Arch Argent Pediatr. 2025;123(3):e202410456

Peripheral precocious puberty secondary to severe hypothyroidism

Melina Gil[1], *Florencia Martino*[1], *Gonzalo Besseghine*[2], *María V. Rojas Ortiz*[2], *Sonia Rojas*[2], *María E. Rodríguez*[1], *Andrea Arcari*[1], *Analía Freire*[1]

ABSTRACT

Van Wyk-Grumbach syndrome is a rare form of severe hypothyroidism.

We present a 10.9-year-old girl who consulted for genital bleeding, Tanner stage 2, and clinical manifestations of hypothyroidism. Severe hypothyroidism was confirmed, secondary to chronic lymphocytic thyroiditis. A pelvic ultrasound showed bilateral evidence of cystic ovarian masses. The hormonal profile confirmed peripheral precocious puberty secondary to hypothyroidism. A pituitary MRI showed significant pituitary elongation due to thyrotropic hyperplasia. After initiating treatment with thyroid hormone, there was a notable clinical improvement and resolution of the adnexal masses and pituitary hyperplasia.

The pediatrician must be able to identify signs and symptoms associated with thyroid dysfunction and prompt referral to a pediatric endocrinologist to avoid the appearance of severe conditions such as the one presented.

Keywords: *hypothyroidism; precocious puberty; ovarian cysts; Van Wyk-Grumbach syndrome.*

doi: http://dx.doi.org/10.5546/aap.2024-10456.eng

To cite: Gil M, Martino F, Besseghine G, Rojas Ortiz MV, Rojas S, Rodríguez ME, et al. Peripheral precocious puberty secondary to severe hypothyroidism. *Arch Argent Pediatr.* 2025;123(3):e202410456.

[1] *Endocrinology Research Center Dr. César Bergadá, National Scientific Research Council and Techniques - FEI, Endocrinology Division;* [2] *Unit 7; Hospital de General de Niños Ricardo Gutiérrez, City of Buenos Aires, Argentina.*

Correspondence to *Melina Gil: melinagil@cedie.org.ar*

Conflict of interest: *None.*

Received*: 5-28-2024*
Accepted*: 9-16-2024*

INTRODUCTION

Precocious pseudopuberty secondary to severe hypothyroidism or Van Wyk-Grumbach syndrome is described in 25% of cases of severe hypothyroidism with plasma thyrotropin (TSH) levels >100 mIU/mL.

Manifestations such as genital bleeding, ovarian masses, visual disturbances, or headaches due to pituitary hyperplasia may be the reason for consultation that stand out to the phenotype of the severe hypothyroid state. Diagnosing this syndrome is essential to avoid possible unnecessary interventions or treatments.

It is essential that the pediatrician, attentive to the longitudinal evaluation of the child's growth, maturational, and intellectual development, recognize hypothyroidism promptly to avoid persistence, which leads to these severe forms.

CLINICAL CASE

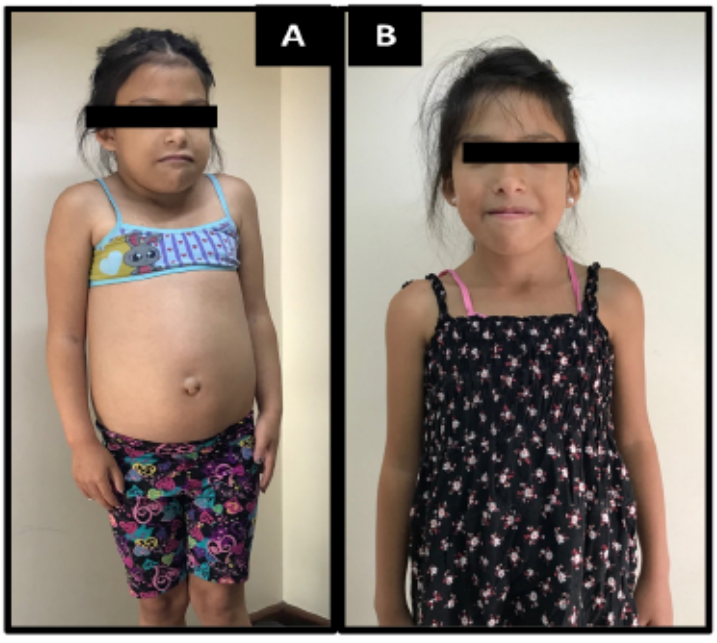
A girl aged 10 years and 9 months consulted the emergency room of a tertiary level hospital for scant genital bleeding of 5 days of evolution with abdominal pain and distension. She appeared chronically ill, with puffy facies, dry and scaly skin, and thin and dry hair. Her abdomen was distended, tympanic, with an umbilical hernia (*Figure 1*). No thyroid gland was palpable. Breast development was stage 2 on the Tanner scale, hypotrophic, but with striking areolar hyperpigmentation, and pubic hair was in stage 1. Vaginal bleeding was scarce but persistent. Her weight was 24.5 kg (-2.06 SD), and her height was 117.5 cm (-2.89 SD), below her genetic target height (25th percentile). She reported a constipated cathartic habit that had evolved for over three years. She had poor school performance and repeated second grade twice. She spoke slowly, with a quiet and withdrawn attitude.

An on-call pelvic ultrasound was performed and reported uterus of preserved shape and size 37 x 17 x 21 mm (6.6 mL) with endometrium of 6 mm. Both ovaries increased in size; the right one showed a simple cystic image of 18 ml and 32 x 22 x 37 mm, and the left one had another cystic image of 10 ml, without fluid in the space of Douglas.

During the ultrasound evaluation, she presented a hypotension episode, so it was decided to hospitalize her. Surgical evaluation was considered to rule out acute surgical abdomen or Hirschsprung's disease.

The patient was clinically evaluated in the

Figure 1. Physical appearance



A. Phenotype of the patient at the time of consultation. She presented puffy facies, a globular abdomen, an umbilical hernia, thin hair on the forehead, and dry skin.
B. Physical appearance of the patient after three months of treatment with levothyroxine.

Division of Endocrinology Gynecology area, who suspected Van Wyk-Grumbach syndrome. The studies requested are summarized in *Table 1*.

Laboratory studies confirmed severe hypothyroidism due to chronic lymphocytic thyroiditis or Hashimoto's thyroiditis and precocious pseudopuberty (Van Wyk-Grumbach syndrome). Treatment was started with LT4 50 mcg/day. The general chemistry laboratory results show hemoglobin 10.6 g/dL (hemacytometric profiles of normochromic normocytic anemia), and mild elevation of transaminases. Skeletal maturation was delayed (bone age 6.8 years for almost 11 years of chronological age).

The study was completed with thyroid ultrasound, which showed both small thyroid lobes with homogeneous echostructure without nodular images. An atrophic variant of chronic lymphocytic thyroiditis was characterized.

Due to elevated TSH levels, the brain's magnetic resonance imaging (MRI) was requested. This revealed pituitary elongation with a cephalocaudal extension of 17 mm, reaching the optic chiasm but with no compressive effect (*Figure 2 A*).

At three weeks of treatment (first outpatient control), there was clear clinical improvement, with no genital bleeding since the third day of treatment. Three months later, an MRI was repeated, which showed normalization of the pituitary size (*Figure 2 B*).

After months, she presented improvement in height Z-score (-2.06 SD) with a growth rate of 14 cm/year, normalization of thyroid function, and reactivation of the gonadotrophic axis in the pubertal range according to age (*Table 1*).

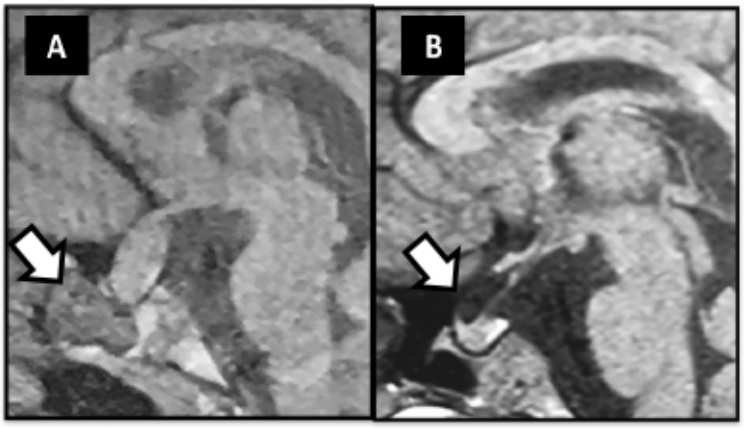
The patient had irregular compliance with clinical controls; she was contacted to reinforce adherence to treatment and controls. She attended at 12 years of age with no changes in pubertal progression, height 132 cm (pc 3) and growth velocity of14 cm/year despite partial adherence to treatment.

DISCUSSION

Van Wyk and Grumbach, in 1960, described for the first time a group of girls with severe hypothyroidism phenotype associated with precocious puberty, delayed bone age, and sellar mass. After treatment with levothyroxine, the symptoms of hypothyroidism improved, and the pubertal changes reversed.[1] At that time, neonatal screening for hypothyroidism was not widespread, so most of these girls had undiagnosed congenital hypothyroidism. Currently, primary congenital hypothyroidism is diagnosed by neonatal screening, and treatment is indicated before one month of life. With early treatment and adequate follow-up, patients have a favorable evolution.[2] The most frequent cause of acquired hypothyroidism is chronic lymphocytic thyroiditis.

The clinical picture varies according to the severity and duration of the hypothyroid state. Growth retardation is usually prominent, associated with delayed skeletal and pubertal

Figure 2. Magnetic resonance imaging of the brain



A. Pituitary elongation of 17 mm in longitudinal axis reaching the optic chiasm without compression effect.
B. Normal size pituitary after 3 months of treatment and normalization of thyroid function.

Table 1. Hormonal determinations

	At diagnosis	After 3 months of treatment	Reference value
TSH (mIU/ml)	2393	0.36	0.5-6.5
T4 (µg/dl)	0.5	13	4.5-12.5
T4L (ng/dl)	0.1	2.2	0.8-2.2
T3 (ng/dl)	<19.5	-	80-220
ATPO (U/ml)	75	-	<35
ATG (U/ml)	2903	-	<50
LH (mIU/ml)	<0.1	9.1	0.3-5
FSH (mIU/ml)	9.1	5.9	1.5-7
Estradiol (pg/ml)	<10	49	30-105
PRL (ng/ml)	82.1	23.4	3-25

TSH: thyrotrophin, T4: thyroxine, T4L: free thyroxine, T3: triiodothyronine, ATPO: antithyroid peroxidase antibody, ATG: antithyroglobulin antibody, LH: luteinizing hormone, FSH: follicle stimulating hormone, PRL: prolactin.

maturation. Asthenia, constipation, learning difficulties, dry skin, and hair are frequent manifestations.[3,4] Although pubertal delay is characteristic in hypothyroidism, paradoxically, girls with Van Wyk-Grumbach syndrome present breast development, with or without galactorrhea and genital bleeding. Pelvic ultrasound usually shows large multicystic ovaries with uterine enlargement.[5] It is less frequent in boys, but they may present testicular enlargement without virilization.[6]

Pituitary enlargement is due to hyperplasia of thyrotropic cells stimulated by lack of negative feedback of free thyroxine (T4L). Hyperplasia of the thyrotropic and lactotropic sectors is stimulated by the hypothalamic TSH-releasing factor (TRH). This hyperplasia can become very important and manifest with headache or visual disturbances due to involvement of the optic chiasm and retrograde under treatment with LT4.[7]

Severe hypothyroidism is that with serum TSH levels > 100 mIU/ml. However, the serum sample requires repeated dilution processing to reach the actual TSH value. In Van Wyk-Grumbach syndrome, peripheral thyroid hormone levels are deficient, prolactin is elevated, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are suppressed, and estradiol is normal or slightly elevated.[6]

The pathophysiology of precocious pseudopuberty is not well known; the most common hypothesis accepted involves the mechanism of cross-reactivity between TSH and FSH because of the similar structure between the glycoproteins and their receptors (> 40% homology in the binding domain).[8-10] Although specificity barriers exist in these ligand-receptor pairs, they would only prevent cross-activation under physiological conditions, whereas, in non-physiological situations, this structural similarity results in natural promiscuity between receptors and ligands. Thus, TSH in high concentrations can act promiscuously on gonadal FSH receptors. This explains the proliferation of ovarian follicles with estradiol production, as in this case. In males, it only causes Sertoli cell hypertrophy manifesting with macroorchidism without increasing steroid activity.[7]

Stimulated ovaries can present large ovarian masses and suffer complications such as hemorrhage with hemoperitoneum or torsion. In our patient, as a differential diagnosis, ovarian stimulation syndrome was considered, which can occur with gonadotrophin-producing germ cell tumors. However, it was ruled out with normal alpha-fetoprotein and beta-human chorionic gonadotropin levels.[7]

After initiating treatment with levothyroxine, the cysts resolve entirely in 3 to 6 months.[11-13]

Galactorrhea, a clinical manifestation of hyperprolactinemia, was frequently reported in the case series of Van Wyk and Grumbach. However, more recent case series describe it in only 2 of 26.[7]

Clinically, unlike true precocious puberty, where growth and skeletal maturation are at an advanced stage accelerated by sex steroid stimulation, in this syndrome, the severe hypothyroid state predominates, and there is no actual activation of the gonadotrophic axis.

All the symptoms of hypothyroidism, pituitary hyperplasia, and other manifestations due to promiscuous action of elevated TSH reverted after normalization by levothyroxine replacement therapy. In cases of severe acquired hypothyroidism, such as our patient, it

is recommended to start treatment at low doses and then titrate the dose to avoid adverse events such as headache or insomnia.[3]

Under treatment, there is usually evidence of catch-up growth, especially during the first year of life. However, adult height may be affected if the period of hypothyroidism is very prolonged.

The pediatrician's role is very relevant in evaluating growth and development; it is essential to identify signs and symptoms suggestive of hypothyroidism or the presence of goiter. Referral to a specialist will allow timely identification to avoid progression in severity. Treatment is simple and accessible, adequately controlled has optimal results. ■

Acknowledgments

To Dr. Ana Chiesa and Dr. Mirta Gryngarten, thank you for your careful review of the manuscript and for unconditionally transferring your extensive clinical experience, which helped us recognize this clinical picture.

REFERENCES

1. Van Wyk JJ, Grumbach MM. Syndrome of precocious menstruation and galactorrhea in juvenile hypothyroidism: an example of hormonal overlap in pituitary feedback. *J Pediatr*. 1960;57(3):416-35.
2. Chiesa A, Papendieck P, Vieites A, Braslavsky D. Hipotiroidismo congénito. *Separata Montpellier*. 2019;27(2):1-65.
3. Comité Nacional de Endocrinología. Alteraciones tiroideas en la infancia y en la adolescencia. Parte 2: hipotiroidismo. *Arch Argent Pediatr*. 2021;119(1):S8-16.
4. Brown RS. Autoimmune thyroiditis in childhood. *J Clin Res Pediatr Endocrinol*. 2013;5(Suppl 1):45-9.
5. 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.
6. Cabrera S, DiMeglio L, Eugster E. Incidence and Characteristics of Pseudoprecocious Puberty Because of Severe Primary Hypothyroidism. *J Pediatr.* 2013;162(3):637-9.
7. Boddu SK, Ayyavoo A, Nagarajappa VH, Kalenahalli KV, Muruda S, Palany R. Van Wyk Grumbach Syndrome and Ovarian Hyperstimulation in Juvenile Primary Hypothyroidism: Lessons from a 30-Case Cohort. *J Endocr Soc*. 2023;7(6):bvad042.
8. Vassart G, Pardo L, Costagliola S. A molecular dissection of the glycoprotein hormone receptors. *Trends Biochem Sci*. 2004;29(3):119-26.
9. Alzebidi JA, Almushri K, Elmoheen R. Spontaneous Ovarian Hyperstimulation Syndrome Associated with Primary Hypothyroidism. *Cureus*. 2023;15(1):e33247.
10. 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.
11. Sultan A, Velaga MR, Fleet M, Cheetham T. Cullen's sign and massive ovarian enlargement secondary to primary hypothyroidism in a patient with a normal FSH receptor. *Arch Dis Child*. 2006;91(6):509-10.
12. Yamamoto K, Saito K, Takai T, Naito M, Yoshida S. Visual field defects and pituitary enlargement in primary hypothyroidism. *J Clin Endocrinol Metab*. 1983;57(2):283-7.
13. Chen CP, Chen CW, Wang KG. Spontaneous ovarian hyperstimulation syndrome and hyperprolactinemia in primary hypothyroidism. *Acta Obstet Gynecol Scand*. 1996;75(1):70-1.