Journal of the Endocrine Society, 2023, **7**, 1–7
https://doi.org/10.1210/jendso/bvad135
Advance access publication 9 November 2023
Mini-Review

Precocious Puberty in Hypothyroidism: Mini-Review of Van Wyk–Grumbach Syndrome

Sara Maria Fernandez-Gonzalez,[1] Marina Maria Perez Vila,[1] and Ana Maria Prado-Carro[2]

[1]Pediatrics Service, Complexo Hospitalario Universitario de A Coruña, 15006 A Coruña, Spain
[2]Endocrinology Department, Complexo Hospitalario Universitario de A Coruña, 15006 A Coruña, Spain

Correspondence: Sara Maria Fernandez-Gonzalez, MD, Complexo Hospitalario Universitario A Coruña, As Xubias 84, 15006 A Coruña, Spain.
Email: sara.maria.fernandez.gonzalez@sergas.es.

Abstract

Severe hypothyroidism can affect a variety of organs and can develop atypical manifestations. Peripheral precocious puberty may be secondary to other endocrinological diseases, which must be taken into account in the differential diagnosis in order to avoid unnecessary additional tests. Van Wyk–Grumbach syndrome is an infrequent manifestation characterized by severe hypothyroidism and incomplete precocious puberty. Diagnosis is made by clinical and complementary tests, and the main treatment goal is to achieve euthyroidism through hormone replacement. Prognosis is good once the treatment is established. The aim of this study is to review the available literature about Van Wyk–Grumbach syndrome following the PRISMA statement, and to present the first clinical case published in Spain. We have included the articles published during the period from 1905 to week 40 of 2022. A total of 68 articles have been selected for study and analysis, within which there are 99 published clinical cases. Girls accounted for 92.1% of cases (median age at the diagnosis 8.5 years). Metrorrhagia was the most prevalent symptom, present in 80.5% of the girls. Abdominal ultrasound was performed in 93.3% of the girls and 97.8% of them had at least one ovarian cyst. All cases were treated with levothyroxine, responding satisfactorily after the first doses of treatment. To conclude, Van Wyk–Grumbach syndrome is characterized by severe hypothyroidism and incomplete precocious puberty, which is important to keep in mind in order to avoid complementary exams and unnecessary surgical interventions.

Key Words: hypothyroidism, vaginal bleeding, precocious puberty, Van Wyk–Grumbach, polycystic ovaries

Abbreviations: FSH, follicle-stimulating hormone; fT4, free thyroxine; KDSS, Kocher-Debré–Semelaigne syndrome; LH, luteinizing hormone; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; TSH, thyrotropin (thyroid-stimulating hormone); VWGS, Van Wyk–Grumbach syndrome.

Acquired hypothyroidism is the most common thyroid affection in childhood and Hashimoto thyroiditis is the main cause. It is estimated to have a prevalence of approximately 1% to 2% in children, especially in girls [1], and higher incidence in patients with autoimmune diseases and chromosomal disorders such as Down and Turner syndrome [2, 3]. Generally, signs and symptoms show a gradual onset, and they are characterized by asthenia, weight gain, dry skin, and bradypsychia as well as growth and developmental delay. Occasionally, hypothyroidism may manifest with precocious puberty, as occurs in Van Wyk–Grumbach syndrome (VWGS) [4].

VWGS is characterized by severe hypothyroidism associated with incomplete precocious puberty. It was described by Kendle [5] in 1905, in his published report of a clinical case of a 9-year-old girl with precocious puberty and metrorrhagia, in addition to obesity, short stature, constipation, and xerosis, which was treated with sheep thyroid extract and had a satisfactory evolution. *After that*, in 1960, Van Wyk and Grumbach [6] described this syndrome as severe hypothyroidism, precocious puberty, and cystic ovaries.

Nowadays, there is a pathophysiological hypothesis that establishes that high thyroid-stimulating hormone (TSH) levels, which are present in cases of severe hypothyroidism due to the negative feedback mechanism secondary to failure of the thyroid gland [7], acts as a "follicle-stimulating hormone (FSH)-like" agent on the FSH receptors in the ovary, due to their common α-subunits. Estradiol levels increase and they generate ovarian hyperstimulation, developing precocious puberty, metrorrhagia, and ovarian cysts in girls as well as development of secondary sexual characteristics, in the absence of pubic or axillary hair. Paradoxically, thyrotropin-releasing hormone (TRH) induces hyperprolactinemia and simultaneously probably suppresses the pituitary gonadotropic axis, especially luteinizing hormone (LH) [8].

Girls with VWGS have metrorrhagia, ovarian cysts, breast enlargement with or without galactorrhea, and delayed bone age. Usually, boys have macroorchidism without virilization. In contrast to many other causes of precocious puberty, this entity is characterized by the absence of axillary and pubic hair, highlighting a clear dissociation between gonadarche and adrenarche [9].

Clinical manifestations and complementary tests findings determine the diagnosis. In the laboratory test we can find very low free thyroxine (fT4) levels, and very high TSH, estradiol, and prolactin levels. High prolactin levels produce LH suppression, increase ovarian sensitivity to circulating gonadotropins, and accelerate follicular maturation [10]. Anti-thyroid antibodies are also elevated in most cases. After GnRH administration, and lack of increase in LH as

Received: 7 June 2023. **Editorial Decision:** 26 October 2023. **Corrected and Typeset:** 16 November 2023

well as FSH are found, with is characteristic of peripheral precocious puberty.

Anemia is a common finding between many published clinical cases of VWGS, and this could be most likely be due to a reduction in red cell production secondary to lower tissue oxygen requirements, in addition to blood loss in vaginal bleeding [8, 11].

Radiological tests usually reveal enlarged ovaries with single or multiple cysts and a pubertal uterus, as well as delayed bone age and pituitary hyperplasia.

Treatment is based on hormone replacement with a synthetic form of thyroid hormone, requiring progressive dose adjustment to achieve euthyroidism [12]. The prognosis is good once the treatment is established. Clinical manifestations disappear and secondary sexual characteristics regress. Prompt treatment enables children to reach a normal final height [13, 14]. Surgical treatment is reserved for complications, such as ovarian torsion [14]. Early diagnosis is important to avoid invasive and unnecessary diagnostic and therapeutic proceedings, and also to make a differential diagnosis with other pathologies like McCune Albright syndrome [15]. This syndrome may have similar symptoms, except for the congenital hyperpigmented spots, polyostotic fibrodysplasia and, very importantly, it usually presents with accelerated bone age [16]. Patients with McCune Albright syndrome do not present a response to the levothyroxine sodium treatment.

Material and Methods

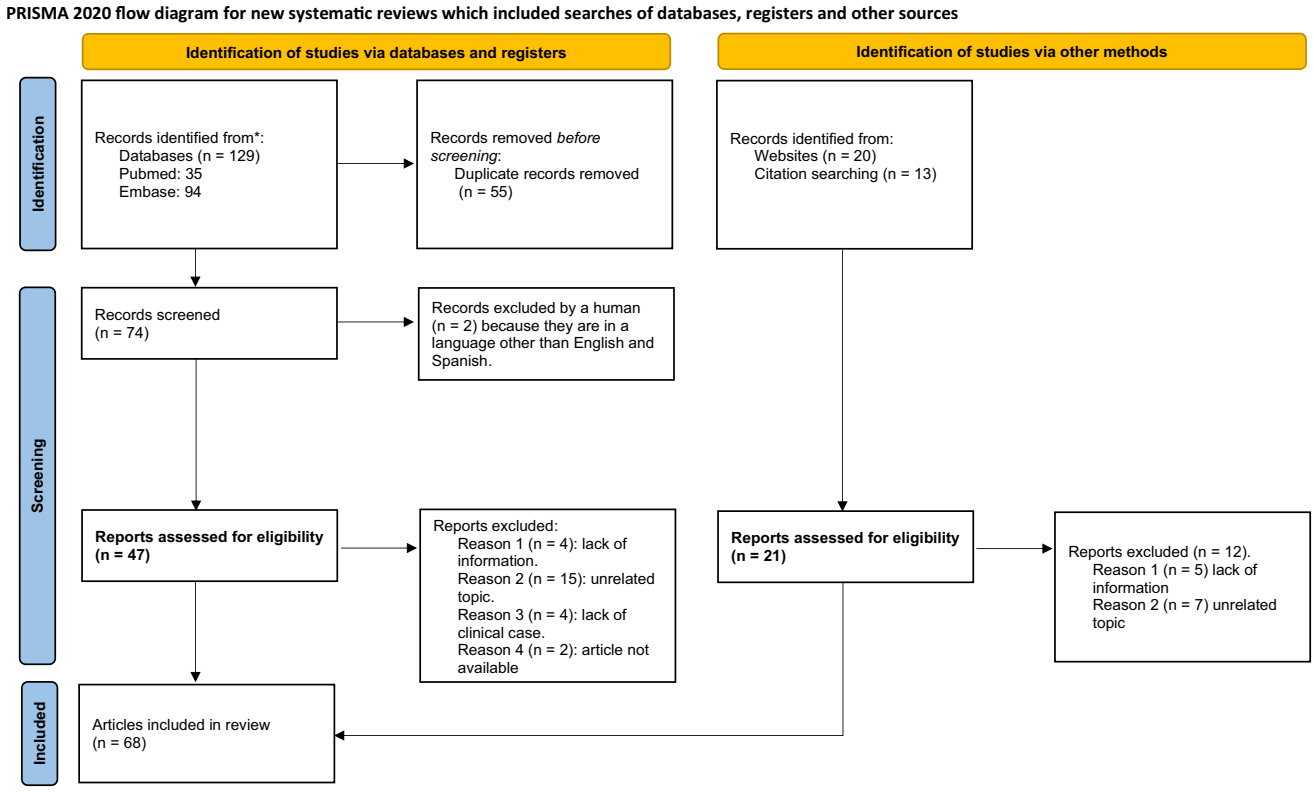
A systematic review of the literature using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement was done for the period from the year 1905 to week 40 of 2022 in the PubMed and Embase databases. In PubMed, the terms "*hypothyroidism*" AND "*puberty, precocious*" OR "*precocious puberty*" AND "*polycystic ovary syndrome*" OR "*van Wyk Grumbach syndrome*" have been included. The articles selected in Embase met the following criteria: "*hypothyroidism*" AND "*precocious puberty*" AND "*polycystic ovary syndrome*" OR "*ovary polycystic disease*" OR "*van Wyk-Grumbach syndrome*."

We have included any type of article written in English or Spanish language, including conference abstracts, because most clinical cases are presented in that format.

Within the inclusion criteria of the articles, they must present at least one clinical case with a diagnosis of VWGS, indicating the patient's age, clinical presentation, blood tests at diagnosis, and the treatment received.

Articles that do not meet these inclusion criteria have been excluded.

A total of 158 articles have been found, 125 of them from these 2 databases (90 from Embase and 35 from PubMed) and 33 from other sources of information. A total of 51 articles have been excluded because they were repeated. Of the remaining, 22 have been eliminated for being inconsistent with the terminology, 2 due to a language other than English or Spanish, 2 because they are not available and 9 for lack of information. Finally, 68 articles have been selected for study and analysis, including 99 clinical cases. Figure 1) presents the flow chart of the article selection.



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Figure 1. Flow-diagram according to the PRISMA statement.

Clinical Case

A 6-year-old Spanish girl consulted the emergency department of a tertiary level hospital with a 1-day history of metrorrhagia and dizziness. She had no relevant data in her personal or family medical background. In the previous 10 days, she had painful breast development and abdominal discomfort. Her appetite was normal, and the symptoms were not associated with vomiting, fever, headache, asthenia, or weight loss.

On general physical examination, her weight was 28.8 kg (according to World Health Organization references, P98, 2.08 SD), her height was 112 cm (P22, −0.79 SD) and her body mass index was 22.55 kg/m^2 (> P99, 3.07 SD). She had very dry skin, mild acanthosis nigricans on the neck and breast development at Tanner stage 2 to 3, without galactorrhea, and she had no pubic or axillary hair development (Fig. 2). The abdominal examination revealed a mass painful to the touch, approximately 5 × 4 cm in size, located in the right hemiabdomen that did not exceed the midline. Female external genitalia were normal, with minimal vaginal bleeding.

Laboratory tests revealed high TSH levels and low fT4 levels, positive thyroid antibodies, in addition to a slight elevation of prolactin, estradiol, and CA-15.3 levels (Table 1). Abdominal ultrasound revealed a pubertal uterus with 6.6 cm of longitudinal diameter, multicystic left ovary and in the right ovary a 5.4 × 3.9 cm cystic image with cysts inside, suggestive of a functional cyst.

As VWGS was suspected, the study was completed with thyroid ultrasound, showing a normal-sized and hypoechogenic thyroid, which was suggestive of autoimmune thyroiditis. We also included a wrist x-ray image, which was in accordance with chronological age, and a brain magnetic resonance imaging, which revealed adenohypophyseal physiological hyperplasia. Treatment was started with levothyroxine (Eutirox®; maximum dose received 2.6 mcg/kg/day). She tolerated the treatment well and she did not suffer adverse effects.

Since then, she has presented a favorable clinical and analytical evolution. Seven months later, her weight was 29.5 kg (P97, 1.82 SD), her height was increased by 6.8 cm (118.8 cm, P46,

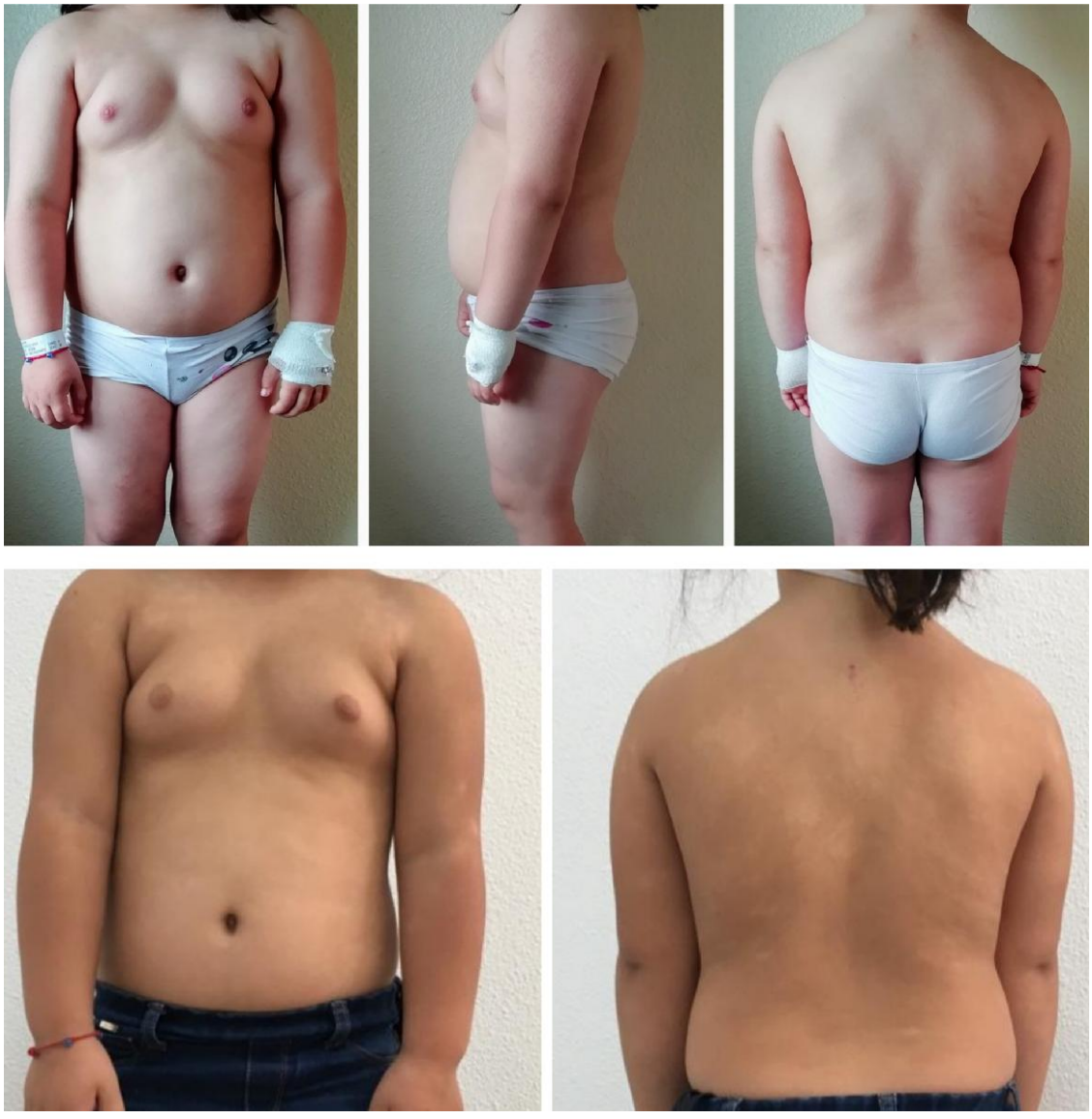


Figure 2. Phenotype before starting treatment (above) and 6 months after treatment (below). Before starting treatment, she had telarchy, dry skin, scratching lesions, abdominal distension, and dorsal hump. Clinical manifestations had favorable evolution thanks to replacement treatment.

Table 1. Laboratory evolution over the clinical course of treatment

	At time of diagnosis	2 weeks after treatment	3 months after treatment	6 months after treatment
TSH (pUI/mL)	1132	95	1.04	17
fT4 (ng/dL)	0.4	1.1	1.1	1.1
Anti-TG (U/mL)	82		103	55
Anti-TPO (U/mL)	>1300		912	>1300
Prolactin (ng/mL)	87			
FSH (mUI/mL)	3.6	0.3	0.8	
LH (mIU/mL)	<0.07	<0.07	<0.07	
Estradiol (pg/mL)	73	26	<12	
Progesterone (ng/mL)	1.8			

Abbreviations: Anti-TG, antithyroglobulin antibody; Anti-TPO, anti-thyroid peroxidase; FSH, follicle-stimulating hormone; fT4, free thyroxine; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

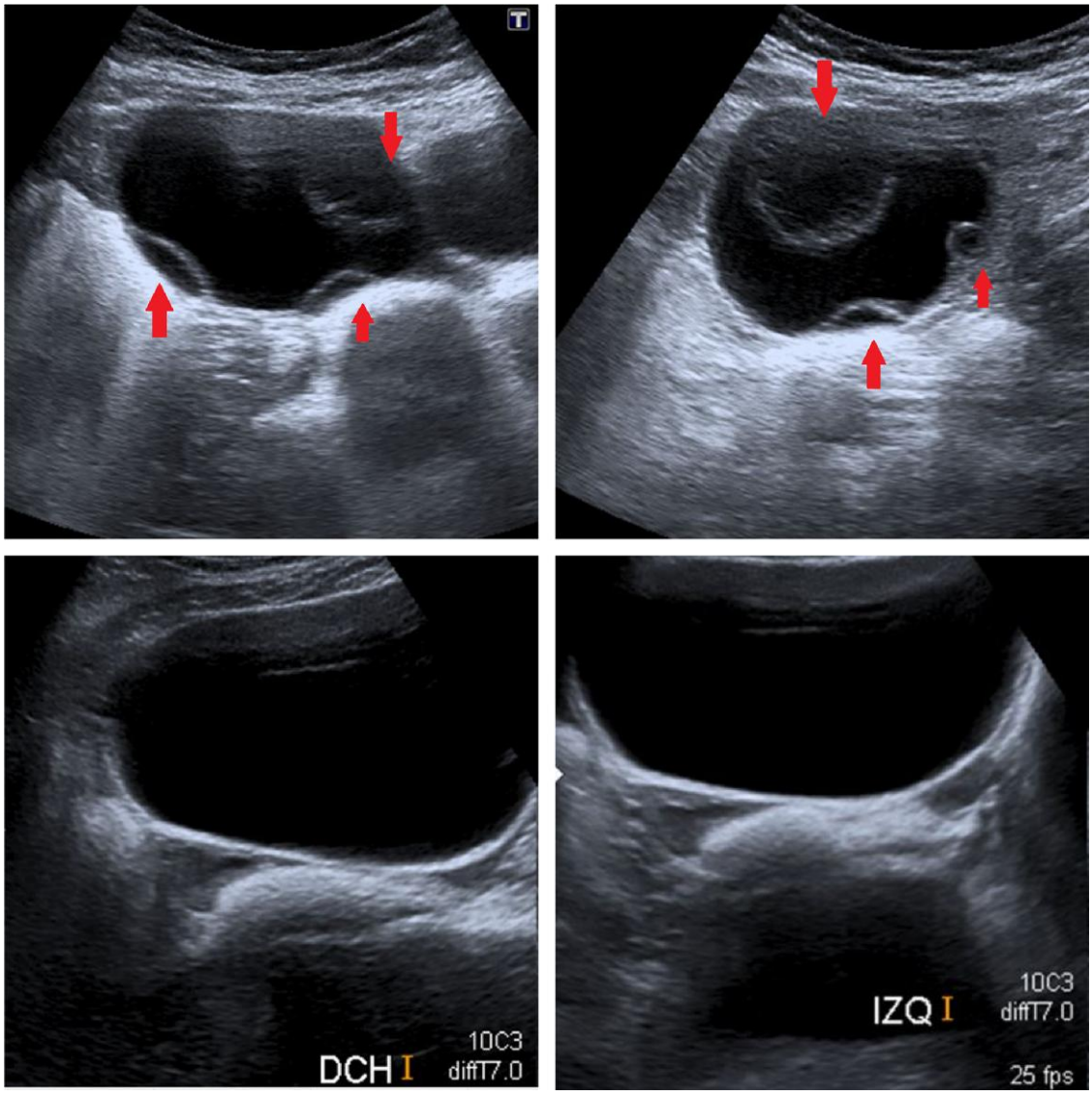


Figure 3. Pelvic ultrasound before (above) and after (below) starting treatment. Arrows point to ovarian cysts.

−0.11 SD) and her body mass index was decreased to 20.9 kg/m^2 (>P99, 2.42 SD). Table 1 shows the analytical evolution and Fig. 2 shows clinical evolution over the course of treatment with levothyroxine. Metrorrhagia was resolved after starting the treatment. Two months later, abdominal ultrasound revealed a normal-size uterus and resolution of the ovarian cysts (Fig. 3).

Results

Ultimately, 68 articles were reviewed, in which we found 99 clinical cases (92.1% girls). The patients were diagnosed at the median age of 8.75 years (range, 1.5-24 years) with 10.3% presenting at 9 years.

Almost half of the cases reported (33.3%) are from India, 14.4% are from the United States, 12.1% are from Pakistan, and 6% are from China. There are 5 cases from Turkey, 3 cases from Italy, 2 from Tunisia, 2 from Japan, 2 from Korea, and 2 from Greece. The remaining cases originate one each from different countries: Mexico, Guyana, Cuba, Bangladesh, Brazil, France, Germany, Georgia, Chile, Nepal, Sri Lanka, Algeria, Qatar, Bali, Croatia, and Jordan.

Metrorrhagia was the most common cause of consultation. It was present in 80.5% of the girls, with a median evolution time of 12 weeks (range, 0.14-576). Abdominal pain was present in 18% and thelarche in 88.9% of the girls. At the diagnosis, the median SD of weight was −0.25 SD (range, −3.87–2.87) and height was −3.24 SD (range, −9.17–0.19). World Health Organization standards of reference were used in cases of children up to 10 years of age and standards of reference from Carrascosa et al [17] were used for patients older than 10 years.

Seven cases were diagnosed as a result of a surgical intervention. Among these 7 cases, 5 [14, 18-21] underwent surgery due to an ovarian torsion and the other 2 [19, 22] on suspicion of neoplastic lesion.

Seven cases have been published in male patients, 2 of them [23, 24] from China, and the others from India [25], Italy [26], Korea [27], Turkey [28] and the United States [29]. These patients presented with weight gain, short stature, delayed bone age, cold intolerance, and poor school performance. On physical examination they had hepatomegaly and increased testicle size, without pubarche.

Ten patients had trisomy 21 [12, 30-36], 3 cases were associated with Kocher syndrome [37-39] and 1 with Alport syndrome [27].

Abdominal ultrasound was performed in 93.3% of the patients; 85.5% had multicystic ovaries, 12.2% a simple cyst, and the abdominal ultrasound was normal in the 2.3% of the patients. Wrist x-ray was done in 75 cases (75.8%) and 97.3% had delayed bone age (mean difference between bone and chronological age was 43.2 months; range, 12-120 months). Thyroid ultrasound was performed in 39.4% of cases, finding autoimmune thyroiditis in 51.3%. Brain magnetic resonance imaging was done in 47.5%, pituitary hyperplasia was observed in 51.1%, pituitary adenoma in 19.1%, and the remaining 29.8% had no alterations.

All cases were treated with levothyroxine (mean dose of 3.2 mcg/kg/day). All reported cases responded satisfactorily to treatment, but there are 17 cases (17.2%) in which there is no reference to response to treatment. Metrorrhagia resolved after first doses, ovarian cysts and the rest of the symptoms disappeared a few months later, and laboratory tests normalized in 4.5 months on average (between 0.25 months and 48 months) with a median of 3 months.

Discussion

VWGS is characterized by severe hypothyroidism and incomplete precocious puberty. As we have seen in our review, it is more common in girls, and usually it presents with metrorrhagia, abdominal pain, bilateral ovarian cysts, and delayed bone age. In male patients, it presents with increased testicle size without virilization, in addition to delayed bone age.

Bone age and height could be the key point in the differential diagnosis because children with precocious puberty usually have advanced bone age and pubertal growth spurt. In contrast, VWGS children are short, have delayed bone age, and lack the concomitant growth spurt [9].

In our review we have found a large number of cases reported in countries where the neonatal screening test for congenital hypothyroidism is not universally implemented in the entire population [40]. The reported patients suffered from acquired autoimmune hypothyroidism, so although in Western countries screening is performed in the neonatal period, this entity could not be diagnosed at that time because thyroid function is normal at birth.

Our patient is the first Spanish case available in the literature. She consulted for metrorrhagia and bloating, revealing bilateral ovarian cysts on abdominal ultrasound, which could be explained by ovarian myxedematous infiltration [4]. Laboratory tests showed normochromic normocytic anemia, elevated Ca 15.3 (75.5 IU/mL, normal value < 35 UI/mL [41]), that we have not found in the clinical cases reviewed, and normal levels of CA125. In some published cases [42, 43] CA125 levels were initially elevated and they normalized after regression of ovarian cysts.

Despite the fact that most of cases consulted in a short period of time since the onset of metrorrhagia, a common finding in the literature is the presence of normocytic and normochromic anemia [4, 8, 15, 19], which could be explained by menstrual blood losses or due to lower metabolic requirements as a result of severe hypothyroidism.

Down syndrome [12, 30-34] could make the diagnosis more difficult, because cognitive impairment and behavioral alterations could be attributed to their condition. In this situation delayed bone age and decreased growth velocity could facilitate the diagnosis [9, 33]. Hypothyroidism is the most common endocrine problem in children with Down syndrome and its prevalence varies between 7% and 40% [2]; therefore, it is important to evaluate thyroid function in children with Down syndrome, due to the increased risk of autoimmune hypothyroidism.

Kocher-Debré–Semelaigne syndrome (KDSS) is a rare disease in childhood characterized by pseudohypertrophy and muscle weakness in patients with untreated long-standing severe hypothyroidism [44]. In our review, 2 cases presented VWGS in relation with KDSS [37, 38]. In these situations, the cause of myopathy is not completely clarified. It could be in relation to glycogen and glycosaminoglycans storage [45], and lower enzymatic activity for generating energy. Myopathy and laboratory alterations (increased creatine kinase) are resolved with levothyroxine treatment. Another clinical case [10] presented rhabdomyolysis, pseudohypertrophy, muscle weakness, and elevated CPK at the diagnosis, which is compatible with KDSS.

There are some limitations in this study. First, there was a lack of information in some of the published articles, and second, some of the data collected are based on abstracts presented in the European Endocrinology Congress.

Conclusions

We have presented here a review of the available literature about Van Wyk–Grumbach syndrome, an infrequent rare

manifestation characterized by severe hypothyroidism and incomplete precocious puberty, along with the first clinical case published in Spain. VWGS is a manifestation more common in girls characterized by severe hypothyroidism and incomplete precocious puberty. It is characterized by metrorrhagia, ovarian cysts, breast development, and delayed bone age. Diagnosis is made by clinical and complementary tests. The main treatment goal is to achieve euthyroidism through hormone replacement with synthetic thyroid hormone.

We believe this is an important topic. Although it is a rare manifestation of untreated hypothyroidism, it is important to suspect and diagnose it early to avoid invasive complementary tests, unnecessary surgical interventions, and to initiate an appropriate treatment for a good prognosis.

Disclosures

The authors declare that they have no conflict of interest.

Author Contributions

Each author listed on the manuscript has read and approved the submission of this version of the manuscript and takes full responsibility for the manuscript.

Informed Patient Consent for Publication

Written informed consent was obtained from the patient's parents.

Data Availability

Original data generated and analyzed during this study are included in this published article or in the data repositories listed in References.

References

1. Cappa M, Bizzarri C, Crea F. Autoimmune thyroid diseases in children. *J Thyroid Res*. 2011;2011:675703.
2. Amr NH. Thyroid disorders in subjects with down syndrome: an update. *Acta Biomed*. 2018;89(1):132-139.
3. Witkowska-Sędek E, Borowiec A, Kucharska A, *et al*. Thyroid autoimmunity in girls with turner syndrome. *Adv Exp Med Biol*. 2017;1022:71-76.
4. Riaz M, Ibrahim MN, Laghari TM, Hanif MI, Raza J. Van Wyk Grumbach syndrome. *J Coll Physicians Surg Pak*. 2020;30(12):1332-1334.
5. Kendle FW. Case of precocious puberty in a female cretin. *Br Med J*. 1905;1(2301):246.
6. Wyk JJV, Grumbach MM. Syndrome of precocious menstruation and galactorrhea in juvenile hypothyroidism: an example of hormonal overlap in pituitary feedback. *J Pediatr*. 1960;57(3):416-435.
7. Kanwal S, Ullah Z, Malik SE. Van Wyk Grumbach syndrome: case report. *Khyber Med Univ J*. 2022;14(2):141-143.
8. Baranowski E, Högler W. An unusual presentation of acquired hypothyroidism: the Van Wyk-Grumbach syndrome. *Eur J Endocrinol*. 2012;166(3):537-542.
9. Indumathi CK, Bantwal G, Patil M. Primary hypothyroidism with precocious puberty and bilateral cystic ovaries. *Indian J Pediatr*. 2007;74(8):781-783.
10. Leonardi A, Penta L, Cofini M, Lanciotti L, Principi N, Esposito S. Rhabdomyolysis in a young girl with van Wyk-Grumbach syndrome due to severe Hashimoto thyroiditis. *Int J Environ Res Public Health*. 2018;15(4):704.
11. Chu JY, Monteleone JA, Peden VH, Graviss ER, Vernava AM. Anemia in children and adolescents with hypothyroidism. *Clin Pediatr (Phila)*. 1981;20(11):696-699.
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. *J Pediatr Surg Case Reports*. 2017;25:5-9.
13. Jimenez Soutelo M, Faraj G. Pseudopubertad precoz por hipotiroidismo severo. *Rev Endocrinol Ginecológica y Reprod*. 2008;15:43-44.
14. Zhang H, Geng N, Wang Y, Tian W, Xue F. Van Wyk and Grumbach syndrome: two case reports and review of the published work. *J Obstet Gynaecol Res*. 2014;40(2):607-610.
15. Rastogi A, Bhadada SK, Bhansali A. An unusual presentation of a usual disorder: Van Wyk-Grumbach syndrome. *Indian J Endocrinol Metab*. 2011;15(6):S141-S143.
16. Soriano Guillén L, Argente J. Pubertad precoz periférica: fundamentos clínicos y diagnóstico-terapéuticos. *An Pediatr*. 2012;76(4):229.e1-229.e10.
17. Carrascosa A. Estudio Longitudinal de Crecimiento Barcelona 1995-2017. *Endocrinología, Diabetes y Nutrición*. 2018;65(6):311-313.
18. Sanjeevaiah AR, Sanjay S, Deepak T, Sharada A, Srikanta SS. Precocious puberty and large multicystic ovaries in young girls with primary hypothyroidism. *Endocr Pract*. 2007;13(6):652-655.
19. 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):538-542.
20. Gregory JL, Wilson DM, Parker B, Wood BP. Radiological case of the month. *AJDC*. 1992;146:1-1.
21. Burns LP, Pennesi CM, Rosen MW, *et al*. Interdisciplinary care and a focus on fertility preservation when multi-cystic ovaries cause ovarian torsion: a case of a 9-year-old girl with severe, undiagnosed hypothyroidism. *J Pediatr Adolesc Gynecol*. 2020;33(6):723-726.
22. Reedy MB, Phillips D. A 7-year-old with bilateral, granulosa cell tumors, severe hypothyroidism, precocious puberty, and delayed bone-age: a case of Van Wyck-Grumbach syndrome diagnosis and recommendations. *Gynecol Oncol*. 2020;159:153.
23. Omran A, Peng J, Shrestha B, Ashhab MU, Yin F. Male child with Van Wyk-Grumbach's Syndrome and other complications of long-standing primary hypothyroidism: a case report. *Case Rep Pediatr*. 2012;2012:1-5.
24. Zhang S, Yang J, Zheng R, Jiang L, Wei Y, Liu G. VanWyk-Grumbach syndrome in a male pediatric patient: a rare case report and literature review. *Exp Ther Med*. 2017;13(3):1151-1154.
25. Acharya SV, Mathew BK, Menon PS, Bandgar TR, Shah NS. Rare cases of precocious puberty with hypothyroidism: a case series with review of literature. *Endocrinologist*. 2010;20(2):78-79.
26. Abstracts of the 51st annual meeting of the European Society for Paediatric Endocrinology (ESPE). Leipzig, Germany. September 20-23, 2012. *Horm Res Paediatr*. 2012;78(Suppl.1):1-349.
27. Lee S-J, Moon J-E, Lee G-M, Cho M-H, Ko CW. An Alport syndrome boy with Van Wyk-Grumbach syndrome induced by prolonged untreated congenital hypothyroidism. *Ann Pediatr Endocrinol Metab*. 2020;25(2):132-136.
28. Esen I, Demirel F. Hypothyroidism-associated testicular enlargement: is it a form of precocious puberty or not? A case report. *Turk J Pediatr*. 2011;53(2):210-212.
29. Friends D. PES 2020 Abstracts. *Horm Res Peadiatr*. 2020;93(Suppl 1):1-185.
30. Gupta J, Lin-Su K. Van Wyk-Grumbach syndrome in a female pediatric patient with trisomy 21: a case report. *Int J Pediatr Endocrinol*. 2020;2020(1):20-22.
31. Selim N, Dououia K, Boutalbi N, Boukadoum N, Bouchair N. Van-Wyk Grumbach syndrome associated with trisomy 21: a case report. *58th Annu ESPE Meet*. 2019;92:P3-330.

32. Sharma Y, Bajpai A, Mittal S, Kabra M, Menon PSN. Ovarian cysts in young girls with hypothyroidism: follow-up and effect of treatment. *J Pediatr Endocrinol Metab*. 2006;19(7):895-900.
33. Chemaitilly W, Thalassinos C, Emond S, Thibaud E. Metrorrhagia and precocious puberty revealing primary hypothyroidism in a child with Down's Syndrome. *Arch Dis Child*. 2003;88(4):330-331.
34. Rivera-Hernández A, Madrigal-González MM, Espinosa-Peniche R, Zurita-Cruz J, Balcázar-Hernández L. Van Wyk-Grumbach syndrome and trisomy 21. *Baylor Univ Med Cent Proc*. 2022;35(4):569-571.
35. Ozgen T, Güven A, Aydin M. Precocious puberty in a girl with down syndrome due to primary hypothyroidism. *Turk J Pediatr*. 2009;51(4):381-383.
36. Dikaiakou E, Vlachopapadopoulou E, Kosteria I, *et al*. A girl with trisomy 21 presents with Van Wyk-Grumbach syndrome. A rare diagnosis. *Eur Soc Paediatr Endocrinol*. 2021;87(3):2021.
37. Oden Akman A, Tayfun M, Demirel F, Ucakturk SA, Gungor A. Association of Van Wyk Grumbach and Debre Semelaigne syndromes with severe hypothyroidism. *J Pediatr Adolesc Gynecol*. 2015;28(6):e161-e163.
38. Razi SM, Gupta AK, Gupta DC, Gutch M, Gupta KK, Usman SI. Van Wyk-Grumbach syndrome with Kocher-Debré-Sémélaigne syndrome: case report of a rare association. *Eur Thyroid J*. 2017;6(1):47-51.
39. 55th annual meeting of the European Society for Paediatric Endocrinology (ESPE), Paris, France. *Horm Res Paediatr*. 2016; 86(Suppl.1):1-556.
40. Therrell BL, Padilla CD, Loeber JG, *et al*. Current status of newborn screening worldwide: 2015. *Semin Perinatol*. 2015;39(3): 171-187.
41. Ocaña E, Isabel Aceituno Azaustre Ma. Utilidad Clínica de Los Marcadores Tumorales Esther. 2014; 2-12.
42. Durbin KL, Diaz-Montes T, Loveless MB. Van Wyk and Grumbach syndrome: an unusual case and review of the literature. *J Pediatr Adolesc Gynecol*. 2011;24(4):e93-e96.
43. Ghosh S, Chowdhury S, Shivaprasad K, *et al*. Huge bilateral ovarian cysts in adulthood as the presenting feature of Van Wyk Grumbach syndrome due to chronic uncontrolled juvenile hypothyroidism. *Indian J Endocrinol Metab*. 2013;17(7): 164.
44. Ariza Mateos M, Cruz Rodríguez A, López-Canti Morales L, Navarro Villén M. Síndrome de Kocher-Debré-Semelaigne asociado a una hiperplasia hipofisaria. Estudio de un caso infrecuente. *Acta Pediátr Esp*. 2017;75(11–12):e214-e218.
45. Luiz N. Kocher-Debre-Semelaigne syndrome. *Indian Pediatr*. 1998;35(11):1115-1116.