

Transient hypothyroxinaemia associated with developmental delay in very preterm infants

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Abstract

In 563 surviving very preterm (<32 weeks gestational age) and/or very low birthweight (<1500 g) infants the relationship between neonatal thyroxine concentration and psychomotor development at 2 years of age (corrected for preterm birth) was studied. A significant association was found between low neonatal thyroxine concentration and a negative score on the three milestones of development. These findings do not support the view that transient hypothyroxinaemia in preterm infants is harmless.

Low thyroxine concentrations are very common in the first weeks of life in preterm and low birthweight infants. The thyroxine values are inversely related to gestational age and birth weight,¹⁻³ and severity of respiratory and other neonatal disease.^{1 4 5} Such transient hypothyroxinaemia is viewed by many as an adaptive process.^{1 2 4 5} However, its significance for later development has not been established for lack of large prospective studies, and the need for thyroid hormone replacement is controversial.⁶

We used the opportunity presented by a nationwide collaborative survey on very preterm and very low birthweight infants in The Netherlands to study the relationship between thyroxine values, as measured routinely in the national screening programme for congenital hypothyroidism, and later psychomotor development of the study infants as assessed in the follow up programme.

Patients and methods

The Project on Preterm and Small for Gestational Age Infants in The Netherlands is a collaborative survey collecting data on 1338 infants, liveborn in 1983 with a gestational age of less than 32 weeks and/or a birth weight of less than 1500 g.^{7 8} The surviving infants all entered a standardised follow up programme up to 2 years of age, corrected for preterm birth. Examinations were performed by the local paediatricians, and the results were recorded on pre-coded forms designed to minimise the risk of interobserver variability.^{9 10}

Psychomotor development was assessed at the corrected age of 2 years, using the Gesell test adapted for Dutch children (revised Van Wiechen test) after oral and written instruction following the standardised guidelines for this test.^{11 12} For the present study, the items obtained by history were omitted because of possible bias in reporting from the mother. The

three developmental milestones chosen for analysis were obtained by direct observation of the child: 'builds tower of three blocks' (fine motor behaviour and coordination), 'walks without support' (gross motor function), and 'puts ball in box upon request' (passive language). Each of these milestones is reached at the age of 24 months by 90% of a group of normal children.¹¹

These items were chosen as indicators of the effect of transient hypothyroxinaemia on development on theoretical grounds: the effect of a noxious influence on the developing nervous system depends on the postconceptional period in which the nervous system is exposed.¹³ The postconceptional period of transient hypothyroxinaemia in the study group resembles the period of prenatal hypothyroidism in early treated (before the age of 1 month) term born patients with congenital hypothyroidism. Prenatal hypothyroidism (retarded bone age, more marked hypothyroidism at birth) increases the risk of developmental delay at the age of 1.5 to 3 years—that is, a delay in psychomotor development which is not confined to one field of behaviour.¹⁴⁻¹⁸ Therefore, based on this analogy, the chosen measure of developmental delay in our study represents developmental delay which is not confined to one area of development: a developmental delay was assumed to be present when at least one of the three selected milestones was not reached.

Although the national screening programme for congenital hypothyroidism prescribes testing between days 6 and 8, in practice only about 70% of all newborn infants are actually screened at that age; 97% are screened within 14 days from birth.¹⁹ In preterm infants, the delay in screening is greater.

Out of 944 children assessed at the corrected age of 2 years, screening values between days 5 and 17 could be obtained and linked to the follow up data in 563 cases (of which 479 (85%) had been tested between days 6 and 11). Missing values were caused mainly by a later start in the collection of thyroxine values (mid-April) compared with the perinatal data (1 January) and missing birth weight and gestational age in screening data, prohibiting linking (n=311); missing thyroxine values because heel puncture was performed before day 5 or after day 17 (n=56); by exclusion of disabling congenital malformations (n=7), permanent primary congenital hypothyroidism (n=1), and infants with temporary thyroid hormone replacement (n=5); and unknown duration of ventilatory support (n=1). Comparison of prenatal and perinatal characteristics showed no

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Table 1 Characteristics of the study group

	Study group (n=563)	Source population* (n=953)
<i>Mean (SD)</i>		
Gestational age (weeks)	31.0 (2.6)	31.0 (2.5)
Birth weight (g)	1275 (257)	1315 (283)
Highest bilirubin concentration (µmol/l)	176 (43)	178 (45)
Average increase in body weight (g/day)	20.1 (4.2)	20.2 (4.4)
<i>Number (%)</i>		
Male	280 (49.7)	486 (51.0)
Small for gestational age	288 (40.5)	354 (37.1)
Apgar score ≥7	471 (83.7)	792 (83.1)
Respiratory distress syndrome	221 (39.3)	371 (38.9)
Intracranial haemorrhage and/or convulsions	97 (17.2)	174 (18.3)
Septicaemia	171 (30.4)	318 (33.4)
Duration of ventilatory support (days):		
0	287 (51.0)	490 (51.4)
1-7	163 (29.0)	267 (28.0)
8-28	95 (16.9)	165 (17.3)
≥29	18 (3.2)	31 (3.3)

*Project on preterm and small for gestational age infants.^{7-10 12 24-26}

important differences (table 1), and therefore we assume that no selection bias has occurred.

Thyroxine values were measured as part of the national screening for congenital hypothyroidism.²⁰ In addition, a second measurement of thyroxine was performed on special request for the present study in 443 infants between 18 and 39 days of age. Thyroxine concentrations from filter paper eluates were determined in duplicate by radioimmunoassay²¹ in five laboratories with permanent laboratory quality control,²² each with an average of 125 samples per day. Thyroxine in the eluates was expressed as standard deviations about the mean calculated on a daily basis.²³ When appropriate, thyroxine (T4) values have been calculated using a regression equation (T4 (SD) = -4.065 + 0.0184 × T4 nmol/l), based on a correlation of simultaneously obtained blood spot thyroxine and serum thyroxine in 115 low birthweight infants on the seventh day of life, determined in the same laboratory.¹

The relationship between thyroxine concentration and developmental outcome was studied using cross tabulations as well as multivariate stepwise logistic regression analysis with unconditional maximum likelihood estimation PROC LOGIST, Statistical Analysis System. Possible confounding factors were agreed before analysis, based on clinical experience and literature^{7-9 24-26}: infant's sex, gestational age, birth weight, weight for gestational age (<10th centile),^{27 28} Apgar score at 5 minutes (<7), age at thyroxine screening (in days), and highest observed neonatal serum bilirubin concentration (µmol/l). Covariables, related to neonatal disease, were: intracranial haemorrhage (clinical

diagnosis based on rapid or saltatory deterioration, fall in erythrocyte sedimentation rate, and/or ultrasound or computed tomography),^{24 26} seizures (irrespective of duration), respiratory distress syndrome (clinical diagnosis based on the need for extra oxygen for more than 24 hours, expiratory grunting, tachypnoea, sternal and intercostal retractions and nasal flaring, and/or typical radiograph),²⁶ and sepsis (haematological findings of typical white cell count and/or positive blood culture).²⁶

To control for severity of disease, two additional variables were included in the analysis: ventilatory support (total number of days of intermittent positive pressure ventilation or continuous positive airway pressure) which indicated the severity of respiratory disease, and the mean weight gain during hospital stay (g/day). Finally, a separate analysis was done in the subset of 228 infants in which grading of intracranial haemorrhage according to Papile²⁹ was possible.²⁴

The adjusted odds ratios are derived from logist regression including all confounding factors listed above.

All statistical tests were two sided and a p value of less than 0.05 was considered to be significant.

Results

Mean thyroxine concentration in the 563 study infants was -2.4 (recalculated as 91 nmol/l), which is considerably below the mean (SD) of the total screened population, which by definition is 0 (1 SD), or 221 (54) nmol/l. The range was -5.0 to +0.5 SD.

Psychomotor development, as assessed by the three items described, was normal in 473 (84%) of the children, scoring all items positively. No relation was found between thyroxine and any of the three items separately. However, there was a significant association between thyroxine concentration and the number of children scoring negatively on at least one of the three items. Crude risks, odds ratios, as well as adjusted odds ratios, showed a linear increase of risk (table 2).

Assuming a linear relation, the overall crude odds ratio (not adjusted for potential confounding) for 1 SD decrease in thyroxine was 1.4 (p<0.01), implying a 40% increase in the odds that developmental delay will occur. After adjusting for the potential confounders, as mentioned in the patients and methods section, the odds ratio did not change appreciably, neither after adjusting for each covariable separately

Table 2 The association of thyroxine and psychomotor development (n=563)

Thyroxine (SD)	Calculated thyroxine (nmol/l)	Psychomotor development		Risk	Odds	Crude OR*	Crude overall OR	OR computed by regression analysis		
		Normal	Delay					Without adjusting	Adjusted†	Adjusted overall OR by 1 SD (95% CI)
≥-1.0	≥164	41	3	0.07	0.07	—	—	—	—	1.4‡ (1.1 to 1.9)
-1.1 to -2.0	110-163	121	15	0.11	0.12	1.7	1.4	1.2	1.1	
-2.1 to -3.0	56-109	177	38	0.18	0.21	2.9		2.0	1.9	
≤-3.1	≤55	134	34	0.20	0.25	3.5		3.5	3.5	

OR, odds ratio.

*Relative to the group with thyroxine ≥-1.0 SD; test for trend, p=0.003.

†Adjusted for possible confounding factors, mentioned in the patients and methods section.

‡p=0.01.

nor after adjusting for all covariables simultaneously. The overall adjusted odds ratio was 1.4 (95% CI 1.1 to 1.9). In the subset of 228 infants with a known degree of intracranial haemorrhage,²⁴ the crude adjusted odds ratios were the same as in the total study group; including the degree of intracranial haemorrhage in the analysis did not alter the odds ratio. Within the group of 90 children with developmental delay (at least one negative item), no relation was found between thyroxine concentration and number of negative items (Kruskal–Wallis one way analysis of variance $p > 0.5$).

Discussion

This study shows an association between thyroxine concentration and later psychomotor development in very preterm and very low birthweight infants who, having survived the first few days of life, took part in the national screening programme for congenital hypothyroidism. Even after adjusting for a number of obvious possible confounding factors representing degree of prematurity and severity of neonatal disease, a significantly increased risk of developmental delay was found in children with relatively lower neonatal thyroxine concentrations.

Preterm birth and severity of neonatal disease are known to be associated with both lower thyroxine values and poor developmental outcome.²⁻⁹ Therefore a major concern in this study was to preclude the possibility that the observed association between lower thyroxine and development delay was an artefact, with a common cause (preterm birth, neonatal disease). In our data, the overall odds ratio remained entirely unaffected after adjusting simultaneously for the carefully selected potential confounders, which virtually precludes the possibility of substantial residual confounding of this overall association. The 13 potential confounders which were included represent immaturity and neonatal disease. It is hardly imaginable that some fourteenth confounder would be able to cause any appreciable shift in the thyroxine developmental odds ratio after adjustment for 13 other confounders.

The systematic increase in the risk of developmental delay with decreasing thyroxine concentrations suggests the possibility of a causal relationship. The available literature on the essential function of thyroid hormones in growth and developmental of the nervous system³⁰⁻³⁶ supports such a hypothesis. Thyroxine and triiodothyronine act on brain development and maturation by binding to triiodothyronine nuclear receptors. Serum thyroxine is the major source of brain triiodothyronine: approximately 70–80% of the triiodothyronine used by the cerebral cortex is produced in situ from thyroxine by a local 5'-deiodinase.³⁷⁻⁴⁰ Thus, low serum thyroxine rather than low serum triiodothyronine indicates poor availability of thyroid hormones for the nervous system. In the animal model a deficiency of thyroid hormones leads to inhibition of cell differentiation and impaired myelination in a short critical age period.³¹⁻³³ In 33

very preterm (≤ 31 weeks) and very low birthweight (≤ 1500 g) infants, prolonged hypothyroxinaemia was associated with a delay in progression in nerve conduction velocity, especially in those infants who also required ventilation.⁴¹ These results suggest that transient hypothyroxinaemia may interfere with neurological maturation. Furthermore, in our study group low thyroxine values were associated with a delay in psychomotor development not confined to one area of development; a similar type of delay was observed in early treated patients with congenital hypothyroidism.^{14-16 18}

As the duration of relevant hypothyroxinaemia may be important, the second measurement of thyroxine (between days 18 and 39, available in 443 infants) was included in an additional analysis. No association with outcome was observed, and neither was the observed association with early thyroxine concentrations changed. Possibly some compensatory mechanisms occur such as observed in the newborn hypothyroid rat⁴²: an increased activity of 5'-deiodinase in the cerebral cortex,³⁷ coincident with a reduction of the rate of degradation of triiodothyronine.³⁹ These mechanisms act to keep the cerebrocortical content of triiodothyronine at euthyroid concentrations even when serum concentrations of thyroxine are severely reduced.³⁹ The nervous system in newborn rats is comparable with the nervous system in humans in the third trimester of gestation and it has been suggested that in the hypothyroid human fetus these protective mechanisms may develop.⁴² As very preterm infants in the first weeks of life have a similar postconceptional age, the same protective mechanisms may develop in reaction to the reduced thyroxine levels. We are not aware of previous epidemiological studies in which the effect of transient hypothyroxinaemia was studied in a large population of very preterm or very low birthweight children. Lucas *et al* reported that low plasma triiodothyronine (lowest recorded concentration < 0.3 nmol/l) in a cohort of 280 infants with birth weight below 1850 g was associated with the risk of developmental disadvantage at 18 months' corrected age.⁴³ Because in the nervous system hypothyroidism is caused by low serum thyroxine rather than low serum triiodothyronine,³⁷⁻⁴⁰ the reported association of low serum triiodothyronine with delayed development may reflect the underlying effect of low serum thyroxine on the development of the nervous system.

In earlier studies^{44 45} such a delay was not observed. However, in one study⁴³ where the number of infants was very small, thyroxine concentrations were measured in cord blood and development was assessed at a younger age. The thyroid hormone replacement trial⁴⁵ compared only five treated children to three non-treated children at 12 months of age, and even fewer at 24 months. In such studies, the detection of a significant relationship is virtually impossible.

Although transient hypothyroxinaemia does not seem to be associated with gross damage, it may contribute to developmental delay. Our

findings do not support the view that low thyroxine concentrations in preterm infants are harmless and that these infants do not require replacement treatment. The presumed undesirable effects of thyroid hormone supplementation on metabolism and oxygenation in the first weeks of life should be weighed against the possible benefits in terms of a more favourable developmental outcome at a later age.

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