Sexual Development in a Two-Year-Old Boy Induced by Topical Exposure to Testosterone

Y. Miles Yu, MD; Natavut Punyasavatsu, MD; Deborah Elder, MD; and A. Joseph D'Ercole, MD

ABSTRACT. Virilization, including penile enlargement and growth of pubic hair and facial acne, developed in a 2-year-old boy over a period of months. This sexual development was induced by incidental and unintentional dermal exposure to a testosterone cream that was applied to his father's arm and back as a part of body building regimen. Except for penile size, the other signs of virilization diminished several months after the exposure was discontinued. ***Pediatrics*** **1999;104(2). URL: http://www.pediatrics.org/cgi/content/full/104/2/e23;** ***testosterone, sexual development, childhood, topical exposure.***

ABBREVIATIONS. T, testosterone; BA, bone age; DHT, dihydrotestosterone.

Virilization in boys before puberty caused by exposure to exogenous androgens is rarely reported. We have evaluated a 2-year-old boy who developed androgenization, including progressive penile enlargement and development of pubic hair and facial acne, over a period of months. We discovered dermal exposure to exogenous androgens and ruled out the other causes of androgenization. Here, we discuss the differential diagnosis, laboratory testing, and outcome of this patient. Given the widespread availability of androgens in our society, we suspect that this is not an isolated event.

CASE PRESENTATION

A 2.7-year-old boy presented to our pediatric endocrine clinic for evaluation of his sexual development. Over the past 4 to 5 months, he developed progressive enlargement of his penis. Over 1 to 2 months before this visit, he also developed facial acne and pubic hair. The patient was otherwise healthy and active. No change in behavior was noticed. There was no history of accidental ingestion of any medications. However, during approximately the past year, his father had been applying a topical cream containing 50 g of testosterone (T) per ounce to his arms and back (4 oz/day) as a part of a body building regimen. Although the cream was not applied directly to the boy, he had close contact with his father, as well as with his father's body building equipment and mats, which were smeared with the T cream.

The patient was born at 31 weeks' gestation and subsequently was diagnosed with congenital hypothyroidism. He had been receiving thyroid replacement therapy successfully since 1 month of age. He had demonstrated a remarkable catch-up growth since birth, and his height crossed the 5th percentile at 21 months of age. He was seen in our pediatric endocrine clinic at 2 years of age. At that time, he was clinically and biochemically euthyroid and had no abnormalities of sexual development.

The family history is unremarkable. His father measures 5 feet 7 inches, and his mother measures 5 feet 5 inches. There is no known family history of any causes of abnormal sexual development such as precocious puberty, intracranial tumor, or adrenal abnormalities.

Physical examination revealed a very active, playful, and healthy boy. Vital signs were normal for his age. His standing height was 90.6 cm (15th percentile), and his weight was 12.2 kg (15th percentile). His height growth velocity calculated from his previous visit was 10.7 cm/year (90th percentile). Fundoscopic examination showed no signs of papilledema. Facial skin was slightly oily with macular papular acne primarily on his forehead. Neck examination revealed no thyromegaly. Abdominal examination showed no organomegaly or masses. Genitourinary examination was remarkable for a significantly enlarged penis with a stretched penile length of 8.5 cm and width of 2 cm. There were 50 to 75 slightly dark curled pubic hairs at the base of his phallus. His testicular sizes were prepubertal, measuring ~2 mL each.

Several laboratory tests were performed, and bone age (BA) was interpreted as 2.5 to 3 years of age using the standards of Greulich and Pyle.[1] Thyroid function tests showed a total T4 of 10.4 μg/dL and a thyroid-stimulating hormone level of 1.37 μU/mL; a serum T level of 48 ng/dL (normal range of 0–25 ng/dL for his age group); a luteinizing hormone level of <2 μU/mL (normal for age); and normal adrenal steroid levels (17-hydroxy-progesterone, 13 ng/dL; dehydroepiandrosterone sulfate, 0.1 μg/mL; androstendione, <10 ng/dL; and cortisol, 5.8 μg/dL).

Approximately 4 months after stopping the exposure to exogenous androgen, the patient returned for follow-up. Although his penis size remained the same, his facial acne and pubic hair were diminished dramatically. Repeat serum T level was decreased to 20 ng/dL, and repeat BA analysis showed no significant change from the previous result.

DISCUSSION

Sexual precocity in males has been defined as the appearance of signs of secondary sexual maturation before 9 years of age.[2] True male precocious puberty results from pituitary gonadotropin stimulation of the testes to secrete the T that is responsible for sexual development or virilization. Premature sexual development also can result from adrenal disorders such as congenital adrenal hyperplasia and adrenal tumors, from testicular diseases such as tumors and familial testotoxicosis, or from exposure to exogenous androgens. In our patient, the physical examination eliminated true precocious puberty as a possibility, because his testes were prepubertal in size. This conclusion was supported by an undetectable serum-luteinizing hormone. The absence of testicular enlargement or masses and the return of the serum T level to the normal range after T exposure was stopped made a testicular etiology unlikely. An adrenal etiology of sexual precocity was excluded by

From the Division of Pediatric Endocrinology, Department of Pediatrics, University of North Carolina, Chapel Hill, North Carolina.
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Reprint requests to (Y.M.Y.) Pediatric Endocrinology, University of North Carolina at Chapel Hill, CB No 7220, 509 Burnett-Womack, Chapel Hill, NC 27599-7220. E-mail: ymy62@med.unc.edu.com

finding normal levels of adrenal steroids from this patient.

Cases of androgenization caused by exogenous androgen exposure rarely have been reported in the medical literature. However, because of the ready availability of steroids in our society, we suspect that this is not an isolated incident. In our patient, the virilization seemed to occur exclusively in response to transdermal absorption of T, and its resulting systemic effects. Dermal application of T to the maxillary or genital area is used to treat patients with hypogonadism and has been shown to result in an elevation of serum T levels and penile enlargement.[3] The kinetics of transdermal absorption and the subsequent biological effects by topical androgens depend on many factors including the area of application, the thickness of the skin, and the androgen concentration in the preparation. Our patient's serum T was increased modestly to 48 ng/mL, which is comparable with the levels found in patients <10 years of age treated with topical T cream for 3 weeks.[4] In that study, Klugo et al[4] found that although the T elevation was modest, the biological response was greatest in younger patients. They suggested that the dermal conversion of T by 5α-reductase to the more potent metabolite, dihydrotestosterone (DHT), is more active in younger children. Subsequently, Ahmed et al[5] demonstrated higher levels of serum DHT in younger children treated with T patches. Although we did not measure the DHT level in our patient, his androgenization might have been mediated by dermal conversion of T to DHT and/or possibly by the direct absorption of DHT contained in the preparation to which he was exposed.

The long-term effects of androgen exposure during early childhood on pubertal development, final adult penile length, and final adult height are not fully known. Elevation of serum T can cause accelerated bone maturation that in turn may result in a compromised final adult height. Accelerated bone maturation has been reported in at least 1 child treated with topical androgens.[6] Children treated with short-term T injection usually exhibit some acceleration of skeletal maturation.[7] However, after cessation of treatment, the rate of bone maturation decelerates and gradually returns to normal. Because our patient's BA was not assessed before the time of T exposure, we do not know whether his skeletal maturation was accelerated; however, his BA was not advanced either at the time of diagnosis or 4 months later. Our finding of a height growth velocity in the 90th percentile suggests that the patient might have some increase of skeletal maturation. Nonetheless, we do not expect that his final adult height will be compromised significantly.

There is conflicting information on the effect of androgen exposure on adult penile length. In studies of rats with luteinizing hormone-releasing hormone analog-induced micropenis, androgen treatment at 7 days of age resulted in subnormal adult penile length, apparently by downregulating androgen receptor number.[8–11] In contrast, a recent clinical study reported that the exposure to T during gestation and/or childhood does not reduce adult penile length.[12]

CONCLUSIONS

In summary, exposure to androgen-containing products should be considered in evaluation of virilization. Our data indicate that androgens can be absorbed transdermally after accidental exposure that in turn may induce early sexual development in children. The diagnosis can be established with a clear history and a few laboratory tests to exclude other sources of androgens. A favorable outcome is predicted, once the exposure is discontinued.

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