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Case Report

An unusual cause of bleeding in primary hypothyroidism

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Highlights

- This case report highlights the importance of excluding primary hypothyroidism in children presenting with unexplained bleeding disorders especially if there is evidence of factor 8 deficiency.
- It illustrates how primary hypothyroidism can cause an acquired von Willebrand Factor deficiency and multi system manifestations with reversal of biochemical and clinical abnormalities after levothyroxine therapy.

Abstract. A 10-yr-old female was referred due to prolonged bleeding lasting for a week following tooth extraction. She had heavy periods since she was 9. Her height was < 0.4th centile. Tanner staging was breast stage B3-4, axillary hair A1, and pubic hair P1. Thyroid function tests showed elevated TSH, low free T4, and negative anti-TPO antibodies. Gonadotrophins showed high FSH and a prepubertal LH. Prolactin was high and ovarian cysts were found on ultrasound. Further investigations revealed low von Willebrand factor (vWF) antigen levels, leading to a diagnosis of acquired von Willebrand disease. She was started on levothyroxine therapy, with normalization of vWF antigen levels, prolactin levels, cessation of her menstrual periods and resolution of ovarian cysts.

Key words: hypothyroidism, acquired von Willebrand disease, Van Wyk-Grumbach syndrome, bleeding, precocious puberty

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Introduction

Primary hypothyroidism (PH) is an insidious endocrine condition that occurs when there is reduced production of thyroid hormones from the thyroid gland. Consequently, patients with PH have low free thyroxine (free T4) levels and high TSH. The symptoms and signs are often subtle especially in the early stages (1).

The typical features of PH in children are: weight gain, fatigue, lethargy, cold intolerance, impaired cognitive function, dry skin, hair loss, low energy levels, constipation and menstrual irregularities (1).

Long standing PH can cause acquired von Willebrand's syndrome (AvWS) which is relatively uncommon (2). There have been reports of raised prolactin levels and ovarian cysts in untreated PH (3).

Precocious puberty is the occurrence of secondary sexual characteristics starting before 8 yr in girls and 9 yr in boys (4). Isosexual pseudo-precocious puberty can occur in association with long standing hypothyroidism and this is known as Van Wyk-Grumbach syndrome. The high level of TSH in hypothyroidism acts through FSH effects causing ovarian stimulation. Therefore, isosexual pseudo-precocious puberty and ovarian cysts can be found as part of this syndrome (5).

The most common cause of isosexual pseudo-precocious puberty in girls is the presence of functioning follicular cysts that secrete oestrogen, leading to premature breast development. Vaginal bleeding may occur when these cysts degenerate. Unlike true (central) precocious puberty, there is no development of pubic or axillary hair in girls with pseudo-precocious puberty. Additionally, affected individuals may exhibit decreased linear growth and delayed bone age, which are important clues for clinicians to investigate for an underlying cause that could combine both manifestations, such as Van Wyk-Grumbach syndrome (4, 5).

The purpose of this case report is to highlight the potential common and rare clinical manifestations of prolonged untreated PH on various body systems and the therapeutic effect of levothyroxine therapy on reversing these multisystem manifestations.

Case Presentation

Our patient presented at the age of 10 yr with excessive bleeding for 7 d following tooth extraction. She started menstrual periods at the age of 9 yr, with reported thelarche a few months before and no pubic or axillary hair development. She had heavy periods lasting for over two weeks every month. On further questioning, she had overwhelming fatigue, extreme daytime sleepiness, dry skin, abdominal pain, constipation, cold intolerance, and weight gain.

Her newborn screening for congenital hypothyroidism was negative and there was no family history of bleeding disorders.

On examination she was short for her parental target centile height range. There was mild puffiness of the face and hands and no goitre. Tanner staging showed breast stage B 3-4, no pubic hair, and no axillary hair.

She was investigated for PH in view of her symptoms and short stature which showed evidence of severe PH with a very low FT4 (1.1 pmol/L) and raised TSH (> 100 mU/L). The clotting profile showed prolonged APTT of 37.5 seconds.

A panel of investigations was done to evaluate for bleeding disorders (as shown in **Table 1**) which showed low levels of vWF. These results were consistent with AvWS.

Prolactin was also high at 1935 mU/L, FSH was 15.4 IU/L, LH less than 0.1 IU/L and oestradiol was 29 pmol/L.

Bone age was delayed (7 yr) at a chronological age of 10 yr and 6 mo.

Thyroid ultrasound showed a small thyroid gland with a lobulated outline. Multiple small nodules (up to 6 mm in diameter) were seen throughout both lobes and the isthmus. The ultrasound picture was suggestive of thyroid inflammation.

Pelvic ultrasound showed an anteverted bulky uterus with 2.7 mm endometrial thickness. The right ovary was enlarged with 28 mm × 15 mm × 27 mm thin walled, septate cystic area and normal left ovary.

She was started on levothyroxine with complete resolution of symptoms, radiological and laboratory parameters as shown in **Table1** and **Fig. 1**.

Discussion

It is well known that long standing untreated autoimmune PH can have varied clinical presentations. The purpose of this case report is to highlight the common and rare clinical manifestations of prolonged untreated PH on various body systems and the therapeutic effect of levothyroxine therapy on reversing these multisystem manifestations. Our patient had a combination of short stature, isosexual pseudo-precocious puberty, raised prolactin levels, ovarian cyst, and AvWS.

Anti-TPO antibodies are detected in > 80% of patients with Hashimoto's thyroiditis (6). The initial work up for our patient showed negative TPO antibodies but she was positive for antithyroglobulin antibodies. Antithyroglobulin antibodies are not routinely measured in paediatric practice; however, they can be raised in > 50% of patients with Graves' disease and Hashimoto's thyroiditis.

If laboratory findings indicate von Willebrand disease (vWD) in a patient who has no personal or family history of bleeding disorders, it is important to investigate conditions that can cause AvWS which is a rare bleeding disorder with laboratory findings similar to those for congenital vWD type 1 (7).

AvWS is defined as either vWF:Ag ≤ 50% and/or vWF ristocetin cofactor activity (VWF:RCo) ≤ 50% (8). The mechanism behind the coagulation disorder is the reduced mRNA transcription for vWF at a nuclear level as an effect of reduced triiodothyronine which causes a

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Table 1. Initial and follow up test results

Initial tests	Follow up tests
Factor VIII level was at the lower end of normal range (55.1 IU/dL) [Reference range 50–150 IU/dL] vWF antigen level was low (36.2 IU/dL) [Reference range 50 and 200 IU/dL] vWF:GP1b was low (38.9 IU/dL) [Reference range 50–200 IU/dL] Ristocetin cofactor level was low (17 IU/dL) [Reference range 50–200 IU/dL] APTT was prolonged (37.5 sec) [Reference range 24.7-31.7]	Factor VIII level improved (80 IU/dL) [Reference range 50–150 IU/dL] vWF antigen level normalised (55.1 IU/dL) [Reference range 50 and 200 IU/dL] vWF:GP1b normalised (58.7 IU/dL) [Reference range 50–200 IU/dL] Ristocetin cofactor level was not repeated as von Willebrand antigen and vWF:GP1b normalised APTT normalised 32.6 sec [Reference range 24.7–31.7] The bleeding profile was repeated 2 wk after levothyroxine (T4) treatment
TSH > 100 mU/L (0.27–4.2) Free T4 1.1 pmol/L (11–25) Anti-TPO antibodies 12.8 U/mL < 34.0 (negative) Thyroid stimulating immunoglobulins < 0.10 IU/L (negative) Thyroglobulin 2.1 µg/L Thyroglobulin antibodies 5 kU/L (positive)	TSH 23.19 mU/L (0.27–4.2) Free T4 18.7 pmol/L (11–25) 2 wk after treatment TSH 0.88 mU/L (0.27–4.2) Free T4 13.9 pmol/L (11–25) 3 mo after T4 treatment
FSH 15.4 IU/L LH < 0.1 IU/L Oestradiol 29 pmol/L Testosterone < 0.1 nmol/L	FSH 4.8 IU/L LH 0.6 IU/L Oestradiol < 20 pmol/L 2 wk after T4 treatment
Prolactin 1935 mU/L	Prolactin 1645 mU/L (100–500) 2 wk after T4 treatment Prolactin 201 mU/L (100–500) 6 mo after T4 treatment

reduction of hormone-induced upregulation of mRNA expression and protein synthesis of vWF. This results in decreased vWF levels due to reduction in its synthesis and secretion; therefore, can lead to a subsequent deficiency in factor 8 (9). Patients with AvWS can present with mucocutaneous bleeding e.g. bleeding following dental extraction or major bleeding following surgery or prolonged menstrual bleed (8).

AvWS is an uncommon presentation of hypothyroidism with a frequency of about 2 to 5% in retrospective studies (2). However, a prospective study including 90 patients diagnosed with hypothyroidism showed that the prevalence of AvWS is 33%. AVWF deficiency in this cohort was found to be either mild or moderate, either VWF:Ag or VWF:RCo of 10–30% or either VWF:Ag or VWF:RCo of 30–50% respectively, with no severe cases reported in this prospective study. The level of VWF in that study showed a positive correlation with the levels of free T4. Free T4 levels were lower in patients with hypothyroidism and AvWS compared to hypothyroid patients without AvWS. All patients in that study had their bleeding profiles normalised following initiation of levothyroxine therapy and establishment of the euthyroid state similar to our patient (8). Therefore, AvWS is likely to be the main cause of bleeding in severe primary hypothyroidism and therefore needs to be excluded in a child presenting with an uncommon bleeding disorder.

Delayed puberty is a common manifestation of untreated hypothyroidism; however, pseudo-precocious puberty can occur in as many as half of the children with severe longstanding untreated PH. The persistently high TSH can cross react with the similar glycoprotein receptor for FSH leading to ovarian stimulation. Additionally, the extremely high TRH in long-standing PH can contribute to the stimulation of the release of FSH and thus adds to the development of ovarian follicles in girls (5).

Reversal of the high TSH, FSH, and oestradiol following normalisation of TSH with levothyroxine treatment can reverse the pubertal changes.

Similar to precocious puberty, resolution of the cystic changes in the ovaries has also been reported after the start of levothyroxine therapy and achievement of a euthyroid state. The time taken for these cystic changes to resolve radiologically ranged between 1 wk and 6 mo in one case series (5).

Prolactin was also raised in our patient, similar to other cases in the literature with PH and subclinical

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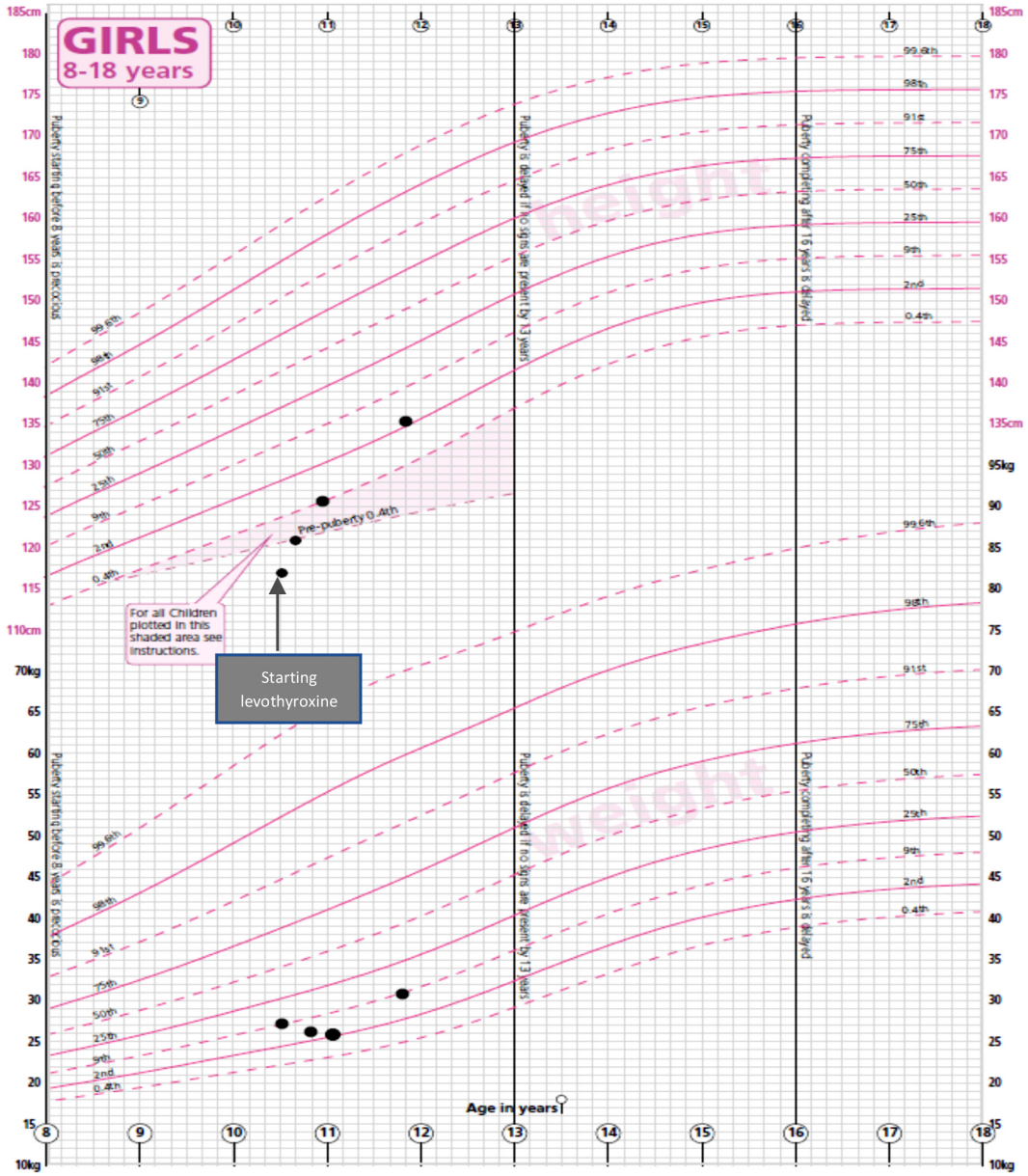

Fig. 1. Growth chart showing the changes in anthropometric measures. Before the start of treatment, the height was < 0.4th centile and the weight was on the 9th centile.

hypothyroidism. The high TRH in patients with PH can increase prolactin secretion which is a reported finding in up to 30% of patients with PH (10).

Conclusion

Severe PH can have both common and rare presentations and can affect several systems in the body.

Monitoring of growth is of utmost importance for early pick up of treatable causes of short stature such as hypothyroidism.

Early recognition and treatment of primary hypothyroidism with levothyroxine can reverse the associated coagulation disorders, pseudo-precocious puberty, ovarian cysts, and help optimise final height.

Conflict of interests: The authors do not have any financial interests or relationships to disclose.

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