal pattern. He showed an enlargement of the tests and penis. Bone age was 8 years at 6 years and 3 months. He was treated with LH-RH analog every other month. Case 2 is a 3 years old boy. At the age of 7 months, his body weight accelerated and pubic hair appeared. MRI showed a hypothalamic hamartoma. At the age of 1 year and 6 months old, he showed an enlargement of the testes, Tunner stage 2 pubic hair, elevated testosterone levels and bone age of 7 years old. Assays revealed LH and FSH levels in the pubertal range both before and after LH-RH stimulation. At the age of 1 year and 11 months old, he received surgical operation for partial removal of hypothalamic hamartoma.

Two cases of central precocious puberty associated with hypothalamic hamartoma were reported and who were treated with LH-RH analog. Several reports state that complete resection of hypothalamus hamartoma causing precocious puberty is curative, but we had better followed up treatment with LH-RH analog for precocious puberty.

- 104** AROMATASE INHIBITOR THERAPY FOR PRECOCIOUS PUBERTY IN 3-YEAR OLD GIRL WITH McCUNE ALBRIGHT SYNDROME

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<Aim>The McCune Albright syndrome is characterized by endocrine hyperfunction including precocious puberty, polyostic fibrous dysplasia and skin pigmentation. We tried to treat with the aromatase inhibitor for precocious puberty seen in McCune Albright syndrome.

<Case>

A 3-year old girl was referred to our clinic for precocious puberty. The enlargement of mammary gland and vaginal bleeding was seen since 1 year old, 1 year and 10 month respectively. MRI revealed the right ovarian cyst. The endocrinological study showed the hyperfunction of ovary independently of gonadotropin secretion. The bone scintigram revealed the multiple abnormal uptake of isotope. These data indicated that the precocious puberty was due to functioning ovarian cyst accompanied by McCune Albright Syndrome. The bone age was 2 year ahead from her chronological age. Since 3 year 5 month vaginal bleeding was regularly seen and the enlargement of mammary gland was increasing. While considering the treatment of medroxyprogesterone, aromatase inhibitor therapy was chosen under the agreement of parents.

<Result>

The aromatase inhibitor therapy for 2 month decreased the enlargement of mammary gland and size of ovarian cyst. The vaginal bleeding, seen every month before treatment, was disappeared at least last 1 month. The high blood value of estradiol before treatment was gradually lowered. The adverse events were not noticed until now. Instead of cyproterone acetate which is unable to use in Japan, the aromatase inhibitor therapy might be able to considered for precocious puberty of McCune Albright Syndrome. The long term observation is necessary for the evaluation of this therapy.