Annals of Case Reports & Reviews

Case Report

doi: 10.39127/2574-5747/ACRR:1000341

Al Jabri A, et al. Annal Cas Rep Rev: ACRR-341

A Rare Association of Mauriac Syndrome and Van-Wyk Grumbach Syndrome Found in A Young Saudi Girl: A Case Report and Brief Literature Review

Aida Al Jabri*[1], Aesha Al Joher[2], Mohamed Tahar Yacoubi[3]

[1]Pediatric Endocrinologist, Department of Pediatrics, AlMoosa Specialist Hospital, Al-Ahsa, Saudi Arabia. In charge of pediatric department, Director, Pediatric residency program

[2]Pediatrics resident, Department of Pediatrics, King Abdulaziz Hospital, Ministry of the National Guard-Health Affairs, Al-Ahsa, Saudi Arabia

[3]Histopathology consultant, Department of Laboratory, King Abdulaziz Hospital, Ministry of the National Guard-Health Affairs, Al-Ahsa, Saudi Arabia

***Corresponding author:** Aida Al Jabri, Pediatric Endocrinologist, Department of Pediatrics, AlMoosa Specialist Hospital, Al-Ahsa, Saudi Arabia. In charge of pediatric department Director, Pediatric residency program. Email: dr_aida_s@hotmail.com

Citation: Al Jabri A, Al Joher A, Yacoubi MT (2022) A Rare Association of Mauriac Syndrome and Van-Wyk Grumbach Syndrome Found in A Young Saudi Girl: A Case Report and Brief Literature Review. Annal Cas Rep Rev: 341.

Received Date: 03 November, 2022; **Accepted Date:** 15 November, 2022; **Published Date:** 21 November, 2022

Abstract

Type 1 Diabetes Mellitus (T1DM) is an autoimmune disease characterized by insufficient insulin production of the pancreatic beta-cells; patients with this disease will have a higher risk of other autoimmune disorders like celiac and thyroid disease. Hypothyroidism is the failure of the thyroid gland to secrete an adequate amount of thyroxine, which has an essential role in physical growth, brain development, and cellular metabolism. Most of the studies showed that children with T1DM have a higher incidence of hypothyroidism than normal children with an incidence of 9.6% of hypothyroidism and 19% with positive anti-TPO antibodies. Hypothyroidism will aggravate the condition in a child with T1DM and vice versa. Uncontrolled diabetes for a long time might increase insulin resistance due to complete depression of the hypothalamus-pituitary thyroid axis. A rare complication of poorly controlled T1DM is Mauriac syndrome, characterized by elevated liver enzymes, hyperlipidemia, cushingoid features, growth retardation, and hepatomegaly due to glycogenic hepatopathy. Van-Wyk Grumbach syndrome as well, is a rare complication of long-standing, untreated hypothyroidism, manifested by breast development, multi-cystic ovary, uterine bleeding associated with lack of pubic and axillary hair growth, and delayed bone age. Here, we report a case with two rare complications of Mauriac syndrome and Van-Wyc Grumbach syndrome, in a child with hypothyroidism and poorly controlled T1DM.

Keywords: *Type 1 Diabetes, Hashimoto Thyroidits, Mauriac syndrome, Van-Wyk Grumbach syndrome, Diabetes complications.*

Introduction

Type 1 Diabetes Mellitus (T1DM) is an autoimmune disease characterized by insufficient insulin production of the pancreatic beta-cells; patients with this disease will have a higher risk of other autoimmune disorders like celiac and thyroid disease [1]. Hypothyroidism is the failure of the thyroid gland to secrete an adequate amount of thyroxine, which has an essential role in physical growth, brain development, and cellular metabolism [2]. In 2017, a study was conducted by Fatourechi A et al, they found that children with T1DM have a higher incidence of hypothyroidism than normal children with an incidence of 9.6% of hypothyroidism and 19% with positive anti-TPO antibodies [3]. Also found, the consanguinity rate is high among the parents of children with T1DM and hypothyroidism than those children with T1DM who had normal thyroid function, and a higher rate of diabetes mellitus in their first-degree relatives as well, also they had significantly higher rates of Diabetic Ketoacidosis (DKA) at initial diagnosis and they required higher doses of insulin to control their disease. Hypothyroidism will aggravate the condition in a child with T1DM and vice versa. The Thyroid hormone enhances glucose uptake into peripheral tissue and has an additive effect on insulin action. Uncontrolled diabetes for a long time might increase insulin resistance due to complete depression of the hypothalamus-pituitary thyroid axis [3]. In tow studies, they found the association between impaired thyroid function and the severe metabolic

imbalance in patients with newly diagnosed T1DM, also showed significantly lower levels of thyroid hormones among newly diagnosed T1DM children who presented with DKA compared to patients without DKA at initial diagnosis. A rare complication of poorly controlled T1DM is Mauriac syndrome, characterized by elevated liver enzymes, hyperlipidemia, cushingoid features, growth retardation, and hepatomegaly due to glycogenic hepatopathy [4]. Van-Wyk Grumbach syndrome as well, is a rare complication of long-standing, untreated hypothyroidism, manifested by breast development, multi-cystic ovary, uterine bleeding associated with lack of pubic and axillary hair growth, and delayed bone age [5]. Here, we report a case with two rare complications of Mauriac syndrome and Van-Wyc Grumbach syndrome, in a child with hypothyroidism and poorly controlled T1DM.

Case Report

Eleven years old female, known case of T1DM diagnosed at age of 9 months and since that time her diabetes was uncontrolled with frequent visits to the endocrine clinic every three to 4 months with poor compliance to medication and lack of laboratory investigation. At age of 4 years, she was diagnosed with Hashimoto Thyroiditis with a high TSH of 23.6 mIU/L, FT4 was 10 pmol/L, and positive thyroid peroxidase (TPO) antibodies, and since that time she was started on levothyroxine medication. In 2017, we have noticed that the patient not growing well on the growth chart and had Lipohypertrophy in all limbs with no other abnormal finding. Education again was given to her and her mother as well. And at age of 11 years, her breast increased in size, the tanner stage was III without other signs of puberty. She had frequent admission to our hospital due to DKA. Upon physical examination during the last admission, the patient has a cushingoid face with a depressed nasal bridge and prominent forehead, significantly short with a Z score of 3.82. Tanner's stages involve breast stage IV without pubic hair and her thyroid gland was not palpable. Abdominal examination revealed hepatomegaly, the liver span was 15 cm (8 cm below the costal margin). Lipohypertrophy over all limbs was recognized. So, we question the complication of hypothyroidism and T1DM, for that reason investigations were done to roll out the rare complication of both diseases. The investigation showed an abnormal thyroid panel with a very high TSH level reaching 392.66 mIU/L and a low free T4 5.2 pmol/L, HgA1C was 15%, Celiac antibodies were negative, ACTH, Cortisol level, insulin-like growth factor were within normal limit. Her bone age study showed delayed Bone age of nine years (Figure 1) and had mild anterior pituitary enlargement with convex upper margin was confirmed by pituitary fossa MRI (Figure 2). Multiple small follicles in both ovaries were seen in the pelvic Ultrasound (Figure 3). Abdomen ultrasound confirmed hepatomegaly (16.1 cm). Although liver transaminase is within an ordinary level, the liver biopsy showed minimal focal inflammation in the portal tract with minimal glycogen deposition (Figure 4).

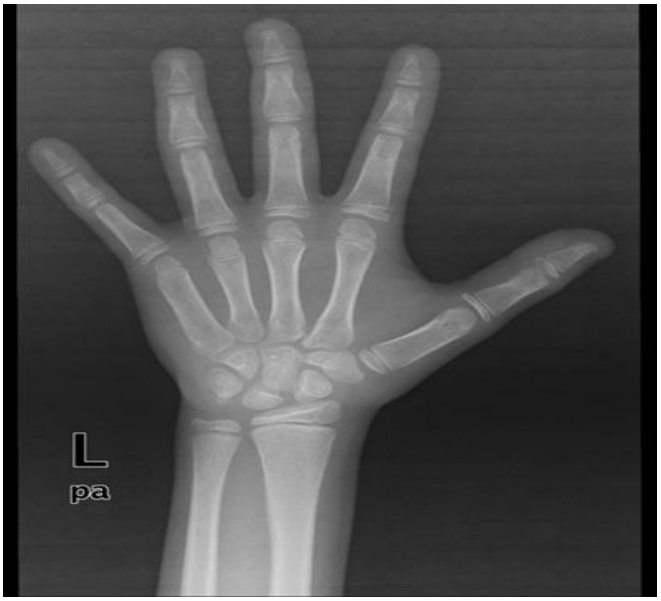

Figure 1: Using Greulich and Pyle atlas; approximate bone age is about 8 years.

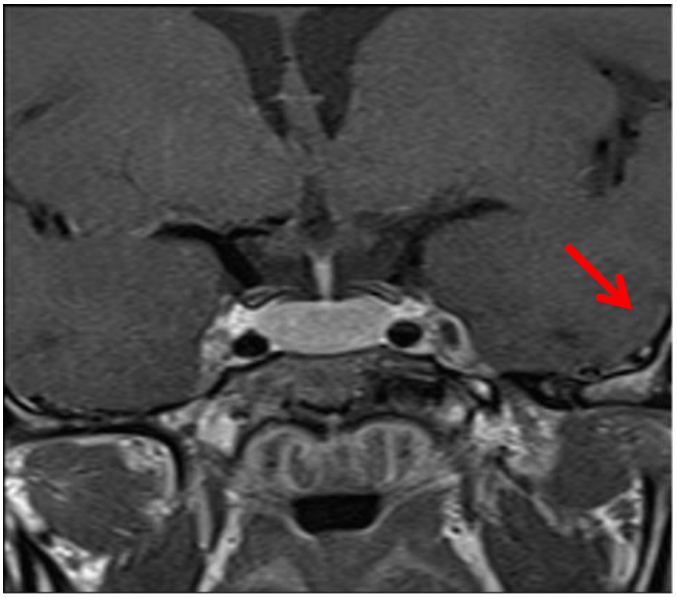

Figure 2: Mildly enlarged anterior pituitary with convex upper margin.

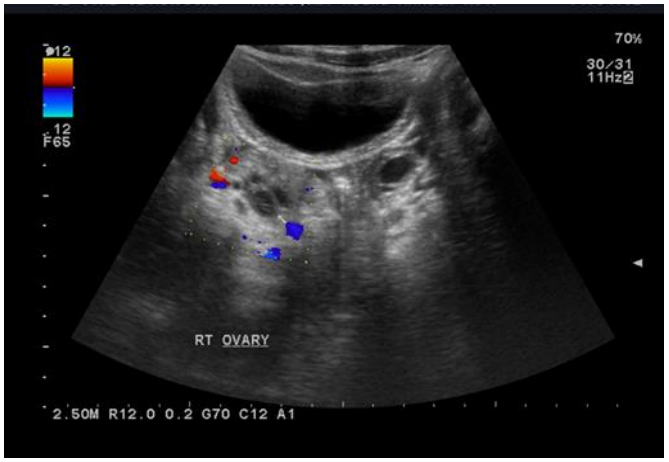

Figure 3: Right ovary measures 2.3 x 1.4 x 1.6 cm with an average volume of 2.8 ml and left ovary measures 2.6 x 1.5 x 2.0 cm with an average volume of 4.1 ml. Multiple small follicles are seen in both ovaries.

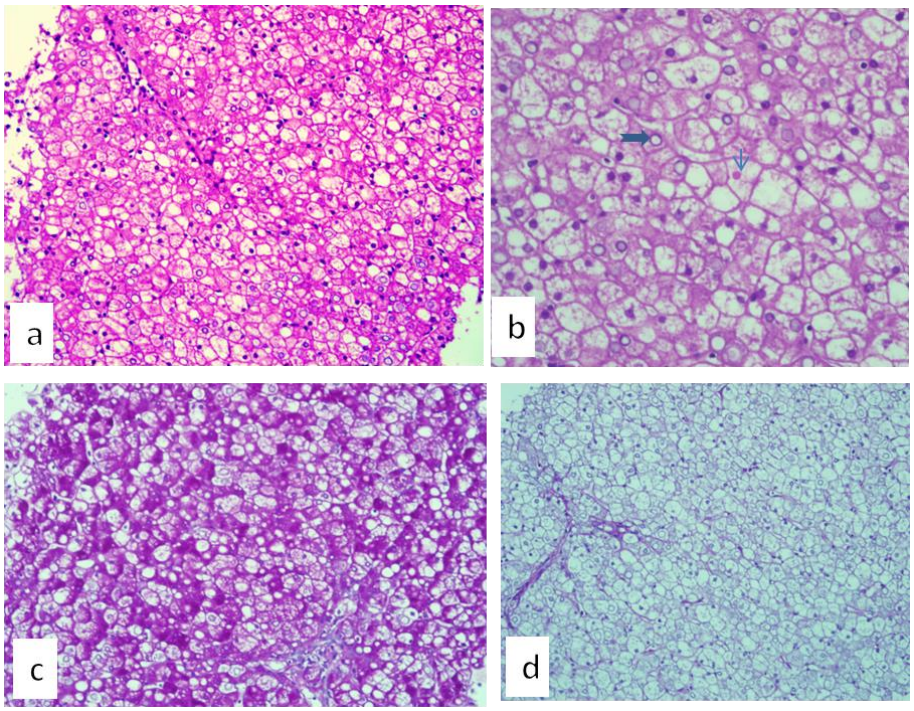

Figure 4: a +b- HE staining x 200, HE staining x 400: the hepatocytes are swollen with pale or eosinophilic cytoplasm and accentuation of the cell membranes. The sinusoids are compressed. Glycogenated nuclei (notched arrow) and megamitochondria (arrow) are identified. c+d: PAS staining, PAS staining with digestion by diastase, showed glycogen accumulation in the hepatocytes.

Discussion

In 1930 Mauriac syndrome was described by Mauriac as hepatic glycogenosis in diabetic children with cushingoid facial features, poor growth, and hyperlipidemia, however, the hepatic glycogenosis without another hallmark of the syndrome was reported [6]. Mauriac syndrome can occur in both children and adults, and it's a complication of neonatal diabetes mellitus, a poorly controlled T1DM, and rarely Type 2 diabetes mellitus [4]. Patients with Mauriac syndrome may present with clinical signs of diabetic ketoacidoses, such as abdominal pain and vomiting as our patient or asymptomatic with elevated liver enzymes and hepatomegaly [6]. Another presentation of this syndrome is signs of acute hepatitis, jaundice, pruritus, and elevated plasma lactate levels with or without diabetic ketoacidosis, as mentioned in a few reports [4]. Our patient had the usual clinical presentation, including hepatomegaly, growth failure, and cushingoid facial feature [4]. Hyperglycemia and hyperinsulinemia are two components in the pathophysiologic process of glycogenic hepatopathy [6]. Passive diffusion leads to an influx of glucose into the hepatocytes in hyperglycemia, then irreversibly converting glucose to glucose-6-Phosphate [4]. Hyperglycemia increases the need for insulin in a patient with poorly controlled DM type 1 and a higher amount of administration of insulin leads to activation of the glycogen synthase, which promotes hepatic glycogen storage [6]. This vicious cycle was described by several authors as the primary mechanism of the excessive accumulation of glycogen in hepatocytes that rapidly lead to liver injury [4]. The fluctuation in the blood glucose level leads to secondary hyperadrenalism that causes cushingoid features in the classic presentation of Mauriac syndrome [4]. Releasing excessive cortisol could result in delayed growth and puberty, decreased circulating insulin-like growth factor-1 (IGF-1) with a relative resistant state of growth hormone [4]. On the other hand, Corticosteroids use, and poorly controlled DM type 1& 2 are the most well-known cause of acquired glycogenic hepatopathy [4,6]. Some reports showed other reasons for glycogen hepatopathy, one of them was a toddler with dumping syndrome associated with gastrostomy feeding without glucose intolerance, and the other one was a well-controlled type 2 DM 15-years old boy, and in three children treated by high-dose glucocorticoid without DM [7]. Also, the development of Mauriac syndrome is associated with some genetic mutations such as KCNJ11 mutation, INS mutation, and PHKG2 mutation that cause prolong permanent neonatal diabetes [4]. The differential diagnosis of a patient with type 1 DM with hepatomegaly or elevated serum liver enzymes should include the classic causes of liver damage and hepatomegaly like nonalcoholic Steatohepatitis (NASH) and congenital glycogen storage diseases. NASH is characterized by cirrhosis and weight loss. While hereditary glycogen storage diseases warrant hypoglycemic episodes, hepatomegaly, lactic acidosis, growth retardation, hyperlipidemia, with hepatic glycogenosis [6]. Other differential diagnoses are acute, chronic, or autoimmune hepatitis [4]. We did several investigations for our patient including serology and liver biopsy which confirmed the diagnosis, which is the gold standard that differentiates Mauriac syndrome from other causes of hepatomegaly as nonalcoholic fatty liver disease

(NAFLD), which can't be distinguished entirely either clinically or radiologically by ultrasound (US) or even computed tomography (CT) [4,7]. Torbenson et al. showed that liver transaminases levels could be dramatically elevated, up to ten times above normal in patients with glycogenic hepatopathy with preserved liver synthetic function [6]. Our patient has normal liver transaminase; for that reason, the other differential diagnosis was excluded, including hepatocellular and cholestatic injury [7]. The features of Glycogenic hepatopathy (GH) in histopathology include swollen hepatocytes caused by glycogen accumulation, without or with mild fatty change, minimal inflammation, minimal spotty lobular necrosis, and intact architecture without significant fibrosis. Mild steatosis may be present or absent and the hallmark of this condition is glycogen accumulation [7]. As we mentioned before, significant fibrosis is usually not exhibited by Mauriac syndrome, but focal portal fibrosis and bridging fibrosis were reported in some cases, which is an unusual finding and the exact mechanism responsible for fibrosis development remains unclear [4]. All the clinical features of Mauriac syndrome include growth failure, hepatomegaly, and glycogen deposition return to normal with optimal insulin therapy and strict blood glucose levels. Regression of Mauriac features differs according to the patient; some take two weeks to be normalized, others take four weeks, but if hepatomegaly persists more than four weeks, should roll out other causes [6]. One case report showed that after four months of changing the insulin treatment regimen GH appeared then resolved rapidly after extensive insulin therapy [7]. Indication of pancreatic transplantation in a patient with type1 DM has been found to reduce diabetic complications by improving glycemic control in patients with Mauriac syndrome [6]. End-stage liver damage, synthetic dysfunction, hepatocellular carcinoma, or portal hypertension were fatal complications of GH itself and fortunately have never been reported [7]. In patients with Mauriac syndrome, deterioration of retinopathy and nephropathy were caused by aggressive insulin treatment, so, patient education is essential in all diabetic patients to minimize complications and to reverse the clinical features of Mauriac Syndrome by optimal insulin therapy [6]. Unfortunately, our patient has another autoimmune disease which is Hashimoto Thyroiditis which consider the most frequent cause of acquired thyroid disorder during childhood and adolescence. Hashimoto Thyroiditis is characterized by the production of thyroid autoantibodies that involve (anti-TPO), thyroglobulin (anti-TG), and thyroid-stimulating hormone receptors (TRABs) through T and B lymphocytes infiltration to the thyroid and reaction against thyroid antigens which lead to fibrous replacement and parenchymal atrophy. The disease outcome is affected by existential/environmental factors and genetic background. The patient has hypothyroidism by clinical and biochemical alterations that result from autoimmune gland injury [8-10]. The prevalent disease among diabetic children is hypothyroidism, associated with higher DKA rates and requiring higher insulin doses and both diseases share common genetic factors and immunologic processes [1,3]. Our patient has the hallmark of Van-Wyc Grumbach syndrome that includes Isosexual precocious puberty, resulting from long-standing untreated hypothyroidism [11]. The first description of this syndrome was in 1960 by Van Wyk and Grumbach and the clinical features of the girls with this syndrome include breast development, follicular cysts which were manifest in the histopathological analysis of resected ovaries and ovarian cysts, and menstruation with an absence of pubic or axillary hair [12]. Myxoedematous infiltration appeared within the affected ovaries and it was noticed by some reports suggesting an independent role in cyst formation and abnormal steroidogenesis in the gonad. Van-Wyk Grumbach syndrome can occur in boys characterized by macroorchidism without significant virilization. The predominance of tubular elements without elevated Leydig cell numbers was manifest in testicular histology consistent with an FSH-mediated response. In early development, thyroid hormone is known to affect the growth and physiology of the testis, while in Van-Wyc Grumbach syndrome, the function of thyroid hormone receptors on Sertoli and Leydig cells is currently poorly understood [12]. These features occur due to the elevation of thyroid releasing hormone caused by the lack of negative feedback on the pituitary from the thyroid hormone deficiency resulting in an 'overlap' in pituitary hormone secretion [13]. The glycoprotein of thyroid-stimulating hormone (TSH) shares a common alpha-subunit with follicle-stimulating Hormone (FSH), Luteinising Hormone (LH), and human chorionic gonadotropin (hCG). Still, each hormone has a unique beta-subunit that is specific for each hormone. Each hormone stimulates cAMP production through adenylate cyclase activation by transmembrane GPCRs. Anasti et al. showed that recombinant human TSH elicited a dose-dependent response at the human FSH receptor. The FSH-like activity of TSH is deficient because the requirement of TSH concentration was several orders of magnitude higher than FSH. The TSH competitively antagonizes FSH because both TSH and FSH are acting on the same receptor. Still, not all glycoproteins have the same response, like the hCG was unresponsive to adenylate cyclase activity in transfected cells [12]. For that, the development of secondary sexual characters results from increased estrogen production by elevation of TSH on the FSH receptor. Furthermore, the absence of pubic and axillary hair results from the unaffected adrenal gland and normal hormones. Another explanation of Isosexual precocious puberty is hyperprolactinemia due to thyrotrophic hyperplasia in the pituitary that compresses the pituitary stalk and disrupts hypothalamic inhibition of prolactin or due to direct stimulation of prolactin release by Thyrotropin-releasing hormone (TRH) [5]. Pituitary gonadotropins suppressed by prolactin through slowing gonadotropin-releasing hormone (GnRH) pulse frequency causes FSH production and suppression of LH [12]. In our case, an MRI of the pituitary gland showed mild anterior pituitary enlargement due to the lack of negative feedback on the pituitary [5]. Patient

with this syndrome may also present with skin hyperpigmentation due to hormonal overlapping with the melanocyte-stimulating hormone (MSH) that act on G protein-coupled receptor (GPCR) [12].

Association of Trisomy 21 or Kocher-Debre-Semelaigne syndrome with this syndrome have been reported in various atypical cases of Van-Wyc Grumbach syndrome; also, the patient can present with unilateral ovarian mass or has a presentation of this syndrome in adulthood [5]. Elevated tumor markers can present in some patients with VWGS like CA-125 and Alpha-Fetoprotein (AFP). Both are non-specific and related to other conditions like endometriosis, uterine fibroids, tubal-ovarian mass, dysgerminomas, and other germ cell tumors. Replacement of thyroid hormone has been found to normalize AFP, so; the tumor marker elevation occurs secondary to ovarian hyper-stimulation and cyst formation not due to cancer [14]. Bone age determines by various methods like appearances of epiphysis in X-ray of wrist and hand that determines linear growth, and another one is to compare the patient's ossification centers with published age-matched standards derived from healthy children using the Greulich and Pyle's atlas [5]. Most precocious puberty causes are associated with advanced bone age, for that delayed bone age is a unique diagnostic clue for VWGS [14]. VWGS can be manifested as hypertrichosis in long-standing untreated hypothyroidism associated with accelerated precocious puberty and delayed bone age while in all other causes of precocious puberty, the bone age will be advanced [15]. Van-Wyk Grumbach syndrome can be found in other causes of hypothyroidism like congenital hypothyroidism, ectopic thyroid tissue, or hypothyroidism tumors [16]. As Mauriac Syndrome, early recognition of the Van-Wyc Grumbach syndrome and initiation of thyroid hormone replacement causes reversal of all symptoms with normalization of hormonal profile through negative feedback on pituitary hyperplasia, and the patient will have appropriate growth velocity resumption [5,13,14].

Also, patients with dysfunctional uterine bleeding may need estrogen treatment in the short term. For that, any exogenous estrogen should be discontinued after normalization of TSH levels to optimize final adult height [13]. Surgical intervention like ovarian cystectomy or oophorectomy should reverse for patients who may have ovarian torsion, ovarian rupture, hemodynamically unstable, or failure to regress with thyroid hormone replacement as by several authors' agreement [14]. Other consequences of prolonged untreated hypothyroidism are macrocytic anemia due to suppression of bone marrow with erythropoietin secretion and pericardial effusion through increased capillary permeability leading to extravasation of the pericardial sac by protein-rich fluid that increased salt and water retention and impaired lymphatic drainage [17].

Conclusion

Our case is peculiar because of the rare association of Mauriac Syndrome with Van-Wyc Grumbach syndrome in the same patient with hypothyroidism and poorly control DM type 1. Patient education and medication compliance are essential in all diabetic patients associated with hypothyroidism to reduce complications and to reverse the clinical features of Mauriac Syndrome with Van-Wyc Grumbach syndrome.

Reference

1. Nederstigt C, Uitbeijerse BS, Janssen LG, Corssmit EP, de Koning EJ, Dekkers OM. Associated auto-immune disease in type 1 diabetes patients: a systematic review and meta-analysis. European journal of endocrinology. 2019 Feb 1;180(2):135-144.
2. Giorda CB, Carnà P, Romeo F, Costa G, Tartaglino B, Gnavi R. Prevalence, incidence and associated comorbidities of treated hypothyroidism: an update from a European population. Eur J Endocrinol. 2017 May 1;176(5):533-542.
3. Fatourechi A, Ardakani HM, Sayarifard F, Sheikh M. Hypothyroidism among pediatric patients with type 1 diabetes mellitus, from patients' characteristics to disease severity. Clinical Pediatric Endocrinology. 2017;26(2):73-80.
4. Medhioub M, Ayedi H, Chelbi E, Khsiba A, Hamzaoui L, Azzouz MM. Mauriac syndrome: An unusual presentation with portal fibrosis. Presse Medicale (Paris, France: 1983). 2019 May 25;48(6):718-720.
5. Pant V, Baral S. Van Wyk Grumbach syndrome with precocious puberty and ovarian cysts: Value of thyroid function tests. Journal of Pediatric Surgery Case Reports. 2019 Apr 1;43:32-34.
6. Topaloğlu Ö. Mauriac syndrome: Case report and review of the literature.
7. Casto C, Pepe G, Li Pomi A, Corica D, Aversa T, Wasniewska M. Hashimoto's thyroiditis and Graves' disease in genetic syndromes in pediatric age. Genes. 2021 Feb;12(2):222.
8. Ruggeri RM, Trimarchi F, Giuffrida G, Certo R, Cama E, Campennì A, Alibrandi A, De Luca F, Wasniewska M. Autoimmune comorbidities in Hashimoto's thyroiditis: different patterns of association in adulthood and childhood/adolescence. Eur J Endocrinol. 2017 Feb 1;176(2):133-141.
9. Won JH, Lee JY, Hong HS, Jeong SH. Thyroid nodules and cancer in children and adolescents affected by Hashimoto's thyroiditis. The British Journal of Radiology. 2018 Jul;91(1087):20180014.
10. Sahana PK, Deshmukh AS, Sengupta N, Das C, Dasgupta R. Case Report: An unusual case of incomplete isosexual precocious puberty in a young girl with juvenile hypothyroidism.
11. Marr A, Hardy K, Curtis J. A 14-year-old girl with short stature, incomplete puberty and severe menstrual bleeding. Paediatrics & Child Health. 2018 May;23(2):85.

12. Ayub SS, Ruzic A, Taylor JA. Ovarian cysts, vaginal bleeding and hypothyroidism in a 4-year-old female with Down Syndrome: A case of Van Wyk-Grumbach Syndrome. Journal of pediatric surgery case reports. 2017 Oct 1; 25:5-9.
13. Reddy P, Tiwari K, Kulkarni A, Parikh K, Khubchandani R. Van Wyk Grumbach syndrome: a rare consequence of hypothyroidism. The Indian Journal of Pediatrics. 2018 Nov;85(11):1028-1030.
14. Kacem FH, Kalthoum M, Ammar M, Sefi W, Mnif M, Abid M. Van Wyk and Grumbach Syndrome: An Unusual Presentation of Acquired Hypothyroidism.
15. Egodawaththe NS, Seneviratne SN, Gunasekara S, Amarasekara SM, Weerasekara K. Van Wyk-Grumbach syndrome and oligosyndactyly in a 6-year-old girl: a case report. Journal of Medical Case Reports. 2020 Dec;14(1):1-7.
16. Lin CH, Lee YJ, Huang CY, Kao HA, Shih BF, Wang AM, Lo FS. Thyroid function in children with newly diagnosed type 1 diabetes mellitus. Acta Paediatrica Taiwanica= Taiwan er ke yi xue hui za zhi. 2003 May 1;44(3):145-149.
17. Balsamo C, Zucchini S, Maltoni G, Rollo A, Martini AL, Mazzanti L, Pession A, Cassio A. Relationships between thyroid function and autoimmunity with metabolic derangement at the onset of type 1 diabetes: a cross-sectional and longitudinal study. Journal of Endocrinological Investigation. 2015 Jun;38(6):701-707.