Hypothyroidism-associated testicular enlargement: is it a form of precocious puberty or not? A case report

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In children with untreated hypothyroidism, the onset of puberty is usually delayed, but gonadotropin-independent precocious puberty may occur in children with severe hypothyroidism of long duration. The association of hypothyroidism, delayed bone age and gonadotropin-independent precocious puberty is defined as Van Wyk Grumbach syndrome (VWGS). VWGS has been described mostly in girls, and only seldom in boys. The manifestation of VWGS in boys is only testicular enlargement without substantial Leydig cell stimulation or testosterone secretion. We report a case of testicular enlargement due to obvious hypothyroidism secondary to autoimmune thyroiditis in a boy who presented with obesity.

With this case report, we would like to emphasize that VWGS is not a real gonadotropin- independent precocious puberty in boys as it is in girls. Additionally, we would like to emphasize that delayed bone age is a special discriminating feature for differentiation of VWGS from the other causes of precocious puberty.

Key words: autoimmune thyroiditis, precocious puberty, testicular enlargement, Van Wyk Grumbach syndrome.

Van Wyk Grumbach syndrome (VWGS) is characterized by association of juvenile hypothyroidism, delayed bone age and isosexual precocious puberty[1]. In children with untreated hypothyroidism, the onset of puberty is usually delayed, but precocious puberty may occur in as many as 50% of children with severe hypothyroidism of long duration[2]. In the medical literature, VWGS is described mostly in girls, and only seldom in boys. Nonetheless, VWGS is not a real gonadotropin-independent precocious puberty in boys as it is in girls[2]. Testicular enlargement occurs without substantial Leydig cell stimulation or testosterone secretion in affected boys. We report herein a case of testicular enlargement due to obvious hypothyroidism secondary to autoimmune thyroiditis in a boy who presented with obesity.

Case Report

A 7-year, 3-month-old boy was referred to our pediatric endocrinology department from his family physician because of obesity and suspicion of precocious puberty. The patient was born at term with normal delivery after an uneventful pregnancy. He had met developmental milestones over time. He received routine immunization and had an uneventful medical history to this age. His parents noted his weight gain especially in the last two years. Physical examination was significant for obesity. There was no sign of acanthosis nigricans or stria on his skin, but he had a swollen face and myxedematous appearance. His weight was 35.2 kg (>97th percentile), height 116 cm (3-10th percentile), body mass index 26.1 (>95th percentile), and weight for height 166%. His blood pressure was 100/60 mmHg and heart rate 78 beats per minute. Both testes were measured as 8 ml in size with orchidometer (Fig. 1). Stretched penile length was 7.5 cm (75-90th percentile). There was no pubic or axillary hair.

The endocrine laboratory profile revealed severe hypothyroidism: thyroid stimulating

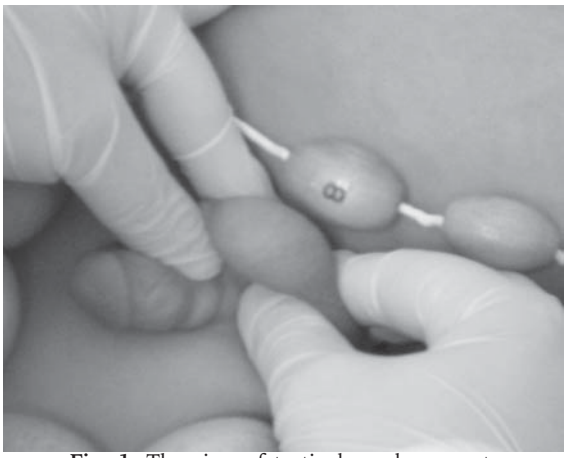

Fig. 1. The view of testicular enlargement.

hormone (TSH) value was above 75 mIU/L (normal range: 0.7-6.4), total T4: 1.0 μg/dl (normal range: 5.5-12.8) and free T4: 0.3 ng/dl (normal range: 0.8-2.2) with increased anti-thyroglobulin and antiperoxidase antibodies, of 39.2 IU/ml and 814 IU/ml, respectively. Basal serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels were 0.14 mIU/ml and 5.09 mIU/ml, respectively. Total testosterone level was 20 ng/dl. The remainder of the laboratory tests including complete blood count, biochemistry and other hormonal analysis were in normal ranges. A luteinizing hormone-releasing hormone (LHRH) test (100 μg/iv) was performed and resulted in a prepubertal response (peak LH and FSH were 3.34 mIU/ml and 3.27 mIU/ml, respectively). Ultrasonography showed heterogeneous ECHO pattern of thyroid parenchyma concordant with autoimmune thyroiditis with normal for age thyroid gland size. According to Greulich and Pyle, his bone age was consistent with 4 years (Fig. 2). Diagnosis of testicular enlargement due to obvious hypothyroidism secondary to autoimmune thyroiditis was considered. Treatment with levothyroxine (50 μg/day) was initiated. Myxedematous appearance regressed following administration of thyroid hormone therapy. His weight was 29.2 kg (90th percentile) and 27.3 kg (75th percentile) at the 1st and 4th month of therapy, respectively. Both testes had regressed in size to 5 ml after nine months of levothyroxine therapy.

Discussion

In 1960, Van Wyk and Grumbach first described a syndrome in girls with juvenile hypothyroidism, delayed bone age and isosexual precocious puberty[1]. VWGS is a unique form of precocious puberty as being related with delayed bone age. After the initial description of this syndrome, several sporadic cases were reported, most of which were described in girls[3-7]. VWGS has been reported in boys only rarely [8-10]. Isosexual precocious puberty in girls consists primarily of breast enlargement and menstrual bleeding. Pelvic sonography may reveal large, multicystic ovaries. The counterpart of enlarged ovaries in boys is testicular enlargement. VWGS in boys is associated with modest or no penile enlargement or pubic hair development in the presence of testicular enlargement. In our case, we determined increased bilateral testicular size without pubic hair or penile enlargement.

Initial evaluation of a child with suspected precocious puberty includes determination of gonadotropin levels and bone age. Our case had elevated FSH and prepubertal LH and testosterone levels with delayed bone age. Thyroid function test results led us to consider testicular enlargement due to severe hypothyroidism secondary to autoimmune thyroiditis.

The pathogenesis of testicular enlargement in VWGS is not clear. Several mechanisms have been considered to date. Van Wyk and Grumbach first proposed a theory to explain the etiology of this syndrome[1]. The low level of T3 and T4 in primary hypothyroidism elicited a rise in thyrotropin-releasing hormone (TRH) secretion, which in turn led to increase in levels of TSH, prolactin and gonadotropins.

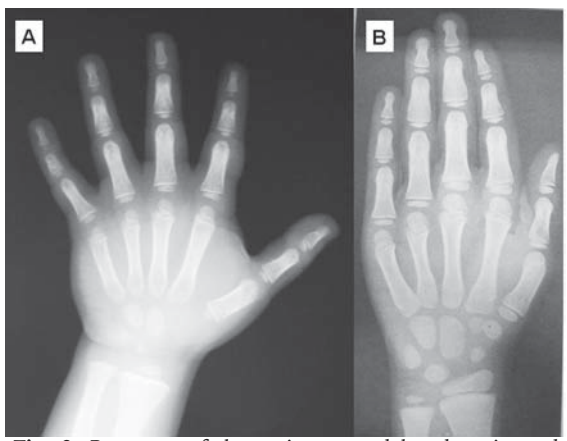

Fig. 2. Bone age of the patient was delayed, estimated at 4 years **(A)**. X-ray of the left wrist and hand, appropriate for patient's chronological age **(B)**.

These glycoprotein hormones (TSH, LH and FSH) have a common alpha subunit. This hormonal overlap results due to negative feedback regulation occurring in primary hypothyroidism considered as a cause of precocious puberty. However, in uncomplicated juvenile hypothyroidism, pubertal development is usually delayed, and subsequent studies have found that gonadotropins are not routinely elevated in juvenile hypothyroidism. Moreover, it is now recognized that only the FSH level is elevated; the LH level is either low or normal[11-13]. In our patient, we determined elevated FSH level despite normal LH level for his age. Testicular enlargement without virilization is a finding suggesting a process mediated through the FSH receptor rather than LH receptor. Another underlying mechanism is that high levels of TSH act via the FSH receptor and cause the gonadal stimulation. *In vitro* studies using recombinant TSH and human FSH receptor bioassays explored this hypothesis[14]. This study demonstrated that TSH could elicit a dose-dependent cAMP response at the FSH receptor, suggesting that the markedly elevated TSH levels in hypothyroidism act on the FSH receptor to induce testicular enlargement.

Another complaint of our patient was excessive weight gain. Physical examination, laboratory investigation findings and clinical course revealed that the underlying cause of weight gain was myxedema. Similar clinical features were reported in a girl by Niedziela and Korman[15]. Myxedema may also have an effect on testicular enlargement. Additionally, a direct effect of hypothyroidism on prepubertal testes leading to overproliferation of Sertoli cells has also been suggested to explain the enlarged testes[16]. We consider that the significant weight loss in our patient in a short time was due to resolution of the myxedema after adequate replacement with thyroid hormone.

In conclusion, VWGS may present in boys by testicular enlargement, and it can be a result of prolonged hypothyroidism due to autoimmune thyroiditis. Nonetheless, VWGS is not a real gonadotropin-independent precocious puberty in boys as it is in girls, since testicular enlargement occurs without substantial Leydig cell stimulation or testosterone secretion. We would like to stress that delayed bone age is a special discriminating feature for differentiation of VWGS from the other causes of precocious puberty.

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