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VAN WYK-GRUMBACH SYNDROME: A CASE SERIES AND REVIEW OF LITERATURE

Endocrinology

Adlyne Reena Asirvatham — Assistant Professor, Department of Endocrinology, Diabetes & Metabolism, Sri Ramachandra Medical College & Research Institute, Chennai -600116. Tamil Nadu.

Shriraam Mahadevan* — Professor & Head, Department of Endocrinology, Diabetes & Metabolism, Sri Ramachandra Medical College & Research Institute, Chennai -600116. Tamil Nadu. *Corresponding Author

Karthik Balachandran — Assistant Professor, Department of Endocrinology, Diabetes & Metabolism, Sri Ramachandra Medical College & Research Institute, Chennai -600116. Tamil Nadu.

Satish Kumar Balasubramaniam — Senior Resident, Department of Endocrinology, Diabetes & Metabolism, Sri Ramachandra Medical College & Research Institute, Chennai -600116. Tamil Nadu.

ABSTRACT

Context: Classic presentation of longstanding hypothyroidism is delayed growth and delayed puberty. However, rarely it may present with paradoxical precocious puberty. Thus awareness about this condition among clinicians is essential to diagnose this not so common syndrome.

Aim: We aimed to study the characteristics of children who presented with Van Wyk-Grumbach syndrome in the last 10 years. We also intended to determine the duration of resolution of symptoms following thyroxine therapy.

Materials & Methods: Three children with classic presentations of Van Wyk-Grumbach syndrome were included in this study. Prompt treatment with thyroxine was initiated and the subjects were followed up.

Results: All three children showed significantly elevated TSH with very low T4 levels. High FSH and suppressed LH were observed in all. Clinical, biochemical and radiological resolution occurred at 8, 9 and 12 months in cases 1, 2 and 3 respectively.

Conclusion: Van Wyk-Grumbach syndrome is quite rare and needs to be suspected for prompt treatment and complete resolution.

KEYWORDS

Van Wyk-Grumbach syndrome; Multicystic ovaries; Hypothyroidism;

INTRODUCTION

Kendle first reported a 9 year old cretin girl presenting with menarche at 5 years and fully developed breasts as an 'Astonishing case' in 1905. After treating the child with thyroid extract, he described that her growth resumed and menses ceased.(1) Later in 1960, Van Wyk and Grumbach described the syndrome as characterized by breast development, uterine bleeding and multicystic ovaries and is now known as Van Wyk-Grumbach syndrome (VWGS).(2) Traditionally, long standing untreated hypothyroidism presents with growth and pubertal delay. This rare condition presents with growth delay and paradoxically precocious puberty thereby posing a diagnostic challenge. Classically, prepubertal girls present with overt hypothyroid appearance, delayed growth, premature breast development and uterine bleeding. The striking feature that differentiates this syndrome from other common causes of precocity is the lack of axillary, pubic hair, short stature and delayed bone age. Laboratory investigations reveal very high levels of Thyroid Stimulating Hormone (TSH) and very low or undetectable levels of T4. Follicle Stimualting Hormone (FSH), Prolactin and 17-β estradiol are high with suppressed Luteinising Hormone (LH). Gonadotrophin Releasing Hormone (GnRH) stimulation also shows a prepubertal response with suppressed LH thereby confirming a GnRH independent precocious puberty.

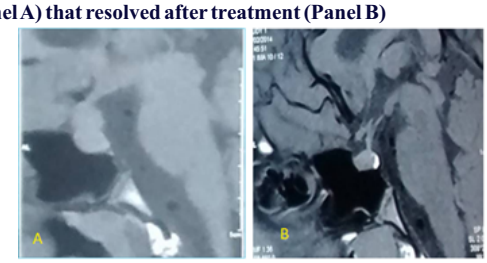
Several theories exist to explain the pathophysiology of this syndrome of overt hypothyroidism with paradoxical precocious puberty. The original hypothesis was the hormonal overlap in the negative feedback mechanism associated with hypothyroidism resulting in elevated gonadotrophins.(2) However this hypothesis does not explain the normal FSH reported in few patients.(3,4) Then came the more acceptable theory wherein it was thought that elevated TSH can act at the FSH receptor as TSH, FSH and LH share a common β-subunit. Interestingly, TRH induced hyperprolactinemia slows down the GnRH pulse frequency causing an increase in FSH production but a decrease in LH release. Another explanation hypothesized for high FSH could be the cross-reactivity of very high TSH levels with standard FSH assays.(5) The rise in FSH results in the follicular enlargement and resultant multicystic ovaries that can be just larger than a normal ovary or even up to 15 cm in diameter. Elevated alpha fetoprotein has also been reported in this syndrome which resolves with thyroxine therapy.(6) Hence when undiagnosed, this presentation could end up in an inadvertent surgery.(7) Estradiol levels are high in the serum more so in the follicular fluid.

Review of literature provides many cases with longstanding hypothyroidism, large multicystic ovaries and precocious puberty.(8,9) Atypical cases have also been reported in the literature where VWGS presented with unilateral mass (10), associated with down syndrome (11), occurred with Kocher-Debre-Semelaigne syndrome (12) and even with late presentation in adulthood.(13) In this paper, we studied the clinical presentations, evaluation, management and follow up of three girls who were diagnosed with VWGS in the last 10 years.

Case: 1

A 9 year old girl presented with constipation and weight gain for one year. She also noticed abdominal distension over last one month. Her mother noticed bleeding per vagina 5 days ago and was worried. She was born to consanguineous parents and her past medical history was insignificant. She weighed 34.9 kg and her height was 122.5 cm. Her breast development was Tanner stage 3 but showed lack of axillary and pubic hair. There was no goitre on clinical examination. She was noticed to have abdominal distension. Her bone age was significantly delayed and laboratory investigations are shown in Table:1. MRI pituitary showed pituitary hyperplasia (Figure: 1). As suspected by clinical examination, she was found to have primary hypothyroidism and was started on thyroxine. On follow up, her ovarian cysts as well as pituitary hyperplasia regressed after 8 months of treatment and menses ceased.

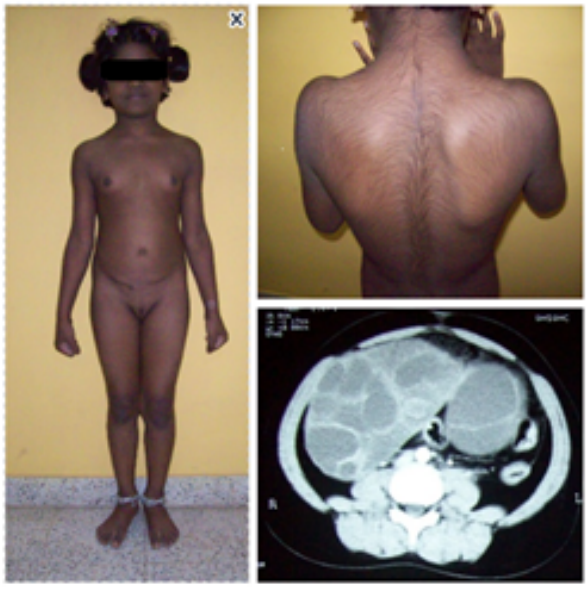
Figure: 1 MRI Pituitary of case 1 who had pituitary hyperplasia (Panel A) that resolved after treatment (Panel B)



Case: 2

A 7 year old girl was brought by her parents with complaints of two episodes of bleeding per vagina over the last 2 months. Her weight was 20 kg and she was 104.5 cm tall. On clinical examination, she had thyromegaly, dry, coarse skin, hypertrichosis and well noticeable Tanner stage 3 breast development. On evaluation, she had primary hypothyroidism (Table:1) and her CT abdomen showed large complex multicystic right ovary and simple cysts in left ovary. (Figure:2) She was initiated on thyroxine and she improved symptomatically in 9 months.

Figure: 2 shows the phenotype of case 2 who presented with Tanner 3 breasts, hypertrichosis and bilateral multicystic ovaries in CT abdomen.



Case: 3

Six year old female child was accompanied by her anxious parents. She was evaluated elsewhere for abdominal pain and was diagnosed to have bilateral ovarian tumour. She was initially referred to an oncology centre for surgery. Her pre-operative evaluation had showed an elevated TSH and was referred for fitness for surgery. Examination showed severe short stature, diffuse goitre, abdominal distension with palpable mass bilaterally, Tanner stage 2 breasts, stage 1 pubic and axillary hair. While suspecting Van Wyk-Grumbach syndrome, further enquiry revealed that the child had an episode of bleeding per vagina few weeks ago. Biochemically she had overt hypothyroidism and was commenced on thyroxine. She showed significant improvement on follow up with resolution of ovarian mass at 12 months.

Table: 1 showing the biochemical parameters of the study cases.

Parameters	Reference range	Case 1		Case 2		Case 3	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
TSH	0.3-5.5 mIu/mL	>75	4.8	1329	7.9	>150	6.3
Free T4	0.7-1.8 ng/dL	<0.4	0.99	0.3	1.0	0.2	1.1
Total T4	4.5-12.5 ug/dL	<1.0	-	-	-	-	-
FSH	0.3-10 mIu/mL	8.15	2.87	12.6	3.4	7.5	2.9
LH	1.5-12 mIu/mL	<0.1	3.52	0.01	0.9	<0.1	1.4
Estradiol	< 10 pg/mL	46	-	36	-	52	-
Prolactin	2-25 ng/mL	60	18	84	28	54	12
AFP	< 10 ng/mL	-	-	5.95	-	257	22

AFP – Alfa-fetoprotein

DISCUSSION

Our study shows that Van Wyk-Grumbach syndrome is not very uncommon and high index of clinical suspicion is required to diagnose this rare syndrome. Our first case presented with classic findings of VWGS with pituitary hyperplasia similar to that had been reported earlier.(14) Usually pituitary hyperplasia resolves like in our case where repeat MRI 8 months after treatment showed shrinkage of the pituitary enlargement. Patients may also present with visual field defect and headache.(15) Second girl showed a classic premature thelarche and hypertrichosis which are commonly associated with untreated hypothyroidism. Her menses ceased 8 weeks after thyroxine therapy and complete resolution occurred 9 months after therapy. The third child was the youngest of all who had a near miss. She was thought to have bilateral ovarian malignancy with elevated alpha-fetoprotein similar to prior reports.(6) Fortunately, she was detected to have elevated TSH and was referred for fitness for surgery. She was then diagnosed to have VWGS and was started on thyroxine. With treatment, she had a significant regression of the ovarian masses likely due to the reduced cross-reactivity of TSH on the FSH receptors. Due to prompt recognition, an inadvertent surgery was evaded in this child.

CONCLUSION

This study shows that VWGS is not rare. Good clinical knowledge, correct suspicion and appropriate laboratory investigations would help in early diagnosis and thus save the patient from unnecessary burden and inadvertent surgery. Complete clinical, biochemical and radiological resolution may take even up to a year in severe cases.

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