Case Report: The Specter of Untreated Congenital Hypothyroidism in Immigrant Families

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Newborn screening has dramatically reduced rates of untreated congenital hypothyroidism (CH). However, in low-income nations where newborn screening programs do not exist, untreated CH remains a significant health and societal challenge. The goal of this report is to alert health care providers about the potential of undiagnosed CH in unscreened immigrant children. We report 3 siblings of Somali descent with CH who started treatment with levothyroxine at age 0.5 years, 7.7 years, and 14.8 years and were followed for 8 years. This case series demonstrates a spectrum of severity, response to treatment, and neurocognitive and growth outcomes depending on the age at treatment initiation. Patient 1, now 22 years old, went undiagnosed for 14.8 years. On diagnosis, his height was -7.5 SDs with a very delayed bone age of -13.5 SDs. His longstanding CH was associated with empty sella syndrome, static encephalopathy, and severe musculoskeletal deformities. Even after treatment, his height (-5.2 SDs) and cognitive deficits remained the most severe of the 3 siblings. Patient 2, diagnosed at 7.7 years, had moderate CH manifestations and thus a relatively intermediate outcome after treatment. Patient 3, who had the earliest diagnosis at 0.5 years, displayed the best response, but continues to have residual global developmental delay. In conclusion, untreated CH remains an important diagnostic consideration among immigrant children.

Congenital hypothyroidism (CH) is a common and preventable cause of irreversible intellectual disability (ID).^{1,2} Laboratory screening allows prompt initiation of treatment during the first month of life.¹ Since the introduction of newborn screening (NBS) programs in 1972, most infants with CH born in countries that have implemented these programs are identified through this type of procedure.³ Unfortunately, there remain countries without adequate NBS programs, including the majority of countries in Africa.³ It is estimated that 71% of newborns worldwide are not included in an NBS program.³ Given the increase

in displacement and migration of individuals from Africa, the diagnosis of previously unrecognized CH is likely to rise.

The average annual number of refugees coming to the United States is 60 000, with the numbers trending upwards.⁴ Thus, unscreened patients with CH arriving in the United States may contribute to the count of unrecognized cases. Centers for Disease Control and Prevention (CDC) guidelines currently recommend no routine metabolic screening of newly arrived refugee children, leaving any testing up to individual state policies and/or health care providers.⁵

abstract

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Dr Hamdoun carried out data collection and drafted the initial manuscript; Dr Karachunski carried out neurological analyses; Dr Nathan, Mrs Torkelson, and Mrs Drilling reviewed and revised the manuscript; Dr Fischer carried out the neuropsychological assessments and revised the manuscript; and Dr Petryk conceptualized and designed the study, reviewed and revised the manuscript, and approved the final manuscript as submitted.

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TABLE 1 Neuropsychological Instruments Used by Domain

IQ	Mullen Scales of Early Learning Kaufman Assessment Battery for Children, 2nd ed
Adaptive Functioning	Adaptive Behavior Assessment System 2nd ed Vineland Adaptive Behavior Scales, 2nd ed
Language	Mullen Scales of Early Learning Clinical Evaluation of Language Fundamentals, 5th ed Peabody Picture Vocabulary Test, 4th ed
Fine-Motor	Mullen Scales of Early Learning The Beery-Buktenica Developmental Test of Visual-Motor Integration, 6th ed Purdue Pegboard
Gross-Motor	Mullen Scales of Early Learning

FIGURE 1

Family pedigree suggests recessive inheritance of CH. There is no report of consanguinity. Mother was reported to be clinically euthyroid, but has never had a TSH or a neck ultrasound performed before the 3 pregnancies.

In this article, we report 3 cases of CH in Somali immigrants, all blood relatives, who were diagnosed with hypothyroidism soon after arrival to the United States. The adverse effects of delayed treatment on growth and cognition and the impact of treatment are discussed.

METHODS

This study has a local institutional review board approval.

Anthropometry

Measurements of weight and height were performed at a minimum of 6-month intervals after diagnosis. Values were plotted on CDC growth charts. SDs and growth velocities

were calculated using GenenCALC, version 3.0 (Genentech Inc., San Francisco, CA).

Endocrine and Developmental Evaluations

Thyrotropin (TSH), free thyroxine, insulin-like growth factor binding protein 3, anti-thyroglobulin, and thyroid peroxidase antibodies were measured by chemiluminescent immunoassay, whereas insulin-like growth factor-1 was measured by total liquid chromatography/mass spectrometry. Growth hormone stimulation testing was performed using clonidine and arginine.⁶

Neuropsychological evaluation (NPE) was performed using measures that

matched the developmental levels of the patients and that were sensitive to their linguistic and cultural background (Table 1). For Patient 1, NPE results were calculated using age-equivalents.^{7,8} A Somali interpreter assisted the caregiver with completion of the rating forms. Mental age refers to age-equivalent performance level on NPE. Areas assessed included IQ,^{9,10} adaptive functioning,^{11,12} language,^{9,13,14} fine-motor,^{9,15,16} and gross-motor abilities.⁹

Imaging Studies

Thyroid ultrasounds, skeletal radiographs, bone age radiographs (based on the Greulich–Pyle method), and pituitary MRI were interpreted by pediatric radiologists.

RESULTS

The family pedigree is shown in Fig 1. There is no reported consanguinity. Patients 1 and 2 were born in Somalia. Patient 3 was born in a Kenyan refugee camp before the family immigrated to the United States. The mother did not have a history of goiter or thyroid disease. Three of 9 siblings were diagnosed with nongoitrous CH shortly after arrival to the United States. All siblings had negative antithyroglobulin and thyroid peroxidase antibodies and small thyroid glands without focal nodularity on ultrasound examination.

Patient 1

Based on history from the parents, Patient 1 was edematous at birth and hypotonic. He did not achieve head control or ability to sit without support until five years of age. Upon arrival to the United States at the age 14.8 years, the main concerns were severe global developmental delay, chronic constipation, and dry skin. He was dull appearing and nonverbal.

FIGURE 3
Patient 1 growth chart: stature-for-age percentiles with bone age and midparental height data. The patient is now 22 years old. Height data beyond age 20 years are shown in Table 3.

FIGURE 4
Patient 1 growth chart: weight-for-age percentiles. The patient is now 22 years old. Weight data beyond age 20 years are shown in Table 3.

FIGURE 2
Photograph of 2 brothers. Patient 1 (right) is 22 years old, height -5.2 SDs. Lower extremity contractures confound height measurements. Patient 3 (left) is 8 years old, height -1.3 SD.

His face was myxedematous, with a large protruding tongue and prominent lips. He was prepubertal, had diminished to absent tendon reflexes, and was nonambulatory, requiring full time use of a wheelchair due to flexion contractures in his lower limbs (Fig 2). Clinical presentation and diagnostic evaluation were consistent with primary hypothyroidism (Table 2, Figs 3 and 4).

Treatment with levothyroxine (L-thyroxine) was started at a dose of 25 mcg per day and increased to 100 mcg over the ensuing 12 months. After 3 years of L-thyroxine therapy, he was able to ambulate with assistance. Although growth improved, he remained short statured without adequate catch-up growth. Insulin-like growth factor-1 was 132 ng/ml (-1.4 SD) and insulin-like growth factor binding protein 3 was 2.6 μ g/ml (-2.3 SD) (Figs 2 and 3, Tables 2 and 3). A growth hormone (GH) stimulation test was consistent with GH deficiency (peak GH level of 8.1 μ g/L after clonidine and 1.6 μ g/L after arginine). His brain MRI revealed an empty sella (ES) (Fig 5A) and a pars intermedia cyst (Fig 5B). A cosyntropin stimulation test was normal (peak cortisol level of 21 μ g/

dL). GH treatment was started and resulted in improved growth velocity (Table 3).

Patient 1 continues to suffer from severe deformities of the lower extremities (Fig 6A) attributed to myopathy and static encephalopathy with spasticity. There were no bony abnormalities on radiographs (Fig 6B). His audiology evaluation showed a normal bilateral sensitivity with some degree of hair cell damage. His NPE demonstrated profound ID (Table 4) with severe deficits in early visual problem-solving (functioning at the 37 month level), gross motor skills (18 months), fine motor skills (36 months), receptive language (28 months), and expressive language (2 months). To date, he remains nonverbal, unable to ambulate without support, and has a level of comprehension and functioning insufficient for independent activities of daily living.

Patient 2

Patient 2 did not achieve head support or the ability to sit up independently until 3 years of age. On presentation at age 7.7 years, she spoke only a few words with grossly normal hearing, ambulated only with support, and had chronic constipation. She had facial myxedema with a large tongue and lips, was hyporeflexive with a delayed recovery phase, had poor weight gain, and short

TABLE 2 Baseline Characteristics and Response to L-thyroxine Treatment of Congenital Hypothyroidism

	Patient 1	Patient 2	Patient 3
Gender	Male	Female	Male
At Diagnosis			
Age (y)	14.8	7.7	0.5
Height (SD)	−7.5	−8.1	−8.1
Weight (SD)	−11.3	−7.3	−3.7
Bone age (y, SDS)	(1.3, −13.5)	(0.8, −8.6)	—
IGF-1 (SD)	−1.4 ^a	—	—
IGFBP-3 (SD)	−2.3	—	—
Tanner stage (breasts)	N/A	1	N/A
Tanner stage (testes)	1	N/A	1
Tanner stage (pubic hair)	1	1	1
Testicular vol (mL)	2	N/A	2
TSH (mU/L)	150	>500	26
FT4 (ng/dL)	Not available	0.36	0.89
At Most Recent Visit 8 y After the Diagnosis and Treatment of CH			
Age (y)	22	15	8
Height (SD)	−5.2	−2.1	−1.3
Δ height (SDS)	2.3	6.0	6.8
Wt (SD)	−4.7	−2.4	−2.5
Bone age (y, SDS)	(14, −6.2)	(14.5, −0.3)	7.4
IGF-1 (SD) (on GH therapy)	0.5 ^b	−1.7	—
IGFBP-3 (SD)	−1.6	−2.7	—
Tanner stage (breasts)	N/A	4	N/A
Tanner stage (testes)	3	N/A	1
Tanner stage pubic hair	4	3	1
Testicular vol (mL)	12	N/A	2
TSH (mU/L)	3.86	2	4.41
FT4 (ng/dL)	0.96	1.03	1.31

FT4, free thyroxine; IGF-1, insulin-like growth factor-1; N/A, not applicable; SDS, SD score.

^a Before GH therapy.

^b On GH therapy.

stature (Figs 7 and 8, Tables 2 and 3). She was diagnosed with primary hypothyroidism with a severely delayed bone age (−8.6 SDS) and had

a normal GH stimulation test (peak GH level of 11.4 μg/L).

After initiation of L-thyroxine, her energy level improved, her

TABLE 3 Change in Height in Siblings With CH Over the Course of L-thyroxine Treatment

Visits	Patient 1				Patient 2				Patient 3			
	Age (y)	Height SD	Height (cm)	Δ Height (SDS)	Age (y)	Height SD	Height (cm)	Δ Height (SDS)	Age (y)	Height SD	Height (cm)	Δ Height (SDS)
Initial	14.8	−7.5	89.1	N/A	7.7	−8.1	84	N/A	0.5	−8.1	52.2	N/A
Year 1	15.8	−7.4	93.1	0.1	8.7	−6.2	98.2	1.9	1.5	−2.9	73	5.2
Year 2	16.7	−8.3	99.8	−0.9	9.6	−4.9	107	1.3	2.4	−2.3	82.3	0.6
Year 3	17.8	−8.7	107.7	−0.4	10.7	−3.8	116	1.1	3.6	−2.2	91.1	0.1
Year 4	18.9	−8.1	116.0	0.6	11.8	−4.1	125.2	−0.3	4.6	−1.9	98	0.3
Year 5	19.4	−8.0	117.5	0.1	12.3	−4.1	128.0	0.0	5.1	−1.7	101.5	0.2
Year 6	20.6 ^a	−6.9	126.5	1.1	13.6	−3.5	136.7	0.6	6.4	−1.4	110	0.3
Year 7	21.5	−6.1	134.4	0.8	14.4	−2.9	142.2	0.6	7.2	−1.5	115.9	−0.1
Year 8	22.0	−5.2	136.0	0.9	15.0	−2.07	148.6	0.83	8.0	−1.3	120.6	0.2

N/A, not applicable; SDS, SD score.

^a Growth hormone therapy was started

FIGURE 5

Brain and pituitary gland MRI of Patient 1 was obtained 3 years after the start of L-thyroxine therapy. The image has T1 weighted sequences, with and without contrast enhancement with gadolinium. Arrows point to an empty sella (A) and pars intermedia cyst (B). The extrapituitary brain structure is normal.

TABLE 4 Comparison Between Chronological and Mental Age (Years) in 3 Siblings With CH

	Patient 1	Patient 2	Patient 3
Chronological Age at diagnosis	14.8	7.7	0.5
Chronological Age at evaluation	21	14	7
Mental Age at evaluation	2.0	7.0	5.1

Mental age is the average of subtest age equivalents for Mullen (Patient 1), Kaufman Assessment Battery for Children, Second Edition (KABC-II) Nonverbal Index (Patient 2), and KABC-II Fluid/Crystallized Index (Patient 3).

FIGURE 6

A, Radiographs of lower extremities of Patient 1 show leg deformities. B, No apparent bony abnormalities were identified on anteroposterior image, suggesting that leg deformities are due to muscle contractures.

constipation resolved, and her speech improved with increased vocabulary. At 12 years, she was started on depot Lupron

to delay epiphyseal closure (Fig 7). Her height SD score has significantly increased (Fig 7, Table 3). Although she showed

some developmental progress, her current NPE shows moderate ID (Table 4).

Patient 3

Patient 3 was diagnosed with CH at 6 months of age (Table 2) after showing symptoms of chronic constipation. His initial physical examination was remarkable for persistent head lag and the inability to sit without support. He had diminished reflexes, dry skin, and grossly normal hearing. He was started on 37.5 mcg of L-thyroxine. After initiation of therapy, he had a remarkable improvement in growth rate and development (Tables 2 and 3). Nevertheless, his NPE still reflects global developmental delay (Table 4).

DISCUSSION

This report should alert health care providers about unrecognized cases of CH among immigrants arriving from countries without NBS. It highlights the phenotypic spectrum of CH and sequelae of delayed treatment based on age at diagnosis. Infants with CH often exhibit subtle or no manifestations at birth, making a clinical diagnosis difficult.¹⁷ In countries without NBS, there is a substantial risk that newborns with CH can pass unnoticed by health care providers. This report is a critical reminder that infants with CH who are detected by NBS and promptly treated on diagnosis have better growth and neurocognitive outcomes.¹⁸

CH complications can extend to involve the pituitary gland as well as the musculoskeletal system. Longstanding CH can induce pituitary thyrotrope hyperplasia (due to lack of negative feedback), which can involute into an ES.^{19,20} A sudden increase in inhibitory feedback to the hypothalamic-pituitary axis caused by thyroid

hormone replacement can result in atrophy of the pituitary gland.²⁰ In this report, the small initial dose of L-thyroxine and gradual dose titrations show that ES syndrome can occur irrespective of the rapidity of TSH normalization. Although Patient 1 did not have a brain MRI before starting L-thyroxine treatment, his initial TSH elevation argues against central hypothyroidism and supports the presence of a pituitary gland at presentation. Evaluation of pituitary function and brain MRI should be considered in the work-up of longstanding CH when clinically indicated.²¹

Prolonged deficiency of thyroid hormones can result in a change of muscle fibers from fast twitch type II to slow twitch type I as well as hypertrophy due to the accumulation of glycosaminoglycans.²² This can manifest clinically as stiffness, muscular pseudohypertrophy, weakness, and painful muscle cramps.^{22–24} Abnormal motor function due to static encephalopathy, proximal myopathy associated with CH, and adaptive positioning in nonambulatory patients who are not receiving physical therapy may contribute to muscle contractures and leg deformities. Although partial improvement of motor function after the start of treatment reflects the reversible myopathic effect of thyroid hormone deficiency, in severe cases, spasticity due to upper motor neuron involvement and musculoskeletal deformities may be irreversible.

This study has several limitations. One of them is lack of genetic testing in the siblings. The negative maternal history for goiter^{25,26} and hypothyroidism makes neurological cretinism from iodine deficiency²⁷ less likely in Patient 1, although there is

FIGURE 7

Patient 2 growth chart: stature-for-age percentiles with bone age, midparental height, and duration of Lupron therapy data.

FIGURE 8

Patient 2 growth chart: weight-for-age percentiles.

still uncertainty about maternal iodine status during pregnancy. In addition, musculoskeletal

deformity in Patient 1 could have underestimated his height. He had no baseline brain MRI to determine

the onset of ES in relation to treatment.

In summary, the assumption that all children undergo NBS could hinder a clinical diagnosis of CH by a US health care provider. There is insufficient epidemiologic data regarding the prevalence of unrecognized CH among immigrants to the United States. Testing for thyroid function is neither routinely recommended nor mandated by the US Department of

Health and Human Services or the CDC for children >1 year of age.⁵ Therefore, screening and early recognition of this diagnosis in immigrant families remains entirely in the purview of the US health care provider.

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ABBREVIATIONS

CDC: Centers for Disease Control and Prevention
CH: congenital hypothyroidism
ES: empty sella
GH: growth hormone
ID: intellectual disability
L-thyroxine: levothyroxine
NBS: newborn screening
NPE: neuropsychological evaluation
TSH: thyrotropin

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