Capillary TSH cut-off levels for congenital hypothyroidism screening: evidence against adopting the UK threshold of 10 mIU/L.

Jeremy H. Jones, Avril Mason and M. Guftar Shaikh
Department of Endocrinology, Royal Hospital for Sick Children, Glasgow, G3 8SJ, UK.

Background: The recommended capillary TSH (cTSH) cut-off level for neonatal screening for congenital hypothyroidism (CH) in the UK is 10 mIU/L. However several of the regional screening laboratories have adopted lower cut-off limits in order to increase detection sensitivity. There is now pressure to standardise the UK screening programme with universal adoption of the recommended cut-off. Scotland has been using a cut-off of 8 mIU/L since the adoption of AutoDELFIA TSH screening methodology in Autumn 2003. We wished to examine what difference this lower cut-off has made to detection of congenital hypothyroidism.

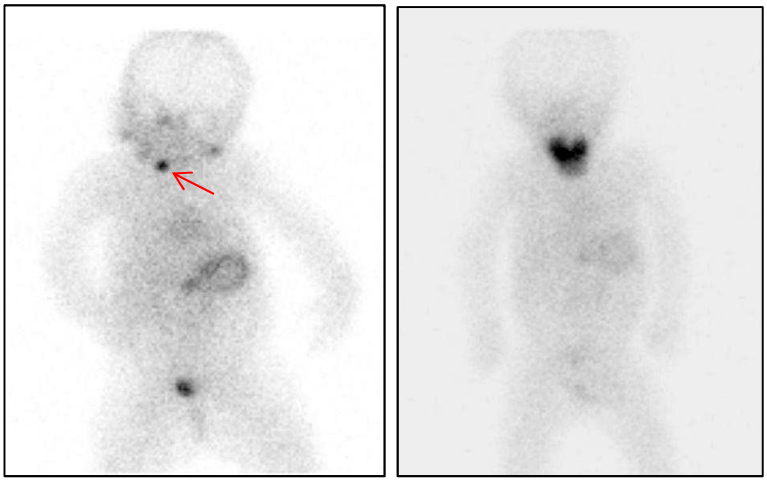
Methods and design: The national congenital hypothyroidism database was searched for referrals in which the first or subsequent capillary TSH (cTSH) results fell between 8.0 and 10.0 mIU/L between January 2004 and March 2014. The outcome of these cases was then examined using well-defined and published diagnostic criteria (Ray M, Muir TM, Murray GD, et al. Audit of screening programme for congenital hypothyroidism in Scotland 1979–93. *Arch Dis Child* 1997;76:411–15).

Results: There were 304 referrals for cTSH of any value in the study period. Twenty five (8.2%) referrals were made because of a cTSH between 8.0 and 10.0 mIU/L. Of these, 15 (60%) have since proven to have had transient elevated TSH in the neonatal period. A further seven (28%) cases have permanent forms of CH; two thyroid ectopia with compensated hypothyroidism (Pts 4, 6), two dyshormonogenesis and decompensated hypothyroidism (Pts 2, 7), three unknown cause: one decompensated pre-treatment (Pt 5); one 100 mcg/day thyroxine at seven years of age (Pt 3) and one who had a diagnostic challenge at the age of 9 years; TSH rose to 15.7 mU/L on 25 mcg/day (Pt 1). The remaining three (12%) have no final diagnosis, either because they are still awaiting diagnostic challenge (n=2; one with proven thyroglobulin mutation c.199 G>A and premature stop codon) or because the challenge was inconclusive (n=1). Table 1 shows the screening and diagnostic features of those infant with definite congenital hypothyroidism.

Pt No	Gender	Cause	cTSH 1 mU/L (age in days)	cTSH 2 mU/L (age in days)	First venous TSH mU/L	First venous fT4 pmol/L	Age in days at initial venous TFTs
1	F	Unknown	9.0 (6)	8.0 (18)	22.0	INSUF	20
2	F	Dyshormonogenesis	8.3 (6)	45.3 (19)	>100.0	3.5	23
3	M	Unknown	8.6 (5)	8.52 (52)	13.7	14.0	63
4	F	Ectopia	9.2 (5)		23.4	15.0	21
5	F	Unknown	9.4 (5)	21.8 (17)	49.9	8.0	20
6	M	Ectopia	8.8 (5)	8.22 (13)	15.5	15.6	24
7	F	Dyshormonogenesis	23.2 (5)	9.5 (12)	22.7	4.8	18

Patient 7 would have been referred after the first screening test elsewhere in the UK as the initial TSH was >20.0 mU/L. Because the immediate referral cut-off is 25 mU/L in Scotland this infant had a second capillary TSH test (9.5 mU/L) on day 12 of life. This second abnormal TSH, notably below the putative 10.0 mU/L cut-off led to a referral and the infant was found to have decompensated hypothyroidism on day 18. Nuclear medicine imaging revealed increased isotope uptake.

Diagnostic imaging Patient 4 – initial cTSH was 9.2 mU/L (d5). At assessment she had compensated CH with TSH 23.4 mU/L and fT4 15.0 pmol/L. Image obtained on day 35 and thyroxine replacement started on d32.



Diagnostic imaging Patient 2 – initial cTSH was 8.3 mU/L (d6). At assessment (d23) she had decompensated CH with TSH >100 mU/L and fT4 3.5 pmol/L. Image obtained on day 29 and thyroxine replacement started on d23.

Conclusion: Less than 10% of referrals made were due to a cTSH of between 8.0 and <10.0 mIU/L. Nearly two thirds of these referrals proved to be transient neonatal hyperthyrotropinaemia. However more than one quarter of all referrals based on a cTSH of between 8.0 and <10.0 mIU/L had permanent forms of CH including both dysgenesis and dyshormonogenesis, half of whom had decompensated CH at pre-treatment assessment. Our data indicate that it would be inappropriate to raise the Scottish TSH threshold from the current level of 8.0 mU/L to 10 mU/L.