Congenital hypothyroidism in Saudi population in two major cities: A retrospective study on prevalence and therapeutic outcomes

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ABSTRACT

Objective: Congenital hypothyroidism (CH) is a common cause of preventable severe neurocognitive impairment in children. Previously conducted studies describing the natural history of CH in Saudi Arabia were either of shorter duration or a limited number of patients. In this study, we aim to assess our experience in the clinical course and therapeutic outcome of CH in two large tertiary centers in Saudi Arabia.

Methods: This is a retrospective chart review of patients <18 years of age diagnosed with CH at King Abdulaziz Medical City in Jeddah and Riyadh, Saudi Arabia, between 2000 and 2018. Data were collected from the patients’ medical records, including epidemiological, clinical, laboratory, and radiological features as well as a long-term outcome of CH. Statistical analysis was carried out using the JMP statistical software. This study was approved by the Institutional Review Board (IRB) at King Abdullah International Medical Research Center (KAIMRC).

Results: Out of the 71 cases, 53.5% were female, and 80.3% of these cases were diagnosed in the 1st week of life. The estimated incidence of CH is 1:2470 in the two study centers. Ectopic thyroid (43%, n = 25/58), dyshormonogenesis (34.5%, n = 20/58), and thyroid agenesis and hypoplasia (22.4%, n = 13/58). Learning difficulty was significantly associated with delayed treatment onset (P = 0.044) and lower compliance with treatment (P = 0.001).

Conclusion: In our study, the incidence of dyshormonogenesis in CH is higher than international rates (34.5% vs. 20%), possibly because of consanguinity. Effective neonatal screening program facilitates early diagnosis that leads to prompt management of CH and avoidance of long-term outcome of neurocognitive impairment.

Keywords: Congenital hypothyroidism, dyshormonogenesis, incidence, newborn screening, Saudi Arabia, thyroid

Introduction

Thyroid hormone is essential for normal growth and neurological development, especially in the early years of life.[1] Congenital hypothyroidism (CH) is one of the most common causes of preventable mental retardation and severe neurocognitive impairment worldwide.[2] In previous reports, the incidence of CH is estimated to be 1:3000–4000 live births; yet, recent data suggested an increased trend.[3] The most common causes of CH include dygenesis, dyshormonogenesis, ectopic thyroid, and iodine deficiency.[4] Symptoms and signs of CH are non-specific and are considered as a result of the absence of effects of thyroid hormone.[5]

In the 1970s, a universal newborn screening program (NBS) has been implemented with enormous success in preventing mental retardation caused by CH.[6] However, with up to a 10% false-negative rate, NBS is certainly inaccurate for the diagnosis of CH if used solely without being combined with clinical judgment and repeat screening results.[7] The Saudi National NBS program for CH was established in November 1989, utilizing cord blood TSH at birth.[8] According to the Saudi screening program, the test is positive if cord TSH is more than 30 mU/L. If TSH is positive, free thyroxin (FT4) level is measured in the same sample, and the infants are recalled to repeat the TSH and FT4 within 24–48 h.[8] If cord TSH is greater than 60 mU/L, this indicates a definite abnormal result and requires immediate intervention.[8] Timely diagnosis and treatment with levothyroxine are effective in achieving an excellent neurocognitive outcome in most patients with CH.[9]
CH had been well characterized in earlier reports. However, epidemiologic, clinical, genetic, radiological, and laboratory characterization of CH is still required for better clinical interventions in the Middle East countries. For instance, most of the previously conducted studies in Saudi Arabia on the epidemiology and outcome of CH were either of short duration or of limited number of patients. It is essential to have a good insight into the epidemiology and natural course of CH in this region with recent advances in therapies, genetic testing, imaging techniques, and other diagnostic procedures.

In this study, we did an assessment of the clinical, laboratory, and radiological features of CH in this region of Saudi Arabia. The study also includes evaluating the different causes, course of the disease, management, and long-term outcome. We aimed to review the current practice and outcome for Saudi children with CH to allow better future planning to match with the globally-approved best therapeutic practices.

Methods

This study was approved by the Institutional Review Board (IRB) at King Abdullah International Medical Research Center (KAIMRC) under IRB number IB/0706/19 (May 19, 2019). A retrospective chart review of CH patients was conducted at King Abdulaziz Medical City in both Jeddah and Riyadh, Saudi Arabia for the period from January 2000 until December 2018. We included all patients <18 years old who were diagnosed with CH in these two tertiary centers. Patients with incomplete data were excluded.

Data were collected from the patients’ medical records. We included all patients diagnosed with CH who had complete clinical, diagnostic, and treatment data. Variables included were patients’ demographics (age, gender), clinical characteristics (clinical presentation, course of the disease, disease duration), investigations (laboratory data, radiological data, and genetic testing), and treatment parameters (medication usage, duration of treatment, adverse events related to the medications). The measurement method of free T4 and TSH assays was by Chemiluminescent Microparticle Immunoassay (CMIA) on the ARCHITECT analyzer (Abbott manufacturer).

Statistical analysis was carried out using the JMP statistical software. Descriptive statistics analysis was conducted to describe and present the study variables. The measures of mean, median, standard deviation, and interquartile range (IQR) were computed for continuous variables. Categorical variables were presented in frequency and percentage distributions. To test for associations or correlations between variables in the study, different statistical tests were conducted, including the Pearson χ² test for independence with Fisher’s exact test or Fisher Freeman-Halton exact test used in cases of small frequencies of contingency table. T-test for independent sample or Mann–Whitney non-parametric test was conducted to test significant differences in FT4 level among the groups of patients’ clinical features. The statistical significance level was set out to be at \( P < 0.05 \).

Results

Demographic and clinical data

The estimated average incidence of CH was 1:2470 in the two tertiary centers of the study, where the average rate of delivery was 9750/year. We included a sample of 71 cases of CH (median current age in these children 9 years, IQR of 7.0 years, and 53.5% were females). Among them, etiology was unknown in 8 patients as they were born in peripheral hospitals and started on L-thyroxin treatment before doing thyroid scans. Five patients had permanent central hypothyroidism. They had no structural brain abnormality and no additional intracranial pathology that could affect the outcome of their development. Most patients in the study were investigated and started on L-thyroxin treatment during the 1st 3 days of life. The results of family history analysis showed a positive family history of a similar condition present in about one-quarter of cases, and about one-third of cases were the outcome of consanguineous parents [Table 1].

Laboratory and imaging data

Descriptive measures of cord TSH and FT4 levels in the study patients showed that TSH levels ranged between 22 and 882 mIU/L with median calculated at 106 mIU/L and SEM was 24.8. The range of values for FT4 was 3–15 pmol/L with a median of 9 pmol/L and SEM was 0.52.

Thyroid scanning results revealed ectopic thyroid in 43.1% of cases, dyshormonogenesis in 34.5% of patients, and thyroid agenesis in 19% of cases [Figure 1].

The majority of infants with CH due to primary hypothyroidism were diagnosed in the 1st week of age, while 80% of central hypothyroidism patients were presented and diagnosed after 1 month of age \( (P = 0.001) \) [Table 2].

| Table 1: Characteristics of patients |
|-------------------------------------|
| **Variable**                        | **n=71** | **%** |
| Gender                              |         |      |
| Male                                | 33       | 46.5 |
| Female                              | 38       | 53.5 |
| Current age (years)                 | Median 9.0 | IQR 7.0 |
| Age at presentation                 |         |      |
| <1 week                             | 57       | 80.3 |
| 1–4 week                            | 5        | 7.0 |
| >1 month                            | 9        | 12.7 |
| Primary hypothyroidism              | 66       | 92.0 |
| Central hypothyroidism              | 5        | 8.0 |
| Positive family history             | 19       | 26.8 |
| Consanguinity of parents            | 24       | 33.8 |
Correlation analysis of study variables

A significant correlation using the Chi-squared test was found between etiological causes of CH (confirmed by thyroid scan) and the categories of TSH levels. Lower levels of cord TSH (less 100 mIU/L) were mainly recognized in patients with ectopic thyroid and to some extent with dyshormonogenesis [Figure 2].

Table 2: Correlation between age at diagnosis and etiological causes

| Cause                  | Age at presentation | P value |
|------------------------|---------------------|---------|
|                        | <1 week | 1–4 weeks | >4 weeks |
| Dyshormonogenesis       | 90.0     | 5.0       | 5.0       | 0.001   |
| Ectopic thyroid         | 96.0     | 4.0       | 0         |
| Thyroid agenesis        | 81.8     | 18.2      | 0         |
| Thyroid hypoplasia      | 50.0     | 50.0      | 0         |
| Central hypothyroidism  | 0        | 20.0      | 80.0      |

Fisher’s exact test (Freeman-Halton test). **Significant at 1%. Values represent percentage in each cause

Figure 1: Etiological causes of primary congenital hypothyroidism in our cohort. *Excluding 8 patients with unknown etiology

Correlation of CH with patient’s gender, family history, age at onset of treatment, treatment compliance, and disease outcome was also assessed [Table 3]. Learning difficulties were significantly associated with age at treatment onset and compliance to treatment, the results reported that 80% of patients who started treatment at 1–4 weeks did not develop learning difficulties, compared to 35% of patients who started the treatment after 1 month of diagnosis. The fast majority, 80.7% of patients with good compliance with treatment, did not develop learning difficulties compared only with 28.6% of patients with poor treatment compliance (P = 0.044). School performance was found to be significantly associated with treatment compliance, 87.7% of patients with good treatment compliance were found to have good school performance (P = 0.008) [Table 3].

Clinical features at presentation correlated well with the initial FT4 level. Patients with positive features had a lower level of FT4 compared with patients who had negative features (P = 0.013). FT4 level < 6 pmol/L significantly correlated with some clinical features, including umbilical hernia and mottled skin (P = 0.048).

Discussion

Our study reports important epidemiological data about CH in a highly consanguineous community with a higher incidence of dyshormonogenesis (34.5%) as an etiology of primary hypothyroidism compared to the international rates (15–20%) [Figure 1].

The worldwide incidence of CH has marked geographical and racial variations ranging from 1:2000–1:4000 live birth.[4] Previous studies from Saudi Arabia reported different incidences from different regions of the country. Incidence rates were 1:1400 live births in Najran,[13] 1:2666 live births in Riyadh,[15] and 1:3500 live births in Dhahran.[16] These data suggested a high incidence of CH in Saudi Arabia. A study from Madinah[12] showed a lower incidence of 1:4208 live births, equivalent to international rates. The lower incidence rate was explained by the heterogeneous population in this city, including Afro-Asian races. In our study, the incidence was 1:2470 live births, which is consistent with the previously reported higher incidence of CH in the country. This high incidence may be related to the implementation of newborn screening programs that led to the detection of milder cases and also due to the lowering of the used TSH cutoff levels.

In previous reports, the majority of CH cases are sporadic due to thyroid dysgenesis (missing, ectopic, or severely underdeveloped).[17] Only 15–20% of cases are due to thyroid dysshormonogenesis, which is a result of inherited defects in one of the steps of thyroid hormone synthesis.[17] In our study, the most common causes of CH were ectopic thyroid (43.1%) and dyshormonogenesis (34.5%). The higher rates may be related to the genetic background of Saudi Arabia and the higher rate of consanguinity, which favors autosomal recessive inheritance of
diseases since most of dyshormonogenesis defects are inherited in an autosomal recessive manner. Consanguineous marriages are common in the Saudi population, with an estimated rate of 51–56%, of which 30% are 1st-degree cousins. In addition, a positive family history of a similar condition was present in 26.8% of our cases, which also indicates a possible genetic influence.

Markedly elevated TSH level is the most sensitive test for the diagnosis of CH in cord serum. Over the last years, several newborn screening programs lowered their TSH cutoff level from 20 to 50 mIU/L to 17–19 mIU/L. In our study, most of CH patients with thyroid agenesis and hypoplasia had high initial TSH more than 100 mIU/L, while most CH children due to dyshormonogenesis and ectopic thyroid presented with initial TSH < 100 mIU/L.

The newborn screening program is based on TSH in Saudi Arabia. Therefore, central hypothyroidism needs a high index of suspicion and there is always a risk of delayed diagnosis. The development and widespread utilization of newborn screening programs enabled early detection and treatment of infants with CH. This advent has been successful in achieving a better neurocognitive outcome. However, in our study and others, not all infants achieve a completely normal neurocognitive outcome due to a variety of reasons, including the age of beginning treatment, levothyroxine-staring dose, severity of hypothyroidism, effect of lower serum T4 levels in the 1st 2 years of life, and non-compliance to treatment. In our study, 18.3% of the patients had poor school performance and 32.3% had learning difficulties as reported by school. Most of the patients with poor school performance and learning difficulties started treatment after the first month of life and/or had poor compliance to treatment. This indicates the importance of early diagnosis, initiation of L-thyroxin, and compliance with treatment to achieve good neurocognitive outcomes. Since no underlying neurological condition was identified in any of the patients with central hypothyroidism in our study, we attributed their learning difficulty to CH.

Clinical manifestations are usually few or absent in about 95% of infants with CH, and most cases are picked by the neonatal screening programs. In our study, clinical signs of CH were subtle or absent in most infants who were asymptomatic initially. These patients were picked up by the cord TSH screening before clinical features appear. Therefore, relying only on the appearance of clinical features of hypothyroidism will delay the diagnosis and treatment and consequently worsen the outcome. These findings suggest that effective neonatal screening programs enable early diagnosis and treatment of asymptomatic infants with CH without delay in starting L-thyroxin.

The retrospective nature of this study is a known limitation, with incomplete data for several subjects being excluded. However, our study involved a larger sample size from different centers collected over a longer period of time. Such studies are important in providing information about outcome data as well as discussing current limitations and ways of further improvement in the healthcare service provided.

**Conclusion**

Our study reports important epidemiological data about CH in two large tertiary centers in Saudi Arabia. Dyshormonogenesis is common as an etiology of primary congenital hypothyroidism in our highly consanguineous community, with a higher incidence (34.5%) compared to international rates (15–20%). CH has a subtle presence in most of the cases. Effective neonatal screening programs facilitate early diagnosis and management of asymptomatic infants without delay in starting L-thyroxin treatment. Future studies should be conducted on a larger, nationwide scale involving more tertiary centers in major cities of Saudi Arabia to further improve the therapeutic outcome of congenital hypothyroidism.

**Ethics Approval and Consent to Participate**

**Availability of data and material**

The data used in this study are available and will be provided by the corresponding author on a reasonable request.
Competing interests

The authors declare that they have no conflicts of interest.

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