Clinical Endocrinology (2005) **62**, 444–448 doi: 10.1111/j.1365-2265.2005.02239.x

ORIGINAL ARTICLE

Proportion of various types of thyroid disorders among newborns with congenital hypothyroidism and normally located gland: a regional cohort study

Rossella Gaudino*, Catherine Garel†, Paul Czernichow* and Juliane Léger*

**Pediatric Endocrinology and Diabetes Unit, INSERM U 457 and †Radiology Department, Hôpital Robert Debré, Paris, France*

Summary

Objective To determine the proportion of the various types of thyroid disorders among newborns detected by the neonatal TSH screening programme, with a normally located thyroid gland.

Patients and methods Of the 882 575 infants screened in our centre between 1981 and 2002, 85 infants with a normally located gland had persistent elevation of serum TSH values (an incidence of 1/10 383). Six of these 85 patients were lost to follow-up and were therefore excluded from the study. During follow-up, patients were classified as having permanent or transient hypothyroidism.

Results Among the 79 patients included in the study, transient ($n = 30$, 38% of cases) and permanent ($n = 49$, 62% of cases) congenital hypothyroidism (CH) was demonstrated during the follow-up at the age of $0{\cdot}7 \pm 0{\cdot}6$ years and $2{\cdot}6 \pm 1{\cdot}8$ years ($P < 0{\cdot}0001$), respectively. The proportion of premature births was significantly higher in the group with transient CH (57%) than in the group with permanent CH (2%) ($P < 0{\cdot}0001$). A history of iatrogenic iodine overload was identified during the neonatal period in 69% of transient cases. Among permanent CH cases ($n = 49$), patients were classified as having a goitre ($n = 27$, 55% of cases), a normal sized and shaped thyroid gland ($n = 14$, 29% of cases) or a hypoplastic gland ($n = 8$, 16% of cases). The latter patients demonstrated global thyroid hypoplasia ($n = 3$), a right hemithyroid ($n = 2$), hypoplasia of the left lobe ($n = 2$), or asymmetry in the location of the two lobes ($n = 1$). Patients with a normal sized and shaped thyroid gland showed a significantly less severe form of hypothyroidism than those with a goitre or a hypoplastic thyroid gland ($P < 0{\cdot}0002$). Among permanent CH cases, those with a goitre ($n = 27$) had an iodine organification defect ($n = 10$), Pendred syndrome ($n = 1$), a defect of thyroglobulin synthesis ($n = 8$), or a defect of sodium iodine symporter ($n = 1$), and in seven patients no aetiology could be determined. Among permanent cases with a normal sized and shaped thyroid gland ($n = 14$), a specific aetiology was found in only one patient (pseudohypoparathyroidism) and two patients had Down's syndrome. Among those with a globally hypoplastic gland, a TSH receptor gene mutation was found in two patients.

Conclusions A precise description of the phenotype can enhance our understanding of various forms of neonatal hypothyroidism as well as their prevalence and management. It also helps to identify cases of congenital hypothyroidism of unknown aetiology, which will need to be investigated in collaboration with molecular biologists.

(Received 28 October 2004; returned for revision 10 December 2004; finally revised 16 December 2004; accepted 26 January 2005)

Introduction

Neonatal biochemical screening programmes for congenital hypothyroidism (CH) allow early diagnosis and treatment of infants with CH, thereby efficiently preventing mental retardation. An absent or ectopic gland is the most common cause of the disease. CH with a normally located thyroid gland is a heterogeneous group accounting for 20% of all CH cases. Defects in hormone synthesis are usually associated with the development of a goitre, while a normal or hypoplastic thyroid gland is classically related to a developmental defect, resistance to thyrotropin (TSH) at the level of the receptor or its signalling pathway, or an as yet unknown aetiology. In addition, in the group with a normally located thyroid gland, hypothyroidism may be permanent or transient. In the latter group the most common causes are iodine deficiency (which varies widely in the world according to iodine status) or iodine overload, particularly in premature newborns through intensive care or transplacental passage of antithyroid antibodies or antithyroid drugs.[1,2] In these patients, normalization of TSH occurs rapidly and most have normal TSH at recall examination. These newborns are classified as false positives at CH screening and do not require L-thyroxine treatment at that time. However, the half-life of maternal antibodies (4–6 weeks) and the effect of iodine overload can therefore last over 1 month past the recall period.[2] When hypothyroidism is confirmed at recall examination, L-thyroxine treatment is usually initiated. In this group of infants with a heterogeneous clinical and biochemical syndrome, there is currently no means of distinguishing those with mild and transient hypothyroidism from those with true permanent hypothyroidism. A re-evaluation of thyroid function is therefore required.[3–5]

Correspondence: Juliane Léger, Pediatric Endocrinology and Diabetes Unit, INSERM U 457, Hôpital Robert Debré, 48 Bd Sérurier, 75019 Paris, France.
Tel.: + 33 1 40 03 23 54; Fax: + 33 1 40 03 24 29;
E-mail: juliane.leger@rdb.ap-hop-paris.fr

The frequency of the different disorders among patients who have persistently elevated serum TSH values at recall examination has not been precisely investigated.

The present study was carried out to analyse, through a regional cohort study, the definitive diagnosis (i.e. transient or permanent CH), the clinical characteristics, the likely aetiology, and the prevalence of the different forms of CH in patients with a normally located gland.

Patients and methods

Of the 882 575 infants screened in our centre between 1981 and 2002, 252 infants were diagnosed as having persistently elevated serum TSH values (TSH ≥ 8 mU/l) at recall, representing an incidence of 1/3502 births. Among them, 167 patients had thyroid dysgenesis (incidence 1/5285) with ectopic thyroid tissue ($n = 125$; 88 females, 37 males) or athyreosis ($n = 42$; 33 females, nine males) and 85 patients (36 females, 49 males) had a normally located gland (incidence of 1/10 383). Seventy-nine of the 85 patients with a normally located gland were included in the study. Of the remaining six, two died during the neonatal period (one with a history of iodine exposure and the other with Down's syndrome) and four were lost to follow-up.

Elevated TSH levels at screening were confirmed in the 79 patients at the age of 18·2 ± 13·0 days by clinical evaluation and by measurement of serum TSH and free thyroxine (FT4) levels. L-thyroxine treatment was started at the age of 19·2 ± 17·8 days in 73 patients. For the remaining six patients, therapy was not initiated because the TSH value was only moderately elevated (TSH = 19·2 ± 17·8 mU/l). The 79 patients were divided into two groups: those with transient and those with permanent CH. Transient CH was defined as normal thyroid function with normal serum TSH level (< 6 mU/l) after therapy had been discontinued for at least 4 weeks. Patients were considered to have permanent CH if the serum TSH showed an increased level (> 7 mU/l) during treatment or after therapy had been progressively withdrawn at various ages.

Methods

The existence of a normally located thyroid gland was ascertained on the basis of thyroid radioiodine scanning (Iodine 123) and/or ultrasonography. Thyroid scanning ($n = 55$) was performed before or within the first 4 days after treatment initiation. The imaging was performed using a gamma camera equipped with a pinhole collimator, 30 min after intravenous injection of 100 μCi 123 Iodine. A perchlorate washout test was performed in 52 cases. Radioactive iodine uptake values with a decrease of more than 10% at 2 h after administration of sodium perchlorate were considered positive for the perchlorate washout test. Thyroid volume and morphology were investigated by thyroid ultrasonography ($n = 69$ cases); this was performed and interpreted by the same experienced radiologist (CG) as previously described.[6] Patients were classified as having a normal sized and shaped thyroid gland, a goitre or a thyroid hypoplasia (hemi or global hypoplasia).

On the basis of clinical history, thyroid scanning, perchlorate discharge test, ultrasonography and serum thyroglobulin measurement, CH was linked in some permanent CH cases, even if the link has not necessarily been proven by molecular investigation, to a specific thyroid dyshormonogenesis, i.e. iodine organification defect (with or without Pendred syndrome), thyroglobulin synthesis or iodide transport defects and to pseudohypoparathyroidism or hyporesponsiveness to TSH (TSH receptor defect).[2,7–9] TSH receptor gene analysis was conducted in selected cases of normal or global hypoplastic gland and sequencing performed as previously described (N de Roux, molecular biological laboratory, Kremlin-Bicêtre, France).[10]

At the time of CH diagnosis, bone maturation was assessed in term neonates ($n = 53$) by the presence or absence of knee epiphyses. Bone maturation was considered delayed if one or both epiphyses were absent. Serum TSH (normal range 0·5–6 mU/l) and FT4 (normal range 11–21 pmol/l) concentrations were measured by competitive immunoassay based on enhanced luminescence (Bayer Corp., Paris, France). Serum thyroglobulin was measured by radioimmunoassay with a lower limit of sensitivity of 2·5 μg/l.[11] Gestational age, possible history of iodine exposure and maternal thyroid disease were also recorded.

Informed consent for therapy and for the evaluations was obtained from the children's parents.

Statistical analysis

Results are expressed as mean ± SD. Data were analysed by non-parametric tests (Mann–Whitney *U*-test and Kruskal–Wallis test as appropriate) for comparison between groups. Frequency rates were compared by χ^2-test.

Results

Among the 79 patients (33 females, 46 males), transient and permanent hypothyroidism was demonstrated during the follow-up in 30 (38%) and in 49 (62%) patients, at the age of 0·7 ± 0·6 years and 2·6 ± 1·8 years ($P < 0·0001$), respectively. The clinical characteristics of these patients are indicated in Table 1. As expected, the proportion of premature births was significantly higher in the group with transient (57%) than in the group with permanent CH (2%) ($P < 0·0001$). A history of iodine exposure was found in 69% of cases of transient hypothyroidism. Six of the full-term transient hypothyroid patients had no history of iodine exposure or maternal autoimmune thyroid disease and presented with either a neonatal goitre with a positive perchlorate test ($n = 3$) or a normal sized thyroid gland ($n = 3$). In the group of transient hypothyroid patients, 25/30 patients (83%) were treated with L-thyroxine for 0·66 ± 0·7 years. In the group of permanent hypothyroid patients, all patients were treated with L-thyroxine, with the exception of one patient who had moderate hyperthyrotropinaemia both at diagnosis (TSH 11·3 mU/l) and during the follow-up.

Among the permanent hypothyroid cases ($n = 49$), patients were classified as having a goitre ($n = 27$, 55% of cases), a normal sized and shaped thyroid gland ($n = 14$, 29% of cases) or a hypoplastic thyroid gland ($n = 8$, 16% of cases). The latter patients had a global thyroid hypoplasia ($n = 3$), a right hemithyroid ($n = 2$), hypoplasia of the left lobe ($n = 2$), or asymmetry in the location of the two lobes

Table 1. Clinical findings of the 79 patients with neonatal hypothyroidism and normally located thyroid gland diagnosed through neonatal TSH screening and according to the evolution of thyroid function: transient or permanent congenital hypothyroidism

	Transient hypothyroidism ($n = 30$)	Permanent hypothyroidism ($n = 49$)
Sex: F/M	13/17	20/29
At diagnosis		
Chronological age (days)	14·9 ± 9·9	20·2 ± 14·3
Serum TSH (mU/l)	102 ± 108	163 ± 200
Serum FT4 (pmol/l)	11·9 ± 7·2	9·8 ± 7·2
Goitre	16 (53%)	27 (55%)
Premature infants	17 (57%)	1 (2%)*
At re-evaluation		
Age (years)	0·7 ± 0·6	2·6 ± 1·8*
Duration of LT4 treatment (years)	0·66 ± 0·7	2·29 ± 1·6*
Serum TSH (mU/l)	2·2 ± 1	18·2 ± 15·9*

*$P < 0.0001$ permanent hypothyroidism group *vs.* transient hypothyroidism group.

($n = 1$). As shown in Table 2, patients with a normal sized and shaped thyroid gland had a significantly less severe form of hypothyroidism (as demonstrated by moderate hyperthyrotropinaemia and normal bone maturation at the time of diagnosis) than those with a goitre or a hypoplastic thyroid gland.

Based on the clinical, radiological and biological findings, patients with a goitre were suspected of having an iodine organification defect ($n = 10$), Pendred syndrome ($n = 1$), a defect of thyroglobulin synthesis ($n = 8$), or a defect of sodium iodine symporter ($n = 1$). In seven patients (26% of cases), no aetiology could be proposed. Among permanent hypothyroid cases with a normally sized and shaped thyroid gland, no aetiology could be found in a high proportion of cases (79%). One patient had pseudohypoparathyroidism and two patients had Down's syndrome. Interestingly, the mother of two siblings with moderate permanent hyperthyrotropinaemia (TSH values of 11 and 8·5 mUI/l of therapy, respectively) had been treated for Graves' disease. The two siblings had a moderate goitre and a normal thyroid gland, respectively. Moreover, among the 10 remaining patients with permanent hypothyroidism of unknown aetiology, no anomaly in the TSH receptor gene was found in the seven cases that were tested for this gene. Among patients with a global hypoplastic thyroid gland, a TSH receptor mutation was found in the two patients who demonstrated no iodine uptake at thyroid scanning.

Discussion

Through our screening programme we established that 1/3 of patients diagnosed as having hypothyroidism at recall examination had a normally located gland. Among these patients, transient hypothyroidism was demonstrated in 38% of cases. Thus, as previously reported,[2] the overall incidence of permanent CH was approximately 1/4000, with thyroid dysgenesis being the most common aetiology. In CH cases with a normally located gland, it is difficult to differentiate between transient and permanent CH. As shown in our study, neither serum thyroid hormone levels at recall examination nor the presence of a neonatal goitre can differentiate those with transient CH from those with permanent CH; they also are not predictors of thyroid function later in life. However, as expected, transient CH was more frequently associated with premature birth, and a history of iatrogenic iodine overload during the perinatal period was identified in 69% of transient cases. In our study, no aetiology could be identified in six transient CH patients who were born at term. Until recently, transient CH was exclusively attributed to environmental, iatrogenic or immune factors.[2] However, monoallelic inactivating mutations in the gene for thyroid oxidase 2 have been shown to be associated with transient mild CH.[9,12] This constitutes the first

Table 2. Characteristics of the 49 patients with permanent congenital hypothyroidism and normally located thyroid gland according to the thyroid gland morphology evaluated during the neonatal period

	Goitre $n = 27$ (55%)	Normal sized and shaped thyroid gland $n = 14$ (29%)	Hypoplastic thyroid gland $n = 8$ (16%)
At diagnosis			
TSH (mU/l)	224 ± 237	47 ± 27**	157 ± 153
FT4 (pmol/l)	5·1 ± 5·1	16·4 ± 3·2***	14·6 ± 4·3
Delayed bone maturation	58% ($n = 11$)	11% ($n = 1$)*	63% ($n = 5$)
Aetiology/subtypes	Iodine organification defect ($n = 10$)† Pendred syndrome ($n = 1$) Defect of Tg synthesis ($n = 8$)† Defect in sodium iodine symporter ($n = 1$) Mother with Graves' disease ($n = 1$)† Unknown ($n = 6$)‡	Pseudohypoparathyroidism ($n = 1$) Down's syndrome ($n = 2$) Mother with Graves' disease ($n = 1$)† Unknown ($n = 10$)	Global hypoplasia ($n = 3$)§ Right hemithyroid ($n = 2$) Left lobe hypoplasia ($n = 2$) Asymmetry of the two lobes ($n = 1$)

†Two patients were siblings; ‡Negative perchlorate test. Thyroglobulin (Tg) measurement not done; §No iodine uptake at thyroid scanning with inactivating TSH receptor defect ($n = 2$).
*$P < 0.05$, **$P < 0.0002$, ***$P < 0.0001$ (Kruskal–Wallis test for comparison among the three groups).

evidence of a genetic origin for transient CH. Molecular investigations would be necessary in order to determine whether there is a genetic component in some of our cases of transient CH of unknown aetiology, notably those cases with a positive perchlorate test during the neonatal period and no other iatrogenic or immune aetiological factors.

It is well established that hypothyroidism at recall examination requires prompt L-thyroxine replacement therapy in newborns to avoid any intellectual impairment. Treatment should be maintained for 2–3 years before re-evaluation of thyroid function after L-thyroxine withdrawal.[2,3,5,13] Those of our patients who were subsequently diagnosed as having a transient form of the disease did not require adjustment of L-thyroxine dose during the first weeks of life. We retrospectively found that re-evaluation of their thyroid function had been carried out significantly earlier than in those with permanent CH. We therefore believe that in most cases with a history of premature birth, iatrogenic iodine overload and/or maternal thyroid disease, the distinction between transient and permanent CH should be made before the end of the first year of life to avoid prolonging treatment unnecessarily. In our study, and as previously reported,[14] a secondary slight rise in the serum TSH level during treatment occurred during the first 3 years of life in most permanent CH cases and only a few patients required a trial off therapy at 2–3 years of age to determine whether CH was permanent or transient. However, it should be borne in mind that subclinical hypothyroidism may be present later in life, even in those patients who have been diagnosed as having transient CH.[15–18] Therefore, repeated thyroid hormone testing after at least 6–12 weeks off therapy should be performed, and a thyrotropin-releasing hormone test might be helpful to confirm thyroid status, particularly in term newborns without any suspected iatrogenic aetiology.

As found in our study, iodine organification defect and defect of thyroglobulin synthesis are among the most frequent causes of inborn abnormalities of thyroid hormone synthesis. The low familial occurrence is related to an autosomal recessive mode of inheritance. In our study, the cause of CH in six patients with a goitre remained unclear but thyroglobulin measurements were unavailable in these infants. To determine whether a defect of thyroglobulin synthesis or secretion or an iodothyrosine deshalogenation defect could be involved would have required further investigations in these patients.[7,9,19] Interestingly, 45% of our patients with permanent CH demonstrated a normal or a hypoplastic thyroid gland. Only one of these cases with a normal sized thyroid gland was related to pseudohypoparathyroidism, a resistance to TSH at the level of the signalling pathway (i.e. Gsα protein encoding by the GNAS1 gene) and two patients had Down's syndrome, which is also known to be associated with a high prevalence of idiopathic mild hyperthyrotropinaemia.[20] In our study, two siblings of a mother treated for Graves' disease were also demonstrated to have permanent CH, one with a moderate goitre and the other with a normal thyroid gland at the time of diagnosis. Transient CH due to antithyroid drug or TSH receptor-blocking antibodies as well as central CH due to gestational hyperthyroidism have been reported in infants born to mothers with Graves' disease.[2,21,22] To our knowledge, there have been no previous reports of permanent cases of hyperthyrotropinaemia related to maternal Graves' disease. The aetiology of the CH in these children remains unclear. A hypoplastic thyroid gland is a well-known but rare congenital anomaly. Inactivating mutations in the TSH receptor gene have been found in several patients with CH and a hypoplastic or normal thyroid gland.[23–25] Two of our patients with a global hypoplastic thyroid gland and no iodine uptake at thyroid scanning were found to have this defect. Nevertheless, as previously shown in some patients with hyperthyrotropinaemia and normal free thyroid hormone levels,[26] no anomaly in the TSH receptor gene was found in 7/10 permanent CH patients with a normal thyroid gland who were tested for this gene. This might imply that other genes involved in the TSH-TSHR-Gsα cascade could be affected.[9,26,27] Finally, although total or partial thyroid hemiagenesis is more frequently found in euthyroid subjects and is a rare condition among CH patients with thyroid dysgenesis, permanent CH was demonstrated in our patients with thyroid hemiagenesis.[28–31] Moreover, our study showed for the first time the precise proportion of this disorder among the various forms of CH with thyroid dysgenesis. A genetic involvement in the disorder is suspected but has been reported in only one case, in which a Pax 8 gene anomaly was found.[32] To date, no clear explanation for this developmental anomaly has been found in humans.[33]

In conclusion, a detailed description of the phenotype can enhance our understanding of the various forms of neonatal hypothyroidism as well as their prevalence and management. It also helps to identify those cases of congenital hypothyroidism of unknown aetiology, which will need to be investigated in collaboration with molecular biologists. Even though a better understanding of congenital hypothyroidism will probably have no impact on long-term treatment, it will be important for establishing an accurate prognosis and for genetic counselling of affected families.

Acknowledgements

We thank Thérèse Sanchis for TSH screening of all subjects during the study period, Aubène Léger (Hôpital Necker-Enfants Malades, Paris, France) for the thyroid radioiodine scanning evaluations and Nicolas De Roux (Hôpital Bicêtre, Kremlin-Bicêtre, France) for TSH receptor gene testing.

References

1 Smerdely, P., Boyages, S.C., Wu, D., *et al.* (1989) Topical iodine-containing antiseptics and neonatal hypothyroidism in very low birthweight infants. *Lancet*, **2**, 661–664.
2 Delange, F. (1997) Neonatal screening for congenital hypothyroidism: results and perspectives. *Hormone Research*, **48**, 51–61.
3 Fisher, D.A. (1991) Management of congenital hypothyroidism. *Journal of Clinical Endocrinology and Metabolism*, **72**, 523–529.
4 Working Group on neonatal screening of the European Society for Paediatric Endocrinology. (1999) Revised guidelines for neonatal screening programmes for primary congenital hypothyroidism. *Hormone Research*, **52**, 49–52.
5 Eugster, E.A., LeMay, D., Zerin, J.M. & Pescovitz, O.H. (2004) Definitive diagnosis in children with congenital hypothyroidism. *Journal of Pediatrics*, **144**, 643–647.
6 Bubuteishvili, L., Garel, C., Czernichow, P. & Léger, J. (2003) Thyroid abnormalities by ultrasonography in neonates with congenital hypothyroidism. *Journal of Pediatrics*, **143**, 759–764.

7 Grüters, A., Finke, R., Krude, H. & Meinhold, H. (1994) Etiological grouping of permanent congenital hypothyroidism with a thyroid gland in situ. *Hormone Research*, **41**, 3–9.

8 Derrien, C., Kosugi, S., Lucidarme, N., David, V., Czernichow, P. & Polak, M. (2002) Novel missense loss of function mutation R124H of the sodium/iodine symporter gene in a French family of African descent. *Hormone Research*, **58**, abstract, P1. 215, 62.

9 Moreno, J.C., de Vijlder, J.J.M., Vulsma, T. & Ris-Stalpers, C. (2003) Genetic basis of hypothyroidism: recent advances, gaps and strategies for future research. *Trends in Endocrinology and Metabolism*, **14**, 318–326.

10 de Roux, N., Misrahi, M., Chatelain, N., Gross, B. & Milgrom, E. (1996) Microsatellites and PCR primers for genetic studies and sequencing of the human thyrotropin receptor. *Molecular Cell Endocrinology*, **117**, 253–256.

11 Van Herle, A.J., Uller, R.P., Matthews, N.C. & Brown, J. (1973) Radioimmunoassay for measurement of thyroglobulin in human serum. *Journal of Clinical Investigation*, **52**, 1320–1327.

12 Moreno, J.C., Bikker, H., Kempers, M.J.E., *et al.* (2002) Inactivating mutations in the gene for thyroid oxidase 2 (THOX2) and congenital hypothyroidism. *New England Journal of Medicine*, **347**, 95–102.

13 AAP Section on Endocrinology and Committee on Genetics, and American Thyroid Association Committee on Public Health. (1993) Newborn screening for congenital hypothyroidism: recommended guidelines. *Pediatrics*, **91**, 1203–1209.

14 Davy, T., Daneman, D., Walfish, P.G. & Ehrlich, R.M. (1985) Congenital hypothyroidism: the effect of stopping treatment at 3 years of age. *American Journal of Disease in Childhood*, **139**, 1028–1030.

15 Miki, K., Nose, O., Miyai, K., Yabuuchi, H. & Harada, T. (1989) Transient infantile hyperthyrotropinaemia. *Archive of Disease in Childhood*, **64**, 1177–1182.

16 Köhler, B., Schnabel, D., Biebermann, H. & Grüters, A. (1996) Transient congenital hypothyroidism and hyperthyrotropinemia: normal thyroid function and physical development at the ages of 6–14 years. *Journal of Clinical Endocrinology and Metabolism*, **81**, 1563–1567.

17 Daliva, A.L., Linder, B., DiMartino-Nardi, J. & Saenger, P. (2000) Three year follow-up of borderline congenital hypothyroidism. *Journal of Pediatrics*, **136**, 53–56.

18 Calaciura, F., Motta, R.M., Miscio, G., *et al.* (2002) Subclinical hypothyroidism in early childhood: a frequent outcome of transient neonatal hyperthyrotropinemia. *Journal of Clinical Endocrinology and Metabolism*, **87**, 3209–3214.

19 Gillam, M.P. & Kopp, P. (2001) Genetic defects in thyroid hormone synthesis. *Current Opinion in Pediatrics*, **13**, 364–372.

20 Van Trotsenburg, A.S.P., Vulsma, T., Van Santen, H.M., Cheung, W. & de Vijlder, J.J.M. (2003) Lower neonatal screening thyroxine concentrations in Down syndrome newborns. *Journal of Clinical Endocrinology and Metabolism*, **88**, 1512–1515.

21 Brown, R.S., Bellisario, R.L., Botero, D., *et al.* (1996) Incidence of transient congenital hypothyroidism due to maternal thyrotropin receptor-blocking antibodies in over one million babies. *Journal of Clinical Endocrinology and Metabolism*, **81**, 1147–1151.

22 Kempers, M.J.E., Van Tijn, D.A., Van Trotsenburg, A.S.P., de Vijlder, J.J.M., Wiedijk, B.M. & Vulsma, T. (2003) Central congenital hypothyroidism due to gestational hyperthyroidism: detection where prevention failed. *Journal of Clinical Endocrinological Metabolism*, **88**, 5851–5857.

23 Sunthornthepvarakul, T., Gottschalk, M.E., Hayashi, Y. & Refetoff, S. (1995) Resistance to thyrotropin caused by mutations in the thyrotropin receptor gene. *New England Journal of Medicine*, **332**, 155–160.

24 Biebermann, H., Schöneberg, T., Krude, H., Schultz, G., Gudermann, T. & Grüters, A. (1997) Mutations of the human thyrotropin receptor gene causing thyroid hypoplasia and persistent congenital hypothyroidism. *Journal of Clinical Endocrinology and Metabolism*, **82**, 3471–3480.

25 Alberti, L., Proverbio, M.C., Costagliola, S., *et al.* (2002) Germline mutations of the TSH receptor gene as cause of nonautoimmune subclinical hypothyroidism. *Journal of Clinical Endocrinology and Metabolism*, **87**, 2549–2555.

26 Xie, J., Pannain, S., Pohlenz, J., *et al.* (1997) Resistance to thyrotropin in three families is not associated with mutations in the TSH receptor or TSH. *Journal of Clinical Endocrinology and Metabolism*, **82**, 3933–3940.

27 Meeus, L., Gilbert, B., Rydlewski, C., *et al.* (2004) Characterization of a novel loss of function mutation of PAX8 in a familial case of congenital hypothyroidism with in-place, normal-sized thyroid. *Journal of Clinical Endocrinology and Metabolism*, **89**, 4285–4291.

28 Shabana, W., Delange, F., Freson, M., Osteaux, M. & De Schepper, J. (2000) Prevalence of thyroid hemiagenesis: ultrasound screening in normal children. *European Journal of Pediatrics*, **159**, 456–458.

29 Maiorana, R., Carta, A., Floriddia, G., *et al.* (2003) Thyroid hemiagenesis: prevalence in normal children and effect on thyroid function. *Journal of Clinical Endocrinology and Metabolism*, **88**, 1534–1536.

30 Castanet, M., Polak, M., Bonaïti, C., Lyonnet, S., Czernichow, P. & Léger, J. (2001) 19 years of national screening for congenital hypothyroidism: familial cases with thyroid dysgenesis suggest the involvement of genetic factors. *Journal of Clinical Endocrinology and Metabolism*, **86**, 2009–2014.

31 Léger, J., Marinovic, D., Garel, C., Bonaïti-Pellié, C., Polak, M. & Czernichow, P. (2002) Thyroid developmental anomalies in first degree relatives of children with congenital hypothyroidism. *Journal of Clinical Endocrinology and Metabolism*, **87**, 575–580.

32 Krude, H., Macchia, P.E., Di Lauro, R. & Grüters, A. (1998) Familial hypothyroidism due to thyroid dysgenesis caused by dominant mutations of the Pax8 mutations gene. *Hormone Research*, **50**, abstract O43, 17.

33 Fagman, H., Grände, M., Gritli-Linde, A. & Nilsson, M. (2004) Genetic deletion of Sonic Hedgehog causes hemiagenesis and ectopic development of the thyroid in mouse. *American Journal of Pathology*, **164**, 1865–1872.