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Research paper

Transient Congenital Hypothyroidism due to maternal autoimmune thyroid disease

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ABSTRACT

The neonatal screening program for congenital hypothyroidism (CH) in Greece shows an overall incidence of the disease of 1:2321. The cases with permanent CH have an incidence of 1:2542, whereas the transient forms of CH account for 8.7% of all cases diagnosed as CH. Transplacental passage of maternal thyrotropin receptor-blocking antibodies is a rare cause of transient CH. In our program, a retrospective analysis of 508,358 screened newborns revealed 6 infants with transient CH caused by maternal thyroid autoimmunity, representing 2.7% of all cases of CH. All the newborns with transient CH, due to maternal autoimmune thyroid disease, had high serum TSH concentration (ranging from 98 to 689 mU/L), whereas serum thyroxine (T4) values were low normal to normal in 3 of them. Replacement therapy with L-thyroxine was initiated at a mean age of 6.5 days. The newborns with transient CH belonged to 4 families, one of which had 4 and another 2 children with the same pathology. Thyrotropin-receptor antibodies (TSH-R Abs), present at the initial examination in newborns' serum, had disappeared from the infants' circulation by the third month of life. One mother carried the Abs for at least 8 years during which period she delivered four babies. The diagnosis of transient CH should be suspected if the mother has autoimmune thyroid disease, if there are siblings with transient CH or if there is no need for an increase in L-thyroxine dose with advancing age. The diagnosis is very important for genetic counseling, early treatment initiation of subsequent offspring and adequate control of the mother's thyroid function during subsequent pregnancies so that any neurodevelopmental abnormality of the fetus could be avoided.

Key Words: transient congenital hypothyroidism, TSH receptor- blocking antibodies, maternal thyroid autoimmunity

INTRODUCTION

Neonatal screening programs for congenital hypothyroidism (CH) on a nationwide basis depict not only cases with permanent CH but also those with transient forms of CH. The incidence of permanent CH is about 1:3000-3500 newborns and is due either to dyshormonogenesis or to thyroid gland dysgenesis (ab-

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sence, hypoplasia or ectopia of the gland). These cases require life-long substitution therapy with L-thyroxine[1].

Transient CH is not common and is usually caused either by maternal ingestion of goitrogenic substances which reach the fetus via placental transfer (i.e. iodine, thioureas, sulphonamides etc.) or by maternal-fetal transfer of thyrotropin receptor-blocking antibodies, which are immunoglobulins of IgG type. It may also be caused by iodine deficiency or overload in the neonatal period[2]. Transient CH persists for a variable period of time postnatally and substitution therapy may be needed for a short period depending on the cause of the condition.

Epidemiological data about the true incidence of transient CH due to maternal thyroid autoimmunity are scarce since most published cases are isolated[3,4].

The present study aims to assess the occurrence, incidence and evolution of transient CH caused by maternal thyroid autoimmunity.

SUBJECTS AND METHODS

A neonatal screening program for CH was begun in Greece in 1979[5]. Thyroid stimulating hormone (TSH) has been measured in dried blood spots by a RIA-TSH method. Blood is routinely obtained by heel-prick on a Schleicher and Schuell 2992 filter paper between the 3rd and 5th day of life. When a newborn is highly suspicious for CH (TSH ≥ 25 mU/L), a serum biochemical examination of thyroid function is requested. For the cohort of TSH values between 10 and 25 mU/L in whole blood, a repeat blood specimen on filter paper is required. Values of TSH below 10mU/L in whole blood are considered normal. When a family already has a child with CH, the next offspring is clinically and biochemically examined during the first postnatal days.

Between 1997 and 2001 a total of 508,358 newborns were screened. Two hundred fifty-seven of them were checked for anti- thyroid Abs, namely anti-thyroglobulin (anti-Tg) and anti-microsomal (anti-TPO), and for thyrotropin-receptor Abs (TSH-R Abs). These cases represent 69% of recalled newborns with spot TSH values >25mU/L in whole blood. The remaining 31% of the cases were examined only for thyroid hormones and TSH, because they were referred for evaluation to other pediatric endocrinological units of the country and were either classified as infants with normal thyroid function or as hypothyroid. Finally 80% of the newborns with hypothyroidism were examined for Abs.

The biochemical examination of the neonates suspected for CH included serum measurements of thyroxine (T4), free T4, (FT4), triiodothyronine (T3), TSH, thyroid Abs (anti-Tg and anti-TPO) and TSH-R Abs. In mothers of babies suspected for CH serum values of T4,T3, TSH and anti-thyroid and TSH-R Abs were determined.

Serum T4 and T3 were determined by radioimmunoassay (RIA) while FT4 and TSH by chemiluminescence immunoassay (Nichols Advantage, Nichols Institute Diagnostics). For RIA-T4 intra- and inter-assay coefficient of variations (CVs) on 3 different T4 levels ranged from 3.0% to 3.9% and 4.6% to 8.5%, respectively. For RIA-T3 the respective figures were 2.0% and 3.5% and 3.7% and 1.8%, for TSH 2.3% and 6.0% and 14.7% and 7.0% and for FT4 6.6% and 4.5% and 7.1% and 3.8%. The thyroid Abs were measured by an immunoradiometric assay (DiaSorin Diagnostics). The CVs for anti-Tg ranged from 3.6% to 4.4% (intra-assay) and 6.7% to 11.6% (inter-assay) and for anti-TPO from 2.4% to 6.1% and 4.8% to 7.8%, respectively. The TSH-R Abs determined by a radioreceptor assay produced by Incstar Corp., Stillwater, MN. This method detects Abs that interfere with the binding of TSH to TSH receptor without differentiating between thyroid-stimulating Abs and thyroid stimulation-blocking Abs. The CVs of the method ranged from 7.0% to 12.0% (intra-assay) and 8.7% to 17.7% (inter-assay).

The criteria used for the diagnosis of transient CH due to maternal autoimmune thyroid disease were: a) the presense of TSH-R Abs in mothers' and infants' serum, b) the disappearance of TSH-R Abs from the infants' circulation, c) normal thyroid function after treatment discontinuation and d) no requirement for adaptation of L-thyroxine dose as the infant increased in size.

RESULTS

Among the 508,358 screened newborns, 219 were found to have CH and replacement therapy with L-thyroxine was initiated at a mean age of 18 days. Two

hundred of them were proved to have permanent CH, thus yielding an incidence of the disease of 1:2542 (Table 1). The remaining 19 newborns had transient CH (8.7% of all cases diagnosed as having CH). Six of them had transient CH due to maternal thyroid autoimmunity (2.7% of CH cases). In the remaining 13 newborns the transient course of the disease was attributed to problems related to prematurity or perinatal complications.

In Table 2 the recalled infants, grouped according to their final diagnosis and the results of Abs measurements are listed. Sixteen of the 19 newborns with transient CH were checked for Abs. One of those not checked for Abs belonged to a family with 3 previous children with positive TSH-R Abs and transient CH and her mother had Hashimoto thyroiditis. This patient was therefore included in the group of transient CH. The remaining two were premature newborns, part of a twin set and the twin siblings did not have thyroid function problems and therefore their transient CH was attributed to prematurity.

The percentage of newborns with positive anti-Tg and anti-TPO Abs is about the same in the groups of normal infants and those with permanent CH, while the group with transient CH had a much higher incidence of positive anti-Tg and anti-TPO Abs (Table 2).

In Table 3 the laboratory data of the 6 cases with transient CH due to maternal autoimmune thyroid disease are listed. Cases 3 and 4 are siblings and there were two more older children in the family with the same course of the disease. The same is true of case 1, who had an older sister with transient CH. All newborns with transient CH presented very high TSH values on dried blood spots during the first days of life. At a mean age of 6.5 days (range 1-14 days), serum TSH concentrations ranged from 98 to 689 mU/L (normal values <5). The T4 values were low-normal to normal in 3 newborns and the T3 values were normal in all but one.

Antithyroid Abs were present (either one or both of them) in all newborns with transient CH due to maternal autoimmune thyroid disease.

Sequential measurements of the Abs in the patients' serum showed that TSH-R Abs were cleared by the second to third month of postnatal life, irrespective of their initial concentration. Antithyroid Abs needed more time for their elimination depending on their initial titre: more than 5 months for anti-Tg (case 2) and more than 8 months for anti-TPO Abs (case 6).

All infants with transient CH due to maternal thyroid autoimmunity were full-term and were born after an uneventful pregnancy. Their birth weight was

Table 1. Results of the Greek screening program for congenital hypothyroidism in 508,358 newborns (1997-2001).

Diagnosis	No of patients	Incidence/percentage of cases
Newborns with CH	219	1:2,321
a. newborns with permanent CH	200	**1:2,542**
b. newborns with transient CH	19	**8.7%** of CH cases
c. newborns with transient CH due to maternal autoimmune thyroid disease	6	**2.7%** of CH cases or **1:84,726** newborns

Table 2. Data on thyroid and TSH-R Abs in newborns with transient or permanent congenital hypothyroidism and in newborns with normal thyroid function.

Recalled newborns	Number of newborns examined for Abs	no. of newborns with positive Abs					
		anti-Tg		anti-TPO		TSH-R Abs	
		no	%	no	%	no	%
A. Newborns with CH	173	5	2.9	24	13.9	5	2.9
a. Transient CH	16	2	12.5	5	31.2	5	31.2
b. Permanent CH	157	3	1.9	19	12.1	-	-
B. Normal newborns	84	1	1.2	10	11.9	-	-
Total	257	6	2.3	34	13.2	5	1.9

Table 3. Laboratory data of infants with transient congenital hypothyroidism due to maternal autoimmune thyroid disease. Cases 3 and 4 are siblings.

Patients	Year of diagnosis	Age (days or months)	Spot TSH (mU/L)	T4 (nmol/L)	FT4 (pmol/L)	T3 (nmol/L)	TSH (mU/L)	Anti-Tg (U/mL)	Anti-TPO (U/mL)	TSH-R Abs (U/L)	Thyroid U/S
1	1997	1d	>125	69.5	4.2	ND	388	84	62	403	Normal
		2m		225.0	25.2	4.78	0.7	23	13	12	
		3m		253.7	31.6	4.56	0.1	17	7	4	
2	1998	14d	>125	28.3	3.5	1.87	673	12,540	1,240	402	Normal
		2m		185.4	20.6	4.20	4.4	3,779	259	136	
		5m		154.5	19.0	2.38	1.2	1,061	75	<2	
		9m		171.3	18.8	2.85	1.6	37	7	<2	
3	1997	3d	>125	69.5	ND	ND	98	80	239	>300	
		1m								580	
		2m								360	ND
		5m								<2	
4	2000	3d	>125	27.0	ND	1.65	287	ND	ND	ND	ND
5	2000	9d	64	148.0	14.1	3.15	198	376	105	400	Normal
		1m		118.5	19.0	2.70	5.7	157	69	190	
		2m		148.0	20.5	4.50	3.4	27	23	8	
		4m		167.4	18.7	3.25	2.4	10	14	<2	
		6m		115.9	17.3	2.74	2.2	6	5	<2	
6	2000	9d	>125	48.9	3.1	1.38	689	19	726	>405	Normal
		1m		118.5	18.8	3.06	76.0	10	598	>405	
		2m		146.8	23.9	ND	2.3	<4.0	260	357	
		3m		115.9	22.0	3.06	0.2	<4.0	92	<2	
		6m		122.3	16.6	3.25	2.9	3.6	29	<2	
		8m		114.6	15.2	2.77	2.7	6.4	16	<2	
Normal Values			<10	77-206	9-28.3	1.5-4.5	0.3-5.0	<100	<10	<10	

ND: Not done

over 3000gr. The most common clinical findings were prolonged jaundice (> 10 days) and large posterior fontanelle (> 0.5 cm). No malformations were present in these patients. Thyroid ultrasound performed by 6 months of age in 4 cases showed normal size and morphology of the thyroid gland with a homogenous parenchyma and without focal abnormalities.

In Table 4 the clinical and laboratory data of the mothers are presented. All of them were hypothyroid on L-thyroxine therapy for a period of 2-8 years before the last delivery and 2 of these had more than one child with transient CH. All were well controlled during pregnancy.

The infants received L-thyroxine replacement therapy immediately after diagnosis was established at a dose ranging from 25 to 50 μg/day, which required no adaptation during the follow-up period. Since treatment discontinuation, thyroid function tests and the physical and psychomotor development of the patients have been normal.

The overall incidence of transient CH attributed to maternal thyroid autoimmunity in our material is 2.7% of all cases diagnosed with CH.

DISCUSSION

The diagnosis and early treatment of infants with CH has been greatly facilitated by the application of neonatal mass screening programs. The administration of replacement therapy during the first days of life has resulted in normal psychomotor development

Table 4. Clinical and laboratory data of mothers of infants with transient CH.

Patients	Clinical history	anti-Tg (U/mL)	anti-TPO (U/mL)	TSH-R Abs (U/L)
1	Hypothyroid on R_x(3)	0.6	91	245
2	Hypothyroid on R_x(3)	> 13,000	> 2,000	402
3,4	Hypothyroid on R_x(8)	ND	ND	ND
5	Hypothyroid on R_x(2)	731	173	137
6	Hypothyroid on R_x(4)	55	988	> 405
Normal values		<100	<10	<10

ND: Not done. Numbers in parenthesis: years of therapy

of the children affected[6,7]. In Greece, a similar program was initiated in the early 80's on a nationwide basis. The overall incidence of CH in the country is 1:2321. One in every 2542 screened newborns suffered permanent CH, whereas the transient forms of the disease, which needed replacement therapy, accounted for 8.7% of all cases.

Transient CH caused by transplacental transfer of TSH-R Abs is a relatively rare condition and epidemiological data in the literature are scarce. In our study, which comprised 508,358 screened newborns, we found 6 newborns with transient CH attributed to maternal Hashimoto thyroiditis. Thus, in every 84,726 newborns one has this condition. These cases represent 2.7% of all neonates with CH (transient and permanent). In North America, Brown et al[8] found this form of transient CH in 1:180,000 screened newborns by measuring the TSH binding inhibitory activity in dried blood spots. This accounted for approximately 2% of CH cases in this study. Data from Switzerland showed an incidence of approximately 1:310,000 live newborns screened. Specifically, among 618,913 infants screened in a 16-year period, only two cases (two siblings) with transient CH due to maternal autoimmune thyroid disease were detected[9].

The presence of TSH-R Abs only in neonates with transient CH provides strong evidence that these Abs are etiologically related to the hypothyroidism observed and are therefore of diagnostic value.

The antithyroid Abs also detected in this group do not seem to be responsible for the development of CH since they had also been found in the other two groups of children recalled who were proved to have either normal thyroid function or permanent CH. These results are in agreement with a study done by Dussault et al who suggested that antithyroid Abs do not play an important role in the pathogenesis of permanent CH[10]. In another study by Dussault et al[11], it was demonstrated that the prevalence of microsomal Abs was similar in mothers of newborns with CH and in a control population (11.6% and 12%, respectively). In our study, we found similar results for anti-TPO Abs in newborns with permanent CH and those who eventually had normal thyroid function. Moreover we noticed the same percentage for anti-Tg Abs in these two groups of newborns (1.2% and 1.9%, respectively). These findings reflect the prevalence of these Abs in the general neonatal population, possibly through transplacental transfer. A higher percentage of these Abs was observed in the group of newborns with transient CH due to transplacental transfer of maternal TSH-R Abs.

The serum concentration of TSH-R Abs does not correlate with the severity of hypothyroidism as it is expressed by serum levels of T4, FT4 and TSH. We found that their clearance from an infant's circulation has been completed by the 3rd month of life. In a study by Matsuura et al[12], who presented data from two siblings with transient CH due to TSH-binding inhibitor immunoglobulins, it was found that the Abs had been cleared from children's blood by 3 months of age in one and by 10 months in the other. Because TSH-R Abs metabolism is crucial for the treatment period, their measurement is expected to help in the decision to terminate therapy with L-thyroxine.

All infants in the present study with transient CH of autoimmune origin were healthy and in good clinical condition when first examined. This is in contrast to descriptions from other studies where the hypothyroid infants had the typical appearance of a cretin[12]. We assume that this is due to well-controlled thyroid

function of the mothers during pregnancy, which allowed an adequate thyroid hormone supply to the fetus through transplacental transfer. The most frequent signs encountered in our infants were prolonged jaundice (more than 10 days) and a posterior fontanelle greater than 0.5cm. A thyroid ultrasound in 4/6 infants revealed normal size and morphology of the thyroid gland. Another important characteristic of our cases was that no adaptation of thyroxine dose was required as the child was growing. After treatment discontinuation, all children had completely normal thyroid function and normal neurodevelopmental outcome.

It must be emphasized that absence of the thyroid gland is reported in thyroid scintiscans performed at the time of diagnosis of CH in such infants[3]. This finding must be attributed to the presence of TSH-R blocking Abs and should not be mistaken for thyroid agenesis. In our cases, thyroid scintiscan was not carried out at diagnosis.

The early differential diagnosis of this type of CH is of considerable importance because it does not require lifelong treatment, which is undesirable for both children and parents. Suspicion for its existence should be raised by a mother's history of autoimmune thyroiditis and the presence of previous siblings with the same clinical course.

It is now well established that maternal thyroid function throughout pregnancy influences the neurodevelopmental outcome of the child[13]. Studies in which both mother and child are hypothyroid,as in areas with severe iodine deficiency[14] or in TSH-R blocking Abs-induced CH[15], the psychomotor development of the offspring is also impaired.

Therefore, in these families genetic counseling is very important to alert the parents to the possibility of recurrence of the disease in subsequent offspring, information which will ensure early evaluation and treatment of the newborn. Furthermore, such findings are of utmost importance for alerting physicians to control the mother's thyroid function in subsequent pregnancies in order to avoid any impairment of fetal neuronal development.

In conclusion, transient CH caused by maternal-fetal transfer of TSH-R Abs is a rare condition, accounting for 2.7% of all cases with CH. This form of CH should be suspected when a) serum TSH-R Abs are detected in the mother and/or the newborn, b) there is a history of maternal autoimmune thyroid disease, c) there are other siblings with transient CH, and d) there is no need for an increase in L-thyroxine dose with advancing age. This diagnosis is very important for the proper management of the patient and for genetic counseling of the family.

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REFERENCES

1. La Franchi S, 1999 Congenital hypothyroidism: etiologies, diagnosis, and management. Thyroid 9: 735-740.
2. Delange F, 1998 Screening for congenital hypothyroidism used as an indicator of the degree of iodine deficiency and of its control. Thyroid 8: 1185-1192.
3. Francis G, Riley W, 1987 Congenital familial transient hypothyroidism secondary to transplacental thyrotropin-blocking autoantibodies. Am J Dis Child 141: 1081-1083.
4. Pacaud D, Huot C, Gattereau A, et al, 1995 Outcome in three siblings with antibody-mediated transient congenital hypothyroidism. J Pediatr 127: 275-277.
5. Mengreli C, Kassiou K, Tsagarakis S, Pantelakis S, 1981 Neonatal screening for hypothyroidism in Greece. Eur J Pediatr 137: 185-187.
6. Komianou F, Makaronis G, Lambadaridis J, et al, 1988 Psychomotor development in congenital hypothyroidism. The Greek screening programme. Eur J Pediatr 147: 275-278.
7. Van Vliet G, 1999 Neonatal hypothyroidism: treatment and outcome. Thyroid 9: 79-84.
8. Brown RS, Bellisario RL, Botero D, et al, 1996 Incidence of transient congenital hypothyroidism due to maternal thyrotropin receptor-blocking antibodies in over one million babies. J Clin Endocrinol Metab 81: 1147-1151.
9. Pasquier S, Torresani T, Werder E, Gnehm HE, 1997 Transitory neonatal hypothyroidism caused by transplacental transfer of anti-receptor antibodies of hypothyseal thyroid stimulation. Case report and estimated incidence. Schweiz Med Wochenschr 127: 1824-1828.
10. Dussault JH, Letarte J, Guyda H, et al, 1980 Lack of influence of thyroid antibodies on thyroid function in the newborn infant and on a mass screening program for congenital hypothyroidism. J Pediatr 96: 385-389.
11. Dussault JH, Fisher DA, 1999 Thyroid function in mothers of hypothyroid newborns. Obstet Gynecol 93: 15-20.
12. Matsuura N, Yamada Y, Nohara Y, et al, 1980 Familial neonatal transient hypothyroidism due to maternal TSH-binding inhibitor immunoglobulins. N Engl J Med 303: 738-741.
13. Glinoer D, 2001 Potential consequences of maternal hypothyroidism on the offspring: evidence and implications.

Horm Res 55: 109-114.
14. Cao XY, Jiang XM, Dou ZH, et al, 1994 Timing of vulnerability of the brain to iodine deficiency in endemic cretinism. N Engl J Med 331: 1739-1744.
15. Matsuura N, Konishi J, 1990 Transient hypothyroidism in infants born to mothers with chronic thyroiditis: a nationwide study of twenty-three cases. The Transient Hypothyroidism Study Group in Japan. Endocrinol Jpn 37: 369-379.

ERRATUM:

Insulin resistance in pheochromocytoma improves more by surgical rather than by medical treatment (Vol. 2, No 1)

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