Precocious Puberty Secondary to Topical Testosterone Transfer: A Case Report

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ABSTRACT

Introduction. Testosterone replacement therapy is the standard of care for androgen deficiency syndrome, and patients and physicians can choose among depot injectable, subcutaneously implanted pellet, transdermal patch, topical gel, and buccal tablet dosage forms. Topical gels have become popular and, although unintentional secondary transfer to a spouse or child is a known hazard, physicians and patients may underestimate the risk.

Aim. We report a case of precocious puberty in a 10-month-old male secondary to transfer of topical testosterone from his father, who was treated for primary hypogonadism.

Results. Once the father's therapy was changed from a topical to a buccal dosage form, the symptoms in his son receded.

Conclusion. The potential for secondary exposure to testosterone—and its consequences—may be underappreciated by patients and by health care providers not involved in managing testosterone replacement therapy. The patient's lifestyle (e.g., contact with children, physical limitations, daily schedule) should be part of the discussion when selecting a method of testosterone replacement therapy. **Cavender RK and Fairall M. Precocious puberty secondary to topical testosterone transfer: A case report. J Sex Med 2011;8:622–626.**

Key Words. Precocious Puberty; Hormone Replacement Therapy; Environmental Exposure

Introduction

The standard of care for androgen deficiency syndrome is testosterone replacement therapy, which is available in many forms: depot injectables, subcutaneously implanted pellets, transdermal patches, topical gels, and buccal tablets (approved by the U.S. Food and Drug Administration [U.S. FDA] in 1953, 1972, 1995, 2000, and 2003, respectively) [1]. Topical gels have become progressively more popular in the primary care arena because of the ease of application, as well as the clinically proven benefits such as stable therapeutic testosterone levels, improvement in metabolic parameters (e.g., blood sugar control in diabetics), and improvement of symptoms commonly expressed by androgen-deficient men (e.g., functional capacity, sexual function, libido, mood, cognition, and bone and body composition). In a competitive whirlwind, the marketing campaigns of the topical gel industry have targeted primary care providers, barraging them with data that demonstrate the ease of administration and testosterone levels achieved without formally educating them about the international testosterone prescribing guidelines [2] and the potential risks, specifically the risk of drug transfer to spouses and/or children (also known as secondary exposure).

Cutaneous transfer of topical testosterone to a spouse or child has long been recognized as a possible complication of this method of administration [3–5], yet cases of secondary transfer are still reported [6,7]. It is standard practice to advise patients to wash their hands following the application of these products and to cover the treated area with clothing. Prior to prescribing a topical testosterone product, it is imperative that physicians be aware of all associated risks and that they conduct a detailed lifestyle and risk assessment for secondary exposure. Moreover, patient circumstances commonly change after the initial assessment, necessitating ongoing lifestyle and

transfer-risk surveillance as well as counseling at each follow-up visit. If a risk of secondary exposure is identified, or if the patient fails to acknowledge transfer precautions, an alternative method of therapy should be employed.

This report describes a case of precocious puberty in a 10-month-old male secondary to transfer of topical testosterone from his father, who was treated for primary hypogonadism.

Case Report

On January 26, 2006, a 32-year-old white male with a past medical history of hypertension presented with the complaint of 1.5 years of progressive generalized sarcopenia with asymmetrical lower extremity atrophy, left greater than right. Symptom onset followed repair of a left anterior cruciate ligament tear and subsequent prolonged immobilization. The patient reported delayed rehabilitation, with generalized decreased muscular strength, tone, and endurance. The patient also reported a 40-lb central weight gain over the 1.5-year period, with associated symptoms of insomnia, fatigue, decreased libido, and mild erectile insufficiency. His score on the Androgen Deficiency in the Aging Male questionnaire was positive for 9 out of 10 variables and the Sexual Health Inventory for Men score was 20 out of 25 points. His International Prostate Symptom Score was 0 out of 35 points, indicating no lower urinary tract symptomatology. His physical exam was significant for generalized lower extremity muscular atrophy, with left greater than right. His genitourinary and prostate exams were normal. His baseline morning hormone laboratory results are shown in Table 1; additionally, glucose, renal and liver function tests, electrolytes, and complete blood count were within normal limits.

The patient was diagnosed with primary hypogonadism, having met both clinical and laboratory criteria, and was counseled regarding pathophysiology and methods of androgen therapy. He subsequently elected topical therapy. On February 8, 2006, following detailed secondary exposure risk counseling and his provision of informed consent, he was started on testosterone 150 mg/mL, 1 mL topically to the shoulder area daily at bedtime. Additionally, he started therapy with anastrozole 0.2 mg sublingually once daily to decrease the supraphysiologic estrone level noted in his baseline laboratory results. Follow-up assessment 2 months later revealed a subtherapeutic response with laboratory results as shown in Table 1 (April 1 data). On April 10, the testosterone dose was increased to 200 mg/mL, 1 mL topically daily at bedtime, with no change in the anastrozole regimen. At the next assessment approximately 6 weeks later, his clinical response had improved and laboratory results were stable (Table 1, May 20 data). His laboratory results for the metabolic panel and complete blood count were also within normal limits.

In early June, approximately 4 months after starting topical testosterone treatment, the patient notified our office that his 10-month-old son had undergone a pediatric endocrinology evaluation secondary to the development of precocious puberty. Further inquiry revealed that the infant had developed progressive penile enlargement

Table 1 Selected laboratory results for father (32 years old)

			Laboratory results (2006)		
Hormone*	Units	Normal range	January 26 (baseline)	April 1	May 20
Total testosterone	ng/dL	241–827	264	369	378
Free testosterone	pg/mL	8.7–25.1	13	15.7	19
Dihydrotestosterone	ng/dL	30–85	—	46	73
Sex hormone binding globulin	nmol/L	13–71	12	—	9
Luteinizing hormone	mIU/mL	1.5–9.3	2.6	—	—
Follicle stimulating hormone	mIU/mL	1.4–18.1	4.7	—	—
Estrone	pg/mL	12–72	69	54	59
Estradiol	pg/mL	3–70	21	9	15
Prostate-specific antigen	ng/mL	0.0–4.0	0.5	0.6	0.6
Dehydroepiandrosterone	μg/dL	120–520	378	—	—
Cortisol	μg/dL	3.1–22.4	8.9	—	—
Thyroid stimulating hormone	μIU/mL	0.350–5.500	4.961	—	—
T4 free	ng/dL	0.61–1.76	0.89	—	—
T3 free	pg/mL	2.3–4.2	3	—	—

*Blood for all laboratory tests was collected in the morning.
— = not tested.

Table 2 Selected laboratory results for son (approximately 10 months old)

			Laboratory results (2006)		
Hormone*	Units	Normal range	May 18	June 5	July 5†
Total testosterone	ng/dL	<3–10	874	938	24
Free testosterone	pg/mL	0.15–0.6	—	159	1.2
Sex hormone binding globulin	nmol/L	60–252	—	78	148
Luteinizing hormone	mIU/mL	0.02–7.0	—	0.03	0.08
Follicle stimulating hormone	mIU/mL	0.16–4.1	—	0.62	0.69
17-Hydroxyprogesterone	ng/dL	3–90	<10	—	—
Progesterone	ng/dL	<10–15	<10	—	—
17-OH Pregnenolone	ng/dL	42–540	<10	—	—
Dehydroepiandrosterone	ng/dL	20–100	84	—	—
Specific S	ng/dL	10–156	18	—	—
Androstenedione	ng/dL	6–68	91	—	—
Deoxycorticosterone	ng/dL	7–49	7.9	—	—
Cortisol	μg/dL	2.8–23	3.7	—	—
Beta human chorionic gonadotropin, quantitative (tumor marker)	NS	NS	—	<1.0	—

*Blood for all laboratory tests was collected in the morning.
†Approximately 4 weeks after father changed from topical to buccal testosterone.
— = not tested; NS = not specified by the laboratory.

over the previous 4-month period. It was not until the infant developed pubic hair that the parents brought this to the attention of their pediatrician. Upon our learning of the child's condition, the patient's testosterone therapy was immediately changed from topical to buccal delivery.

The infant's birth history and development were documented as normal until the development of precocious pubertal signs. Pediatric endocrinology records provided to us revealed that the father had been practicing diligent hand washing, as counseled when he started topical testosterone therapy. However, rather than applying the testosterone to his shoulders at bedtime, he was applying it to his forearms in the morning. Additionally, the parents worked split shifts with the father serving as his son's primary caretaker during the day, and the mother serving as the primary caretaker in the evening. On May 18, 2006, the infant's physical exam revealed a weight of 11.3 kg and length of 76.2 cm, both values just above the 97th percentile. The infant was alert and active, and healthy in appearance with no facial hair. His head, eye, ear, nose, and throat examinations were normal, with no thyromegaly. His cardiovascular and respiratory examinations were also normal. His abdomen was soft and nontender, with no hepatosplenomegaly. His genitourinary exam revealed an enlarged penis (approximately 5 cm long) and Tanner stage II pubic hair. His testes were 2 mL, descended bilaterally with no palpable nodules, and his scrotum was hyperpigmented with pubertal appearance. There was no skin hyperpigmentation elsewhere. His neurologic exam was intact. A congenital adrenal hyperplasia laboratory evaluation revealed markedly elevated testosterone and androstenedione, with adrenal hormones within normal limits (Table 2). His bone age was reported as within the normal range. Follow-up laboratory tests on June 5, 2006 revealed no change in total testosterone concentration (Table 2). Approximately 4 weeks after the father discontinued topical testosterone therapy, the son's testosterone levels declined to age-appropriate ranges (Table 2, July 5 data) and his penis size receded. The son's history was then uneventful until, as a toddler, the child was diagnosed with developmental delay and subsequently with Asperger's disorder.

Discussion

Despite patient education on the risks of skin-to-skin transfer with topical testosterone gel products, the U.S. FDA has received reports of secondary exposure to testosterone in children and, on May 7, 2009, announced a requirement for boxed warnings about the risks of secondary transfer on the labels of topical testosterone gel products [7]. At that time, FDA had received information for eight cases of secondary exposure to testosterone in children of age 9 months to 5 years. In December 2009, the FDA Drug Safety Newsletter reported that between 2000 (initial market approval of testosterone gel) and May 2009, the FDA had received 20 reports (18 U.S., 2 non-U.S.) describing adverse events in children who were exposed to testosterone gel that was used

by another person. The mechanism of secondary exposure is not always clear. Although skin-to-skin contact may be most common, some secondary exposure may occur via shared washcloths or bed linens [6–8].

This case illustrates the importance of preventing secondary testosterone exposure. This case also raises the question as to whether supraphysiologic testosterone levels, either endogenous or iatrogenic, at this stage of development could contribute to the development of a neurological or autism spectrum disorder, such as autistic disorder or Asperger's disorder (also known as Asperger's syndrome). Autism spectrum disorders are complex neurodevelopmental disorders characterized by impaired social interactions and communication patterns, and by repetitive behaviors [9,10]. These characteristics typically appear by the age of 3 years. Although autism spectrum disorders are relatively common, occurring in at least 6 of every 1,000 children in developed countries, the cause(s) of these disorders has yet to be determined. Searches of the PubMed database on October 13 and December 3, 2009 using the terms *testosterone replacement* or *male hypogonadism* and *Asperger syndrome; Asperger*, *Asperger's*, or *Asperger syndrome* and *precocious puberty;* and *testosterone* or *androgen*, when combined with the terms *Asperger*, *Asperger's* or *Asperger syndrome*, identified no publications which suggested any relationship between postnatal testosterone exposure and autism or Asperger's disorders.

This case also illustrates several important principles for physicians and other health care providers who prescribe topical testosterone replacement therapy for any patient, male or female (note: use in women is not yet FDA-approved). First, health care providers should extensively evaluate the patient's lifestyle, including the number of small children in the home and the patient's role as caregiver. Alternatives to topical testosterone therapy should be considered as needed, to completely avoid any risk of drug transfer. The currently available intramuscular injections, crystalline subcutaneous pellet implants, transdermal patches, and buccal testosterone products are safe and effective [2], and each has important benefits and limitations. Deep intramuscular injections and subcutaneous pellet implants have a long duration of action and provide no opportunity for secondary drug transfer. Deep intramuscular injections are administered every 1 to 4 weeks; however, many patients experience undesirable peaks and troughs in both symptoms and circulating testosterone levels. Crystalline subcutaneous pellets are implanted every 3 to 6 months and provide sustained eugonadal testosterone levels [11]. Transdermal patches and buccal systems, which are less frequently utilized, are self-administered by the patient and are shorter acting. Transdermal patches, like gels, are applied once daily, while buccal systems are applied twice daily. Secondary transfer of testosterone is unlikely with either of these methods.

Selection of the testosterone preparation should be a joint decision by an informed patient and health care provider (e.g., physician, nurse practitioner, physician assistant), and should include discussion about the patient's contact with children or grandchildren, and any physical limitations that might affect treatment choice (e.g., arthropathy, limited range of motion). When the patient and health care provider decide to proceed with topical testosterone therapy, the health care provider should repeat the transfer-risk assessment at each clinical follow-up and provide ongoing counseling relative to transfer risks and precautions to avoid secondary exposure. The health care provider should be cognizant of and inquire about any unusual health situations involving members of the patient's household. Health care providers should also advise patients that, should any unusual health issues arise among household members, the patient should inform other health care providers that an adult in the home is using topical testosterone therapy.

In the case presented, had the recently implemented black box warning about the risks of secondary transfer with topical testosterone therapy been in place at the time the father initiated therapy, all health care providers involved in this case, as well as the patient himself, may have been more aware of the skin-to-skin transfer risks. Further, when the patient's infant son developed signs and symptoms of excess testosterone, the connection with the father's treatment regimen may have been more quickly identified and corrected.

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