Acquired primary hypothyroidism with profound anemia in an adolescent girl: a case report and a brief narrative review

Astrid Leeuwerck [a], Johan Hellinckx [b], Saskia van der Straaten [c]

[a] Ghent University, Faculty of Medicine and Health Sciences, Ghent, Belgium
[b] AZ Klina, department of Pediatrics, Brasschaat, Belgium
[c] Ghent University Hospital, department of Pediatric Endocrinology and Diabetology, Ghent, Belgium

astrid.leeuwerck@gmail.com

Keywords

autoimmune thyroiditis, adolescent, anemia, hypothyroidism

Abstract

Autoimmune thyroiditis is the most common cause of acquired thyroid disease in children and adolescents. Because the initial presentation can be very heterogeneous, diagnosis can be a challenge. Untreated, hypothyroidism has a significant impact on overall health and quality of life. Best outcome requires early detection as well as appropriate treatment. We present a case report of primary acquired hypothyroidism with a special presentation and a brief narrative review about hypothyroid autoimmune thyroiditis. Besides, we want to warn for delayed diagnosis in children with developmental disabilities.

Introduction

Hypothyroidism is characterized by an inadequate action of thyroid hormone at tissue level, with a decrease in metabolism as a consequence. A normal thyroid action through childhood is necessary for normal growth and neurodevelopment and is essential to the function of most organ systems.

Hypothyroidism may present at birth (congenital hypothyroidism) or appear later in life (acquired hypothyroidism). The cause of hypothyroidism can be at any level of the hypothalamic-pituitary-thyroid axis. Central hypothyroidism refers to disorders with decreased production of thyroid stimulating hormone (TSH) in the pituitary gland (secondary hypothyroidism) or decreased production of thyrotropin releasing hormone (TRH) in the hypothalamus (tertiary hypothyroidism). In central hypothyroidism, serum free thyroxine (FT4) is low and serum TSH is usually low or normal. By contrast, primary hypothyroidism is due to a defect in the thyroid gland itself, characterized by a low or normal FT4 and free triiodothyronine (FT3) and an increase of TSH (1).

In developed countries, autoimmune thyroiditis (AIT), also known as Hashimoto thyroiditis, is the most common cause of primary hypothyroidism in children and adults, with an estimated prevalence of 1-2%. In developing countries, hypothyroidism due to iodine-deficiency is the most common cause (1).

The clinical presentation of hypothyroidism reflects mainly the decrease of metabolic rate, which leads to fatigue, decreased heart rate, constipation, mild to moderate weight gain and decreased growth velocity. In severe forms, accumulation of matrix glycosaminoglycans in the interstitial spaces occurs, leading to myxedema, coarse hair and skin, puffy facies. The signs and symptoms can vary greatly between patients and is influenced by the rate of onset. Anemia is a clinical sign that can also be present at time of diagnosis (1).

Anemia can be defined as a reduction in red blood cell mass or blood hemoglobin concentration. For the pediatric population, normal ranges for hemoglobin vary with age and sex. Thresholds for defining anemia is a hemoglobin below the 2.5th percentile for age and sex based upon normative data from healthy individuals (2).

The diagnostic approach starts with assessing the mean corpuscular volume of the red blood cell (MCV). Anemia is classified in microcytic (MCV < 2.5th percentile for age and sex), normocytic (MCV 2.5th-97.5th percentile for age and sex) and macrocytic anemia (MCV > 97.5th percentile for age and sex). Consideration of the reticulocyte response can be helpful in differentiating the normocytic anemias. The reticulocyte response shows the reaction of the bone marrow to the anemia. In an anemia due to hypothyroidism, normocytic anemia with a low reticulocyte count is expected (2).

In this case report, we describe an unusual presentation of hypothyroidism with anemia in an adolescent girl. In the narrative review of autoimmune thyroiditis, we want to raise awareness of the diversity in clinical presentation. Especially in children with developmental disability diagnosis can be a challenge (3).

Method

We present clinical and biochemical data of a thirteen-year-old Caucasian girl with an acquired primary hypothyroidism and a profound anemia due to autoimmune thyroiditis. Additionally, a brief narrative review on the hypothyroid phenotype of autoimmune thyroiditis is presented.

Case report

We report the case of a 13-years old girl known with autism spectrum disorder (ASD), for which she is attending a school for children with special needs. She is not taking any medication.

She consulted a general practitioner (GP) because of pain and important blood loss during her periods. The GP assessed the girl as rather pale and decided to do an exploratory blood test. Two striking results were found: a normochromic anemia with a hemoglobin of 4.8 g/dl (12.1 – 14.6 g/dl) and an MCV of 100 fL (80 – 100 fL).and a severe primary hypothyroidism with a TSH of > 950.5 mIU/l (0.51 – 4.3 mIU/l) and an FT4 of < 1.5 pmol/l (12.6 – 21.0 pmol/l). Hepatic function tests were normal. Creatinine was slightly elevated. An increase of total cholesterol and triglycerides was seen. The GP transferred the patient to the pediatric ward of a regional hospital for further elaboration and blood transfusion.

At presentation in the hospital, we found a very pale girl. Her blood pressure was 85/55 mmHg with a heart rate of 90 bpm. During the inspection dry hair and puffy facies were noticed. There was no goiter in the region of the thyroid gland. Her tanner stage was 4.

It was only possible to have very little interaction with the adolescent girl. When we asked the parents, they did not notice any change in behavior. They said she has always been very slow, tired, withdrawn, and introverted, but parents framed this in the context of ASD and intellectual disability. No deterioration of these symptoms was noticed. She was having little appetite, but this has been the case for a long time. No cold intolerance, constipation, or weight gain was present. Further inquiry revealed that the maternal grandmother had a thyroid problem, but the exact diagnosis could not be reported.

Further laboratory test were done in the hospital. Blood tests confirmed primary hypothyroidism, and severe anemia. Very low vitamin D, folic acid deficiency and hypercholesterolemia were also found. On the other hand, iron status was normal, as well as vitamin B12 level.

To determine the cause of the hypothyroidism, autoimmune antibodies were obtained. Thyroperoxidase antibodies (TPOAb) were normal (12.3 IU/ml, ref value < 34 IU/ml), but thyroglobin antibodies (TgAb) were raised (351 IU/ml, ref value < 115 IU/ml). A blood transfusion with two units of packed cells was given to treat the severe anemia. Vitamin D and folic acid supplementation were also started.

Although little growth data were available, plotting data on the growth curve, showed a height declining from the mean at the age of 5 years to -2.5 SDS. Weight started around -1 SDS, and diminished to below -2.5 SDS. Bone age, according to Greulich and Pyle was 11 years, at a calendar age of 13 years. Ultrasound examination of the thyroid region demonstrated a heterogeneous thyroid gland with cystic and hypoechogenic zones, indicating thyroiditis. Diagnosis of autoimmune thyroiditis with severe hypothyroidism was made.

Treatment with L-thyroxin substitution was started with a low dose, approximately 1 µg/kg/day, assuming a long-standing hypothyroidism. During outpatient follow-up, L-thyroxin was gradually up-titrated. Two weeks after diagnosis, the dose was increased to 1.5 µg/kg/day. Normalization of thyroid hormones and TSH occurred within one month (Table 1).

Although character-wise she remained quiet and withdrawn, interaction with her became much more easy.

The tentative explanation of the normocytic anemia was the overt hypothyroidism along with substantial blood loss with her menses and concomitantly a folic acid deficiency.

Discussion

Pathophysiology of autoimmune thyroiditis

The development of autoimmune thyroiditis (AIT) is a multifactorial disease caused by genetic and environmental factors that initiate a complex autoimmune pathway. The onset is marked by lymphocytic infiltration with subsequent cytotoxicity and a humoral immune response producing antibodies against thyroid antigens that leads to inflammation and destruction of the thyroid follicular cells (4).

At the genetic level, mutations in major histocompatibility genes, immunoregulatory genes, thyroid-specific genes, and genes associated with thyroid peroxidase antibody synthesis are described in patients with auto-immune thyroiditis. Familial co-aggregation with Graves' disease, or other auto-immune diseases like celiac disease, diabetes mellitus type 1, vitiligo, or Addison disease is seen (5). In several syndromes, an increased prevalence of autoimmune thyroiditis is seen. Turner syndrome, Down syndrome, Klinefelter syndrome and Noonan syndrome being the most frequent (Table 2) (6). AIT can also be part of autoimmune polyglandular syndrome and IPEX (immunodysregulation polyendocrinopathy enteropathy X-linked) syndrome (1). Regarding the environmental factors, the influence of iodine intake, selenium intake, and vitamin D is suggested, as well as lifestyle factors such as smoking and alcohol (5). Passing through infections in infancy, or therapies which modulate the immune system (e.g., lithium, irradiation) might play a role, but further research is necessary to clarify this (4, 5).

Different phenotypes of autoimmune thyroiditis exist. Distinction can be made based on the concentration of thyroid hormones in the circulation. In this regard, children with auto-immune thyroiditis can present with euthyroidism, subclinical hypothyroidism, overt hypothyroidism, or they can present with subclinical or overt hyperthyroidism. The latter is a temporary phase caused by the release of stored thyroid hormone as the follicles get destroyed. This may also be promoted by the concomitant presence of anti-TSH stimulating antibodies.

The subclinical hypothyroid, euthyroid and hyperthyroid phenotype can evolve to an overt hypothyroid state. de Vries et al. studied 114 children with various clinical presentations leading to diagnosis of auto-immune thyroiditis and referral to a tertiary hospital. The reason for referral was thyroid gland enlargement in 39.5%, clinical symptoms of hypothyroidism in 28.9 %, incidental finding of thyroid dysfunction in 22 %, finding of thyroid dysfunction at routine screen of high-risk group and, hyperthyroid symptoms in 2%. At the moment 37% was hypothyroid, 42% was subclinical hypothyroid, 21% was euthyroid and 1% was hyperthyroid at time of diagnosis (reversed to hypothyroidism within weeks) (7). A German study of 43 children with severe acquired hypothyroidism, all due to Hashimoto thyroiditis, showed 66% of the children had a goiter, 2% had a hypoplastic thyroid and 32% did not have any palpable changes (8). Another study described the presence of a goiter in 40% of children with severe hypothyroidism due to autoimmune thyroiditis (9).

Usually, children with acquired hypothyroidism present with symptoms of fatigue, a remarkably decreased growth velocity and a modest weight gain (1). Other clinical findings that can be present are cold intolerance, dry rough skin and poor tolerance to cold. As mentioned before, goiter is a common finding. Occasionally loss of head hair, hypertrichosis, delayed tendon reflexes, myxedema of the face and extremities is noted. Precocious pseudopuberty (breast development in girls or testicular enlargement in boys, both without virilization), precocious menarche, as well as delayed puberty, irregular menses, excessive menstrual bleeding are described. The most frequent biochemical disturbance in severe hypothyroidism (TSH > 100 U/L, low fT4) are anemia (38%) and lipid disorders. In some cases liver and

Table 1: Thyroid hormone levels at follow-up

Day	Day 0	Day 3	Day 9	Day 26	Day 47	Day 79	Reference value
TSH (mIU/L)	950.5	950.1	349.9	22.02	2.41	1.57	(0.51 – 4.3)
FT4 (pmol/L)	< 1.3	4.7	10.48	17.85	18.41	15.54	(12.6 – 21.0)
Dose	1 µg/kg/d	1 µg/kg/d	1 µg/kg/d	1.5 µg/kg/d	1.5 µg/kg/d	1.5 µg/kg/d	

Table 2: Prevalence of autoimmune thyroiditis by syndrome (6)

Syndrome	Prevalence of autoimmune thyroiditis
Turner syndrome	10-42%
Down syndrome	13-46%
Klinefelter syndrome	5.4-10%
22q11.2 deletion syndrome	5%
Williams syndrome	Rare
Prader-Willi syndrome	Rare
Noonan syndrome	14.3-60%
Neurofibromatosis type 1	2.5%

kidney function tests are impaired. The degree of disturbance correlates with the degree of hypothyroidism (4, 9). Hyperprolactinemia has also been found with hypothyroidism (9). Unexpectedly, severe hypothyroidism can also be found on a random blood check in asymptomatic children (8).

Going back to our patient with hypothyroidism and a severe anemia. Anemia is an underestimated clinical condition that can accompany thyroid diseases. It can be the first and most prominent clinical sign of hypothyroidism (10). Anemia can either be microcytic, normocytic or macrocytic, because of different mechanisms which can play a role in the etiopathogenesis. Thyroid hormones stimulate the proliferation of erythrocyte precursors both directly and via erythropoietin production enhancement (11). Kucharska et al. found a positive correlation between fT4 and red blood cell count, as well as a positive correlation between fT4 and hemoglobin level (9). Uncomplicated mild anemia due to hypothyroidism can recover by starting thyroid hormone supplementation alone (10).

Questioning if the autism spectrum disorder of the patient plays an important role in the diagnostic process, a phenomenon of diagnostic overshadowing is described. In patients with intellectual disability, symptoms can sometimes be mistakenly attributed to the intellectual disability, which can cause a delay in the diagnosing of coexisting somatic disorders. In this regard, people with intellectual disability should be regularly screened for somatic comorbidity, and be re-evaluated in case of behavioral changes (3).

Diagnosis of hypothyroid auto-immune thyroiditis in children

Diagnosis is made by determining TSH and fT4 in the blood, as well as antithyroglobulin antibodies (TgAb) and antithyroid peroxidase antibodies (TPOAb) (12). Antithyroid peroxidase antibodies

are present in 90–95% and antithyroglobulin antibodies 20–50% of patients (1). An ultrasound of the thyroid has a typical appearance, but does not change the treatment, clinical course or outcome of children with AIT (7). Bone age is usually delayed correlated to the duration and degree of hypothyroidism (9).

Treatment of hypothyroid auto-immune thyroiditis in children

Levothyroxine is indicated for hypothyroidism. The treatment of choice are tablets, administrated daily 15-30 minutes prior to food intake. Levothyroxine should not be given at the same time with soy containing foods, iron or calcium supplements. The recommended dose is based on age, weight, and severity of hypothyroidism. For children around the age of 12, a dose of 2-4µg/kg/day is recommended (13). In cases of long-standing hypothyroidism, it is important to uptitrate the dose slowly. Pseudotumor cerebri or changes in behavior can occur when correcting the thyroid axis too quickly (14). Regular outpatient follow-up is necessary every 3 to 6 months and 4 to 6 weeks after dose adjustment. The goal of treatment is to maintain TSH in the age-specific normal range (1)

Prognosis of hypothyroid auto-immune thyroiditis in children

When focusing on growth, the severity of growth retardation has a significant correlation with the severity of hypothyroidism at the time of diagnosis. When starting adequate thyroid hormone supplementation, catch-up growth occurs in most children. The time of initiation of thyroid supplementation in relation to puberty has a major impact. There is a superior catch-up growth when starting thyroid hormone supplementation before the start of puberty (8). When starting thyroid hormone supplementation, the time to euthyroidism does not influence the final adult height. Trials with growth-promoting therapy were not effective (15).

Currently, research considering the association between autoimmune thyroiditis and thyroid cancer is ongoing (16-18). In children and adolescents, some studies show a growing coexistence between autoimmune thyroiditis and Papillary Thyroid Carcinoma (PTC) (17). As a result, some studies suggest an annual thyroid ultrasound in patients with autoimmune thyroiditis. More research is needed to clarify the link between autoimmune thyroiditis and PTC, and to determine the value of ultrasound in follow-up of children with autoimmune thyroiditis (18).

Conclusion

We presented a case of a 13-year-old with acquired overt hypothyroidism with an impressive initial presentation with severe anemia. The diagnosis seemed in this case to be delayed because of the lack of complaints of the girl with ASD. Awareness should be raised about the heterogeneous clinical presentation of autoimmune hypothyroidism. Therefore a check of the thyroid status should be performed in children with vague complaints, especially in children or adolescents with ASD and/or intellectual disabilities for whom anamnesis is more difficult.

Conflict of interest

The authors have no conflict of interest to declare with regard to the subject discussed in this manuscript.

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