Case Report

Van Wyk- Grumbach Syndrome – An Unusual Presentation of Severe Hypothyroidism

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Abstract

Van Wyk- Grumbach syndrome (VWGS) is characterized by juvenile hypothyroidism, delayed bone age, and precocious puberty with a complete reversal to the pre-pubertal state following thyroid hormone replacement therapy. In this study, a 7 years and 1 month old girl presented with precocity having premature menarche, short stature, constipation, delayed bone age and enlarged bilateral multicystic ovaries. She presented with acute abdomen due to torsion of left ovary and had to undergo left sided oophorectomy and right ovarian cystectomy. High serum TSH, low FT_4 with high FSH but low LH within pre-pubertal range suggestive of 'severe hypothyroidism with FSH dominant precocious pseudopuberty' confirmed the diagnosis of VWGS.

Key-words: Grumbach syndrome, hypothyroidism, precocious pseudopuberty.

Introduction

Kendle, in 1905, first described the association of severe primary hypothyroidism and isosexual precocious puberty in females[1,2]. In 1960, Van Wyk and Grumbach first reported the clinical syndrome of long standing primary hypothyroidism associated with isosexual precocious pseudopuberty and multicystic enlarged ovaries in young female child[1-5]. Boys of VWGS having macroorchidism with no significant signs of virilization have also been reported[1,2]. In this study, a 7 year and 1 month old girl is presented with bilateral enlarged ovaries with twisted left ovarian cyst, isosexual precocious puberty, short stature and constipation due to un-noticed and untreated long standing hypothyroidism.

Case Report

A girl of 7 years 1 month reported to emergency department of a private hospital with the features of acute abdomen having left sided abdominal pain and vomiting for several hours. She also had history of scanty per vaginal bleeding for the preceding 7 days, but no history of fever or burning micturition. She was of short stature in respect of her age; often suffered from constipation since her 3 years of age. Her parents mentioned that she was less sweaty even in summer and was slow in every aspect since her 3 years of age. The girl was a meritorious student of her class but her performance was gradually deteriorating. She was born of non-consanguineous parents at full-term through lower uterine caeserian section (LUCS) and the milestone of development was normal. General examination revealed, she was restless due to pain in abdomen, her pulse rate was 124/min (though pulse rate recorded on previous occasion was 64/min), temperature 98ºF and was mildly dehydrated. Her height was 104 cm (<3rd centile) (z score -3.77), weight was 21 kg (26th centile) (z score -0.5), in contrast 50th centile weight for age 22 kg and height for age 121cm. Her thyroid gland was not enlarged. As per Tanner's staging, her sexual maturation score was B1 and PH1 for breast and pubic hair, respectively, and her axillary hair was absent. On palpation, abdomen was soft, non-distended, but tender on right and left iliac fossa. She had mild anaemia with haemoglobin level of 9.5 gm/dl, ESR 15 mm in 1st hour and non specific findings in peripheral blood film. Urine routine examination revealed no abnormality. Fasting blood sugar 5.1 mmol/L. Hormonal investigations revealed TSH > 100 µIU/ml (normal range=0.7– 5.7), free T_4 0.9 pmol/L (normal range=11.8–24.6), total T_4 13.6

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nmol/L (normal range=66–181), suggestive of severe hypothyroidism and anti-TPO was positive with 888 IU/ml (< 5.61) confirmed autoimmune thyroiditis, FSH 8.0 mIU/ml (normal range=0.2–5.8), LH < 0.08 mIU/ml (normal range=0.7–2.0), suggestive of FSH dominant precocious pseudopuberty, Basal Growth Hormone 2.0 ng/ml (normal range=0.06-5.0), Morning Serum Cortisol 304 nmol/L (normal range=138-690). Her radiological bone age was about 3½ years. USG revealed grossly enlarged ovaries, left ovary 148 cm^3 and right ovary 86 cm^3 with bilateral large ovarian cysts having multiple internal septations. Left ovarian cyst measuring about 75.7 x 65.4 x 66.5 mm and right ovarian cyst measuring about 57.8 x 45.2 x 63.2 mm, and uterus measuring 6.1 x 1.7 cm. Possibility of torsion of left ovary could not be ruled out by USG. After clinical evaluation and supportive investigations, she was diagnosed as a case of 'torsion of left ovary with right ovarian cyst with severe hypothyroidism'. Exploratory laparotomy was done and after opening of the peritoneum left ovarian cyst was found gangrenous, so left oophorectomy was done. Right ovary was healthy, so right ovarian cystectomy was carried out. Histopathology revealed follicular cyst with haemorrhage within the stroma of left ovary and follicular cyst of right ovary. Replacement therapy with tab. thyroxine was initiated and carefully dose was adjusted. So, this young female child is a classic presentation of the Van Wyk-Grumbach syndrome consisting of primary hypothyroidism, isosexual precocious pseudopuberty and multicystic enlarged ovaries. She suffered more complications due to unnoticed and untreated long standing primary hypothyroidism. On follow up she had no further episodes of vaginal bleeding and all her hormones returned to normal. At her last review, after 6 months of thyroid hormone replacement therapy, her height was 113 cm (<3rd centile) and weight was 19 kg (3rd centile), meaning that she had lost her weight than before and attained a height of 9 cm by 6 months with thyroid hormone therapy.

Discussion

Van Wyk - Grumbach syndrome (VWGS) is a rare disorder. Incidence of VWGS is not known. Only sporadic cases are reported. Clinically VWGS is often a diagnostic challenge, because long-standing primary hypothyroidism in children is known to cause delayed puberty as well as growth delay, whereas, in this rare syndrome, hypothyroidism leads to growth delay with paradoxical precocious puberty[5,6].

In 1905, Kendle first reported an "astonishing case" of a 9-year-old girl, who had menarche at age 5, fully developed breasts, and the clinical symptoms of female cretinism. After treatment with thyroid extract, her growth resumed, her menstruation stopped, and her symptoms of cretinism resolved[6]. Girls with VWGS have breast development with or without galactorrhoea, follicular cysts of ovaries causing bilateral ovarian masses, and menstruation in absence of pubic or axillary hair, whereas, boys have macroorchidism i.e. testicular enlargement with minimal penile enlargement but no significant signs of virilization[1-6]. Sexual precocity in VWGS is always isosexual and incomplete with lack of pubic and axillary hair growth. Delayed bone age, and high TSH with low T_4 are characteristic of VWGS[1,2].

In contrast, other causes of precocity are usually associated with increase in linear height, advanced bone age and epiphyseal fusion leading to final short stature[2]. For this, delayed bone age in patients with precocious puberty appears to be an important clue for the diagnosis of VWGS[1]. Usual consistent finding of VWGS is autoimmune thyroiditis and peri-pubertal onset of symptoms. FSH dominated pre-pubertal response with suppressed LH confirms GnRH-independent precocious pseudopuberty in VWGS[3]. The secretion of gonadotropin or gonadal steroids independent of pulsatile GnRH stimulation leads to GnRH-independent sexual precocity. Pituitary enlargement may occur due to thyrotroph hyperplasia in VWGS[1] which may lead to misdiagnosis of pituitary tumour and may cause expansion of sella turcica[5]. So, it is important to recognize this syndrome because initiating simple thyroid hormone replacement completely resolves the symptoms and hormone abnormalities, avoiding unnecessary investigations for malignancies or surgical intervention[2]. Similar to other reported cases this patient also exhibited breast development vaginal bleeding, and bilateral ovarian masses due to multicystic ovaries. The exact mechanism of development of precocious puberty in VWGS still remains speculative. Van Wyk and Grumbach postulated that an "overlap" in negative feedback response or non-specificity of stimulated by TRH, due to low thyroid hormones[1,3,4]. Alternatively, others

have suggested that the proximate nature of the TRH centre to the GnRH centre in the hypothalamus leads to excessive production of both the releasing factors[4]. Another explanation is, pituitary gonadotropins(FSH, LH) are glycoprotein hormones like TSH and all have a common alpha subunit, can be triggered by positive feed-back effect of low serum thyroxine, described as 'specificity spill over'[2,3]. But, the serum gonadotropins levels in these patients are relatively low in contrast to the degree of gonadal stimulation. Thus, elevated gonadotropins alone cannot completely explain the gonadal stimulation seen in severe juvenile hypothyroidism. Whereas, TSH level remain consistently elevated in such patients and the tendency to manifest sexual precocity may be directly related to the severity of TSH elevation[2]. It is also proposed that prolactin may play a primary role in the disease process, perhaps by sensitizing the ovaries to gonadotropins or that TSH itself sensitizes the ovaries to gonadotropin stimulation[4]. Besides, the majority of human hormones act through 7-transmembrane G protein-coupled receptors (GPCRs), all of which share common intracellular signalling pathways but little is known about their distribution, activity and cross reactivity in hormone excess conditions. TRH-induced TSH excess may be the common stimulator of the FSH receptor and possibly other GPCRs[3]. So, high circulating level of TSH act directly on FSH receptors may be the actual mediator of precocity[1,5].

Using recombinant tools, it has been shown that human TSH can interact with the human FSH receptor to stimulate the adenylyl cyclase activity, without simultaneous stimulation of LH receptors explaining the low prepubertal LH[1,5]. So, relatively low FSH-like activity of TSH can be clinically significant at very high concentrations of TSH, present in severe primary hypothyroidism. Hyperprolactinemia, another common finding, also present in our patient, has two etiologies. Some postulate that the thyrotroph hyperplasia in the pituitary compresses the pituitary stalk, thereby disrupting hypothalamic inhibition of prolactin. Besides, TRH is also known to stimulate prolactin. So, when thyroid hormone is low, TRH increases and can lead to high prolactin[6]. Again TRH induced hyperprolactinaemia likely to suppress the pituitary gonadotrophic axis particularly LH level[3]. The increased FSH or FSH like activity of TSH and low LH cause a high FSH/LH ratio in contrast to high LH/FSH ratio in normal puberty, thereby causing the increased ovarian estrogen secretion and multicystic ovaries[2]. In females, the multicystic ovaries may result from elevated levels of circulating gonadotropins acting on it. However, ovarian enlargement may be secondary to a myxedematous infiltration[1]. A direct effect of severe hypothyroidism on the pre-pubertal testis leads to over proliferation of Sertoli cells is responsible for testicular enlargement in boys[1,5]. Another unique feature of VWGS is short stature and delayed bone age which differs from other causes of precocious puberty where growth acceleration is the norm. This can be explained on the basis that thyroid hormone mediated bone maturation involves both direct and indirect actions. The indirect action is mediated by the regulation of growth hormone gene expression and the insulin-like growth factor (IGF) system, while T3 directly regulates the endochondral ossification and also controls chondrocyte differentiation in the growth plate both in vitro and in vivo[5]. Summary of findings in Van Wyk and Grumbach syndrome[1-6]:

Physical characteristics:
- Hypothyroid facies
- Short stature
- Precocious uterine bleeding
- Precocious thelarche
- ± Galactorrhoea
- Absence of pubic hair or axillary hair.

Radiological characteristics:
- Enlarged and multicystic ovaries
- Pubertal uterus.
- Delayed bone age
- Enlarged pituitary

Endocrine abnormalities:
- Extremely raised TSH and low undetectable free T4
- High/ high normal FSH
- Suppressed LH
- Raised Prolactin
- Flat response on LHRH stimulation test

Conclusion

The precocious puberty in VWGS is unique in that it is classically associated with delayed bone age and short stature with severe hypothyroidism. However, the bone age is advanced in all cases of precocious puberty other than VWGS. The delayed bone age in our case along with high TSH, low T3, low T4, low

LH levels and precocious puberty helped us to think of VWGS. In the absence of suspected ovarian torsion, surgery is unnecessary, as ovarian cyst regression occurs and all the hormones return to normal after appropriate thyroid hormone replacement.

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