Down Syndrome and Van Wyk-Grumbach Syndrome: A Rare Presentation

Jesmin E[1], Mohsin F[2]

DOI: https://doi.org/10.3329/jafmc.v18i1.61270

Abstract

Van Wyk-Grumbach Syndrome (VWGS) is presented by juvenile hypothyroidism, delayed bone age and isosexual precocious puberty. All of the features will be reversed with treatment of the underlying thyroid hormone deficiency. It has been described, a 3-year-old girl with Down Syndrome who presented with per vaginal bleeding. Physical examination showed typical morphologic features of Down Syndrome and hypothyroidism. Pubertal developments in tanner stages were: breast at stage II and pubic hair at stage I. Serum TSH level was very high. Serum FSH, LH and Estrogen level were also high for her age. On radiological examination her bone age was 2 years. Her pelvic sonogram revealed enlarged uterus with ovarian cysts. These findings confirmed the diagnosis of VWGS. Treatment with Levothyroxine, her vaginal bleeding did not recur and ovarian cyst size decreased after 4 weeks and disappeared after 2 months. In conclusion, thyroid hypo-function must be investigated in children who have precocious puberty with multicystic enlarged ovaries.

Introduction

Van Wyk-Grumbach Syndrome (VWGS) is an uncommon cause of precocious puberty due to hypothyroidism[1]. The pulsatile release of gonadotropin releasing hormone (GnRH)-activates the hypothalamic-pituitary-gonadal axis which leads to central precocious puberty (CPP). In this case the gonadotropins (LH and FSH) secretion is independent of pulsatile GnRH stimulation which leads to pseudoprecocious puberty, or GnRH-independent sexual precocity[2]. It is the association of long standing primary hypothyroidism, isosexual precocious puberty and multicystic enlarged ovaries in young female. A case of Down Syndrome with VWGS is described here who presented to the Paediatric Endocrine outpatient department (OPD).

Case

A 3 years old girl with Down Syndrome was diagnosed as hypothyroidism 1 year back. But she did not take any treatment for this problem. For last one weak she developed per vaginal bleeding. She had also history of developmental delay, constipation and repeated RTI since early infancy. Her physical examination showed typical morphologic features of Down Syndrome and hypothyroidism (Figure-1). Her pubertal developments in Tanner stage were: breast at stage II, pubic hair at stage I and active per vaginal bleeding.

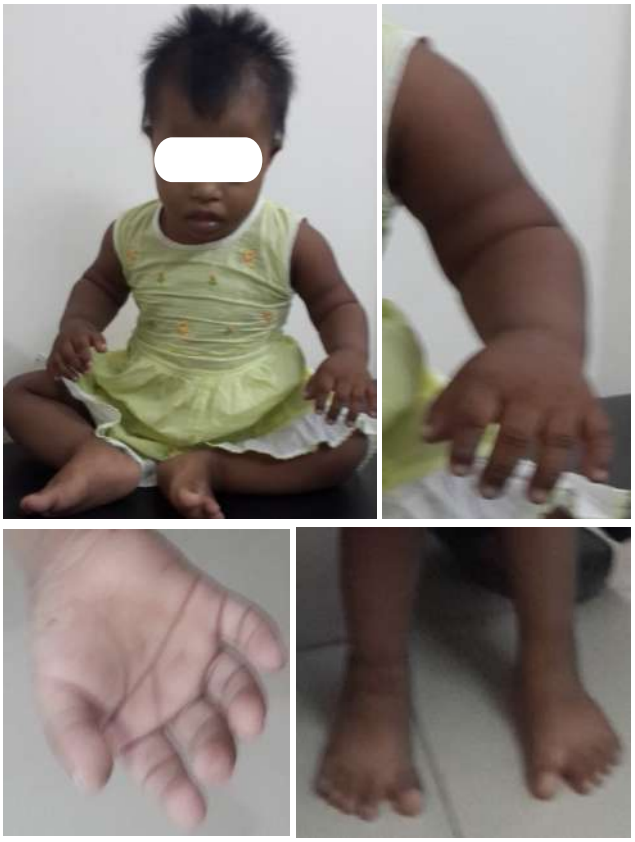

Figure-1: Down Syndrome and hypothyroidism

On investigations her serum FT4 was 0.24ng/dl (0.8 – 1.9), serum TSH was >150µ iu /ml (·80-9) FSH was 8.17 m IU /ml (0.2-3.8), LH was 0.92mIU/ml (<0.5) and Estrogen level was 25.85pg/ml (3-15). USG of lower abdomen revealed Grossly thick walled vagina (36mm in length and 14mm in breadth), Relatively large uniform Uterus(5.26x1.7cm), no endometrial or endovaginal collection or any foreign body. A left ovarian cyst (3.4 x 3cm) was found which had thick wall with marginal septation & content clear fluid (Figure-3). These findings confirmed the diagnosis of VWGS.

1. **Lt Col Eva Jesmin**, MBBS, DCH, FCPS, Classified Child Specialist and Paediatric Endocrinologist, Combined Military Hospital (CMH), Dhaka (*E-mail:* jesmin882@gmail.com) 2. **Professor Fauzia Mohsin**, MBBS, FCPS, Head of Paediatrics Endocrinology Unit, Department of Paediatrics, BIRDEM General Hospital-II.

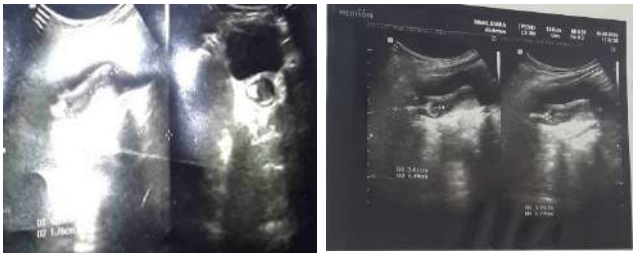

Figure-2: USG at the time of 1st report

She was treated with levothyroxine. Her vaginal bleeding was stopped after 3 days of treatment and her ovarian cyst size was decreased after 4 weeks and disappeared after 2 months (figure 3 and 4). And her thyroid function test became normal within 4 weeks.

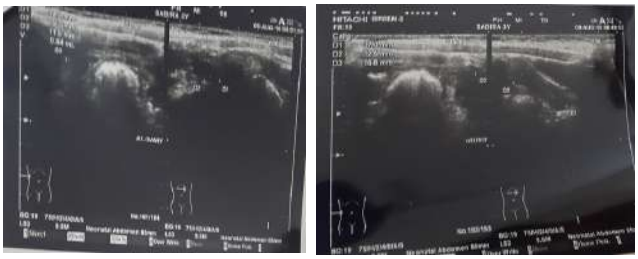

Figure-3: Follow up USG after 4 weeks of treatment

Figure-4: Patient after 4 weeks of treatment

Discussion

The exact pathogenesis of precocious puberty in VWGS remains speculative. The initial theory which explained the etiology of this syndrome was proposed by Van Wyk and Grumbach in 1960[3]. Primary hypothyroidism causes a rise in TRH, which leads to increase the levels of TSH, prolactin and gonadotropins (LH and FSH). There is a possible hormonal overlap due to TSH, LH, FSH have a similar alpha subunit. This explanation for precocious puberty in primary hypothyroidism remains uncertain, because in uncomplicated juvenile hypothyroidism, the development of puberty is usually delayed[1]. In addition to this, it is now recognised that only FSH level is elevated, but the level of LH is either low or normal[4,5]. The increased level of FSH and high FSH/LH ratio is thought to be responsible for the increased ovarian oestrogen secretion in girls. However, in normal puberty, the LH/FSH ratio is high[6]. In contrast, in males with this clinical presentation, the testes may be enlarged with relatively minimal virilization, possibly due to the predominant effect on the FSH receptor, without substantial testosterone secretion[1,7]. Therefore, the isosexual precocity associated with hypothyroidism behaves as an incomplete form of gonadotropin-dependent puberty[7].

High serum TSH (with normal LH levels) is consistent with van Wyk-Grumbach syndrome, in which the high TSH may act directly on the FSH receptor to mediate the precocious puberty[1]. The diagnostic features include long-standing hypothyroidism, high levels of TSH, isosexual precocious puberty with the absence of pubic and axillary hair growth, and delayed bone age[3,8]. The precocious puberty is always isosexual and is not complete in patients of VWGS[8]. High circulating levels of TSH directly acts on FSH receptors which might be the actual mediator of precocity[9]. The syndrome generally responds well to thyroid hormone replacement therapy with complete resolution of symptoms[10]. Although younger age and features of true precocious puberty were present, the patient was better on follow up after 2 weeks with proper diagnosis and appropriate management.

Conclusion

Children who have precocious puberty with multicystic enlarged ovaries, thyroid function tests must be investigated for proper management.

References

1. Backeljauw PF, Dattani MT, Cohen P et al. Sperling's textbook of Pediatric Endocrinology. 4th ed. Philadelphia: Saunders (Elsevier, 2014). Disorder of Growth hormone / Insulin-Like growth factor secretion and actions; 2014:292–404.

2. Styne DM, Grumbach MM. William's textbook of Endocrinology. 11th ed. Philadelphia: Saunders (Elsevier, 2008). Puberty: Ontogeny, neuroendocrinology, physiology and disorders; 2008:969–1166.

3. Van Wyk JJ, Grumbach MM. Syndrome of precocious menstruation and galactorrhea in juvenile hypothyroidism. An example of hormonal overlap in pituitary feedback. J Pediatr. 1960; 57:416–35

4. Pringle PJ, Stanhope R, Hindmarsh P. Abnormal pubertal development in primary hypothyroidism. Clin Endocrinol (Oxf). 1988; 28:479–86.

5. Buchanan CR, Stanhope R, Adlard P. Gonadotropin, growth hormone and prolactin secretion in children with primary hypothyroidism. Clin Endocrinol. 1988; 29:427–36.

6. TK Jagadhish. Van Wyk and Grumbach Syndrome (A Syndrome of Incomplete Isosexual Precocity and Juvenile Hypothyroidism). Med J Armed Forces India. 2002; 58(4):343–5.

7. Garibaldi LR, Chemaitilly W. Disorder of pubertal development. In: Behrman RE, Kliegman RM, Staton BF, St. Geme JW, Schor NF, editors. Nelson textbook of Paediatrics. 20th ed. Philadelphia: Elsevier, 2016:2656.

8. Ever JL, Rolland R. Primary hypothyroidism and ovarian activity evidence for an overlap in the synthesis of pituitary glycoproteins. Br J Obstet Gynaecol. 1981; 88:195–202.

9. Rastogi A, Bhadada SK and Bhansali A. An unusual presentation of a usual disorder: Van Wyk-Grumbach syndrome. Indian J Endocrinol Metab. 2011 Jul; 15(Suppl2):S141–S143.

10. Zhang H, Geng N, Wang Y et al. Van Wyk and Grumbach syndrome: Two case reports and review of the published work. J Obstet Gynaecol Res. 2014; 40(2):607-10.