Varied presentations of hypothyroidism in children

Maj Sanjeev Khara*, Wg Cdr V Venkateshwar*, Col Madhuri Kanitkar#, Col Amit Devgan*

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INTRODUCTION

Hypothyroidism is among the most common endocrine disorders in children. Congenital hypothyroidism is reported to occur with an incidence of 1:2640 live births in India,¹ and the most common cause is thyroid dysgenesis. Acquired hypothyroidism in children is less common, and in a hospital based study of 100 hypothyroid children in a developing country, only 9% were acquired.²

Hypothyroidism is an endocrine disorder of varied clinical presentation. Manifestations range from subclinical hypothyroidism, which requires high index of suspicion for diagnosis to myxoedema coma. There may be situations where in a given patient an alternative diagnosis may explain the clinical features, and hypothyroidism may be missed. We report four such cases of cryptic hypothyroidism, which we encountered in different clinical situations.

CASE REPORT

First Case: A fifteen month old female toddler, a known case of pulmonary stenosis with global developmental delay, was referred from cardiothoracic centre, when following cardiac catheterisation and balloon dilatation, she developed acute onset anasarca, which was not explained by her cardiac condition. Acute kidney injury due to intravenous contrast administration was considered. However, her urine output, blood pressure, urine examination, renal function tests, renal ultrasonography and Doppler studies were normal. In view of history of global developmental delay and generalised oedema not explained by other conditions, hypothyroidism was suspected. Weight 8.1 Kg (25th centile), length 71 cm (<3rd centile). Thyroid function tests revealed low T3-0.24 ng/mL (normal 1.27–2.21) and T4-1.30 µg/dL (normal 5.6–14.9), while TSH was raised 512 µIU/mL (normal 0.7–6.4). Bone age was delayed. USG neck revealed non-visualisation of thyroid gland. With a diagnosis of hypothyroidism, she was started on tablet thyroxine 50 µg daily, and on follow-up has no oedema and is gaining milestones.

Second Case: A nine year old male child was a known case of single kidney (Lt) with vesicoureteric reflux (ureteric reimplantation done) with chronic kidney disease (CKD) stage IV since early infancy. He was on conservative care for CKD. He was admitted with complaints of excessive gain of weight for last three months. There was no history of developmental delay, lethargy, poor scholastic performance, prolonged steroid intake or decreased urine output. On examination, he was normotensive, had proportionate short stature (height-110 cm), weight-30 Kg (75th centile), bilateral non-pitting pedal oedema and rounded facies (Figure 1). Mild goitre was present. Investigations revealed serum albumin 3.2 g/dL, serum creatinine-2.8 mg/dL (eGFR of 21 mL/min/1.73 m² BSA), serum calcium 8 mg/dL, Phosphorous 4 mg/dL, Alk phosphatase 340 IU/L, random plasma glucose 80 mg/dL. Lipid profile was normal. Bone age was delayed, estimated at 6 years. Ultrasonography of neck showed presence of normal thyroid gland. Thyroid function study revealed low levels of free T3-1.7 pg/mL (normal 2.3–4.2) and free T4-0.29 ng/dL (normal 0.71–1.85), while TSH was raised to 150 µIU/mL. Serum thyroid peroxidase antibodies and antithyroglobulin antibodies were negative. Serum cortisol level at 8 AM was 8.42 µg/dL (normal). He was diagnosed to have hypothyroidism and was started on tablet thyroxine 75 µg daily. Presently child is on follow-up and has lost 8 Kg weight and gained 2 cm height in last 6 months. His TSH is 12.8 µIU/mL presently.

Third Case: An eight year old girl, a known case of steroid resistant nephrotic syndrome with chronic kidney disease was being managed conservatively since one and half year age. Her serum creatinine level was 3.5 mg/dL and eGFR was

Figure 1 Photograph of child with CKD showing obesity and short stature.

*Graded Specialist (Paediatrics), CH (SC) Pune – 40, *Reader, Department of Paediatrics, AFMC, Pune – 40, #Prof & Sr Advisor (Paediatrics), Base Hospital, Delhi Cantt – 10.

Correspondence: Maj Sanjeev Khara, Graded Specialist (Paediatrics), CH (SC) Pune – 40.

E-mail: kherakherakhera@gmail.com

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20 mL/min/1.73 m² BSA. Her height was below third centile and she had a weight of 21 Kg (25th centile). She had anaemia and her haemoglobin levels ranged from 6.8–8.4 g/dL. In spite of erythropoietin, the peripheral blood smear showed normocytic normochromic anaemia with occasional macrocytes. Reticulocyte count was 0.8% and serum iron studies were normal. Bone marrow examination revealed megaloblastic picture and B₁₂ therapy was started. There was no improvement of haemoglobin with iron, folic acid, vitamin B₁₂ and erythropoietin therapy over the past three months. In view of refractory anaemia and presence of macrocytes on PBS, thyroid function tests were carried out, which revealed low T3-0.8 ng/mL (1.27–2.21) and T4-4.1 µg/dL (5.6–14.9), while TSH was raised 13.7 µIU/mL (0.7–6.4). Hypothyroidism was confirmed and she was started on tablet thyroxine 50 µg daily which was subsequently increased to 75 µg. However there were no other sign/symptoms of overt hypothyroidism. After 3 months of thyroxine therapy, her haemoglobin increased to 10 g/dL with peripheral smear showing normocytic normochromic picture.

Fourth Case: A eleven year old girl with no family history of thyroid disorder presented with complaints of poor growth, lethargy, dry skin and poor scholastic performance, for last seven years. She had taken multiple consultations for the same from different medical practitioners. She was treated with multivitamins, haematinics and nutritional 'tonics'. When she reported to our hospital, she was found to have short stature (height 114 cm, 3rd centile: 130 cm), hoarse voice, brittle hair, coarse facial features, periorbital oedema, skin pallor out of proportion to mucosal pallor, coarse dry skin (Figure 2). There was no goitre. Sexual maturity rating was stage 1 (pre-pubertal). Bone age was delayed, estimated at five years (Figure 3). Ultrasonography of neck showed normal presence of thyroid gland. In view of typical symptomatology, a thyroid function tests were done, which revealed low free T3 <0.2 pg/mL (normal 2.3–4.2) and free T4 0.09 ng/dL (normal 0.71–1.85), while TSH was raised >150 µIU/mL (0.7–6.4). Thyroid scan (Tc99) showed no uptake. Serum thyroid peroxidase antibodies and anti-thyroglobulin antibodies were negative.

She was diagnosed to have congenital hypothyroidism (dyshormonogenesis), and started on tablet thyroxine 50 µg daily. The dose was gradually increased. Presently the child after four months of follow-up has lost weight and oedema with improved scholastic performance and has gained 3 cm in height.

DISCUSSION

Hypothyroidism is an eminently treatable condition, which should always be considered in the differential diagnosis of unexplained symptoms, as our case series above reveals. In paediatric patients, congenital hypothyroidism can present late, and acquired hypothyroidism can have unusual causes. Our first patient probably had undiagnosed congenital hypothyroidism and the disease was unmasked following the invasive procedure. The patient developed non-pitting oedema following cardiac catheterisation and balloon valvuloplasty, for which contrast induced nephropathy was initially suspected. Hypothyroidism has been reported in literature following cardiac procedures. The potential causes of decreased thyroid hormone levels during and after cardiac surgery (cardiac catheterisation in this case) are varied and include hypothermia, reduced peripheral cytokines and tumour necrosis factor on thyroid function, iodine skin preparations and cortisol-induced effects on TSH secretion.³ The cause of oedema in hypothyroidism is due to accumulation of glycosaminoglycan in soft tissues and the large volume of hydrated glycosaminoglycan molecules in subcutaneous areas causes oedema of the overlying skin. In addition, absent compensatory increases in lymph flow in hypothyroid patients leads to generalised lymphoedema.⁴ It is unclear why our patient developed such severe and diffuse oedema, although alterations in free water excretion from both the hypothyroid state and renal insufficiency and further cardiac procedure related reductions of thyroid hormone levels in an untreated patient with long-standing severe hypothyroidism, may have precipitated her dramatic clinical appearance.

Figure 2 Photograph of child showing coarse facial features and periorbital oedema.

Figure 3 Radiograph of hands showing delayed bone age in the 11-year-old child.

Our second and third patients had chronic kidney disease (CKD). In chronic kidney disease, there are several mechanisms for hypothyroidism, involving both hypothalamo-pituitary thyroid axis, as well as peripheral thyroid hormone metabolism. Serum TSH levels are normal or elevated, total and free serum T3 and T4 levels are either normal or low.⁵ In CKD, the prevalence of hypothyroidism correlates with GFR. A study showed prevalence of subclinical hypothyroidism increasing from 7% in patients with estimated GFR 90 mL/min per 1.73 m² to 17.9% with <60 mL/min per 1.73 m².⁶ In our patients, eGFR levels were 21 and 20 mL/min/1.73 m², respectively. Data from recent research suggest that TH, especially T3, can be considered as a marker for survival in patients with kidney disease.⁵

In the second patient, short stature was explainable by CKD, but the excessive weight gain remained a concern. There were no features to suggest a central cause of obesity. Cushing syndrome was excluded by absence of other features and a normal serum cortisol level. Therefore we ascribe the short stature and weight gain to hypothyroidism.

Our third patient had refractory anaemia which we initially presumed to be due to CKD itself. The anaemia was however not responding to haematinics and erythropoietin therapy. Anaemias are diagnosed in 20–60% patients with hypothyroidism and is often the first sign of hypothyroidism.⁷ Diagnosis of hypothyroidism should be considered in every case of anaemia with uncertain aetiology because sometimes signs of overt hypothyroidism may not be evident. Our patient had normocytic anaemia with macrocytes seen on peripheral blood smear. Macrocytoses are found in up to 55% patients with hypothyroidism and may result from the insufficiency of the thyroid hormones themselves without nutritive deficit. The response of anaemia to thyroid hormone therapy, in retrospect further substantiated our diagnosis of hypothyroidism.

Our fourth patient presented with the classical symptoms of hypothyroidism in the form of growth failure, lethargy, skin pallor and coarse skin. She had been seen by various medical practitioners, but the diagnosis was apparently missed and she was being administered haematinics, multivitamins and tonics. This shows the importance of high index of suspicion of hypothyroidism in any child with growth failure. On investigations, the thyroid gland was present on ultrasonography, but the thyroid scan (Tc99) showed no uptake of the dye, supporting a diagnosis of dyshormonogenesis. The child most probably had inherited defects in hormone biosynthesis or iodine uptake defect. Dyshormonogenesis account for 10–15% children with hypothyroidism.^{1–8} Dyshormonogenesis results from a deficiency or absence of one or more of the enzymes involved in

the thyroid hormone synthesis or secretion, the most common abnormality being absent or insufficient thyroid peroxidase (TPO) activity. The children with dyshormonogenesis may have no evidence of primary hypothyroidism in the neonatal period, either clinically (normal growth velocity) or biochemically (normal plasma levels of thyroid stimulating hormone and/or thyroid hormone). However, in early childhood, these children develop severe hypothyroidism.⁹

This case series has thus brought to light hypothyroidism in different settings which was initially not suspected, but was subsequently unravelled. Hypothyroidism may manifest variedly as unexplained oedema, excessive weight gain or refractory anaemia in a case of CKD or as growth failure and should not be missed.

CONFLICTS OF INTEREST

None.

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