Replacement therapy of secondary hypothyroidism in children born with low body weight improves mental development

Iwona Ben-Skowronek, Magdalena Wisniowiecka

Department of Paediatric Endocrinology and Diabetology, Medical University, Lublin, Poland


Abstract

Background. Secondary hypothyroidism is observed in children after brain damage. The aim of the study was evaluation of the mental development in preterm-born children during replacement therapy with l-thyroxin because of secondary hypothyroidism.

Materials and Methods. The motor and mental development of preterm newborns with secondary hypothyroidism treated with l-thyroxin since the second week of life were compared with the development of preterm newborns with secondary hypothyroidism treated since the fourth week, or later. Motor development was evaluated, and the mental development and IQ assessed by the Wechsler Intelligence Scale for Children in the seventh year of life.

Results. Earlier achievement of the milestones of motor development, i.e. sitting, standing, and walking, was observed in children from the group who received early treatment with modest doses of l-thyroxin. In this group, all infants acquired the motor functions statistically significantly earlier in comparison to the infants from group with delayed treatment. In the seventh year of life, the IQs were significantly higher in group I treated since the second week of life, compared to group II.

Conclusions. The early replacement therapy with l-thyroxin initiated in the second week of life may improve long-term mental development in children.

Key words

secondary hypothyroidism, motor development, mental development, replacement therapy

Introduction

The thyroid gland produces triiodothyronin (T3) and thyroxin (T4) in response to pituitary gland stimulation. The body can convert T3 to T4, and a biofeedback mechanism maintains adequate levels of thyroxin for body metabolism and, in new-borns, normal growth and brain development: proliferation of neurons including dendrite formation, and synaptogenesis, such as the process of myelin formation [1, 2]. Thyroxin deficiency in infancy can cause severe, irreversible mental and physical retardation, a condition known historically as cretinism.

Secondary hypothyroidism is observed in children after brain damage and insufficiency of the hypothalamus or/and the pituitary gland. This disorder is not detected by screening tests, as only TSH levels greater than 15 IU/ml can be detected by screening.

Even children who receive too late thyroid hormone replacement therapy for congenital hypothyroidism have motor and cognitive deficits that persist until late childhood [3]. Infants born prematurely also have a high incidence of motor and cognitive deficits that are worse at lower gestations [4]. There is insufficient evidence from controlled clinical trials to determine whether the use of thyroid hormones for the treatment of preterm infants with transient hypothyroxinaemia results in changes in neonatal morbidity and mortality, or reductions in neurodevelopmental impairments [5].

Thyroid hormones have effects not only on neurological development, but also on the respiratory and cardiovascular systems, and somatic growth. Separate reviews address the use of prophylactic postnatal thyroid hormones for prevention of morbidity and mortality in preterm infants, and postnatal thyroid hormones for treatment of preterm infants with respiratory distress syndrome [6, 7].

One underpowered randomized trial reported no significant difference in mortality before discharge, or any neonatal morbidity in infants with transient hypothyroxinaemia treated with thyroxine 10 μg/kg/day beginning on day 15 and continuing for 7 weeks. The standard therapeutic recommendations described in the Newborn Screening Programme and in Recommendations of Neonatology Society and Paediatric Endocrinology Society recommend beginning the l-thyroxine replacement therapy in the second week of life, but delayed diagnosis may delay administration of the treatment. However, neurodevelopmental follow-up was inadequate so that no conclusions can be made for long-term effects. Researchers hypothesize benefits from thyroid hormone supplementation [8, 9].

Objectives. Evaluation of mental development the preterm-born children during early replacement therapy with l-thyroxin due to the secondary hypothyroidism in comparison with late therapy.

Patients and methods. The study involved two groups of children who were observed from the newborn period to...
the end of the seventh year of life. 45 children – premature neonates (24-35 Hbd) were qualified for group I. All the premature infants had low birth weight <2500 g (LBW): 20 were LBW (2500-1500 g), 17 were very low-birth weight (VLBW 1500-1000 g), and 8 were extremely low-birth weight infants <1000 g (ELBW). All the newborns had suffered from intrauterine asphyxia, infections, and intracranial haemorrhages in the perinatal period. The intracranial haemorrhages were diagnosed by ultrasonography. In all the children, concentrations of TSH and free T4 in serum from peripheral vein blood were determined between weeks 1-4 of life and regularly monitored by ELISA assay (Abbott). In all the neonates, the free T4 concentration was decreased. The children were treated with l-thyroxin in doses 5-10 µg/kg b.w./day since the second week of life (recommendations described in the Newborn Screening Programme and in Recommendations of Neonatology Society and Paediatric Endocrinology Society) and were during treatment clinical and biochemical euthyroid. Five children died in the neonatal or infant period due to sepsis or infections of the respiratory system. The treatment was continued in 40 children during 7 years of life.

Group II included 52 children born as premature neonates (24-35 Hbd): 21 as LBW, 24 as VLBV, and 7 as ELBW with intracranial haemorrhages, intrauterine infection, or intrauterine asphyxia. Ultrasonography revealed brain damage. The TSH and free T4 blood concentrations were estimated in the children. The free T4 levels were decreased, but no l-thyroxin treatment was initiated before week 4 of life (Tab. 1). Twelve children died in the neonatal or infant period due to infections of the respiratory system or sepsis. Forty children were observed, and l-thyroxin treatment was started at decreased TSH and decreased fT4 levels in the second month of life, or later. The children with chromosomal disorders (Down Syndrome, Edwards syndrome), with meningo(myelo)cele and with important brain defects were excluded from the study.

The psychomotor development of children was evaluated based on our Outpatient-Clinic documentation, compared with the development scale of Zdanska-Brincken [4], a scale for Polish children used routinely for evaluation of motor development. The milestones in motor development in the infant period: sitting time, standing time, and walking time were observed.

The mental development was examined in the 7th year of life by the Wechsler Intelligence Scale for Children-Revised (WISC-R) [10].

No statistically significant differences between the TSH and free T4 levels were observed in both groups. The children were controlled in our Outpatient Clinic. All parents signed an informed consent before the investigations which were accepted by the local Ethical Committee at the Medical University in Lublin.

The statistical analysis was performed using the Mann-Whitney test.

RESULTS

In preterm newborns with LBW, VLBV, and especially with ELBV, decreased levels of free T4 and normal or decreased levels of TSH were observed. In this situation, secondary hypothyroidism and/or thyroid sick syndrome were usually diagnosed. The differential diagnosis was often difficult or impossible. In group I of the children receiving early treatment with modest doses of l-thyroxin, an earlier achievement of the milestones of motor development, i.e. sitting, standing and walking, was noticed. In the entire infant group, the motor functions developed earlier than in the infants from group II with delayed l-thyroxin treatment. The differences were statistically significant (Tab. 2). In the 7th year of life, the IQs in the Wechsler Intelligence Scale for Children were significantly higher in group I treated since the second week of life with l-thyroxin, compared with group II. These differences were statistically significant in all the birth weight classes (Tab. 3). However, a modest reverse correlation between the time of achievement of the milestones of motor development and IQ was observed in the 7th year of life in children in both groups. In group I, the correlation coefficient between IQ in the 7th year of life and sitting time was -0.68, between IQ and standing time -0.58, and between IQ and walking time -0.62. In group II, respectively: -0.69 (IQ vs. sitting time), -0.63 (IQ vs. standing time), -0.54 (IQ vs. walking time).

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LBW 17 30-35 0.000-12.651 0.0-8.2</td>
<td>19 30-35 0.000-11.423 0.0-7.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLBW 15 28-35 0.000-7.824 0.0-8.1</td>
<td>14 29-35 0.000-8.534 0.0-7.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELBW 8 26-31 0.000-3.12 0.0-6.7</td>
<td>7 25-29 0.000-4.22 0.0-7.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean 0.518±8.451 6.8±0.7</td>
<td>0.65±10.231 7.4±0.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal ranges 0.49-15.00 9.1-23.8</td>
<td>0.49-15.00 9.1-23.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Milestones of motor development in preterm born children

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total 9.6±1.4 12.2±2.3 0.009</td>
<td>12.7±2.1 16.2±2.6 0.003</td>
<td>15.5±2.5 18.6±2.7 0.002</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBW 8.9±0.9 11.4±2.16 0.004</td>
<td>11.2±0.6 15.5±2.4 0.002</td>
<td>14.5±1.3 17.6±2.4 0.005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLBW 10.0±1.5 13.0±2.5 0.012</td>
<td>13.4±2.0 17.3±2.5 0.007</td>
<td>15.4±2.2 18.7±2.3 0.004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELBW 10.3±1.7 12.7±1.5 0.021</td>
<td>14.6±2.6 17.0±1.9 0.005</td>
<td>18.0±3.8 21.0±3.1 0.004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Statistic significant p<0.01.
Thyroid hormones play an important role in the development and maturation of the all tissue in the foetus. By 7 weeks of gestation, before the onset of foetal thyroid functioning, thyroid hormone has been demonstrated in foetal serum, FT4 concentrations being at least one third of the mother’s FT4 concentration [11]. By that time, the thyroid hormone receptors and the deiodinating enzymes are present in human foetal cerebral cortex [12]. Nuclear thyroid hormone receptors sensitive to bioactive T3 have been found in human brain and lung tissue since the 9th week of foetal life. Although the hypothalamic and pituitary start to synthesize hormones by 12 weeks, significant thyroid hormone production does not occur before the 20th week of gestation [13]. In the first half of the pregnancy, maternal-foetal transfer of T4 is therefore pivotal for the foetal thyroid hormone status. Foetal thyroid function and the hypothalamic-pituitary-thyroid axis continue to mature throughout pregnancy [14]. Serum levels of TT4 increase from about 5 nmol/l at 12 weeks of gestation to about 120 nmol/l at term, while the increase in the serum TT3 is much lower: from 0.5 nmol/l at 12 weeks to about 1.5 nmol/l at term [11, 14]. Serum FT4 in cord blood seems to increase from about 5 pmol/l at 12 weeks of gestation to about 20 pmol/l at term [11, 14].

During foetal life, the concentration of TT3 is controlled in the tissues. The already abundantly present T4 is preferably converted by type III deiodinase to reverse T3, which is present in high concentrations during foetal life and only decreases in the last weeks, while T3 is readily converted to diiodothyronine [15]. In addition, sulphatation by hepatic sulphotransferase enzymes to the inactive sulphated diiodothyronine [15]. In addition, sulphatation by hepatic sulphotransferase enzymes to the inactive sulphated diiodothyronine [15]. In addition, sulphatation by hepatic sulphotransferase enzymes to the inactive sulphated diiodothyronine [15]. In addition, sulphatation by hepatic sulphotransferase enzymes to the inactive sulphated diiodothyronine [15].

Thyroid hormone receptors, and possibly mechanisms regulating T4 uptake in the cells, also play a role in this ontogenetically programmed production and action of T3 [12].

The described regulatory mechanisms are also important in protecting against thyroid dysfunction. In the human foetal brain, type II deiodinase was found to increase in response to a plasma T4 decrease, but the onset of this regulatory mechanism was only found at mid-gestation [16].

After preterm birth, the total T4 and total T3 levels remain lower than in term born infants during the first weeks [16].

<table>
<thead>
<tr>
<th>Group</th>
<th>IQ</th>
<th>Group</th>
<th>IQ</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>102.6±20.1</td>
<td>82.3±21.3</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>LBW</td>
<td>107.2±22.7</td>
<td>89.1±23.5</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>VLBW</td>
<td>99.3±23.7</td>
<td>83.3±13.4</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>ELBW</td>
<td>99.0±11.8</td>
<td>62.0±19.0</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

Statistical significant p<0.01.

Table 3. The mean IQ on the Wechsler scale for Children – Revised (WISC-R)

There is no consensus definition for levels of thyroid hormones consistent with ‘transient hypothyroxinaemia’ in preterm infants. The FT4 measurements between days 3-8 in infants <30 weeks gestation, by a two-step RIA, was found to be between 10.1-21.1 pmol/l [32]. TSH has a variable time course, but comes down to about 2-4 μU/l by 4 weeks after birth [8]. The postnatal time course of T3 in preterm infants misses the sharp peak after birth and only slowly rises to term values in the course of 6-8 weeks [8]. The question is whether the transient decrease in the serum concentration of free T4 that occurs in some preterm
infants during the first weeks after birth contributes to these neurodevelopmental problems? Three cohort studies [21, 33, 34, 35, 36] have documented an association between low thyroid hormone levels (T3 or T4) in the first weeks after birth and the abnormal neurodevelopmental outcome. All the studies similar to our observations documented a measure of abnormal mental development in children who had low neonatal thyroid hormone levels. One study [37], found a 4.4 fold increase in risk of disabling cerebral palsy at 2 years of age. The hypothyroxinaemia in the first weeks of life is connected with worse mental development – in our study the consequence of this situation is a lower IQ in the WISC-R in the in 7th year of life. Den Ouden [36] described children who had low neonatal T4 levels having an increased risk of school failure at 9 years. The associations in the cohorts persisted despite correction for potential confounders, including gestation, measures of foetal growth (either birth weight or presence of growth restriction) and, in some studies, factors relating to severity of illness in preterm infants and independent risk factors of an abnormal neurodevelopmental outcome.

A separate review [5] found no significant effect of prophylactic postnatal thyroid hormone treatment in preterm infants on neonatal morbidity, mortality, or the neurodevelopmental outcome. Additionally, no significant effect was found from the use of thyroid hormones in preterm infants with respiratory distress syndrome, although neurodevelopmental outcomes were not reported by the 2 included trials [6].

Our observations indicate that we can diagnose hypothyroxinaemia as the result secondary hypothyroidism and/or thyroid sick syndrome in premature newborns with intracranial haemorrhagiae, respiratory distress, and infections. The early replacement therapy in newborns can be beneficial for quicker motor development and better mental development in the 7th year of life.

The preterm newborns with secondary hypothyroidism have no chance for early diagnosis in a screening programme. In Poland, primary newborn screening for congenital hypothyroidism involves a fluorometric assay to determine the thyroid-stimulating hormone (TSH) level after 72 hours of life. If the TSH level is elevated above 35 IU/l the newborn is referred to the paediatric endocrinologist, and the TSH, T4 and T3 levels are also tested. If the TSH level is between 35 IU-1 – 15IU-1, the blotting test for TSH is repeated. In preterm born newborns and in newborns with low body weight, the screening test is repeated after 6 weeks. In the preterm newborns from our study, the screening test was negative since the levels of TSH were decreased. Checking the levels of free T4 can only allow diagnosis of hypothyroidism.

Immediate diagnosis and treatment of congenital hypothyroidism in the neonatal period is critical for normal brain development. Treatment is usually effective if started within the first few weeks of life, whereas delayed treatment may result in decreased intellectual capacity.

The doses of l-thyroxin used in preterm infants are still being discussed. Using different treatment protocols in each of the randomized controlled trials, researchers have not been able to demonstrate a positive effect of T4 and/or T3 treatment on the clinical outcome. Presumably, improvement of the clinical outcome should not be the aim of studies, but rather of the neuro-developmental outcome when thyroid hormone supplementation studies are designed [38].

Vanhole et al [39] in1997 and Smith et al. [40] in 2000 used 20 ug/kg doses of l-thyroxin and observed no difference in the clinical outcome and development. The observations lasted only 7 months. Van Wassenaer et al and Briet et al. [8] noticed no difference in the total groups, but a better outcome with T4 at 8 mg/kg doses at 2 and 5years. The results of the post-hoc subgroup analyses seem to show that T4 supplementation may be beneficial in infants of less than 28-29 weeks of gestation [8, 41]. In the presented study, the treatment usually started with doses from 7-10 ug/kg/bw/day, and were followed by 5-7 ug/kg/day because the growth of the children. The doses were modified for maintenance of the normal levels of free T4.

**CONCLUSIONS**

Analysis of the cohort studies and the presented study shows that replacement therapy with l- thyroxin initiated from the second week of life may improve the long-term mental development in children (7 years). The achievement of the milestones of the motor development is earlier in infants with early replacement therapy, and may be a predictor of the cognitive outcome in future. The 7-10mg/kg/day l-thyroxin doses were sufficient to produce the desired effect. In this situation, the diagnosis of the pituitary-thyroid axis action (by measurement of TSH and free T4) in the second week after birth in preterm newborn with brain damage give a chance for optimal development.

**REFERENCES**


36. van Ouden AL, Kok JH, Verkerk PH, Brand R, Verloove-Vanhorick SP. The relation between neonatal thyroxine levels and neurodevelopmental outcome at age 5 and 9 years in a national cohort of very preterm and/or very low birth weight infants. Ped Res. 1996; 39: 142-5.
