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Thyroid Hemiagenesis: Prevalence in Normal Children and Effect on Thyroid Function

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Thyroid hemiagenesis prevalence was studied by neck ultrasound examination in 24,032 unselected 11- to 14-yr-old schoolchildren from southeastern Sicily. Twelve cases of thyroid hemiagenesis were identified, with a prevalence of 0.05%. The female to male ratio was 1:1.4. Thyroid hemiagenesis was always due to the absence (11 cases) or severe hypoplasia (1 case) of the left lobe. The hemiagenetic thyroid volume was within the normal total thyroid volume range normalized to age in 4 of 12 cases, enlarged in 3, and significantly reduced in 5. Thyroid function (thyroid hormones and TSH, both basal and 30 min after administration of 200 μg TRH, iv) was evaluated in 9 of 12 children and was always within the normal range. However, children with thyroid hemiagenesis had an average serum TSH significantly higher than that of 18 matched controls (2.8 ± 0.6 *vs.* 1.9 ± 0.5 mU/liter; $P < 0.001$). This study confirms that thyroid hemiagenesis is nearly always due to left lobe defect, and that its prevalence is similar to the cumulative prevalence of thyroid agenesis and ectopia. Compensatory hypertrophy of the residual thyroid lobe occurs in most, but not all, cases and is due to thyroid tissue overstimulation by TSH. The high risk of goiter and hypothyroidism suggests systematic follow-up of all identified cases of thyroid hemiagenesis. (*J Clin Endocrinol Metab* 88: 1534–1536, 2003)

THYROID HEMIAGENESIS IS a rare congenital abnormality in which one thyroid lobe fails to develop. The true prevalence of this congenital abnormality is uncertain because the absence of one thyroid lobe usually does not cause clinical symptoms by itself. Therefore, only the coincidental presence of other thyroid diseases leads to the occasional detection of thyroid hemiagenesis. This has led to the erroneous conclusion that thyroid hemiagenesis is more frequent in the female sex, because of a selection bias due to the fact that thyroid diseases are more frequent in women. In addition, as most epidemiological studies (based on autopsy, surgery, and imaging) have been carried out in adults, when postinflammatory sclerosis of one thyroid lobe may have occurred, a pathological bias is also possible for epidemiological studies.

A large meta-analysis (1) has estimated a 0.05% prevalence of thyroid hemiagenesis. Very recently, an ultrasound study in 2,845 schoolchildren has reported a 0.2% prevalence (2). We now report the first systematic thyroid ultrasound study in a large cohort of 24,032 unselected 11- to 14-yr-old schoolchildren living in southeastern Sicily. A prevalence of 0.05% of thyroid hemiagenesis was observed.

Subjects and Methods

Schoolchildren (n = 24,032 ; 11,752 males and 12,280 females), aged 11–14 yr, all attending primary school in southeastern Sicily were evaluated by thyroid ultrasound examination during a survey for iodine deficiency goiter in Sicily. The survey was carried out between December 1999 and June 2001. Review board approval was obtained as well as written informed consent from parents of the children studied. Age, weight, and height were recorded for all children. Thyroid volume and morphology were investigated by a 7.5-MHz linear transducer. The length, width, and depth of each lobe were measured, and the volume was calculated by the mean of the elliptical shape volume formula ($\pi/6 \times$ length $\times$ width $\times$ depth). Reference values for thyroid volume in children were obtained from the literature (3), and values normalized to the individual body surface were also considered (4). Thyroid hemiagenesis was defined as either the total absence (11 of 12 cases) or severe hypoplasia of 1 thyroid lobe (<1/10th of the normal thyroid lobe volume for the subject age, 1 in 12 cases). In all cases of thyroid hemiagenesis we calculated the thyroid volume and compared it to normal total thyroid volume for subject age and also to its half value in order to evaluate the residual hemiagenetic thyroid volume in comparison with the volume of a normal single thyroid lobe. In all subjects with thyroid hemiagenesis a careful family history for goiter and thyroid diseases was carried out. Thyroid function was studied in 9 of 12 of these children (3 refused to enter the biochemical study) by measuring thyroid hormones [free T_4 (FT_4) and free T_3 (FT_3)] and thyroid antibodies (antithyroid peroxidase and antithyroglobulin) by commercially available methods. Serum TSH was measured under basal conditions and 30 min after administration of TRH (200 μg, iv) by an ultrasensitive method (TSH Axsym, Abbott Laboratories, Inc., Rome, Italy). The same measurements (except the TRH test) were carried out in a group of 18 children, matched for sex and age, born and living in southeastern Sicily and with normal thyroid glands.

Results

Among the 24,032 schoolchildren examined, 12 cases of thyroid hemiagenesis were identified, indicating a prevalence of thyroid hemiagenesis of 1 in 2,000 (0.05%). As an area of moderate iodine deficiency is present in eastern Sicily (5, 6), we analyzed whether this abnormality was more frequent in the endemic areas. Three cases of thyroid hemiagenesis were observed among the 2,986 children living in the endemic area (1:995), a prevalence higher than that observed in the iodine-sufficient area (1:2,338). The difference, however, is not statistically significant at the χ^2 test ($P = 0.186$). A history of thyroid diseases in the family (at least 1 individual among relatives up to the third grade) was present in 4 children.

Abbreviations: FT_3, Free T_3; FT_4, free T_4.

TABLE 1. Clinical, biochemical, and thyroid ultrasound measurements in children with thyroid hemiagenesis

Patient	Sex	Age	Thyroid volume (ml)		Normal total thyroid volume (ml) (normalized for age)	Hemiagenetic thyroid volume with respect to normal total thyroid volume[a]	Living in iodine-deficient area	Familiarity for thyroid diseases[b]	Serum TSH[c] (mU/liter)		FT_4[c] (pmol/liter)	FT_3[c] (pmol/liter)
			Left lobe	Right lobe					Basal	30 min after TRH		
1	M	11.0	0	3.0	4.9 ± 1.5	R	+	n.a.	/	/	/	/
2	F	12.1	0	6.2	5.3 ± 1.4	N	−	+	3.6	24.7	11.5	4.0
3	M	12.0	0	2.6	5.3 ± 1.4	R	−	−	3.0	/	14.2	6.1
4	F	12.1	0	4.0	5.3 ± 1.4	N	−	n.a.	/	/	/	/
5	F	12.0	0	3.2	5.3 ± 1.4	R	−	n.a.	/	/	/	/
6	M	12.0	0	7.5	5.3 ± 1.4	E	+	+	2.3	/	11.5	6.1
7	M	12.5	0	4.4	5.3 ± 1.4	N	+	−	3.5	19.2	12.8	6.3
8	F	12.5	0.76	2.4	5.3 ± 1.4	R	−	−	2.5	21.2	15.4	4.4
9	F	13.0	0	6.2	6.1 ± 1.6	N	−	+	3.7	25.6	14.2	4.9
10	M	13.1	0	4.2	6.1 ± 1.6	R	−	−	2.3	13.2	11.5	5.1
11	M	13.6	0	9.3	6.1 ± 1.6	E	−	+	2.2	8.2	15.4	5.8
12	M	14.3	0	12.3	6.3 ± 1.5	E	−	−	3.0	17.5	11.5	6.4

M, Male; F, female; n.a., not assessed.
[a] N, Normal (within average value for age ± 1 SD); R, reduced; E, enlarged.
[b] At least one individual among relatives up to the third grade.
[c] Normal values for: TSH, 0.49–4.67 mU/liter; FT_4, 9.1–23.8 pmol/liter; FT_3, 2.2–5.4 pmol/liter.

Seven of 12 hemiagenesis cases occurred in male children, with a female to male ratio of 1:1.4 (0.71), which is in contrast with previous data in the literature (1, 7, 8). The relative prevalence of thyroid hemiagenesis in our cohort was 1:1,678 (0.06%) among males and 1: 2,456 (0.04%) among females. The difference between male and female prevalence was not statistically significant at the χ^2 test ($P = 0.527$).

According to the already reported observations, thyroid hemiagenesis was nearly always due to agenesis of the left thyroid lobe. In our series the left lobe was completely absent in 11 children and severely hypoplasic in the remaining subject. The hemiagenetic thyroid was within the normal total thyroid volume (average value normalized for patient age ± 1 SD) (3) in 4 of 12 cases; it was enlarged in 3 subjects (no. 6, 11, and 12), and it was significantly reduced in 5 cases (no. 1, 3, 5, 8, and 10). In most cases (7 of 12) a compensatory hypertrophy of the right lobe occurred if compared with half the normal total thyroid volume; in 3 subjects (no. 6, 11, and 12) it reached the relevance of a monolateral diffuse goiter (Table 1).

Although thyroid function measurements were within the normal range in all children with thyroid hemiagenesis, both average serum TSH value and average FT_3 serum value were significantly higher compared with those in the control group [TSH, 2.8 ± 0.6 *vs.* 1.9 ± 0.5 mU/liter ($P < 0.001$); FT_3, 5.5 ± 0.8 *vs.* 4.5 ± 1.1 pmol/liter ($P = 0.01$); Table 2]. There was no difference in FT_4 values in the two groups (14.1 ± 2.6 *vs.* 14.1 ± 2.6 pmol/liter). Thyroid antibodies were negative in all but one subject with a hemiagenetic thyroid (antithyroglobulin antibodies, 165.0 IU/ml) as well as in all control children.

TABLE 2. Serum TSH and thyroid hormones in children with thyroid hemiagenesis and control children

	Children with thyroid hemiagenesis (n = 9)	Control children (n = 18)	*P*
TSH (mU/liter)	2.8 ± 0.6	1.9 ± 0.5	<0.001
FT_4 (pmol/liter)	14.1 ± 2.6	14.1 ± 2.6	0.78
FT_3 (pmol/liter)	5.5 ± 0.8	4.5 ± 1.1	0.01

Discussion

Thyroid hemiagenesis is a morphological abnormality once considered very rare (9), but that actually occurs rather frequently; a recent review of the literature indicates an estimated prevalence between 1 in 1,900 and 1 in 2,675 (1), similar to that calculated for congenital hypothyroidism due to agenesis or ectopia of the thyroid. The incidence of hemiagenesis in the normal population was expected to increase with the widespread use of thyroid ultrasound; however, our study using thyroid ultrasound screening of a large sample (>24,000) of 11- to 14-yr-old schoolchildren, has confirmed the previous reported prevalence (0.05% or 1:2,000). By screening healthy children attending secondary school, we have avoided the possible bias due to selection for either gender or pathology. Most previous studies were based on observations in adult patients affected by thyroid diseases, studied in hospitals and thyroid centers. The higher estimated prevalence of thyroid hemiagenesis in women, therefore, was a possible consequence of the fact that thyroid diseases are more frequent in women than in men. In fact, when the estimated ratio was recalculated based on equal numbers of females and males, the female to male ratio was 1.3:1 (1). By systematic screening of a population of normal children we actually observed a higher prevalence of thyroid hemiagenesis in males (male to female ratio, 1.4:1.0). By studying children we have also greatly reduced the possibility of classifying as hemiagenesis the presence of a single thyroid lobe caused by a pathological process earlier in life, resulting in fibrotic atrophy of one thyroid lobe.

The cause(s) of the abnormal development of the thyroid that leads to thyroid hemiagenesis is not known. It must first be underlined that the large majority of thyroid hemiagenesis is due to the lack of the left lobe. In many normal subjects the thyroid is asymmetric, with the right lobe larger in size in respect to the left lobe. Thyroid hemiagenesis, therefore, could be considered an exaggeration of this difference, producing an extreme asymmetry of the thyroid gland because

of some imbalance in the descent and/or development of the bilobed gland during embryogenesis. The thyroid gland develops from a duct-like invagination of the primitive pharynx endoderm and expands ventrally along the thyroglossal duct line as a spherical thyroid gland primordium. Only at the end of the second month does the thyroid rudiment begin to expand laterally and acquire the bilobed structure (10). It is unknown whether disturbance of the lobulation process is due to the interference of environmental factors or to some genetic abnormality. A genetic component is suggested by the occurrence of thyroid hemiagenesis among monozygotic twins (11), among members of the same family (12), and together with other thyroid (13) or other neck structure pathological conditions (14). Several genes are known to control thyroid descent, development, and morphogenesis (15, 16), but these genes have not been investigated in thyroid hemiagenesis. In our series of asymptomatic children with hemiagenetic thyroid, we observed an association with thyroid diseases (hypothyroidism, hyperthyroidism, or multinodular goiter) in one or more relatives up to the third grade in four of nine cases studied. This association is not significantly higher than that in the control population. We also observed a higher prevalence of hemiagenesis in children born and living in areas with mild iodine deficiency, but this difference also does not reach statistical significance because of the small number of cases. In most subjects with thyroid hemiagenesis we observed a compensatory hypertrophy of the right lobe. Among the three children with hemiagenetic thyroid goiter, two had familiarity for thyroid disease, and one was from an iodine-deficient area. The thyroid lobe enlargement was a likely consequence of thyroid tissue overstimulation by endogenous TSH; although thyroid function was within the normal range in all subjects studied, the average serum TSH and FT_3 values were significantly higher in children with thyroid hemiagenesis than in control children. The compensatory hypertrophy, however, did not occur in all subjects: in five cases the hemiagenetic thyroid size roughly corresponded to the volume of a single normal thyroid lobe. Serum TSH levels, in these subjects, were not different from those in subjects without thyroid volume reduction. Overstimulation, therefore, occurred in these subjects also, but it was unable to cause thyroid hypertrophy. These observations suggest that different situations may occur in different patients and suggest that different causes may be involved in the pathogenesis of thyroid hemiagenesia.

One last comment regards thyroid function in the presence of thyroid hemiagenesis. Although these subjects cannot be considered as affected by subclinical hypothyroidism, they certainly have a pituitary-thyroid axis set at a different level. This may be the reason for the higher frequency of hypothyroidism or other thyroid diseases in adult patients with thyroid hemiagenesis (1, 17–19). We have previously reported (20) a high prevalence (10.7%) of hemiagenesis in a group of 56 newborns who were identified at neonatal screening with congenital hyperthyreotropinemia and with persistent high serum TSH values (>4 mU/liter) at 2–3 yr of age, during a period of life when thyroid function is critical for physical and mental development.

Our studies indicate that thyroid hemiagenesis in most cases has a causative effect, producing subtle abnormalities of thyroid function that, in the absence of other intervening factors, are not clinically relevant, although they maintain the subject in a situation of thyroid tissue overstimulation. We would recommend systematic follow-up of all identified cases of thyroid hemiagenesis because of the high risk of goiter and hypothyroidism. Treatment should be limited only to subjects with either a hemiagenetic goiter or documented functional abnormalities.

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References

1. **Mikosh P, Gallowitsch HJ, Kresnik E, Molnar M, Gomez I, Lind P** 1999 Thyroid hemiagenesis in an endemic goiter area diagnosed by ultrasonography: report of sixteen patients. Thyroid 9:1075–1084
2. **Shabana W, Delange F, Freson M, Osteaux M, De Shepper J** 2000 Prevalence of thyroid hemiagenesis: ultrasound screening in normal children. Eur J Pediatr 59:456–458
3. **Vitti P, Martino E, Aghini-Lombardi F, Rago T, Antonangeli L, Maccherini D, Nanni P, Loviselli A, Balestrieri A, Araneo G, Pinchera A** 1994 Thyroid volume measurements by ultrasound in children as a tool for the assessment of mild iodine deficiency. J Clin Endocrinol Metab 70:600–603
4. **WHO and International Council for Control of Iodine Deficiency Disorders.** 1997 Recommended normative values for thyroid volume in children aged 6–15 years. Bull WHO 75:95–97
5. **Vigneri R** 1988 Studies on the goiter endemia in Sicily. J Endocrinol Invest 11:831–843
6. **Trimarchi F, Vermiglio F, Finocchiaro MD, Battiato S, Lo Presti VP, La Torre N, Calaciura F, Regalbuto C, Sava L, Vigneri R** 1990 Epidemiology and clinical characteristics of endemic cretinism in Sicily. J Endocrinol Invest 13:543–548
7. **Melnick JC, Stemkowski PE** 1981 Thyroid hemiagenesis (hockey stick sign): a review of the world literature and a report of four cases. J Clin Endocrinol Metab 52:247–251
8. **Bergami G, Barbuti D, Di Mario M** 1995 Echographic diagnosis of thyroid hemiagenesis. Minerva Endocrinol 20:195–198
9. **Mc Henry CR, Walfish PG, Rosen IB, Lawrence AM, Palnyan E** 1993 Congenital thyroid hemiagenesis. Am Surg 61:634–639
10. **Pintar JE** 2000 Normal development of the hypotalamic-pituitary thyroid axis. In: Braverman LE, Utiger RD, eds. The thyroid. Philadelphia: Lippincott Williams & Wilkins; vol 2:7–19
11. **McLean R, Howard N, Murray IP** 1985 Thyroid dysgenesis in monozygotic twins: variants identified by scintigraphy. Eur J Nucl Med 10:346–348
12. **Rajmil Ho, Rodriguez-Espinosa J, Soldevila J, Ordonez-Llanos J** 1984 Thyroid hemiagenesis in two sisters. J Endocrinol Invest 7:393–394
13. **Rosemberg T, Gilhoa Y** 1980 Familial thyroid ectopy and hemiagenesis. Arch Dis Child 8:6–39
14. **Woods RH, Laury M** 1992 Thyroid hemiagenesis in a patient with parathyroid adenoma. Otolaryng Head Neck Surg 5:469–471
15. **Fabbro D, Pelizari L, Teli G, Damante G** 1998 Pax-8 protein levels regulate thyroglobulin gene expressions. J Mol Endocrinol 12:1100–1105
16. **Macchia PE, Mattei MG, Lapi P, Fenzi G, Di Lauro R** 1999 Cloning chromosomal localization and identification of polymorphism's in the human thyroid transcription factor 2 gene TTF2). Biochemie 81:433–440
17. **Burmann KD, Adler RA, Wartofsky L** 1975 Hemiagenesis of the thyroid gland. Am J Med 58:143–146
18. **Mortimer PS, Tomlinson TW, Rosenthal FD** 1981 Hemiaplasia of the thyroid with thyrotoxicosis. J Clin Endocrinol Metab 52:152–155
19. **Shibutani Y, Inoue D, Koshiyama H, Mori T** 1995 Thyroid hemiagenesis with subacute thyroiditis. Thyroid 5:133–135
20. **Calaciura F, Motta RM, Miscio G, Fichera G, Leonardi D, Carta A, Trischitta V, Tassi V, Sava L, Vigneri R** 2002 Subclinical hypothyroidism in early childhood: a frequent outcome of transient neonatal hyperthyrotropinemia. J Clin Endocrinol Metab 87:3209–3214