

Neonatal transient hypothyroidism: aetiological study

G Weber, M C Vigone, A Rapa, G Bona, G Chiumello, on behalf of the Italian Collaborative Study on Transient Hypothyroidism

Abstract

Aims—To define the aetiology of neonatal transient hypothyroidism (NTH) and recommend preventive measures.

Methods—Maternal and perinatal clinical data on the use of antiseptics, drugs, and contrast agents containing iodine were collected from 40 subjects. Thyroid stimulating hormone (TSH), free thyroxine (FT4), thyroxine (T4), thyroglobulin (TG), TSH receptor antibodies, thyroid peroxidase antibodies and urinary iodine were measured in random neonatal samples. In the mothers with known or suspected thyroid disorders, TSH, FT4, TSH receptor antibodies and thyroid peroxidase antibodies were also measured.

Results—The NTH aetiology was identified in 85% of cases. More than 50% of the babies with transient hypothyroidism had been exposed to iodine; maternal transfer of antibodies had occurred in a third of them.

Conclusions—It is suggested that the practice of using iodine containing disinfectants should be withdrawn, and chlorhexidine substituted instead; that pregnant women should be advised of the adverse effects of using iodine products; and that thyroid function should be monitored whenever iodine is used.

(Arch Dis Child Fetal Neonatal Ed 1998;79:F70-F72)

Keywords: transient hypothyroidism; screening; iodine; thyroid antibody

Neonatal screening programmes for congenital hypothyroidism can detect permanent and transient thyroid gland dysfunction.¹ The incidence of transient hypothyroidism varies from 1 in 8400 in Berlin² to 1 in 700 in Belgium, an iodine deficient area.³ In Italy neonatal screening for congenital hypothyroidism indicates that the incidence of transient hypothyroidism has increased. In one region of northern Italy the incidence was 1 in 2707 and 1 in 2741, in 1994 and 1995, respectively.

Environmental, maternal, and neonatal factors have an important role in determining the extent of neonatal transient hypothyroidism (NTH) (table 1). NTH may be due to either too much or too little iodine. In moderate to severe iodine deficiency, up to 10% of neonates have transient hypothyroidism, characterised by high thyroid stimulating hormone (TSH) and low thyroxine (T4). An even higher percentage have hyperthyrotropinaemia with normal T4.^{4,5} Paradoxically the iodine excess blocks iodine uptake by the thyroid gland and

inhibits hormone synthesis. This phenomenon is called the Wolff-Chaikoff effect.⁶⁻¹⁰ The risk of this effect is the same in an iodine sufficient area as it is in an iodine deficient one.¹¹ Premature infants are considered to be particularly susceptible to iodine excess.¹²⁻¹⁸ Maternal thyroid antibodies are another important aetiopathogenic cause of permanent and transient congenital hypothyroidism.¹⁹ A recent report described the prevalence of thyroid transient disorder, due to maternal thyrotropin receptor blocking, as 1 in 180 000 normal infants in North America, or put another way, roughly 2% of babies have congenital hypothyroidism.²⁰

The neonatal screening programme detects many cases of transient dysfunction, but the high recall rate increases costs and causes unnecessary psychological stress in many families. In any case, the consequences of NTH on the long term neurological development of infants are unknown. Therefore, to determine possible preventive measures we investigated the aetiology of transient hypothyroidism.

Methods

We performed a collaborative study from 1994 to 1996 with 10 paediatric centres. We studied 40 babies (26 boys, 14 girls), seven of whom were preterm neonates, with a normally sited thyroid gland on ultrasonography and who were positive on screening for congenital hypothyroidism (TSH \geq 20 mcU/ml, on dried blood on filter paper, collected at 3-5 days of life). High TSH values were confirmed in a second sample performed on blood spots. When TSH was evaluated on serum samples, lower TSH values were recorded in 35 patients. These patients' TSH values normalised by day 30 of life. Five patients had raised TSH activities both in spot and serum samples. Therefore, L-thyroxine treatment was maintained until 2 years of age, when a complete re-evaluation of thyroid function was performed.

Table 1 Environmental, maternal and neonatal factors in neonatal transient hypothyroidism

<i>Environmental factors</i>
Iodine deficiency
<i>Maternal factors</i>
Immunological: Thyroid antibodies (microsomal and TSH receptor)
Iatrogenic: Drugs (amiodarone, mucolytic, anti-asthmatic, antithyroid Iodine disinfection (caesarean section, vaginal application, epidural anaesthesia)
<i>Neonatal factors</i>
Iatrogenic: Iodine disinfection (umbilical cord, presurgical intervention)
Contrast media (venous catheterisation, radiological investigation)

The Members of the Italian Collaborative Study on Transient Hypothyroidism are:

P Torresani
R Longhi
P Bini
M Maccabruni
F Frisone
E Cacciari
A Cassio
F Severi
D Larizza, C de Sanctis
A Corrias
R Zannini
R Masperi
I Moschini
P Costa

Department of Paediatrics, Scientific Institute H San Raffaele University of Milan
G Weber
M C Vigone
G Chiumello

Department of Paediatrics Ospedale Maggiore Novara University of Torino
A Rapa
G Bona

Correspondence to:
Dr Giovanna Weber
Clinica Pediatrica III
H San Raffaele
Via Olgettina 60
20132 Milano
Italy.

Accepted 14 January 1998

We obtained maternal and perinatal histories, focusing in particular on the use of disinfectants, drugs, and contrast agents containing iodine.

Serum TSH, free thyroxine (FT4), T4, thyroglobulin (TG), TSH receptor antibodies, thyroid peroxidase antibodies and urinary iodine were measured in random samples from 35 neonates at diagnosis and in five treated children at 2 years of age, after L-thyroxine had been withdrawn. TSH, FT4, TSH receptor and thyroid peroxidase antibodies were also measured in mothers with known or suspected thyroid disorders and in those whose babies had anti-thyroid antibodies.

TSH and T4 were measured using an enzyme linked immunoabsorbent assay (ELISA; Enzymum testTSH, Boehringer Mannheim Immunodiagnosics, Germany); FT4 was measured using a radioimmunoassay (Free T4 solid phase component system, Becton Dickinson Immunodiagnosics, Orangeburg, New York); thyroglobulin was measured using time resolved fluoroimmunoassay (DEL-FIA thyroglobulin (hTG), Wallac, Oy, Turkyu, Finland); thyroid microsomal antibodies were measured using an agglutination test (SERODIA-AMC, Fujirebio Inc., Tokyo); TSH receptor autoantibody was measured using a radioreceptor assay (TRAB ¹²⁵I, RADIM, Angleur, Liège); urinary iodine was measured using the Sandell-Kolthoff method. Urine samples were frozen in plastic tubes at -20°C until tested. The specimens were digested with perchloric acid under mild conditions and iodine content was measured according to its catalytic action to reduce ceric ammonium sulphate (yellow) to the cerous form (colourless) in the presence of arsenious acid.²¹ Urinary iodine excretion was expressed as mcg/l.

Results

The 40 neonates examined were divided into three groups on the basis of clinical history and biochemical data: group A: iodine exposure (23 neonates, 58%); group B: positive antibodies (11 neonates, 27%); group C: no suggestive data (6 neonates, 15%).

In group A neonatal transient hypothyroidism from iodine overload was caused by maternal iodine exposure in 11 cases and neonatal exposure in 12 cases. Antiseptics containing iodine were used for vaginal applications before and after giving birth in two mothers, in seven mothers at delivery (caesarean section in five cases), while a skin disinfectant was applied in the second trimester of pregnancy to two mothers.

Among the neonates topical iodine antiseptics were applied for skin disinfection (before and after surgical intervention) in three cases and for umbilical cord disinfection in four neonates; moreover, iodine containing contrast media were used in four subjects for venous catheterisation and in one case for urography. The urinary iodine excretion of group A is shown in fig 1. We found a remarkably high urinary iodine excretion (>1000 mcg/l) in six subjects (26%); urine collection was performed

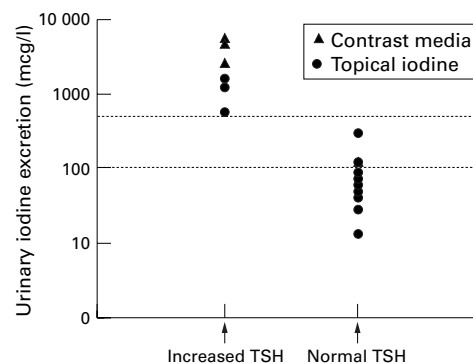


Figure 1 Association between urinary iodine excretion and TSH values. TSH was collected soon after exposure (raised) and when it had returned to normal values (normal).

soon after iodine exposure. In the other 17 cases (74%) a low value of iodine excretion was found in the urinary samples collected when TSH had already returned to normal values. Serum thyroglobulin was high (> 100 ng/dl) in all cases evaluated in the first month of life, returning to normal values by the third month of life.

Group B was identified by the presence of thyroid antibodies: positive thyrotropin receptor blocking antibodies were found in four neonates and positive thyroid peroxidase antibodies in seven. Maternal history was positive for autoimmune thyroid disease in five cases (three Hashimoto's thyroiditis, one Graves' disease, and one thyromegaly during the second trimester of pregnancy), while the six other mothers had positive antibodies. We found normal urinary iodine excretion in eight neonates and low values of iodine excretion in the other three. Serum thyroglobulin was measured in only four subjects, with heterogeneous results.

In group C clinical and biochemical data could not determine the aetiology of NTH. Low urinary iodine excretion was found in one subject but it was normal in the others. Serum thyroglobulin was high in all three cases examined.

Discussion

We were able to determine NTH aetiology in 85% of the cases. We documented maternal or neonatal iodine exposure in more than 50% of the subjects with transient hypothyroidism. Our study shows that there are several pathways of iodine overload in infants. Maternal skin disinfection with iodine (povidone iodine) is widely used by obstetricians during delivery or for vaginal application. Povidone solution applied at delivery increases iodine concentrations in breast milk even as late as the 5th postpartum day.¹¹ Neonates are particularly sensitive to iodine excess because their skin is especially permeable, iodine trapping processing in the thyroid gland is very active, and iodine renal clearance is low. Premature babies are even more susceptible and a lower iodine overload may impair their thyroid function. Escobar *et al* reported that thyroid complications due to iodine exposure should

be suspected in those premature infants with urinary iodine concentrations greater than 200 mcg/l.¹⁶

We underline the importance of obtaining an accurate clinical history of iodine exposure. We have often found that mothers are not fully aware that iodine products were used during pregnancy, delivery, and after birth. Moreover, our experience tells us that mothers are rarely aware of the topical treatments used in obstetric wards. Consequently, it is often difficult to obtain the necessary clinical data; therefore, we suggest contacting the hospital where the baby was born when a positive result on neonatal screening for congenital hypothyroidism is obtained in neonates with a normally sited thyroid gland.

Our data show that only one patient had NTH caused by iodine deficiency, but other studies have shown that neonates born in iodine deficient areas have impaired thyroid function.^{5 22 23}

In our study the second most frequent cause of NTH was transplacental passage of thyroid antibodies, either anti-thyrotropin receptor or anti-thyroid peroxidase. Thyroid autoimmunity might be involved in the pathogenesis of some forms of permanent and transient congenital hypothyroidism.¹⁸ Recently, a change in thyroid function has been detected in 20% of mothers of neonates with congenital hypothyroidism compared with 8–10% of normal pregnancies (Abstract presented at the Fifth Joint Meeting of the European Society for Paediatric Endocrinology, Stockholm June 1997). We underline the fact that maternal history was negative for autoimmune thyroid dysfunction in more than half of the neonates with positive antibodies; therefore, maternal thyroid dysfunction is often unknown.

In conclusion, we identified the aetiology of NTH in most cases. For this, it is essential to obtain an accurate clinical history and to measure urinary iodine excretion. However, we would like to point out that urinary iodine excretion data are strongly influenced by the timing of iodine exposure. It is also important to exclude maternal thyroid disease by assay of thyroid antibodies and hormones.

Our data, like those of Chanoine,²⁴ suggest that iodine exposure is the most common cause of NTH. We suggest the following preventive measures:

- (1) withdrawing iodine disinfection from obstetric clinics and neonatal departments, using chlorhexidine as a skin disinfectant instead²⁵;
- (2) informing pregnant women of the adverse effects of iodine disinfectants or products;
- (3) using radio opaque catheters for venous catheterisation;
- (4) monitoring thyroid function when iodine is used.

These measures should help to decrease the recall rate after screening for congenital hypothyroidism and unnecessary psychological stress in many families. However, to prevent

any delay in treatment, it is better to start treatment and then, later in childhood, confirm the transient nature of the condition: we treated five patients for 2 years in this way. Long term neuropsychological follow up of neonates with NTH is desirable to identify possible negative effects on their neurological development.

- 1 American Academy of Pediatrics. Newborn screening for congenital hypothyroidism: recommended guidelines. *Pediatrics* 1993;**91**:1203-9.
- 2 Gruters A, Kohler B, Schnabel D, Helge H. Follow up of thyroid function, thyroid size, and development in children with transient neonatal hypothyroidism up to the age of 14 years. *J Endocrinol Invest* 1994;**17**:59.
- 3 Delange F, Dodion J, Walter R, et al. Transient hypothyroidism in the newborn infant. *J Pediatr* 1978;**92**:974-6.
- 4 Calaciura F, Mendola G, Distefano M, et al. Childhood IQ measurements in infants with transient congenital hypothyroidism. *Clin Endocrinol* 1995;**43**:473-7.
- 5 Sava L, Delange F, Belfiore A, Purrello F, Vignieri R. Transient impairment of thyroid function in newborns from an area of endemic goiter. *J Clin Endocrinol Metab* 1987;**59**:90-5.
- 6 Delange F. Iodine. *Annales Nestlé* 1994;**52**:81-93.
- 7 Braverman LE. Thyroid dysfunction induced by excess iodine. In: Delange F, et al, eds. *Iodine Deficiency in Europe*. New York: Plenum Press, 1993:79-88.
- 8 Lin C-P, Chen W, Wu K-W. Povidone-iodine in umbilical cord care interferes with neonatal screening for hypothyroidism. *Eur J Pediatr* 1994;**153**:756-8.
- 9 Gordon CM, Rowitch DH, Mitchell ML, Kohane IS. Topical iodine and neonatal hypothyroidism. *Arch Pediatr Adolesc Med* 1995;**149**:1336-9.
- 10 Chabrolle JP, Rossier A. Gotre and hypothyroidism in the newborn after cutaneous absorption of iodine. *Arch Dis Child* 1978;**53**:495-8.
- 11 Harada S, Ichihara N, Arai J, Honma H, Matsuura N, Fujieda K. Influence of iodine excess due to iodine containing antiseptics on neonatal screening for congenital hypothyroidism in Hokkaido prefecture, Japan. *Screening* 1994;**3**:115-23.
- 12 Fisher DA. Euthyroid low thyroxine (T4) and triiodothyronine (T3) states in prematures and sick neonates. *Pediatr Clin North Am* 1990;**37**:1297-312.
- 13 Van Wassenaeer AG, Kok JH, Endert E, Vulsma T, de Vijlder JM. Thyroxine administration to infants of less than 30 weeks' gestational age does not increase plasma triiodothyronine concentrations. *Acta Endocrinol* 1993;**129**:139-46.
- 14 Meijer WJ, Verloove-Vanhorick SP, Brand R, van den Brande JL. Transient hypothyroxinaemia associated with developmental delay in very preterm infants. *Arch Dis Child* 1992;**67**:944-7.
- 15 Smerdely P, Boyages SC, Wu D, et al. Topical iodine-containing antiseptics and neonatal hypothyroidism in very low birthweight infants. *Lancet* 1989;**ii**:661-4.
- 16 Ares S, Pastor J, Quero J, Morreale de Escobar G. Thyroid complications, including overt hypothyroidism, related to the use of non-radiopaque silastic catheters for parenteral feeding in prematures requiring injection of small amounts of an iodinated contrast medium. *Acta Paediatrica* 1995;**84**:579-81.
- 17 L'Allemand D, Gruters A, Beyer P, Weber B. Iodine in contrast agents and skin disinfectants is the major cause for hypothyroidism in premature infants during intensive care. *Hormone Res* 1987;**28**:42-9.
- 18 Chiovato L, Lapi P, Santini F, et al. Autoimmunità tiroidea e ipotiroidismo congenito. *Ann Super Sanità* 1994;**30**:317-23.
- 19 Brown RS, Bellisario RL, Botero D, et al. Incidence of transient congenital hypothyroidism due to maternal thyrotropin receptor-blocking antibodies in over one million babies. *J Clin Endocrinol Metab* 1996;**81**:1147-51.
- 20 Parravicini E, Fontana C, Paterlini GL, et al. Iodine, thyroid function, and very low birth weight infants. *Pediatrics* 1996;**98**:730-4.
- 21 Wawshinek O, Eber O, Petek W, Wakonig P, Gurakar A. Bestimmung der harnjodausscheidung mittels einer modifizierten-cer-arsenitmethode. *Berichte OGKC* 1985;**8**:13-15.
- 22 Vermiglio F, LoPresti VP, Scaffidi AG, et al. Maternal hypothyroxinemia during the first half of gestation in an iodine deficient area with endemic cretinism and related disorders. *Clin Endocrinol* 1995;**42**:409-15.
- 23 Trimarchi F, Vermiglio F, Finnochiario MD, et al. Epidemiology and clinical characteristics of endemic cretinism in Sicily. *J Endocrinol Invest* 1990;**13**:543-8.
- 24 Chanoine JP, Boulvain M, Bourdoux P. Increased recall rate at screening for congenital hypothyroidism in breast fed infants to iodine overloaded mothers. *Arch Dis Child* 1988;**63**:1207-10.
- 25 Alder VG, Burman D, Simpson RA, Fysh J, Gillespie WA. Comparison of hexachlorophane and chlorhexidine powders in prevention of neonatal infections. *Arch Dis Child* 1980;**55**:277-80.