ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at: www.ijmacr.com

Volume – 5, Issue – 1, January –February - 2022, Page No. : 256 – 269

Correlation between complexities of Van-Wyk Grumbach Syndrome with prolonged hypothyroidism among pediatric age group: Reviewing the consequences and possible treatment

[1]Dr. Bishwajit Mishra, Department of Paediatrics, Hitech medical college and hospital, Bhubaneswar, India.

[2]Dr. Bibhudatta Mishra, Department of Paediatrics, Jagannath hospital, Bhubaneswar, India.

[3]Dr. Arjit Mohapatra, Department of Paediatrics, Jagannath hospital, Bhubaneswar, India.

[4]Dr. Vidya Patwari, Department of Paediatrics, Jagannath hospital, Bhubaneswar, India.

[5]Dr. Manoj Dehury, Department of Paediatrics, Jagannath hospital, Bhubaneswar, India.

[6]Dr. Brutiranjan Rout, Department of Paediatrics, Jagannath hospital, Bhubaneswar, India.

[7]Dr. Pratap Behera, Department of Paediatrics, Jagannath hospital, Bhubaneswar, India.

Corresponding Author: Dr. Bibhudatta Mishra, Department of Paediatrics, Jagannath hospital, Bhubaneswar, India.

How to citation this article: Dr. Bishwajit Mishra, Dr. Bibhudatta Mishra, Dr. Arjit Mohapatra, Dr. Vidya Patwari, Dr. Manoj Dehury, Dr. Brutiranjan Rout, Dr. Pratap Behera, "Correlation between complexities of Van-Wyk Grumbach Syndrome with prolonged hypothyroidism among pediatric age group: Reviewing the consequences and possible treatment", IJMACR- January – February - 2022, Vol – 5, Issue - 1, P. No. 256 – 269.

Type of Publication: Review Article

Conflicts of Interest: Nil

Abstract

Van Wyk Grumbach Syndrome (VGWS) has been considered an atypical endocrinal disorder that majorly affects pediatrics by limiting their growth rate with prolonged hypothyroidism and delaying their bone age. It has been observed among prepubertal girls and boys and can be represented during their sexual developmental phases of life. There is a need for evolving possible treatment among the patients of VWGS by involving thyroid hormone replacement as the major step in the treatment. This management approach of treating the patients of VWGS will be effective in eradicating the symptoms of VWGS and improving the normal growth efficacy rate among pediatrics. The present study has reviewed the aspects of Van Wyk Grumbach Syndrome (VGWS) and the correlation between complexities of Van-Wyk Grumbach Syndrome with prolonged hypothyroidism among pediatrics have been represented in the present review paper. The implication of the major consequences and possible treatment for VWGS with prolonged hypothyroidism have been presented in this study. Various cases studies of Van-Wyk Grumbach Syndrome with prolonged hypothyroidism along with the efficacy of treatment have been represented in the study. The present study has helped in intervening the treatment for VWGS with prolonged hypothyroidism in the form of precautionary measures, related therapies,

interventions, and medication, and the involvement of existing literature has helped in analyzing the reasons behind the correlation of Van-Wyk Grumbach Syndrome with prolonged hypothyroidism that further helps in filling the gap.

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

Introduction

Van Wyk Grumbach Syndrome (VWGS) was initially explained in 1960 as an array of hypothyroidism with precocious puberty, and massive ovarian cysts (Van Wyk & Grumbach, 1960). The lack of treatment of hypothyroidism and its long-lasting impact results in the development of hormonal overlap syndrome. The precocious puberty in Van Wyk Grumbach Syndrome (VWGS) shows association with delayed bone age and is often considered to be isosexual and incomplete (Rastogi et al., 2011). The syndrome consisting of VWGS is known to be a challenging approach due to the prolonged hypothyroidism that results in pubertal and growth delay. The occurrence of large and multi cystic ovarian masses evolves the development of precocious puberty in hypothyroidism (Hunold et al., 2009; Panico et al., 2007; Kubota et al., 2008; Sanjeevaiah et al., 2007; Mohsin et al., 2007). The occurrence of abnormalities among the affected individuals such as pituitary hyperplasia or pituitary adenomas evolves the formation of abnormal levels of prolactin and FSH (Singh et al., 2005; Campaner et al., 2006; Takeuchi et al., 2004). The hypothyroidism in cases of precocious puberty in the female pediatrics results in early thelarche and vaginal bleeding without adrenarche. It has been found that different cases of Van Wyk and Grumbach syndrome have been observed among the prepubertal girls and boys and can be represented during their sexual developmental phases of life (Hunold et al., 2009; Panico et al., 2007; Kubota et al., 2008; Browne et al., 2008).

Occurrence of Van Wyk Grumbach Syndrome (VWGS) among affected individuals is often characterized by the development of hypothyroidism. Hypothyroidism is considered the most common endocrine disorder occurring among children. The major symptoms of hypothyroidism among children involve the delaying of sexual development. The severe cases of hypothyroidism among children cause precocious puberty, thus evolving the occurrence of Van Wyk Grumbach Syndrome with certain symptoms of enlargement of breasts, multi cystic ovaries, and menstrual bleeding in females, and the boys observed with symptoms of enlargement of testicles and minimal penile enlargement (Indumathi et al., 2007). Hence, it has been revealed that Van Wyk and Grumbach syndrome is characterized by the combination of juvenile hypothyroidism, delayed bone age, and precocious puberty with several cases found in girls (Baranowski and Högler, 2011; Rastogi et al., 2011; Panico et al., 2007; Browne et al., 2008) and also in boys (Castro-Magaña et al., 1988; Esen and Demirel, 2011). The imbalance in the hormonal changes among the patients of Van Wyk Grumbach syndrome is represented by an increased level of prolactin, presence of estradiol, thyroid-stimulating hormone (TSH) with the combination of decreased level of free thyroxine (Zhang et al., 2017). The response of prepuberty among the patients of VWGS has been considered to be isosexual and arbitrated by an increased level of TSH that shows activity of follicle-stimulating hormone (FSH) that results in the induction of follicle-stimulating hormonal effect by the receptors (Indumathi et al., 2007). Hence, there is a need for evolving possible treatment among

the patients of VWGS by involving thyroid hormone replacement as major step in the treatment. This management approach concerning patients' treatment of VWGS will be effective in eradicating the symptoms of VWGS and improving the normal growth efficacy rate among pediatrics.

The present article reviews the complexities of Van-Wyk Grumbach Syndrome with prolonged hypothyroidism among pediatrics. Its correlation with each other will be explained by involving the existing literature that will help in better understanding of implementing the review paper. Also, the major consequences and its possible treatment among the pediatrics will be implicated while representing different case studies of Van-Wyk Grumbach Syndrome with prolonged hypothyroidism.

Literature Review

Van-Wyk Grumbach Syndrome among pediatrics

Van Wyk and Grumbach (1960) explained the syndrome by representing its characters in the form of breast development, uterine bleeding and multicystic ovaries in females, and testicular enlargement with minimal penile enlargement in the presence of long-standing primary hypothyroidism. Several case reports of Van-Wyk Grumbach Syndrome (VWGS) have been studies that represent the characterization, differences, imaging techniques, and biochemical changes among the patients. It has been observed that girls in pediatrics have shown the presence of classical hypothyroid appearance, delayed growth, follicle-stimulating hormone (FSH)-mediated secondary sexual characteristics with breast development with or without galactorrhoea, uterine bleeding with the absence of pubic or axillary hair development (Baranowski and Högler, 2011). The occurrence of hypothyroidism mainly evolves from the destruction of autoimmune thyroid and all the externalization reverts after management with replacement of thyroid hormone. This unusual mechanism occurs due to the initiation of structural homology between different glycoprotein hormones acting through G-protein-coupled receptors (Van Wyk and Grumbach, 1960). Precocious puberty is known to be the major characterization issue among pediatrics. The correlation of hypothyroidism with precocious puberty, results in hormonal overlapping in the hypothalamic-pituitary-ovarian axis which was first explained in 1960. The conduction of laboratory analysis has revealed an increased level of Thyroid Stimulating Syndrome (TSH) and Follicle Stimulating Hormone (FSH), Prolactin, and 17-β estradiol with suppressed Luteinising Hormone (LH). The precocious puberty observed among the pediatrics in VWGS is mainly isosexual and incomplete. The girls have been characterized by the appearance of the situation with irregular menstrual bleeding along with uncommon enlargement of breasts and galactorrhoea (Gordon et al., 1997). Lack of pubic hair among them has been also characterized as a major symptom for VWGS. The boys have been characterized as macroorchidism with the absence of axillary hair. Hence, it has been revealed that autoimmune thyroiditis has been considered the most common cause of hypothyroidism among the pediatrics of VWGS. the prevalence of VWGS among pediatrics constitutes approximately 2.5% of the total population that is 1.3%-4% among the children across the globe (Pant and Baral, 2019).

The hypothalamic-pituitary-gonadal axis with activation of gonadotropin-releasing hormone (GnRH) results in the occurrence of central precocious puberty (CPP). Also, the occurrence of pseudo precocious puberty along with GnRH-independent sexual precocity has been

observed among the pediatrics suffering from VWGS with hypothyroidism (Ashraf et al., 2015). The occurrence of incomplete isosexual precocity is considered as one of the major consequences of premature sex hormone secretion with an increasing level, iatrogenic exposure of gonadal steroids, the occurrence of juvenile hypothyroidism either in boys and girls, and, in boys, rarely hCG- or LH-secreting tumors. Hence the characterization of Van Wyk-Grumbach syndrome (VWGS) is represented by juvenile hypothyroidism, delayed bone age, and isosexual precocious puberty with a reversal to a prepubertal state following thyroid hormone replacement therapy (Van Wyk and Grumbach, 1960).

Impact of prolonged hypothyroidism among pediatrics

The hormones in the thyroid gland have been considered important for the growth and neurologic development of children. The thyroid gland in the body mainly acquires its shape from 7 weeks of the gestation period and the production of thyroid hormone (T4, thyroxine) is initiated at the gestation period of 12 weeks. The dysfunction Ing of the thyroid among neonates, infants, and children has led to a major impact on development. Therefore, the major aim for the treatment of thyroid deficiency involves the assurance of normal growth and prevention from developmental delay.

Hypothyroidism has been considered as the condition in which the thyroid gland, is located in the front of the neck is not capable of producing enough thyroid hormones that basically work for monitoring the overall function and metabolism of the body. The autoimmune disorder is a major cause for hypothyroidism, also known as Hashimoto's disease involves the condition of the body where the immune system causes the destruction of its own thyroid gland due to some mistake. Hence, among adolescents this condition causes underactive thyroid when compared with other causes. Hypothyroidism also develops in the adult phase of life as its incidence tends to increase as per the age of the individuals. Congenital hypothyroidism tends to cause a major impact among children and newborns.

Hypothyroidism can be characterized by several signs and symptoms. It mainly presents the broader symptoms of subclinical hypothyroidism. The occurrence of congenital hypothyroidism has been known as the most preventable cause of mental retardation and is often diagnosed with simple and cost-effective biochemical tests in the neonatal period. The diagnosis of congenital hypothyroidism among children has a major impact on the skeleton and bone maturation along with affecting the central nervous system in the form of mental development (Moran et al., 2013). The increased level of TSH results in the development of abnormal skeletal while suppressing the growth of the children (Endo and Kobayashi, 2013). Hence, it is clear from the above studies that hypothyroidism has a major impact on the normal growth rate of children and their developmental functions within their bodies. This majorly involves the dysfunction of sexual development among children. Also, hypothyroidism results in decreasing the levels of red blood cells in the blood causing anemia, decreasing the body temperature, heart failure, and issues in the nervous system, mainly involving lower IQ and difficulties with motor skills.

The major function of the thyroid gland involves the secretion of thyroxine (T4) and triiodo thyroxine (T3) and the pituitary thyrotropin are responsible for regulating the production of these thyroid hormones. The defects of the autosomal chromosomes in the

organification of iodine (thyroid hormone synthesis) and dysfunction of the enzymatic reactions of T4 synthesis and release result in the occurrence of hypothyroidism. Acquired hypothyroidism has been found to be more common among children and adults by affecting the autoimmune system of the body. The prevalence of congenital hypothyroidism has been found to affect 1 per 4000 newborns across the globe. Hypothalamic or pituitary insufficiency evolves from tertiary hypothyroidism that affects 1 per 60,000-140,000 newborns across the globe. The acquired hypothyroidism includes the prevalence of 10% of young females who have been observed with the occurrence of autoimmune thyroid disease, mainly considered as chronic lymphocytic thyroiditis (CLT). These types of patients are mainly prone to the risk of acquired hypothyroidism when compared with the general population. The prolonged occurrence of congenital hypothyroidism among in fants results in growth failure and lack of development of the central nervous system that further evolves cretinism with a developmental cognitive delay while hypothyroidism among children results in growth failure along with decreased metabolic functions and impaired memory.

Hypothyroidism affects both males and females with the prevalence of ratio in terms of 2:1 (female to male ratio). Also, chronic lymphocytic thyroiditis tends to occur in the ratio of 4:1 in terms of female-to-male preponderance in childhood. The occurrence of congenital hypothyroidism is observed among the individuals at the time of birth with the development of symptoms for several months (Chung, 2014). The prediction of occurrence of symptoms at appropriate age group among children suffering from hypothyroidism has been ineffective due to the initial increase in TSH level which results in overcoming the insufficiency of the thyroid gland. The occurrence of chronic lymphocytic thyroiditis has been found among the adolescent age group at any time in their phase of life.

Correlation between complexities of Van-Wyk Grumbach Syndrome with prolonged hypothyroidism among pediatrics

The prolonged hypothyroidism among the children results in decreasing the pubertal and growth delay along with the occurrence of precocious puberty and delayed bone age in some exceptional cases. The Van-Wyk Grumbach Syndrome consists of hypothyroidism and precocious puberty which was initially explored in 1905 and then explained in 1960. Cases for the occurrence of VWGS have been reported among the prepubertal girls with major symptoms of enlargement of breast showing abnormal condition, vaginal bleeding, and cystic ovaries, but in boys, it has been found to show rare cases with a testicular enlargement (Nebesio and Eugster, 2007). Different studies have been represented for describing the paradoxical precocious puberty showing correlation with prolonged hypothyroidism. Van Wyk and Grumbach (1960) have revealed the mechanism showing overproduction of gonadotropins and other heterologous hormones from the pituitary hypothalamic axis including estradiol. The studies have shown a demonstration of in vitro experiments concerning the stimulation of TSH that regulates weakly with FSH receptors without appropriate LH receptors being stimulated that reveals the pre- pubertal level to below concerning LH. The increasing level of TSH results in gonadal stimulation and precocious sexual changes (Bhansali et al., 2000). The cautious secretion of the high level of thyrotropin-releasing hormone (TRH) revives the secretion of FSH (Chemaitilly et al., 2003). The hypothyroidism in boys

shows a correlation with the isosexual and incomplete precocious puberty having testicular enlargement without virilization (Evers and Rolland, 1981). The severity of hypothyroidism in males results in over proliferation of Sertoli cells which causes enlargement of testicles and a higher level of testicular damage (Jannini et al., 1995).

Van Wyk-Grumbach syndrome is concerned with prolonged hypothyroidism among pediatrics showing a correlation with the pubertal phase. Van Wyk-Grumbach syndrome occurs as prolonged hypothyroidism is not treated for a longer duration. The complex interactions in Van Wyck-Grumbach syndrome occur in the hypothalamic-pituitary axis. The studies have shown the functionality of recombinant TSH which interacts with FSH receptors for assessing the functions of adenylyl cyclase (Anasti et al., 1995). The higher level of FSH results in ovarian hyperstimulation while evolving the characterization of multi cystic ovaries of this syndrome (Sharma et al., 2006). The patients suffering from VWGS consist of a higher level of FSH. Lack of axillary and pubic growth facilitates the non-stimulation of adrenarche that describes lack of development at puberty in the case of VWGS. The lack of thyroid hormones among children results in causing pituitary hyperplasia which tends to occur secondary to thyrotroph hyperplasia (Passeri et al., 2011). The prolonged hypothyroidism among children represents limitations in growth rate and more weight gain with moderate to severe obesity. The prolonged hypothyroidism also includes the occurrence of macrocytic anemia due to reduced aging of bone marrow showing less functions (Marzuillo et al., 2016). The decreased metabolic demand, dietary deficiency, menorrhagia, and autoimmune cluster evolves from reduced hematopoiesis showing mechanism of anemia among hypothyroid patients (Chu, 1981).

The occurrence of acquired hypothyroidism among pediatrics has been known to be the common endocrine disorder and its early diagnosis results in preventing the complexities of VWGS. The delay in puberty is considered the major consequence of VWGS with the prevalence of prolonged hypothyroidism. But as it can be identified at the initial phase due to the appearance of pubertal symptoms, it can be improved. The symptoms of sexual precocity with breast development in girls and testicular enlargement in boys have been observed due to prolonged hypothyroidism showing a correlation of VWGS.

Case studies showing the correlation between Van-Wyk Grumbach Syndrome with prolonged hypothyroidism

Several cases of Van-Wyk Grumbach Syndrome with prolonged hypothyroidism have been observed and described in the existing literature. Precocious puberty has been considered as the major consequence which is related to the delayed bone age and is also known to be isosexual and incomplete. The resolution on same aspect is only done after the initiation of thyroid hormone replacement therapy. The existing literature has evolved illustration of different cases by several authors regarding the pediatric cases with an appropriate exploration of Van- Wyk Grumbach Syndrome with prolonged hypothyroidism.

The case of 11 years and 7 months old female child was considered by one of the pediatric surgeons showing progressive abdominal distension for the past 2 years along with the appearance of symptoms of dull aching pain, decreased appetite, and lassitude (Reddy et al., 2018). She had vomited for 3 days before the

presentation. After carrying out a specific examination for the same, adynamic ileus was observed. The X-ray revealed multiple air-fluid levels representing intestinal obstruction and multiloculated cystic mass was observed after ultrasonography. Hence, the occurrence of ovarian mass was found by the sonologist as both ovaries were not seen separately. Also, the slow growth rate and irregular scanty vaginal spotting were observed in the patient. The observation of the sexual maturity rate of the girl was found to be four for breast development and one for pubic hair. Hence, the appearance of some of the major symptoms such as constipation, dry skin, slow growth, weakness, and adynamic ileus have evolved the suspicion of hypothyroidism. Thyroid profiling was also done confirming the severity of hypothyroidism due to the presence of autoimmune thyroiditis. Hence, the presence of autoimmune thyroiditis and ovarian mass together involved the diagnosis approach for Van- Wyk Grumbach Syndrome. Also, more investigation regarding pubertal status was carried out that revealed the prepubertal levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH) but pubertal levels of estradiol. The delaying of the bone age was also observed in the patient. Therefore, the presence of hypothyroidism, isosexual precocious puberty, ovarian mass, and pituitary adenoma revealed appearance of VWGS. Therefore, treatment with thyroxin and metformin showed efficacy in monitoring the levels of TSH along with improvement in the ovarian cyst.

Another case of an 11-year-old female was reported to the neurologist as she suffered from the frequent occurrence of headaches (Durbin et al., 2011). The MRI for the same was conducted revealing the appearances of sellar mass with a differential diagnosis including macroadenoma or craniopharyngioma. Pediatric endocrinology was suggested for the resolution of this lesion. Also, severe abdominal pain was observed in her after two weeks of lesion occurrence in her brain. Computed tomography (CT) imaging of the abdomen revealed the appearance of bilateral ovarian masses. The gynecological tests were done and the Tanner stage III revealed the breast enlargement and absence of axillary hair in pubic hair. The complexities in the masses of the ovary resulted in the occurrence of ovarian tumor markers. Also, the levels of estradiol, cancer antigen 125 (CA-125), lactate dehydrogenase (LDH), inhibin-A, and alpha- fetoprotein (AFP) were increased. The abnormal functioning of the thyroid was observed with the increased level of thyroid-stimulating hormone (TSH) and thyroxine (T4). This case showed hypothyroidism as bilateral ovarian masses were observed, but did not exhibit precocious puberty. Pubic hair and breasts were observed at Tanner Stage III. The patient had experienced one menstrual cycle at age 11, and was considered to be precocious puberty secondary to her pathologically elevated estrogen levels, given that menses ceased once she was treated. It further showed a unique case of Van Wyk and Grumbach syndrome as the appearance of abnormal tumor markers has been observed. Also, the existing literature has revealed that there is the possibility of having unilateral ovarian mass in young women and still can be seen with the occurrence of Van Wyk Grumbach syndrome (Browne et al., 2008).

One of the cases of 12 years old male child from Asia was reported with progressive weight gain, short stature, cold intolerance, constipation, and poor school achievement with low average IQ (Omran et al., 2012). The appearance of myxedematous appearance in facial features, absence of axillary and pubic hair, the bilateral

testicular volume of 14 ml in size was observed. Delayed bone age was observed by x-ray examination. MRI brain represented diffuse enlargement of the pituitary gland, with no limitation in the lesion size. The laboratory testings represented the increased level of TSH and decreased level of T3 and T$ with ATG. Also, the appearance of Hashimoto's thyroiditis was reported showing major complexities with hypothyroidism, delayed bone age, and testicular enlargement. Hence, mentioned symptoms have been associated with the occurrence of VWGS along with showing association with pericardial effusion, and pituitary hyperplasia.

Another study of 12 years old female was reported with weight gain from the last 2 years along with abdominal pain from the last 1 year (Joshi and Matti, 2014). Her parents were non- consanguineous. No appropriate symptoms of hypothyroidism were observed in her case. Tanner's staging was B5 and P4 for breast and pubic hair. Microcytic hypochromic anemia was reported after investigations. The radiological investigations have revealed the delayed bone age and ultrasonography have shown the enlargement of multi cystic ovaries. These symptoms have revealed the presence of hypothyroidism in the patient with precocious puberty which represents the diagnosis of Van Wyk-Grumbach syndrome. The weight gain and insulin resistance reveal the appearance of polycystic ovarian disease with prolonged hypothyroidism in the patient. Hence all these symptoms show the appearance of Van Wyk-Grumbach syndrome with prolonged hypothyroidism.

Treatment for preventing Van-Wyk Grumbach Syndrome and prolonged hypothyroidism

Van-Wyk Grumbach Syndrome is mainly associated with the prolonged occurrence of hypothyroidism along with the appearance of precocious puberty and massive ovarian cysts which has been already explained since 1905 and gained its importance in 1960. The clinical and biochemical findings have been carried on as the patients of Van-Wyk Grumbach Syndrome with prolonged hypothyroidism are treated with appropriate thyroid replacement therapy. This syndrome has been conisdered as a major challenging approach for its treatment as it results in pubertal and growth delay. The treatment for VWGS with prolonged hypothyroidism is mainly initiated by replacement therapy with thyroid hormone. The thyroid replacement therapy results in a relapse of all clinical symptoms and signs. The need for excluding the signs and symptoms of hypothyroidism is first excluded. The resolution of ovarian cysts is carried out by initiating hormonal treatment. One of the recent approaches for the treatment of VWGS involves the implementation of the direct action of TSH on FSH receptors (Anasti et al., 1995). The circulation of the increased level of TSH has been observed in all the patients of VWGS. The thyroxine hormone replacements help in the resolution of endocrine abnormalities and the large cysts in the ovaries tend to disappear effectively. Surgeries are only recommended in the major complexities of ovarian cyst including the formation of torsion.

Radiological investigations have played an important role in identifying the clinical and imaging features of VWGS which evolves the better understanding of showing the association between juvenile hypothyroidism and cystic ovarian enlargement, for avoiding unnecessary surgery. The TSH levels have been found to be increased in VWGS patients and the sexual precocity is directly associated with the increased level of TSH. The circulation of high TSH levels directs acts with the FSH receptors that are considered as the

mediator of precocity (Anasti et al., 1995). The use of recombinant tools helps in representing the interaction of human TSH with FSH receptors for stimulating adenylyl cyclase activity. Approximately 1000-fold greater than hFSH dose of human recombinant TSH evolved a dose-dependent cyclic AMP response in Chinese hamster ovary (COS-7) cells which was transfected with human FSH receptor. It low FSH-like activity of TSH can be clinically significant at very high concentrations of TSH in the case of hypothyroidism.

Thyroid replacement therapy utilizes the replacement of an appropriate amount of hormone from the thyroid gland through the use of medication. Thyroxine is the medication mainly used for this therapy. It is the form of oral medication that is taken by the patients for increasing the level of thyroid hormone while balancing the other thyroid hormones within the body. This therapy is capable of replicating the normal functioning of the thyroid. Blood testing has been used for recommending the appropriate dosage of thyroid hormone as per the level of hormones required by the patients' body. The results of the blood tests help in estimating the level of thyroid hormones in the blood along with the release of thyroid-stimulating hormone (TSH) by the pituitary gland. A high TSH level represents the presence of underactive thyroid and the thyroid hormone level needs to be elevated.

Research Gap

The overview of Van-Wyk Grumbach Syndrome among pediatrics has been implicated in this paper. The prevalence of Van-Wyk Grumbach Syndrome among pediatrics has been discussed for analyzing its complexities in the population. The important information on prolonged hypothyroidism and its impact and consequences among pediatrics has been discussed here. All these sections explain the complexities, consequences, and impact affecting the health of pediatrics and the emergence of Van-Wyk Grumbach Syndrome among them. Also, the existing literature has evolved that association of Van-Wyk Grumbach Syndrome with prolonged hypothyroidism. Therefore, this review has shown relevancy and provided a discussion on the update showing the correlation between the complexities of Van-Wyk Grumbach Syndrome with prolonged hypothyroidism among pediatrics. The case studies concerning this correlation have been implicated in this paper. The research gap involves the absence of any particular interventions or treatment that would be effective in reducing the impact of prolonged hypothyroidism among pediatrics in VWGS patients. Therefore, the present study has helped in intervening the treatment for VWGS with prolonged hypothyroidism in the form of precautionary measures, related therapies, interventions, and medication, and the involvement of existing literature has helped in analyzing the reasons behind the correlation of Van-Wyk Grumbach Syndrome with prolonged hypothyroidism that further helps in filling the gap.

Findings and Discussions

Case representation: Prolonged hypothyroidism in pediatrics has been reported with continuity of delayed growth rate and puberty. In some cases, prolonged hypothyroidism is connected with precocious puberty. The Present study has involved the case representing the Van Wyk-Grumbach syndrome among the children. The case involves the female patient belonging to the age group of 4 years showing a history of vaginal bleeding for 10 days along with reduced physical activity, lack of height growth, abdominal distension, and poor scholastic performance from the last 12 months. The previous

symptoms of the female child represent her activities to be playful while she was capable of participating in all other normal activities appropriately. Her birth history represented her birth weight to be 2.70 kg and she had no history concerning her health deterioration involving no headaches, visual disturbances, vomiting, head trauma, frequent illnesses, or hospitalization. Menstrual bleeding was observed in her for 10 days with prior history of serosanguinous discharges per vagina intermittently since last 2 months. Her vital signs were normal for age. She also represented dull, had pallor, and was hypotonic with coarse facial features. Her puberty examination test was conducted that showed the results with the occurrence of Tanner 2 breasts and pubic hair. The absence of axillary hair and abnormal body odor was also observed in the female child patient. The external genitalia was found to be normal with a small amount of blood being observed at the vaginal orifice during the puberty examination. Her weight was on the 15th centile and her height was less than 3 rd centile as per IAP growth charts. Another systemic examination was unremarkable apart from the abdomen looking protuberant with a lordotic stance.

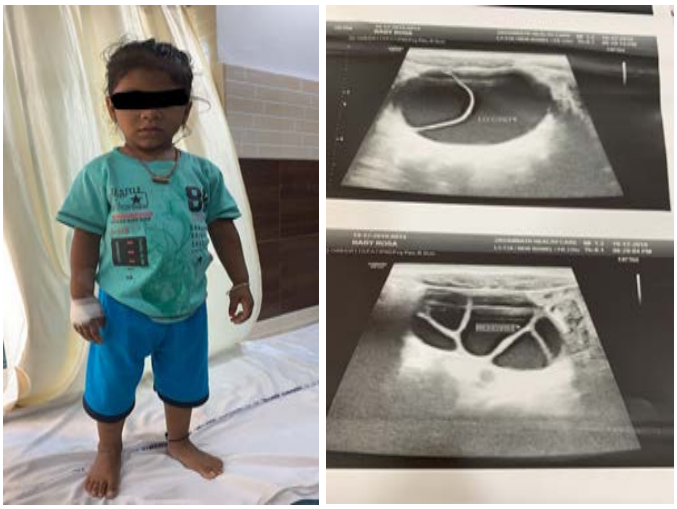

Figure 1: 4 year female child.

Fundus examination was also conducted in the female child that represented normal report while other examinations revealed the occurrence of normocytic normochromic anemia with a hemoglobin of 8.7g% along with TLC to be estimated as 6000cu mm/l with a normal differential count. The reports of X-ray bone age showed delayed bone age of 2 years. Thyroid hormone analysis showed free T3 4.01pg/ml, free T4 0.9ng/dl, TSH >100micro IU/ml, serum T3 30.19ng/dl, serum T4<0.42 micro g/dl. USG of the abdomen represented bilateral loculated benign ovarian cysts with measurements of 4.7 x2.6cm of the right ovary and 4.8 cm x 3.4 cm of the left ovary. The USG reports of neck represented hypoplastic thyroid gland with the presence of few small cysts in both lobes. Her LH level was prepubertal at < 0.02 mIU/mL. FSH level was 12.67 mIU/mL and estradiol levels were elevated at 151.0 pg/mL. Hence, these examined reports evolved the diagnosis for Van Wyk-Grumbach syndrome with the initiation of dosage of levothyroxine at 50 micrograms per day. Her follow-up was conducted regularly that eventually improved her TSH level with 9.2 mIU/mL along with observation of normalization of her thyroxine level to 01.6 ng/dL within 2 months of initiation of treatment. The examination of her mother has also conducted that represented resolution of vaginal bleeding and remarkable improvement in her energy level and school performance after 6 months.

Discussion

Many theories have been explained for justifying the correlation of Van Wyk Grumbach Syndrome with prolonged hypothyroidism. Also, appropriate treatment of this syndrome has been implicated in different studies. Thyroid replacement theory is one of the most effective treatments that utilize the use of thyroid

hormone for maintaining the balance within the patients' body in case of hypothyroidism. The thyroid hormones are usually recommended as an oral medication to maintain the level of hormones within the body. In this case, hypothyroidism occurred due to the hypoplastic thyroid gland presenting with both the typical features like lethargy, short stature, constipation, and also atypical features involving precocious puberty and ovarian cysts.

The laboratory examinations of these patients have revealed severe, uncompensated hypothyroidism with a high level of TSH. Also, FSH and LH have been found to be normal or prepubertal among affected patients. The present case has represented the increased level of prolactin and estrogen that integrates with FSH receptors as TSH and FSH share a common beta-subunit resulting in precocious puberty among affected patients. The occurrence of pituitary hyperplasia was observed in the present case which is correlated with the long-standing thyrotrope cell hyperplasia due to low circulating thyroid hormones responsible for decreasing the negative feedback mechanism. Also, the presence of hyperprolactinemia in this case clearly represented the case of VWGS. Ultrasound of the abdomen showed the presence of bilateral ovarian cysts in the present case. The existing literature has revealed that most of the patients of VWGS bilateral rather than unilateral masses which can present as pain abdomen due to torsion in some cases (Takeuchi et al., 2004; Campaner et al., 2006). Also, the fact regarding multi cystic ovaries revealed the increased level of circulating gonadotropins (Waghmare et al., 2016). The representation of delayed bone age among patients with precocious puberty has been considered as one of the major symptoms for diagnosing VWGS. The diagnosis of VWGS has been done by identification of specific characteristics with clinical features, initial knowledge regarding VWGS, and appropriate confirmatory endocrine laboratory examinations which are considered as an important aspect towards avoiding of risk of surgeries and eliminating the occurrence of any future disease. The present case mentioned in this study has evolved the significance in three major aspects involving the identification of growth faltering with regular plotting of height with consideration of thyroid screening in the early phase, the importance of identifying the atypical characteristics of hypothyroidism for avoiding any major risk of surgeries, and importance of identifying the late phase of hypothyroidism that mainly occurs due to hypoplastic thyroid or autoimmune thyroiditis which is presented after infancy but can show efficacy on growth, development and overall health of the child.

Conclusion

VGWS has been considered an atypical endocrinal disorder that majorly affects pediatrics by limiting their growth rate with prolonged hypothyroidism and delaying their bone age. Hypothyroidism in this syndrome has been included and resented in different cases with several subtle signs. Precocious puberty is mainly evolved only during the severe cases of prolonged hypothyroidism. The sexual precocity has been considered to be isosexual which is represented by breast enlargement, multi cystic ovaries, and menstrual bleeding in girls while in boys it is represented as testicular enlargement along with minimal penile enlargement. The appropriate knowledge of various types of cases of VWGS with prolonged hypothyroidism along with its correlations has been helpful in the early diagnosis of these types of conditions with related signs

and symptoms. It further recommends taking preventive measures along with undertaking the important investigations, treatments, and surgical explorations if needed as per the case severity.

References

1. Van Wyk, J.J. and Grumbach, M.M., 1960. Syndrome of precocious menstruation and galactorrhea in juvenile hypothyroidism: an example of hormonal overlap in pituitary feedback. The Journal of Pediatrics, 57(3), pp.416-435.
2. Rastogi, A., Bhadada, S.K. and Bhansali, A., 2011. An unusual presentation of a usual disorder: Van Wyk-Grumbach syndrome. Indian journal of endocrinology and metabolism, 15(Suppl2), p.S141.
3. Hunold, A., Alzen, G., Wudy, S.A., Bluetters< Sawatzki, R., Landmann, E., Reiter, A. and Wagner, H.J., 2009. Ovarian tumor in a 12< year old female with severe hypothyroidism: A case of Van Wyk and Grumbach syndrome. Pediatric blood & cancer, 52(5), pp.677-679.
4. Panico, A., Lupoli, G.A., Fonderico, F., Colarusso, S., Marciello, F., Poggiano, M.R., Del Prete, M., Magliulo, R., Iervolino, P. and Lupoli, G., 2007. Multiple ovarian cysts in a young girl with severe hypothyroidism. Thyroid, 17(12), pp.1289-1293.
5. Kubota, K., Itho, M., Kishi, H., Igarashi, S. and Minegishi, T., 2008. Primary hypothyroidism presenting as multiple ovarian cysts in an adult woman: a case report. Gynecological Endocrinology, 24(10), pp.586-589.
6. Sanjeevaiah, A.R., Sanjay, S., Deepak, T., Sharada, A. and Srikanta, S.S., 2007. Precocious puberty and large multicystic ovaries in young girls with primary hypothyroidism. Endocrine Practice, 13(6), pp.652-655.
7. Mohsin, F., Nahar, N., Azad, K. and Nahar, J., 2007. Vaginal bleeding with multicystic ovaries and a pituitary mass in a child with severe hypothyroidism. Mymensingh medical journal: MMJ, 16(2 Suppl), pp. S60-62.
8. Browne, L.P., Boswell, H.B., Crotty, E.J., O'Hara, S.M., Birkemeier, K.L. and Guillerman, R.P., 2008. Van Wyk and Grumbach syndrome revisited: imaging and clinical findings in pre-and postpubertal girls. Pediatric radiology, 38(5), pp.538-542.
9. Singh, B.M., Ammini, A.C. and Kriplani, A., 2005. Ovarian cyst in juvenile hypothyroidism. Archives of gynecology and obstetrics, 271(3), pp.263-264.
10. Campaner, A.B., Scapinelli, A., Machado, R.O., Dos Santos, R.E., Beznos, G.W. and Aoki, T., 2006. Primary hypothyroidism presenting as ovarian tumor and precocious puberty in a prepubertal girl. Gynecological endocrinology, 22(7), pp.395-398.
11. Takeuchi, K., Deguchi, M., Takeshima, Y. and Maruo, T., 2004. A case of multiple ovarian cysts in a prepubertal girl with severe hypothyroidism due to autoimmune thyroiditis. International Journal of Gynecologic Cancer, 14(3).
12. Indumathi, C.K., Bantwal, G. and Patil, M., 2007. Primary hypothyroidism with precocious puberty and bilateral cystic ovaries. The Indian Journal of Pediatrics, 74(8), pp.781-783.
13. Baranowski, E. and Högler, W., 2011. An unusual presentation of acquired hypothyroidism: the Van Wyk-Grumbach syndrome. European journal of endocrinology, 166(3), pp.537-542.
14. Rastogi, A., Bhadada, S.K. and Bhansali, A., 2011. An unusual presentation of a usual disorder: Van Wyk-Grumbach syndrome. Indian journal of endocrinology and metabolism, 15(Suppl2), p.S141.

15. Castro-Magaña, M., Angulo, M., Cañas, A., Sharp, A. and Fuentes, B., 1988. Hypothalamic-pituitary gonadal axis in boys with primary hypothyroidism and macroorchidism. The Journal of pediatrics, 112(3), pp.397-402.

16. Esen, I. and Demirel, F., 2011. Hypothyroidism-associated testicular enlargement: is it a form of precocious puberty or not? A case report. The Turkish journal of pediatrics, 53(2), p.210.

17. Zhang, S., Yang, J., Zheng, R., Jiang, L., Wei, Y. and Liu, G., 2017. Van Wyk< Grumbach syndrome in a male pediatric patient: A rare case report and literature review. Experimental and therapeutic medicine, 13(3), pp.1151-1154.

18. Gordon, C. M., Austin, D. J., Radovick, S., & Laufer, M. R. (1997). Primary hypothyroidism presenting as severe vaginal bleeding in a prepubertal girl. Journal of pediatric and adolescent gynecology, 10(1), 35-38.

19. Pant, V. and Baral, S., 2019. Van Wyk Grumbach syndrome with precocious puberty and ovarian cysts: Value of thyroid function tests. Journal of Pediatric Surgery Case Reports, 43, pp.32-34.

20. Ashraf, F., Nandi, E. R., Akhter, P., & Yasmin, N. (2015). Van Wyk Grumbach Syndrome-A rare case report. Journal of Current and Advance Medical Research, 2(1), 24-27.

21. Moran, C., Schoen makers, N., Agostini, M., Schoen makers, E., Offiah, A., Kydd, A., Kahaly, G., Mohr-Kahaly, S., Rajanayagam, O., Lyons, G. and Wareham, N., 2013. An adult female with resistance to thyroid hormone mediated by defective thyroid hormone receptor α. The Journal of Clinical Endocrinology & Metabolism, 98(11), pp.4254-4261.

22. Endo, T. and Kobayashi, T., 2013. Excess TSH causes abnormal skeletal development in young mice with hypothyroidism via suppressive effects on the growth plate. American Journal of physiology-endocrinology and metabolism, 305(5), pp. E660-E666.

23. Chung, H.R., 2014. Adrenal and thyroid function in the fetus and preterm infant. Korean journal of pediatrics, 57(10), p.425.

24. Nebesio, T.D. and Eugster, E.A., 2007. Current concepts in normal and abnormal puberty. Current problems in pediatric and adolescent health care, 37(2), pp.50-72.

25. Bhansali, A., Kashyap, A., Lodha, S., Kotwal, N., Ganapathi, B., Mittal, B. and Dash, R., 2000. Isosexual precocity: uncommon presentation of a common disorder. Postgraduate medical journal, 76(893), p.177.

26. Chemaitilly, W., Thalassinos, C., Emond, S. and Thibaud, E., 2003. Metrorrhagia and precocious puberty revealing primary hypothyroidism in a child with Down's syndrome. Archives of disease in childhood, 88(4), pp.330-331.

27. Evers, J.L.H. and Rolland, R., 1981. Primary hypothyroidism and ovarian activity evidence for an overlap in the synthesis of pituitary glycoproteins: case report. BJOG: An International Journal of Obstetrics & Gynaecology, 88(2), pp.195-202.

28. Jannini, E.A., Ulisse, S. and D'Armiento, M., 1995. Thyroid hormone and male gonadal function. Endocrine reviews, 16(4), pp.443-459.

29. Anasti, J.N., Flack, M.R., Froehlich, J., Nelson, L.M. and Nisula, B.C., 1995. A potential novel mechanism for precocious puberty in juvenile hypothyroidism. The Journal of Clinical Endocrinology & Metabolism, 80(1), pp.276-279.

30. Sharma, Y., Bajpai, A., Mittal, S., Kabra, M. and Menon, P.S.N., 2006. Ovarian cysts in young girls with hypothyroidism: follow-up and effect of treatment. Journal of Pediatric Endocrinology and Metabolism, 19(7), pp.895-900.

31. Passeri, E., Tufano, A., Locatelli, M., Lania, A.G., Ambrosi, B. and Corbetta, S., 2011. Large pituitary hyperplasia in severe primary hypothyroidism. The Journal of Clinical Endocrinology & Metabolism, 96(1), pp.22-23.

32. Marzuillo, P., Grandone, A., Perrotta, S., Ruggiero, L., Capristo, C., Luongo, C., Del Giudice, E.M. and Perrone, L., 2016. Very early onset of autoimmune thyroiditis in a toddler with severe hypothyroidism presentation: a case report. Italian journal of pediatrics, 42(1), pp.1-5.

33. Chu, J.Y., Monteleone, J.A., Peden, V.H., Graviss, E.R. and Vernava, A.M., 1981. Anemia in children and adolescents with hypothyroidism. Clinical pediatrics, 20(11), pp.696-699.

34. Reddy, P., Tiwari, K., Kulkarni, A., Parikh, K. and Khubchandani, R., 2018. Van Wyk Grumbach syndrome: a rare consequence of hypothyroidism. The Indian Journal of Pediatrics, 85(11), pp.1028-1030.

35. Durbin, K.L., Diaz-Montes, T. and Loveless, M.B., 2011. Van Wyk and Grumbach syndrome: an unusual case and review of the literature. Journal of pediatric and adolescent gynecology, 24(4), pp. e93-e96.

36. Omran, A., Peng, J., Shrestha, B., Ashhab, M.U. and Yin, F., 2012. Male child with Van Wyk-Grumbach's syndrome and other complications of long-standing primary hypothyroidism: a case report. Case reports in pediatrics, 2012.

37. Joshi, S.N. and Matti, M., 2014. Van Wyk-grumbach syndrome: a rare result of prolonged hypothyroidism.

38. Kendle, F.W., 1905. Case of precocious puberty in a female cretin. British medical journal, 1(2301), p.246.

39. Riddles Berger Jr, M.M., Kuhn, J.P. and Mun Schauer, R.W., 1981. The association of juvenile hypothyroidism and cystic ovaries. Radiology, 139(1), pp.77-80.

40. Desai, M.P., Mehta, R.U., Choksi, C.S. and Colaco, M.P., 1996. Pituitary enlargement on magnetic resonance imaging in congenital hypothyroidism. Archives of pediatrics & adolescent medicine, 150(6), pp.623-628.

41. Philip, R., Saran, S., Gutch, M. and Gupta, K.K., 2013. An unusual case of precocious puberty and macroorchidism. Thyroid Research and Practice, 10(1), p.29.

42. Takeuchi, K., Deguchi, M., Takeshima, Y., & Maruo, T. (2004). A case of multiple ovarian cysts in a prepubertal girl with severe hypothyroidism due to autoimmune thyroiditis. International Journal of Gynecologic Cancer, 14(3).

43. Campaner, A. B., Scapinelli, A., Machado, R. O., Dos Santos, R. E., Beznos, G. W., & Aoki, T. (2006). Primary hypothyroidism presenting as ovarian tumor and precocious puberty in a prepubertal girl. Gynecological endocrinology, 22(7), 395-398.

44. Waghmare, Mukta & Shah, Hemanshi & Kumbhar, Vikrant & Jayaswal, Shalika. (2016). Van Wyk Grumbach syndrome - a rare association of a common prepubertal condition.