Van Wyk-Grumbach syndrome: A rare cause of precocious puberty

Le syndrome de Van Wyk-Grumbach syndrome : une cause rare de puberté précoce

Introduction

Profound primary hypothyroidism in children causes generally delayed pubertal development. Rare association with precocious puberty may occur especially in long standing untreated patients.

The cardinal features of hypothyroidism inducing isosexual precocious puberty include thelarche, galactorrhea and/or menarche. Other characteristics features are the absence of sexual hair and retardation of linear growth [1,2]. This condition was described in 1960 by Van Wyk-Grumbach in a report of three cases of long standing hypothyroidism, presented with menarche, premature thelarche and galactorrhea [3]. We report an 8 year-old-girl who presented with vaginal bleeding and short stature. Subsequent investigations led to a diagnosis of autoimmune hypothyroidism.

Case report

An 8 year-old girl presented with complaints of growth failure and regular vaginal bleeding. She was born at 37 weeks gestation with a birth weight of 2.8 kg. She had a healthy sister. Parental height target was 152 cm. There was no family history of short stature. Since the age of 4 years, her parents noticed a decreased physical activity, easy fatiguability, intolerance to cold, excessive weight gain and lack of growth spurts. Her mother noticed a breast development and 3 episodes of vaginal bleeding occurred for the last 3 months. She had no family history of thyroid disease, autoimmunity or precocious puberty. Physical examination revealed pallor, facial puffiness, dry skin and myxedema, she had a protuberant abdomen without organomegaly or palpable mass. Her weight was 24 kilograms (–0.25 SDs), height was 91 cm (more than 4 SDs below her target height). She had an elevated body mass index (29 kg/m²). She had breast development at Tanner’s stage 3, but no pubic or axillary hair development. The thyroid gland was not palpable. Her motor and mental development was retarded.

Thyroid function tests showed profound hypothyroidism with free thyroxin (FT4) 0.5 pmol/L (normal ranges: 9-21), thyroid stimulating hormone (TSH) > 100 μU/mL (normal ranges: 0.25-5). Follicle stimulating hormone (FSH) was elevated 7.7 mIU/mL (normal ranges: 3-2), luteinizing hormone (LH) 0.07 m UI/mL (normal ranges: 0.1-6), estradiol: 19.2 pg/mL (normal ranges: 6-25). IGF1 was normal. Thyroid peroxidase antibodies were significantly increased; TPO antibody titre was > 1000 UI/ml (normal < 70 UI/ml), anti-thyroglobulin antibodies were strongly elevated: 1335 UI/mL (normal < 100 UI/mL). Her bone age corresponded to one year. Thyroid ultrasound showed a normal volume for age and normal echopattern. Pelvic ultrasonography revealed normal sized uterus and ovaries. The MRI of the brain revealed a pituitary adenoma measuring 1.9 × 1.5 cm extending up to, but not compressing the optic chiasm (figure 1). She was started on l thyroxine treatment at a dose of 5 μg/kg/d. After a 4-year-treatment, she had dramatic improvement; symptoms like myxedema and dry skin resolved, vaginal bleeding was not seen again, breast development regressed and showed a catch up height increase of 44 centimeters over 4 years (figure 2). A repeated brain MRI, performed 12 months later, showed a massive reduction in pituitary size. At her last review, at the age of 16 years and 7 months, her height was 146 cm (–3 SDs) with a weight of 59 kg (–1.5 SDs), she had a body mass index of 27.7 kg/m². Pubertal assessment revealed the following development:

- breast, stage 5;
- pubic hair, stage 5;
- regular menstrual cycle.

A hand X ray revealed a bone age of 14 years. She had normal thyroid function tests with a daily dose of 3.5 μg/kg of L thyroxin.

Discussion

Delayed pubertal development is a common manifestation of long standing untreated hypothyroidism. PP may occur rarely. Some cases have been reported in the literature [1,3-7] (table I). The exact incidence of PP attributable to hypothyroidism is unknown; a retrospective review conducted over ten years report a 24% incidence of PP among 33 children with profound hypothyroidism [8]. The cause of hypothyroidism in these patients is often undiagnosed lymphocytic thyroiditis although it may be seen in association with congenital hypothyroidism also [4,5]. In our case, positive thyroid antibodies were consistent with autoimmune hypothyroidism.

Acquired pediatric hypothyroidism is most commonly caused by chronic autoimmune thyroiditis and occurs in 1.3 to 4% of children [9]. The etiology of autoimmune thyroiditis is not completely understood but is considered to be multifactorial...
and is attributed to genetic and environmental factors [10]. In our case, there is no family history of hypothyroidism or personal history of recent infection, obscuring the cause of her disease.

The onset of PP is with thelarche with or without galactorrhea followed by menarche with absence of hair development as a characteristic feature, which depends on adrenal androgens [1,6]. Another clinical clue to hypothyroidism in our case is the decreased linear growth and delayed bone age, quite opposite of what is seen in patients with true PP which is usually associated with increase of linear height and acceleration of bone maturity.

The mechanism of this condition is not clear yet; however, there are several theories to explain the mechanism of PP due to hypothyroidism. Van Wyk and Grumbach suggested increased pituitary production of TSH, FSH, LH and prolactin when there was no negative feed back from thyroid hormone [3]. Another hypothesis is overproduction of prolactin resulting in either an increased level of gonadotropin-releasing hormone or an increased level of estrogen by upregulation of follicle-stimulating hormone receptors [5].

The current and most widely accepted theory is that high levels of TSH act on FSH receptors because the molecular similarities between the glycoprotein receptors of the two hormones, which share a common α subunit [5]. TSH elevation induces FSH like effects on the gonads resulting in multicystic ovaries, uterine bleeding and breast enlargement. In our case, FSH level was raised and estrogen level was in the normal range. The prolactin dosage was not performed. Hyperprolactinemia, a finding seen in several cases of Van Wyk-Grumbach syndrome, has two etiologies; some postulate that the thyrotrope hyperplasia in the pituitary compresses the pituitary stalk, thereby disrupting hypothalamic inhibition of prolactin. TRH is also known to stimulate prolactin. When thyroid hormone is low, TRH increases to increased levels of prolactin [5]. It has been shown that hyperprolactinemia can stimulate the secretion of adrenal androgens [11] and can enhance ovarian progesterone responsiveness to gonadotropins resulting in precocious puberty [12].

Pituitary hyperplasia or pituitary adenoma, as was seen in our case, occurs as a consequence of the loss of negative feedback from decreased circulating thyroid hormones and resultant thyrotroph hyperplasia [7].

Polycystic ovaries, which was described in several cases [4-7], is due to the direct action of TSH on FSH receptor resulting in ovarian stimulation, thus, TSH, which is present and elevated in all patients with this syndrome, may be the actual mediator for the development of ovarian cysts [7]. Our patient did not have cystic ovaries.

Although there is no definite consensus regarding the precise etiopathogenesis of the disorder, the treatment approach is clear. With thyroxin hormone replacement, all symptoms subside, the endocrine abnormalities resolve, as we witnessed in our case during follow up.
Conclusion
Our case is particular because of the absence of multicystic ovaries and breast development, which have been described in several cases of Van Wyk–Grumbach syndrome. The presence of a delayed bone age, a growth delay with precocious puberty in our patient was the important clue for the diagnosis of Van Wyk–Grumbach syndrome. Although there is little consensus regarding the precise etiopathogenesis of the disorder, the treatment approach is clear; in fact, with thyroxin replacement therapy, all endocrine abnormalities disappear.

Ethic statement: we declare that we have received written informed consent from the parents of the patient presented here-in to publish this article.

Disclosure of interest: the authors declare that they have no competing interest.

References

TABLE I
Characteristics of some cases of Van Wyk and Grumbach syndrome reported in the literature

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Presentation</th>
<th>Imaging</th>
<th>Biochemistry</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharma et al. [1]</td>
<td>5.5</td>
<td>Vaginal bleeding</td>
<td>Polycystic ovaries</td>
<td>Elevated FSH, LH, oestradiol and prolactin</td>
</tr>
<tr>
<td>Chattopadhyay et al. [4]</td>
<td>9</td>
<td>Breast enlargement</td>
<td>Multicystic ovaries</td>
<td>Raised FSH and oestradiol Normal LH</td>
</tr>
<tr>
<td>Durbin et al. [5]</td>
<td>11</td>
<td>Vaginal bleeding</td>
<td>Cystic ovaries</td>
<td>Elevated FSH and prolactin</td>
</tr>
<tr>
<td>Baranovski and Högler [6]</td>
<td>8</td>
<td>Breast development</td>
<td>Polycystic ovaries</td>
<td>Raised oestradiol, High FSH Suppressed LH Raised prolactin</td>
</tr>
<tr>
<td>Tran et al. [7]</td>
<td>10</td>
<td>Vaginal bleeding</td>
<td>Polycystic ovaries</td>
<td>Normal FSH and LH Raised prolactin</td>
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