CASE REPORT

# Congenital hypothyroidism as cause of short stature in a 17-year-old Zambian female – A case report

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## ABSTRACT

Congenital hypothyroidism (CH) is a disorder characterized by a deficiency of thyroid hormones at birth. This results in delayed mental and motor milestones with short stature. A 17-year-old female presented to the University Teaching Hospitals - Children's Hospital (UTHs - CH), with a history of delayed developmental milestones and growth since the age of 6 months. Examination revealed an open anterior fontanel, short stature, coarse facies, thick skin, a distended abdomen with reducible umbilical hernia, and kyphoscoliosis. Thyroid function tests showed features of primary congenital hypothyroidism and the patient was put on Levothyroxine with drastic improvements noted. Despite the significant improvement in the patient's condition after the introduction of Levothyroxine, the delay in diagnosis and treatment due to late presentation to the hospital has left some irreversible consequences, especially in terms of growth and skeletal development, this case emphasizes the importance of newborn screening programs which can help detect hypothyroidism early, allowing timely treatment that can prevent long term complications as seen in our case.

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## INTRODUCTION

Congenital hypothyroidism (CH) is a disorder that affects 1 in 2000 to 4000 newborns, commonly females more than males (2:1), and is characterized by the deficiency of thyroid hormones at birth [1,2,3]. The Thyroid gland produces thyroid hormones, including triiodothyronine (T3), thyroxine or tetraiodothyronine (T4), and calcitonin. These hormones are important for the development of the brain, muscles, and heart; they are also responsible for normal skeletal growth, oxidative metabolism, and heat production in all body cells [1, 3, 4, 5]. Thyroid hormones promote the absorption and metabolism of carbohydrates and lipids by optimizing glycolysis and gluconeogenesis, increasing insulin activity, and stimulating lipogenesis and lipolysis. Studies have also shown that thyroid hormones also play a role in Molecular mechanisms such as activation of Thyroid Hormone Receptor (TR) isoforms (α and β) to influence gene expression and nuclear receptor Interactions such as Vitamin D Receptor (VDR) to regulate bone metabolism[6,7], therefore, reduction or total absence of thyroid hormones in the body, in the case of congenital hypothyroidism, causes delayed growth, and mental disability[7,8].

There are three main types of congenital hypothyroidism based on the cause which are primary, secondary, and

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tertiary congenital hypothyroidism. Primary congenital hypothyroidism may be due to thyroid dysgenesis (most common cause), defective thyroid hormone synthesis, transient hypothyroidism, maternal iodine deficiency or end-organ unresponsiveness to TSH, T3, and T4 (pseudo hypothyroidism). Secondary congenital hypothyroidism occurs due to TSH deficiencies either because of isolated causes or multiple pituitary deficiencies. Tertiary congenital hypothyroidism is due to inadequate secretion of Thyrotropin-releasing hormone (TRH) from the hypothalamus [1, 3, 5]. One type is differentiated from the other based on Thyroid function test findings. In primary congenital hypothyroidism, TSH is high (> 100 µ unit/L) with low T3 and T4. There are low T3, T4, and TSH levels in secondary congenital hypothyroidism, however, TSH levels may be normal or slightly above >10 µ unit/L. There is decreased TRH, TSH, T3, and T4 in tertiary congenital hypothyroidism [1, 9].

The clinical presentation of CH includes a history of poor feeding, prolonged neonatal jaundice, decreased activity, delayed teething in early life and later on, delayed mental and motor milestones with short stature. On physical examination of the head and neck, they have coarse facial features with a hoarse voice, coarse brittle hair with a low anterior hair line and delayed closure of anterior fontanel. The eyes may be puffy and narrow with short palpebral fissures and a depressed nasal bridge. They may also have a short neck with supraclavicular fat pads[4, 5, 10]. Thyroid hormones are essential for skeletal development and are important regulators of bone maintenance. Therefore, Congenital hypothyroidism has profound impact on the skeletal system such as delayed bone age, dwarfism and thickened bands at the metaphyseal ends being the most common findings, as well as epiphyseal dysgenesis . Because thyroid hormones are essential for normal brain development, congenital hypothyroidism causes neurologic sequelae, including impaired intellectual and motor development and generalized hypotonia . Cardiovascular manifestations include bradycardia, pericardial effusion, and cardiomegaly. Manifestations in the digestive system include umbilical hernia and constipation. They can present with short broad hands, with occasional reversible generalized pseudohypertrophy most prominent in the calf (Kocher Debre Semelaigne Syndrome), the skin may be cold, dry (myxedematous tissue), pale (resistant anemia), or yellow (raised carotene) in the musculoskeletal system. They also present with delayed sexual maturation [1, 2, 4, 5.]

When evaluating a case of congenital hypothyroidism, a detailed history should be obtained with a careful clinical examination performed[9]. Thyroid function tests confirm the diagnosis of congenital hypothyroidism . Other diagnostic tests, such as thyroid radionuclide uptake and scan, thyroid sonography, or serum thyroglobulin determination may help pinpoint the underlying etiology, although treatment may be started without these tests[3]. Treatment of CH is hormone replacement with Levothyroxine with the starting dose typically being 10-15 µg/kg [9, 16.] We reported a case of a 17-year-old female who presented to the UTHs - CH with a history of delayed developmental milestones and growth. After performing thyroid function tests, the diagnosis of primary congenital hypothyroidism was made, and the patient was started on Levothyroxine, resulting in significant improvements.

## CASE PRESENTATION

A 17-year-old female was referred to The UTHs - CH in Lusaka from Malambanyama Rural Health Centre in Chibombo District, which is in the Central province of Zambia, with a history of delayed growth and limb weakness since the age of six months. From history, she had delayed attaining motor milestones, such as head support, crawling, standing, and walking. Currently, she was able to stand unsupported but got fatigued easily. Her Speech was impaired, with limited ability to construct two-word sentences. Her birth history was unremarkable as she was born at term weighing 4.5 kg via spontaneous vaginal delivery. She cried immediately after birth and had no feeding difficulties. Other systems were unremarkable and there was no history of similar presentation in the family.

On general examination, she had short stature with a height of 80cm (below the 5$^{th}$ percentile for age and sex), coarse facies, and thick skin. She had an open anterior fontanel, macroglossia, and a short neck. The respiratory examination revealed mild pectus carinatum with a short sternum, increased anterior-posterior diameter and kyphoscoliosis. The gastrointestinal examination revealed abdominal wall laxity with a reducible umbilical hernia. In the central nervous system, she had cognitive impairment and her limbs were both hypotonic and hyporeflexic. In the musculoskeletal examination, she

had stubby fingers and toes with pes planus. Her sexual maturity rating was at Tanner stage II. From the history and examination, the differential diagnoses made by the attending doctor included; mucopolysaccharidosis and congenital hypothyroidism.

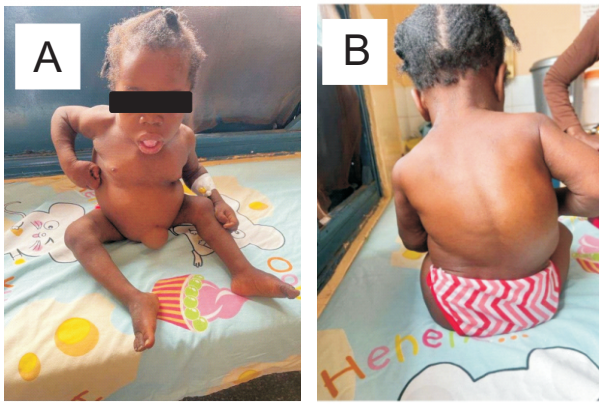


**Figure 1:** Pictures showing features of congenital hypothyroidism on 1st admission before the administration of levothyroxine, **A)** shows course facial features with a protruding tongue and umbilical hernia. **B)** Shows skeletal abnormality (kyphoscoliosis).

While at UTHs - CH, routine laboratory tests were performed as shown in **Table 1**. These tests included thyroid function tests which revealed low triiodothyronine (T3; 0.47 ng/ml), low thyroxine (T4; 2.49$\mu g/dl$), and elevated serum Thyroid Stimulating Hormone (TSH; 100.0$\mu IU/ml$). Since mucopolysaccharidosis was a strong differential diagnosis, urine lysosomal marker profiling was done which revealed high total Urine Glycosaminoglycan (U-GAGs = 99mg/mmol).

The imaging tests performed were an Echocardiogram (ECHO), X-ray of left hand and wrist for bone age determination and computed tomography (CT) scan of the brain, neck, thorax, abdomen, and lower extremities. The ECHO revealed mild pericardial effusion. X-ray of the left hand and wrist for bone age determination showed that all the epiphyses in the hand and wrist were evident and not fused to the long bones, the degree of difference in the width between the smaller epiphyses and the larger metaphases in the middle and distal phalanges was noted, all carpal bones were recognizable except the pisiform, and had not attained adult size, the bone age was in keeping with 8 years of age. CT of the neck revealed soft tissue thickening in the circumscribed oropharyngeal region and mild congestive changes in the bilateral epiglottic fold with partial luminal narrowing while, the chest CT revealed bilateral pleural effusion. CT of the lower extremities revealed epiphyseal dysplasia as seen in **figure 2**.

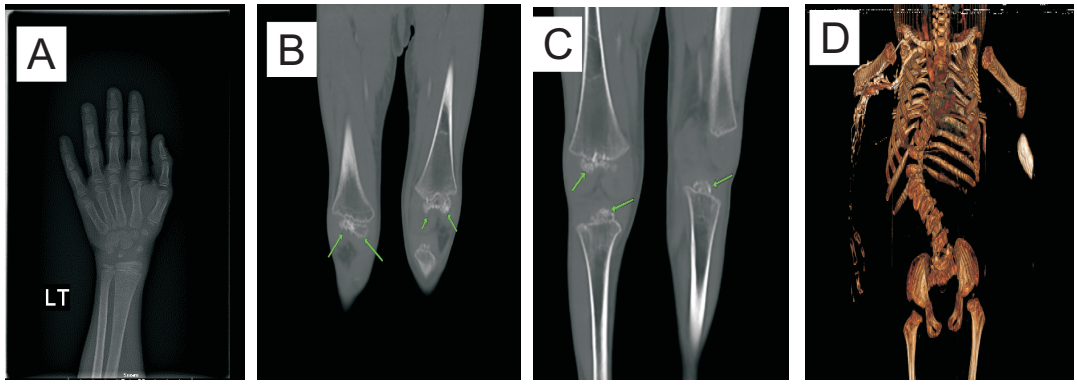


**Figure 2** shows the skeletal manifestations in the patient. **A)** X-ray of the left hand and wrist showing bone age consistent with 8 years of age, **B** and **C)** CT images showing heterogeneous epiphysis with irregular ossification. **D)** showing reconstruction images demonstrating severe thoracic kyphoscoliosis apexed at the T12/L1 level.

The decision was made to start the patient on Levothyroxine 50µg once daily. During her second admission, which was two months after initiation of levothyroxine, the Thyroid function tests were repeated and revealed normal levels of T3 (1.48 ng/ml) and T4 (7.74 *µg/dl)*, with slightly raised TSH (24.4 *µIU/mL*). Her height had improved, increasing to 86cm, and the coarse facies and appearance of the skin had also improved. According to her mother, she was now able to walk unsupported for longer distances and could communicate with a few new words. During her third admission (6 months after the commencement of levothyroxine), lysosomal marker profiling tests were repeated and U-GAGs had reduced from 99 mg/mmol to 21.5 mg/mmol, her mother noted that the patient's motor function and speech had greatly improved. It was due to this drastic response to levothyroxine that a definitive diagnosis of congenital hypothyroidism was made instead of mucopolysaccharidosis, which usually has a progressive course. The patient continues to be followed up in the paediatric clinic and continues to make tremendous improvements on levothyroxine.

**Table 1: Laboratory investigations.**

| **Parameters** | 1st Admission | 2nd Admission | 3rd admission | Normal values |
|---|---|---|---|---|
| **FBC with Differential count** | | | | |
| White blood cell count | $5.4\times10^9$/l | $4.62\times10^9$/l | $5.16\times10^9$/l | $3.80 – 4.80\times10^9$/l |
| Hemoglobin | **9.4 g/dl** | **10.1 g/dl** | **10.1 g/dl** | 12.1 – 16.3g/dl |
| Hematocrit | 27.1% | 30.2% | 31.5% | 36.0 – 46.0% |
| MCV | 95.6 fl | 88.6 fl | 91.6 fl | 79 - 98 fl |
| MCH | 33.0 pg | 29.6 pg | 29.4 pg | 27.0 - 32 pg |
| Platelets | $303\times 10^9$/l | $328\times10^9$/l | $309\times 10^9$/l | $150 - 400\times10^9$/l |
| Neutrophils | $1.78x10^9$/l | $2.70x10^9$/l | $1.78x10^9$/l | $2.00 – 7.00\times10^9$/l |
| Lymphocytes | $3.0\times 10^9$/l | $2.52\times10^9$/l | $2.58\times 10^9$/l | $1.00 - 3.00\times10^9$/l |
| Monocytes | $0.32\times10^9$/l | $0.34\times10^9$/l | $0.72\times10^9$/l | $0.2 - 1.00\times10^9$/l |
| **Liver Function Tests** | | | | |
| AST | **81.24 U/l** | - | - | 0 – 37 U/l |
| ALT | 41.70 U/l | | | 0 – 42U/l |
| ALP | 149.11U/l | | | 40 - 279 U/l |
| Albumin | 3.72 g/dl | - | - | 2.3 – 3.5g/dl |
| **Lysosomal Marker profiling** | | | | |
| U-GAGs | **99mg/mmol** | - | **21.5mg/mmol** | <5.4 |
| **Thyroid Function Tests** | | | | |
| T3 | **0.47 ng/mL** | 1.08 ng/mL | 1.48 ng/mL | 0.51 – 1.80 |
| T4 | **2.49 µg/dL** | 8.13 µg/dL | 7.74 µg/dL | 4.50 – 12.0 |
| TSH | **>100.0 µIU/ml** | **24.8 µIU/ml** | **24.4 µIU/ml** | 0.25 – 5.50 |

***The bold figures in Table 1 denote abnormal laboratory values found in our case.**

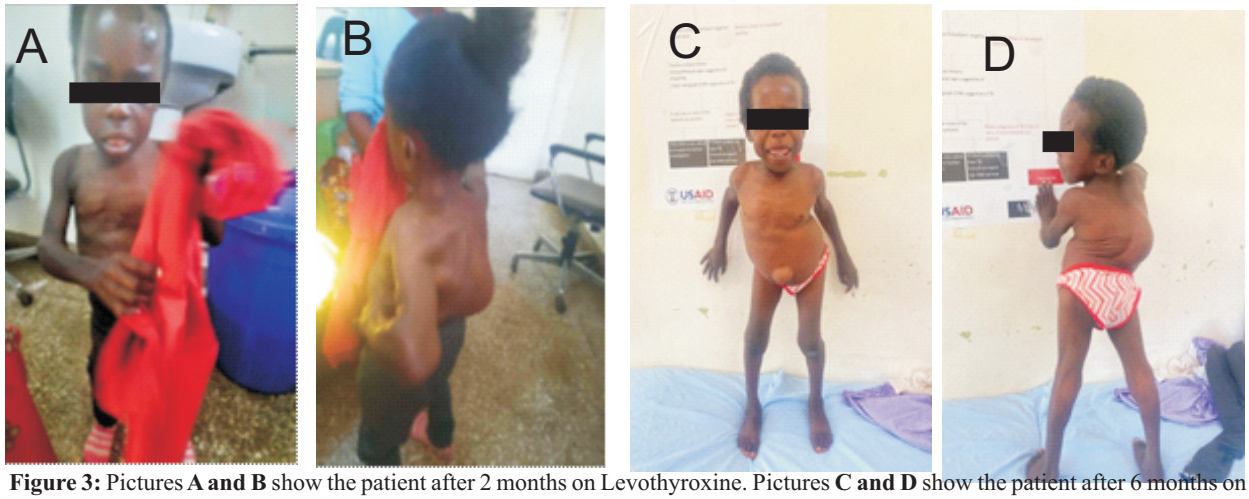


**Figure 3:** Pictures **A and B** show the patient after 2 months on Levothyroxine. Pictures **C and D** show the patient after 6 months on Levothyroxine.

## DISCUSSION

This case highlights the importance of early detection and management of congenital hypothyroidism, which when left untreated or diagnosed late can result in irreversible complications such as cognitive impairment, short stature, and musculoskeletal deformities, as seen in this 17-year-old female.

Congenital hypothyroidism presents with a variety of symptoms affecting different organ systems. In early infancy it can present with features such as poor feeding, prolonged neonatal jaundice, noisy breathing due to macroglossia, reduced activity, delayed teething and delayed closure of the anterior fontanel. Later, these patients have more pronounced symptoms like delayed mental and motor milestones and short stature [1, 2, 17]. Our patient presented with delayed growth and delay in achieving motor milestones, such as head support, crawling and walking, which was noticed from the age of 6 months.

Physical examination of a patient with congenital hypothyroidism reveals general signs such as dry-pale skin, coarse facial features which include puffy eyes, protruding tongue and depressed nasal bridge, they also present with a short stature[4,5,10]. Skeletal abnormalities such as delayed bone age, kyphoscoliosis, epiphyseal dysgenesis, and thickened bands at the metaphyseal ends are also common. Patients with congenital hypothyroidism may sometimes have cardiovascular complications such as pericardial effusion and bradycardia [1, 2]. Sexual maturity is also delayed[1]. On examination, our patient had course facies, thick and dry-pale skin, a depressed nose bridge, a protruding tongue, puffy eyes and an umbilical hernia. She had a short stature with a height below the 5$^{th}$ percentile. Skeletal abnormalities included, delayed bone age, with X-ray of the left hand and wrist showing bone age consistent with 8 years of age in a 17-year-old, kyphoscoliosis and epiphyseal dysplasia confirmed by CT scan. The patient had pericardial effusion which was confirmed by echocardiogram. She also exhibited intellectual disability, evident in her failure to construct sentences at the age of 17 years. She had delayed puberty and her sexual maturity rating was at Tanner stage II.

Confirmatory tests for congenital hypothyroidism are thyroid function tests. In primary congenital hypothyroidism, TSH is high (> 100 µ unit/L) with low T3 and T4 [1, 2]. In our patient the TSH was found to be high (100.0 *µIU/ml*), T3 was low (0.47 ng/ml) as well as T4 (2.49 *µg/dl*), these test results coupled with our clinical findings, confirmed the diagnosis of primary congenital hypothyroidism. Due to limited investigative capacity, we were not able to establish the exact cause of the primary congenital hypothyroidism in our patient.

Mucopolysaccharidosis (MPS) was considered a differential diagnosis due to the overlap in clinical features between MPS and CH. MPS is a group of rare metabolic disorders caused by failure to degrade large carbohydrate molecules due to some enzyme deficiencies, leading to the accumulation of glycosaminoglycan's (GAGs) in the lysosomes and these are excreted through urine as Urine Glycosaminoglycan's (U-GAGs) [18, 19, 22, 23]. Both MPS and CH present with developmental delay, coarse facial features, short stature, and skeletal abnormalities, making MPS a reasonable differential diagnosis [18,19,24]. Mucopolysaccharidosis is associated with progressive mental decline and progressive physical symptoms and signs[18]. The diagnosis of Mucopolysaccharidosis is confirmed by performing quantitative analysis of GAGs in urine and clinical evaluation. Other tests include enzyme assays and molecular testing [18-21, 24]. In our patient, to rule out MPS, we tested for U-GAGs which were found to be as high as 99mg/mmol. Due to limited resources, enzyme assays could not be performed.

The patient was commenced on Levothyroxine based on the clinical picture and abnormal thyroid function tests. At follow-up visits, she had normal T3 and T4 and TSH had reduced from >100 *µIU/mL* to 24.4 *µIU/mL*. She also had notable improvements in height, skin appearance, and both motor and cognitive functions. The level of U-GAGs had also reduced from 99 mg/mmol to 21.5 mg/mmol. This improvement on levothyroxine ruled out mucopolysaccharidosis which is a progressive condition that typically shows no improvement without enzyme replacement therapy and has no cure[18]. This response indicated that the glycosaminoglycan accumulation was secondary to hypothyroidism rather than MPS. Since thyroid hormones facilitate carbohydrate metabolism, a reduction in these hormones can lead to the accumulation of GAGs in the cells just like in MPS[6].

The prognosis of congenital hypothyroidism is generally favorable and symptoms are prevented by early diagnosis

through newborn screening and early treatment with levothyroxine[12]. Thyroid hormone replacement stimulates catch-up growth and bone maturation, but recovery may be incomplete depending on the duration and severity of hypothyroidism before treatment[11]. In our patient, treatment with levothyroxine resulted in improved thyroid function tests, increased height, improved facial features and better motor skills. Despite these improvements, the patient still has irreversible complications such as cognitive delay, short stature and musculoskeletal deformities like kyphoscoliosis.

After a patient with CH is started on Levothyroxine, frequent follow up throughout childhood and adolescence is recommended for better treatment outcomes [25, 26]. Visits are recommended to be made every 6-12 months or more frequently in the case of poor compliance, and each follow-up visit should include a full physical examination and measurement of T4 and TSH levels[26], psychometric tests are also recommended to ensure adequate compliance and cognitive development[25]. Therefore, Long term follow up of this patient will include; regular monitoring of thyroid function tests to ensure proper levothyroxine dosing. Growth, cognitive development and skeletal health will be closely monitored. Patient will be reviewed every 6 months in the general paediatric clinic at the UTHs-CH in Lusaka Zambia.

Early identification and treatment of CH in affected newborns from high income countries, through Newborn screening (NBS) protocols has been shown to be effective in preventing developmental sequelae [27]. However, the same cannot be said about most low and middle income countries where Newborn screening tools are limited to urban hospitals [16,27] and adequate treatment options in resource limited settings are scarce. As seen in this case, our patient traveled all the way from Chibombo District of Central province to access thorough treatment in Lusaka province. This suggests that implementing newborn screening programs in rural areas, providing access to CH treatment and training more health care professionals in the diagnosis and treatment of CH will prevent late diagnosis of the disease, and consequently prevent most of the abnormalities seen in this case.

## CONCLUSION

Congenital hypothyroidism (CH) is characterized by the deficiency of thyroid hormones at birth, it presents with a variety of symptoms affecting different organ systems. A detailed history and clinical examination, supported by thyroid function tests are needed to confirm the diagnosis of congenital hypothyroidism. Timely diagnosis and intervention are critical to prevent long-term complications. This case illustrates the impact of late-diagnosed CH, as seen in the 17-year-old patient who presented with developmental delay, short stature and musculoskeletal deformities. Treatment with levothyroxine yielded significant improvements in thyroid function, physical growth and motor skills, although some irreversible effects, such as cognitive impairment and skeletal abnormalities remain. This case emphasizes the necessity of newborn screening for early CH detection and highlights the need for continuous follow-up and appropriate management to optimize outcomes for affected individuals.

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**Conflict of interest**

There are no conflicts of interest.

**Ethical consideration**

Not applicable

**Consent**

The patient's mother provided written informed consent for the publication of the case.

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**Authors Contribution**

DKM and SM wrote the first draft of the manuscript which was revised several times by HM, and the rest of the Authors.

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