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Increased Prevalence of Renal and Urinary Tract Anomalies in Children with Congenital Hypothyroidism

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Abstract

Objective—We investigated the prevalence of congenital renal and urologic anomalies in children with congenital hypothyroidism to determine whether further renal and urologic investigations would be of benefit.

Study design—Prevalence of congenital hypothyroidism was obtained from the New York State Congenital Malformation Registry. The occurrence of urinary tract anomalies were calculated for children with congenital hypothyroidism and compared to children without congenital hypothyroidism. In addition we obtained congenital hypothyroidism data from New York State newborn screening, and the cases were matched to Congenital Malformation Registry.

Results—Analysis of Congenital Malformation Registry data showed 980 children with congenital hypothyroidism and 3 661 585 children without congenital hypothyroidism born in New York State (1992-2005). Children with congenital hypothyroidism have a significantly increased risk of congenital renal and urological anomalies with the odds ratio (OR) of 13.2 (10.6-16.5). The other significantly increased defects in congenital hypothyroidism were cardiac, gastrointestinal, and skeletal. Analysis of matched data confirmed an increase of congenital renal and urologic anomalies with OR of 4.8 (3.7-6.3).

Conclusions—Children with congenital hypothyroidism have an increased prevalence of congenital renal and urologic anomalies. We suggest that these children should be evaluated for the presence of congenital renal and urologic anomalies with renal ultrasonography, and that further studies of common genes involved in thyroid and kidney development are warranted.

Congenital malformations are the leading cause of infant mortality in the United States.[1] Congenital hypothyroidism is the most common congenital endocrine disorder, affecting 1 in 3000 to 4000 newborns.[2] Its incidence has increased 138% from 1978 to 2005 in New York State and 73% in the US from 1987 to 2002.[3] Nearly all newborns are routinely screened for congenital hypothyroidism at birth in the United States.[4] Thyroid dysgenesis is responsible for about 85% of cases of congenital hypothyroidism; dyshormonogenesis accounts for the remaining cases.[5]

Congenital hypothyroidism is associated with increased prevalence of congenital malformations.[6-11] There are case reports of children with congenital hypothyroidism having defects in the development of the renal and urogenital systems.[12-14] However, there

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are no studies specifically examining prevalence of congenital renal and urologic anomalies in the congenital hypothyroidism population. Congenital renal and urologic anomalies are the most common cause of end-stage kidney disease in children, accounting for almost 50% of the cases.[15] Most children with congenital hypothyroidism are not routinely screened for the presence of congenital renal and urologic malformations.

Recently, mutations in PAX 8, TITF1, or FOXE1 genes have been associated with congenital hypothyroidism in patients with either isolated thyroid dysplasia or thyroid dysplasia with associated malformations involving kidney, lung, forebrain, and palate.[16-20] PAX 8 is expressed in the developing central nervous system and kidney, including the ureteric bud, mesonephric ducts, and the main collecting ducts.[17]

PAX 2 and PAX 8 transcription factors are central regulators of kidney development. In mouse pronephros and mesonephros, they are found in both the mesenchymal primordium and the epithelial components. PAX 8 expression starts at the renal vesicle stage and is maintained until the end of nephron differentiation. PAX 2 and PAX 8 genes are necessary and sufficient to induce the nephric lineage. Embryos that are mutant for both genes fail to generate the nephric (Wolffian) duct and subsequently all 3 embryonic kidneys are defective.[20,21]

We hypothesized that children with congenital hypothyroidism have an increased prevalence of congenital renal and urologic anomalies. Our objective was to compare the prevalence of renal and urinary tract anomalies in children with and without congenital hypothyroidism and to determine whether renal ultrasound scanning would be beneficial in management of children with congenital hypothyroidism.

METHODS

Prevalence data for congenital hypothyroidism and congenital anomalies was obtained from the New York State Department of Health. The Congenital Malformations Registry of the New York State Department of Health is a repository of case reports on children who are born or reside in New York State and are diagnosed before the age of 2 years with any structural, functional, or biochemical abnormality determined genetically or induced during gestation and not due to birthing events.[22]

Since there are published reports of increased incidence of malformations of other major organ systems, we also examined prevalence of congenital malformations of heart, gastrointestinal, and skeletal systems in the data set. In addition we obtained congenital hypothyroidism data from the New York State newborn screening database and matched it to the Congenital Malformation Registry data.

Statistical Analysis

Prevalence, odds ratios (OR), and 95% confidence intervals (CI) were calculated for the risk of having congenital anomalies in children with hypothyroidism and in those without. Statistical analysis was done with SAS (Cary, North Carolina).

RESULTS

There were 980 children with congenital hypothyroidism and 3 661 585 children without congenital hypothyroidism born in New York State from 1992-2005 (Table I). Children with congenital hypothyroidism had a significantly increased risk of congenital anomalies, with all ORs achieving statistical significance with $P < .0001$ (Table II).

Odds of having congenital renal and urologic anomalies were much higher in children with congenital hypothyroidism with OR of 13.2 (10.6-16.5). OR for hydronephrosis, hypospadias, and renal agenesis were especially significant as evidenced by the narrower confidence intervals. Composite ORs calculated for renal, cardiovascular, gastrointestinal, and skeletal anomalies were all highly significant, with *P* values < .0001 (Table II).

There were 1538 children with congenital hypothyroidism and 3 654 033 children without congenital hypothyroidism born in New York State from 1992 to 2005 registered in the New York State newborn screening database. A total of 418 of these (27%) matched to the Congenital Malformation Registry database. Data from the New York State newborn screening database was matched to the Congenital Malformation Registry data (Table III). Analysis of this data confirmed significantly increased prevalence of congenital renal and urological anomalies in congenital hypothyroidism with OR of 4.8(3.7-6.3). Hydronephrosis, UPJ obstruction, renal dysplasia and renal agenesis remained significantly increased in the matched data. There was, however, only 1 case of hypospadias and hydroureter in the matched data, resulting in nonsignificant OR. We observed differences in the distribution of congenital renal and urologic anomalies amongst congenital hypothyroidism and noncongenital hypothyroidism groups (Figure). Hydronephrosis was the major defect in congenital hypothyroidism population while hypospadias was most often seen in the general population. Of note, the renal and urologic anomalies seen in the congenital hypothyroid population are not discernible on a routine physical examination, but can easily be detected by a noninvasive renal ultra-sound. This is in contrast to hypospadias, which can be easily diagnosed on a routine physical examination.

DISCUSSION

Our study shows significantly increased prevalence of specific congenital renal and urologic anomalies in congenital hypothyroidism. Although Cassio et al[7] showed increased incidence of internal urogenital system malformations from 0.11% in noncongenital hypothyroidism to 0.43% in subjects with congenital hypothyroidism, these differences did not reach statistical significance, because they had only 1 child with congenital renal and urologic anomalies and the number of subjects with hypothyroidism were 235. Our findings of increased prevalence of gastrointestinal, cardiac, and skeletal anomalies among the congenital hypothyroidism group are consistent with other published reports.[6-11]

The strength of our study is that we used data from one of the largest population-based congenital malformation registries in the United States. About 80% of children in the Congenital Malformation Registry have only 1 malformation reported, but despite this we were able to demonstrate significant ORs. We further matched the data obtained from the newborn screening database to the Congenital Malformation Registry database, which confirmed the finding of increased odds of having congenital renal and urologic anomalies in children with congenital hypothyroidism.

This finding is biologically plausible, because recently there has been discovery of common genes involved in both thyroid and renal organogenesis. Pax 8 is one of these common genes expressed in the developing central nervous system and kidney, including the ureteric bud, mesonephric ducts, and the main collecting ducts. Mouse embryos that do not have Pax 8 and Pax 2 proteins fail to develop any pronephros. Pax 8 mutant mice show normal kidney development but die postnatally because of defective thyroid gland development. Bouchard et al[20] used double mutant mice embryos to show that both Pax 2 and Pax 8 work cooperatively in the development of the kidney. $Pax2^{+/-}Pax\ 8^{+/-}$embryos had hypoplastic kidneys with decreased nephric tubules and glomeruli and increased stromal component. $Pax2^{+/-}Pax\ 8^{-/-}$ embryos failed to develop a kidney, ureter, and genital tract.[16]

Another possible explanation for the multiple organ system malformations seen in children with congenital hypothyroidism could be that the thyroid hormones play an important role during early embryogenesis. However, to our knowledge there are no conclusive studies in human beings.

Limitations of our study include absence of any demographic data so we cannot make any observations about the prevalence on the basis of demographic variables. The Congenital Malformation Registry is compiled on the basis of hospital-generated data, so we may be underestimating the true prevalence of congenital renal and urologic anomalies. Another limitation of our study is that Congenital Malformation Registry is limited to children under 2 years of age, and, hence, we may be missing children who are diagnosed after that age. We do not know whether the cases of congenital hypothyroidism were transient or true hypothyroids. However, Oakley et al[8] have reported an increased incidence of congenital malformations even with transient elevation in thyroid-stimulating hormone. Another potential limitation is that we do not have any information regarding the prenatal sonograms of the subjects in our study, and we do not know the timing and the reason for postnatal sonograms. Sensitivity of prenatal sonograms in detecting hydronephrosis is 80%, and because hydronephrosis can spontaneously resolve, we do not know whether cases reported to the Congenital Malformation Registry as having hydronephrosis were transient or persistent. On the other hand it is plausible that children who had abnormal renal ultrasounds were not admitted to the hospital and thus had not been reported to the Congenital Malformation Registry, in which case we may be underestimating the true prevalence of renal/urologic anomalies.

This is an observational study, and associations can be implied, but causality cannot be proven. Despite these limitations we show that children with congenital hypothyroidism are at increased risk of having associated renal and urologic anomalies. On the basis of our results, we recommend routine postnatal screening with renal ultrasound imaging to look for renal and urologic anomalies in children with congenital hypothyroidism. Since the most common types of congenital renal and urologic anomalies in congenital hypothyroidism, not identifiable on physical examination were hydronephrosis and renal dysplasia, early detection of these defects may prevent or delay the morbidity and mortality associated with end-stage kidney disease.

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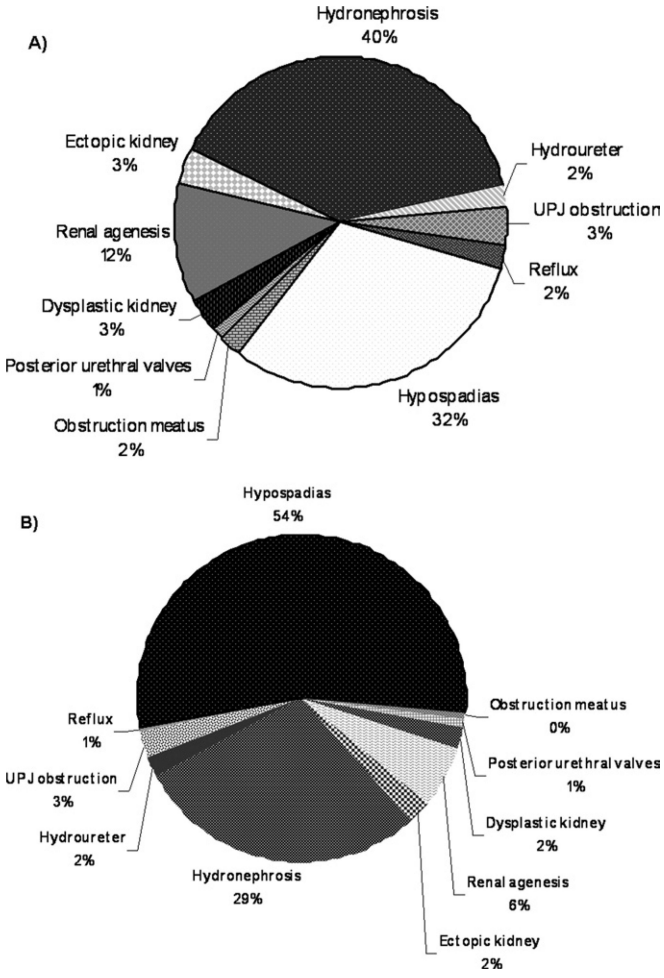

Figure.
Congenital renal anomalies in **A**, CHT and **B**, non-CHT populations.

Table I

Prevalence rates of congenital anomalies in congenital hypothyroidism (CHT) and in general population (Non-CHT)

Congenital anomalies	CHT (RATE/10 000)	Non-CHT (RATE/10 000)
Renal		
Dysplastic kidney	30.6	1.7
Renal agenesis	102	4.3
Ectopic kidney	30.6	1.7
Hydronephrosis	346.9	21.1
Hydroureter	20.4	1.5
UPJ obstruction	30.6	1.9
Reflux	20.4	0.4
Hypospadias	275.5	39.6
Obstruction meatus	20.4	0.3
Posterior urethral valves	10.2	0.7
Cardiovascular		
Atrial septal defect	622.4	29
Ventricular septal defect	602	36.6
Coarctation of aorta	81.6	4.1
Tetralogy of Fallot	183.7	4.6
Endocardial cushion defect	275.5	3.1
Gastrointestinal		
Duodenal atresia/stenosis	51	1.6
Gastroschisis	10.2	1.4
Omphalocele	40.8	1.3
Oral clefts	91.3	12.9
Pyloric stenosis	40.8	17.1
Tracheoesophageal fistula	61.2	2.4
Skeletal		
Craniosynostosis	51	4
Congenital hip dysplasia	30.6	1.7
Limb reduction	40.8	3.3

Table II

Odds ratios of congenital anomalies with 95% confidence intervals in Congenital Malformation Registry data

Congenital anomalies	CHT (n = 980)	Non-CHT (n = 3 661 585)	OR (95% CI)
Renal			
Dysplastic kidney	3	622	18.1 (5.8-56.3)
Renal agenesis	10	1574	23.9 (12.8-44.8)
Ectopic kidney	3	622	18.1 (5.8-56.3)
Hydronephrosis	34	7726	16.9 (12.1-23.9)
Hydroureter	2	549	13.6 (3.4-54.7)
UPJ obstruction	3	696	16.2 (5.2-50.3)
Reflux	2	146	51.1 (12.7-207.3)
Hypospadias	27	14 499	7.1 (4.9-10.5)
Obstruction meatus	2	110	68.1 (16.8-275.9)
Posterior urethral valves	1	256	14.6 (2.0 to 104.2)
Composite	87	26 800	13.2 (10.6-16.5)
Cardiovascular			
Atrial septal defect	61	10 619	22.8 (17.6-29.6)
Ventricular septal defect	59	13 401	17.4 (13.4-22.7)
Coarctation of aorta	8	1501	20.1 (9.9-40.3)
Tetralogy of Fallot	18	1684	40.7 (25.4-64.9)
Endocardial cushion defect	27	1135	91.4 (62.1-134.5)
Composite	173	28 340	27.5 (23.3-32.4)
Gastrointestinal			
Duodenal atresia/stenosis	5	586	32.0 (13.3 to 77.4)
Gastroschisis	1	513	7.3 (1.0-59.0)
Omphalocele	4	476	31.5 (11.8-84.5)
Oral clefts	9	4723	7.2 (3.7-13.8)
Pyloric stenosis	4	6261	2.4 (0.9-6.4)
Tracheoesophageal fistula	6	879	25.7 (11.5-57.4)
Composite	29	13 438	8.3 (5.7-11.9)
Skeletal			
Craniosynostosis	5	1464	12.8 (5.3-30.9)
Congenital hip dysplasia	3	622	18.1 (5.8-56.3)
Limb reduction	4	1208	12.4 (4.6-33.2)
Composite	12	3294	13.8 (7.8-24.4)

Table III

Odds ratios of congenital anomalies with 95% confidence intervals in data matched between Congenital Malformation Registry and New York State newborn screening database

Congenital anomalies	CHT (n = 1538)	Non-CHT (n = 3 654 033)	OR (95% CI)
Renal			
Dysplastic kidney	10	629	38.0 (20.3-71.1)
Renal agenesis	4	1631	5.8 (2.2-15.6)
Ectopic kidney	2	632	7.5 (1.9-30.2)
Hydronephrosis	30	8055	8.7 (6.0-12.6)
Hydroureter	1	564	4.2 (0.6-29.9)
Atresia/Stenosis of ureter	1	135	17.6 (2.5-126)
Hypospadias	1	14 585	0.16 (0.02-1.2)
Anterior urethral obstruction	1	31	76.7 (10.5-562.1)
UPJ obstruction	4	691	13.8 (5.2-36.9)
Composite OR	53	26 953	4.8 (3.7-6.3)
Cardiovascular			
Atrial septal defect	37	10 619	8.5 (6.1-11.7)
Ventricular septal defect	44	13 401	8.0 (5.9-10.8)
Coarctation of aorta	8	1501	15.9 (8.5-29.7)
Tetralogy of Fallot	8	1684	11.3 (5.7-22.8)
Endocardial cushion defect	10	1135	21.1 (11.3-39.3)
Composite OR	109	28 340	9.8 (8.0-11.9)
Gastrointestinal			
Duodenal atresia/stenosis	4	586	16.1 (6.1-43.5)
Oral clefts	4	4723	2.0 (0.8-5.4)
Pyloric stenosis	3	6261	1.1 (0.4-3.5)
Composite OR	11	11 570	2.3 (1.3-4.1)
Skeletal			
Craniosynostosis	1	1464	1.6 (0.2-11.5)