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Original Articles

Extra-Thyroid Congenital Abnormalities Associated with Thyroid Dysgenesis in Turkey

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Abstract A higher frequency of extra-thyroidal congenital malformations (ETCM) has been reported in children with congenital hypothyroidism (CH) compared with the general population. The most commonly reported one, congenital cardiac malformation (CCM), is reported to be in the range of 2-29% which is much higher than in normal population with a prevalence of 0.8%. Our aim is to investigate the frequency and type of additional ETCM in children with congenital hypothyroidism due to thyroid dysgenesis (TD) born between 1991 and 2013. We included 41 children with confirmed primary CH due to TD and excluded patients with Down syndrome. Age at diagnosis ranged from 4 days to 4 years. The aetiology of TD was determined with thyroid ultrasound and scintigraphy. Malformations were identified by physical examination, echocardiography abdominal/renal ultrasound and X-ray. Twenty-seven of the 41 patients had ectopic thyroid (66%), 12 had thyroid agenesis (29%) and 2 had hemiagenesis (5%). A high level of ETCM (48%, n:20) was observed. Nine patients had more than one system malformation. The most frequent malformation was CCM (22% n:9), consisting of atrial septal defect (15%, n:6), mitral insufficiency (5%, n:2), pulmonary stenosis (2%, n:1). There was a high prevalence of ETCM in patients with thyroid dysgenesis especially cardiac. Patients at least should be screened for cardiac anomalies.

Key words Abnormalities; Cardiac; Dysgenesis; Thyroid development

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Introduction

Hypothyroidism is the most frequently encountered endocrine pathology in childhood. Permanent congenital hypothyroidism constitutes 85% of all cases of hypothyroidism.[1,2] This group includes structural malformations in the thyroid gland. This entity, generally referred to as thyroid dysgenesis, includes agenesis, ectopia, hypoplasia and hemiagenesis. An increase in the incidence of additional anomalies has been reported in cases of thyroid dysgenesis (TD).[2] These may include numerous additional anomalies, from cardiac anomalies to the skeletal system. This shows that genes involved in thyroid development and differentiation are also involved in the development of other organs.

Methods

Forty-one patients aged between 0.4 and 19 years, born and monitored at the Kocaeli University, Faculty of Medicine, Department of Pediatrics during the years 1991 to 2013 were included in the study. Parents of all patients were given a form describing the study protocol and informed consent was taken. Patient data were obtained retrospectively from files. Thyroid hormone profiles were measured by immunochemiluminescence, (TSH-mIU/L) (0.6-4.5), free T4 (ng/dl) (0.88-1.72) and free T3 (pg/ml) (1.63-4.23), (reference levels denoted in parenthesis), Colour Doppler ultrasound (Phillips scanner at 7.5-12 MHz) and 99 Tc scintigraphy data were accessed at time of diagnosis for all patients. Patients were classified as athyroid, ectopic thyroid or hemiagenesis on the basis of imaging data. If the gland was not observed in its location by both imaging technique, the condition was described as athyroidism; abnormal location was considered as ectopic thyroid and cases of agenesis in any lobe were classified as hemiagenesis. Cases of thyroid hypoplasia were excluded from the study so as to evaluate the relationship between major development defect of thyroid and other organs.

Physical examination was performed to screen for additional anomalies. All patients underwent abdominal and renal ultrasound, echocardiography M-Mode and skeletal survey. Identifiable ocular findings were also recorded.

Results

We included 41 children with confirmed primary congenital hypothyroidism (CH) due to TD and excluded patients with Down syndrome. Age at diagnosis ranged from 4 days to 4 years. Twenty-seven of the 41 patients had ectopic thyroid (66%), 12 had thyroid agenesis (29%) and 2 had hemiagenesis (5%). A high level of extra-thyroidal congenital malformations (ETCM) (48%, n:20) was observed. Nine patients had more than one system malformation. The most frequent malformation was congenital cardiac malformation (CCM) (22%, n:9), consisting of atrial septal defect (ASD) (15%, n:6), mitral insufficiency (MI) (5%, n:2), pulmonary stenosis (PS) (2%, n:1). Seven patients (17%) had skeletal abnormalities, including developmental dysplasia of the hip (7%, n:3), polysyndactyly (7%, n:3), pes planus (2%, n:1) and pectus excavatum (2%, n:1). Two patients had ophthalmological abnormalities, consisting of strabismus (2%, n:1) and synkinesia (2%, n:1). Two patients (2%) had urogenital tract malformations: one with horse shoe kidney and one with testicular atrophy.

Nine patients (21%) had some dysmorphic facial features, and one had the diagnosis of Fanconi syndrome.

Mean gestational age was 38 weeks (32-41). Distribution by sex was 27 female (66%) and 14 (34%) male. Mean birth weight was 3625 g (2100-5250 g). Mean age at diagnosis was 25 days of life (4-120 days).

The most prominent clinical data were hyperbilirubinemia (34%) and constipation (20%). The medians and ranges at diagnosis for thyroid stimulating hormone (TSH) were 233 (7-987 mIU/L) and for FT4 0.5 ng/dl (0.06-1.2). Values in the ectopic group (n:27) were TSH 180±227 mIU/L and FT4 0.5±0.3 ng/dl; in the thyroid agenesis group (n:12) TSH 321±366 mIU/L and FT4 0.39± 0.22 ng/dl; and in the hemiagenesis group (n:2) TSH 461±441 mIU/L and FT4 0.84±0.5 ng/dl. A high level of ETCM (48%, n:20) was observed (Table 1) and one patient was diagnosed as Fanconi syndrome.

Moderate-severe mental retardation which was attributed to late diagnosis and delayed commencement of treatment was present in 4 (10%) of the 41 patients.

Table 1 Extra thyroidal defects in thyroid dysgenesis patients

Type of extra-thyroidal congenital malformations	%	N
I- CARDIAC defects		
• Atrial septal defect	15	6
• Mitral insufficiency	5	2
• Pulmonary stenosis	2	1
II- SKELETAL abnormalities		
• Hip (Perthes/dysplasia)	7	3
• Polysyndactyly	7	3
• Pectus excavatus	2	1
• Pes planus	2	1
II- OPHTHALMOLOGICAL		
• Strabismus	2	1
• Synkinesia	2	1
IV- RENAL		
• Horse shoe kidney	2	1
V- DYSMORPHIC appearance & syndrome	21	9
TOTAL	**48**	**20**

Discussion

We investigated additional anomalies in cases of hypothyroidism due to thyroid dysgenesis. When all anomalies were evaluated cumulatively, the incidence of additional anomaly in this patient group was 48%. This shows that defects in thyroid development affects other organs and systems and that this can be attributed to various unknown mechanisms in early embryogenesis. One study investigated defects at birth in 212 cases of thyroid agenesis and determined an incidence of 24%.[3] Although the reason for this comorbidity is not definitively understood, it may be due to the effect of the genetic component in early morphogenesis and the irregularity created by this in organ and other systems. Another mechanism may be the role of thyroid hormones in early embryogenesis.[4,5]

In agreement with previous studies[2,3,5] the pathology most commonly accompanying TD in our study, too, was cardiac defects, the most frequent being ASD. This was followed by MI and PS. Compared with the incidence of heart disease in the normal population (0.8%), the level in our study was significantly high (22%). The frequency of cardiac abnormalities in patients with TD is reported to be 2-29%.[2,6]

NKX2.5 is one of the genes responsible for thyroidogenesis and is also expressed in cardiac tissue explaining the association between thyroid and cardiac tissue.[6] In one of our previous studies we investigated mutation in genes responsible for thyroid organogenesis in 35 of our cases (unpublished data). No mutation was identified in our patients with TD and cardiac malformation.

Netrin1 (Ntn1) is another important link between heart and thyroid development. A recent study demonstrated that Ntn1a-deficient embryos displayed defective aortic arch artery formation and abnormal thyroid morphogenesis.[7]

Assessment of abdominal/renal pathologies with renal and abdominal USG performed for each patient revealed pelviectasis in 2 patients and horse shoe kidney in one. One large scale study investigating renal pathologies and urogenital tract anomalies reported a high incidence of anomaly in 1538 cases of CH compared to the normal population, at OR:13.1. Hydronephrosis, ureteropelvic junction obstruction, renal dysplasia and renal agenesis were markedly higher compared to the control group.[8] Cassio et al determined an incidence of internal renal anomaly of 0.43% in cases of congenital hypothyroidism, compared to 0.11% in cases of non-congenital hypothyroidism.[2]

Comorbid renal and thyroid anomaly can be explained biologically. PAX 8 is a gene involved in thyroid development and is also expressed in the central nervous system, mesonephric duct, ureteric bud and main collecting tubules.[1,5,9] Our 2 cases with renal anomaly had no PAX 8-related mutation

Neural tube defects are also commonly reported to be associated with TD. One study from India reported spina bifida occulta in 7 (41%) of 17 TD cases, making it the second most frequent accompanying anomaly.[4] By using vertebral X-ray for diagnosis, the frequency of spina bifida in our cases was 17%.

Eye defects reported in cases of TD include strabismus, cataract, ptosis and cranial nerve involvements[1,3] Considering the frequency of strabismus and cataracts in the general population the defects may be coincidental. Strabismus was present in one case in our series and synkinesis of the 5th-7th cranial nerves in another.

A study from Mexico reported syndromes or multiple organ involvement in 7 out of 212 cases of CH.[3] These syndromes included Hirschsprung, Albright's Hereditary Osteodystrophy, Pierre Robin sequence, Beckwith Wiedemann, VATER and frontonasal dysplasia. Although 7 of our cases had dysmorphic facial appearance, only one had a specific syndromal diagnosis, namely Fanconi syndrome.

Moderate-severe mental retardation was found in 4 of our patients, and this was attributed to late commencement of treatment associated with late diagnosis. Anomalies such as hypo-hypertelorism, epicanthal fold, depressed nasal bridge, micro-macrognathia, low-sited ears and a high-arched palate were detected in 7 of our cases. The highest reported incidence of these anomalies in normal population is 10%, and the increased frequency in TD cases (17%) shows a powerful correlation between thyroid hormone and organogenesis.[10]

The effect of thyroid hormones on bone growth is quite clear. Thyroid hormones are essential at every stage of bone growth. Defects such as delayed chondrocyte differentiation, delayed endochondral ossification and delayed linear growth occur together with TD in mouse models.[11] Severe vertebral involvement associated with late diagnosis was observed in one of our cases, and severe developmental disturbance in the form of rotatory and severe kyphosis has occurred. Syndactyly and flat arches, bilateral Perthes and polydactyly with pectus excavatum were also present. We also think that these anomalies are associated with direct and indirect effects of thyroid hormones. The

frequency of skeletal abnormalities including hip dysplasia, polysyndactyly, pectus excavatum and pes planus was 18% in our cases. This is much higher than reported in the Mexican study which was 2%.[3]

Extrathyroidal abnormalites were seen much more frequently not only in patients with dysgenesis but also dyshormonogenesis. Nineteen patients with dyshormonogenesis were evaluated for ETCM and 5 had associated extrathyroidal malformations. Two of them had urogenital malformations and the other 2 had cardiac anomalies.One patient reported to have features of dysmorphism.[12] So, this is quite clear that thyroid hormone itself besides transcription factors of thyroid development is also very important in the organogenesis of other systems of the body.

Limitation of the study is that the number of patients participating in the study is inadequate. We have found ETCM frequency around 48% in our study.This rate was reported to be 8.4% in Italy[13] 24% in Mexico[3] and 59% in South India.[4] Cardiac abnormalities is the most common associated anomaly in all studies.[3,4,13]

In conclusion, the high incidence of additional anomalies detected in cases of TD should alert all physician for detailed physical examination and investigations for associated congenital anomalies.

Declaration of Interest

No conflict of interest to declare.

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