Neonatal Pituitary-Thyroid Axis Dysregulation with Combined Thyroid Hormone and Thyrotropin Resistance in Infant with Trisomy 21 and Maternal Subclinical Hypothyroidism

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Abstract

Trisomy 21 is commonly associated with thyroid problems. Although autoimmune hypothyroidism is the commonest thyroid problem in Trisomy 21, infants with this chromosomal disorder are also known to have dysregulated pituitary thyroid axis. This results in elevated thyrotropin (TSH) levels in absence of autoimmunity and structurally normal thyroid gland. The mechanism for this phenomenon is not clearly understood and it is possible that this may be due to genomic imbalance from trisomy of chromosome 21. Some authors have proposed that thyroid hormone resistance (RTH) might be a contributing factor to this. However, the genes coding for TSH receptor and the two proteins known to be implicated in TSH resistance are normal in patients with Trisomy 21. In newborns, transient hyperthyrotropinaemia is considered to be associated with maternal thyroperoxidase (TPO) antibody positivity.

We describe a case of term infant with Trisomy 21, who was identified on newborn congenital hypothyroidism screening. The infant had high TSH and raised plasma free T4 (FT4) with clinical signs and symptoms of congenital hypothyroidism. We discuss the management of this case and possible mechanisms contributing to the uncommon presentation.

Keywords: Thyrotropin resistance; Hypothyroidism; Neonatal

Case Report

A term infant born to a primigravida mother was confirmed to have Trisomy 21. The mother had subclinical hypothyroidism with plasma TSH of 7 mU/L, FT4 of 11 pmol/L and positive TPO antibodies during the third trimester. She was not on thyroxine replacement. Her thyroid function tests (TFT) and antibody status normalised following delivery [1-6].

The infant was identified to have raised TSH indicating CH on the neonatal screening program. His TFTs confirmed raised TSH at 30.9 mU/L and T4 of 23.8 pmol/L. The TPO antibodies were absent. Ultrasound scan showed normal appearance of the thyroid gland in the neck (Figure 1). 99mTc-Pertechnetate scan showed uptake within a bilobed structure in the lower neck (Figure 2). Scan time was 5 min and 17 seconds, at the upper limit of normal. No treatment was started as he was clinically well.

On day 16 of life, his plasma TSH remained elevated. He had prolonged jaundice and a widely open posterior fontanelle. Levothyroxine replacement was started at 37.5 µg daily as the neonatal screening program in the UK recommends treatment of all infants with congenital hypothyroidism by Day 21. Treatment had to be reduced progressively (Table 1) due to mild features of overtreatment despite raised plasma TSH, similar to what has been well described in RTH. The elevated plasma thyroid hormones (FT4, FT3) failed to normalise TSH with high plasma FT4 initially could be due to transient thyroid hormone resistance (RTH). In the absence of any known mutations, this phenomenon has been previously described in the literature as case Trisomy 21 than in general population. Infants can have congenital hypothyroidism as well as subclinical compensated hypothyroidism characterised by elevated TSH levels, but normal plasma thyroxine (FT4) and triiodothyronine (FT3) levels [7,8]. In our case, raised TSH with high plasma FT4 initially could be due to transient thyroid hormone resistance (RTH). In the absence of any known mutations, this phenomenon has been previously described in the literature as case Trisomy 21 than in general population. Infants can have congenital hypothyroidism as well as subclinical compensated hypothyroidism characterised by elevated TSH levels, but normal plasma thyroxine (FT4) and triiodothyronine (FT3) levels [7,8]. In our case, raised TSH with high plasma FT4 initially could be due to transient thyroid hormone resistance (RTH). In the absence of any known mutations, this phenomenon has been previously described in the literature as case

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In this unusual case, plasma TSH and FT4 were both very high and pituitary thyroid feedback appeared to be dysregulated. Maternal subclinical hypothyroidism may have resulted in prolonging the physiological neonatal TSH surge that usually elevates plasma TSH and causes dynamic FT4 changes in the first few days after birth. However, baby showed a combination of both thyroid hormone resistance and TSH resistance associated with the Trisomy 21 state. Maternal hypothyroidism could also be partly responsible for elevated plasma TSH. The authors recommend that monitoring of TFTs is recommended and TSH significantly raised above 10 μu/L should warrant consideration of thyroxine supplementation in the early years of life.

**Conclusion**

In this unusual case, plasma TSH and FT4 were both very high and pituitary thyroid feedback appeared to be dysregulated. Maternal subclinical hypothyroidism may have resulted in prolonging the physiological neonatal TSH surge that usually elevates plasma TSH and causes dynamic FT4 changes in the first few days after birth. However, baby showed a combination of both thyroid hormone resistance and TSH resistance associated with the Trisomy 21 state. Maternal hypothyroidism could also be partly responsible for elevated plasma TSH. The authors recommend that monitoring of TFTs is recommended and TSH significantly raised above 10 μu/L should warrant consideration of thyroxine supplementation in the early years of life.

**References**


