SMALL THYROID VOLUME ON ULTRASOUND IN INFANTS WITH TRANSIENT TSH ELEVATION FOLLOWING REFERRAL BY NEWBORN SCREENING

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INTRODUCTION

- Between 15 and 25% of Scottish infants referred with elevated capillary thyroid stimulating hormone (TSH) on newborn screening are found to have transient TSH elevation (Jones et al, 2006)
- Transient TSH elevation may be associated with neonatal sickness, prematurity, iodine exposure, maternal thyroid antibodies and some forms of dyshormonogenesis (e.g. DUOX.2 mutation).
- Correct identification of these infants is needed in order to avoid unnecessarily prolonged treatment with thyroxine
- While evaluation of thyroid size by ultrasound or scintigraphy forms part of the assessment of infants with TSH elevation there is little information on thyroid size in transient TSH elevation

AIMS AND HYPOTHESIS

- **Aim:** To determine thyroid volume by ultrasound in infants with transient TSH elevation, defined as capillary TSH elevation on newborn screening but normal venous thyroid function tests subsequently off thyroxine treatment.
- **Hypothesis:** That most subjects with transient TSH elevation would show thyroid glands which were normal in volume when compared with population-specific data .

PATIENTS AND METHODS

- Evaluation of thyroid ultrasound in infants found to have eutopic glands following referral to the Royal Hospital for Sick Children in Glasgow between 2007 and 2013 after capillary TSH elevation on newborn screening.
- For 37 infants with eutopic thyroid in whom satisfactory US images were available, two observers (MG and SS) rated thyroid size by subjective (Sx) evaluation as small, small-normal, normal, large-normal and large, and then reached consensus where possible. On two separate occasions two observers (MG and JJ) measured volume of each lobe by objective evaluation (Ox).
- Ox thyroid volume was determined according to the formula length x breadth x depth x $\pi/6$ for each lobe and expressing total gland volume as the sum of both lobes.
- Using the Scottish population-specific mean (SD) volume of 1.61 (0.4) ml, Ox volumes corresponding to small, small-normal, normal, large-normal and large were set at < 0.8, 0.8-1.0, >1 -<2.2, 2.2-2.4, and >2.4 ml.
- Ultrasound was 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.
- Infants who were subsequently found to have transient TSH elevation were analysed as a separate subgroup

RESULTS

TABLE : Data on fifteen infants with transient TSH elevation. Ox = objective evaluation; Sx = subjective evaluation; RIS = radioisotope scan. NB Ox volumes equivalent to small, small-normal, normal, large-normal and large are; <0.8, 0.8-1.0, >1.0-<2.2, 2.2-2.4, >2.4 ml

	Sex	BW	Gestation	Mean Ox volume (ml)	Agreed Sx volume (ml)	RIS uptake	RIS size	Comment
1	F	2.85	40	2.42	Large	↑	N	Pendrin heterozygote with large thyroid isthmus effect. Initial thyroglobulin 2301 ng/ml. Treated initially with L-T4
2	M	2.86	37	1.80	Large	N	N	Thought to have large gland on initial assessment and treated with L-T4. Now off treatment
3	M	3.80	39	0.86	Large	N	N	Thought to have large gland on initial assessment and treated with L-T4 for suspected DHG. No mutation found
4	F	2.82	37	0.76	Large/normal	N	↓	Turner's syndrome
5	F	3.06	38	1.17	Normal	N/D	N/D	Sick due to placental abruption. birth asphyxia and renal failure
6	F	2.37	37	0.84	Normal	↓	↓	Cause unknown. Never treated
7	F	3.57	40	0.83	Normal	N/D	N/D	Transient TSH elevation, no obvious cause.
8	M	3.42	40	0.75	Normal	↓	↓	Never treated; no cause found
9	M	3.00	42	0.62	Normal	N/D	N/D	Transient TSH elevation, no obvious cause.
10	F	3.42	40	0.61	Normal	↓	↓	Heterozygous TSH receptor mutation. treated with L-T4 initially
11	M	3.80	39	0.72	Small/normal	↓	N	Treated initially with L-T4 for suspected blocking antibodies but none found
12	M	2.48	37	0.60	Small/normal	↓	N	Never treated; no cause found
13	M	3.65	41	0.48	Small/normal	Absent	Absent	Blocking antibodies (TPO +ve)
14	M	3.60	41	0.63	No agreement reached	Absent	Absent	Blocking TSH receptor antibodies (sibling affected)
15	M	2.55	33	0.43	No agreement reached	↓	↓	Allo-immune thyroiditis with very high TSH receptor antibodies. Image hard to interpret due to surrounding oedema (see Figure)

- Of 37 infants with eutopic glands, 15 **(M 9 : F 6)** were found to have transient TSH elevation **(see Table)**
- Median (range) birthweight and gestation for the fifteen infants was 3.06 (2.37-3.8) kg and 39 (33-42) weeks with **one baby** preterm (<37 weeks) and **two infants** with low birth weight (<2500g). **Their details are shown in the Table**
- Principal findings
  - ✓ Three infants were scored subjectively as having large glands.
    - **(i)** One infant, a Pendrin heterozygote had large gland on Ox assessment (volume 2.42 ml)
    - **(ii)** Volume was normal at 1.8 ml in another infant and small-normal in a third **(Figure 1)**. In both of theses infants the shape of the gland gave the impression of large size
  - ✓ One infant with perinatal sickness due to placental abruption had a normal gland on both Sx and Ox assessment (volume 1.17 ml).
  - ✓ Assessment was not possible in one infant with allo-immune thyroiditis (TSH-receptor antibodies >405 U/l, Thyroglobulin 253 □g/l) whose image showed peri-thyroidal oedema **(Figure2)**.
  - ✓ The remaining 10 infants showed median (range) Ox volume was to be small/small-small-normal - <0.8 (0.48-0.76) ml in **8** infants; and 0.82, 0.83 ml in the other two.
  - ✓ Sx evaluation was normal in **6** and small-normal in **4** of the infants, gland shape normal in all **(Figure 3)**
  - ✓ Uptake of radioisotope was decreased in 5 and absent in 2 of the 10 infants **(See Table)**
  - ✓ Cause of transient TSH elevation was attributable to blocking antibodies **(3),** heterozygous TSH receptor mutation **(1)** and cause unknown **(6).**

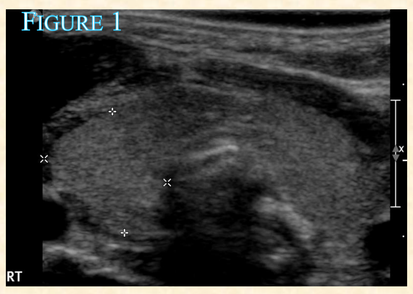

FIGURE 1:
Ultrasound image of patient **3** (see Table), an infant in whom gland size was considered large on Sx assessment when Ox assessment on two occasions (observers blinded) gave R lobe volume 0.36/0.40 ml, L lobe volume 0.48/0.47, combined volume 0.84/0.87 mean 0.86 ml (small-normal). The impression of large size is attributable to flattening of the anterior margin of the gland and deep isthmus. An initial diagnosis of dyshormonogenesis was made but mutational analysis was negative and thyroid function was normal after L-T4 was discontinued aged 3 years.

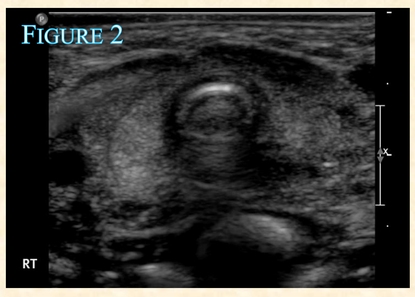

FIGURE 2:
Ultrasound image of patient **15** (see Table), an infant with allo-immune thyroiditis associated with ↑↑ TSH receptor antibody levels. There is an obvious difference in echogenicity between what appears to be the "core" of the lobes and the outer margins. The observers were unable to agree on what constituted actual gland and what constituted possible peri-thyroid oedema so that neither Sx nor Ox assessment was possible

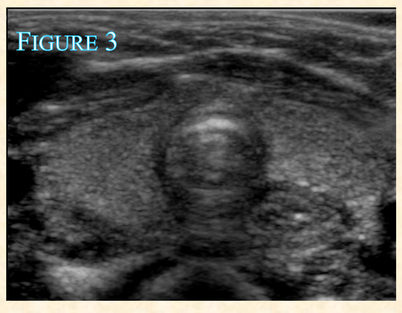

FIGURE 3:
Ultrasound image of patient 6 (see Table) with transient TSH elevation of unknown cause, never treated with L-T4. Gland shape is normal with a narrow isthmus and pronounced anterior margin curve proximal to this with more gentle, bilateral curves at the anterior surfaces of the lobes.

DISCUSSION

- Our hypothesis that objective evaluation of thyroid volume would be normal in most infants with transient TSH has not been supported by this study.
- Thyroid volume was unexpectedly reduced on objective measurement in 11 of 14 patients in whom Ox measurement was possible – small in 6 and small-normal in 5.
- One explanation for the discrepancy between Ox and Sx evaluation is that of artefact due to our Scottish reference range being set too high, the Scottish reference range for newborn thyroid size being higher than in other studies from countries such as Poland, Turkey, China, Germany and Belgium.
- Moreover, Scottish data are from term infants (37-42 weeks gestation) and it is known that thyroid volume increases with gestation.
- However even according to other populations (e.g. Poland, Germany) thyroid volumes in 10 of our transient cases are at the lower end of the reference range.
- The combination of ultrasound and scintigraphy was particularly useful in this groups of infants with transient TSH elevation, reduced or absent uptake on RIS being seen in nearly half of the patients

CONCLUSION

- Transient TSH elevation is not synonymous with a normal thyroid gland. The question of reduced thyroid volume in transient TSH elevation requires further study with larger numbers. It is possible that at least some cases merit follow up imaging in later childhood to confirm normal thyroid size.

55ESPE 923--P1
Thyroid
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DOI: 10.3252/pso.eu.55ESPE.2016
Poster presented at: ESPE 2016 PARIS