

CLINICAL STUDY

Risk factors for congenital hypothyroidism: results of a population case-control study (1997–2003)

Emanuela Medda, Antonella Olivieri¹, Maria Antonietta Stazi, Michele E Grandolfo, Cristina Fazzini¹, Mariangiola Baserga², Massimo Burroni⁴, Emanuele Cacciari⁵, Francesca Calaciura⁶, Alessandra Cassio⁵, Luca Chiovato⁷, Pietro Costa⁸, Daniela Leonardi⁶, Maria Martucci³, Lidia Moschini⁸, Severo Pagliardini⁹, Giuseppe Parlato³, Alberto Pignero¹⁰, Aldo Pinchera¹¹, Danielle Sala¹⁰, Lidia Sava⁶, Vera Stoppioni⁴, Francesco Tancredi¹⁰, Fabiola Valentini⁸, Riccardo Vigneri⁶ and Mariella Sorcini¹

Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute and ¹Dipartimento di Biologia Cellulare e Neuroscienze, Istituto Superiore di Sanità, Rome, Italy, ²Istituto di Pediatria and ³Servizio di Chimica Clinica, Facoltà di Medicina e Chirurgia, Università di Catanzaro, Catanzaro, Italy, ⁴Neuropsichiatria Infantile, Ospedale, Fano, Italy, ⁵Clinica Pediatrica Università di Bologna, Bologna, Italy, ⁶Cattedra di Endocrinologia, Università di Catania, Catania, Italy, ⁷IRCCS Mangeri, Università di Pavia, Pavia, Italy, ⁸Dipartimento Scienze Ginecologiche Perinatologia e Puericultura, Università 'La Sapienza', Rome, Italy and ⁹Dipartimento di Patologia Clinica A.O. OIRM, S. Anna, Turin, Italy, ¹⁰Centro Screening, Ospedale S.S. Annunziata, Naples, Italy ¹¹Dipartimento di Endocrinologia e Metabolismo, Ortopedia e Traumatologia, Medicina del Lavoro, Università di Pisa, Pisa, Italy

(Correspondence should be addressed to M Sorcini, Dipartimento di Biologia Cellulare e Neuroscienze, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy; Email: olivieri@iss.it)

Abstract

Objective: To identify risk factors for permanent and transient congenital hypothyroidism (CH).
Design: A population-based case-control study was carried out by using the network created in Italy for the National Register of Infants with CH.
Methods: Four controls were enrolled for each new CH infant; 173 cases and 690 controls were enrolled in 4 years. In order to distinguish among risk factors for permanent and transient CH, diagnosis was re-evaluated 3 years after enrolment when there was a suspicion of transient CH being present. Familial, maternal, neonatal and environmental influences were investigated.
Results: An increased risk for permanent CH was detected in twins by a multivariate analysis (odds ratio (OR) = 12.2, 95% confidence interval (CI): 2.4–62.3). A statistically significant association with additional birth defects, female gender and gestational age >40 weeks was also confirmed. Although not significant, an increased risk of CH was observed among infants with a family history of thyroid diseases among parents (OR = 1.9, 95% CI: 0.7–5.2). Maternal diabetes was also found to be slightly associated with permanent CH (OR = 15.7, 95% CI: 0.9–523) in infants who were large for gestational age. With regard to transient CH, intrauterine growth retardation and preterm delivery were independent risk factors for this form of CH.
Conclusion: This study showed that many risk factors contribute to the aetiology of CH. In particular, our results suggested a multifactorial origin of CH in which genetic and environmental factors play a role in the development of the disease.

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Introduction

Screening programmes for congenital hypothyroidism (CH), which have been extensively implemented in developed countries, provide the opportunity to investigate the aetiology and the pathogenesis of CH (1, 2). In Italy, where the CH incidence is 1:3100 live births, neonatal screening for CH was established in 1977 and then progressively developed all over the country. All the Italian centres in charge of screening, treatment and follow-up of CH infants participate in the Italian National Register of Infants with CH (INRICH) which was established in 1987 as a programme of the

Health Ministry. Information on CH infants, including results of screening and confirmation tests, demographic data, assessment of clinical state in the neonatal period, birth and family background, maternal history during pregnancy, diagnostic investigation, onset and dose of replacement therapy, is collected by the INRICH (3). The aim of the register is to provide disease surveillance, to monitor efficiency and effectiveness of neonatal screening and to allow identification of possible aetiological risk factors for CH.

The majority of patients with CH are characterized by dysgenesis of the thyroid gland represented by complete absence of the thyroid (agenesis), ectopic or

hypoplastic gland (4, 5). Inherited defects of thyroid hormone biosynthesis, secretion and utilization represent a minor fraction of all CH cases (6). The identification of genes related to gland organogenesis or thyroid hormone biosynthesis has allowed the formulation of hypotheses on molecular mechanisms causing CH. Mutations of the human thyrotrophin receptor gene are considered a possible cause of hypoplasia and persistent CH (7–9). Mutations of the PAX8 gene have been found in familial as well as in sporadic cases of thyroid dysgenesis (10). Again, mutations of thyroglobulin and thyroid peroxidase genes are reported to be responsible for defects in the synthesis or iodination of thyroid hormones (11, 12). More recently, mutations in the THOX2 gene, encoding part of the thyroid oxidase system, have been reported to result in disruption of thyroid-hormone synthesis and associated with transient and permanent CH (13). However, as the occurrence of genetic mutations has been observed only in a small proportion of the patients, the aetiology of CH due to thyroid dysgenesis is still largely unknown. Hence, it is clear that the investigation of modifiable risk factors for CH is important because of the potential to prevent CH. To date, many authors have consistently reported that females have about twice the prevalence of males and that birth prevalence of CH is lower in black subjects and higher in Asian and Hispanic subjects (14–17).

Also an increased birth weight has been reported to be associated with CH (17–19) but no other risk factors, such as maternal or familial risk factors, have been identified.

The results of a population-based case-control study are presented in this paper. Familial, maternal and neonatal exposure was investigated with the aim of identifying the most important risk factors for permanent and transient CH.

Subjects and methods

Enrolment

Twenty-six regional or inter-regional CH screening centres operate in Italy. Eight of these centres were selected to participate in the study. These were considered representative of the whole country for their geographical location and for the high number of screened infants every year. In fact, these eight centres are in the north, centre and south of Italy and the total number of CH infants who were diagnosed in these centres represented about 30% of the total number of CH infants recorded in the INRICH during the study period.

The study enrolment started in 1997 and was carried out for 4 years. Only newly diagnosed cases of CH screened by the selected centres were included in the study. The screening test for CH was performed on dried blood spots and thyroid-stimulating hormone (TSH) and thyroxine (T4) were measured. The positive results of the first screening test were then confirmed by serum TSH, T4 and free T4. Infants with a normalization of TSH between screening and recall were not included in the sample because infants who do not start substitutive therapy are not recorded in the INRICH.

Four controls were then enrolled for each new CH case. These controls were the first four infants born in the same maternity clinic where a new CH case was born. They were recruited a few days after the CH diagnosis was confirmed. Cases and controls included in the study were resident in the same region where the screening centres were located. Parents were interviewed by a trained physician and gave their informed consent for participation in the study. Their socio-economic level was assessed by evaluation of education and occupation level. The mother's reproductive history as well as the present pregnancy were investigated. Information on threatened abortion, gestational diabetes and smoking habits were recorded to assess the effect of these factors during pregnancy. Neonatal features of cases and controls were collected directly from medical records. An extensive family history of metabolic and autoimmune disorders was also recorded. Thyroid ultrasound and/or scintigraphy were performed in most of the CH cases.

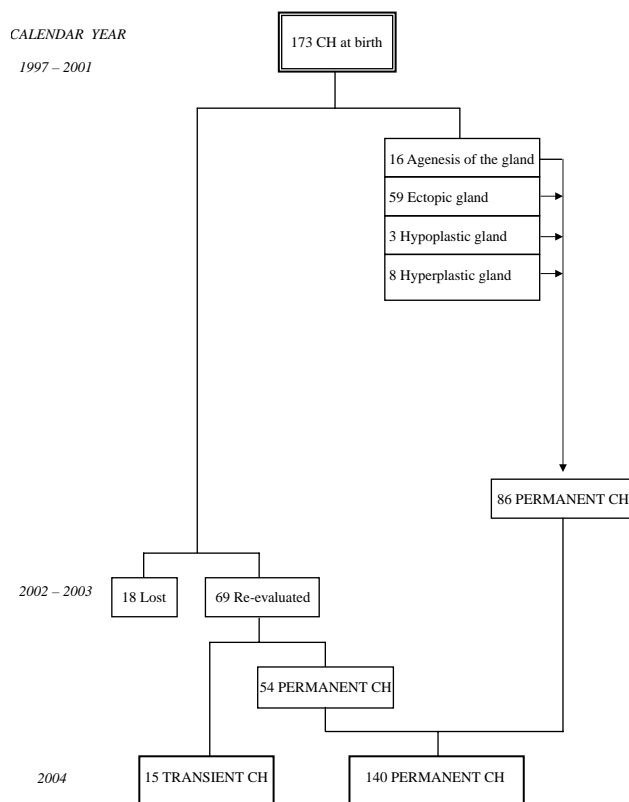


Figure 1 Enrolment procedure for cases.

Case definition

The enrolment was carried out for 4 years and the study ended in 2003 when all the cases were at least 3 years old. Cases were classified as permanent or transient CH on the basis of diagnosis re-evaluation performed at 2–3 years of age after withdrawal of replacement therapy according to international guidelines (20). Children for whom there was no information about the persistence of CH were not included in the analysis.

Statistical analysis

Analyses by two-by-two contingency tables were performed to estimate the association between CH (permanent and transient) and possible risk factors. Continuous variables were categorized according to biological considerations or to conventional cut-off points. Matched crude odds ratios (OR) were estimated by the Mantel–Haenszel method. The Mantel–Haenszel summary χ^2 test was used to test the significance of the matched ORs. A conditional logistic regression was performed to evaluate the adjusted effect of the considered variables on the risk of being a CH case.

Results

During the first 4 years of the study 173 cases and 690 controls were enrolled. As shown in Fig. 1, 140 permanent CH cases with 559 matched controls, as well as 15 transient CH infants with 60 matched controls were considered for statistical analysis.

The distribution of clinical signs at birth and scintigraphy and/or ultrasound findings of CH cases enrolled in this study were consistent with those of the CH Italian population recorded in the INRICH. In this case-control study, a thyroid scan with ^{99}Tc was performed before the onset of therapy in 70.7% of the permanent cases; among these, ectopic gland was 57.6%, eutopic gland 17.2% and agenesis 25.2%.

Permanent CH

Table 1 shows the selected demographic and neonatal characteristics of permanent and transient CH cases compared with their matched controls. With regard to permanent CH, the mother's age at delivery was slightly higher in CH cases than in controls (8.6 vs 4.3%; age at delivery ≥ 40 years). Both parents of the cases reported a lower, although not statistically significant, level of education than that observed in the control group (37.8 vs 30.8%). No differences in risk factors related to pregnancy (parity, previous spontaneous abortion, threatened abortion, gestational diabetes and smoking) were observed between the two groups.

With regard to neonatal risk factors, the frequency of females was significantly higher in the permanent CH infants than in the control group ($P < 0.01$). Also an advanced gestational age was significantly associated with permanent CH. In fact, 35.2% of permanent CH infants were born after 40 weeks of gestation as compared with 15.9% of the controls ($P < 0.01$). Overall, no statistically significant difference was found in birth weight between cases and controls, although a higher percentage of cases than controls was observed in the extreme weight classes. Moreover, the distribution of sex-adjusted OR for birth weight showed a high risk of CH among infants with low (≤ 2000 g; OR = 4.3, 95% confidence interval (CI): 0.6–32) or high (≥ 4500 g; OR = 9.7, 95% CI: 0.8–111) birth weight. In this analysis, birth weight ranging between 3001 and 3500 g was considered to be the reference category. Infants were also classified using the normal curve (21) as small for gestational age (SGA) when weights were below the 10th centile, normal for gestational age (NGA) when weights were between the 10th and 90th centile and large for gestational age (LGA) for those above the 90th centile. The percentage distribution reported in Table 1 did not show significant differences between cases and controls although the percentage of SGA infants was slightly higher among cases and LGA infants were more frequent among controls. However, to verify whether high birth weight for gestational age in the permanent CH cases may be associated with maternal diabetes during pregnancy, a restricted analysis on CH infants with a birth weight above the 90th centile was performed. The estimated OR of permanent CH was 15.7 (95% CI: 0.9–523) in the cases whose mothers had diabetes during pregnancy.

With regard to the other neonatal features, a higher frequency of twinning was observed among cases compared with controls (5.1 vs 0.7%, $P < 0.01$). Neonatal and clinical features of CH twins enrolled into the study are presented in Table 2. None of the seven permanent CH twins belonged to the same pair and two of them were monozygotic (MZ). Ultrasound and/or ultrascan diagnosis was performed on six permanent CH twins. Among these, three eutopic glands, two ectopies and one agenesis were found.

On the basis of the results obtained in our previous study (22), an expected high frequency of additional birth defects was found in permanent CH cases while the control infants showed a frequency similar to that expected in the general population (14.3 vs 2.1%, $P < 0.01$). Among the observed malformations the most frequent were cardiac in both cases and controls (60 and 40% respectively). As already described (22), a higher frequency of infants with atrial septal defects was found in cases than in controls (42.1 vs 16.7%).

Table 1 Demographic and neonatal characteristics of permanent and transient CH cases and matched controls.

Characteristic	Permanent CH					Transient CH				
	Cases (n = 140)		Controls (n = 559)		P	Cases (n = 15)		Controls (n = 60)		P
	n	%	n	%		n	%	n	%	
Socio-demographic factors										
Mother's age										
≤ 25 years	18	12.9	64	11.4		5	33.3	9	15.0	
25–39 years	109	78.4	471	84.3		9	60.0	48	80.0	
≥ 40 years	12	8.6	24	4.3	0.09*	1	6.7	3	5.0	0.24*
Parent's education ≤ 8 years	51	37.8	171	30.8	0.12	9	60.0	24	40.7	0.18
Consanguinity	2	1.5	8	1.5	0.99	0	—	2	3.4	—
Pregnancy										
First pregnancy	75	57.2	321	58.6	0.78	7	46.7	33	55.9	0.52
Previous spontaneous abortion	29	22.1	109	20.1	0.61	2	13.3	11	19.3	0.59
Threatened abortion	16	11.5	83	14.9	0.31	2	13.3	14	23.3	0.40
Gestational diabetes	4	2.9	16	2.9	0.99	1	6.7	0	—	—
Smoking	15	11.0	79	14.2	0.34	1	6.7	12	20.0	0.22
Neonatal characteristics										
Femal gender	88	62.9	271	48.5	<0.01	5	33.3	27	45.0	0.41
Gestational age										
< 37 weeks	9	7.0	24	4.6		4	26.7	3	5.0	
37–40 weeks	74	57.8	411	79.5		8	53.3	47	78.3	
≥ 41 weeks	45	35.2	82	15.9	<0.01*	3	20.0	10	16.7	0.02*
Birth weight										
< 2500 g	9	6.6	30	5.4		4	26.7	5	8.3	
2500–3500 g	84	61.3	346	61.9		6	40.0	32	53.3	
3500–4500 g	42	30.7	182	32.6		5	33.3	22	36.7	
> 4500 g	2	1.5	1	0.2	0.20*	0	—	1	1.7	0.25*
Small for gestational age	17	13.5	55	10.6	0.36	5	33.3	7	11.7	0.04
Large for gestational age	8	6.3	48	9.3	0.29	1	6.7	3	5.0	0.80
Twin	7	5.1	4	0.7	<0.01	4	26.7	0	—	—
Additional birth defects	20	14.3	12	2.1	<0.01	0	—	0	—	—

* Overall χ^2 test.

None of the other neonatal or pregnancy-related risk factors considered in the analysis was associated with permanent CH.

Familial risk factors were also investigated. With regard to the family history of thyroid diseases (Table 3),

no differences were observed in the frequency of hyperthyroidism in parents between cases and controls (0.8 vs 1.7%, $P = 0.47$). However, permanent CH cases were more likely to have parents with hypothyroidism and/or goitre (including hypothyroidism due to an

Table 2 Neonatal and clinical features of CH twins enrolled in the study.

	Mother's age (years)	Gender	Birth weight (g)	Gestational age (weeks)	Zygoisty†	Birth defects	Thyreopathy in parents	Ultrascan and/or ultrasound diagnosis
Permanent CH twins								
1	28	Male	3150	42	MZ	No	No	Ectopy
2	35	Female	2850	38	DZ	No	No	Eutopic gland
3	43	Female	2540	38	MZ	No	No	Agnesis
4	33	Female	2370	38	DZ	No	No	Ectopy
5	25	Female	880	31	DZ	No	No	Eutopic gland
6	34	Female	2750	37	DZ	No	No	—
7	17	Female	2990	38	DZ	No	No	Eutopic gland
Transient CH twins								
1	36	Female	2810	38	MZ	No	No	Eutopic gland
2*	23	Female	2000	35	DZ	No	No	—
3*	23	Female	1680	35	DZ	No	No	—
4*	23	Male	2410	35	DZ	No	No	—

* Concordant triplets.

† MZ, monozygotic and DZ, dizygotic twins.

Table 3 Family history of diseases in permanent and transient CH.

Family history	Permanent CH					Transient CH				
	Cases (n = 140)		Controls (n = 559)		P	Cases (n = 15)		Controls (n = 60)		P
	n	%	n	%		n	%	n	%	
Hyperthyroidism										
Parents	1	0.8	9	1.7	0.47	0	—	0	—	—
Mother	1	0.8	9	1.6	0.48	—	—	—	—	—
Father	0	—	1	0.2	0.63	—	—	—	—	—
Hypothyroidism and/or goitre										
Parents	9	7.1	17	3.2	0.04	3	20.0	1	1.7	<0.01
Mother	6	4.7	15	2.7	0.25	3	20.0	1	1.7	<0.01
Father	3	2.4	2	0.4	0.02	0	—	0	—	—
Autoimmune diseases										
Parents	2	1.6	11	2.1	0.74	2	13.3	0	—	—
Mother	1	0.8	8	1.5	0.56	2	13.3	0	—	—
Father	1	0.8	3	0.6	0.76	0	—	0	—	—

autoimmune aetiology) than controls (7.1 vs 3.2%, $P = 0.04$). Specifically, a significant difference was observed when the father reported a positive history of thyroid disease (2.4% in the cases vs 0.4% in the controls, $P = 0.02$). The overall prevalence of a family history of autoimmune diseases other than thyroid autoimmune diseases (i.e. rheumatoid arthritis, psoriasis, inflammatory bowel disease, diabetes type 1 and vitiligo) did not show any significant difference between permanent CH cases and controls (1.6 vs 2.1%, $P = 0.74$).

Table 4 reports the OR for permanent CH estimated by the conditional logistic regression. In the multivariate analysis, four neonatal features were significantly associated with the birth of a permanent CH infant: female gender (OR = 2.0, 95% CI: 1.2–3.3), twinning (OR = 12.2, 95% CI: 2.4–62.3), additional birth defects (OR = 7.5, 95% CI: 2.9–19.0) and gestational age >40 weeks (OR = 3.0, 95% CI: 1.8–5.1). Although not significant, an increased risk of CH was still observed among infants with a family history of

hypothyroidism and/or goitre among the parents (OR = 1.9, 95% CI: 0.7–5.2).

Transient CH

No significant differences were found in the mother's age and the parents' educational level between transient CH cases and controls (Table 1). However, with regard to the risk factors related to pregnancy, gestational diabetes was present in the mother of a transient CH infant and in none of the controls' mothers.

With regard to neonatal features, no significant difference in gender was found between cases and controls while low gestational age (OR = 2.9, 95% CI 0.7–12.0) and intrauterine growth retardation (SGA infants) (OR = 5.4, 95% CI 1.0–29.4) were independently associated with transient CH in the multivariate analysis. Four out of fifteen transient CH newborns were twins: one triplet (female, female, male) concordant and one MZ pair discordant for CH were detected while none of the controls were twins. None of the CH twins reported additional congenital malformations (Table 2).

In relation to family history (Table 3), three mothers of transient CH children reported a personal positive history of hypothyroidism and/or goitre as compared with only one mother in the controls ($P < 0.01$).

Table 4 ORs for permanent CH estimated by conditional logistic regression.

Risk factors	Permanent CH (140 cases–559 controls)	
	OR	95% CIs
Female gender	2.0	1.2–3.3
Mother's age		
≤ 25 years	1.7	0.96–3.4
≥ 40 years	1.6	0.6–4.6
Gestational age		
< 37 weeks	1.4	0.5–3.9
> 40 weeks	3.0	1.8–5.1
Twin pregnancy	12.2	2.4–62.3
Additional birth defects	7.5	2.9–19.0
Hypothyroidism and/or goitre in parents	1.9	0.7–5.2

Discussion

Important results have been obtained in the early diagnosis, treatment and follow-up of CH infants and progress has been made in the search for genes involved in the dysgenesis and dyshormonogenesis of the thyroid gland. However, the aetiology of CH has not been completely elucidated. As far as we know, this is the first aetiological study performed with a population-based case-control approach aiming at identifying the most relevant risk factors for permanent and transient CH.

Our study confirmed the already known higher prevalence of CH among females than males (14–17). In fact, in this case-control study a twofold higher risk of permanent CH was estimated in females than in males. However, it is still unclear why females are more susceptible to developing CH. It has been reported that the ratio of females to males among hereditary cases of CH was approximately 1.0 (23). This finding is also confirmed by the INRICH database in which the ratio is about 1.0 for the CH cases with a eutopic gland and about two among cases with ectopy and agenesis (24). It follows that the preponderance of female cases is mostly associated with dysgenesis of the thyroid gland. For the female to male ratio in the group of infants with transient CH it was approximately 1, the same as that expected in the general population.

Some authors have suggested that infants with CH have a tendency to a prolonged gestation, although only a few have presented data on gestational age (19, 25). In our case-control study a significant association was observed between advanced gestational age (≥ 41 weeks) and permanent CH. Moreover, our results showed that the high birth weight frequently observed in permanent CH infants was associated with maternal diabetes rather than a prolonged gestation. On the other hand, in infants with transient CH, low gestational age and growth retardation were found independently associated with this form of CH. These findings are consistent with the fact that transient hypothyroidism is frequent in pre-term infants and possibly results from a transient immaturity of the thyroid gland with respect to thyroid hormone biosynthesis and adaptation to variations in the external iodide supply (26).

The restricted analysis conducted on permanent CH infants classified as LGA allowed us to estimate a high risk of CH (OR = 15.7) when any form of diabetes is present during pregnancy, while gestational diabetes was found associated with transient hypothyroidism. The causal relationship between diabetes in pregnancy and CH is not clear. However, it is well known that maternal diabetes affects embryonic development, leading to increased morbidity in the offspring (27) and a more frequent neonatal hyperthyrotropinaemia has been reported in pregnancies with gestational diabetes than in non-diabetic pregnancies with normal glucose tolerance (28). Our results are also consistent with those obtained by other authors in an experimental model (29). They reported that maternal diabetes in pregnancy negatively affects foetal thyroid hormone status in pregnant rats with streptozotocin-induced diabetes mellitus. The same authors suggested that if adequate control of the maternal diabetic condition is achieved, the alterations in foetal thyroid hormone economy would be avoided. Moreover, in a previous study (30), we reported an increased risk of subclinical hypothyroidism during pregnancy in a group of women with gestational diabetes. Taken together, all these findings highlight the importance of an adequate metabolic

control during pregnancy in order to reduce maternal and foetal morbidity, including transient and permanent forms of neonatal hypothyroidism.

With regard to the other neonatal risk factors, our results showed that twins, although almost always discordant for CH, have a high risk for either permanent or transient CH. In particular, the risk of permanent CH among twins (OR = 12.2) was estimated taking into account the effect of potential confounding variables, such as birth weight, gestational age, birth defects and maternal age. The high adjusted risk for twinning indicates a strong association with CH. This finding is also consistent with data collected in the INRICH data set showing a proportion of multiple deliveries threefold higher (3.5%) in the CH pregnancies than in the Italian general population (1%) (31). As far as we know no other studies have reported such a strong association between CH and twinning. Moreover, given the high discordance rate for CH our data suggest the importance of environmental risk factors in the aetiology of CH and a possible role of competitive conditions regarding metabolic factors *in utero*. However, further investigations are needed to understand the causal association between twinning and CH.

As expected (22, 32, 33), a high frequency of malformations has been observed among cases with permanent CH (14.3%) while a frequency similar to that expected in the general population was found in the control group (2.1%). Although the association of congenital birth defects and CH has already been well documented, the inclusion of that variable in the multivariate model allowed an adjusted estimate of the relative risk for other factors, such as twin pregnancy (34, 35), related to both CH and malformations. At least some types of congenital malformations are potentially detectable during foetal life (36). This is of concern in view of also preventing CH and malformations. In fact, the high frequency of extrathyroidal congenital malformations observed in the group of permanent CH cases represents a strong argument supporting the role of a common genetic component in the aetiology of permanent CH and at least some types of congenital defects. With this in view, investigations of the molecular mechanisms underlying the developmental events of the formation of the thyroid and other organs represent critical steps in the knowledge of CH and malformation aetiology and can be considered the starting point to achieve prevention of these pathologies even during foetal life.

Another important result was the high frequency of family history of goitre and/or hypothyroidism (included autoimmune pathogenesis) observed among both permanent and transient CH infants. Since the questionnaire used to collect information on CH infants did not distinguish between goitre and autoimmune hypothyroidism, it was not possible to consider these two maternal risk factors separately. However, it is reported that maternal thyroid autoimmunity is not a

frequent cause of permanent CH (37) but rather of transient CH (38, 39), likely as a consequence of a transplacental transfer of TSH receptor-blocking antibodies (40). Concerning the presence of goitre in the mothers, it is important to remember that, in this study, cases and controls were matched for geographic areas and the same exposure to environmental iodine deficiency could be assumed. However, no information about rural or urban and mountainous or coastal residence of the families and about the use of iodized salt was collected. Therefore, a different exposure to iodine deficiency in case and control families cannot be excluded. It has been reported that the worldwide incidence of CH shows local differences ranging between 1:2500 and <1:5000 (41–44). Although methodologically influenced biases can still be present in a few cases (only T4 as a screening approach or a high cut-off of the TSH test), according to worldwide data on iodine supply provided by the World Health Organization and the activities of the International Council for the Control of Iodine Deficiency Disorders working group, regional differences in CH incidence are suggested to be more likely to be due to iodine deficiency thyroid disorders than to ethnic affiliation (42). In fact, the CH incidence is lower in countries where the iodine supply is sufficient (e.g. USA 1:4000, Japan 1:5000, Taiwan 1:5700) than in those where iodine supply is deficient (Italy, Turkey 1:2400) (42–44). Unfortunately, iodine deficiency is still prevalent in a large part of the world, including our country which is characterized by a moderate–mild iodine deficiency and a high prevalence of goitre has been reported in the Italian population (45, 46). Iodine deficiency is the main cause of potentially preventable mental retardation in childhood, as well as causing goitre and hypothyroidism in people of all ages, including neonates (47, 48). Specifically, the most important and frequent alterations of thyroid function due to iodine deficiency in Europe occur in neonates and young infants and the frequency of transient neonatal hypothyroidism is almost eight times higher in Europe than in North America where iodine sufficiency is present (49). The reason for the particular sensitivity of newborns, especially of preterm infants, to the effects of iodine deficiency is explained by the fact that the turnover rate of intrathyroidal iodine is markedly accelerated in iodine-deficient neonates. Thyroid failure is therefore more likely to occur (50).

With regard to autoimmune diseases in parents, these do not represent a risk factor for permanent CH. However, if present in the mothers, autoimmune diseases are associated with the transient form of CH. This finding supports the idea that maternal autoimmune response towards autoantigens may transiently affect foetal and neonatal thyroid function. This hypothesis is consistent with previous studies in which a specific anti-thyroid antibody-dependent cell-mediated cytotoxic activity was found in CH infants

born to mothers with subclinical thyroid autoimmune disorders, suggesting that in these cases CH may be immunologically mediated (51, 52).

In conclusion, this population-based case-control study has shown that many risk factors contribute to the aetiology of CH. In particular, our results suggest a multifactorial origin of CH in which genetic (high frequency of additional malformations) and environmental factors (especially iodine deficiency and maternal diabetes) play a role in the development of the disease. Although the prevention of the neuropsychological consequences of CH through the use of replacement therapy represents an important public health success, knowledge about the modifiable risk factors could reduce the number of infants affected by this disease.

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