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Case Report Open Access

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 hypothydoidism 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 hypothyrodism 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 plasma TSH. No mutations of TSH receptor were found and urinary iodine levels were reported to be normal.

He has remained stable on 12.5 µg of levothyroxine with normal plasma FT4 levels till 2 years of age. His development has been appropriate for children with Trisomy 21 with concerns from his parents.

Discussion

Prevalence of thyroid dysfunction is higher in newborns with 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

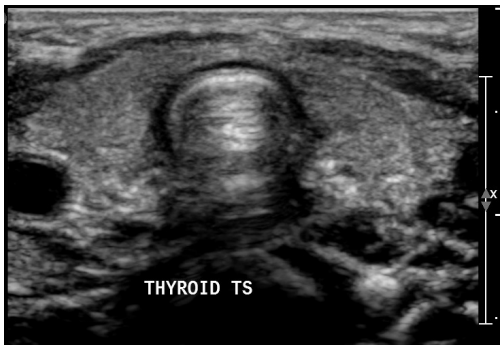

Figure 1: Ultrasound of thyroid gland.

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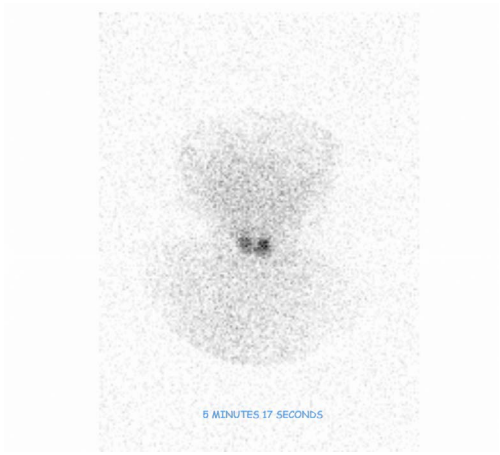

Figure 2: 99mTc-Pertechnetate scan.

Age	FT4 (normal 11-22 pmol/l)	TSH (ref 0.3-5.0 mU/l)	FT3 (ref pmol/l)	Thyroxine Replacement/ comments
10 days	23.8	30.99	n/a	Nil
16 days	28.3	22.98	n/a	Started on Thyroxine 37.5 µg daily
24days	31.2	6	n/a	Thyroxine reduced to 25 µg daily due to features of overtreatment
32 days	29.3	7.5	n/a	Thyroxine 25 µg daily
40 days	27.9	6.58	7.5	Thyroxine reduced to 12.5 µg due to features of overtreatment
50 days	22.2	9.42	7.2	Thyroxine 12.5 µg daily
60 days	21.1	10.94	7.4	Thyroxine 12.5 µg daily
3 months	22	6.8	n/a	Thyroxine 12.5 µg daily
6 months	18	7.2	n/a	Thyroxine 12.5 µg daily
1 year	17.8	4.71	n/a	Thyroxine 12.5 µg daily
1 year 6 months	18.8	5.06	n/a	Thyroxine 12.5 µg daily
2 years	17.9	5.6	n/a	Thyroxine 12.5 µg daily

Table 1: Treatment.

reports of RTH and Trisomy 21 [3]. Some authors have challenged this hypothesis as proteins involved in mild TSH resistance were normal in patients with Trisomy 21 as well as bioactivity of TSH was normal in children with Trisomy 21 and mildly raised TSH [9]. It has been proposed that these thyroid abnormalities are likely to be thyroidal in origin [10]. Sharav et al. have concluded that the immaturity of hypothalamic pituitary axis is responsible for transient elevation in TSH in children with Trisomy 21 [2].

A case series of 320 infants with Trisomy 21, had a 28% incidence of thyroid problems [11]. They had described similar case to the one described above, where the infant's TSH was raised at 40.3 mu/l and high T4. Patient was diagnosed as compensated hypothyroidism and also received treatment with thyroxine for 3 months. Our patient was also started on thyroxine treatment because of elevated TSH. This was in keeping with current recommendation to start thyroxine for children with Trisomy 21 and elevated TSH [12]. As thyroxine treatment is easy to carry out and beneficial effects on growth and mental development have been observed in early years, it was thought to be clinically beneficial for the patient. His TSH remained high but we had to wean treatment very quickly because of features of overtreatment.

Another complicating factor which might have contributed to high TSH in our case was maternal TPO positivity. High prevalence of transient congenital hypothyroidism has been reported in infants of mothers with TPO positivity [6].

This case also highlights the dilemma of starting treatment in an infant with features of compensated subclinical hypothyroidism. It could be argued that this infant should have been monitored without treatment as initial plasma FT4 was high but VanTrotsenburg et al. have shown significant benefit in development of children with persistent raised TSH when treated with thyroxine. It has also been shown that low level of TSH has a positive correlation with speed of growth [13].

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 levels 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 mu/L should warrant consideration of thyroxine supplementation in the early years of life.

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