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The Critical Role Of Newborn Screening In Congenital Hypothyroidism: Insights From A Case Study

Jayakrishnan VY[1], Sourabh Bhutani[2], R Nagamahendran[3], Vaibhav Dubey[4]
[1,2,3,4]*Armed Forces Medical Services, India*

Abstract
This case report discusses a 6-year and 5-month-old girl presenting with poor growth noticed by her parents from 2-3 years of age. Detailed examination and investigations revealed congenital hypothyroidism due to thyroid dyshormonogenesis. The child showed significant clinical improvement with Levothyroxine therapy. This report underscores the importance of early diagnosis and management of congenital hypothyroidism to ensure optimal growth and development. The role of newborn screening programs is crucial for early detection and intervention, reducing the risk of intellectual disability and growth failure. Regular anthropometric assessment in children is essential for monitoring growth and identifying deviations that may indicate congenital hypothyroidism. Recognizing red flags, such as poor growth and developmental delays, allows for timely investigations and management.

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I. Background

Congenital hypothyroidism (CH) is the most frequent neonatal endocrine disorder, affecting approximately 1 in 2000 to 1 in 4000 newborns worldwide. It is a significant cause of preventable intellectual disability and growth failure if not diagnosed and treated early. Thyroid hormones play a crucial role in brain development, growth, and metabolism. The condition can result from thyroid dysgenesis (abnormal thyroid development), dyshormonogenesis (defects in thyroid hormone synthesis), or central hypothyroidism (deficiency of thyroid-stimulating hormone, TSH) [1].

The introduction of newborn screening programs has significantly reduced the incidence of intellectual disability due to severe congenital hypothyroidism in many parts of the world. However, not all countries have implemented such screening programs, and the incidence of CH can vary significantly depending on the population and region studied. For instance, in East Asian populations, mutations in the DUOX2 gene are commonly implicated, whereas in European and Middle Eastern populations, mutations in the TG gene are more prevalent [2].

CH can have various etiologies, including genetic mutations, environmental factors, and maternal iodine deficiency. Genetic studies have identified multiple genes associated with CH, with varying prevalence depending on the population and methodology used. For example, mutations in the DUOX2 gene are found in 16-32% of CH patients in East Asia, whereas mutations in the TG gene are more common in European cohorts. Additionally, thyroid dysgenesis and dyshormonogenesis can sometimes share genetic etiologies, complicating the clinical presentation and diagnosis.

II. Case Report

A 6-year and 5-month-old girl, the second child of non-consanguineous parents, presented with poor growth first noticed by her parents at 2-3 years old. She was born full-term and appropriate for gestational age, with no significant antenatal or perinatal history. Exclusively breastfed for six months, followed by complementary feeds, the child had a good appetite, was non-vegetarian, and had no history of fussy eating or constipation. Her developmental milestones were normal, and she had good scholastic performance.

Anthropometric measurements indicated severe growth retardation (Weight: 16.4 kg; Height: 98 cm). Her mid-parental height (MPH) was 158.5 cm, with a target height range of 152 cm to 165 cm. She exhibited features such as a periorbital puffiness, broad nasal bridge, large tongue, short phalanges, protruded abdomen, and a small umbilical hernia. Vital signs were stable, and systemic examination revealed no organomegaly or abnormalities in the external genitalia. There was no history of recurrent infections or hospital admissions, but delayed dentition and umbilical swelling since infancy were noted.

Initial laboratory tests showed normal complete blood count and metabolic panel, but thyroid function tests were markedly abnormal: fT3: 2.37 pg/ml (Normal: 1.04 to 4.4), fT4: 0.32 ng/dl (Normal: 0.8-1.8), TSH: 408.1 mIU/l (Normal: 0.45-4.5), T3: 129 ng/dl (Normal: 59-237), T4: 3.91 mcg/dl (Normal: 5.91-11.5), Anti-

TPO: 0.40 IU/ml (Negative). Ultrasound of the neck revealed altered echotexture of the thyroid with colloid nodules in both lobes. Bone age assessment via X-ray of the wrist showed a bone age of approximately 2 years, indicating significant delay.

The diagnosis was congenital hypothyroidism due to thyroid dyshormonogenesis [3]. The patient was started on Levothyroxine at a dose of 3 mcg/kg/day, titrated based on follow-up thyroid function tests. Additionally, Vitamin D3 and calcium supplementation were initiated. Thyroid function tests were monitored at 2 weeks, 4 weeks, 2 months, and 3 months intervals. Improvements were noted: T3 increased from 129 ng/dl to 184 ng/dl, T4 increased from 3.91 mcg/dl to 10.4 mcg/dl, TSH decreased from 408.1 mIU/l to 0.9 mIU/l. The dose of Levothyroxine was adjusted to 4 mcg/kg/day. Anthropometric measurements at 3 months showed increased height (104 cm) and weight (19 kg), indicating a positive response to treatment.

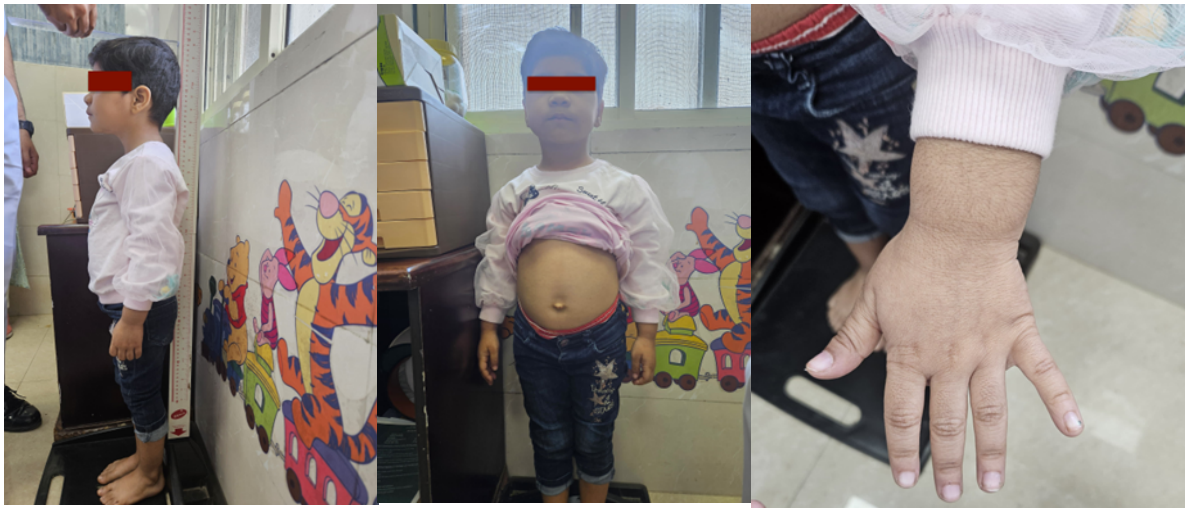

Fig 1. Short Stature In A 6 Yr 5-Month Old Girl
Fig 2. Umbilical Hernia, Facial Puffiness, Broad Nasal Bridge
Fig 3. Shorthand (Metatarsal & Phalanges)

III. Discussion

Early diagnosis and treatment of congenital hypothyroidism are crucial for preventing severe developmental delays and growth impairment. Newborn screening programs, where available, have been instrumental in early detection and management, leading to improved neurocognitive outcomes. The recommended treatment for CH is Levothyroxine, which should be started as soon as possible after diagnosis. The initial dose is typically 10-15 µg/kg/day, with adjustments based on regular monitoring of thyroid function tests[4].

Despite advancements in screening and treatment, challenges remain in managing CH. One significant issue is the variability in screening practices and TSH cutoff values across different regions and countries. For instance, in India, newborn screening (NBS) for congenital hypothyroidism is gradually gaining importance, though it is not yet universally implemented across the country. Screening usually involves measuring the levels of thyroid-stimulating hormone (TSH) in the blood collected from a heel prick sample. The Indian Society for Pediatric and Adolescent Endocrinology recommends TSH levels to be less than 10 mU/L for neonates screened at 48-72 hours of life. If the TSH levels are elevated, a repeat test and a confirmatory serum free T4 and TSH test are conducted [5].In Iran, the TSH cutoff for newborn screening is 5 mU/l for samples taken in the first week of birth and 4 mU/l for samples taken thereafter [6]. Such differences can impact the detection rates and subsequent management of CH. In the U.S., NBS for congenital hypothyroidism is mandatory and includes measuring TSH and/or T4 levels. Typically, a blood sample is taken within the first 24-48 hours of life. If TSH levels are elevated (above 20 mU/L) or if T4 levels are low, further testing is conducted to confirm the diagnosis. Most European countries have well-established NBS programs[7]. The European Society for Paediatric Endocrinology recommends screening with TSH as the primary test. The cutoff value for TSH in Europe varies but generally ranges between 10-20 mU/L depending on the country[8]. In Japan, the NBS program includes both TSH and T4 measurements, with specific follow-up protocols for abnormal results. In some countries in the Middle East, the NBS programs are emerging, with varying degrees of implementation and protocols.

Furthermore, genetic studies have shown that many patients with CH have mutations in more than one gene, suggesting a complex genetic basis for the disorder. This complexity is highlighted by findings that some genes associated with thyroid dysgenesis are also implicated in dyshormonogenesis, indicating an overlap in the

pathogenesis of these conditions. For example, the JAG1 gene, critical for thyroid gland formation, has been associated with both thyroid dysgenesis and eutopic thyroid glands [9].

CH can have various etiologies, including genetic mutations, environmental factors, and maternal iodine deficiency. Genetic studies have identified multiple genes associated with CH, with varying prevalence depending on the population and methodology used. For example, mutations in the DUOX2 gene are found in 16-32% of CH patients in East Asia, whereas mutations in the TG gene are more common in European cohorts[10]. Additionally, thyroid dysgenesis and dyshormonogenesis can sometimes share genetic etiologies, complicating the clinical presentation and diagnosis . Several antenatal factors can increase the risk of congenital hypothyroidism, including iodine deficiency, maternal thyroid disorders, medications (such as antithyroid drugs, lithium, and iodine-containing medications), and environmental factors like exposure to goitrogens. Familial cases of thyroid dysgenesis and dyshormonogenesis due to mutations in genes like TSHR, PAX8, DUOX2, and TG also contribute to the risk.

Management of CH involves not only medical treatment but also regular follow-up and monitoring to ensure optimal growth and development. Levothyroxine therapy should be adjusted based on periodic thyroid function tests, and growth parameters should be closely monitored. In addition to medical management, addressing any developmental delays through early intervention programs is essential for improving long-term outcomes [11]. Dietary factors play a critical role in thyroid health, with adequate iodine intake being essential for thyroid hormone synthesis. Sources include iodized salt, dairy products, seafood, and certain vegetables. Selenium is important for the metabolism of thyroid hormones, with sources including nuts, seafood, and cereals. Excessive soy intake can interfere with thyroid hormone absorption and should be consumed in moderation. While generally healthy, cruciferous vegetables (e.g., cabbage, broccoli) contain goitrogens that can interfere with thyroid function if consumed in large amounts without adequate iodine intake.

Overall, while significant progress has been made in the early detection and treatment of congenital hypothyroidism, ongoing research and refinement of screening and management strategies are needed to further improve outcomes for affected children. Genetic studies continue to uncover new insights into the etiology of CH, which may lead to more personalized and effective treatment approaches in the future.

IV. Conclusion

Early detection and treatment of congenital hypothyroidism (CH) are essential to prevent developmental delays and growth impairment. Newborn screening programs enable early identification and timely treatment, reducing intellectual disabilities. Regular anthropometric assessments help monitor growth and identify deviations indicating CH, supporting optimal development. Recognizing red flags, such as poor growth and developmental delays, allows for swift investigations and interventions.

Global standardization of screening practices is crucial for consistent detection, as differences in TSH cutoff values affect diagnosis. Genetic research shows the complex etiology of CH, necessitating comprehensive genetic screening and personalized treatments. Regular monitoring and follow-up optimize Levothyroxine therapy and support normal growth.

Advancements in genetic research and standardized screening programs will enhance early detection and management of CH, improving the quality of life for affected individuals.

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