Testolactone treatment of precocious puberty in McCune-Albright syndrome

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Abstract. Current medical and surgical therapies of precocious puberty in McCune-Albright syndrome are often unsatisfactory. We used an aromatase inhibitor, testolactone, to treat precocious puberty in a girl with McCune-Albright syndrome. This child was unresponsive to 28 weeks of treatment with the long-acting agonist of LRH, D-trp6-pro9-NEt-LRH. During testolactone therapy, menarche ceased, bone age advancement and height velocity diminished, and plasma oestradiol levels were suppressed. Serum gonadotrophin levels remained in the prepubertal range. Testolactone may be an effective therapy of precocious puberty in girls with McCune-Albright syndrome.

Precocious puberty in girls with McCune-Albright syndrome is usually due to ovarian oestrogen secretion that is independent of pubertal hypothalamic-pituitary activation. Previous attempts to treat the precocious puberty of McCune-Albright syndrome have met with limited success. Surgical wedge resection of the ovaries or excision of ovarian cysts has resulted only in temporary remission of the symptoms of sexual precocity (Foster et al. 1984a; Scully & McNeely 1975). Agents that suppress pituitary secretion of gonadotrophins, such as the long-acting agonist of LRH, D-trp6-pro9-NEt-LRH, have also failed to achieve remission of menses and secondary sexual development (Foster et al. 1984b; Comite et al. 1981). We have treated a girl with McCune-Albright syndrome with the aromatase inhibitor, testolactone, which inhibits the conversion of androstenedione to oestrone and testosterone to oestradiol (Segaloff et al. 1960). Testolactone treatment was associated with cessation of menses, decreases in height velocity and the rate of bone age advancement, and suppression of plasma oestradiol levels.

Materials and Methods

Subjects
The patient, a 2 3/12 year old girl, was the 2770 g product of a 24 year old G1P0 mother, who had an uncomplicated pregnancy, labour, and delivery. The child developed normally until she had an episode of vaginal bleeding at age 8 months. She continued to have periods every 4–6 weeks and was referred to the National Institutes of Health at the age of 15 months. There was no known exposure to oestrogens. The child’s height was 82.5 cm (97th percentile). Height velocity between 11 and 15 months was 34.2 cm/year. (Height velocity of girls between 11 and 15 months is 13.5 ± 2.0 (SD) cm/year (Tanner 1965)). The weight was 10.6 kg (67th percentile), and the blood pressure was 90/60 mmHg. She had Tanner stage III breasts and no pubic hair. Her external genitalia were normal but her vaginal mucosa appeared oestrogenized and had a white mucoid discharge. The vaginal smear had 100% intermediate cells. There was no abnormal skin pigmentation. The remainder of the physical examination was normal. Computed tomography of the head and ultrasonography of the adrenal glands showed no abnormalities. Pelvic ultrasound indicated a
right ovarian volume of 1 ml and a left ovarian volume of 13 ml, which included a > 1 cm diameter cyst (normal prepubertal ovarian volume: < 0.9 ml) (Sample et al. 1977). The bone age was 2 years. A radiographic skeletal survey demonstrated bone lesions consistent with fibrous dysplasia in the sphenoid bone, the left radius, and in both tibia. Thyroid function tests were normal (T4 9.9 μg/dl; TSH 3.4 μIU/ml). 17-Hydroxyprogesterone, 11-deoxycortisol and cortisol were normal before and after an 8 h iv infusion of 250 μg Cosyntropin. Day and night serum LH and FSH levels were prepubertal with no evidence of nocturnal LH or FSH pulses (mean LH 1.0 mIU/ml, mean FSH 0.2 mIU/ml). Administration of LRH resulted in no stimulation of either LH or FSH (peak LH 1.2 mIU/ml; peak FSH 0.3 mIU/ml). Mean plasma oestradiol was 133 pg/ml (normal < 20). LRH analogue
The long-acting agonist of LRH, D-trp6-pro9-NEt-LRH (LRHα), was provided by Dr. Jean Rivier and was prepared and stored as previously described (Cargille & Rayford 1970).

Protocol
The protocol was approved by the Clinical Research Committee of the National Institute of Child Health and Human Development, and informed consent was obtained from the child’s mother. The child was admitted to the Clinical Center of the National Institutes of Health. During each hospital admission serum gonadotrophins were determined every 20 min from 10.00 to 14.00 h and from 22.00 to 02.00 h. Plasma oestradiol, oestrone, androstenedione and testosterone levels were obtained at 10.00, 14.00, 22.00 and 02.00 h. An LRH stimulation test was performed on the morning of the following day. Serum gonadotrophin levels were obtained at -30, -15, 0, 15, 30, 45, 60, 90, 120 and 180 min following a 100 μg iv bolus of LRH at time 0. Height was determined at 08.00 h from the average of 10 measurements on a stadiometer. Pelvic ultrasonography was employed to determine ovarian volume. Left hand and wrist films were obtained for bone age. The bone age was read by a radiologist who was unaware of the treatment status. Outpatient evaluations, which were performed monthly between inpatient evaluations, consisted of 10 measurements of height by stadiometer and three determinations, 20 min apart, of plasma oestradiol, oestrone, androstenedione, testosterone and serum gonadotrophins. The patient was observed for 12 weeks before therapy with LRHα (4 μg/kg/day, sc) was initiated. She was treated with LRHα for 28 weeks. Testolactone (Teslac, ER Squibb and Sons) was started at an initial dose of 20 mg/kg/day in 4 oral doses at 52 weeks. The dose was increased weekly by 10 mg/kg/day to a maximum dose of 40 mg/kg/day from week 72 to 104. Inpatient evaluations were repeated at weeks 12, 20, 40, 52, 64 and 72.

Hormonal measurements
Serum LH and FSH, and plasma oestradiol, oestrones, androstenedione and testosterone were determined by modifications of previously described methods (Cargille & Rayford 1970; Cutler et al. 1978; Loriaux et al. 1971; Nieschlag & Loriaux 1972; Odell et al. 1967). The intra- and inter-assay coefficients of variation were 7 and 12 per cent for LH, 5 and 14 per cent for FSH, 8 and 16 per cent for oestradiol, 5 and 14 per cent for oestrone, 5 and 10 per cent for androstenedione, and 8 and 27 per cent for testosterone. The sensitivity limits for these assays were 0.3 mIU/ml for LH (2nd International Reference Preparation of human menopausal gonadotrophin), 0.2 mIU/ml for FSH, 20 pg/ml for oestradiol, 12–20 pg/ml for oestron and 10 ng/dl for androstenedione and testosterone. Hormone assays for weeks 0 through 40, 52 through 68 and 72 through 100 were performed within a single assay.

Statistical analysis
Analysis of changes in height and bone age advancement were performed by a least squares regression of bone age or height on time. Student’s t-test was employed in all other analyses.

Results
The course of this patient’s growth curve, bone age, oestradiol levels and serum gonadotrophin levels during LRHα and during testolactone therapy are shown in Fig. 1. During LRHα treatment, serum gonadotrophins remained in the prepubertal range while oestradiol levels fluctuated strikingly. Menses continued to occur at 4–6 week intervals.

LRHα therapy was discontinued and, 12 weeks later, testolactone therapy was instituted. Oestradiol levels fell below the detection limit of the assay (Fig. 1). When testolactone was discontinued a 3 cm ovarian cyst appeared and plasma oestradiol concentration rose to 200 pg/ml. Testolactone therapy was re-instituted and the plasma oestradiol level fell to < 20 pg/ml and remained undetectable throughout the next 7 months. Ovarian volume diminished to the prepubertal range. Menses occurred 2 weeks after re-institution of testolactone therapy and then ceased. Height velocity (18 to 24 months) while on LRHα therapy was 12.2 ± 0.7 (SE) cm/year. During testolactone therapy (27 to 38 months), height velocity decreased to 7.5 ± 0.8 cm/year (P < 0.001). Since the height velocity deceleration may in part be explained by the normal decrease in velocity which occurs between 21 and
23 months of age (9.8 ± 1.7 (SD) cm/year to 8.2 ± 1.3 cm/year for girls (Tanner 1965)), we also compared bone age velocities during the periods before and on testolactone treatment. Bone age advancement was 2.8 ± 0.3 (SE) bone age years/chronological year before testolactone and fell to 1.9 ± 0.1 bone age years/chronological year during testolactone treatment (P < 0.05).

![Bone Age, Height, Oestradiol, FSH and LH Levels, and Ovarian Volume During LRHα Therapy and During Testolactone Therapy](image)

**Fig. 1.** Bone age, height, oestradiol, FSH and LH levels, and ovarian volume during LRHα therapy and during testolactone therapy. For hormonal measurements, closed symbols represent inpatient determinations and open circles represent outpatient determinations as described in Methods. The hatched area represents the detection limit of the oestradiol assay. MOV represents mean ovarian volume.

Plasma oestrone, androstenedione and testosterone levels before and after 2 and 6 months of testolactone therapy. Each level is the mean of four determinations at 10.00, 14.00, 22.00 and 02.00 h. *P < 0.05.

![Plasma Hormone Levels](image)

**Fig. 2.**

Serum gonadotrophin levels during testolactone were not significantly different from pretreatment levels and remained in the prepubertal range. Similarly, peak responses of LH and FSH to LRH stimulation were not different (data not shown).

Inhibition of aromatase could potentially cause an elevation in precursor steroids such as androstenedione or testosterone. No clinical evidence of increased androgen was seen. Additionally, no significant increase of testosterone or androstenedione levels during therapy was observed (Fig. 2). As expected, oestrone levels fell significantly during therapy (P < 0.05).

The major side effects of testolactone are gastrointestinal (Segaloff et al. 1960). Our patient had two episodes of diarrhoea, lasting 2–3 days, during which testolactone was discontinued. No nausea, vomiting or dehydration occurred. Blood counts, urine analysis, liver function tests, serum calcium, blood urea nitrogen, serum electrolytes and serum creatinine did not change during treatment (data not shown).

**Discussion**

Testolactone therapy appears to have been successful in this patient. Menses ceased, and height velocity and the rate of bone age advancement
diminished. Oestradiol fell during treatment, rose during the 2 months off treatment, and then fell again when treatment was re-instituted.

Serum oestradiol levels in McCune-Albright syndrome are elevated only intermittently (Comité et al. 1984; Foster et al. 1984a,b), and appear to rise with the appearance of large ovarian cysts (Foster et al. 1984a). Thus, the fall of oestradiol that occurred in this patient could conceivably re-appear the intermittent pattern of her disease. However, two points argue against this. First, the patient's menses occurred every 4–6 weeks from 9 months of age until institution of testolactone therapy at the age of 26 months. Only a single menstrual period occurred during the next 12 months, and this occurred in association with the 2 month period of testolactone withdrawal ($P < 0.001$, Chi-square test). Second, the patient's oestradiol levels rose with the discontinuation of testolactone and these levels fell when testolactone therapy was re-instituted. No increase in plasma oestradiol levels were seen during testolactone treatment. Chi-square test showed a significantly greater percentage of undetectable oestradiol levels during testolactone therapy. We conclude that testolactone suppressed ovarian oestrogen production in this patient.

Ovarian volume, which was consistently elevated during the year prior to testolactone, returned to normal during testolactone treatment. Since oestradiol plays a critical role in normal follicular development, we postulate that inhibition of intra-ovarian oestradiol formation by testolactone may have contributed to the decrease in ovarian volume. Thus, in addition to inhibiting the oestrogen secretion of established ovarian cysts, testolactone may interrupt the pathophysiologic event leading to ovarian cyst formation.

Testolactone shows promise as a therapy for precocious puberty due to ovarian oestrogen secretion that is independent of pubertal gonadotrophin secretion in the McCune-Albright syndrome. Further studies with testolactone in patients with the McCune-Albright syndrome appear warranted.

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References


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