OBJECTIVE VERSUS SUBJECTIVE MEASUREMENT OF THYROID VOLUME BY ULTRASOUND IN INFANTS REFERRED WITH TSH ELEVATION ON NEWBORN SCREENING

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INTRODUCTION

- Thyroid imaging by ultrasound, scintigraphy, or both is an integral part of the assessment of infants referred with elevation of thyroid stimulating hormone (TSH) on newborn screening.
- Assessing thyroid size when the gland is eutopic is important since:
  - An enlarged gland suggests either iodine deficiency or dyshormonogenesis due for example to a thyroperoxidase (TPO or thyroglobulin (Tg) defect
  - The finding of a hypoplastic gland is an indication to rule out a PAX8 or a TSH receptor mutation.
- But what constitutes a small, normal or large gland **(see Figure 1)?** Should the evaluation be made by a subjective assessment by the radiologist or radiographer; or by objective measurement compared with normative data; or both?

AIMS OF STUDY

To compare intra-observer variation in the objective (Ox) measurement of thyroid volume (vol) by ultrasound (US); and to examine the correlation between subjective (Sx) and Ox assessment

PATIENTS AND METHODS

- A radiographer and a clinical scientist reviewed the images of available images from ultrasound scans in infants referred with TSH elevation on newborn screening to the Royal Hospital for Sick Children in Glasgow between 2007 and 2013 who were found to have *in situ* glands
- Ultrasound had been performed using a Philips iU22 (Koninklijke Philips Electronics N.V., Groenewoudsweg 1, 5621 BA, Eindhoven, The Netherlands), featuring a 7 - 15 MHz hockeystick transducer with coupling gel.
- The observers measured length, breadth and depth of each thyroid lobe from each eligible infant on two separate occasions, and were blinded as to the identity/diagnosis in each patient. Intra-observer error was calculated as mean +/- SD
- The volume of each lobe was calculated using the formula: length x depth x breadth x π/6. Combined thyroid volume was derived as the sum of the volume of each lobe, ignoring the contribution of the thyroid isthmus.
- The radiographer and a radiologist then carried out Sx assessment by blindly reviewing images from the same infants and placing them into 5 categories: small, small-normal, normal, large-normal and large.
- Equivalent Ox size was determined using Scottish population-specific data[1] which gave mean ± SD (range) thyroid volume as 1.62 ± 0.4 (0.7-3.3) ml. Corresponding ranges to Sx assessment were set at: <0.7,0.7-<0.9,0.9-<2.1, 2.1-2.3 and >2.3 ml.
- Correlation between Ox and Sx was defined as concordant, partial or discordant if categories were equivalent, one apart or two apart.

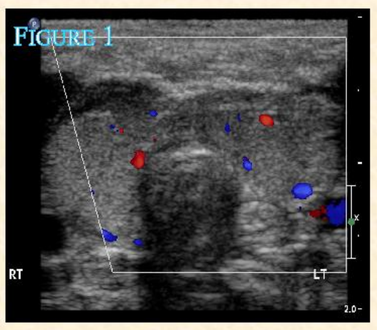

FIGURE 1 :
Is this gland large, normal or small in volume? The impression is of an enlarged or "bulky" gland, but combined thyroid volume is only 0.93 ml. This infant was originally thought to have dyshormonogenesis with an enlarged gland but is now believed to have Thyroid-Brain-Lung syndrome due to a *de novo* 0.82Mb deletion at 14q13.2-13.3 impacting on NKX2-1 function.

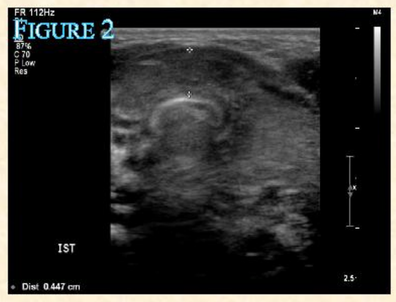

FIGURE 2:
In this image of an infant with proven TPO mutation the left lobe of the thyroid is so big that its edge has to be estimated by extrapolation, leading to inaccuracy. The calculated volumes (2.8 and 3.3 ml on two occasions) are within the range (0.7-3.3 ml) described by Perry et al. This may be because the isthmus is not included in our volume calculations.

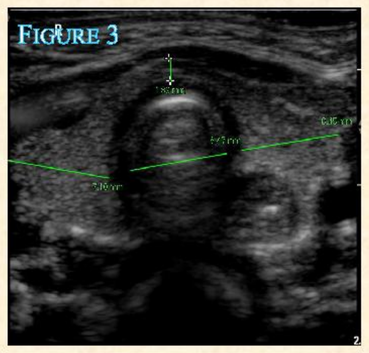

FIGURE 3:
Normal-shaped thyroid gland with three curves to the ventral margin. In this image the size of isthmus and lobes are being compared with the trachea.

RESULTS

- Images were reviewed for 65 children scanned 2007-2013. Of these, 23 were excluded (4 found to have thyroid dysgenesis, images unavailable in 19) leaving 42 for analysis.
- Prior to the study the diagnosis, based on clinical, biochemical, radiological and molecular genetic analysis was:
  - ✓ Congenital hypothyroidism due to hypoplasia in situ in 4 patients (2 with heterozygous and 1 with homozygous TSH-R mutation, one with Down's syndrome and PAX-8 mutation)
  - ✓ Congenital hypothyroidism due to dyshormonogenesis in 15 with proven mutation in 5 (2 with Tg, 2 with TPO and 1 with DUOX.2 defect)
  - ✓ Transient hypothyroidism in 13 (including 1 with Down and 1 with Turner syndrome)
  - ✓ Status uncertain in 9 (including 3 with Down's syndrome).

TABLE 1: INTRA-OBSERVER ERROR FOR BLINDED EVALUATION OF THYROID SIZE ON ULTRASOUND DURING TWO SEPARATE SESSIONS.

Difference in measurement of combined thyroid volume (ml) between sessions 1 & 2					
Gland volume [n=]		Mean	SD	Median	Range (min-max)
Small (<0.7 ml)	[14]	0.078	0.114	0.04	0.003-0.436
Small-normal (0.7- <0.9 ml)	[8]	0.07	0.04	0.06	0.031-0.13
Normal (0.9- <2.1 ml) all patients	[9]	0.077	0.073	0.052	0.0009-0.208
Normal (0.9- <2.1 ml) excluding infant in whom extrapolation needed	[8]	0,083	0,075	0,060	0.0009-0.208
Large-normal (2.1-2.3)	[0]				
Large (>2.3 ml) all patients	[7]	0.34	0.42	0.13	0.038-1.302
Large (>2.3 ml) excluding infants in whom extrapolation needed	[5]	0.15	0.14	0.11	0.038-0.439

- Table 1 show intraobserver differences in Ox assessment of thyroid size. Differences were small after excluding two patients with large glands in whom thyroid length had to be estimated by extrapolation because the lobes were too large to be contained on a single image.
- Thyroid volume was only modestly increased (combined volumes ranging between 2.7 and 3.4 ml) in 3 patients with proven dyshormonogenesis (Tg defect in 2 and TPO in one). **Figure 2** shows one of these infants in whom the isthmus is very large, and in whom lobe length had to be estimated by extrapolation.

TABLE 2: COMPARISON BETWEEN OBJECTIVE (OX) AND SUBJECTIVE (SX) EVALUATION OF COMBINED THYROID VOLUME IN 38 (SEE METHODS).
key to symbols: * = sx concordant with ox ,+ = sx partially concordant with ox ! = sx discordant with ox

Ox / Sx	Small (<0.7) [n=14]	Small-normal (0.7-<0.9) [n=8]	Normal (0.9-<2.1) [n= 9]	Large-normal (2.1-2.3) [0]	Large (>2.3) [n=7]
Small	****				
Small-normal	+++	**			
Normal	!!!!	+++	**		
Large-normal		!!	+		
Large		!	!!!!!!		*******

- Table 2 compares Ox vs Sx assessment, showing * for concordance, + for partial concordance and ! for discordance.
  - ✓ Sx assessment never underestimated thyroid size in comparison to Ox.
  - ✓ Sx assessment frankly overestimated thyroid volume in 7 infants diagnosed as dyshormonogenesis, all of whom were mutation negative, had normal or small glands and retrospectively normal uptake on RIS. One of these patients is now off thyroxine
  - ✓ A Sx impression of large size or a "bulky" gland in a thyroid which was small/normal **(Figure 1)** is attributable to relatively broad isthmus and lobes which seem to expand into the ventral area of the thyroid fossa.
  - ✓ Mean ±SD (range) thyroid volume in the 13 patients with transient TSH elevation was 0,082 ± 0,116 (0,006 - 0,436) ml indicating thyroid size small or small/normal rather than normal.

DISCUSSION

- Subjective assessment of thyroid size on ultrasound in infants referred with TSH elevation on newborn screening may be grossly misleading, with a tendency to overestimate volume and hence to overdiagnose thyroid dyshormonogenesis.
- The impression of large size in a normal or small gland may relate to the shape of the ventral margin of the gland which normally has three distinct (usually convex) curves to the gland margin **(See Figure 3).** If the gland shape changes to show a single curved ventral margin **(see Figure 1)** it "looks" enlarged
- Thyroid volume is relatively small in the infants with transient TSH elevation in this study. This might reflect
  - ✓ A gland which is not always normal, even if the TSH has normalised and the infant does not require thyroxine replacement
  - ✓ A problem with the Scottish reference range for thyroid volume, which is larger than that seen in other countries such as Poland [2,3]
- The current formula method of calculating thyroid volume by taking each lobe as a prolate ellipsoid and ignoring the isthmus will underestimate thyroid volume when thyroid shape is altered and when the isthmus is enlarged (as in dyshormonogenesis). New models for assessing thyroid volume are needed
- The accuracy of subjective assessment of thyroid volume may be improved by
  - ✓ Critical evaluation of the shape of the ventral surface of the gland
  - ✓ Assessing size in relation to the trachea, including ratio of lobe width:tracheal width; and isthmus depth:tracheal depth **(see Figure 3).**

CONCLUSION

- Subjective assessment of thyroid size on ultrasound in infants with TSH elevation may grossly overestimate true size and should always be carried out in conjunction with objective measurement
- Objective measurement using the current formula (ignoring the isthmus) may underestimate volume
- Ultrasound examination in infants with TSH elevation and a gland in situ can only be one part of a wider assessment which should include radioiosotope scanning, molecular genetic assessment, and clinical follow up.

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ESPE 2015 558--P2
Thyroid.
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DOI: 10.3252/pso.eu.54espe.2015
Poster presented at: 54th Annual Meeting 1-3 October ESPE 2015 BARCELONA European Society for Paediatric Endocrinology
PosterSessionOnline.com