

# Primary congenital hypothyroidism complicated by persistent severe anaemia in early infancy: a case report with a literature review

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Keywords: congenital hypothyroidism, persistent anaemia, infants

Peer reviewed. (Submitted: 2013-12-24. Accepted: 2014-05-27 .) © SEMDSA

JEMDSA 2014;19(2):85-88

## Introduction

Although anaemia is a common finding in adults with hypothyroidism, there is a general paucity of studies on anaemia in infants with congenital hypothyroidism.<sup>1</sup> The degree of anaemia is usually mild to moderate, with a haemoglobin concentration that is rarely less than 8-9 g/dl.<sup>2</sup> The associated anaemia in hypothyroidism is generally normochromic and normocytic, and occasionally mildly macrocytic.<sup>1</sup> This heterogeneity has been attributed to coexisting deficiencies of iron, vitamin B<sub>12</sub> and folic acid, largely due to impaired absorption.<sup>2,3</sup> Anaemia in hypothyroidism has been linked to impaired haemoglobin synthesis due to a deficiency of thyroxine (T<sub>4</sub>).<sup>3</sup> There is evidence of a direct effect of the thyroid hormone on erythropoiesis. The pathogenesis of anaemia in hypothyroidism has been linked to either a lack of erythropoietin production, or a physiological adaptation to the decreased tissue oxygen requirements resulting from a decrease in the basal metabolic rate.<sup>4</sup> The red cell life span is normal and the results of ferrokinetic studies are compatible with hypoproliferative erythropoiesis in hypothyroidism.<sup>5,6</sup> Thyroid hormones affect oxygen needs at cellular level. Therefore, the responses are compatible with an appropriate physiological adjustment.<sup>2</sup> In vitro studies have shown that thyroid hormones potentiate the effect of erythropoietin on erythroid colony formation.<sup>7</sup> Conversely, iron deficiency impairs T<sub>4</sub> synthesis by reducing the activity of haeme-dependent thyroid peroxidase.<sup>8</sup> White blood cell and platelet counts are usually unaffected in hypothyroidism.<sup>2</sup> Indeed, it has been stated that the presence of pancytopenia suggests that hypothyroidism is not primary, but instead relates to hypopituitarism.<sup>9</sup> In their report, Antonijevic Nesovic, Trbojevic and Milosevic<sup>10</sup> state that the presence of acanthocytosis in a peripheral blood smear suggests hypothyroidism in approximately 90%

of cases. The response to thyroid hormone therapy is gradual. A slow improvement in haemoglobin concentration is seen over several months.<sup>11</sup> Children with a haematocrit value less than 21% and 15%, are considered to have severe anaemia and very severe anaemia, respectively.<sup>12</sup> We report on a case of a six-month old infant who presented with persistent severe anaemia, and who was found to have primary congenital hypothyroidism after a prolonged stay in hospital.

## Case study

A six-month-old infant was referred to the Lagos University Teaching Hospital (LUTH) from a private hospital on account of a low packed cell volume (PCV) of 14%. She underwent blood transfusion in a private hospital the previous month. Her pre-transfusion PCV then was 11%. On presentation at LUTH, the complaints were a two-day history of "whiteness of the body and palms" and a history of a blood transfusion in the preceding month. There was no history of fever. The pregnancy, delivery and the neonatal period were all uneventful. The infant had delayed developmental milestones. The patient is the younger of two children. The brother is five years old without any history suggestive of sickle cell anaemia. The family is of relatively high socio-economic status. The father is a 42-year-old civil engineer and the mother a 38-year-old civil servant.

A physical examination revealed an ill-looking, pale, anicteric infant with a normal temperature that ranged from 36.2-37°C. Anthropometry revealed a weight of 6.5 kg (< 5<sup>th</sup> percentile), a length of 50 cm (< 5<sup>th</sup> percentile) and a head circumference of 43 cm (50<sup>th</sup> percentile). The pulse rate was 128 per minute, was regular, of moderate volume and with normal heart sounds. The patient was in respiratory distress, but the lung fields were clear. There was no hepatosplenomegaly. She

had an umbilical hernia measuring 2 x 3 cm. Following evaluation at the emergency unit for children, the considered diagnosis was haemoglobinopathy or red cell aplasia. During hospitalisation at LUTH, the patient underwent two blood transfusions in two months, a total of three blood transfusions over three months. The pre-transfusion PCV during the second episode of blood transfusion at LUTH was 18%. The post-transfusion PCV for each of the three episodes of blood transfusion was 25%, 34% and 25%, respectively. The PCV remained above 35% following commencement of T<sub>4</sub> replacement therapy, together with haematinic substances. The dose of levothyroxine was 50-75 µg daily. The infant was subsequently discharged after three weeks of commencement T<sub>4</sub> therapy and followed-up at the clinic. The patient did not receive anti-heart failure therapy. As shown in Table I, the packed cell volumes reflected severe anaemia, but the white blood cells and platelet values were within normal limits.

As shown in Table II, the initial free T<sub>4</sub> and thyroid-stimulating hormone (TSH) values were very low and high respectively, suggesting primary congenital hypothyroidism. In addition, during the

course of therapy, the patient also had iatrogenic hyperthyroidism, as revealed by the free T<sub>4</sub> and TSH values on 9 April 2013.

### Discussion

The clinical presentation and laboratory findings in this patient were consistent with persistent severe anaemia. However, some of the clinical features in this patient need to be considered. Five months was the age of onset in this infant. This clearly shows that as well as in adults, anaemia could complicate hypothyroidism in early infancy.<sup>1</sup> The anaemia was normocytic normochromic and the white blood cell and platelet counts were both within normal reference intervals. These haematological indices are in consonance with anaemia associated with hypothyroidism.<sup>1,2</sup> The inconclusive bone marrow aspiration result, which was attributed to haemodilution, may be a reflection of the well known hypoproliferative erythropoietic state associated with hypothyroidism.<sup>5,6</sup> The persistent nature of the anaemia is exemplified by the PCV which ranged from 11-18% over three months, despite repeated blood transfusions. A review of the literature revealed that with this condition, the degree of anaemia is usually mild to moderate, with haemoglobin

**Table I:** Summary of haematological laboratory findings at weeks 1 and 4

Week 1		Week 4	
Parameter	Comments	Parameter	Comments
RBC count: 1.84 x 10 <sup>12</sup> /l	Very low	RBC count: 2.56 x 10 <sup>12</sup> /l	Low
Hb: 4.7 g/dl	Severe anaemia	Hb: 5.6 g/dl	Severe anaemia
PCV: 14%	Severe anaemia	PCV: 17%	Severe anaemia
MCV: 74 fl	Normal	MCV: 66 fl	Low
MCH: 26 pg	Normal	MCH: 21 pg	Low
MCHC: 35 g/dl	Normal	MCHC: 32 g/dl	Normal
WBC* count: 9.10 x 10 <sup>9</sup> /l	Normal	WBC count: 12.1 x 10 <sup>9</sup> /l	Normal
Neutrophils: 3.67 x 10 <sup>9</sup> /l (46.2%)	Normal	Neutrophils: 5.82 x 10 <sup>9</sup> /l (48.1%)	Normal
Lymphocytes: 4.21 x 10 <sup>9</sup> /l (10.3%)	Normal	Lymphocytes: 4.99 x 10 <sup>9</sup> /l (41.2%)	Normal
Monocytes: 0.94 x 10 <sup>9</sup> /l (10.3%)	Normal	Monocytes: 0.96 x 10 <sup>9</sup> /l (7.9%)	Normal
Eosinophils: 0.22 x 10 <sup>9</sup> /l (2.4%)	Normal	Eosinophils: 0.28 x 10 <sup>9</sup> /l (2.3%)	Normal
Basophils: 0.80 x 10 <sup>9</sup> /l (0.95)	Normal	Basophils: 0.06 x 10 <sup>9</sup> /l (0.5%)	Normal
Platelets: 155 x 10 <sup>9</sup> /l	Normal	Platelets: 202 x 10 <sup>9</sup> /l	Normal

Hb: haemoglobin, MCH: mean corpuscular haemoglobin, MCHC: mean corpuscular haemoglobin concentration, MCV: mean corpuscular volume, PVC: packed cell volume, RBC: red blood cell, WBC: white blood cell

\*: Percentage of the total white blood cell count

Other results included haemoglobin phenotype AA, the bone marrow aspirate being inconclusive owing to haemodilution, no occult blood in the stool before commencement of the haematinic therapy the post-transfusion packed cell volume value was 25%, and the packed cell volume value was ≥ 35% following levothyroxine therapy

**Table II:** A summary of the results of the thyroid function tests

Date	Free T <sub>4</sub> (pmol/l)	Comments	Free T <sub>3</sub> (pmol/l)	Comments	TSH (mIU/l)	Comments
6 July 2012	< 3.2	Very low	1.5	Very low	100	Very high*
6 August 2012	29.2	High	9.4	High	0.9	Very low**
10 September 2012	15.7	Normal	7.1	High normal	4.13	High
2 November 2012	13.5	Normal	6	Normal	7.24	High
30 November 2012	36.7	Very high	9.2	High	0.04	Very low**
11 January 2013	22.3	High	7.1	High normal	0.04	Very low**
15 February 2013	14	Normal	4.6	Normal	7.41	High
9 April 2013	22.3	High	5.9	Normal	0.87	Normal
7 June 2013	10.1	Normal	4.3	Normal	3.63	Normal***

T3: triiodothyronine, T4: thyroxine, TSH: thyroid-stimulating hormone

\*: Thyroid function test results on diagnosis of primary congenital hypothyroidism

\*\* : Thyroid function test results indicating iatrogenic hyperthyroidism

\*\*\*: Thyroid function test results indicating a euthyroid state

Reference values: Free thyroxine of 7.2-16.4 pmol/l, free triiodothyronine of 4.4-7.3 pmol/l and thyroid-stimulating hormone of 0.37-3.5 mIU/l

concentration rarely less than 8-9 g/dl,<sup>2</sup> corresponding to a PCV of 24-27%. By contrast, the index patient had a persistently severe form of anaemia, with a PCV range of 11-18% and evidence of decompensation, warranting blood transfusion. The clinical implication is that hypothyroidism should still be considered in the aetiology of anaemia, even if the anaemia is severe (contrary to popular knowledge that the anaemia is usually mild or moderate in severity).<sup>2</sup>

The lack of overt clinical signs of hypothyroidism in this patient may have contributed to the delay in the diagnosis of hypothyroidism. This is unsurprising because of the subtle nature of the clinical manifestations of hypothyroidism in infancy, a well documented phenomenon.<sup>13</sup> Indeed, in standard paediatric endocrinology textbooks, it is documented that the diagnosis of pre-existing thyroid disease during critical illness is extremely difficult.<sup>14</sup> Developmental delay and weight for height of less than the fifth percentile were the two clinical features in keeping with congenital hypothyroidism in this index patient. The extent of the clinical findings depends on the cause and severity of the congenital hypothyroidism. For instance, infants with athyreosis or a complete block in hormonogenesis have more signs and symptoms at birth than infants with ectopic thyroid, the most common cause of congenital hypothyroidism.<sup>13</sup> The practical implication is that clinicians should be more alert to the possibility that when anaemia is persistent, its aetiology might relate to undiagnosed primary congenital hypothyroidism. Considering the subtle nature of the clinical manifestations of congenital hypothyroidism in

infancy, it is reasonable to recommend that a thyroid function test should be performed in all cases of anaemia of uncertain aetiology in the paediatric age group, particularly during infancy. At diagnosis, the free triiodothyronine and free T<sub>4</sub> levels were both low, while the TSH level was markedly elevated, indicating primary congenital hypothyroidism. The tachycardia reflects the anaemia, rather than the typical bradycardia of hypothyroidism.

The resolution of persistent anaemia following levothyroxine therapy represents indirect proof that the anaemia in the index patient was due to hypothyroidism. This is not surprising as previous reports have documented the resolution of anaemia following thyroid hormone therapy in patients with hypothyroidism.<sup>6,11</sup> The pathogenetic mechanisms of anaemia in hypothyroidism include deficiencies of iron, vitamin B<sub>12</sub> and folic acid, largely due to impaired absorption.<sup>2,3</sup> Anaemia in hypothyroidism has also been linked to impaired haemoglobin synthesis because of the deficiency of T<sub>4</sub>.<sup>3</sup> Thyroid hormones affect the oxygen needs at cellular level. Therefore, the response (a reduction in red cell mass) is compatible with an appropriate physiological adjustment.<sup>2</sup> There is reduced oxygen need in hypothyroidism, resulting in reduced erythropoietin secretion.<sup>15</sup> In vitro studies have shown that thyroid hormones potentiate the effect of erythropoietin on erythroid colony formation.<sup>7</sup> If not all, at least some of the aforementioned factors, may have played a role in the persistent severe anaemia observed in the index patient. During the follow-up period, the clinical condition of the patient fluctuated

from severe hypothyroidism to overtreatment, then from stabilisation to overtreatment again. The reason for this observation is unclear. It might relate to compliance on the part of the patient's parents. The development of anaemia in patients with hyperthyroidism has been linked to impairment of the utilisation of iron.<sup>4</sup>

In conclusion, primary congenital hypothyroidism in infancy may be complicated by severe anaemia, and this possibility should be considered in all cases of anaemia with uncertain aetiology, and particularly if the anaemia is persistent.

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