Iran Red Crescent Med J. 2015 November; 17(11): e20306. doi: 10.5812/ircmj.20306

Published online 2015 November 1. **Case Report**

Delayed Diagnosis of Hypothyroidism in Children: Report of 3 Cases

Nosrat Ghaemi,[1] Sepideh Bagheri,[1] Saghi Elmi,[1,*] Saber Mohammadzade Rezaee,[2] Sam Elmi,[1] and Reza Erfani Sayyar[3]

[1]Department of Pediatrics, School of Medicine, Mashhad University of Medical Sciences, Mashhad, IR Iran
[2]Department of Pediatrics, School of Medicine, Birjand University of Medical Sciences, Birjand, IR Iran
[3]Department of Anesthesiology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, IR Iran

*Corresponding Author: Saghi Elmi, Department of Pediatrics, School of Medicine, Mashhad University of Medical Sciences, Mashhad, IR Iran. Tel: +98-9155181130, Fax: +98-5137273943, E-mail: saghi_elmi_106@yahoo.com

Received 2014 May 18; **Revised** 2015 April 23; **Accepted** 2015 May 11.

Abstract

Introduction: Hypothyroidism is the most common endocrine disorder in children and presented with various sign and symptoms; its diagnosis needs a high index of suspicion.

Case Presentation: We report 3 cases with unusual presentations of hypothyroidism and with delay in diagnosis that referred to Pediatric Endocrine Outpatient Clinic in Mashhad University of Medical Sciences, Mashhad, Iran with different clinical manifestations. They had decreased Thyroxin (T4) and increased thyroid stimulating hormone (TSH) levels. One case had mental retardation and deafness, but the other two cases had normal neurodevelopment. Some additional interesting findings were as follows: short stature, delayed bone age, teeth eruption impairment, hair loss, anemia and hypercholesterolemia, persistent and long-term constipation that had led to several abdominal surgeries. After a year of hormonal replacement therapy, their growth parameters and hematological values improved.

Conclusions: We recommend thyroid hormonal evaluation for any children with short stature, especially with delayed bone age, in order to detect and treat hypothyroidism at the right time. It seems that more attention to pediatric growth is necessary.

Keywords: Hypothyroidism, Deafness, Constipation, Short Stature, Mental Retardation, Bone Age

1. Introduction

Hypothyroidism can manifest with different signs and symptoms. This disorder has a wide range of presentation from subclinical hypothyroidism to overt form. Congenital hypothyroidism is one of the most common preventable causes of mental retardation and is detectable with simple and cost-benefit biochemical test in neonatal period. The most severe effect of undiagnosed congenital hypothyroidism is on skeleton and bone maturation, also central nervous system as mental development (1). High serum TSH level causes abnormal skeletal development in hypothyroidism via its suppressive effects on the growth plate (2).

The primary thyroid-stimulating hormone screening has become standard in many parts of the world. However, newborn thyroid screening is not yet implemented in some countries (3). Neonatal screening for congenital hypothyroidism (NSCH) has obviously eradicated the severe irreversible neurodevelopment damage also reversed the chances of growth failure during infancy and early childhood (4). When clinical symptoms and signs suggest hypothyroidism, regardless of newborn screening results, serum free thyroxin and thyroid-stimulating hormone (TSH) should be evaluated (3). A strategy of rapidly identifying and treating infants with congenital hypothyroidism (CH) by using high-dose levothyroxine replacement will result in normal intellectual and motor development (5).

The aim of this article was to emphasize on the fact that any physician must be alert of considering hypothyroidism in its nonclassical presentations.

2. Case Presentation

From January 2008 to September 2011, three cases with hypothyroidism and different clinical presentations were referred to our outpatient clinic in Imam-Reza Hospital in Mashhad University of Medical Sciences, Mashhad, Iran. They were females and 9 to 11 years old. All patients had short stature with Z-scores of -2.5, -2, and -5.8. We used growth parameters (weight and height) by SECA balance and stadiometer 3 times and calculated the average growth rate of them (Table 1, Figure 1).

The patients showed unusual symptoms. In the first case, her teeth were rapidly lost; she also had massive dental carries (Figure 2). Second case was evaluated for

progressive obesity with no response to diet restriction on the supervision of nutritionist. Third case had more problems. She had chronic constipation from infancy and a history of two times abdominal surgery with Hirschsprung disease impression without any improvement (Figure 3). She also had ear trumpet due to deafness for more than 5 years and delay in development. Wrist X-ray showed delay bone age for her chronological age (Figures 4 and 5). Thyroid function test revealed very low T4 and high TSH levels. Thyroid isotope scan with technetium-99m approved thyroid agenesis in the third case but it had normal result in the first and second cases.

Thyroid peroxidase antibody and thyroglobulin antibody were in normal range in the third case but were high in two others. The results of complete blood count, lipid profile, level of serum iron, ferritin, total iron binding capacity (TIBC), TFT (thyroid function test) are shown in Table 2. Moreover, we did not use ELISA for measurement of laboratory data and instead used ECL method by calibrated automatically devices.

Treatment with levothyroxine 3 μg/kg/day as thyroid hormone replacement started for all 3 cases under close supervision. During recovery process we observed remarkable improvement in growth parameters indicated by evaluating Z-score and standard growth charts (Table 3). After suitable hormone replacement therapy, severe constipation in the third case becomes much better. She had defecation once every 10 days; which after treatment, it changed to every day. According to the parents, all children's general conditions and physical activities got better. They started to participate in daily activities with other children despite the fact that before treatment they were unsociable. Also, teeth lost stopped in the second case and she gained 4 kg. Improvement in laboratory data after sufficient treatment has been shown in Table 4.

Table 1. Growth Parameters Before Treatment

Variable	Case 1	Case 2	Case 3
Age, y	11	9.5	10.5
Gender	female	female	female
Weight, kg	31.6	42	20
Weight z-score	-1	1.7	-2.8
Height, cm	126	119	100
Height z-score	-2.5	-2	5.8

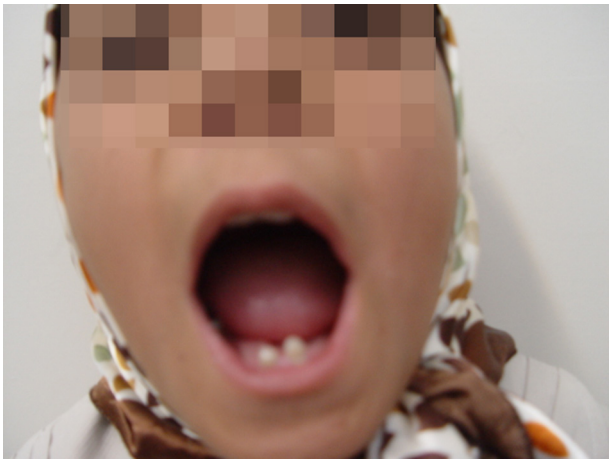

Figure 1. Dental Growth Impairment

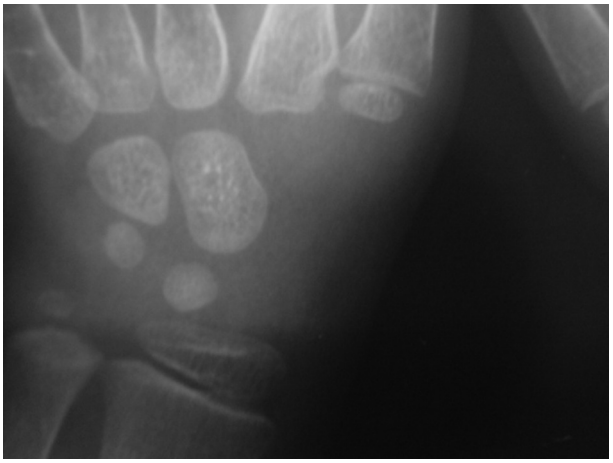

Figure 2. Delayed Bone Age (Case 1)

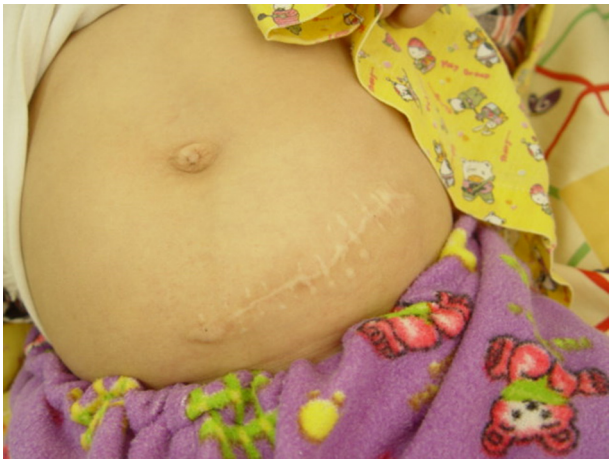

Figure 3. Abdominal Surgery Scar Due to Persistent Constipation

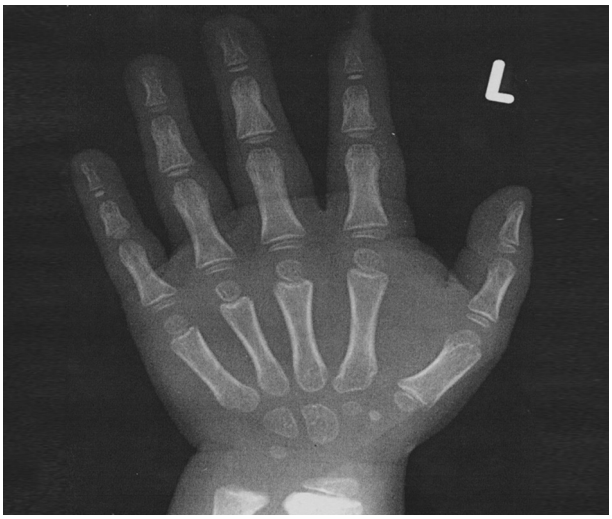

Figure 4. Delayed Bone Age (Case 3)

Figure 5. Short Stature

Table 2. Laboratory Data of All Patients Before Treatment[a]

Variable	Normal Range	Case 1	Case 2	Case 3
Age, y		11	9.5	10.5
Gender		female	female	female
Hb, g/dL	11.5 - 15.5	10	8.9	8.5
MCV, fL	80 - 100	98	105	79
Choles, mg/dL	Up to 200	230	225	180
TG, mg/dL	40 - 200	130	160	102
Ferritin, ng/mL	7 - 140	25	126	41
Serum iron, µg/dL	50 - 120	24	80	45
TIBC, µg/dL	250 - 425	314	260	420
T4, µg/dL	4.7 - 12	0.9	2.7	0.5
TSH, mIU/mL	0.3 - 5	100	110	100
Anti TPO Ab	< 34	690	998	29
TG-Ab	2 - 150	95	400	120

[a]Abbreviations: Anti-TPO Ab: Anti-Thyroid Peroxidase Antibody; Choles: Cholesterol; Hb: Hemoglobin; MCV: Mean Corporal volume; TG: Triglyceride; TG-Ab: Thyroglobulin Antibody; TIBC: Total Iron Binding Capacity; TSH: Thyroid stimulating hormone; T4: Thyroxin.

Table 3. Growth Parameters After One Year of Treatment

Variable	Case 1	Case 2	Case 3
Age, y	12	10.5	11.5
Weight, kg	30	38	27
Weight z-score	-0.8	1	-1.9
Height, cm	140	129	120
Height z-score	-1	-1	-3.5

Table 4. Laboratory Data After Treatment

Variable	Normal Range	Case 1	Case 2	Case 3
Age, y		12	10.5	11.5
Gender		female	female	female
Hb, g/dL	11.5 - 15.5	11.5	12.5	12.7
MCV, fL	80 - 100	85	93	91
T4, μg/dL	4.7 - 12	4	7.3	4.8
TSH, mlU/mL	0.3 - 5	15	13.9	12.3

3. Discussion

Hypothyroidism is the most common disturbance of thyroid function in children presented with various signs and symptoms. Therefore, physicians must be alert not to miss the diagnosis of hypothyroidism. The most common manifestation of acquired hypothyroidism is the suppression of growth which leads to short stature. It was notable that short stature was observed in all 3 patients but missed by previous physicians.

Our third patient probably had congenital hypothyroidism that was missed because screening test for congenital hypothyroidism initiated in Iran since 8 years ago. She had been seen by various medical practitioners and undergone abdominal surgery for 2 times due to severe constipation (Figure 3). She also suffered from deafness and had ear trumpet since she was 3 years old, but all symptoms were attributed to her mental retardation. Unfortunately her diagnosis was apparently missed. On investigations using thyroid scan (T99), showed no uptake supporting the diagnosis of thyroid agenesis.

Hearing loss is more common in hypothyroid patients than normal population (6). Median age for detection of hearing impairment was 7 in a Paris study that showed 17% of samples required hearing support in early adulthood. Despite major improvements in prognosis, hearing loss remains a significant problem, particularly in patients with severe congenital hypothyroidism (6), as it was seen in our third patient. The individual roles of receptors in cochlear hair cells are still unclear, and thyroid hormone may act through different thyroid hormone receptor activities to permanently alter the sensitivity of auditory neurotransmission (7). Mutations in SLC26A4 can cause deafness and goiter in Pendred syndrome as one of the most common hereditary causes of deafness (8). Parents and primary care providers should be aware of deafness risk, because early diagnosis and intervention for hypothyroidism could improve the long-term prognosis in these patients (6).

The symptom of first patient was misleading, because she had premature loss of permanent teeth (Figure 1). Children who suffer from hypothyroidism may have a wide variety of dental problems, including malocclusion, delay in teeth eruption, swelling gums, and enamel hypoplasia that are reported by many researchers but loss of teeth was rarely reported. Recent studies have pointed to the potential periodontal risk indicators; however, no information is available on the impact of changes in thyroid hormone levels on the progression of periodontitis and quality of alveolar bone. It may be concluded that decreased serum levels of thyroid hormones may enhance periodontitis-related bone loss (9).

The oral health care professionals can play a significant role in the screening of patients with undiagnosed thyroid disease (as it was seen in our first patient). Thus, a dentist can detect thyroid abnormalities. Modifications of dental care must be considered when treating hypothyroid patients (10). Obesity that is seen in hypothyroidism is mild but our second patient had moderate obesity. It was notable that 1 month after treatment with levothyroxine she lost 5 kg weight without any change in her diet and 10 kg after 1 year treatment. Untreated hypothyroidism in children usually results in delayed puberty, but juvenile hypothyroidism causes isosexual precocious puberty (11).

In addition to above symptoms, hypothyroidism may have some cardiac manifestations, like myxedema, presenting with even and hemodynamically significant pericardial effusion or cardiac tamponade. It is suggested that patients with hypothyroidism-associated pericardial effusion be monitored for development of cardiac tamponade (12). Subclinical hypothyroidism (SH) is defined as an elevated thyroid stimulating hormone (TSH) associated with normal levels of free thyroxin. In obese people, the prevalence of subclinical hypothyroidism is significantly higher than general population. It is suggested that this hormonal state is rather a consequence than the cause of the overweight status (13).

As the bright side of our study, we saw considerable response to treatment because of good follow up of children and their parents. Growth parameters of all 3 patients improved remarkably and they had 10 - 12 cm catch up in a year. Plotting on the CDC growth charts, they were crossing the growth percentiles upwards. Regarding the limitations of our study, we did not have per chlorate discharge test in Mashhad, and despite our situation we had to spend much money for laboratory tests. Thyroid diseases are frequently associated with erythrocyte abnormalities, including normocytic, macrocytic, and microcytic anemia (14, 15). Macrocytic anemia was observed in our 3 patients via laboratory evaluations that were missed previously.

In a Turkish study in which 100 hypothyroid patients were compared with 100 subclinical hypothyroid patients and also 200 healthy control people, anemia was more common in hypothyroid group than 2 other groups (16). Anemia secondary to hypothyroidism responded to thyroid replacement therapy alone and after restoration of euthyroid state, most erythrocyte abnormalities will be corrected (14). Anemia also was resolved after treatment with levothyroxine in our patients. In patients with mild to moderate anemia of unknown origin, especially those with decline in linear growth and increased mean corpuscular volume for erythrocyte (MCV), hypothyroidism should be considered in the differential diagnosis of the anemia (17).

Although hypothyroidism is a cause of secondary hyperlipidemia, hypothyroidism in other healthy hypercholesterolemic children should be considered (18). Spanish researchers also mentioned hypercholesterolemia even in patients with congenital hypothyroidism (19). According to a study in New Zealand, high titer of thyroid antimicrosomal antibodies, as well as overt hypothyroidism were found in apparently healthy people with plasma cholesterol concentration above 7-mmol/L (20). It was interesting that hypercholesterolemia was found in our patients. The diagnosis of many childhood endocrine disorders can be facilitated by considering the associated dermatologic findings. Skin as an endocrine organ itself may help us understanding disease mechanisms as well as providing targeted therapy (21).

Hypothyroidism is a common and well recognized cause of diffuse hair loss. Zinc and other trace elements such as copper and selenium are required for the synthesis of thyroid hormones, and deficiency of these can result in hypothyroidism (22). Predominant cutaneous symptom in hypothyroid patients includes dry coarse skin, hair loss, puffy edema, xerosis and altered skin texture. Coarse scalp hair, puffy face, hair loss attributed to hypothyroidism may not improve with thyroxin unless zinc supplements are added (23). Our first case also suffered from hair loss. Her nail and hair growth was slow too.

Thyroid hormones are crucial for proper development of the central nervous system. They are important from the early stages of fetal development. The level of intelligence on verbal scale, correlated negatively with the mean value of TSH (24). Our study had some notable and wonderful unusual manifestations of hypothyroidism such as short stature, anemia, severe constipation, teeth loss, etc. One of the most considerable points in our report was neurodevelopmental delay as well as other symptoms. It is worrying that all 3 cases were missed for about 3 - 4 years by the parents and physicians, especially in the third case who was missed about 9 years, because she had delay in her developmental milestones or IQ assessment and also deafness due to congenital hypothyroidism.

Considering the high prevalence of congenital hypothyroidism (CH) in Isfahan, our Iranian researchers studied on a total of 120 children with CH in 3 groups assessing for IQ score (verbal IQ, performance IQ, and full scale IQ). There was a negative relationship of these values with screening TSH and age of treatment onset. Since CH screening and early treatment has improved the prognosis of patients, so they recommended early and high dose of treatment in children with CH (25). Therefore, if the second case was diagnosed earlier, her IQ impairment and social damage could be prevented.

The screening test for evaluation of congenital hypothyroidism in 3 - 5 days of life, is a good program that were done since 10 years ago in Iran but our patients were born before that time. WHO emphasized on the cost-benefit of this screening test. This program can prevent complications of congenital hypothyroidism and mental retardation. Introduction of screening test has increased the frequency of reported congenital hypothyroidism in many countries like the UK, India, and Saudi Arabia. Ozgelen et al. explained that before initiation of the screening program, 48.4% of cases were diagnosed in the first month; after the program the percentage increased to 62.8%, which was significant. While mental retardation was detected in 13.3% of patients before the screening, it was decreased to 4% after initiation of the program (26).

In Iran the incidence of congenital hypothyroidism is high according to the report of the Health Ministry of Iran. Unfortunately, our patient's parents had not considered their children's developmental delay and short stature; especially in the third case in which they were only worried about child's constipation, so that she had undergone twice abdominal surgery at the age of 5.5 and 7 for this problem with suspicion of Hirschsprung disease.

Veisani et al. by identifying 25 samples, including 1425124 neonates in our country, showed that considering TSH $\geq$ 5 mIU/L as a cut-off point for recalling neonates and low positive predictive value (14%) of this point, more investigation is needed for establishing accurate level of TSH as a criterion for recalling patients (27). Hypothyroidism should be considered in any child with short stature or abnormal growth. Pediatricians and general practitioners should be aware of this disease and have a high index of suspicion in order to detect and treat such patients to minimize the unwanted sequels.

Acknowledgments

It is necessary to appreciate the unwavering efforts of the staff of Pediatric Endocrinology Ward and Laboratory and Nuclear Imaging Center in Imam-Reza Hospital, Mashhad as well as Sadra laboratory (Dr .Mehri Tafazzoli).

Footnote

Authors' Contributions: Study concept and design: Nosrat Ghaemi; acquisition of data: Sam Elmi; analysis and interpretation of data: Reza Erfani Sayyar; drafting of the manuscript: Sepideh Bagheri; critical revision of the manuscript for important intellectual content: Saghi Elmi; statistical analysis: Saber Mohammadzade Rezaee; administrative, technical, and material support: Saghi Elmi; study supervision: Nosrat Ghaemi.

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