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Case report

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Diagnostic challenges in precocious puberty: A case of a 7-year-old girl

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Abstract

Immune-mediated destruction of two or more endocrine glands results in a cluster of deficits in multiple glands, known as autoimmune polyglandular syndrome. Autoimmune hypothyroidism is a common presentation of autoimmune polyglandular syndrome type II (APS–II). Long-standing, untreated hypothyroidism may cause isosexual precocious puberty, which is termed Van Wyk Grumbach syndrome. A 7-year-old girl was diagnosed with autoimmune hypothyroidism and type 1A diabetes mellitus and hence termed as autoimmune polyglandular syndrome type II. She had a history of menarche at the age of 2 years and 6 months and presented with bilateral ovarian cysts and delayed bone age. She was treated with thyroxine along with insulin. Thyroxine therapy stopped her menstruation with a reduction of ovarian cyst size. *[J Assoc Clin Endocrinol Diabetol Bangladesh,* July 2025;4(2)*: 90-95]*

Keywords: Precocious puberty, Van Wyk Grumbach syndrome, Hypothyroidism, Autoimmune polyglandular syndrome type II

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Introduction

Autoimmune polyglandular syndromes are rare disorders characterized by deficient hormone production from multiple endocrine glands, often in association with other non-endocrine autoimmune diseases.[1] A person is classified as having autoimmune polyglandular syndrome (APS) type II if two or more of the following conditions occur in them: primary adrenal insufficiency (Addison's disease), Graves' disease, autoimmune thyroiditis, type 1A diabetes, primary hypogonadism, myasthenia gravis, and celiac disease. Patients with this disease and members of their family also have higher rates of vitiligo, alopecia, serositis, and pernicious anaemia.[2] Approximately 1.4-2 occurrences of this syndrome occur for every 100,000 people.[3] APS type II is more prevalent than APS type I. It is more common in female patients than male, typically manifests in adulthood, and shows signs of familial aggregation.[2]

An uncommon cause of incomplete isosexual precocity in both girls and boys is long-standing, untreated primary hypothyroidism, which is typically the result of autoimmune hypothyroidism. Van Wyk and Grumbach, in 1960, proposed that the syndrome was caused by hormonal overlap in the regulation of negative feedback, resulting in increased release of gonadotropin, prolactin, and thyroid-stimulating hormone (TSH) due to persistent hypothyroidism. The increased release of thyrotropin-releasing hormone (TRH), the greater sensitivity of the mammotrophs and gonadotrophs to TRH, or both, are probably the causes of the inadequate sexual precocity, increased prolactin secretion, and galactorrhea. It is associated with stunted growth and delayed skeletal maturation. Girls often do not develop pubic hair, but they do have breast development, enlarged labia minora, and estrogenic changes in the vaginal smear. Some girls experience irregular vaginal bleeding that may progress to metrorrhagia, and pelvic sonography or physical examination may reveal a single

or multiple ovarian cyst.[4]

Recognition of the situation is necessary to prevent needless surgery for the ovarian cysts or the associated pituitary growth, which would be a serious error given the efficacy of medicinal treatment. Levothyroxine therapy reverses or corrects the pituitary hypertrophy, hypothyroidism, inadequate sexual maturation, and galactorrhea within a few months.[4]

We present a 7-year-old girl who had a history of premature menarche at two and a half years presenting with APS–II.

Case summary

A 7-year-old girl was admitted to the department of Endocrinology of Dhaka Medical College Hospital, with the complaints of generalized body swelling for 6 months and an episode of vaginal bleeding 1 month back. Swelling was insidious in onset, gradually progressive, and more marked in the abdomen. Swelling was associated with constipation, cold intolerance, and somnolence, but not with scanty or frothy micturition, jaundice, chest pain, cough, or breathlessness. She also developed a single episode of per vaginal bleeding 1 month back. Bleeding was not related to trauma, moderate in amount (she had to change two pads per day), not associated with the passage of clots, lower abdominal pain, and bleeding persisted for 5 days. Bleeding was preceded by the gradual enlargement of breasts. But there was no appearance of axillary or pubic hair or rapid increase in height. She had a similar history of per vaginal bleeding at two and a half years of age, which was cyclical, occurred monthly, and episodes of bleeding stopped at around three and a half years of age. On query, the mother stated that her child was not growing well. According to her mother, she was diagnosed with hypothyroidism at three and a half years of age and was on tablet levothyroxine, which she stopped 9 months back. She was also diagnosed with diabetes mellitus 1 year back, presenting as diabetic ketoacidosis, and was treated accordingly. She had no history of dizziness, recurrent vomiting, hypopigmentation or hyperpigmentation of skin, chronic diarrhoea, oral thrush or skeletal dysmorphisms. On examination, she appeared ill-looking, with a puffy face and non-pitting edema. Her pulse was regular at 88 beats/min, blood pressure was 90/55 mmHg with no postural drop, respiratory rate was 16 breaths/min, and her temperature was 98.6°F. Her skin was dry and rough. Height was 98 cm, weight was 16 kg (both below the third percentile). As per Tanner staging, her sexual maturation score was B2, A1 and P1 for breast, axillary and pubic hair respectively. There was no clitoromegaly. Abdominal examination revealed an ill-defined mass measuring approximately 3×2 cm in the left lumbar and iliac regions, which was firm in consistency, non-tender, had a smooth surface, and moved from side to side but did not move vertically. There was no organomegaly. All other systemic examinations revealed no abnormality.

Table-I: Routine investigations with age-specific reference range

Test	Result	Reference range
CBC	Hb 11.5 gm/dL	-
	WBC 8.79 × 109 /L	-
	Platelet 319 × 109 /L	-
	MCV 89.3 fL	-
	MCH 29 pg/dL	-
	MCHC 32.4%	-
Urine RME	Glucose +	-
	Protein - nil	-
	Ketone - nil,	-
	Pus cell -1-2/HPF	-
FPG (mmol/L)	19.1	3.9-5.5
PG 2HABF (mmol/L)	22.7	4.4-7.7
HbA1c (%)	15.7	<5.7
Serum sodium (mmol/L)	141	134-144
Serum potassium (mmol/L)	4.2	3.3-4.6
Serum chloride (mmol/L)	95	98-106
Serum creatinine (mg/dl)	0.54	0.22-0.59
SGPT (U/L)	27	5-45
Total cholesterol (mg/dL)	299	<170
HDL-c (mg/dL)	46	>45
LDL-c (mg/dL)	231	< 110
TG (mg/dL)	321	<75
Corrected calcium (mg/dL)	7.88	8.8-10.3
Phosphate (mg/dL)	4.4	4.5-6.5

CBC– complete blood count, Hb – hemoglogin, WBC – white blood cell, MCV – mean corpuscular volume, MCH – mean corpuscular hemoglobin, MCHC – mean corpuscular hemoglobin concentration, RME – routine and microscopic examination, FPG – fasting plasma glucose, PG 2HABF – plasma glucose 2 hours after breakfast, HbA1c – Glycated hemoglobin, SGPT – serum glutamic pyruvic transaminase, HDL-c – high density lipoprotein cholesterol, LDL-c – Low density lipoprotein cholesterol, TG – triglyceride

Table-I displays her routine investigations showing hyperglycemia, dyslipidemia, hypocalcemia, and hypophosphatemia. The results of laboratory estimation of hormonal analytes imply low free T4 (FT4) and elevated TSH, estradiol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and intact parathyroid

Table-II: Results of biochemical and hormonal analysis before and after treatment

Test	Initial result	After treatment	Reference range (age specific)
Serum TSH (IU/mL)	>50.5	2.32	0.7-4.17
Serum FT4 (ng/dL)	0.61	0.97	1-2.4
Serum Estradiol (pg/mL)	225.6	5	0-16
Serum FSH (mIU/mL)	20.1	-	0.5-4.5
Serum LH (mIU/mL)	1.15	-	0.02-0.18
Serum Prolactin (ng/mL)	107	10.6	2.6-18
Serum Cortisol (µg/dL)	9.1	-	2-17
Plasma ACTH (pg/mL)	10.02	-	9-57
Serum iPTH (pg/mL)	88.5	-	12-65
Serum Calcium (mg/dL)	7.4	8.79	8.8-10.3

TSH – thyroid stimulating hormone, FT4 – free thyroxine, FSH – follicle stimulating hormone, LH – luteinizing hormone, ACTH – adrenocorticotropic hormone, iPTH – intact parathyroid hormone

hormone (iPTH) (Table-II). Table-III shows that the patient had positive anti-glutamic acid decarboxylase (GAD65) antibody, positive anti-thyroid peroxidase (TPO) antibody, and low 25(OH) vitamin D. Her bone age was 4 years (Figure-1). The computed tomography

Table-III: Routine investigations with age-specific reference range

Test	Result	Reference range
C-Peptide (ng/mL)	0.04	0.7-3.6
GAD 65 antibody (IU/mL)	55.5	<17
Anti-TPO (IU/mL)	37.7	1-16
Anti-TG (IU/mL)	19.1	5-100
25(OH) vit D (ng/mL)	5.5	20-50

GAD 65 antibody – glutamic acid decarboxylase 65 antibody, Anti-TPO – anti-thyroid peroxidase antibody, Anti-TG – anti-thyroglobulin antibody, 25(OH)vit D – 25-hydroxyvitamin D

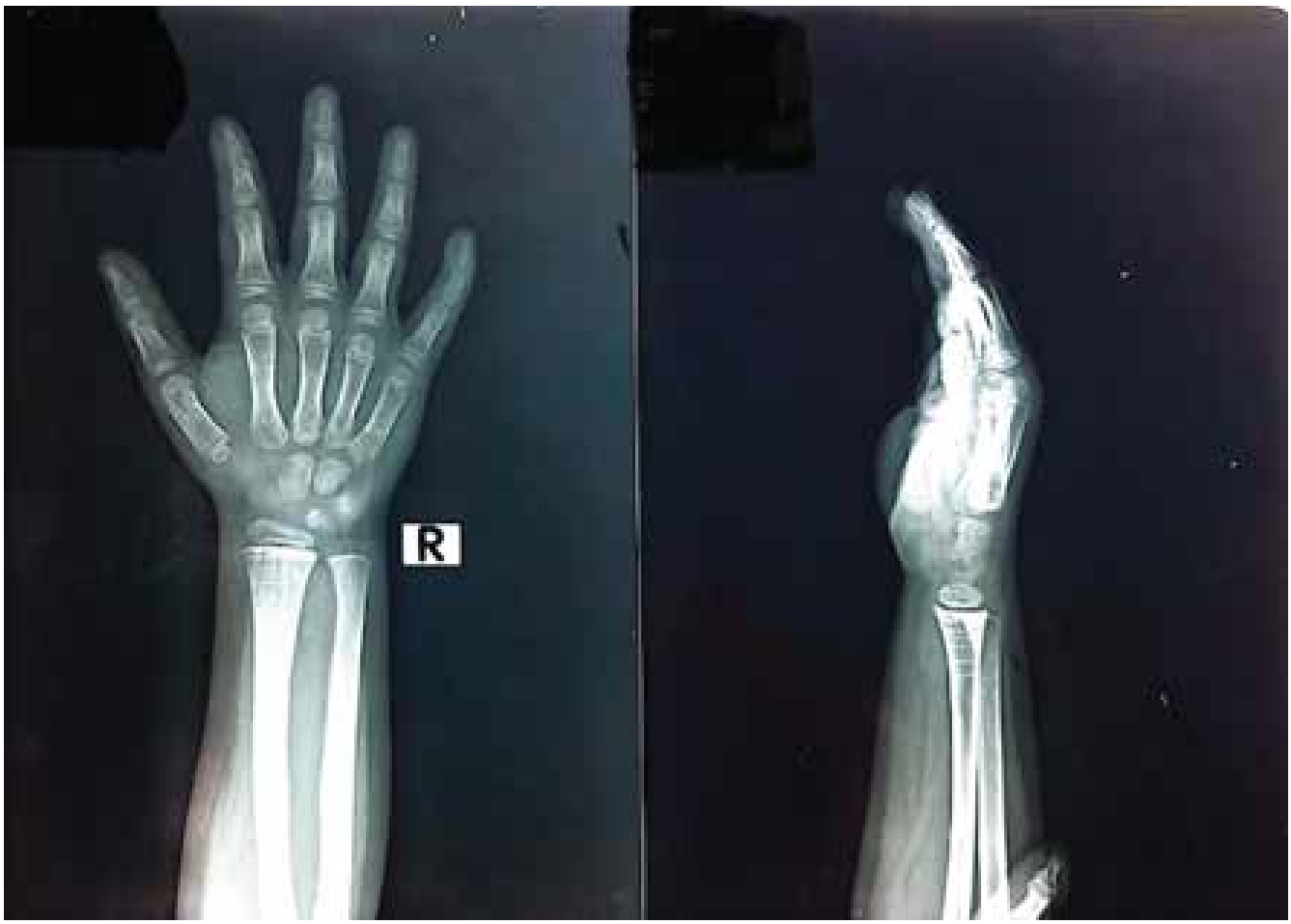

Figure-1: X-ray wrist joint indicating radiological bone age of 4 years

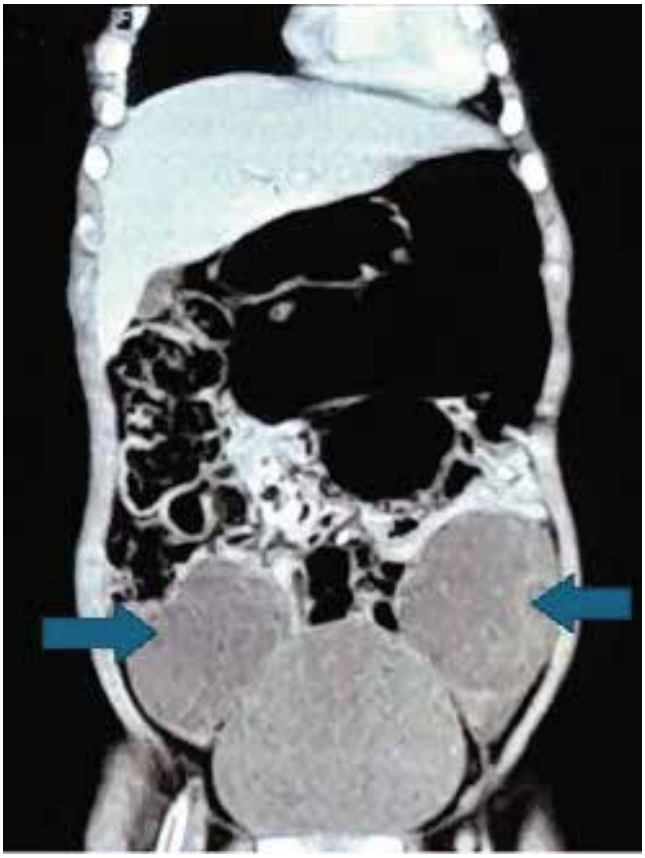

Figure-2: Computed tomography scan of abdomen with contrast, coronal view showing bilateral ovarian cyst

(CT) scan of the abdomen showed bilateral ovarian cysts (right 5.5×5×5 cm3 and left 6.5×5×4 cm3) (Figure-2).

With the pathologic and radiological findings, she was diagnosed as a case of APS-II with Van Wyk Grumbach Syndrome (VWGS) with short stature and vitamin D deficiency. She was then promptly started on oral levothyroxine 75 µg/day, basal bolus insulin, and vitamin D 2000 IU daily. After 2 months, she came for a follow-up. Her generalized swelling had reduced, and her constipation had subsided. There was no further occurrence of menstrual bleeding. Follow up ultra-sonogram revealed marked reduction of size of the ovarian cysts (right 1.3×0.7 ×0.6 cm, left 0.9×0.6×0.4 cm). We further plan to follow up with her to ensure glycemic control, maintenance of euthyroidism, and monitoring of growth. Her follow-up investigations are also shown in Table-II.

Discussion

Autoimmune polyendocrine syndrome (APS) is a rare combination of various autoimmune disorders having at least two endocrine deficiencies. Based on clinical characteristics and inheritance patterns, APS is classified into four main groups: APS types I, II, III, and IV. APS type II is more prevalent compared to APS type I. Environmental or genetic variables are most likely the aetiology. Alleles of the HLA genes, particularly HLA-DR3 and HLA-DR4, are genetically predisposed to APS type II, which increases the risk of the condition in first-degree relatives. Since the occurrence of a single autoimmune condition is uncommon, the advancement of any one of them should prompt evaluation for endocrine autoimmune diseases such as Addison's disease (which affects 50%–70%), Graves' disease (which affects 15%–69%), autoimmune hypothyroidism (which affects 15%–30%), type 1 diabetes (which affects 41%–50%), and non-endocrine autoimmune diseases such as primary hypogonadism, alopecia, vitiligo, and celiac disease.[2,5] Adrenal insufficiency may be present concurrently, may be delayed up to two decades or even may not occur.[6] Our patient presented with Autoimmune hypothyroidism and type 1 DM, evidenced by positive antithyroid peroxidase antibody and GAD 65 antibody, respectively, but no adrenal insufficiency was present.

Acquired hypothyroidism in children is most commonly caused by autoimmune thyroiditis and occurs in 1.3–4% of children.[7] In our case, the cause of hypothyroidism is also autoimmune thyroiditis, as evidenced by elevated anti-TPO antibody. Long-standing hypothyroidism with high levels of TSH causes isosexual precocity with lack of pubic and axillary hair growth, and delayed bone age.[8] Stimulation of the gonadal FSH receptor by TSH in this syndrome is supported by the specific FSH/oestrogen dominant clinical features, including breast development, follicular cysts, and menstruation. This syndrome is known as Van Wyk-Grumbach Syndrome (VWGS).[9] The TSH level was very high, which was above 50 IU/L, and the anti-TPO antibody was also above the normal range.

Elevated TSH levels enhance the development of secondary sexual characteristics by stimulating the gonadal glands and increasing the synthesis of oestrogen through the FSH receptor.[10] At a median age of 10.5 (±2) years, girls transition from Tanner stage 1 to Tanner stage 2.[11] However, in the index instance, the youngster had already attained Tanner stage 2 at the age of seven. Pubic and axillary hair are typically missing because there is no rise in the synthesis of adrenal hormone, which is also true for our index case.

The development of epiphysis, which defines linear growth, in wrist and hand X-rays is typically used to estimate bone age. There are several methods for determining the bone age. The patient's ossification

centers are compared to published age-matched standards obtained from healthy youngsters using Greulich and Pyle's technique.[12] An X-ray of the left wrist using the Greulich and Pyle atlas showed that our patient's bone age was only four years. Due to chronic hypothyroidism, VWGS is the only kind of premature puberty in which there is a delay in bone age.

In VWGS, hyperprolactinemia is caused by either direct stimulation of prolactin production by TRH or thyrotrophic hypertrophy in the pituitary, which compresses the pituitary stalk and impairs hypothalamic regulation of prolactin.[13] In this instance, there was hyperprolactinemia but no galactorrhea, headache, or blurred vision-symptoms that could be brought on by hyperprolactinemia.

In a peripheral primary care clinic, the cystic ovarian enlargement that was observed in our case was mistakenly diagnosed as a hormonally active ovarian tumour that was causing precocious puberty. After that, she was recommended for surgery. To prevent needless surgery, it is crucial to identify VWGS based on clinical and laboratory results, especially the connection between hypothyroidism and cystic ovarian enlargement. Only after completing a thyroid function test and other hormonal profile analyses was this case of VWGS identified. The development of ovarian cysts is caused by hypothyroidism-induced myxedematous infiltration of the ovarian stroma and enhanced ovarian sensitivity to gonadotropins.[14] The bilateral ovarian cyst in the index case probably developed as a result of a high level of FSH and increased ovarian sensitivity. Numerous uncommon examples of VWGS, such as the presence of a unilateral ovarian mass, adult presentation, and correlation with Kocher-Debre-Semelaigne syndrome or Down's syndrome, have also been documented.[15-18] Consequently, a complex mechanism involved in the pathogenesis of VWGS is primarily driven by TSH acting on FSH receptors.

All symptoms of VWGS disappear after thyroid hormone replacement therapy, and the hormonal profile returns to normal. This also eliminates the need for unnecessary surgery, worry about cancer, and additional diagnostic testing. Following two months of thyroxine treatment, our patient experienced regression of the ovarian cyst, total cessation of vaginal bleeding, and normalisation of thyroid function test results.

Conclusion

The diagnosis of APS prompts a search for other autoimmune endocrine diseases after the initial diagnosis. Early recognition of VWGS and initiation of thyroid hormone replacement in a female child with an ovarian mass and precocious puberty can avoid unnecessary investigations and surgical intervention.

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Disclosure

The authors declare that no conflict of interest could be perceived as prejudicing the impartiality of the research reported.

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Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethical Approval and Consent to Participate

Written informed consent was obtained from the patient. All methods were performed in accordance with the relevant guidelines and regulations.

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References

1. Gupta AN, Nagri SK. Schmidt's syndrome – case report. Australas Med J 2012;5(6):292–5. DOI:10.4066/AMJ.2012.987.
2. Styne DM. Physiology and disorders of puberty. In: Melmed S, Koenig R, Rosen C, Auchus R, Goldfine A, editors. Williams Textbook of Endocrinology. 14th ed. Vol. 2. India: Elsevier; 2020. p. 1664–6.
3. Arram N, Riyaz R, Khatroth S, Shrestha AB. A case report on autoimmune polyglandular syndrome type 2 with pernicious anemia. Clin Case Rep 2023;11(6):e7413. DOI:10.1002/ccr3.7413.
4. Jaume JC. Endocrine autoimmunity. In: Gardner D, editor. Greenspan's Basic and Clinical Endocrinology. 10th ed. New York: McGraw-Hill Education; 2017. p. 44–5.
5. Torok KS, Arkachaisri T. Autoimmune thyroiditis in antinuclear antibody positive children without rheumatologic disease. Pediatr Rheumatol 2010;8(1):15. DOI:10.1186/1546-0096-8-15.
6. Ryan GL, Feng X, d'Alva CB, Zhang M, Van Voorhis BJ, Pinto EM, et al. Evaluating the roles of follicle-stimulating hormone receptor polymorphisms in gonadal hyperstimulation associated with severe juvenile primary hypothyroidism. J Clin Endocrinol Metab 2007;92(6):2312–7.

7. Takeuchi K, Deguchi M, Takeshima Y, Maruo T. A case of multiple ovarian cysts in a prepubertal girl with severe hypothyroidism due to autoimmune thyroiditis. Int J Gynecol Cancer 2004;14(3):543–5. DOI:10.1111/j.1048-891x.2004.14318.x.
8. Anasti JN, Flack MR, Froehlich J, Nelson LM, Nisula BC. A potential novel mechanism for precocious puberty in juvenile hypothyroidism. J Clin Endocrinol Metab 1995;80(1):276–9.
9. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child 1969;44(235):291.
10. Bayley N, Pinneau SR. Tables for predicting adult height from skeletal age. J Pediatr 1952;40(4):423–41. DOI:10.1016/S0022-3476(52)80205-7.
11. Browne LP, Boswell HB, Crotty EJ, O'Hara SM, Birkemeier KL, Guillerman RP. Van Wyk and Grumbach syndrome revisited: imaging and clinical findings in pre- and postpubertal girls. Pediatr Radiol 2008;38(5):538–42.
12. Pant V, Baral S. Van Wyk Grumbach syndrome with precocious puberty and ovarian cyst: value of thyroid function tests. J Pediatr Surg 2019;43:32–4.
13. Tran S, Kim EE, Chin AC. Severe menorrhagia, unilateral ovarian mass, elevated inhibin levels, and severe hypothyroidism: an unusual presentation of Van Wyk and Grumbach syndrome. J Pediatr Surg 2013;48(1):e51–4.
14. Lim HH, Kil HR, Kim JY. Unusual presentations of a girl with Down syndrome: Van Wyk-Grumbach syndrome. J Pediatr Endocrinol Metab 2012;25(11–12):1209–12. DOI:10.1515/jpem-2012-0195.
15. Razi SM, Gupta AK, Gupta DC, Gutch M, Gupta KK, Usman SI. Van Wyk-Grumbach syndrome with Kocher-Debre-Semelaigne syndrome: case report of a rare association. Eur Thyroid J 2017;6(1):47–51.
16. Kubota K, Itho M, Kishi H, Igarashi S, Minegishi T. Primary hypothyroidism presenting as multiple ovarian cysts in an adult woman: a case report. Gynecol Endocrinol 2008;24(7):420–3.