Original Article

Archives of Clinical & Experimental Surgery

Prevalence of Congenital Heart Diseases in Children with Congenital Hypothyroidism

Mohamed Abdel Megied Abo El-Magd[1], Mohamed Adel El-Maraghy[1], Mohamed E.A. Abdelrahim[2], Khaled Refaat Abd El Meguid[1], Mohamed Hussein Meabed[1]

Abstract

The aim of the work was to assess the prevalence of cardiac anomalies in primary congenital hypothyroidism (PCH) patients. Fifty patients with PCH recruited after diagnosis by ultrasonography or scintigraphy (64% Dysgenesis, 36% Dyshormonogenesis). The prevalence of cardiac anomalies was 18%, with renal anomalies being 8%. There was no significant difference in the longitudinal follow-up of growth and sexual maturation between a hypothyroid with and without anomalies. Statistically significant difference was found with replacement therapy of both groups. Hence, echocardiography should be done to screen this birth defect as soon as possible so as to prevent or delay the possible complications.

Key words: *Congenital hypothyroidism (CH), cardiac anomalies*

[1]Department of Pediatrics
Faculty of Medicine
Beni-Suef University
Beni-Suef, Egypt

[2]Department of Clinical Pharmacy
Faculty of Pharmacy
Beni-Suef University
Beni-Suef, Egypt

Received: September 18, 2012
Accepted: November 18, 2012
Arch Clin Exp Surg 2013;2: 85-91
DOI:10.5455/aces.20121118032848

Corresponding author:
Mohamed E.A. Abdelrahim
Department of Clinical Pharmacy
Faculty of Pharmacy
University of Beni Suef
Beni Suef, Egypt
mohamedemam9@yahoo.com

Introduction

Congenital hypothyroidism (CH) is defined as thyroid hormone deficiency present at birth. Thyroid hormone deficiency at birth is most commonly caused by a problem with thyroid gland development (dysgenesis) or a disorder of thyroid hormone biosynthesis (dyshormonogenesis). These disorders result in primary hypothyroidism. Secondary or central hypothyroidism at birth results from a deficiency of a thyroid stimulating hormone (TSH). Congenital TSH deficiency may rarely be an isolated problem (caused by mutations in the TSH β subunit gene), but it is most commonly associated with other pituitary hormone deficiencies, as part of congenital hypopituitarism. Peripheral hypothyroidism is a separate category resulting from defects of thyroid hormone transport, metabolism, or action [1].

Newborn screening for congenital hypothyroidism (CH) is one of the major achievements of preventive medicine, as the condition occurs frequently. An early diagnosis and treatment prevent brain damage and the ensuing mental retardation [2].

Neonatal screening for CH is an essential, productive and preventive public health program.

The Egyptian Ministry of Health and Population started to implement the screening program for CH in year 2000, and by the end of year 2003, all 27 governorates were covered [3].

In a small series of infants identified with CH, there is an increased incidence of extrathyroid abnormalities [4].

Approximately 10% of infants with CH have associated congenital anomalies. Cardiac anomalies are most common, but anomalies of the nervous system and eye have been reported [5].

In our clinic, follow-up of thyroid patients does not include screening for cardiac anomalies, and detection of any other anomaly is by accidental discovery, not by a routine screen for the association, so the aim of this study was instituted.

Methods

This study included 50 patients (males and females) with primary congenital hypothyroidism, recruited from Beni-Suef University Hospital and the Health Insurance Hospital, and the study was a cross-sectional study. This study was conducted in six months.

Inclusion criteria

1. Patients with congenital primary hypothyroidism (depending on the documented etiology of congenital hypothyroidism from the files of the patients).
2. Age between neonatal period and 19 years old.

Exclusion criteria

Patients with:

1. Acquired hypothyroidism
2. Autoimmune thyroiditis
3. Secondary hypothyroidism

All patients were subjected to the following:

I- Full history taking including:

- Date of birth, age, sex, residence, and age of presentation.
- Presenting symptom.
- Perinatal history was taken with emphasis on prenatal insult, history of complications during delivery, premature labor, prolonged neonatal jaundice or admission to NICU.
- Developmental history, either normal or delayed.
- Family history for consanguinity and similar condition in the family.
- We monitored the documented data in the files of the patients, including etiology of congenital hypothyroidism, thyroid profile (TSH & FT4) at the time of diagnosis (before treatment) and in the last follow-up, and the dose of replacement therapy.

II- General clinical examination:

- The examination included a general examination as well as an examination of all systems, laying stress on detecting congenital anomalies or presence of any dysmorphic features.

III- Anthropometry

- Weight & weight by standard deviation score (SDS), height and height SDS, body mass index (BMI), and pubertal assessment.

Weight:

- From birth to 2 years, patients were weighed wearing light clothing on a digital scale.

Older patients were weighed while standing on a scale, with weight equally placed on both feet. Weight was measured and recorded to the nearest 0.1 kg and then plotted on the curves, and standard deviation scores were obtained using the GROWTH VERSION II program supplied by NOVONORDESC, constructed on the Egyptian Growth Curves for children (2002).

Height

<u>Supine length:</u>

- From birth to 2 years, patients were measured as supine by two persons with appropriate equipment featuring a headboard and moveable footboard (infantometer). Whilst one person held the head against the headboard, with the head facing upward in the Frankfurt plane (an imaginary line between the outer eye canthus and the external auditory meatus), a second person measured the length by bringing the footboard up to the heels.

<u>Standing height:</u>

- From 2–3 years onward, a wall-mounted stadiometer was used for height measurement. Patients were standing as erect as possible with his/her head, thoracic spine, buttocks, and heels all placed together touching the vertical plane of the stadiometer.

The head was centered and positioned with the Frankfurt plane (an imaginary line between the outer eye canthus and the external auditory meatus) parallel to the floor.

- Length/Height was recorded in centimeters, to

the nearest 0.1 cm, and then plotted on the curves, and standard deviation scores were obtained using the GROWTH VERSION II program supplied by NOVONORDESC, constructed on the Egyptian Growth Curves for children (2002).

Body mass index (BMI):

- BMI was calculated by dividing the weight in kg by the square height in m^2
- By then using Egyptian Growth Percentile Charts, patients whose BMI was equal or above the 95th centile were considered obese. Patients with BMI equal or above the 85th centile, but less than the 95th centile, were considered overweight. But patients whose BMI was below the 3rd centile were considered significantly underweight.

Pubertal assessment:

- Puberty was assessed by Tanner staging. The onset was defined by the beginning of breast development (B2) in girls, and the enlargement of testicular volume to 4 ml (G_2) in boys.

IV- Investigations

- New FT4 and TSH level at the time of study (when needed).
- Echocardiography.

Statistical Methods:

- The Statistical Package for Social Sciences (SPSS) program (version 15.0) was used for analysis of data. Data was summarized as mean, SD and percentage.
- A non-parametric test (Mann-Whitney U) was used for analysis of two independent quantitative data, as data were not symmetrically distributed.
- A chi-square test was used for analysis of qualitative data.
- The p-value is considered significant if < 0.05*.

Results

50 children with primary congenital hypothyroidism were included in the study.

The mean age of patients at the time of examination was 10.9 ± 6.4 years, with the range being 2 months to 19 years. The age of patients at the time of presentation ranges from 1 week to 11 years, with a mean of 3 ± 2.7 years. Seventy percent (35 patients) of the studied cases were females, while thirty percent (15 patients) were males, with a female-to-male ratio of 2.3:1.

About 18% of the studied cases had a positive family history of congenital hypothyroidism (CH). About 38% of cases were diagnosed early by a neonatal screening program. Most of the cases (56%) were diagnosed after a developmental delay. Only 2 cases were diagnosed by prolonged physiological jaundice. 1 case was referred to our hospital by a goiter.

By chest and heart examination, 6% of cases had a systolic murmur by clinical examination.

About 24% of cases were short (below -2 SDS), but 76% of cases were within normal height (above -2 SDS). Delay of the onset of treatment led to retardation of height. Patients diagnosed between 2 years and 6 years and after 6 years were the shortest (mean height SDS = -1.97 and (mean height SDS = -1.9 respectively). Patients diagnosed between 1 month and 2 years of life were less short (mean height SDS = -1.4), while those diagnosed by screening at birth had the best attented height (mean height SDS = -0.84).

About 63.9% of cases were at a pre-pubertal age, 16.8% of cases were delayed in puberty, and 19.3% of cases reached puberty at a normal age.

Patients with delayed puberty comprised 6 patients with an age range of 15 years to 19 years, with a mean of 17 ± 1.9 years. They presented with a mean of 6.5 ± 4.4 years, with their age range being from 2 years to 11 years. 4 patients (66.7%) were females, while 2 patients (33.3%) were males.

About 2% of the studied cases were obese, 4% of cases were overweight, and 94% of cases had a normal body mass index (BMI).

Congenital hypothyroidism was due to dyshormonogenesis in 36% of patients, and dysgenesis in 64% (thyroid agenesis 48%, ectopic thyroid 14%, and hypoplasia 2%), as shown in Table 1.

The thyroid profile at the time of diagnosis was compared among different causes of congenital hypo-

Table 1. Etiology of congenital hypothyroidism.

Etiology	Number	Percent (%)
Dyshormonogenesis	18	36
Dysgenesis		
Agenesis	24	48
Ectopic	7	14
Hypoplasia	1	2

thyroidism. Agenesis had the lowest FT4 and the highest TSH, with a highly significant difference compared to other etiologies, as shown in Table 2.

By echocardiographic examination, 18% of cases had cardiac anomalies in the form of an atrial septal defect (ASD) in 4 cases, ventricular septal defect (VSD) in one case, aortic regurgitation (AR) in 2 cases, pulmonary stenosis (PS) in one case, and tricuspid regurgitation (TR) in one case.

On doing a renal ultrasound for medical cases, 4 cases (8%) were discovered to have renal anomalies, as shown in Table 3.

Patients with no cardiac anomalies were the shortest (mean height SDS = -1.5), while those with cardiac anomalies had the best attainment of height (mean height SDS = -0.8).

There was no statistically significant difference between patients with normal echocardiography and patients with cardiac anomalies, regarding BMI.

There was no statistically significant difference between patients with normal echocardiography and patients with cardiac anomalies, regarding puberty.

There was no statistically significant difference between patients with normal echocardiography and patients with cardiac anomalies, regarding thyroid profile.

There was statistically significant difference between patients with no cardiac anomalies and patients with cardiac anomalies, regarding the dose of L-troxine (LT4). Patients with cardiac anomalies need a larger dose of L-troxine, as shown in Table 4.

Table 2. Comparison of FT4 and TSH serum levels at the time of diagnosis in between different causes of hypothyroidism.

Causes of CH	N	T4 (ng/dl)	TSH (μIU/ml)
Dyshormonogenesis	18	0.40±0.06	76.05±19.51
Agenesis	24	0.32±0.02	148.18±31.71
Ectopic	7	0.39±0.04	108.38±35.75
Hypoplasia	1	0.44±0.01	130.66±10.01
p-value	50	0.001**	0.001**

Table 3. Renal ultrasound finding.

Renal ultrasound finding	Number	Percent (%)
Normal US	46	92
Abnormal renal sonar		
Malrotated kidney	1	2
Bilateral pelvic dilatation	1	2
LF hydronephrosis	1	2
Small kidney for age	1	2

Table 4. Comparison between dose of LT4 in patients with no cardiac anomalies and patients with cardiac anomalies.

Items	No cardiac anomalies Mean ± SD	Cardiac anomalies Mean ± SD	P-value
Dose of L-troxine	3.4 ± 1.6	6.7 ± 4.4	0.001*

Discussion

CH is the most common congenital endocrine disorder, affecting 1:3000–4000 newborns [6].

Several studies tried to estimate the prevalence of CH in Egypt. Abd El-Sallam (1995) [7] screened 3000 Egyptian newborns for CH and it was reported to be 1:1000.

Similarly, Hassan et al. (1998) [8] screened 6128 newborns in Egypt, with an overall incidence of 1:613.

The Egyptian Ministry of Health screened 4,778,549 neonates out of 6,434,844, declaring an incidence of 1/2020 in the year 2005 [9].

CH is associated with an increased prevalence of congenital malformations [10].

However, the prevalence of these has been variable in the different ethnic groups [11].

Recently, the significantly higher frequency of ETA reported in CH than in the general population represents further arguments supporting the role of a genetic component in the etiology of CH [12]. Several cases of TD have been shown to be associated with mutations in genes (TTF1, TTF2, PAX8, and TSHR). However, thyroid organogenesis is a complex process and other genes are expressed during thyroid gland formation. In the last decade, a high frequency of congenital anomalies, mostly cardiac, has been reported in infants with CH detected by neonatal screening, representing precocious structure in the developing embryo and orienting molecular biologists to focus their investigations on genes involved in both heart and thyroid development [13].

Anomalies in our study comprised 9 cases (18%): 2 cases had ASD (with agenesis of the thyroid), 2 with AR (with ectopic thyroid gland and hypoplasia), one with ASD & VSD (agenesis), one with PS (dys-

hormonogenesis), and one with TR (agenesis).

Other anomalies (renal anomalies 8%) were detected accidently by abdominal ultrasound examination due to abdominal pain which revealed renal anomalies in the form of a malrotated kidney, a small-sized kidney for the age, and hydronephrosis. It is important to think of the association, not of the coincidence.

Gu et al. [14](2009) studied the prevalence of ETA in 1520 Japanese CHs with and without Down syndrome: ETA was found in 222 (222/1520) (14.6%) hypothyroid patients without Down syndrome and in 86 (86/1520) (5.7%) patients with Down by a retrospective review of a questionnaire based on medical records. In CH patients without Down syndrome, cardiac anomalies were the most prevalent (135 patients) (8.9%) and they recorded urogenital anomalies in 24 patients (1.58%) in the form of hypospadias, bifid scrotum, bladder exstrophy, and polycystic kidney disease.

El Kholy et al. (2005) [15] studied 48 CH Egyptian children at Ain Shams University for congenital anomalies. Its prevalence was 12.7%. Cardiac anomalies were the most prevalent (10.6%), and other congenital anomalies included absent kidney, pelvic kidney and imperforate hymen.

Shaltout et al. (2006) [16] studied 30 Egyptian CH patients at the Diabetic, Endocrine, Metabolic and Pediatric Unit (DEMPU) clinic at Cairo University, revealing 6 patients (20%) with congenital heart disease and one patient (3.3%) with a malrotated kidney.

Amaresh et al. (2010) [17] studied 17 Indian patients (6 months to 17 years) with CH detected by scintigraphy and ultrasonography (13 had dysgenesis: 11 with agenesis, one with hemiagenesis and one with ectopia, and 4 had dyshormonogenesis). 94% of children had dysmorphic features, 29% with congenital heart disease, 41% with spina bifida occulta, and no renal anomalies detected was attributed to the small number of patients and no correlation to the type of anomaly.

Kreisner et al. (2005) [10] screened 76 Brazilian CH cases (9 with dyshormonogenesis and 67 with dysgenesis (1 with hemiagenesis, 24 with ectopia & 42 with agenesis)) for ETA by clinical examination only. Its prevalence is 13.2%, mostly cardiac, and he only found the malformation in the dysgenetic group. They did not screen for renal anomalies.

Regarding the growth and sexual maturation, no statistically significant difference existed between CH with cardiac anomalies and no data regarding the longitudinal growth and sexual maturation in CH with ETA, especially the cardiac ones, as few studies have looked at the prevalence of cardiac anomalies because it was considered a coincidence rather than association before the era of molecular biology which started to unfold the fascinating story of CH.

We assume that those hypothyroid cases with cardiac anomalies and their longitudinal follow-up will not differ from those without, except that they need follow-up of their cardiac condition and special care to prevent any possible complication to their already existing disease.

A statistically significant difference occurred in the replacement therapy among hypothyroid patients with cardiac anomalies, and L-troxine has a narrow therapeutic index, so careful dosage titration is necessary to avoid the consequence of over- or under-treatment [18].

Demographic data in our study showed a female:male ratio of 2.3:1. The age of presentation was 38% under 1 month of age by neonatal screening and 4% by prolonged neonatal jaundice — others present late and delayed beyond 2 years of age.

Delay in the diagnosis and, therefore, treatment is still a problem in our community, which should not be existent in the era of molecular diagnosis. The age group diagnosed between 3 and 12 years of age may explain the shortness observed in some of our patients.

Hypothyroidism and its late diagnosis is still a problem in our community, like with our set-up (36%) being diagnosed over 2 years. In part it may explain that some of our included patients were before the era of screening.

But on the other hand, neonatal screening offered early diagnosis in 40% of cases. The start of therapy should start within 2 weeks of age so it can normalize cognitive development as the hypothyroid fetus appears to be protected, at least in part, by the placental transfer of maternal thyroid hormones; this is true as

long as postnatal therapy is adequate and maternal thyroid function is normal.

In contrast to the excellent outcome in infants with CH that is treated early, the prognosis for normal mental and neurologic performance is less certain for infants with CH that is not detected early by newborn screening [19-21].

It is generally accepted that the degree of hypothyroidism at diagnosis, the timing of the onset of treatment, and the doses of replacement L-troxine are the major determinants of an intellectual outcome, and whether these factors affect growth and sexual maturation is controversial [20].

Growth rate, adult height and sexual maturation are normal in children with CH in whom replacement therapy is consistently maintained. Although physical recovery is good and stature is normal, when replacement therapy has begun later, but within the first 2 months of life, early diagnosis and adequate treatment from the first weeks of life result in normal linear growth and intelligence comparable with that of unaffected siblings [21].

Delay in diagnosis, inadequate treatment, and poor compliance in the first 2–3 years of life result in variable degrees of brain damage, delayed puberty, and growth retardation [1]. This explains the small percentage in our study with the short stature and delayed puberty because of their late presentation. However, molecular diagnosis of CH will not differ in management of the hypothyroid patients who will still depend on periodic adjustments of L-troxine daily doses, which should be guided by clinical observation of TSH and FT4 levels. The rapid pace of development in our understanding of the genes regulating thyroid embryogenesis and growth as well as of basic genetic mechanisms in general suggests strongly that the further important insights in the etiology of thyroid dysgenesis are likely to be reported in the years ahead.

Our study did not perform molecular analysis to determine the true etiology of the anomalies, despite it showing that children with CH are at increased risk of having cardiac anomalies, since most of these common types, e.g., ASD and AR, are not identifiable by physical examination; therefore, early detection of these birth defects should be done by the non-invasive, non-expensive echocardiography so as to prevent or delay the morbidity and mortality associated with any complication of these cardiac anomalies.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. LaFranchi S. Thyroid Development and Physiology. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF (eds.) Nelson textbook of pediatric, 18th Edition, Elsevier, United states, 2007;2317-2319.
2. Rastogi MV, LaFranchi SH. Congenital hypothyroidism. Orphanet J Rare Dis 2010;5:17.
3. Kumar J, Gordillo R, Kaskel FJ, Druschel CM, Woroniecki RP. Increased prevalence of renal and urinary tract anomalies in children with congenital hypothyroidism. J Pediatr 2009;154:263-266.
4. Hamza RT, Youssef AM, Mouharam WA, El Danasoury AS. Maternal and Neonatal Iodine Nutrition In Cairo. The Internet Journal of Pediatrics and Neonatology 2008;Volume 8 Number 2. DOI: 10.5580/1d4a.
5. Bamforth JS, Hughes I, Lazarus J, John R. Congenital anomalies associated with hypothyroidism. Arch Dis Child 1986;61:608-609.
6. Toublanc JE. Comparison of epidemiological data on congenital hypothyroidism in Europe with those of other parts in the world. Horm Res 1992;38:230-235.
7. Abd El-Salam E. Neonatal screening of inherited and congenital disorders. The Gazette of the Egyptian Pediatric Association 1995;4:95-108.
8. Hassan AA, Fedora L, Samsa SG. Study of phenylketonuria and congenital hypothyroidism in 6128 screened newborns. The Medical Journal of Cairo University 1998:66:255-266.
9. Abdel-Raouf RK. Capacity building for the transfer of genetic knowledge into practice and prevention. Faculty of medicine, Ain-Shams University, Egypt, 2008.
10. Kreisner E, Neto EC, Gross JL. High prevalence of extrathyroid malformations in a cohort of Brazilian patients with permanent primary congenital hypothyroidism. Thyroid 2005;15:165-169.
11. El Kholy M, Fahmi ME, Nassar AE, Selim S, Elsedfy HH. Prevalence of minor musculoskeletal anoma-

lies in children with congenital hypothyroidism. Horm Res 2007;68:272-275.
12. Olivieri A, Stazi MA, Mastroiacovo P, Fazzini C, Medda E, Spagnolo A, et al. Study Group for Congenital Hypothyroidism. A population-based study on the frequency of additional congenital malformations in infants with congenital hypothyroidism: data from the Italian Registry for Congenital Hypothyroidism (1991-1998). J Clin Endocrinol Metab 2002;87:557-562.
13. Olivieri A. Study Group for Congenital Hypothyroidism. The Italian National Register of infants with congenital hypothyroidism: twenty years of surveillance and study of congenital hypothyroidism. Ital J Pediatr 2009;35:2.
14. Gu YH, Harada S, Kato T, Inomata H, Aoki K, Hirahara F. Increased incidence of extrathyroidal congenital malformations in Japanese patients with congenital hypothyroidism and their relationship with Down syndrome and other factors. Thyroid 2009;19:869-879.
15. El-Kholy MS, El-Sedfy HH, Fahmi ME, Nassar ASM. Congenital anomalies associated with congenital hypothyroidism. Thesis submitted in partial fulfillment of M.Sc in pediatrics, Faculty of Medicine, Ain Shams University, 57-70, 2005.
16. Shaltot MF, Taha SA, Ammar RA, Abd El-Meged OM. Congenital anomalies associated with congenital hypothyroidism. Thesis submitted in partial fulfillment of M.Sc in pediatrics, Faculty of Medicine, Cairo University, 68-77, 2006.
17. Reddy PA, Rajagopal G, Harinarayan CV, Vanaja V, Rajasekhar D, Suresh V, et al. High prevalence of associated birth defects in congenital hypothyroidism. Int J Pediatr Endocrinol 2010;2010:940980.
18. Levothroxine. Available via: http://www.drugs.com/pro/levothyroxine.html (Accessed: June 01, 2012).
19. American Academy of Pediatrics, Rose SR; Section on Endocrinology and Committee on Genetics, American Thyroid Association, Brown RS; Public Health Committee, Lawson Wilkins Pediatric Endocrine Society, Foley T, Kaplowitz PB, Kaye CI, Sundararajan S, Varma SK. Update of newborn screening and therapy for congenital hypothyroidism. Pediatrics 2006;117:2290-2303.
20. Salerno M, Micillo M, Di Maio S, Capalbo D, Ferri P, Lettiero T, et al. A. Longitudinal growth, sexual maturation and final height in patients with congenital hypothyroidism detected by neonatal screening. Eur J Endocrinol 2001;145:377-383.
21. Morin A, Guimarey L, Apezteguía M, Ansaldi M, Santucci Z. Linear growth in children with congenital hypothyroidism detected by neonatal screening and treated early: a longitudinal study. J Pediatr Endocrinol Metab 2002;15:973-977.

DOI:10.5455/aces.20121118032848