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Clinical Presentations of Congenital Hypothyroidism and Associated Abnormalities in Children Treated at Western Saudi Arabia

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Research Article

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ABSTRACT

Objectives: To determine the various clinical presentations of and abnormalities associated with congenital hypothyroidism among children diagnosed at King Abdulaziz University Hospital (KAUH), Jeddah, Western Region, Saudi Arabia.

Methods: A retrospective, descriptive study of congenital hypothyroidism and associated abnormalities was conducted in Jeddah, Saudi Arabia from January 2010 to January 2015 and included 173 children aged 0 to 12 months. Data were obtained by reviewing KAUH medical records and laboratory results via the hospital's electronic "Phoenix" system. Results were analyzed using descriptive statistics.

Results: Of the 173 diagnosed cases, primary hypothyroidism was most common (95% of cases), while secondary hypothyroidism was diagnosed in 5% of cases. Of all cases diagnosed via the neonatal screening program, 57% were asymptomatic at the time of diagnosis and 43% were symptomatic. Prolonged jaundice (79%) was the most common clinical presentation. Other signs were constipation (7%), hypotonia (6%), goiter (4%), macroglossia (3%), and facial puffiness (1%). Associated congenital anomalies were found in 13% of cases.

Conclusion: The findings confirm the importance of the neonatal thyroid screening program, as 57% of diagnosed children were not symptomatic at diagnosis. Pediatricians should be aware of the various clinical presentations of congenital hypothyroidism, particularly prolonged neonatal jaundice.

INTRODUCTION

Congenital hypothyroidism (CH) is a common endocrine disease, with a worldwide prevalence of 1:3500–1:5000, and prevalence in Saudi Arabia of 1:2500 [1]. It is one of the most common preventable causes of mental and growth retardation in children [2].

It is classified as either primary or secondary/tertiary (central) hypothyroidism. Primary causes include defects of thyroid gland development (such as thyroid ectopia, hypoplasia, and aplasia) and dyshormongenesis [3]. Central hypothyroidism is a rare cause of hypothyroidism [4] and refers to defects in the production of thyroid stimulating hormone (TSH) due either to hypothalamic or pituitary dysfunction. Rare genetic causes result from mutations in the genes for thyrotropin-releasing hormone (TRH), the TRH receptor [5] or TSH [6,7]. Congenital central hypothyroidism can also be caused by inadequate treatment of maternal Graves' hyperthyroidism during pregnancy [8,9].

Neonatal screening is the most effective method of diagnosis because of the absence of clinical features at birth in most cases[2] due to the ameliorating effect of transplacental maternal thyroid hormone to the fetus [3]. Clinical features include decreased feeding, increased sleeping time, hoarse cry, constipation and cold or mottled skin [3]. Birth weight is greater than the ninetieth percentile in up to one third of patients [3]. The most common signs are umbilical hernia and macroglossia. Other features include jaundice, a puffy face and a wide posterior fontanel with open sutures. Further examination may reveal bradycardia, a protuberant abdomen (with a large umbilical hernia), hypotonia and delayed reflexes on neurological examination [3].

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Early diagnosis via neonatal screening for CH and treatment result in normal development in the vast majority of cases. However, all studies on outcomes report that up to 10% of patients have residual problems with mental development and neurological signs, despite early diagnosis [10].

A study published in 2013 reported that the risk of developing an associated chronic disease in patients with CH was twice that of the reference population, and neurological or mental diseases and congenital malformations were the most frequent sequelae [11].

In the last decade, a high frequency of congenital malformations has been described in infants with congenital hypothyroidism [12]. Extrathyroidal manifestations of CH have been reported at rates between 10.5% and 59% [13]. Olivieri et al. [14] reported that the prevalence of additional congenital anomalies was more than four-fold higher than that reported in the Italian population.

We aimed to determine the various clinical presentations of and abnormalities associated with CH among children diagnosed at King Abdulaziz University Hospital (KAUH), Jeddah, Western Region, Saudi Arabia.

METHOD

This retrospective, descriptive study was conducted by reviewing the medical records of all children with congenital thyroid diseases who were being followed up at the pediatric endocrinology clinic at KAUH between January 2010 and January 2015. A total of 173 children between the ages of birth to 12 months were included in the study. All laboratory data were obtained using the KAUH electronic Phoenix system. The data collected comprised age at diagnosis, gender, thyroid profile (TSH and free thyroxine [fT4]), clinical presentation, weight, height, family medical history, drug history and past medical history. The patients included in the study were those diagnosed with CH defined according to the KAUH laboratory protocol (thyroid hormone deficiency present at birth: TSH level>5 mIU/L; fT4<12 pmol/L).

The Saudi neonatal thyroid screening program measures cord blood TSH and has a cut-off value of 30 mIU/L [15]. All positive screening test results are confirmed by further thyroid function tests.

This study was approved by the Research and Ethics committee at KAUH, Jeddah.

We performed descriptive statistical analysis using Microsoft Excel® 2013 (Redmond, Washington, USA). Data were entered, coded and then analyzed. Frequency and percentages were calculated for qualitative variables including most common age at diagnosis, methods of diagnosis, most common presentations, whether CH was primary hypothyroidism or central hypothyroidism, and presence or absence of developmental delay and associated congenital anomalies. Clinical presentations were presented on a bar graph.

Inclusion criteria

Newborn and infants aged 0-12 months old. Males and females were selected randomly among children diagnosed at King Abdulaziz University Hospital.

Exclusion criteria

The exclusion criteria were age more than 1 years and TSH level<5 mIU/L; fT4>12 pmol/L.

RESULTS

The study included 173 children diagnosed with congenital hypothyroidism. Primary congenital hypothyroidism was the most common (n=165, 94%), while secondary/tertiary hypothyroidism was diagnosed in 8 cases (6%). The age ranges for diagnosis were 0-3 months (n=144, [83%]), 4-8 months (n=8 [5%]), 7-9 months (n=5 [3%]) and 10-12 months (n=16 [9%]). Most patients diagnosed by neonatal thyroid screening testing were asymptomatic at the time of diagnosis and CH was detected solely by screening tests (n=98 [57%]); 75 patients (43%) were symptomatic. The most frequently observed clinical presentation in symptomatic patients was prolonged jaundice. A summary of clinical presentations is presented in **Figure 1.**

Of the 173 patients, 11 (6%) presented with development delay because of either prematurity (27%), fetal distress with prolonged labor (27%), Down syndrome (73%) or cerebral palsy (18%). Congenital heart disease (such as atrial septal defects, ventricular septal defects and patent ductus arteriosis) was present in 13% of patients. This compares with a prevalence of congenital heart defects of 45% in all patients with Down syndrome.

After a positive neonatal screening test result for CH (due to high TSH and low fT4 levels), most diagnoses of CH are confirmed by further testing. In our study sample, three patients underwent thyroid ultrasound scanning because of the presence of goiter; however, no patients underwent radioactive iodine thyroid isotope scanning, as it is not routinely practiced at KAUH.

DISCUSSION

A Saudi national neonatal thyroid screening program was established in November 1989. Screening is compulsory for all hospitals in Saudi Arabia and measures cord serum TSH using a DELFIA® time-resolved fluorescence assay (PerkinElmer,

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Waltham, Massachusetts, USA). A positive cord test result is then confirmed by both TSH and fT4 assays and, if necessary, is supplemented with an fT4 assay, also carried out using a DELFIA® assay [16]. The most frequently used investigation for diagnosing CH was a laboratory assay. Previous studies have reported that TSH screening is a more specific investigation for diagnosing CT [13], whereas fT4 screening is a more sensitive method, particularly for those neonates with rare hypothalamic-pituitary-hypothyroidism; however, fT4 is a less specific method and results in a high frequency of false positive results, mainly in low birth weight and premature infants [17].

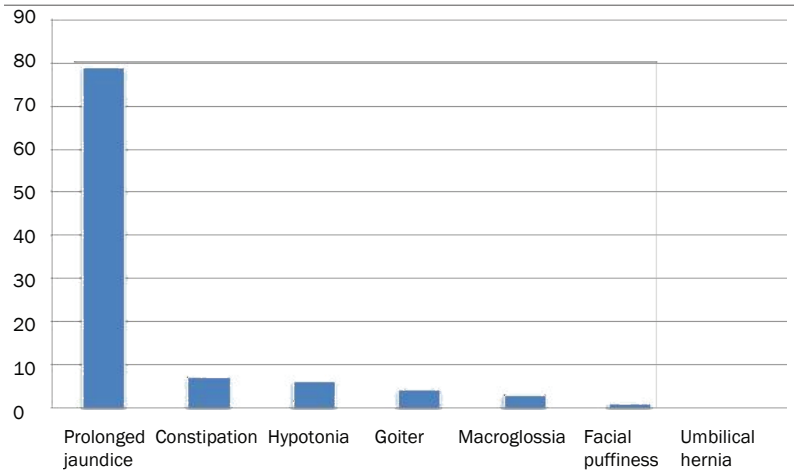

Figure 1. Clinical presentation of patients with congenital hypothyroidism.

In the current study, the first three months of life was the most common age of diagnosis. In a study conducted in Denmark of 436 959 live infants born between 1970 and 1975, 72 patients (49 girls and 23 boys) developed primary hypothyroidism; of these, 40% were diagnosed within the first 3 months and 70% within the first year of life [18]. In the current study, the diagnosis rate, at 83%, was much higher.

In our study, primary hypothyroidism was the most common type of CH. This finding is similar to that of a study of newborn screening for congenital hypothyroidism conducted in Turkey; this study found that primary CH was the most common type, while true central hypothyroidism, which is characterized by low Ft4 and normal TSH levels, was quite rare [17].

Signs, such as constipation, macroglossia, obesity and developmental delay, were variably present among the patients with CH; however, the most frequently observed sign was prolonged jaundice. Several studies have also reported severe persistent jaundice as the most common sign, together with other signs such as macroglossia, umbilical hernia, and constipation [19]. One study reported an association between neonatal TSH concentrations and developmental delay, with TSH concentrations lowers than the present newborn screening thresholds being associated with poor developmental outcomes [20].

CONCLUSION

Furthermore, congenital anomalies associated with CH, most frequently Down syndrome, have been reported in some studies. In one study, which reported congenital anomalies, the most common congenital cardiac anomaly was associated with Down syndrome [21].

Kreisner et al. [12] reported that 13.2% of infants with CH had major congenital malformations. In another study of 1420 infants with congenital hypothyroidism, the prevalence of extrathyroidal congenital malformations was 8.4%, and the majority of malformations were cardiac [3].

A limitation of the study was incomplete data due either to incomplete medical records or patients having been transferred to other hospitals to continue their management before complete data on CH ware recorded.

Congenital hypothyroidism is one of the preventable childhood causes of mental retardation and developmental delay, and can easily be diagnosed by neonatal screening and thyroid function tests. Pediatricians should be aware of the various clinical presentations.

Assays of TSH alone should not be relied upon, since false negative results may be reported in cases of central CH; a delay in diagnosis of this condition could lead to mental sub normality. As the Saudi neonatal thyroid neonatal screening program tests for TSH using cord blood, most cases of central congenital hypothyroidism were diagnosed late, with consequent delayed developmental milestones. We found that primary CH was the most common type of hypothyroidism; however, the prevalence of central hypothyroidism should not be underestimated.

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