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Review Article

Van Wyk Grumbach Syndrome - A Diagnostic Dilemma in Gynec- Oncology

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Abstract

Background: Van Wyk Grumbach syndrome is characterized by isosexual precocious puberty, delayed bone age & raised tumor markers (CA-125, AFP, LDH) in the background of severe hypothyroidism & these symptoms completely reverse to pre-pubertal state on supplementing thyroxin. High circulating levels of TSH with pre-pubertal LH is confirmatory of Van Wyk Grumbach Syndrome. These juvenile girls usually have delayed bone age and present with enlarged multiseptate cystic ovaries mimicking ovarian Germ cell tumor in the background of raised tumor markers adding to confusion. High levels of circulating TSH acting directly on FSH receptors are the cause of precocity in such patients. There is no role of surgery in this entity. Supplementing thyroxin in sequentially increasing dosages reverses the symptoms completely including normalization of tumor markers.

Keywords: Hypothyroidism; Precocious puberty; Tumor markers

Introduction

Central precocious puberty occurs due to GnRH dependant activation of hypothalamic pituitary gonadal axis. Pseudo-precocious puberty or GnRH independent sexual precocity is characterized by extra-pituitary secretion of gonadotropins. In 1960, Van Wyk & Grumbach were treating three juvenile girls with history of precocious menstruation. During evaluation all three girls were found to be hypothyroid & had delayed bone age & enlarged cystic ovaries. They supplemented them with thyroxin & symptoms regressed over a period of 6 months to 1 year. This is how this syndrome came into light.

Van Wyk-Grumbach syndrome is characterized by juvenile hypothyroidism, delayed bone age Isosexual precocious puberty with ovarian enlargement & completely reverts back to pre-pubertal state on treatment of hypothyroidism [1,2]. The precocious puberty is always isosexual & incomplete in VWGS [3]. The presence of precocious puberty in the background of enlarged ovaries usually suggests an estrogen secreting ovarian tumor. However, presence of delayed bone age & severe hypothyroidism narrows down the diagnosis to Van Wyk Grumbach Syndrome. High circulating TSH with pre-pubertal LH further confirms the diagnosis. Auto-immune thyroiditis needs to be ruled out in these patients as a cause of hypothyroidism [4]. So these patients can be diagnosed by their clinical profile & confirmatory lab investigations without doing surgery [5].

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Clinical Findings

Role of high TSH

Precocious puberty: TSH, FSH & LH all share the same alpha subunit & all of them act through the trans-membrane G protein coupled receptors. TSH in high concentrations starts acting on FSH receptors. In VWGS GnRH independent precocious puberty is due to TSH mediated activation of gonadal FSH receptors [6]. This causes raised estrogen levels leading to premature thelarche, menstruation & multi-follicular cysts in the ovaries.

Effect on ovaries: Ovaries are sensitized to GnRH as Granulosa cells TSH receptors are activated which causes ovarian hyper-stimulation & myxedematous infiltration of the ovary [7].

Effect on bones: High TSH causes slow chondrocyte differentiation leading to arrested growth & delayed bone age. High levels of TSH further add to insult by causing excessive bone loss.

Effect on hemoglobin: Severe Hypothyroidism causes decreased metabolism and oxygen requirement of the body. As a result there is decreased RBC production which subsequently causes anemia (Table 1).

Why there is high Prolactin in case of Van Wyk Grumbach Syndrome?

Due to high TSH levels, there is no negative feedback from thyroid hormones. Due to increased TRH levels, there is thyrotrophic hyperplasia in pituitary which compresses the pituitary stalk & disrupts hypothalamic inhibition of Prolactin leading to raised Prolactin levels.

Effects of high prolactin: Due to decreased GnRH there is suppression of Pituitary Gonadotropins which causes slow GnRH pulse. This causes selective suppression of LH with increased production of FSH. This leads to increased sensitization of ovaries to circulating GnRH causing increased follicular maturation.

Tumor markers in van wyk grumbach syndrome: CA125, LDH & AFP may be raised in Van Wyk Grumbach Syndrome adding to confusion in diagnosis for the clinician and increases anxiety for

the patients & their relatives. At times these patients are referred to tertiary centers with suspicion of Germ Cell Tumors. There have been instances in literature where patients have been subjected to surgery in view of ovarian mass with raised tumor markers due to lack of knowledge about this rare entity.

Reasons for rise in tumor markers in VWGS

1. AFP-T3 inhibits the production of AFP from hepatoma cells.
2. LDH- Hypothyroidism causes myopathy & elevation of muscle enzymes. There is linear relation of TSH to LDH.
3. CA-125-Antigen is secreted by mesothelial cells in response to stress- mechanical (fluid over-load) or inflammatory (mediators like TNF & Interleukins).

Management

1. Sequential increasing supplementation of Thyroxin hormone for 9-12 months.
2. Results in complete regression of symptoms to pre-pubertal state.
3. Early recognition & initiation of treatment avoids unnecessary surgery & investigations.

Follow-up

1. 3 Monthly with clinical examination including weight & height measurement, TSH levels & USG Pelvis.
2. MRI Pelvis is not mandatory for follow-up.
3. Even tumor markers which are raised need to be repeated 3 monthly as they normalize in 3 to 6 months of treatment (Table 2).

Conclusion

Van Wyk Grumbach Syndrome though rare, must be entertained in juvenile girls with precocious puberty, delayed bone age & hypothyroidism. These features completely regress on thyroxin supplementation including elevated tumor markers & enlarged ovaries [8]. There is no role of surgery in such cases despite having enlarged multi-cystic ovaries. Elevated tumor markers do cause anxiety to the treating physician and patient & her relatives but return to normal with thyroxin in six to nine months.

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Table 1: Patho-physiology of Van Wyk Grumbach Syndrome.

Phenotype	Imaging	Biochemistry
Typical Hypothyroid appearance	Enlarged ovaries with multi -follicular cysts on USG/MRI	Extremely raised TSH & low undetectable FreeT4
Delayed Growth	Pubertal uterus on USG	Raised estradiol
Precocious uterine bleeding	Delayed bone age on X-ray Lt Hand	High /High -Normal TSH
Precocious Thelarche	Enlarged pituitary on MRI Brain	Suppressed LH
Galactorrhoea		Flat response on LHRH Stimulation test
Anemia		Raised Prolactin
Absence of pubic/axillary hair		CA125, LDH&AFP may be enlarged

Table 2: Trends in follow-up with blood investigations.

Test (Normal Range)	Initial results	After 3 months of treatment	After 9 months of treatment
Free Thyroxin (10.7-21.8 pmol/l)	<3.9	10.8	11.8
TSH (0.4-3.5 mU/l)	955	7.9	20.7
Prolactin(mU/l)	1310	218	198
LH (0.7-2.2 U/l)	0.2	0.5	-
FSH (0.2-6 U/l)	5	2.4	4.9
ESR (0-9 mm/h)	50	18	28
Hb (12-14 g/dl)	8.4	10	12.6