

3-1-1996

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Repository Citation

Brown, Rosalind S.; Bellisario, Ronald L.; Botero, Diego; Fournier, Lawrence; Abrams, Cyril A. L.; Cowger, Marilyn L.; David, Ralph; Fort, Pavel; and Richman, Robert A., "Incidence of transient congenital hypothyroidism due to maternal thyrotropin receptor-blocking antibodies in over one million babies" (1996). *Open Access Articles*. 987.
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Citation: J Clin Endocrinol Metab. 1996 Mar;81(3):1147-51. [Link to article on publisher's website](#)

Incidence of Transient Congenital Hypothyroidism due to Maternal Thyrotropin Receptor-Blocking Antibodies in Over One Million Babies*

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ABSTRACT

To determine the incidence of transient congenital hypothyroidism due to TSH receptor-blocking antibodies, we screened dried blood specimens obtained from 788 neonates identified as having possible congenital hypothyroidism (from a total population of 1,614,166 babies) and 121 controls. A RRA was used. The potency of blood spot TSH binding inhibitory activity was compared with the severity of congenital hypothyroidism to assess the possible etiological relationship. Maternal serum was studied to confirm the presence of blocking antibodies by both RRA and bioassay.

Blood spots obtained from 9 infants contained potent TSH receptor-blocking activity. Samples from 2 additional babies, studied because of clinical suspicion of the disease, were also positive. Long term outcome was known in 8 of the 11 babies, and all had transient

disease. Neonates with TSH receptor-blocking activity greater than 132 U/L had a significantly lower T_4 level ($P < 0.05$) and higher TSH ($P < 0.005$) than those in whom TSH binding-inhibitory activity was less than 132 U/L. All 9 mothers had autoimmune thyroid disease, and 3 had more than 1 affected child. Potent blocking activity was present in 7 maternal serum samples as long as 7 yr after the births of their affected babies.

We conclude that measurement of TSH binding-inhibitory activity in dried neonatal blood specimens is a simple and effective method to predict the occurrence of transient congenital hypothyroidism. The incidence of this disorder in North America is 1 in 180,000 normal infants, or approximately 2% of babies with congenital hypothyroidism. (*J Clin Endocrinol Metab* 81: 1147-1151, 1996)

CONGENITAL hypothyroidism occurs in 1 in 4000 newborn babies and is one of the most frequent preventable causes of mental retardation (1). Although the majority of affected infants have a defect in thyroid gland development or thyroid hormone synthesis and will, therefore, require lifelong thyroid hormone replacement (2), in approximately 10% of babies detected by newborn screening, the abnormality in thyroid function will be transient (1). Recent interest has focused on the possible etiological role in some of these transient cases of maternal TSH receptor-blocking antibodies. Although difficult to distinguish at birth from those with the more common thyroid gland dysgenesis, affected infants differ from the latter in a number of important ways (3-5). They do not require lifelong therapy, results of thyroid imaging may be misleading in them, and there is a high recurrence rate in subsequent offspring due to the tendency of these antibodies to persist for many years in the

maternal circulation (3-5). Furthermore, others have suggested recently that the intellectual outcome of babies with maternal blocking antibody-induced congenital hypothyroidism may be less favorable than that of babies with a permanent abnormality of the thyroid gland, especially if unrecognized maternal hypothyroidism was present *in utero* (6).

The incidence of transient congenital hypothyroidism secondary to maternal TSH receptor-blocking antibodies is unknown, and most information derived about this syndrome to date has been obtained from isolated case reports (3-5, 7). In the present study, we have taken advantage of the recent observation that affected babies can be identified by evaluation of [125 I]TSH binding inhibitory activity in dried neonatal blood specimens obtained for routine screening purposes (8). We have employed this technique to evaluate the incidence of this disorder in more than 1.6 million babies born in New York State over a 6-yr period and have analyzed the clinical and immunological data in a total of 9 babies so discovered as well as in their mothers. Data from 2 additional infants in whom the diagnosis was suspected clinically were evaluated similarly. We also sought to establish whether an etiological relationship was present by relating the potency of the blocking antibodies to the severity of congenital hypothyroidism.

Received July 27, 1995. Revision received September 14, 1995. Accepted September 21, 1995.

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* This work was supported in part by grants from Boots Pharmaceuticals, Inc., and the March of Dimes (6-492).

Subjects and Methods

Study population

A total of 899 dried blood specimens were obtained from 788 newborn infants in whom the screening levels of T_4 were less than the tenth percentile for the assay and whose TSH concentrations were equal to or greater than 40 U/L; infants who had an initial diagnosis of congenital hypothyroidism reported to the New York State Newborn Screening Program were also studied. These infants were selected from among 1,614,166 babies screened for congenital hypothyroidism in New York State over the 6-yr period from 1984–1989. Blood spots from 121 normal or T_4 -binding globulin-deficient babies screened during the same period served as control specimens. The results with 465 test specimens and 88 controls obtained between 1987–1988 were reported in a previous pilot study (8). Dried blood specimens from an additional 2 babies were studied because of suspicion of the disease and are included in the clinical analysis. Blood spots were stored desiccated at -20°C before use and were studied without knowledge of the diagnosis. The study was approved by the University of Massachusetts Medical Center Committee for the Protection of Human Subjects in Research.

Methods

Dried blood specimens were eluted overnight in either 50% Coon's F-12 medium or 10 mmol/L Tris-HCl, pH 7.5, containing 50 mmol/L NaCl; both solutions gave equivalent results. The presence of TSH receptor-blocking activity was estimated in duplicate by evaluation of [^{125}I]TSH binding inhibition to solubilized porcine receptor by the method of Southgate *et al.* (9) using either materials we prepared (8) (part 1) or a commercial kit (Kalibre, Kronus, Dana Point, CA; part 2). In part 1, blocking activity was expressed as the percent TSH binding inhibition according to the formula $(1 - [\text{I}^{125}\text{I}]\text{bovine TSH binding in the presence of test IgG}/1 - [\text{I}^{125}\text{I}]\text{bovine TSH binding in the presence of normal IgG}) \times 100$. In part 2, results were expressed as the TSH receptor antibody (TRAb) concentration in units per L by comparison with a standard curve. A value greater than 2 sd above the mean for normal infants was considered abnormal. We repeated the measurement if the level of blocking activity was greater than 1.5 sd above the normal mean. Only spots with significant blocking activity in at least two assays were considered positive. After a positive spot was confirmed, clinical information was sought and, if not performed previously, a blood sample was obtained from the mother for measurement of blocking antibodies.

To ascertain whether the maternal serum blocked the bioactivity of TSH as well as its binding, we measured the inhibition of TSH-induced stimulation of adenylyl cyclase using recombinant human TSH receptor that had been stably transfected into Chinese hamster ovary cells; the latter were a generous gift from Dr. Leonard Kohn, NIH. Cells were grown overnight to confluence in Costar 24-well plates containing Coon's Modified F-12 buffer and 0.2% FBS. Before assay, cells were

washed twice with hypotonic HBSS containing 0.5 mmol/L 3-isobutyl-L-methyl-xanthine (10) and incubated for 1 h at 37°C in the same buffer plus 100 mU/L recombinant human TSH (Genzyme Corp., Cambridge, MA). cAMP released into the medium was measured by RIA (Incstar Corp., Stillwater, MN).

Thyroid peroxidase (TPO) antibodies were measured by RIA (Kronus). Values greater than 1 U/L were considered abnormal. In one case in which data obtained previously was used for the analysis, the assay in current clinical use was employed.

Statistics

The significance of the difference between groups was evaluated by Student's *t* test. $P < 0.05$ was considered significant.

Results

Dried blood specimens from a total of 11 neonates were found to contain significant TSH binding inhibitory activity. Nine of these were obtained from the screening portion of the study; 2 additional babies were identified because of clinical suspicion of the disorder. Three of the former cases have been reported previously (8). In all instances, blocking activity was extremely potent, being at least 3 sd above the mean for normal newborns. In 7 of the cases, the level was more than 4 sd, and in 3, it was greater than 20 sd.

The available clinical data for the 11 infants are presented in Table 1. All 8 babies in whom follow-up information was available had transient disease. Those babies with the most potent TSH binding inhibitory activity had the most severe hypothyroidism, as determined by comparison with results of thyroid function tests performed in the same spots at the time of newborn thyroid screening. Furthermore, in this group of babies, the antibodies were sufficiently potent to block TSH-induced uptake of radioactive iodine on thyroid scan, leading to the misdiagnosis of thyroid agenesis. In part 2, a sufficient number of babies was studied to permit statistical analysis. As demonstrated in Fig. 1, the 3 infants with the highest TSH binding inhibitory activity (>132 U/L) had a significantly lower mean T_4 concentration on neonatal screening (mean \pm sd, 47 ± 21 vs. 93 ± 39 nmol/L; $P < 0.05$) and a significantly higher TSH level (>200 vs. 85 ± 48 mU/L; $P < 0.05$) than those with TSH binding inhibitory activity less than 132 U/L.

TABLE 1. Clinical and laboratory data of 11 infants with transient congenital hypothyroidism due to maternal TSH receptor-blocking antibodies

Spot No.	Spot TBI/TRAb (% U/L) ^a	Spot T_4 (nmol/L)	Spot TSH (mU/L)	Clinical course	Thyroid scan
Part 1					
157	61	84	>200	Unknown	No uptake
394	55	116	>200	Transient	Normal
320	51	116	75	Transient	Not done
Part 2					
747	>132	39	>200	Transient	No uptake
574	>132	71	>200	Transient	No uptake
A188	>132	<31	>200	Transient	No uptake
A118	57	<31	150	Unknown	Not done
A135	61	84	120	Transient	Normal
784	87	103	120	Transient	Normal
1002	58	84	75	Transient	Not done
A186	72	148	45	Still on Rx.	Not done
Normal	<23/ <37	103–309	<20		

^a In part 1, blocking activity was calculated according to the formula $(1 - [\text{I}^{125}\text{I}]\text{bTSH binding in the presence of test IgG}/1 - [\text{I}^{125}\text{I}]\text{bTSH binding in the presence of normal IgG}) \times 100$ and expressed as percent TSH binding inhibition, TBI. In part 2, the TSH receptor antibody (TRAb) concentration was expressed as units per L by comparison with a standard curve, according to the instructions of the manufacturer.

T₄ (nmol/L) TSH (mU/L)

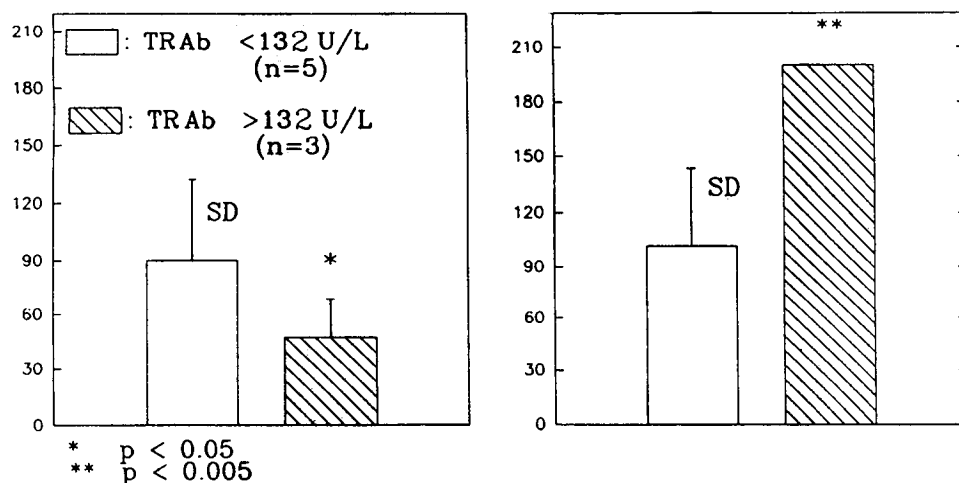


FIG. 1. Relationship between TSH receptor-blocking antibodies and neonatal thyroid function. Infants with the most potent blocking activity (TRAb, >132 U/L; ▨) had a significantly lower T₄ and higher TSH when measured at the time of neonatal screening on the same blood spots than did those with less potent blocking activity (TRAb, <132 U/L; □).

Clinical information in the mothers is presented in Table 2. The 11 babies were born to 9 mothers, all of whom had been diagnosed as having hypothyroidism and were being treated with thyroid hormone. Three of the mothers had been treated initially for Graves' disease. None of the 4 mothers examined had a palpable goiter. Two mothers had more than 1 affected child, and 1 has had, in turn, a normal infant, one with hyperthyroidism, and one with hypothyroidism (11). The presence of TRAb was confirmed around the time of delivery in 3 of the 9 mothers. Blood was obtained in 5 mothers 2.3–7.6 yr after birth (or, in mothers 320 and A188, after the birth of their first affected infants). Potent [¹²⁵I]TSH binding inhibitory activity persisted in all sera at a dilution of 1:40 to 1:160 (Fig. 2). Similarly, all sera studied contained potent *in vitro* blocking activity, as measured by inhibition of TSH-induced stimulation of cAMP, which was detectable in serum at a dilution of 1:50 (Fig. 2). In comparison, the stimulatory effect of most Graves' IgG cannot be demonstrated using unextracted serum in this assay system, but requires prior IgG purification.

There was no apparent loss of blocking activity for at least 6 yr; two positive spots were identified in each of the years 1984, 1985, and 1986, and one in 1989. Furthermore, no significant difference in TSH binding inhibitory activity was observed between spots from control babies with T₄-binding globulin deficiency from 1984 vs. 1989 (13.0 ± 3.6 vs. 14.3 ± 3.9 U/L; P = NS).

In contrast to the striking TSH receptor-blocking activity, TPO antibody concentrations were variable and, in fact, were of only borderline significance in two patients.

Discussion

In this study, we screened neonatal blood spots for TSH binding inhibitory activity to estimate the incidence of transient blocking antibody-induced congenital hypothyroidism in North America and elucidate whether the potency of the blocking antibodies is related to the degree of neonatal hypothyroidism. To attempt to identify all such affected infants,

TABLE 2. Clinical and laboratory data of mothers of infants with transient congenital hypothyroidism

Spot No.	Clinical history	Serum TBI/TRAb (% U/L)	Serum TPO Abs
157	Hypothyroid on Rx.	85.5 ^a	376 ^b
394	Hypothyroid S/P GD on Rx, MGM hypothyroid	82.8 ^a	17.0 ^c
320	Hypothyroid on Rx. MGGM, + maternal aunt with GD	>132	1.3 ^c
747	Hypothyroid on Rx for 9 yr	Not done	Not done
574	Hypothyroid S/P GD on Rx	90.0 ^a	Not done
A188	Hypothyroid on Rx for 7 yr, 2nd infant with CH, MGM with GD	>132	28.0 ^c
A118	Hypothyroid on Rx, GM + aunt with "thyroid problem"	Not done	Not done
A135	Hypothyroid S/P Graves; on Rx	>132	1.5 ^c
784	Hypothyroid on Rx for 2 yr	>132	5.8 ^c
1002	Same as no. 320		
A186	Same as no. 320		
Normal		<15/ <15	

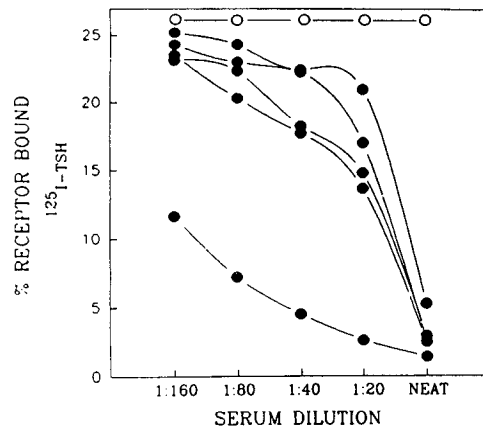
TBI, TSH binding inhibition; TRAb, TSH receptor antibody; Rx, treatment; S/P, status post; GD, Graves' disease; MGM, maternal grandmother; GM, grandmother; MGGM, maternal great grandmother; CH, congenital hypothyroidism.

^a Performed at Nichols Institute (San Juan Capistrano, CA).

^b Performed elsewhere, details not available (normal, <25).

^c Performed in this laboratory, as described in *Materials and Methods* (normal, <1 U/L).

1. Binding Assay



2. Functional Assay*

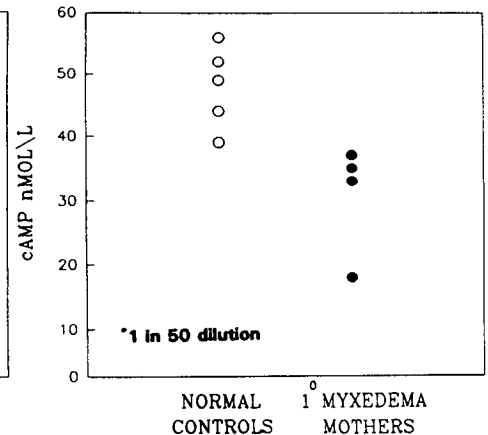


FIG. 2. TSH receptor-blocking activity of maternal serum. Maternal serum (●) obtained 2.3–7.6 yr after delivery of the affected infant still contained potent blocking activity whether measured by RRA (left) or bioassay (right). See text for details. ○, Normal nonpregnant women.

we studied dried blood specimens obtained not only from babies with confirmed congenital hypothyroidism, but from any baby whose initial T_4 was in the lowest 10% for the assay or whose TSH was 40 U/L or more. Nine babies from a total population of 1,614,166 were found to have TSH receptor blocking antibody-induced congenital hypothyroidism, giving an incidence of about 1 in 180,000. As the incidence of congenital hypothyroidism in North America has been estimated to be 1 in 4,000, this suggests that 1 in 45 infants, or approximately 2% of cases of congenital hypothyroidism, are caused by maternal TSH receptor-blocking antibodies.

In all cases, the finding of a blood spot with significant TSH binding inhibitory activity correctly identified a baby with transient congenital hypothyroidism. Furthermore, potent TSH receptor-blocking activity was confirmed in all maternal sera studied. In fact, dose-response studies revealed that the inhibitory activity in maternal serum, which was evaluated as long as 7 yr after the baby's birth, was sufficiently potent that it could be demonstrated at a 1:40 to 1:200 dilution of serum in the RRA and at a 1:50 dilution in the bioassay employed. Although the underlying immunological mechanisms remain unclear, the persistence of these blocking antibodies in some patients for many years explains the tendency for a mother to have multiple affected offspring. The tendency for others to switch from secreting a preponderance of stimulatory to blocking antibodies complicated in some cases by decreased thyroid gland responsiveness is the basis for the change from hyperthyroidism to hypothyroidism (11, 12). Hypothyroidism can also precede hyperthyroidism (13). In rare instances, a more complicated neonatal picture can result due to the coexistence of blocking antibodies and stimulatory ones. In this case, a delayed onset of neonatal Graves' disease occurs because of the progressive dilution of the more potent inhibitory effect over time (14). In the present study, two mothers had more than one affected infant, and one patient has had successively a normal, a hyperthyroid, and a hypothyroid baby. For these reasons, genetic counselling is of utmost importance to alert mothers of the high risk of recurrence and to ensure prompt evaluation (and treatment) of all subsequent offspring.

Babies with the most potent TSH binding inhibitory ac-

tivity had the most profound hypothyroidism, as determined by thyroid function testing on the same dried blood specimens and had the most severe inhibition of radioisotopic uptake on thyroid scan. These findings as well as the transient course in all babies identified provide strong evidence that the maternal blocking antibodies were of etiological importance in the hypothyroidism observed. This relationship between blocking activity and the severity of congenital hypothyroidism in the offspring has been reported previously in maternal serum (15, 16). Maternal sera also inhibited recombinant human TSH-induced adenyl cyclase stimulation of recombinant human TSH receptor, verifying that the blocking antibodies inhibited the action of TSH on the human receptor *in vitro*.

Despite being exposed to potent TSH receptor-blocking activity *in utero*, these infants did not develop any long term abnormality in thyroid function. This is consistent with the fact that TSH receptor-blocking antibodies, like other IgG, do not cross the placenta until 16 weeks (17) and, therefore, could not play a role in early thyroid embryogenesis.

All mothers, like those identified in previous studies (3–5, 7) had underlying autoimmune thyroid disease. All were receiving thyroid replacement because of hypothyroidism, and in three, this had been preceded by a hyperthyroid phase. This suggests that only babies born to mothers with underlying autoimmune thyroid disease are at risk for the development of blocking antibody-induced congenital hypothyroidism. However, severe hypothyroidism in some mothers was not diagnosed until they were postpartum, and their babies were found to have congenital hypothyroidism due to TSH receptor-blocking antibodies (18). Also, it should be emphasized that TPO antibodies, although detectable in all mothers, were of no use in predicting the development of transient disease in the neonate.

In summary, we estimate the incidence of TSH receptor-blocking antibody-induced congenital hypothyroidism to be 1 in 180,000, or about 2% of all cases of congenital hypothyroidism. Whether routine screening for the presence of maternal TSH receptor-blocking antibodies should be performed in all babies with congenital hypothyroidism and whether mothers or babies should be studied will

depend on further information about the prevalence of these antibodies in pregnant women, a careful cost analysis, and whether decreased intellectual ability occurs in some of these infants despite adequate postnatal therapy. In the meantime, the diagnosis should be suspected whenever congenital hypothyroidism is diagnosed in the baby of a mother with hypothyroidism due to autoimmune thyroid disease, particularly if previous offspring have had congenital hypothyroidism. Similarly, any baby with eutopic thyroid tissue evident on thyroid ultrasound should be studied regardless of the thyroid scan result.

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