Case report

Late diagnosis of severe long-standing autoimmune hypothyroidism after the first lockdown for the Covid-19 pandemic: clinical features and follow-up

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Abstract. *Background and aim*: Hashimoto's thyroiditis (HT) is a common endocrinopathy in children, particularly in females. Clinical overt presentation of hypothyroidism in HT includes mild to very severe forms, characterised by impairment of many body functions and organs, such as heart, brain, muscles, ovaries and liver. *Case*: we report the case of a 14-year-old girl, with severe hypothyroidism due to a late diagnosis of HT during the Covid-19 pandemic. Routine biochemical and hormonal exams were carried out at presentation. Moderate pericardial effusion was detected by echocardiography and polycystic ovarian morphology (PCOM) was found on the pelvic ultrasound. Furthermore, high levels of creatine phosphokinase (CPK), Lactic Acid Dehydrogenase (LDH) and hepatic liver enzymes, associated with muscular pseudohypertrophy and bilateral weakness of the lower limbs, were suggestive of a rare presentation of long-standing hypothyroidism defined Kocher-Debre-Semelaigne syndrome (KDSS). Levothyroxine replacement therapy was started immediately, leading to a rapid improvement of symptoms and a progressive normalization of the biochemical parameters. Due to persistent lower limb weakness, further neurological investigations were performed, showing bilateral peripheral polyneuropathy (PNP), ascribable to the longstanding and severe hypothyroidism. A pelvic ultrasound, performed after thyroid hormones had normalised and menses had turned to be regular, showed normal ovarian features supporting the hypothesis of the Van Wyk and Grumbach syndrome in a post-menarcheal girl. *Conclusions*: although clinical manifestation of hypothyroidism are usually mild, more severe and rare presentations such as ovarian dysfunction and myopathy are possible, particularly if the diagnosis is delayed and replacement therapy is not promptly administered.

Key words: autoimmunity, hypothyroidism, autoimmune thyroiditis, muscular pseudohypertrophy, Kocher-Debre-Semelaigne syndrome, polycystic ovarian morphology.

Background

Hashimoto's thyroiditis (HT) is the most common form of thyroiditis during paediatric age. Its prevalence has been reported to be around 3% in childhood, with a peak at adolescence (1,2). In early childhood, the female/male ratio varies across studies between 2:1 to 9.7:1 (1,3,4) and a female predominance occurs at puberty, suggesting the influence of sex hormones in the autoimmune process (1,4). At the time of diagnosis, children with HT could present with thyroid function ranging from euthyroidism (52,1% of cases) to overt hypothyroidism (22,2% of cases), less frequently subclinical hypothyroidism (19,2% of cases) or hyperthyroidism (6,5% of cases) (1,2) can be present. The clinical presentation of overt hypothyroidism includes systemic symptoms such as fatigue, weight gain, constipation, growth delay, dry skin, intolerance to cold, difficulty to concentrate. If undiagnosed, bradycardia, slow movements, blurred speech and general psychomotor retardation can present. Rarely, continuative TSH stimulation may cause pituitary hyperplasia (5). The association between long-standing hypothyroidism and muscle pseudo-hypertrophy has been rarely described in childhood in a condition called Kocher-Debre-Semelaigne syndrome (KDSS) (6). Polycystic ovarian morphology (PCOM) can be also a manifestation of clinical hypothyroidism (7). In adults, hypothyroidism and non-alcoholic fatty liver disease (NAFLD) have been reported to be associated, whereas very few studies have described this in childhood (8).

Case Presentation

A 14-year-old Chinese girl presented to our A&E department with a clear slowdown of body functions. Vital parameters showed bradycardia with a heart rate (HR) of 50 beats/minute and hypotension with a systolic blood pressure (BP) of 80 mmHg and a diastolic BP of 60 mmHg. At presentation weight was 62.5 kg and she had a final height of 158 cm, within her family range. Body mass Index was 25 kg/m^2, compatible with overweight. At physical examination we noticed muscle pseudo-hypertrophy of the lower limbs. No goitre was detected by palpation. The patient referred menarche at age 12 years, irregular menstrual cycles during the previous 6 months followed by amenorrhea in the last 3 months, fatigue over the last 4 months, episodes of intermittent diplopia, cold intolerance, constipation, myalgia and poor school performance.

Biochemical and hormonal investigations

Biochemical and endocrine examinations on admission and after starting replacement therapy are reported in Tab. 1.

Table 1. Biochemical and endocrine examinations at diagnosis and at different timepoints after starting L-thyroxine replacement therapy.

	On Admission	Week 1	Week 2	One month	Three months
Hb (g/dl) [NL.: 11.8 – 15.1]	9.3	9.5	9		11.4
ALT/GPT (U/l) [NL: 4 – 49]	395		130		30
AST/GOT (U/l) [NL: 2 – 40]	428		55		26
LDH (U/l) [NL: 208 – 378]	1321	610	552		312
CPK (U/l) [NL: 33 – 211]	2291	1089	653		57
UREA (mg/dl) [NL: 9 – 23]	17.4	17.5	15.8		14.9
CREATININE (mg/dl) [NL: 0.5 – 1.1]	1.2	1	1.06		0.52
TSH (µU/ml) [NL: 0.35 – 4.5]	277.75	198.97	142.71	34.11	3.23
fT3 (pg/ml) [NL: 2.3 – 4.2]	0.2	1.6	2.3	3.6	2.8
fT4 (pg/ml) [NL: 8 – 18]	2.2	6.4	9	14	12.1

NL: normal levels; Hb: hemoglobin; PTL: platelets; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; LDH: Lactic Acid Dehydrogenase; CPK: Creatine phosphokinase; TSH: thyroid stimulating hormone; fT3: free triiodothyronine; fT4: free thyroxine.

HT was confirmed biochemically: severe hypothyroidism was detected associated with positive antithyroid-peroxidase and antithyroglobulin antibodies. Anemia, high levels of total cholesterol (237 mg/dl, NL: 130-200 mg/dl), triglycerides (254 mg/dl, NL: 30 - 180 mg/dl), ALT, AST, CPK LDH and serum creatinine were found. Progressive normalisation of these data was observed on treatment with Levothyroxine (Tab. 1). Vitamin D deficiency was also present. Screening for other autoimmune diseases, such as coeliac disease and Type 1 Diabetes Mellitus was performed and was negative, as well as anti-nucleus antibodies, anti-liver, anti-kidney, anti-muscle, anti-neutrophil cytoplasm and anti Saccaromyces Cerevisiae antibodies. Insulin basal levels were high (23 μU/ml, NL:3-20) with a fasting glucose/insulin ratio of 4.2 and a HOMA-IR index of 5.51 (NL: 0.23-2.5) compatible with insulin resistance (9). Basal PRL levels were within the normal range (16 ng/ml, NL:3-30 ng/ml).

Imaging studies

On admission, the thyroid ultrasound showed a normal size of the gland (right lobe 16 x 14 mm and left lobe 11 x 15 mm) (10) and a dyshomogeneous aspect compatible with chronic autoimmune thyroiditis.

The electrocardiogram showed low voltage sinus bradycardia (HR:50 beats/minute), aspecific changes in ventricular repolarization with a right cardiac conduction delay.

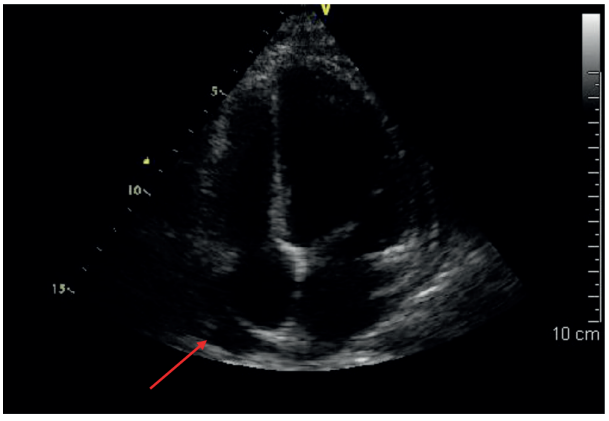

Figure 1. US of the heart with evident pericardial effusion. Pericardial effusion of moderate entity (red arrow), maximum width of 18-19 mm, with minor signs of hemodynamic impairment were present.

On transthoracic echocardiography, pericardial effusion of moderate entity with minor signs of hemodynamic impairment were observed (Fig. 1).

The MRI scan of the pituitary gland and hypothalamus showed a normal morphology, with no signs of pathological enhancement. The ventricular system was normal with the description of a 26 mm cyst in the temporal-mesial left lobe.

A complete ultrasound of the abdomen was performed ruling out the presence of NAFLD.

A pelvic ultrasound showed bilateral ovarian cysts, compatible with polycystic ovarian morphology (PCOM). A subsequent pelvic US, performed after thyroid hormones had normalised and menses had turned to be regular, showed normal ovarian features.

Other Investigations

Electromyography (EMG) and Electroneurography (ENoG) were performed after thyroid function had normalised on L-thyroxine replacement therapy. EMG was normal, but ENoG showed chronic sensorimotor axonal polyneuropathy of the lower limbs compatible with longstanding hypothyroidism. MRI of the lumbar spine was performed to exclude other causes of neuropathy and was negative.

During hospitalization, the patient was started on L-thyroxine replacement therapy, initially at a dose of 25 μg, that was gradually increased to 75 μg/day. During the 10 days of admission, the patient showed a gradual global improvement in cognitive functions, muscular strength and reduction of fatigue. After five days on replacement therapy, pericardial effusion improved as well as BP and HR (mean BP: 95/60 mmHg; HR: 70 beats/minute).

After 14-days on replacement therapy, TSH levels had more than halved with thyroid hormones at the lower limit of normal (Tab. 1). CPK, LDH, ALT/AST normalized within 2 months.

Discussion

The onset of hypothyroidism in childhood is usually insidious. This patient presented with signs and

symptoms of severe, long-standing hypothyroidism due to HT. Cardiac involvement was documented by clinical signs (bradycardia ad hypotension) and pericardial effusion detected at ultrasound. Pericardial effusions associated with severe hypothyroidism have been reported in 10% to 30% of adult cases of HT but are very rare in childhood (11, 12).

Hypothyroidism has been associated with metabolic syndrome as it can play a role in the pathogenesis of NAFLD (13). Studies in adults report this feature as independent of BMI (13), and increased TSH concentration in obese/overweight children has been identified as a predictor of fatty liver disease, and of lipid and glucose derangement, independent of the degree of total and visceral obesity (14). The patient described was slightly overweight and presented initial biochemical signs of insulin resistance, however, NAFLD was excluded by hepatic ultrasound and the increase in hepatic liver enzymes was transient and a consequence of severe hypothyroidism.

An increase in ovarian volume and the development of cysts have been reported in primary hypothyroidism, hypothesizing an association between hypothyroidism and PCOS through different mechanisms. First, the increase in thyrotropin-releasing hormone (TRH), subsequent to hypothyroidism, can lead to increased prolactin levels besides TSH. Prolactin may then contribute to polycystic ovarian morphology through inhibition of ovulation as a result of inhibition of follicle stimulating hormone (FSH) and luteinizing hormone (LH), and an arrest of follicular maturation by increasing dehydroepiandrosterone production from the adrenal gland (7,15). Second, increased TSH could contribute due to its spill-over effect on FSH receptors, promoting collagen deposit in the ovaries (7). An increase in ovarian size in hypothyroid women has been described and its decrease and normalization after starting replacement therapy has been documented, highlighting the impact of thyroid hormone levels on ovarian morphology (16).

The effects of long-standing untreated hypothyroidism have been described by Van Wyk and Grumbach who reported a case of isolated pseudoprecocious puberty and multicystic ovaries in a prepubertal girl (17). In our patient, the menstrual irregularities associated with bilateral ovarian cysts on ultrasound support the hypothesis of the Van Wyk and Grumbach syndrome in a post-menarcheal girl and have been identified as a consequence of severe long-standing untreated hypothyroidism, reversible after replacement therapy. Hyperprolactinaemia and pituitary hyperplasia (5,18) were excluded by hormonal assessment and radiological exams.

A higher prevalence of PCOS has been reported in euthyroid pubertal girls with chronic lymphocytic thyroiditis compared with euthyroid controls, (46,8% vs 4,3%, p = 0,001) suggesting possible role of autoimmune phenomenon in the etiopathogenesis of PCOS (19).

The association between muscle pseudohypertrophy (known as "Herculean" appearance) and severe long-standing hypothyroidism in childhood was previously described as the Kocher-Debre-Semelaigne syndrome (6). Biochemical abnormalities such as high levels of CPK, LDH, altered liver function tests and increased serum creatinine are due to muscular damage owe to hypothyroidism that can result in the most severe cases in rhabdomyolysis (20). Muscle pseudohypertrophy is reversible with L-thyroxine therapy (6). EMG can be either normal or show myopathic low amplitude and short motor unit potentials (20), muscular biopsy findings are reported to be nonspecific (21). Muscle pseudohypertrophy was clinically detected in this patient, and biochemical signs of initial muscle damage were found. EMG and ENoG were performed after thyroid function had normalised. EMG was normal, but ENoG showed a PNP which could be ascribed to longstanding hypothyroidism, and that will require further follow-up. Lumbar MRI was normal, further confirming this hypothesis (22).

In conclusion, we reported a case of severe-long standing hypothyroidism subsequent to HT in an adolescent. The diagnosis was delayed because of the Covid-19 pandemic and the difficulties for the family to obtain correct medical advice due also to language barrier problems. The patient presented to our attention some months after the national "lockdown" in Italy in a compromised clinical situation, showing how important it is to promptly recognise and treat hypothyroidism at onset.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity

interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Received: 20 April 2021
Accepted: 6 May 2021
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