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Potential consequences in children of a testosterone gel used by their fathers☆

Posibles consecuencias en los niños del uso de gel de testosterona por sus padres

Testosterone replacement therapy has been used for male hypogonadism since 1930. In recent decades, gel preparations of this hormone have been preferred by many patients, since in most cases a daily application suffices to obtain stable physiological concentrations. It is important to warn about the side effects that result when the drug is transmitted to someone other than the patient for whom it has been prescribed. In this regard, it is advisable for the user to cover the application zone with clothing or to wash it before coming into contact with other people.[1]

We report two cases of children seen for the early development of sexual characteristics to different degrees, whose fathers had been receiving treatment with testosterone gel.

The first case was a two-year-old boy referred due to penile growth with frequent erections, pubarche, and exaggerated growth in stature in the previous few months. A physical examination revealed tallness for the age of the patient and the height of the parents, a muscled body, pubarche, enlarged penis (Tanner class III), and a rough and pigmented scrotum, but no change in testis volume. Laboratory tests showed a very high total testosterone level for his age, with suppressed LH and FSH, and no response of these hormones to leuprolide stimulation. The bone age was advanced by three years. His testosterone level normalized after gel exposure was discontinued, with a regression of the phenotypical changes. The boy had a normal growth rate and prepubertal testicular volume over the subsequent four years.

The second case was a 6-year-old boy seen due to the appearance of pubic hair and penile growth over the previous three months. The examination also revealed tallness and a testicle volume of 3 mL. Laboratory tests showed isolated total testosterone elevation with suppressed gonadotropins and no response to leuprolide. The bone age was advanced by 1.5 years. Three months after the suppression of exposure to the gel, the testicle volume had increased to 4 mL, indicating the start of puberty, with a high growth rate. The testosterone concentrations remained high, and an increase in gonadotropin levels was also noted, indicative of central activation. Hypothalamic-pituitary magnetic resonance imaging showed no abnormal findings, and treatment was started with monthly triptorelin.

In both cases, the fathers had undergone orchiectomy due to seminoma and were receiving replacement therapy with testosterone gel. The fathers were aware of the risk of transferring the gel to their partners, and followed the

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Table 1 Patient clinical and laboratory test data.

	Patient 1	Patient 2	Normal values
Height of the father	170.1 cm (p 16)	175 cm (p 36)	
Height of the mother	153.7 cm (p 6)	160.5 cm (p 28)	
Target height	168.3 cm (p 8)	174.2 cm (p 31)	
Age at 1st[a] consultation	2 years	6.25 years	
Weight	18.7 kg	26 kg	
Height	97 cm (3.04 SD)	130.6 cm (2.32 SD)	
Body mass index	19.8 kg/m^2 (2.42 SD)	15.24 kg/m^2 (p 32)	
Penis	70 mm × 26 mm	55 mm × 25 mm	
Testicular volume	3 mL	3 mL	
Bone age	Advanced 3 years	Advanced 1.5 years	
Testosterone, nmol/L	3.3	1.8	<0.6
DHEA sulfate, μmol/L	0.1	0.8	<1
Androstenedione, nmol/L	2.9	2.6	<4.2
17-Hydroxyprogesterone (mmol/L)	0.59	0.34	<3
LH/FSH/βHCG, U/L	0.1/0.2/0.1	0.1/0.3/0.1	<0.2/<0.5/<0.4
LH 180′ after leuprolide, U/L	0.7	0.7	<5
After testosterone gel discontinuation			
Penis	53 mm × 18 mm	50 mm × 20 mm	
Testicular volume	3 mL	4 mL	
Growth rate, cm/year	6.7 (p 3)	7.8 (p 98)	
Testosterone, nmol/L	0.1	1.5	<0.5
LH/FSH, U/L	0.1/0.2	1.3/1.5	<0.2/<0.5

βHCG: beta-human chorionic gonadotropin; SD: standard deviation; DHEA: dehydroepiandrosterone; FSH: follicle-stimulating hormone; LH: luteinizing hormone; p: percentile.

recommendations for avoiding exposure. However, they did not apply such measures in the case of their children, and played and hugged them while naked from the waist up after applying the gel to the abdomen or chest (both patients were seen during the summer months). Table 1 shows the clinical and laboratory data for the two patients.

The immediate consequence of testosterone gel transmission from father to prepubertal offspring is hyperandrogenism, which produces precocious virilization (an increase in size of the penis or clitoris, with no associated increase in testicle size in males, early pubarche, accelerated growth and advanced bone age). A number of such cases have been documented in the literature.[2–5] There has even been a report of prenatal virilization in a female fetus.[6] Hyperandrogenism was transient in all those cases, with a normalization of testosterone levels once exposure was ended.

Another less common consequence is the triggering of central early puberty due to exposure to testosterone, a situation which is not reversible. It is known that children with high exogenous or endogenous sex steroid levels, such as those induced by a tumor, congenital adrenal hyperplasia, McCune-Albright syndrome, or testotoxicosis, may develop central early puberty by two possible mechanisms: hypothalamic priming by the high steroid levels if not adequately treated[7] or after a sudden decrease in such levels once control of the disease has been achieved, or the discontinuation of exposure in the case of an exogenous origin,[8] as occurred in the second case reported. The former mechanism was implicated in the case of a 5-year-old boy who developed central precocious puberty after 5 years of exposure to testosterone, and that persisted after the ending of this exposure.[9]

In 2009, the United States Food and Drug Administration published a warning on the risk of testosterone transfer to children.[10] Patients who use the drug should be warned about the possible consequences for their offspring and for other children in the family, and a potential history of exposure should be sought in children seen for early sexual characteristics or excess growth.

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Thyroid involvement by Rosai-Dorfman disease☆

Afectación tiroidea por enfermedad de Rosai-Dorfman

Rosai-Dorfman disease (RDD) or sinus histiocytosis with massive lymphadenopathy, is a rare disease of unknown origin histologically characterized by the infiltration of abundant lymphocyte-containing histiocytes (emperipolesis) within the lymph nodes.[1] Forty percent of patients may have signs outside the lymph nodes, of which skin involvement is the most common. Its location within the thyroid gland is unusual, with only 9 cases reported to date.[2–5]

We report the case of a 58-year-old woman admitted in October 2010 to the department of neurology for clinical manifestations suggesting stroke, including unstable gait, generalized weakness, left hemiparesis, right deviation of conjugate gaze, and decreased consciousness. Following initial improvement in the first week of admission, the patient experienced acute confusion, being unable to recognize her relatives. The patient had a history of primary hypothyroidism and received replacement therapy with levothyroxine 50 μg/day starting in September 2010. Upon admission, thyroid gland test results were as follows: TSH 5.51 mIU/mL (reference range 0.55–4.78 mIU/mL); free T4 14.38 pmol/L (10–20 pmol/L); peroxidase antibodies > 1000 IU/mL (0–35 IU/mL); and thyroglobulin antibodies 61.9 IU/mL (0–40 IU/mL). Both blood immunological testing (ANA, anti-DNA, ENA, anticardiolipin, and ECA) and HIV and RPR proved negative. Thyroid gland ultrasound revealed a hypoechogenic nodule measuring 22 mm × 20 mm in size located in the left thyroid lobe, together with another nodule measuring 11 mm located in the right lobe, and multiple bilateral lateral neck adenopathies—the largest measuring 17 mm in size—without evidence of malignancy. During admission, an ischemic vascular process was ruled out based on CT and MRI of the brain, which only showed an altered signal in the supratentorial white matter consistent with nonspecific leukopathy, with no signs of acute ischemic disease. The electroencephalogram showed a nonspecific decrease in electrical activity. Cerebrospinal fluid tests revealed a slight increase in protein levels, while the other parameters and the culture were negative. Thyroid antibodies were not measured. Treatment was started with prednisone 50 mg/day, followed by a good clinical and radiological response. Based on the foregoing, and after other possible etiologies had been eliminated, the case was tentatively diagnosed as autoimmune corticosteroid-responsive encephalitis associated with autoimmune thyroiditis or Hashimoto's encephalopathy, despite the fact that this disease entity is highly controversial in the medical literature.

Outpatient endocrine monitoring was started, consisting of thyroid laboratory tests, neck ultrasonography, and two successive fine needle aspirations (FNAs) of the dominant nodule. The cytological findings were consistent with Hashimoto's chronic lymphocytic thyroiditis. After thyroid function was normalized with 75 μg/day of sodium levothyroxine, the patient showed a progressive increase in size of the thyroid nodules. In February 2014 she developed compressive symptoms and intense pain on mobilizing the neck. Ultrasound exploration at this time showed an increase in thyroid size at the expense of a nodule in the left lobe measuring over 5 cm in diameter, with a significant bilateral increase in size of the lateral neck adenopathies already noted on the occasion of the previous exploration. A repeat FNA showed signs of granulomatous lymphadenitis. A differential diagnostic study of granulomatous peripheral adenopathies was carried out by Internal Medicine using bacterial and viral serological tests (PPD and PCR for tuberculosis, HIV, HCV, HBV, CMV, *Toxoplasma gondii*, *Treponema pallidum*, *Chlamydia trachomatis*, *Yersinia* spp. and *Bartonella quintana*), tumor markers and autoimmune markers—all of which proved negative. In view of the lack of a specific diagnosis, an adenopathy was removed for histological study, which revealed granulomatous lymphadenopathy with microabscesses. Nine months later, a new ultrasound of the neck showed a sustained enlargement of the entire thyroid gland, of a nodular appearance, with a bilateral increase in size of the lateral neck adenopathies. Thyroidectomy and lymphadenectomy were indicated. A pathological examination of the surgical specimen found a thyroid gland in which the parenchyma had been almost totally replaced by a histiocytic infiltrate. The histiocytes had large nuclei and cytoplasm, with the presence of intact lymphocytes within the cytoplasm (emperipolesis) (Fig. 1). The histological diagnosis was consistent with nodal and

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