

RESEARCH ARTICLE

Congenital hypothyroidism: a five-year retrospective study at Children's University Hospital, Damascus, Syria

Mariam Saoud¹, Sahar Al-Fahoum¹, Younes Kabalan²

Address for Correspondence:

Mariam Saoud

¹Department of Biochemistry and Microbiology,
Faculty of Pharmacy, Damascus University,
Damascus, Syria

²Faculty of Medicine, Damascus University,
Damascus, Syria

Email: Mariam-saoud@hotmail.com

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ABSTRACT

Background: Congenital hypothyroidism (CH) is a treatable thyroid hormone deficiency that causes severe mental retardation and growth deficiency if not detected and treated early. The treatment of CH is simple, inexpensive, and effective. With early detection and treatment, infants usually develop normally without mental retardation and become productive members of society. In Syria, a screening program is not available, and there is no published information about the actual incidence of CH.

However, an unpublished pilot study supported by the International Atomic Energy Agency showed that the incidence of CH in Syria is more than the global incidence, indicating the importance of the application of a CH screening program in Syria.

Objectives: The present study aimed to collect baseline information about CH in Syria to estimate the potential need of a screening program.

Materials and methods: This retrospective study was performed at Children's University Hospital, Damascus. The study included the medical records of patients who had CH as the final diagnosis between 2008 and 2012. Some patients were diagnosed elsewhere and were then admitted to the hospital within the same period.

Results: In this study, 70 cases registered as CH, 67 of them had confirmed, 40 (57.1 %) were male and 30 (42.9%) were female. Among the patients, (51.4%, n = 36) involved parental consanguinity and 6 had a family history of hypothyroidism. Additionally, 74.3% were not diagnosed during the first month of life. The signs and symptoms most commonly detected were cretinoid face (60%), pallor (44.3%), delayed neuropsychomotor development (37.1%), growth

failure (36.7%), jaundice (35.7%), and hypotonia (35.7%).

Conclusion: A CH screening program is necessary in Syria owing to the low specificity of the signs and symptoms of CH, which can lead to delayed diagnosis, and the presence of asymptomatic cases (subclinical hypothyroidism).

Keywords: Congenital Hypothyroidism, Newborn Screening, high TSH values, low fT₄ values

INTRODUCTION

Congenital hypothyroidism (CH) involves thyroid hormone deficiency at birth. Issues with thyroid gland development (dysgenesis) or disorders of thyroid hormone biosynthesis (dyshormonogenesis) most commonly cause thyroid hormone deficiency at birth.¹

CH is one of the most common treatable endocrine diseases, which can affect the growth and mental development of newborns if not treated promptly. Early diagnosis and treatment during the first weeks of life are extremely important for the normal intellectual development of affected children.^{2,3} An early clinical diagnosis of CH is difficult to achieve based on clinical manifestations, which are often subtle or not present at birth,⁴ but it is achievable with simple, low-cost diagnostic laboratory tests for thyroid function. Therefore, in many developed countries, infants routinely undergo thyroid screening, which involves the measurement of thyroid-stimulating hormone (TSH) and thyroxine (T₄) in cord blood or neonatal heel blood.⁵ The incidence of CH varies from 1 in 3000 to 1 in 4000 live births in different parts of the world,² and there is significant variation in the incidence of CH among regions in some countries, such as Iran (1 in 1433, 1 in 914, and 1 in 370 live births in Fars province, Tehran, and Isfahan, respectively).²

Published data demonstrate relatively high incidences of CH in some Arab countries, including Lebanon (1 in 1823),⁶ Bahrain (1 in 2967),⁷ United Arab Emirates (1 in 1778),⁷ Palestine (1 in 2133),⁸ Oman (1 in 2200),⁹ Saudi Arabia (1 in 2931),¹⁰ and Egypt (Fayoum: 1 in 3587¹¹; Alexandria: 1 in 3974¹²).

In Syria, there is no published information about the actual incidence of CH due to the lack of research concerning CH and the absence of an active newborn screening program. In light of the absence of a

screening program and the lack of novel diagnostic tools and facilities, the diagnosis of CH depends on high suspicion of early indicative signs and symptoms.

The present retrospective study aimed to clarify the importance of CH screening programs in Syria, similar to the rest of the world, by reviewing all children with confirmed CH admitted between 2008 and 2012 to Children's University Hospital, Damascus, which is the largest medical center for children in Syria. Additionally, we compared the results with the findings of unpublished retrospective studies performed in Syria over the past 30 years.

MATERIALS AND METHODS

This retrospective study reviewed all medical records of patients with CH admitted to Children's University Hospital, Damascus, between January 1, 2008 and December 31, 2012, as well as those of patients diagnosed elsewhere and then admitted to the hospital within the same period. All data were obtained with the approval of the hospital administration.

The presumptive diagnosis was based on nonspecific clinical signs and symptoms, such as cretinoid face, delayed neuropsychomotor development, growth failure, jaundice, and umbilical hernia.

The quantitative determination of serum free T₄ (fT₄) and TSH levels in a sandwich chemiluminescence immunoassay using the Liaison® Kit (Via Crescentino, snc. – 13040 Saluggia (VC) – ITALY), in accordance with the normal ranges mentioned in Table 1, confirmed the diagnosis.

Data collected from each medical record included the following: age at diagnosis, sex, skeletal age, family

Table 1. Normal range for fT₄ and TSH.

Age	fT ₄ (ng/dL)	TSH (mIU/L)
1–3 d.	2.2–5.3	1.0–17.4
1–2 wk.	1.6–3.8	1.7–9.1
2 wk. – 4 mo.	0.9–2.2	1.7–9.1
4–12 mo.	0.7–1.9	0.8–8.2
1–5 y.	0.8–2.3	0.8–8.2
5–10 y.	0.7–2.1	0.7–7.0
10–15 y.	0.6–2.0	0.7–5.7

fT₄: Free Thyroxine – TSH: Thyroid-Stimulating Hormone.
d.: day – wk.: week – m.: month – y.: year.

history, parental consanguinity, signs, symptoms, and diagnostic study. All data were analyzed using Microsoft Office Excel 2010 (Microsoft Corporation, Redmond, WA, USA).

RESULTS

Between 2008 and 2012, 158,149 patients were admitted to the hospital, and only 70 had CH, with an incidence of 1 in 2259 patients. Three of the patients had CH according to presumptive diagnosis, but they did not undergo confirmatory testing, 40 (57.1%) were male and 30 (42.9%) were female.

The mean age at diagnosis was 8 months (range, 4 days to 6 years). Table 2 shows the distribution of patients according to the age at diagnosis.

Consanguineous marriage was noted in 36 (51.4%) of the 70 patients, and a family history of hypothyroidism was noted in 6 (8.5%) patients.

Among the patients, 42% had clinical manifestations, with more than one of the clinical signs and symptoms of the disease, whereas 58% did not have any signs or symptoms suggestive of the disease, although they were diagnosed according to the serum fT_4 and TSH levels.

The clinical signs and symptoms (umbilical hernia, dry skin, cretinoid face, growth failure, jaundice, macroglossia, abdominal swelling, pallor, constipation, hypotonia, vomiting, feeding problems, delayed neuropsychomotor development, lethargy, and weight deficit) were assessed through parent interview and clinical examination by specialists. Table 3 summarizes the frequencies of the most important signs and symptoms demonstrated by patients.

Table 2. The distribution of patients according to the age at diagnosis.

Age	Current Study % n = 70	Study 2011 ¹⁵ %	Study 1984 ^{15*} %
< 1 mo.	25.7	11.5	7
1 – 3 mo.	24.3	20	24
3 – 6 mo.	11.4	31	10
6 mo. – 1 y.	12.9	20	0
> 1 y.	25.7	17.5	59

*Number of cases not determined according to the reference. mo.: month - y.: year - n.: number of cases.

Table 3. The frequency of the most important ratios signs and symptoms that demonstrated by CH patients.

Signs/Symptoms	%
Cretinoid face	60
Pallor	44.3
Delayed neuropsychomotor development	37.1
Growth failure	36.7
Jaundice	35.7
Hypotonia	35.7
Abdominal swelling	28.6
Lethargy	28.6
Feeding problems	27.1
Vomiting	27.1
Fever	25.7
Constipation	22.9
Umbilical hernia	20
Dry, rough and mottled skin	18.6
Weight deficit	17.1
Macroglossia	15.7

The patients experienced clinical manifestations at different ages. The signs and symptoms of jaundice, poor feeding, constipation, abdominal swelling, and cretinoid face were most common at < 3 months of age, whereas delayed neuropsychomotor development, macroglossia, and weight deficit were most common at > 6 months of age. Table 4 shows the frequencies of the most important signs and symptoms according to the age at diagnosis.

Among the patients, 22 (31.4%) underwent bone age assessment and 17 were found to have delayed bone age. The laboratory data of patients diagnosed in the hospital (50 patients had been diagnosed by external doctors before admission to the hospital) revealed that 56% had high TSH levels, with 12% showing a large increase (TSH levels exceeding 100 mUI/L), and 64% had low fT_4 levels.

DISCUSSION

CH is a common preventable cause of mental retardation. The overall incidence of CH ranges from 1 in 3000 to 1 in 4000 live births in different parts of the world,² and the incidence is greater in females

Table 4. The percentages of the frequency of the most important signs and symptoms that patients demonstrated by comparison with diagnosis' age.

Signs/Symptoms	Age at diagnosis		
	< 3 m.	3 – 6 m.	> 6 m.
Umbilical hernia	43	21	36
Dry, rough and mottled skin	44	19	38
Cretinoid face	45	14	40
Growth failure	28	24	48
Jaundice	80	0	20
Abdominal swelling	45	15	40
Macroglossia	27	0	73
Lethargy	70	15	15
Pallor	32	16	52
Constipation	56	0	44
Hypotonia	44	12	44
Feeding problems	68	11	21
Delayed neuropsychomotor development	19	0	81
Weight deficit	25	25	50
Vomiting	41	18	41
Fever	29	14	57

m.: month.

than in males (2:1).¹³ CH is usually a sporadic disorder and accounts for 85% of cases, and hereditary inborn errors account for approximately 15% of cases.¹³

There is no published information about the actual incidence of CH in Syria. However, the incidences in Arab countries are as follows: Lebanon, 1 in 1823⁶; Bahrain, 1 in 2967;⁷ United Arab Emirates, 1 in 1778⁷; Palestine, 1 in 2133⁸; and Oman, 1 in 2200.⁹ These statistics indicate that the incidence of CH in Arab countries is greater than the global incidence. A study performed by the Atomic Energy Commission of Syria with the aid of the International Atomic Energy Agency and the collaboration of the ministries of Higher Education, Health, and Defense between 1995 and 2002 confirmed this finding.¹⁴ The aforementioned study screened > 40,000 newborns and noted a CH prevalence of 1 in 2176.¹⁴ However, unfortunately, there is no screening program in Syria. The present retrospective study performed for 5 years at Children's University Hospital, Damascus, identified 70 patients with CH, and the incidence of CH was 1 in 2259. Three of these patients had not

undergone confirmatory testing (two were discharged after their parents took responsibility and one died before confirmation); therefore, 67 patients were included. This number of cases obtained does not reflect the frequency of this disease as specialist doctors can diagnose the condition in outpatient clinics and follow-up tests can be performed at any private laboratory. Additionally, the symptoms of hypothyroidism might not be severe and hospitalization might not be required. These factors might be responsible for the low number of cases recorded in this study. Table 5 summarizes the results of retrospective CH studies performed worldwide.

In this study, most of the patients were male, with a female:male ratio of 1:1.33. This is inconsistent with the information in the medical literature (female:male ratio of 2:1).¹³ Furthermore, our finding is inconsistent with the results of a Syrian study,¹⁵ an Iraq study (female:male ratio of 1.6:1),¹⁶ a Turkish study (female:male ratio of 1.15:1),¹⁷ and a Danish study (female:male ratio of 2:1).¹⁸ This could be explained by a coincidental high rate of male births during the

Table 5. Results of retrospective CH studies conducted worldwide.

Authors of study	Number of cases/ study duration	The medical center where the study took place
Ramadan A. 2011 ¹⁵	29/2 years	Children's Hospital of Damascus
Nasheiti NA. 2005 ¹⁶	40/10 years	Endocrine and Diabetes Clinic for Children in Al Kadhymia Teaching Hospital College of Medicine, Al-Nahrain University Baghdad, Iraq
Tarim ÖF. et al. 1992 ¹⁷	1000/25 years	The Pediatric Endocrinology Unit at Hacettep University Children's Hospital, Turkey
Jacobsen BB. et al. 1981 ¹⁸	72/6 years	All departments of pediatrics in Denmark (a total number of 20)
Alm J. et al. 1978 ¹⁹	112/7 years	All Children's Hospitals and Pediatric Wards in Sweden
Current study	70/5 years	Children's Hospital of Damascus

study period or by the nature of our society that tends to prefer and recognize males and pays more attention to males than to females.

High rates of parental consanguinity are associated with a high prevalence of such disorders. In the present study, 53.7% of confirmed cases involved parental consanguinity. Additionally, 8.5% of patients had a family history of hypothyroidism. A previous Iraq study reported parental consanguinity in 80% of patients and a family history of hypothyroidism in 60.7% of patients.¹⁶ Thus, it is important to educate the relatives of patients about the disease.

Our results indicated a high age at diagnosis (inpatients and outpatients), with a mean age of 8 months, and 74.3% of patients were diagnosed > 1 month after birth because symptoms and clinical diagnostic signs were not clear. This delayed diagnosis of CH in Syria might be associated with the lack of a newborn screening program. We compared our results with the results of previous studies. In a Danish study,¹⁸ 10% of patients were diagnosed within the first month, 40% within the first three months, and 70% within the first year of life. In a Turkish study,¹⁷ the mean age at diagnosis was 49.22 months, with 55.4% of patients diagnosed after 2 years of age and only 3.1% diagnosed during the neonatal period. In an Iraq study,¹⁶ the mean age at diagnosis was 2.3 years, and the authors diagnosed only 10 (25%) patients in the neonatal period. In a Swedish study,¹⁹ the diagnosis was delayed until after the age of 3 months in 52% of patients. In the present study, we diagnosed

> 25% of patients within the first month of life, and this proportion is higher than that in previous local studies¹⁵ of CH (Table 2). Improvements in health awareness and clinical orientation of CH might explain this finding. However, our finding did not correspond to the age reported in other countries with neonatal screening programs.

Our study showed that the most common symptoms during the first 3 months of age were jaundice, lethargy, poor feeding, and constipation and that these might be strong indicators of CH, although they are not specific for CH. On the other hand, the most common symptoms at > 6 months of age were delayed neuropsychomotor development and macroglossia, which are more specific to CH (Table 4).

There were two limitations in our study, the first was the lack of perception of CH among parents, and this was clear in cases in which parents took responsibility and removed their children from the hospital before diagnosis completion. The second was that communication with children's hospitals in other cities was difficult.

CONCLUSION

Our study findings indicated a delay in CH diagnosis within the Children's University Hospital, Damascus, Syria. We were unable to make an early diagnosis in more than half of the patients (74.3%), and there was low specificity with regard to the signs and symptoms of CH. Additionally, only 42% of patients had a correct diagnosis according to clinical examination.

These findings indicate that newborn screening is important in the Syrian society to reduce morbidity and decrease the time needed to reach the correct diagnosis. Thus, healthcare providers, especially pediatricians, should maintain a high level of suspicion for CH in symptomatic children.

List of abbreviations:

CH	Congenital hypothyroidism
TSH	Thyroid-stimulating hormone
T ₄	Thyroxine
fT ₄	Free thyroxine

Competing interests

The authors do not have any competing interests with any personal or financial relationship with an individual or an organization.

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Authors' contributions

Conception and design: all authors.

Collection of the medical records of patients, assembly of data, data analysis and interpretation, manuscript writing: Mariam Saoud.

Supervision, manuscript revising critically for important intellectual content and final approval of manuscript: Sahar Al-Fahoum and Younes Kabalan.

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