CASE REPORT

VAN WYK-GRUMBACH SYNDROME: A RARE RESULT OF PROLONGED HYPOTHYROIDISM

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Abstract

Van Wyk-Grumbach syndrome is a rare disease characterized by prolonged hypothyroidism, precocious puberty with multicystic enlarged ovaries and features of polycystic ovarian disease (PCOD). Thyroxin replacement resolves symptoms of hypothyroidism and also symptoms of PCOD. Diagnosing this syndrome is important as unnecessary investigations for cystic enlarged ovaries can be avoided. We report a 12 years old girl who presented with obesity and features of insulin resistance. On evaluation she was found to be hypothyroid with high levels of thyroid stimulating hormone (TSH) and ultrasound of pelvis revealed ovarian cysts.

Keywords: Hypothyroidism, precocious puberty, PCOD, Van Wyk–Grumbach syndrome.

Introduction

Hypothyroidism usually causes delayed puberty. Rarely, prolonged hypothyroidism can present as precocious puberty. It was in 1960 when Van Wyk and Grumbach found association between the long-standing primary hypothyroidism, isosexual precocious pseudopuberty and multicystic enlarged ovaries(1). We present a 12 years old girl with Van Wyk-Grumbach syndrome who responded to oral thyroxine supplement.

Case Report

A 12 year old girl presented with increasing weight gain for last 2 years and pain in abdomen for 1 year. She was born to non-consanguineous parents, had normal milestones and had attained menarche at the age of 10 years. Her appetite was normal and she did not have other features of hypothyroidism like excessive somnolence, cold intolerance, or constipation except dry skin.Her height was 129 cm (< 3rd centile,) cm and weight was 45 kg and body mass index (BMI) was 27.04(> 97th centile). She had pallor, dry scaly skin and acanthosis negricans Random blood sugar was 140 mg/dl, subsequent blood sugars done at follow up were normal and urine sugar was nil. There was no goiter. Tanner's staging was B5 and P4 for breast and pubic hair respectively. On investigation, she had microcytic hypochromic anemia with a hemoglobin level of 9.0 g/dl (normal 12–14 g/dl). Hormonal investigations revealed thyroid stimulating hormone (TSH)> 150 mIU/L (0.7–6.4), free T3 35 pg/ml (60–181), free T4 0.08 ng/ml (4.5–12.6). Her radiological investigations revealed a delayed bone age (bone age 9 years). Ultrasonography of the pelvis showed a uterine size of 71 × 28 × 43 mm with enlarged multicystic ovaries (left ovary measuring 54x31x44 mm with multiple cysts with largest one measuring 17x10mm and right ovary not visualized). The girl was started on thyroxin 100 mcg/m2/day and was advised follow up. After 1½ months of therapy she had lost 11 kgs and pain in abdomen subsided.

Discussion

The pathophysiology of the Van Wyk–Grumbach syndrome involves a complex interaction between different hypothalamic–pituitary hormonal axes. In the original description, Van Wyk and Grumbach hypothesized that there was hormonal overlap in the pituitary feedback mechanism. These overlaps was thought to be partly at the hormone molecular level, given that both TSH and gonadotropins are glycoproteins, and/or partly due to a lack of specificity at the hypothalamic level. (1) Stimulation of the gonadal follicle stimulating hormone (FSH) receptor by TSH is supported by the specific FSH/estrogen dominant clinical picture. TSH also stimulates prolactin secretion and prolactin also sensitizes the ovary to circulating gonadotropins and accelerates follicular maturation via a poorly understood mechanism. (2) The other explanatory mechanism was an overlap in negative feedback response in which not only TSH but also other pituitary hormones such as FSH and luteinizing hormone (LH) are stimulated bythyrotropin releasing hormone(TRH). (3) Alternatively, others have suggested that the proximate nature of the TRH center to the gonadotropin releasing hormone (GnRH) center in the hypothalamus leads to excessive production of both releasing factors. (4) Still others have proposed that prolactin plays a primary role in the disease process, perhaps by sensitizing the ovaries to gonadotropins, or that TSH itself sensitizes the ovaries to gonadotropin stimulation. (5) Anasti et al showed the interaction of TSH with the human FSH receptor using recombinant human TSH(hTSH). (6) Similarly Ryan et al demonstrated actions of the elevated concentrations of TSH on the wild-type human FSH receptor (hFSHR), thereby causing gonadal hyper stimulation. (7) The precise etiopathogenesis of this disorder is unclear, but the treatment is clear.

The presence of palpable pelvic mass in cases of isosexual pseudo precocity would suggest ovarian tumors. In such cases hypothyroidism is not observed. Hence, the presence of hypothyroidism in patients with precocious puberty is an important clue for the diagnosis of Van Wyk-Grumbach syndrome. The acanthosis negricans which indicates insulin resistance and the obesity were part of polycystic ovarian disease. All symptoms subside with thyroxine replacement, the endocrine abnormalities resolve, and even the ovarian cysts decrease in size or disappear, hence this syndrome should be suspected when a clinician gets case of precocious puberty, obesity or features of PCOD along with hypothyroidism.

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