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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Background

Trisomy 21 may be associated with a dysregulated pituitary thyroid axis with higher plasma TSH and lower Free thyroxine (FT4) than controls. This may be due to genomic imbalance from trisomy of chromosome 21.Some workers have considered this to be a form of congenital hypothyroidism(CH) and a randomised control trial[1] has demonstrated significant benefit from treatment with thyroxine. Transient (CH) in newborns is recognised in association with maternal thyroperoxidase (TPO) antibody positivity. 'Thyroid hormone resistance' (RTH) in infancy has also been described in CH.

Case Report

A term infant born to a primigravid mother was confirmed to have Trisomy 21. The mother had plasma TSH of 7mU/L, FT4 of 11 pmol/L and TPO positivity during the third trimester. Her thyroid function tests (TFT)and antibody status normalised following delivery.
The infant was identified as a possible baby with CH on the neonatal screening program. He was observed on Day10 despite his TFTs (table 1) as he appeared well. TPO antibodies were absent. 99mTc-Pertechnetate scan showed uptake within a bilobed structure in the lower neck. (Figure 1) Scan time was 5 min and 17 seconds, at the upper limit of normal. Ultrasound scan showed normal appearance of the thyroid gland in the neck (Figure 2).
His plasma TSH was elevated on Day 16 as compared with the largest published study[1] involving neonates with trisomy 21. He had prolonged jaundice and a widely open posterior fontanelle, consistent with CH. Thyroxine replacement was started at 37.5 micrograms daily as the neonatal screening program in the UK demands treatment of all infants with CH by Day 21. Treatment had to be reduced progressively (table 1) due to mild features of overtreatment despite raised plasma TSH reminiscent of what has been well described in RTH. The elevated plasma thyroid hormones failed to normalise plasma TSH.
He remains well on 12.5 mcg of thyroxine with normal FT4 , but mildly elevated TSH at 6 months of age.

Table 1: TFTs and thyroxine replacement

Age (Days)	FT4 (11-22pmol/l)	TSH (0.3-5.0mU/l)	FT3 (3.5-7.8pmol/l)	Thyroxine Replacement
10	23.8	30.9		Nil
16	28.3	22.9		Started on 37.5 mcg
24	31.2	6.0		Reduced to 25 mcg
40	27.9	6.5	7.5	Further reduced to 12.5 mcg
50	22.2	9.4	7.2	12.5 mcg
60	21.1	10.9	7.4	12.5 mcg
160	23.0	6.8		12.5mcg

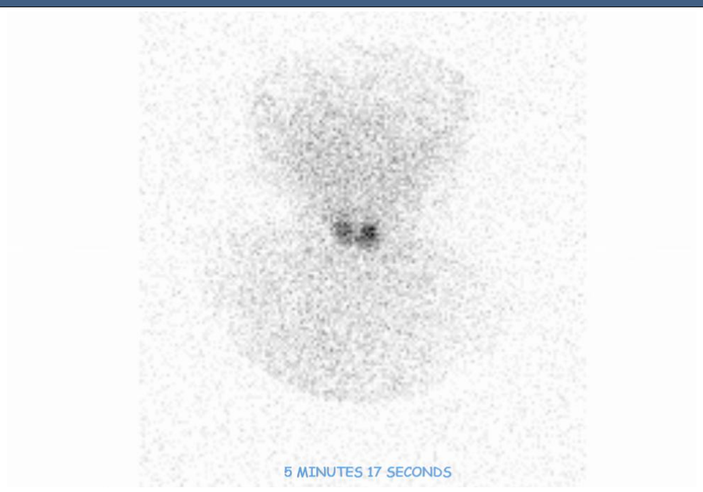

Fig. 1: NM Thyroid Scan (Pertechnetate)

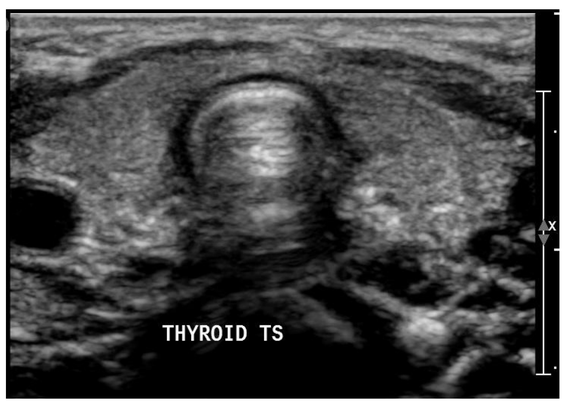

Fig.2:. Ultrasound Scan thyroid gland

Discussion

RTH has been described in Trisomy 21 in the literature in the absence of any mutations[2, 3] known to affect TSH or thyroid hormone receptors. Maternal TPO positivity might have additionally contributed to the picture. Treatment with a small dose of thyroxine was needed to lower the TSH which still remained above the reference range. The unusual thyroid function and its subsequent behaviour in this infant with Trisomy 21 and CH are not completely explained by combined thyroid hormone and TSH resistance that has been previously described.

Conclusion

There may be genes other than the TSH receptor or thyroid hormone receptor implicated in patients with trisomy 21 who display unusual features of the pituitary thyroid axis as in this patient.

References

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