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Case Report

Delayed diagnosis of congenital hypothyroidism in an adolescent results in avoidable complications: a case report

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Delayed diagnosis of congenital hyporhyroidism (CH) remains a serious problem. A retrospective analysis of 1,000 CH cases in Turkey found a mean age of 49 months at the time of clinical diagnosis. Only 3.1% of cases were diagnosed during the neonatal period and 55.4% were diagnosed after 2 years of age.[1] In Cipto Mangunkusumo Hospital, Jakarta, 53% cases were diagnosed at 1-5 years, 3.3% at 6-12 years, and 6.7% after 12 years of age, while the remainder were diagnosed at < 1 year of age.[2] The majority of affected children exhibit signs and symptoms that are highly non-specific, as most infants with CH are asymptomatic at birth, and only 5% of cases can be diagnosed based on clinical examination during the first day of life.[3] The other factors that contribute to delayed diagnosis are uneducated parents, who do not notice or dismiss the importance of mild/moderate deviations in physical and mental growth, as well as constipation, feeding difficulties, or other vague, non-specific symptoms in infancy. Parents are often unaware of the importance of early diagnosis and commencement of therapy for CH.[4]

Newborn screening for hypothyroidism is not routine in many third world countries. Only an estimated one-third of the worldwide birth population is screened. It is, therefore, important that clinicians be able to recognize and treat the disorder. Also, health education with early signs and symptoms of the condition is very important, especially in areas where neonatal screening for hypothyroidism is not performed.[5,6]

Untreated CH may manifest different levels of mental retardation, as well as delayed linear growth and bone maturation.[4] Early diagnosis and adequate treatment in the first weeks of life result in normal linear growth and intelligence, but delayed diagnosis and treatment beyond the first 1-3 months of life is likely to result in irreversible neuropsychological deficits. CH has a variety of adverse effects on adaptive neurocognitive functioning including general intelligence, complex attention and concentration, memory, perceptual and visuospatial function, and language. Eventually, patients with CH reach puberty, and they may be fertile. But their mental development lags for their age, which is easier to diagnose this

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condition in later life. A child with CH treated at less than 3 years of age will likely reach a mean IQ of 89; those treated at the age of 3-6 years attain a mean IQ of 70; while those treated at 7 years of age attain a mean IQ of 54.[7] The aim of therapy in CH patients with delayed diagnoses is to optimize their growth and development. Although treatment was started at late age, significant improvements in social interaction and motor development may be attained.[8]

In this case report of a delayed CH diagnosis in a child of advanced age, we discuss the importance of neonatal screening programs for early detection of CH, that are, unfortunately, still neglected in some regions in developing countries. We also show the value of early and adequate replacement therapy for detected cases, as this may protect patients from growth and mental retardation. Delayed diagnosis is associated with many complications and poor outcomes, as manifested in this case. **[Paediatr Indones. 2017;57:108-16. doi: http://dx.doi.org/10.14238/pi57.2.2017.108-16]**.

The case

A Minang girl aged 14 years and 1 month was referred by a pediatrician in Batusangkar, West Sumatera, to the Pediatric Ambulatory Department at M. Djamil Hospital. She was diagnosed with severe congenital hypothyroidism. The patient's chief complaint was that she often failed to advance to the next grade in school. She entered elementary school at the age of six and a half years, had failed several grades, and was, at the time of the study, in the 5th grade, for the second year in a row. She had difficulty concentrating, was unfocused, had problems in mathematics, and did not like the sports/physical education. She was born vigorous, during the 42nd week of gestation, by normal delivery, with birth weight of 4,000 grams, and body length of 46 cm. Her skin had looked rough since birth and she was often constipated. Although her development was delayed, she could lift up her head at 3 months, sit well at 7 months, stand up at 15 months, and walk properly at 18 months. She could speak two-syllable words such as "ma-ma" and "da-da" beginning at the age of 18 months, but her speech, while unclear, was understandable. Her reading and math skills were poor. She could dress herself by the age of 8 years. She was an introverted, melancholy, and uncommunicative. All of her teeth were deciduous, and she had never lost a tooth. Breast development began at 7 years old and her menstruation cycle began at 10 years old. Every 2-3 months she had some spotting for 5-7 days. From 2 years prior to our examination, her weight increased 18 kg and she looked more corpulent every day. She also looked shorter than many of her friends. Rough, black, rash patches had appeared in her armpits and upper nape of her neck since 1 year prior. She had never been brought for medical treatment because her mother thought that her disorders were not serious. But when the patient failed several grades in school, her mother became suspicious and worried, and upon the suggestion of a neighbor, the patient was brought to a pediatrician in her hometown of Batusangkar. The patient was diagnosed with severe CH, with laboratory findings of very elevated TSH (> 100 mIU/L) and very low free T4 (0.107 ng/mL).

On physical examination, the girl was alert but she is usually inactive. Her blood pressure was 140/90 mmHg, pulse rate 88 x/minute and regular, respiratory rate 22x/minute and regular, as well as body temperature 36.7 °C. Her body weight was 48 kg (25-50th percentile) and she had very short stature, with body height 116 cm (< 3rd percentile), and a corresponding height age of a 6 3/12-years old. Body mass index (BMI) was 35.67 (> 97th percentile), which was classified as obese. She looked myxedematous with coarse facial features, and frontal bossing. Her head circumference was 55 cm (normal based on Nellhaus standard) and the anterior fontanelle was closed. Her hair was scanty, coarse, and brittle. The nasoorbital configuration was retained with narrow and swollen palpebral fissures, with normal conjunctivae. She had a flat nose, and short, thick neck. Her skin was dry and rough. Conjunctivae were not anemic, sclera were not icteric, and pupil and corneal reflexes were normal. Intraoral examination showed that the palate was not highly arched, but the tongue was not protruding or broad. The patient's oral hygiene was good, though her teeth were covered by only small calculus, we found no caries. Her dentition was delayed, with only 20 erupted teeth. Mixed dentition was seen with permanent first molar, as well as deciduous incisors, canines, and premolars in each quadrant. The thyroid gland was not palpable. Micropapular plaques, gray-brown to black, hyperpigmented, as well as excessive keratosis were found in her armpits and trunk, extending to the posterior

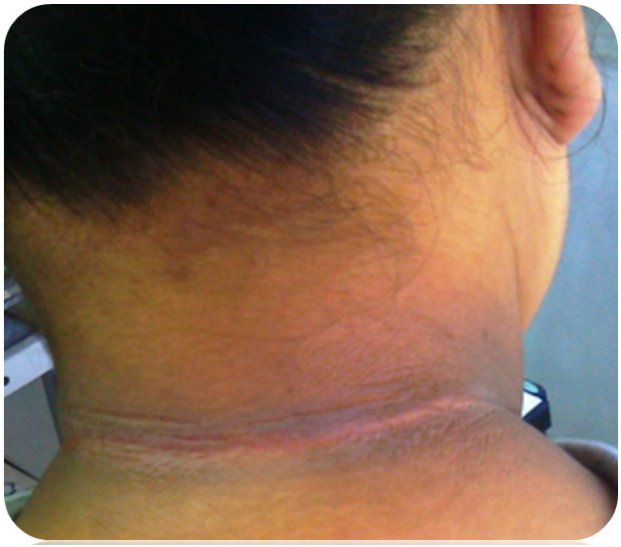

Figure 1. Acanthosis nigricans grade III

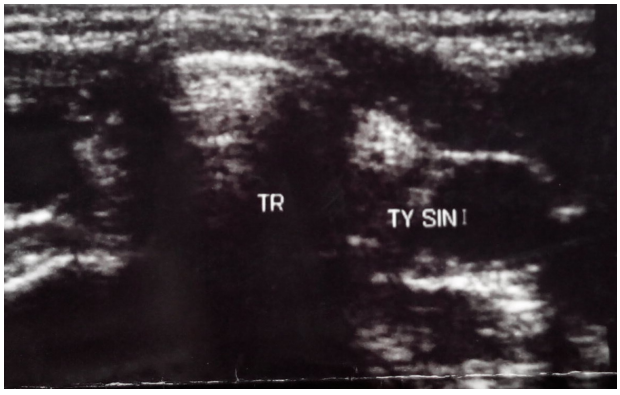

Figure 2. Thyroid USG revealed hemiagenesis of thyroid gland

grade III) (**Figure 1**).

We observed no abnormalities of the lungs. Heart sounds were not distant and no murmur was detected. The abdomen was not distended and there was no umbilical hernia. Waist circumference was 90 cm (> 90th percentile). The external genitalia were edematous. Her sexual maturity rating (SMR) was Tanner stage 3 breast development and Tanner stage 1 axilla and pubic hair (A1M3P1). The extremities were broad, with short fingers and myxedema. Physiological reflexes were normal without any pathological reflex. Motor strength was normal and not hypotonic. Her limbs were short with upper segment to lower segment ratio of 64:52 cm.

Laboratory examinations revealed hemoglobin level 11.2 g/dL, white blood cell 8,600/mm3, and differential count 0/1/1/67/23/8. Urine and feces were normal. Other blood test results were as follows: total cholesterol 180 mg/dL, HDL 40 mg/dl, LDL 84 mg/dL, triglycerides 290 mg/dL, fasting blood glucose 102 mg/dL, serum glutamic oxaloacetic transaminase (SGOT) 7 U/L, and serum glutamic pyruvic transaminase (SGPT) 13 U/L. Ultrasonography (USG) revealed hemiagenesis of the thyroid (right lobe agenesis and left lobe hypoplasia) (**Figure 2**).

Pelvic USG revealed no abnormality in her reproductive organs, as the uterus and both ovaries were normal and without cysts. A panoramic x-ray showed delayed eruption of teeth. Examination of the hand revealed a bone age of 6 year and 10 month girl, with a chronological height of 75.1% of her estimated final height (**Figure 3**).

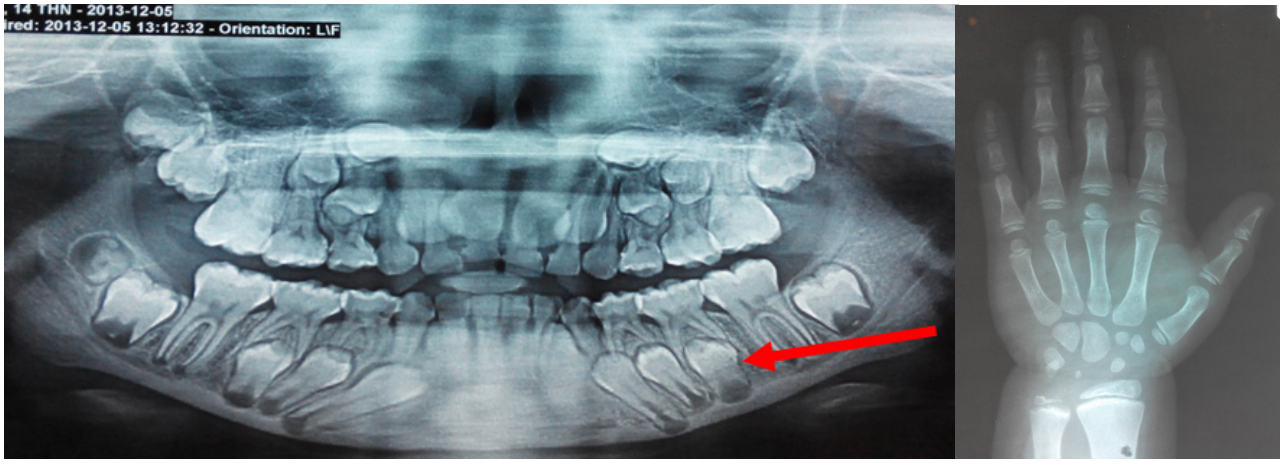

Figure 3. Panoramic and bone age x-rays

The Pediatric Symptom Checklist (PSC) score was 42, with noted psychological impairment. ECG examination revealed sinus rhythm, heart rate 90x/minute, normal QRS voltage, and no widened QRS, nor signs of cardiac enlargement. The patient received a consult from the Mouth and Dentistry Department. The dentist suggested gradual tooth extraction. The pediatric psychologist performed a cognitive function test and found an IQ index of 73 (borderline) and disturbed social maturity. The pediatric psychologist suggested that the parents give more mental stimulation at home, such as actively talking to the patient, teaching her to sing, as well as encouraging her to play and interact more often with her surroundingS. Attention and learning disorders were noted by the Physical and Rehabilitation Department. The patient performed some occupational tests, and was found to be able to recognize objects and colors well, accept instruction, and write well. But the patient had memory and counting problems. She made errors in her first attempt at a mathematics test, but after being taught, she could accomplish it. So the parents were asked to teach their daughter more often and patiently.

The patient had a delayed diagnosis of congenital hypothyroidism with several complications: developmental delay (psychosocial problems, cognitive and learning problems), growth problems (obese, short stature, delayed tooth eruption), precocious puberty, and metabolic syndrome. She was treated with levothyroxine 1x100 μg and colcatriol (vitamin D) 1x 0.25 μg.

On follow up, the patient's condition was improved. Her mother reported that the girl's activity had increased, and she became less disoriented and interested in her surroundings. Her skin became smoother, and she slimmed down. Permanent teeth began to erupt, with the two front teeth already erupted. The black rash patches in her armpits and trunk vanished. Patient defecation became more regular at about once in a day. Patient had just finished her menstrual cycle 5 days prior to the follow-up visit, and reported that it was more normal, with the usual 1-2 times of changing the pad daily, and length of 7 days. The patient was alert and looked more active than before. Her blood pressure had returned to normal. Her body weight decreased 8 kg in one month (from 48 to 40 kg), and to 36 kg after 3 months (**Figure 4**). Her height increased 2 cm in one month, and 4 cm after 3 months of therapy. Social interaction and physiological well-being also improved, with her PSC score changing to 22 after 1 month of therapy and to 14 after 3 months of therapy. One month after therapy her TSH level decreased (30 mIU/L) and free T4 was normal (1.04 ng/mL). TSH level returned to normal after 3 months of treatment.

Figure 4. Physical body composition at admission and after 3 months of treatment

Discussion

Delayed diagnosis of CH was a main problem in this case. The combination of parental unawareness of the signs and symptoms of CH in early life and the girl's non-specific symptoms were reasons for delayed diagnosis. Most infants with CH are asymptomatic at birth. But during the first few months of life, the symptoms of hypothyroidism such as feeding problems, failure to thrive, constipation, hoarse crying, rough skin, and hypotonia, may be noted. Our patient came with symptoms including failure to advance to the next grade in school, developmental delay, constipation, rough skin, and coarse facies in the early months of her life. Unfortunately, the parents were unaware of the serious nature of these clinical features, so they did not bring the child to the health center. Malik *et al.* reported that the common CH symptoms are lethargy /lack of activity (47%), developmental delay (44%), generalized body swelling (25%), and constipation (14%), while common signs are short stature (59%), coarse facies (34%), periorbital puffiness (25%), and obesity (25%).[4]

The lack of a neonatal screening program for CH in the region also contributed to the delayed diagnosis in this case. Neonatal screening programs play an important role for the early detection of CH in apparently healthy newborn infants. Before the screening programs were implemented, children were diagnosed clinically, and the reported incidence of CH was considerably lower, varying from 1:5,800 to 1:6,900.[9] Danish study found that only 10% of affected children were diagnosed clinically during their first month of life, 35% in the first 3 months, and 70% by the age of 1 year. The remaining affected children were not diagnosed until their third or fourth years of life.[10] A retrospective analysis of 1,000 cases of CH in Turkey found that the mean age at clinical diagnosis was 49 months. Just 3.1% of the cases were diagnosed during the neonatal period and 55.4% were diagnosed after 2 years of age.[1] In Indonesia, CH screening was not a routine, government-sponsored program before 2006. A preliminary *Ministry of Health Screening program* was started in 7 provinces: West Sumatra, Jakarta, West Java, Central Java, East Java, Bali, and South Sulawesi. By 2009, CH screening had been done in 171,825 babies and diagnosed in 48 babies (1:3,850).[11]

Determining the cause of CH guides patient management and the need for a genetic consultation, because diagnoses may have prognostic implications. The etiology of CH in this case was thyroid hemiagenesis based on USG examination. USG does not involve the risk of ionizing radiation and can be used to differentiate between thyroid dysgenesis and other causes of CH, in which the thyroid gland has normal morphological features.[12] Ultrasound examination can reduce the need for scintigraphy in more than half (54%) of patients with possible CH.[13] Compared to 99mTc-pertechnetate scanning, USG has high (100%) specificity and low (44%) sensitivity for detection of sublingual thyroid glands.[14] Thyroid hemiagenesis, meaning the absence of one lobe, is occasionally detected among asymptomatic individuals, with prevalence figures from 0.05% to 0.2%. It is three times more common in females than males. Interestingly, hemiagenesis almost invariably affects the left lobe (80%). In this condition, thyroid hormone levels are usually within the normal range in early infancy, however, compensatory growth does not always seem to be sufficient.[15,16]

Longstanding hypothyroidsim affects multiorgan systems. Growth failure is a known complication of congenital hypothyroidism (CH). Patients who receive treatment after a delayed diagnosis are frequently short in stature and unable to reach their final height target, but can show improvement in some physical growth. The patient may lose 6-7 cm from their predicted final height.[17,18] Boersma *et al.* described two children with CH who were left untreated for several years. Although they experienced marked catch-up growth, both of them reached an adult height below their target height.[19] In our case, the patient had short stature with delayed bone maturation. Although replacement therapy was started at 14 years of age, the girl achieved some significant improvement in physical growth, including decreased body weight, increased height, and eruption of permanent teeth. Untreated primary hypothyroidism is associated with decreased growth hormone (GH) pulsatile secretion, attenuation of the GH response to secretagogues, and reductions in insulin-like growth factor-1 (IGF-1) and IGF-binding protein-3 (IGFBP-3).[20]

Our patient had a low IQ of 76. It is well known that CH diagnosed at an advanced age often leads to severe cognitive and motor delays but in CH patient detected by neonatal screening programs and treated early, IQ level can be within normal range and

children can also have normal school attainments.[21] Mean IQ score of CH patients before establishment of CH screening have reported to be 76, whereas after that it increased to 104 comparing with control normal children with mean IQ score of 106.[22] Other findings indicate that cognitive problems may persist into adolescence including memory, attention, and visuospatial issues.[23]

Children with CH were found to have lower arithmetic skills and overall cognitive functioning at school, but no differences in other school performances, such as reading and writing. Some of CH subjects failed in final math examinations.[24] Our patient had below average skills in mathematics and sports. In addition, she was unfocused and easily bored, but she had no serious problems in reading and writing lessons. Deficits in arithmetic may have been caused by impaired concentration as well as difficulty handling numbers.[23,24] Lower IQ was associated with lower scores in cognitive functioning and poor motor skills tended to be associated with low self-worth regarding athletic competence.[25]

The limited literature has shown that children and adolescents with CH have more behavior problems, particularly in the areas of introversion and social negativity, than normal controls.[26] Behavior deviance was two and a half times more common in children with IQ below 90 than in those with IQ above 90. The behavior problems were more neurotic than antisocial in kind, and included poor attention span, fearfulness, speech difficulties, and wetting or soiling at school. Parents also identified speech problems as being major areas of concern.[27] The CH patients cannot reach the mental development expected according to age. Patients receiving treatment after a delayed diagnosis may gain the skills to improve their daily functioning and engage in more physical activity.[28] Before treatment, our patient's personality was introverted, melancholy, and uncommunicative, with PSC score of 42. After thyroxin replacement therapy, she became more outgoing, made more friends, and spent a lot of time with them. Thyroid hormone affects serotonin in the brain and has a modulating effect on mood. It works by increasing serotonergic neurotransmission, specifically by reducing the sensitivity of 5-hydroxytriptamine 1A (5-HT1A) autoreceptors in the raphe area of the brain, and by increasing 5-hydroxytriptamine 2 (5-HT2) receptor sensitivity.[29]

Long-term severe hypothyroidism impairs craniofacial growth and dental development. Disrupted mandibular ramus growth and failed normal resorption of the internal aspect of the ramus, results in insufficient space for proper eruption of teeth.[30,31] Our patient's oral hygiene was good, with only a small calculus and no caries. Dental extraction should be made with care, because patients with long-standing CH may have increased subcutaneous mucopolysaccharides due to decreased degradation of these substances. Hence, the ability of small vessels to constrict when cut may result in increased bleeding.[32]

Our patient fulfilled the criteria of metabolic syndrome based on the IDF consensus definition of in children and adolescents, which is abdominal obesity with dyslipidemia (hypertriglyceridemia and low HDL) and hypertension.[33] Metabolic syndrome in this girl was caused by CH. The prevalence of obesity/overweight among children with CH was 32.2%.[34] A previous study reported that dyslipidemia was found in 83 (46.11%), from 180 patients with hypothyroidism.[35] Metabolic syndrome in CH patients is caused by a disturbance in cholesterol metabolism. Thyroid hormones induce 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase, which is the first step in cholesterol biosynthesis. Moreover, triiodothyronine (T3) upregulates LDL receptors by controlling LDL receptor gene activation.[36]

Total cholesterol and low density lipoprotein cholesterol (LDL-C) levels are increased in patients with hypothyroidism. This is due to decreased LDL-receptors activity, resulting in decreased catabolism of LDL. Decreased lipoprotein lipase (LPL) activity causes decreased clearance of trigliseride-rich lipoproteins. Therefore, overt hypothyroid patients may also present with elevated TG levels associated with increased levels of very low density lipoprotein (VLDL), and occasionally fasting chylomicronemia. Hypothyroid patients may also exhibit elevated levels of high density lipoprotein cholesterol (HDL-C), mainly due to increased concentration of HDL2 particles. Indeed, a reduction of HL activity decreases HDL2 catabolism. Moreover, decreased activity of the cholesteryl ester transfer protein (CETP) results in reduced transfer of cholesteryl esters from HDL to

VLDL, thus increasing HDL-C levels. Hypothyroid patients have increased lipoprotein (a) levels, which are associated with increased cardiovascular disease risk. Decreased thyroid function not only increases the number of LDL particles, but also promotes LDL oxidability. Thyroid failure is strongly associated with arterial hypertension (especially diastolic) via sympathetic and adrenal activation, and increased vascular stiffness.[36]

The American Heart Association recommends that children with normal-borderline LDL (110-129 mg%) make the following changes to their diet: <10% calories from saturated fat, 30% calories from fat, and <300 mg/day from cholesterol. Intake of polyunsaturated fats, mono-unsaturated fats, omega-3 fatty acids, and high fiber foods should be encouraged. No pharmacological lipid-lowering therapy is indicated. Children should be encouraged to engage in physical activity. Sedentary time should be reduced as possible, with a focus on minimizing time spent on television, internet, and video games.[37,38] Our patient was advised to make such lifestyle changes.

Administration of L-thyroxin substitution therapy significantly improves lipid metabolism abnormalities. A period of 4-6 weeks of thyroxin replacement therapy is usually needed to correct dyslipidemia in overt hypothyroidism. In general, changes in serum lipoproteins in hypothyroid patients are correlated with changes in free T4 (FT4).[36] A statistically significant decrease in mean total cholesterol, triglycerides, and LDL-cholesterol levels and a statistically significant increase in mean HDL-cholesterol level followed replacement therapy with L-thyroxin.[35]

Serum 25-hydroxyvitamin D decreases in children with metabolic syndrome.[39] Vitamin D has an important role in glucose and insulin metabolism. It affects pancreatic islet cells through its receptors and may increase insulin secretion.[40] Vitamin D deficiency leads to elevated parathyroid hormone (PTH) levels, and in turn to decreased insulin sensitivity. Moreover, vitamin D has anti-inflammatory and immunomodulating effects, that may decrease insulin resistance and increase in insulin secretion. Low serum levels of vitamin D have been associated with insulin resistance and cardiometabolic risk factors, even in children of a young age.[41] Vitamin D supplementation had favorable effects on reducing insulin resistance and cardiometabolic risk factors in obese children.[42] Our patient received both replacement therapy with thyroxin and vitamin D supplementation. This combination therapy was successful for treating her metabolic syndrome.

Within several months of treatment with thyroxin and vitamin D supplementation, significant improvements were achieved in our patient, including FT4 level returning to normal limits and disappearance of the acanthosis nigricans on her trunk after one month. Also, her body weight decreased 12 kg and her waist circumference, blood pressure and TG returned to normal levels after 3 months.

Longstanding hypothyroidism can interfere with gonadotropin secretion by increasing serum prolactin levels. Clinical manifestations, including menstrual irregularities and impaired fertility, are the results of an ovulation and/or luteal phase defect. Basal ovarian size of patients with hypothyroidism (with or without polycystic ovaries) was significantly larger compared to controls. In humans, hypothyroidism is characterized by deposition of mucopolysaccharides (hyaluronic acid and chondroitin sulfate) within the connective tissue ground substance of various organs. Moreover, similar myxedemetous changes of the ovarian stroma together with an increase in collagen content and sclerosis. Changes in ovarian stroma may alter the paracrine and autocrine mechanisms of communication within the ovary, resulting in disrupted follicular development and altered steroidogenesis. Cyst formation may also cause ovarian enlargement. Animal studies have shown that perinatal exposure to TSH in vivo and in vitro causes a "hormonal imprinting effect", which leads to amplification of the response to subsequent FSH receptor binding. Elevated TSH in combination with normal serum FSH levels may get activated with FSH receptors, causing profound stimulation of ovarian follicles.[43,44,45]

The aim of the therapy in delayed CH diagnosis is to optimize growth and development. Patients who receive treatment after a delayed diagnosis may not reach their target height, but can improve in physical growth, social interaction, and motor development. These children may gain better function in their day-to-day activities, and show improvements in speech, walking, physical activity, thermogenesis, and skin condition. In addition, bone health can benefit from support therapies such as vitamin D.[8]

In conclusion, our patient had a good response to thyroxine treatment. Her FT4 and TSH returned to normal levels after 1 month and 3 months of therapy, respectively. Signs and symptoms of metabolic syndrome disappeared, permanent teeth began to erupt, menstrual cycle became regular, and body height increased. Although physical growth, social interaction, and motor development improved, cognitive function may not reach normal levels due to the delayed diagnosis and treatment.

The child will need thyroid supplementation for life, because her CH was caused by thyroid hemiagenesis. Parents must be educated on the importance of therapy and the severe consequences if therapy is discontinued. School progression should be monitored and the parents should provide additional mental stimulation at home for optimization of therapy. The patient should be trained in specific skills for independent living in the future.

Conflict of interest

None declared.

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