Title: Frequency of Different Congenital Disabilities in an Infant with Congenital Hypothyroidism: A Systematic Review

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Abstract

Objectives: Congenital hypothyroidism (CH) is one of the most prevalent endocrine disorders in children. According to the literature, there is a high prevalence of other anomalies and syndromes in infants diagnosed with CH. In this study, we aim to find the prevalence of concurrent anomalies and the prevalence of each one.

Methods: This was a systematic review study based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).The research question was the comparing of children with and without CH in terms of having extra-thyroidal congenital anomalies. A systematic literature search through PubMed, Science Direct, Scopus, and the Web of Science databases used the following keywords: congenital hypothyroidism, congenital disabilities and congenital anomalies.

Results: From the 655 initially retrieved articles, 24 articles remained, and 4 additional references were found by reviewing the references of the final articles . Finally, 28 articles were selected. The prevalence of extra-thyroidal anomalies ranged from 5 to 50% in girls and from 4 to 80% in boys. 20% of the permanent CH patients and 13% of the patients with transient CH had extra-thyroidal congenital malformations. Cardiac anomalies were more prevalent in girls (F: M ratio 1.6[0.7 to 5.5]), and urogenital anomalies were more reported in boys. Most of the studies did not report the association between non-thyroidal anomalies and TSH, gender, etiology of CH, and transient and permanent CH.

Conclusion: Congenital anomalies are more common in CH patients compared with the general population, even in the absence of congenital syndromes or chromosomal abnormalities. The most common anomalies are cardiac, craniofacial, urogenital, and nervous system.

Key words: Congenital hypothyroidism, Congenital disabilities, Congenital anomalies

Introduction

Congenital hypothyroidism (CH) is one of the most common endocrine disorders in children, which can cause permanent mental retardation if untreated. Nowadays, CH is diagnosed through neonatal screening (1). It affects nearly 1:3,000 to 1:4,000 newborns worldwide. It can be secondary or primary, and permanent or transient based on the laboratory findings. In permanent cases, the patient needs lifelong replacement of levothyroxine. Although in some cases, hypothyroidism is a part of a congenital syndrome such as Pendred syndrome, anomalies related to the various systems are reported in CH patients, even in non-syndromic cases of this disorder (2). In most cases, thyroid dysgenesis is the cause of CH(3).

In addition, a higher prevalence of CH was reported in Down syndrome. Many studies have shown that it is associated with an increased incidence of other congenital malformations (1, 3-5). It is assumed that teratogens and a few genes lead to CH and congenital malformations. However, the exact etiology of the high prevalence of congenital disabilities observed in CH infants is unknown (4, 6). The presence of concurrent anomalies in CH patients raises the role of genetic components in this disorder. Based on available data, most of the reported anomalies are related to the cardiovascular system. However, environmental factors also may be related (6). Mutations in TTF1 (thyroid transcription factor 1), TTF2 (thyroid transcription factor 2), FOXE1 (forkhead box E1), PAX8 (paired box 8), and TSHR (Thyroid-stimulating hormone receptor) are shown to be associated with thyroid dysgenesis and also anomalies such as renal anomalies (7).

It is suggested that determining the rate of different concurrent congenital anomalies in these patients would help us in better understanding of the CH pathogenesis, including both genetic and environmental factors as well as improving the protocol of CH screening in order to determine the disorders early in life and following a routine screening program. A well-designed screening program could help us better manage the diseases. Current study aims to investigate the congenital anomalies.

Methods

Search strategy, research question, and databases

This systematic review study was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). The research question and PICO of this study was comparing children with and without CH in terms of having extra-thyroidal congenital anomalies. A systematic literature search based on the keywords listed in Appendix 1 through

PubMed, Science Direct, Scopus, and the Web of Science databases was performed from December 2021 until January 2022.

Inclusion and exclusion criteria

English language articles, including cross-sectional, cohort, and case-control studies, were included, and case reports, letters, and articles without an available full text were excluded. Studies that evaluated extra-thyroidal anomalies in CH patients were included. Duplicates, reviews, unrelated and low-quality studies were excluded. Meeting abstracts were not included.

Study selection and Quality assessment process

After removing duplicates, the title and the abstracts were evaluated by two reviewers separately (RC & JY). Unrelated ones, reviews, letters, case reports, and articles published before 1990 were ignored. The full text of the remaining articles was reviewed by two reviewers separately, and unrelated items were removed. To finding more related studies, references to the final articles were also reviewed. The final articles entered quality assessment using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist, and were done by two independent reviewers (RC & JY). Consult with an expert (MH) was considered in the case of disagreement.

Data extraction

Data extraction was done by two independent authors using a checklist with the following items: name of the author, year of publication, country, sample size, gender, type of CH, inclusion and exclusion criteria, the number of CH patients with concurrent anomalies, and the type of anomalies and the number of each one. Data of the patients with cardiovascular, craniofacial, urogenital, gastrointestinal, and musculoskeletal anomalies and anomalies related to the nervous system are reported as numbers and percent. Anomalies related to the other systems are reported as others. Considering the known association between Down syndrome and prematurity and congenital anomalies, data from the studies that have excluded these patients are reported separately.

Results

Characteristics of the studies

From the 655 initially retrieved articles, 178 were duplicates, and 430 were excluded based on the title and the abstract. Finally, among the remaining 47 articles, 24 articles entered the data

extraction process, and 4 additional references were found by reviewing the references of the final articles. Finally, 28 articles were selected (Figure 1).

In total, 7401 patients (3067 females, 1987 males, others not reported) with CH were studied. The studied population in 12 studies were primary CH patients, 11 permanent CH patients, and in 4 studies, both permanent and transient cases.

In 5 studies, patients with known syndromes such as Down syndrome were excluded, and 5 studies excluded preterm newborns (Table 1). In 2 studies, patients with Down syndrome and prematurity were not included.

Concurrent congenital anomalies from all of the studies (n=28)(1-28)

The prevalence of extra-thyroidal anomalies ranged from 5 to 50% in girls and from 4 to 80% in boys. Accordingly, 20% of the permanent CH patients and 13% of the patients with transient CH had non-thyroidal congenital malformations.

Multiple anomalies were reported in 1-22% of the studied population (5, 9-12, 17, 18, 21-23, 25, 28). Studies from Turkey (22%) (10)and India (12%) reported a higher rates of multiple defects(9).

Chromosomal anomalies were reported in 1-14% of the studied population (4, 5, 8, 17, 19, 22, 23, 27, 28). The most common chromosomal anomaly was Down syndrome. Higher rate of chromosomal anomalies were reported from Iran (14%) (4)and Saudi Arabia (10%)(27).

Regarding non-thyroidal congenital anomalies, most of the studies (18 out of 28) have reported cardiac anomalies as the most common non-thyroidal anomalies ranging from 2-47%(1, 5, 6, 8, 11-15, 17-20, 22-24, 27, 28).In most European countries, the rate of cardiac anomalies was in the lower range. Higher rate of cardiac anomalies were reported from Turkey (47%)(13), India (29%)(9), Iran (22-24%)(1), Poland (19%) (8), and Saudi Arabia (14%)(27).

Other more frequent non-thyroidal anomalies were urogenital, gastrointestinal, musculoskeletal and nervous system. In one study from Iran, the rate of urogenital anomalies among CH patients has been reported to be 32% (7).

Limb anomalies were more prevalent than cardiac ones in Italy (21).

In a study in India, spina bifida was more prevalent than cardiac ones (41% vs. 29%)(9).

In a study in Egypt, the rate of skeletal anomalies was higher than cardiac ones (45% vs.9%)(3).

In a study in Turkey, the rate of craniofacial anomalies was similar to cardiac ones (22%)(10).

The most common cardiac anomalies were atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA), pulmonary stenosis, persistent foramen ovale (PFO), pulmonary valve dysplasia and endocardial cushion defect, respectively.

The female to male (F/M) ratio ranged from 0.4 in one study from Georgia (26)to 4 in one study from India(2).

Cardiac anomalies were more prevalent in girls (F: M ratio 1.6[0.7 to 5.5]), and urogenital ones were more reported in boys. Among the four studies that have reported the gender of the patients with urogenital anomalies, in three studies, all of the patients were boys (7, 8, 23), and in the other one, out of the 24 patients with urogenital anomalies, 21 patients were male (17). Among the patients with gastrointestinal or respiratory anomalies, 23 patients were male, and 24 were female. In one study, there were 15 female patients and 20 male patients with concurrent gastrointestinal or respiratory anomalies (17), and in the other one, there were 8 female patients and 4 male patients with these anomalies (8). In three studies, the gender of the patients with nervous system anomalies is reported. In two of these, all of the patients were male (8, 23), and in one of them, there were 8 girls and 6 boys (17). In total, there were 10 male patients and 8 female patients with CH and nervous system anomalies (F: M ratio: 0.8). Musculoskeletal anomalies were reported in 11 girls and 6 boys (F: M ratio 1.8) (8, 17).

Consanguinity or its association with the anomalies has been evaluated in six studies. In one study, 57.14%(4 out of 7) of patients with two or more anomalies had parental consanguinity(25). Razavi et al., and Ghandi et al. did not report any association between parental consanguinity and the presence of anomalies (1, 4). Rather et al. (2) reported no consanguineous marriages between their patients. Gu et al. (17)also reported no consanguineous marriages in patients with other anomalies. In the study by Caiulo et al.(21), out of 22 patients with other malformations, 4 patients were born to consanguineous parents.

Concurrent anomalies form the studies that have excluded Down syndrome patients(n=5)(6, 10, 14-16)

In this group of studies, 590 CH patients were evaluated. Multiple anomalies were evaluated only in one study with a prevalence rate of 22% (10)and chromosomal anomalies in 1-2%(5, 12). The most common non-thyroidal anomaly was cardiac, ranging from 4-24%(5, 6, 10, 12, 14, 15).

Other anomalies were craniofacial 22% and skeletal 17%(10). Some studies evaluated only cardiac anomalies(6, 15). A study from Iran reported a high rate of PFO in CH patients (24%) in comparison with other cardiac anomalies (6).

Concurrent anomalies from the studies that have excluded preterm infants(n=5)(1, 4, 8, 19, 25)

In this group of studies, 646 CH patients were evaluated. Some of them only evaluated the cardiac anomalies (1). Multiple anomalies were reported only in one study (25), and chromosomal defects were reported in 1-14% of the patients(4, 8). The most common chromosomal case was Down syndrome (14%)(4).Cardiac anomalies with a range of 4-22% were the most common anomalies. Other more frequent anomalies were gastrointestinal and skeletal.

ASD and PDA were the most common cardiac malformations in this group.

Concurrent anomalies from the studies that have excluded Down syndrome patients and preterm infants (n=2)(5, 12)

1617 patients were evaluated. In this group, the common non-thyroidal anomaly was cardiac anomalies ranging between 5-12%. The rate of multiple defects and chromosomal anomalies was reported in 2-6% and 1-2% of the studied population.

The most common cardiac anomalies were PDA, ASD, VSD and PS in order.

Association between non-thyroidal anomalies with screening characteristics of the CH patients

Most of the studies did not report an association between non-thyroidal anomalies and TSH, gender, etiology of CH, and transient and permanent CH(3-6, 8, 19, 28). Few studies indicated that the anomalies are more prevalent in CH patients with dysgenesis of the thyroid gland (12, 15). One study reported that the rate of cardiac and non-cardiac anomalies was 8 times and 4 times higher in CH patients with transient CH(11). Some studies showed that the anomalies were significantly higher in CH patients with low T4 levels, prematurity, or low birth weight (5, 28). One study from Iran reported that maternal age and parental consanguinity were not associated with anomalies (4).

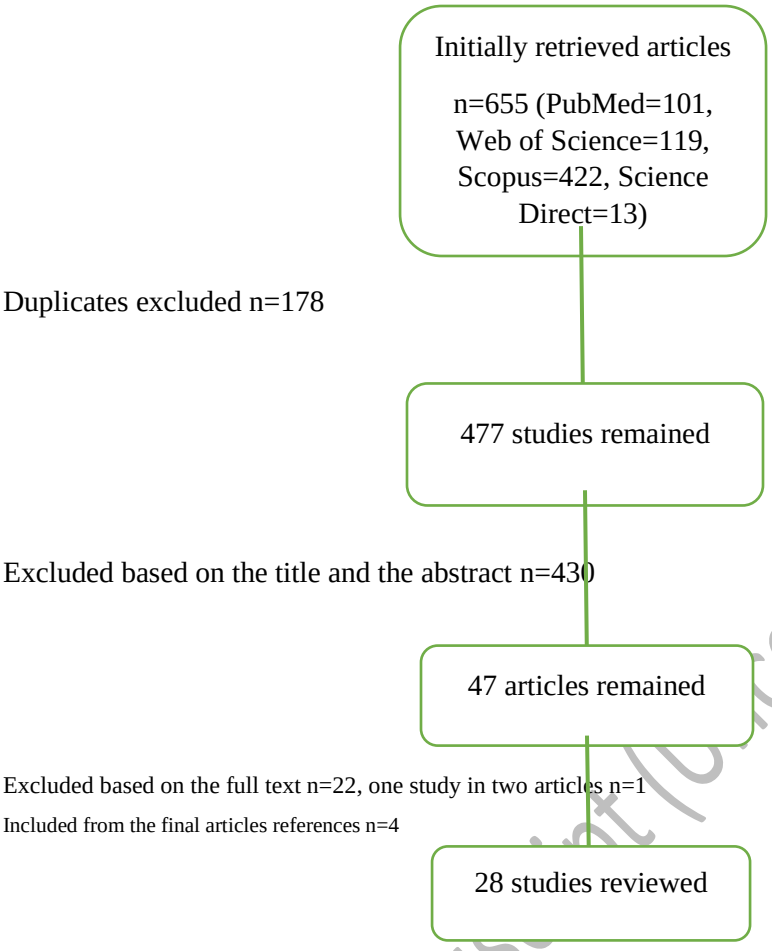

Figure 1. Study selection flowchart

Discussion

In this study, we review the studies that evaluated the rate of non-thyroidal anomalies in patients with CH. Our findings indicated that the most common anomalies were cardiac anomalies. It seems that cardiac malformations were more prevalent in countries with a high rates of CH and in girls. Most of the studies did not report a significant association between screening TSH, gender and etiology of CH. Some studies indicated that gestational age and screening T4 level were associated with the anomalies.

This study showed that although CH is more diagnosed among females(3), concurrent anomalies are more prevalent among male patients with permanent CH. The most common anomalies were cardiac, craniofacial, urogenital, and nervous system malformations. The most common cardiac anomalies were ASD, VSD, and PDA. Among the studies that have excluded Down syndrome

patients, craniofacial anomalies were the most prevalent, and cardiac anomalies were the second one. The most cardiac anomaly in this group was PFO, and ASD was the second most prevalent cardiac anomaly (5, 6, 10, 12, 14-16).In the studies that have excluded preterm infants and studies that have excluded both preterm infants and Down syndrome patients, cardiac anomalies were the most common. ASD and PDA were the most common cardiac anomaly in these studies (1, 4, 5, 8, 12, 19, 25).

Congenital malformations occur in 3–4% of newborns (12). CH affects nearly 1 in 4000 infants (3), and in the current study, the prevalence of congenital malformations in CH patients was found to be higher than the average population (12).

Patients with central CH may have midline facial anomalies (13, 21). In patients with CH, congenital syndromes such as Down syndrome are more prevalent than in the general population, and CH is more common among Down syndrome patients (4).

In the included studies, several syndromes such as Jacobsen syndrome, Di George syndrome, Fanconi syndrome, Turner syndrome, Beckwith Wiedemann syndrome, VATER association, VACTERL association, Albright's hereditary osteodystrophy, and Pierre Robin sequence were reported among the CH patients (4, 12, 17, 21).

In general, the exact etiology of the higher incidence of congenital disabilities in CH patients is unclear (4). Though, based on our review, congenital cardiac malformations were the most common concomitant anomaly in these patients, but in different populations, the types of anomalies may be different from each other (17). For example, in the study by El Kholy et al. in Egypt, the most common concomitant anomaly was musculoskeletal malformations(3). It is assumed that during the embryonic period, several genes that are involved in the thyroid gland formation, are also involved in the other parts of organogenesis. For instance, the NKX2.5 gene involved in the pathogenesis of congenital heart defects, and is also involved in thyroidogenesis (6). This may explain the high prevalence of cardiac malformations in patients with CH. The most common form of CH is thyroid dysgenesis, and mutations in genes such as FOXE1, NKX2.1, and PAX8 are related to this disorder(2). These mutations also lead to other malformations, such as renal, craniofacial, and nervous system anomalies(29). The high prevalence of musculoskeletal anomalies also suggests the possible role of another genetic component, which should be investigated in future studies(3). Although in most cases, CH is reported to be sporadic, Castanet et al. found a high frequency of positive family history of

thyroid dysgenesis in these patients. All of these findings support the role of genetic components in this disorder (20).

Thyroid agenesis is associated with a higher rate of extra-thyroidal malformations(12). However, Rather et al. showed a high incidence of anomalies in patients with dyshormonogenesis (2). Considering the critical role of thyroid hormones in cellular growth and differentiation, the lack of sufficient amounts of thyroid hormones in the early stages of organogenesis is another hypothesis for the high incidence of congenital malformations observed in CH patients (12, 29).

It is recommended that in future studies the presence of different anomalies will be evaluated by genetic studies, in order to determine the possible association between CH-related genetic factors and the anomalies.

Recent evidence shows that environmental factors mainly, pollutants during the prenatal period, may have a role in fetal development. Considering that there are not many studies in this field, this issue is considered as an essential issue in studying the pathogenesis of CH and its related anomalies(30).

The wide range of the prevalence of concomitant anomalies reported in patients with CH might be related to differences in the studied populations, or different study methods and criteria (15). Overall, considering the high frequency of extra-thyroidal anomalies in CH infants, a complete evaluation of the child diagnosed with CH, especially for cardiac, renal, and nervous system anomalies, is needed.

Studies have shown that cardiac and musculoskeletal malformations are more prevalent in girls with CH, nervous system and urogenital abnormalities are more common in boys(8, 17). In the study by Gu et al., 1520 patients with CH were evaluated, and 222 patients showed concurrent anomalies. In this study, cardiac anomalies were 1.25 times more prevalent in girls than boys (10% of the girls and 8% of the boys showed cardiac anomalies, respectively), urogenital anomalies were 10 times more common in boys (3% of the boys and 0.3% of the girls showed urogenital anomalies, respectively), and nervous system anomalies were present in 8 girls and 6 boys (the prevalence of nervous system anomalies was near 1% in both genders) (17).

These findings would be help plan the future screening protocol for the evaluating non-thyroidal anomalies.

Studies from countries with a high rates of CH indicated that parental consanguinity could be a potential risk factor for CH(31, 32).

It is suggested that consanguinity may also be a risk factor for the presence of the mentioned anomalies. In reviewed studies, this factor had not been investigated in most of the studies, and only in 1 study the rate of consanguinity was higher in CH patients with two or more anomalies than those without (25). Ghandi et al. reported a high prevalence (22.7%) of congenital heart defects in CH infants. They observed that consanguinity marriage was not related to the occurrence of cardiac anomalies (1).

According to our findings, it seems that cardiac anomalies were higher in countries with a higher rates of CH than in European countries, which both rates of CH and consanguinity were not high. It is recommended to study the rate of different anomalies in association with consanguinity to find out the possible role of some genetic factors in the development of CH and its related anomalies.

Regarding the association between familial, demographic, and screening factors associations with CH-related anomalies, some studies indicated that low T4 level and prematurity, and low birth weight are associated with the anomalies (5, 28). These findings confirm the role of thyroid hormone in fetal development and its possible role in CH-related anomalies. The association between prematurity and anomalies in CH patients is a challenging issue. However, prematurity itself is associated with a high rate of CH and also anomalies(33, 34).

Further studies are needed to investigate the role of the mentioned factors in this field.

This study has several limitations. First, in a number of the included studies, male to female ratio, CH type (transient or permanent), and the type of anomalies are not reported. In patients with multiple anomalies, the type of each anomaly has not been reported. Also, due to the lack of complete information about the anomalies found in each patient, it is not possible to exclude all patients with Down syndrome and preterm babies in all of the studies. The number of patients with concurrent anomalies, excluding patients with Down syndrome and preterm infants, is only reported from the studies that have excluded these patients. In addition, included studies have not examined intervening variables such as race, consanguineous marriage, and family history. However, this study highlights the impotence of at-birth screening in CH infants for other congenital anomalies considering the high frequency of extra-thyroidal malformations in these patients.

Conclusion

Congenital anomalies are more common in CH patients compared with the general population, even in the absence of congenital syndromes or chromosomal abnormalities. The most common anomalies are cardiac, craniofacial, urogenital, and nervous system. Cardiac anomalies are more frequent among girls. The most common cardiac anomalies are septum defects. It is recommended that we can use the data for revising the CH screening program in order to screen the most common anomalies.

Table 1. Studies on congenital anomalies in CH infants

No	Name of author, Country, Year of publication	Sample size/ Female/male	Type of CH (Primary, transient, permanent)	Etiology of CH	Patients with other anomalies (number)	Multiple defects/ Congenital syndromes/ Chromosomal abnormalities	Anomalies (Cardiac, Urogenital, Gastrointestinal /Respiratory, Nervous system /Musculoskeletal)	Associations
1	Caiulo et al, Italy, 2020 (21)	119 58/61	Permanent, transient	Dygenesis n=52, dyshormonogenesis n=14, transient CH n=53	22 (8 with transient and ' with hypothalamic CH)	-***Multiple defects:***n=7 (6%*)(Down Syndrome+ double urethral meatus and anal stenosis n=1, Jacobsen syndrome+ left renal agenesis, double outlet right ventricle, and VSD n=1, Down Syndrome+ ASD and duodenal atresia n=1, ASD+ dysplastic pulmonary valve n=1, Angioma+ ASD n=1, Down Syndrome+ sensorineural hearing loss and aganglionic megacolon n=1, Down Syndrome+ duodenal atresia, annular pancreas, inferior vena cava agenesis n=1) -***Syndromes:*** one patient with Di George syndrome	-***Cardiac:*** n=3 (3%) (Aortic coarctation n=1, AV canal defect+ Down syndrome n=1, Transposition of the great vessels n=1) -***Urogenital:*** n=4 (3%) (Hypospadias n=2, left megaureter n=1, bilateral cryptorchidism n=1) -***Gastrointestinal:*** n=1 (1%) (giant omphalocele) -***Nervous system:*** n=2 (2%) (Septo-optic dysplasia n=1, Partial agenesis of the corpus callosum n=1) -***limbs:***n=5 (4%); syndactyly n=2, Tendon agenesis n=1, club foot n=2 (one with Di George syndrome)	
4	Yousefichaijan et al, Iran, 2017 (7)	100 60/40	Primary CH	NR	32 (only boys)		-***Urogenital:*** n=32 patients (21 controls, (OR=2.04; 95%CI: 1.1-3.6; p=0.014) *The most prevalent:* 37 (40.2%) hypospadias, 26 (28.2%) cryptorchidism, and 9 (9.7%) hydrocele	
5	Kurtul et al, Turkey, 2016 (13)	121 56/65	Primary CH	Dysgenesis n=9 dyshormonogenesis / iodine deficiency n=112	90	-***Down syndrome***n=21 (17%)	-***Cardiac:*** n=57 (47%) (ASD n=38, PDA n=12, VSD n=7, AV septal defect n=3, Aortic valve stenosis n=3, PS n=3, Tetraology of Fallot n=3, Aortic coarctation n=1) -***Urogenital:*** (3%) Inguinal hernia n=2, Cryptorchidism n=2 -***Gastrointestinal:*** Liver hemangioma n=2 (2%) -***Nervous system:*** n=46 (38%) (Mental retardation n=30, Epilepsy n=18, Cerebral palsy n=3, Microcephaly n=3) -***Skeletal:*** (3%) Pelvis subluxation n=4 -***Others:*** Atopic dermatitis n=10	
6	Rather et al, India, 2014 (2)	19 13/ 6	Permanent CH	Dyshormonogenesis n=12	5 (1 male, 4 females)	-	-***Cardiac:*** n=2 (10%) (pulmonary hypertension and tricuspid regurgitation n=1, mitral regurgitation and stenosis n=1) -***Urogenital:*** n=2 (10%) (left ectopic kidney and penoscrotal hypospadias n=1, malrotated ectopic left kidney with diminished function n=1) -***Craniofacial*** n=1 (5%) (microcephaly, high-arched palate, and low-set ears)	
8	Amaresh Reddy et al, India, 2010 (9)	17 8/9	Primary CH	*In patients with other anomalies:* Dysgenesis n=8, dyshormonogenesis n=2 *In total:* Dysgenesis n=13, dyshormonogenesis n=4	10 (4 females, 6 males)	-***Multiple defects:*** n=2 (12%) (both ASD+ spina bifida, excluding dysmorphic features)	-***Cardiac:*** n=5 (29%) (ASD n=3, PDA n=1, PDA+ ASD n=1) -***Spina bifida:*** n=7 (41%) -***Others:*** High arched palate n=6, low set ears n=8, micrognathia n=4, depressed nasal bridge n=10, epicanthic folds n=6, pectus excavatum n=5	
9	Gu et al, Japan, 2009 (17)	1520 839/673(8 unknown)	Primary CH	25 patients with other congenital abnormalities had thyroid anomalies	222 (101 males and 119 females, 14.6%; 95%	-***Multiple defects:*** n=26 (2%) -***Chromosomal abnormalities:*** n=95	-***Cardiac:*** n=135 (9%) (81 females, 53 males)(VSD n=28, ASD n=27, PDA n=24, PS n=9, Endocardial cushion defect n=8, Pulmonary hypertension n=6, Interrupted	Prevalence of congenital anomalies was significantly higher in CH patients compared to

				(agenesis, hypoplasia, ectopic, and dyshormonogenesis)	CI, 12.8–16.4)	(6%) (Pierre-Robin's syndrome, Down syndrome, Kabuki's syndrome, and Turner's syndrome; Down syndrome n=86 (44 males)	aortic arch n=3, Pulmonary atresia n=3, Total anomalous pulmonary venous return n=3, Hypoplastic left heart syndrome n=2, Tricuspid regurgitation n=1, Tetralogy of Fallot n=2, Coarctation of aorta n=2, aortic valve stenosis n= 2, Congenital AV block n=1, others n=14) -***Urogenital:*** n=17 (1%) (21 males and 3 females) (Hypospadias n=7, bifid scrotum n=2, inguinal hernia n=2, other scrotal anomalies n=2, undescended testis n=1, polycystic kidney n=1, bladder exstrophy n=1, others n=1) -***Respiratory and gastrointestinal:***n=33 (2%) (20 males, 15 females) (duodenal or intestinal atresia n=9, anal atresia n=8, biliary atresia and dilatation n=3, annular pancreas n=3, esophageal atresia n=3, omphalocele n=2, upper tracheal stenosis n=1, umbilical hernia n=1, pulmonary hypoplasia n=1, Hepatorrhexis n=1, anal stenosis n=1) -***Nervous system:*** n=16 (1%) (8 girls and 6 boys) (Hydrocephaly n=5, microcephaly n=3, Spina bifida n=2, Arnold-Chiari malformation n=1, corpus callosum agenesis n=1, congenital hypopituitarism n=1, others n=1, Hirschsprung's disease n=2) -***Limb anomalies:*** n=11 (1%), 7 females, 4 males -***Ocular:***n=4 (1 female, 3 males) -***skin:*** n=3, only females. -***Others:*** cleft lip or palate n=6 (3 females, 3 males), ear problems n=5 (3 females, 2 males), (female), choanal atresia n=1 (female), laryngomalacia n=1 (male), vocal cord paralysis n=1 (male), others n=6	the normal population (excluding Down syndrome patients)
10	El Kholy et al, Egypt, 2007 (3)	44 26/18	Permanent CH	All dysgenesis	22 (major anomalies n=7)		-***Cardiac:*** n=4 (9%) (VSD n=1, PS n=1, PDA n=1, mitral valve prolapse n=1 (Patients with cardiac anomalies also showed some dysmorphic features.) -***Urogenital*** n=2 (5%) Imperforate hymen, pelvic right kidney and absent left kidney n=1, absent left kidney n=1 -***Skeletal:*** n=20 (45%) digitalization of thumbs n=11, brachydactyly n=9 -***Ophthalmological:*** strabismus n=2 -***Others:*** cleft palate n=1	There was no significant correlation between non-thyroidal anomalies and etiology of CH or T4 or TSH at diagnosis.
11	Castanet et al, France, 2001 (20)	681 NR		In the group with other anomalies: all dysgenesis	56		-***Cardiac:*** n=16 (28%) -***Others:*** Facial n=9 (16%), urogenital, nervous system, gastrointestinal	
12	Devos et al, Canada, 1999 (18)	273 147/83 (permanent cases with thyroid scan results)	Primary CH (234 with permanent, 37 with transient, and 2 unknown)	Dyshormonogenesis n=52, dysgenesis n=178	12 with persistent (9 girls, 3 boys), 5 with transient	-***Multiple defects:*** n=4 (1%) Permanent CH: Cleft palate, dextrocardia, and imperforate anus n=1; Neurofibromatosis n=1; PS, ectopic ureterocoele, and duplication of the left pyeloureteral system n=1 Transient CH: VACTERL association n=1	-***Cardiac:*** n=7 (3%) (VSD n=3, ASD n=2, ASD+PS n=1, PS n=1) (permanent CH) -***Gastrointestinal:*** n=2 (<1%) (Gastroschisis n=1, pyloric stenosis n=1 (transient CH) -***Nervous system:*** n=1 (<1%) Septo-optic dysplasia n=1 (permanent CH) *Others:* n=3 (transient CH)	
13	Oakley et al, Scotland, 1998 (11)	344 219/ 125	Primary CH (224 definite cases, 11 probable, 21 uncertain, 88	NR	31 (13 with transient)	-***Multiple defects:*** n=15 (4%) Definite CH: n=4 (cleft palate n=1, hip dysplasia and cleft palate n=1, Deafness n=2) Uncertain CH: n=4 (tracheooesophageal	-***Cardiac:*** n=12 (3%) Definite CH: n=4 (PDA n=1, VSD n=2, Truncus arteriosus n=1) Uncertain CH: n=3 (ASD/PDA+ Down syndrome n=1, AV canal defect+ Trisomy 18 n=1, Coarctation n=1) Transient CH: n=5 (VSD+ Down syndrome n=1, AV canal defect n=1, Coarctation n=1, Coarctation + Down syndrome n=1, AS+	The incidence of congenital heart disorders was three times the expected amount in the definite group (the incidence of non-cardiac malformations was not increased.) and eight

			transient)			fistula+ Down syndrome+ ASD/PDA n=1, tracheooesophageal fistula+ horsehoe kidney+ Trisomy 18 n=1, cleft palate +coarctation n=1, cleft palate n=1) Transient CH: n=7 ***-Congenital syndromes:*** n=16 (5%) (Definite CH: n=6 Uncertain CH: n=4 Transient CH: n=6	MS n=1)	times higher than the expected in the transient group (non-cardiac malformations was four times higher in this group).
14	Law et al, UK, 1997 (22)	136 88/48	Primary CH	Dysgenesis n=3; dyshormonogenesis n=3 (others unknown)	11 (5 males, 8% [95% CI 3·4–12·6%])	***-Down syndrome***n=1 (<1%) ***-Prevalence of chromosomal anomalies:*** 1·5%; 95% CI 0·5–3·5% (three times higher than the general population) ***-Multiple defects:*** cleft palate, spiky hair syndrome and choanal atresia n=1 (<1%)	***-Cardiac:*** n=4 (3%) (95% CI 0·2–5·8%) VSD, PDA n=1; PDA n=1; PS n=1; ASD, spinal and kidney abnormalities n=1 (*Significantly higher than the normal population) ***-Urogenital:*** n=2 (1%) Bilateral hydrocele n=1; Urethral stricture and renal failure n=1 ***-Skeletal:*** n=2 (1%) Bilateral talipes, broken left clavicle n=1; Dysmorphic, small and extra digits n=1; ***-Nervous system:*** Lumbosacral myelomeningocele and hydrocephalus n=1 (<1%)	
15	Roberts et al, Georgia, 1997 (26)	87 56/31	Permanent CH	NR	10 (5 males, 2 females; 3 with Down syndrome; 2 males and 1 female)(OR= 2.2 95%CI 1.03–4.11)	*-Down syndrome* n=3	*-Anomalies:* cleft palate, sagittal synostosis, posterior urethral valves, VSD, clubfoot, lipoma of the spermatic cord, and situs inversus totalis	
16	Al-Jurayyan et al, Saudi Arabia, 1997 (23)	81 NR	Primary CH	*In patients with other anomalies:* Dyshormonogenesis n=3, dysgenesis n=5, others unkown	16 (9 males)	***-Multiple defects:***n=5 (6%) ***-Down syndrome:*** n=2 (2%)	***-Cardiac:*** n=7 (9%) ASD n=1 (female), VSD n=3 (2 female, 1 male), PDA n=1 (male), hypoplastic heart n=1 (male), others n=1 (male) ***-Urogenital:*** n=1 (1%) Hypospadias n=1 (male) ***-Nervous system:*** n=1 (1%) hydrocephalus n=1 (male) ***-Others:*** Neonatal insulin-dependent diabetes mellitus n=1 (male), ichthyosis n=1 (female), unilateral ptosis n=1 (female)	
17	Cassio et al, Italy, 1994 (28)	235 161/74		In patients with other anomalies: Dysgenesis n=15, others unknown	22 (7 males and 15 females)	***-Trisomies****:* n=3 (1%) ***-Multiple defects:*** n=2 (<1%)	***-Cardiac:*** n=8 (3%) ***Urogenital:*** n=1 (<1%) ***Gastrointestinal*** n=2 (<1%) ***Nervous system:***n=1 (<1%) ***Others:*** n=5	The prevalence of congenital anomalies was significantly higher than the general population. In these patients, T4 level and gestational age and birth weight were significantly lower at screening compared to isolated CH. There was no significant difference between patients with and without extra thyroidal anomalies in terms of TSH and type of CH.
18	Majeed-Saidan et al, Saudi Arabia, 1993 (27)	21 11/10	Permanent primary CH	Dyshormonogenesis n=9, dysgenesis n=8, unknown n=4	9	***-Chromosomal anomalies:*** n=2 (10%) Trisomy 21 n=1, Ring chromosome 9 n=1	***-Cardiac:*** n=3 (14%) PDA n=2, PS n=1, VSD n=1) ***-Lung disease*** n=2 (10%) *-Cleft lip* n=1 (5%) *-Erb's palsy* n=1	
19	Sorcini et al, Italy, 1993 (24)	759 506/253		Dysgenesis n=300	25		***-Cardiac:*** n=13 (2%) (Male/Female = 1/5.5 n=12 (non-cardiac)	
Studies that have excluded preterm infants								

1	Wędrychowicz et al, Poland, 2019 (8)	54 33/21	Primary CH	Dysgenesis=29, dyshormonogenesis n=2, unknown n=23	20 (13 females, 7 males)	-***Down syndrome:*** n=1 (2%)	-***Cardiac:*** n=10 (19%) (7 girls, 3 boys) PDA n=1, ASD n=1, aortic valve stenosis n=1, Tetralogy of Fallot n=1, total anomalous pulmonary venous return n=1, Aortic valve insufficiency n=1, persistent foramen ovale n=1, hypoplastic left heart syndrome n=1, ASD+PDA n=2 (Eight children also had other malformations) -***Urogenital:***n=5 (10%) (all boys) (cryptorchidism, hypospadias, inguinal hernia, hydrocele, hydronephrosis, 3 concurrent gastrointestinal and cardiac anomalies) -***Gastrointestinal:***n=7 (13%) (5 girls, 2 boys, 3 concurrent heart defects)(umbilical hernia, bile reflex, tracheoesophageal fistulas, cleft palate, and meconium plug syndrome) -***Respiratory system:*** n=5 (10%) (3 girls, 2 boys, 3 concurrent heart defects) -***Nervous system:*** n=3 (6%) (all boys, epilepsy, deafness, developmental problems, 2 concurrent heart defects) -***Musculoskeletal:***n=6 (11%) (4 females and 2 males) (varus and valgus deformities, differences in limb length, microcephaly, decreased muscle tone) -***Dermatological:*** n=3 (6%) (2 females, 1 male)	There was no significant difference in terms of type of CH or TSH between subjects.
2	Ghandi et al, Iran, 2018 (1)	79 34/36	Primary CH	NR	18		-***Cardiac:*** ASD n=8, PDA n=3, Endocardial cushion defect n=3 (all with Down syndrome), PS n=2, VSD n=1, dilated cardiomyopathy n=1 (In total, six patients had Down syndrome)	Patients with cardiac anomalies in the control group: n=0 (*the difference was statistically significant)
3	Razavi et al, Iran, 2012 (4)	150 72/78	Primary CH	NR	30	***Down syndrome*** n=21 (14%) VACTERL association n=1	-***Cardiac:*** n=7 (5%) (ASD n=3, VSD n=2, PS n=1, PDA n=1) -***Urogenital:*** Severe hypospadias n=1 (1%) -***Skeletal:*** n=7 (5%) DDH n=3, club foot n=2 Dolicocephaly n=1, Hydrocephaly n=1 -***Others:*** Cleft lip and palate n=1, cataract n=1	There were no significant differences in terms of gender, TSH, T4 or parental consanguinity or maternal age between patients with and without other anomalies
4	Chao et al, Taiwan, 1997 (19)	120 NR	Primary CH (24 with transient)	*In total:* Dysgenesis n=37, dyshormonogenesis n=62, unknown n=7 *In patients with other anomalies:* Dysgenesis n=3, dyshormonogenesis n=9, unknown n=2	14 (5 females, 9 males), all with permanent	-***Syndromes:*** Sotos syndrome n=1 (<1%)	-***Cardiac:*** n=5 (4%) (truncus arteriosus, PS, PDA, ASD, sick sinus syndrome) -***Respiratory:*** Tracheoesophageal fistula n=1 (<1%) -***Gastrointestinal:*** n=2 (2%) omphalocele n=1, hypertrophic pyloric stenosis n=1 -***Nervous system:*** n=3 (2%) Hirschsprung's disease n=1, meningomyelocele n=1, infantile spasm n=1 -***Others:*** Cleft lip n=1, bilateral ptosis n=1	There was no significant difference in disease severity or etiology between patients with and without concurrent anomalies.
5	Siebner et al, Israel, 1992 (25)	243 156/87	Permanent primary CH	Dysgenesis n=101, dyshormonogenesis n=32, unknown n=110	38 (26 girls and 12 boys, 15.6 %)	-***Multiple defects:***n=7 (3%)	-***Cardiac:*** n=14 (6%) (VSD n=7, PDA n=3, PS n=2, mitral insufficiency n=1, congenital atrial flutter n=1) -***Urogenital:*** n=4, Inguinal hernia n=5 (total n=9, 4%) -***Gastrointestinal:***n=2 (<1%) -***Nervous system:*** n=2 -***Skeletal:*** n=7, *Congenital dislocation of the hip:* n=8 (total n=15, 6%) -***Facial:*** n=2 -***Skin:*** n=1 -***Others:*** n=1	Prevalence of these anomalies was significantly higher in CH patients: hydrocephalus, diaphragmatic hernia, hydronephrosis, polydactyly, syndactdy, esophageal atresia, cleft lip.
Studies that have excluded Down syndrome patients								
1	Ozsu et al, Turkey, 2016 (10)	41 27/14	Permanent CH	All dysgenesis	20	-***Multiple defects:*** 9 (22%) -***Syndromes:*** One patient (2%) was diagnosed with Fanconi syndrome	-***Cardiac:*** n=9 (22%) (ASD n=6, PS n=1, mitral insufficiency n=2) -***Urogenital:*** n=2 (5%) testicular atrophy n=1, horse shoe kidney n=1 -***Skeletal:***n=7 (17%) (polysyndactyly n=3, pectus excavatum n=1, pes planus n=1, developmental dysplasia of the hip n=3) -***Ophthalmological:*** n=2 (5%) synkinesia n=1, strabismus n=1 -***Craniofacial:*** n=9 (22%)	

2	Kempers et al, The Netherlands, 2009 (16)	242 165/77	Permanent CH	Dysgenesis=185 Dyshormonogenesis n=57	33.1% major and 96.3% minor craniofacial and morphologic alabnormalities		-Percentage of *craniofacial and morphological* abnormalities was significantly higher in CH children compared to the control group (21.8% major and 82.5% had minor abnormalities).	Subgroup analysis showed that this difference was only significant between children with thyroid ectopia and the control group. However, there was no significant difference between etiologies in terms of anomalies.
3	Sabri et al, Iran, 2006 (6)	96 45/51	Primary CH	NR	29 (9 controls; OR=2.4, P-value=0.03, more prevalent among males)		***Cardiac:*** Patent foramen ovale (PFO) n=23 (CH patients) and n=8 (healthy controls); ASD n=2 CH patients; PS n=1 CH patient; PFO+PDA n=2; PFO + VSD + minimal Aortic insufficiency + dilated left ventricle with borderline function n=1	Cardiac anomalies other than PFO were not significantly different between healthy children and children with CH. Prevalence of these anomalies did not show any significant difference between permanent and transient cases and different etiologies
4	Kreisner et al, Brazil, 2005 (15)	76 47/29	Permanent CH	Dysgenesis n=67, dyshormonogenesis n=9	10 (4 males and 6 females, 3 with ectopia and 7 with agenesis)		-***Cardiac:*** n=8 (11%) (VSD n=2, ASD n=2, atrial-ventricular septal defect n=2, valve disorders n=3 [PS n=2, tricuspid and mitral valve disorders n=1], aortic outlet obstruction [sub-aortic ring] n=1) Bifid spine n=1 (1%) -***Others:*** Cleft palate n=2	There were no significant differences between patients with other anomalies and isolated CH in terms of T4 or TSH at diagnosis, sex, and birth weight. Prevalence of malformations in CH children (only children with thyroid dysgenesis) was significantly higher than the normal population (RR=2.6; 95% CI: 1.3–4.8; p=0.005)
5	Kurinczuk et al, Australia, 2002 (14)	126 90/36	Permanent CH	NR	13 (9 females) (OR=2.20[95 % CI 1.24, 3.91])	-***Syndromes:*** n=3	-***Cardiac:*** n=5 (4%) OR= 4.48[CI 1.90, 10.58]) -***Skeletal:*** n=2 (2%) -***Craniofacial;*** n=2 (2%) -***Urogenital:*** n=2 (2%) -***Nervous system:*** n=2 (2%) -***Gastrointestinal*** n=1 (<1%) -***Ocular:*** n=1 (<1%) -Case 1, Fetal alcohol syndrome; case 2, PDA, ASD, partial VATER syndrome; case 3 right ventricular hypoplasia, PDA, pulmonary valve atresia, tricuspid incompetence; case 4, PDA, PS; case 5 hypoplastic toes; case 6 congenital hip dislocation; case 7 facial dysmorphy, bifid scrotum, undescended testis, Dandy Walker malformation, and coloboma; case 8 VSD; case 9 Neurofibromatosis; case 10 ear malformation; case 11 Klinefelter syndrome; case 12 vesico-ureteric reflux, biliary atresia, cystic dysplastic kidney, congenital (Ladd's) bands, hydronephrosis, Tetralogy of Fallot, aberrant hepatic artery and portal vein; case 13 iris tumour and cataract	
Studies that have excluded preterm infants and Down syndrome patients								
1	Monroy-Santoyo et al, Mexico, 2011 (12)	212 150/62	Permanent primary CH	Dysgenesis= 182, dyshormonogenesis n= 2, Undiagnosed n= 28	52	-***Multiple defects:*** n=12 (6%) -***Syndromes:*** n=4 (2%) (Beckwith Wiedemann syndrome n=1, VATER association n=1, Albright's hereditary osteodystrophy n=1, Pierre Robin sequence n=1)	-***Cardiac:*** n=26 (12%) PDA n=8, ASD n=5, PS n=2, VSD n=1, ASD+VSD n=1, VSD+ PDA n=1, ASD+PDA+ tricuspid insufficiency n=1, PDA+ pulmonary stenosis n=1, VSD+ tricuspid insufficiency n=1, PDA+ strabismus n=1, ASD+ strabismus n=1, PDA+ congenital midriasis n=1, ASD+ cleft lip and palate n=1, PS+ hepatic hemangioendothelioma n=1 -***Urogenital:*** n=2 (1%) Cryptorchidism n=1, Phymosis n=1 -***Gastrointestinal:*** Hepatic hemangioendothelioma n=1 (2%) -***Nervous system:*** n=4 (2%) Frontotemporal	Thyroid agenesis was significantly more prevalent in children with concurrent anomalies compared to children with CH alone.

							agenesis n=1, Hydrocephalus n=1, Hirschsprung disease n=2 -***Skeletal:***n=4 (2%) Inferior limbs asymmetry n=1, Talipes equinovarus n=1, Lumbosacral dysraphia n=1, hip dysplasia n=1 -***Ophthalmological:*** n=5 Strabismus n=3, Congenital bilateral cataract n=1, Affected 3th and 4th cranial nerves and palpebral ptosis n=1 -***Craniofacial:***n=4 (8%) Sella Turcica dysplasia n=1, Right microtia n=1, Neonatal teeth n=1, Facial hemangioma n=1, -***Others:*** Frontonasal dysplasia n=1, Cleft palate+ dermoid cyst n=1, Right microtia+ strabismus n=1	
2	Olivieri et al, Italy, 2002 (5)	1405 NR	Primary CH (1372 with permanent and 33 with transient CH)	*Isolated CH:* Dysgenesis 82.6% dyshormonogenesis 17.4% *CH+ major congenital anomalies:* Dysgenesis 80.6% dyshormonogenesis 19.4%	169 with permanent (major abnormalities n=115), 3 with transient	-***Multiple defects:***n=23 (2%) -***Chromosomal:***n=4 (<1%) -***Non-chromosomic syndromes:*** n=1 (<1%)	-***Cardiac:*** n=76 (5%) (OR= 5.5 [4.3–7.0])(the most prevalent ASD [13.8 of 1000, OR=10.6{6.4 –16.5}]) tetralogy of Fallot (OR=8.6[3.1–18.7]) PS (OR=7.8[3.1–16.0]) In transient cases: VSD and persistent fetal circulation -***Urological:*** n=5 (<1%) (OR=1.4[0.4–3.2]) -***Genital:*** n=1 (<1%) (OR= 0.2[0–1.2]) (n=6, 3.5%) -***Gastrointestinal:*** n=7 (<1%) (OR=1.4[0.6–2.9]) -***Respiratory and lungs:*** n=1 (<1%) (0.5%) (OR=0.5[0-2.9]) -***Nervous system:*** n=12 (<1%) (OR= 2.7[1.4–4.7]) -***Skeletal:***n=14 (<1%) (OR= 1.2[0.6–2.0]) -***Cleft palate/lip:*** n=6 (<1%) (OR=2.6[1–5.7]) -***Ophthalmological:*** n=6 (OR= 5.5[2.0–11.9]) -***Skin:*** n=2 -***Others:*** n=1 ***In transient cases:*** clubfoot	Children with other anomalies had significantly lower T4 levels at screening and birth weight. No significant difference between children with transient and permanent CH was found for congenital anomalies. Prevalence of different etiologies was not significantly different in CH patients with and without other birth defects

Table abbreviations: PDA: Patent ductus arteriosus; CH: congenital hypothyroidism; VSD: ventricular septal defect; ASD: atrial septal defect; PDA: Patent ductus arteriosus; DDH: Developmental dysplasia of the hip; VATER: vertebral defects, anal atresia, esophageal atresia /tracheo-esophageal fistula, renal dysplasia, radial-limb anomalies; VACTERL: vertebral abnormalities, anal atresia, cardiac defects, tracheal-esophageal abnormalities, including atresia, stenosis and fistula, renal and radial abnormalities, limb abnormalities; NR; not reported.

Refernces

1. Ghandi Y, Sanatkar SA, Habibi D, Dorreh F, Sadeghizadeh B, Sharahee M. Frequency of congenital cardiac malformations in the neonates with congenital hypothyroidism. Iranian Journal of Neonatology. 2018;9(2):66-70.
2. Rather TA, Khan SH, Masoodi S, Alai MS. Thyroid dyshormonogenesis and associated non-thyroidal anomalies in a tertiary care hospital in India. Horm Res Paediatr. 2014;81(5):314-8.
3. El Kholy M, Fahmi ME, Nassar AE, Selim S, Elsedfy HH. Prevalence of minor musculoskeletal anomalies in children with congenital hypothyroidism. Horm Res. 2007;68(6):272-5.
4. Razavi Z, Yavarikia A, Torabian S. Congenital anomalies in infant with congenital hypothyroidism. Oman Med J. 2012;27(5):364-7.
5. Olivieri A, Stazi MA, Mastroiacovo P, Fazzini C, Medda E, Spagnolo A, et al. 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). The Journal of clinical endocrinology and metabolism. 2002;87(2):557-62.
6. Sabri MR, Shahriari H, Hashemipour M. Congenital cardiac malformations in congenital hypothyroid patients in Isfahan. Journal of Research in Medical Sciences. 2006;11(4):234-9.
7. Yousefi Chaijan P, Dorreh F, Sharafkhah M, Amiri M, Ebrahimimonfared M, Rafeie M, et al. Congenital urogenital abnormalities in children with congenital hypothyroidism. Med J Islam Repub Iran. 2017;31:7.
8. Wędrychowicz A, Furtak A, Prośniak A, Żuberek M, Szczerkowska M, Pacut P, et al. Extrathyroidal congenital defects in children with congenital hypothyroidism – observations from a single paediatric centre in Central Europe with a review of literature. Pediatr Endocrinolog Diabetes Metabol. 2019;25(3):114-21.
9. Reddy PA, Rajagopal G, Harinarayan CV, Vanaja V, Rajasekhar D, Suresh V, et al. High prevalence of associated birth defects in congenital hypothyroidism. International journal of pediatric endocrinology. 2010;2010:940980.
10. Ozsu E, Çizmecioglu FM, Mutlu GY, Hatun S, Altun G, Yildirim B, et al. Extra-thyroid congenital abnormalities associated with thyroid dysgenesis in Turkey. Hong Kong Journal of Paediatrics. 2016;21(1):3-6.
11. Oakley GA, Muir T, Ray M, Girdwood RW, Kennedy R, Donaldson MD. Increased incidence of congenital malformations in children with transient thyroid-stimulating hormone elevation on neonatal screening. J Pediatr. 1998;132(4):726-30.
12. Monroy-Santoyo S, Ibarra-González I, Fernández-Lainez C, Greenawalt-Rodríguez S, Chacón-Rey J, Calzada-León R, et al. Higher incidence of thyroid agenesis in Mexican newborns with congenital hypothyroidism associated with birth defects. Early Human Development. 2012;88(1):61-4.
13. Kurtul BE, Ozer PA, Kabatas EU, Gürkan A, Aycan Z. Ophthalmic Manifestations in Children With Congenital Hypothyroidism. J Pediatr Ophthalmol Strabismus. 2016;53(1):29-34.
14. Kurinczuk JJ, Bower C, Lewis B, Byrne G. Congenital hypothyroidism in Western Australia 1981-1998. J Paediatr Child Health. 2002;38(2):187-91.
15. 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(2):165-9.
16. Kempers MJ, Ozgen HM, Vulsma T, Merks JH, Zwinderman KH, de Vijlder JJ, et al. Morphological abnormalities in children with thyroidal congenital hypothyroidism. American journal of medical genetics Part A. 2009;149a(5):943-51.
17. 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(8):869-79.

18. Devos H, Rodd C, Gagné N, Laframboise R, Van Vliet G. A search for the possible molecular mechanisms of thyroid dysgenesis: sex ratios and associated malformations. The Journal of clinical endocrinology and metabolism. 1999;84(7):2502-6.
19. Chao T, Wang J-R, Hwang B. Congenital hypothyroidism and concomitant anomalies. Journal of Pediatric Endocrinology and Metabolism. 1997;10(2):217-22.
20. Castanet M, Polak M, Bonaïti-Pellié C, Lyonnet S, Czernichow P, Léger J. Nineteen years of national screening for congenital hypothyroidism: familial cases with thyroid dysgenesis suggest the involvement of genetic factors. The Journal of clinical endocrinology and metabolism. 2001;86(5):2009-14.
21. Caiulo S, Corbetta C, Di Frenna M, Medda E, De Angelis S, Rotondi D, et al. Newborn screening for congenital hypothyroidism: The benefit of using differential TSH cutoffs in a 2-screen program. J CLIN ENDOCRINOL METAB. 2021;106(1):E338-E49.
22. Law WY, Bradley DM, Lazarus JH, John R, Gregory JW. Congenital hypothyroidism in Wales (1982-1993): demographic features, clinical presentation and effects on early neurodevelopment. Clinical Endocrinology. 1998;48(2):201-7.
23. Al-Jurayyan NA, Al-Herbish AS, El-Desouki MI, Al-Nuaim AA, Abo-Bakr AM, Al-Husain MA. Congenital anomalies in infants with congenital hypothyroidism: is it a coincidental or an associated finding? Human heredity. 1997;47(1):33-7.
24. Sorcini M, Balestrazzi P, Grandolfo M, Carta S, Giovannelli G. The National Register of infants with congenital hypothyroidism detected by neonatal screening in Italy. Journal of endocrinological investigation. 1993;16(8):573-7.
25. Siebner R, Merlob P, Kaiserman I, Sack J. Congenital anomalies concomitant with persistent primary congenital hypothyroidism. American journal of medical genetics. 1992;44(1):57-60.
26. Roberts HE, Moore CA, Fernhoff PM, Brown AL, Khoury MJ. Population study of congenital hypothyroidism and associated birth defects, Atlanta, 1979-1992. Am J Med Genet. 1997;71(1):29-32.
27. Majeed-Saidan M, Joyce B, Khan M, Hamam HD. Congenital hypothyroidism: the Riyadh military hospital experience. Clinical endocrinology. 1993;38(2):191-5.
28. Cassio A, Tatò L, Colli C, Spolettini E, Costantini E, Cacciari E. Incidence of congenital malformations in congenital hypothyroidism. Screening. 1994;3(3):125-30.
29. 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(2):263-6.
30. Street ME, Bernasconi S. Endocrine-disrupting chemicals in human fetal growth. Int J Mol Sci. 2020;21(4):1430.
31. Hashemipour M, Amini M, Talaie M, Kelishadi R, Hovespian S, Iranpour R, et al. Parental consanguinity among parents of neonates with congenital hypothyroidism in Isfahan. EMHJ-Eastern Mediterranean Health Journal, 13 (3), 567-574, 2007. 2007.
32. Mehran L, Azizi F, Mousapour P, Cheraghi L, Yarahmadi S, Amirshekari G, et al. Development of a risk prediction model for early discrimination between permanent and transient congenital hypothyroidism. Endocrine. 2021;73(2):374-83.
33. Kaluarachchi DC, Allen DB, Eickhoff JC, Dawe SJ, Baker MW. Increased congenital hypothyroidism detection in preterm infants with serial newborn screening. J Pediatr. 2019;207:220-5.
34. Hashemipour M, Samei P, Kelishadi R, Hovsepian S, Hani Tabaei Zavareh N. A systematic review on the risk factors of congenital hypothyroidism. Journal of Pediatrics Review. 2019;7(4):199-210.