ORIGINAL ARTICLE

Combined ultrasound and isotope scanning is more informative in the diagnosis of congenital hypothyroidism than single scanning

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Background: Thyroid imaging is helpful in confirming the diagnosis of congenital hypothyroidism and in establishing the aetiology. Although isotope scanning is the standard method of imaging, ultrasound assessment may be complementary.
Aim: To determine the strengths and weaknesses of thyroid ultrasound and isotope scanning in neonates with thyroid stimulating hormone (TSH) elevation.
Methods: Babies from the West of Scotland with raised capillary TSH (>15 mU/l) on neonatal screening between January 1999 and 2004 were recruited. Thyroid dimensions were measured using ultrasonography, and volumes were calculated. Isotope scanning was carried out with a pinhole collimator after an intravenous injection of 99m-technetium pertechnetate.
Results: 40 infants (29 female) underwent scanning at a median of 17 days (range 12 days to 15 months). The final diagnosis was athyreosis (n = 11), ectopia (n = 12), hypoplasia (n = 8; 3 cases of hemi-agenesis), dyshormonogenesis (n = 5), transient hypothyroidism (n = 2), transient hyperthyrotropinaemia (n = 1) and uncertain status with gland in situ (n = 1). 6 infants had discordant scans with no isotope uptake but visualisation of thyroid tissue on ultrasound. This was attributed to TSH suppression from thyroxine (n = 3); maternal blocking antibodies (n = 1); cystic degeneration of the thyroid (n = 1); and possible TSH receptor defect (n = 1).
Conclusions: Isotope scanning was superior to ultrasound in the detection of ectopic tissue. However, ultrasound detected tissue that was not visualised on isotope scanning, and showed abnormalities of thyroid volume and morphology. We would therefore advocate dual scanning in newborns with TSH elevation as each modality provides different information.

Congenital hypothyroidism is a relatively common congenital disorder with an incidence of 1 in 4350 live births in Scotland.[1] It is one of the few preventable causes of mental retardation. Congenital hypothyroidism is usually seen in otherwise healthy term neonates who are found to have a significant increase in the thyroid stimulating hormone (TSH>50 mU/l) on Guthrie screening carried out between 5 and 7 days of age.[1] Approximately 80% of congenital hypothyroidism is caused by thyroid dysgenesis due to absence, hypoplasia or ectopia of the gland, which is almost always sporadic in nature. The other 15–20% of cases are caused by a variety of autosomal recessive defects affecting thyroxine (T4) synthesis (dyshormonogenesis). In such cases the gland is nearly always normal or enlarged.

Transient thyroid dysfunction (TTD) is usually seen in association with prematurity, sickness and congenital malformation.[2] Congenital hypothyroidism and TTD with increased TSH level cannot always be distinguished on clinical grounds, and current practice is to treat all but the mildest cases with thyroxine and re-evaluate thyroid status after 2 or 3 years.[3] Re-evaluation constitutes either phasing out T4 treatment or converting to T3 treatment and then stopping for 2 weeks, followed by biochemical evaluation and isotope imaging. We have found this problematic; it is time consuming, technically difficult owing to poor cooperation in young children, and may render the child symptomatic from hypothyroidism.

With true congenital hypothyroidism, there has always been a case for carrying out thyroid imaging to determine the aetiology, as 20% of cases will be due to dyshormonogenesis, which carries a 1 in 4 recurrence risk. Neonatal screening was started in Scotland in 1979[4] and isotope scanning was regularly carried out until 1983 when enthusiasm began to wane, possibly due to the practical difficulties.[5]

Since the initial description of the thyroid transcription factor Pax-8 in 1992,[6] advances have been made in the understanding of both normal thyroid development and the aetiology of congenital hypothyroidism. These include the identification of further transcription factors, TTF-1 in 1995[7] and TTF-2 in 1997,[8] and the description of people with inactivating TSH receptor defects.[9 10] Infants with congenital hypothyroidism due to a thyroid gland in situ show a greater diagnostic yield in terms of specific aetiology.[11] Determining the thyroid site and size by imaging is therefore desirable.

Currently, isotope scanning is the gold standard in imaging babies and children with congenital hypothyroidism, and the only reliable method of disclosing an ectopic gland, although it is less helpful in the assessment of thyroid size and morphology. However, most scanning is carried out in adult units and the results may be difficult to interpret, especially in babies who have received iodine in the course of antiseptic procedures, as this interferes with the uptake of isotope.[12] Moreover, it is not practical to carry out isotope scanning in sick, preterm infants.

Although ultrasound is a promising technique for thyroid imaging in newborn infants with congenital hypothyroidism,[13 14] it is still relatively underutilised, especially in the UK. In 1990, De Bruyn *et al*[15] reported that thyroid ultrasound was only of limited value in the assessment of congenital hypothyroidism. However, there has been renewed interest

Abbreviations: TSH, thyroid stimulating hormone; TTD, transient thyroid dysfunction

Table 1 Summary of all infants with increased thyroid stimulating hormone level (>15 mU/l) who underwent dual scanning

Sex	Guthrie TSH (days)	Ven TSH (days)	Ven T4 (days)	Age at Rx (days)	Ultrasound report	Isotope scanning		Diagnosis	Conc
						Report; TSH/age (days)	Day of Rx		
F	173 (7)	477 (13)	7 (13)	13	No tissue	Faint uptake base of tongue; 5.8/27	15	E	Yes
F	152 (8)	155.3 (16)	10 (16)	15	No tissue	Small area base of tongue; NA/17	2	E	Yes
M	83 (5)	NA (11)	79* (11)	11	Lingual thyroid	Uptake thyroid region; 76.8/14	4	E	Yes
F	465 (8)	464 (14)	7.2 (14)	14	No tissue	Sublingual thyroid; 26/20	7	E	Yes
F	238 (7)	514 (11)	5.7 (11)	11	No tissue	Small area midline of tongue; NA/15	5	E	Yes
F	135 (7)	>100 (9)	66 (9)	9	No tissue	Lingual uptake in midline; 70.8/15	7	E	Yes
M	78 (7)	370 (12)	9.2 (12)	12	No tissue	Small area post. to tongue; 13.2/17	6	E	Yes
F	165 (6)	>100 (9)	26.7 (9)	10	No tissue	Lingual thyroid; NA/15	6	E	Yes
F	42 (5)	22.6 (12)	15.7 (12)	58	No tissue	Uptake higher, more post; NA/30	0	E	Yes
M	149 (7)	354.5 (13)	6.2 (13)	13	No tissue	Tiny area base of tongue; 354 (13d)/14	2	E	Yes
F	41 (7)	20.7 (10)	16.3 (10)	155	No tissue	Small sublingual; NA/49	0	E	Yes
F	140 (5)	>100 (8)	70* (8)	8	No tissue	Focal tracer base of tongue; NA/13	6	E	Yes
F	447 (6)	>150 (10)	29* (10)	10	No tissue; cysts on left	No uptake; NA/17	8	A	Yes
M	246 (5)	141.1 (11)	5 (11)	11	No tissue	No uptake; NA/27	7	A	Yes
M	271 (5)	>100 (11)	3.7 (11)	11	No tissue	No uptake: extravasation; NA/14	4	A	Yes
F	301 (5)	660 (10)	8 (10)	10	No tissue	No uptake; 59.5/15	6	A	Yes
F	285 (5)	>150 (9)	4.1 (10)	8	No tissue	No uptake; 49.7 (35 days)/17	10	A	Yes
F	159 (5)	>150 (10)	<20* (10)	10	No tissue	No uptake; 204/16	7	A	Yes
M	279 (5)	561 (12)	<6 (12)	12	No tissue	No uptake; 44.6/20	9	A	Yes
F	146 (5)	>150 (11)	3 (11)	11	No tissue	No uptake; 70.4/16	6	A	Yes
F	258 (6)	616.9 (12)	3.6 (12)	11	No tissue	No uptake; 7.1 (14.5 months)/15 months	15mo	A	Yes
F	221 (6)	>150 (13)	<20* (13)	13	No tissue	No uptake; 6.7 (22 days)/16	4	A	Yes
F	163 (5)	>150 (9)	35* (9)	9	No tissue	No uptake; 2.8/23	15	A	Yes
F	27 (7)	7.4 (16)	18 (16)	None	Left hemi-agenesis	Slightly asymmetrical; 7.3/8 months	0	L Hemi	Yes
F	54 (7)	55 (12)	17 (12)	15	Right hemi-agenesis	Uptake but formless oval; NA/19	5	R Hemi	Yes
F	23 (9)	16.2 (22)	14 (22)	207	Rounded nodule	Rounded area of uptake; NA/5 months	0	Hypo	Yes
F	255 (6)	>150 (8)	84 (8)	8	Small	Faint uptake midline; 11.7/15	8	Hypo	Yes
F	208 (7)	72.3 (10)	4.5 (10)	12	Large	Good uptake; NA/17	6	D	Yes
F	49 (7)	>100 (14)	8 (14)	14	Large	Globally enlarged; 68.3/20	7	D	Yes
M	16 (4)	14.8 (36)	9 (36)	0	Large	Normal; NA/2 months	0	D	Yes
F	300 (6)	>150 (11)	<20* (11)	11	Large	Normal; NA/17	7	D	Yes
M	29 (6)	55 (10)	11 (10)	10	Normal	Normal ; 5.3/17	8	D	Yes
M	41 (13)	117.8 (21)	6.6 (21)	21	Normal	Normal; 10.2/28	8	TH (prem)	Yes
F	27 (9)	33.6 (31)	92* (31)	None	Small	Normal; 24.4/47	0	TETSH	Yes
F	55 (5)	77 (10)	14.1 (10)	10	Right hemi-agenesis	No uptake; NA/16	7	R Hemi	No
F	104 (5)	>150 (10)	<5 (10)	10	Small	No uptake; 71.9 (14 days)/16	7	Hypo	No
F	120 (5)	>100 (12)	9 (12)	12	Small	No uptake; 1/19	8	Hypo	No
F	77 (5)	68.4 (10)	14.3 (10)	10	No right lobe; cysts on left	No uptake; 7.7 (22 days)/21	12	Hypo	No
M	248 (5)	>150 (11)	40 (11)	11	Normal size but hypoechoic	No uptake; 30.8/28	18	TH (mat. abs)	No
M	33 (5)	11.87 (4)	220* (4)	13	Normal	No uptake; 2.2/20	8	SU	No

A, athyreosis; conc, concordance; D, dyshormonogenesis; E, ectopia; F, female; hemi, hemi-agenesis; hypo, hypoplasia; M, male; mat. abs, maternal blocking antibodies; NA, not applicable; prem, prematurity; Rx, start of thyroxine treatment; SU, status uncertain; T4, free thyroxine (pmol/l); TETSH, transient hyperthyrotropinaemia; TH, transient hypothyroidism; TSH, thyroid stimulating hormone; Ven, venous.
The age at neonatal (Guthrie card) screening, venepuncture and Rx is given in days. Guthrie TSH is capillary TSH on neonatal screening.
*Total thyroxine (nmol/l).
The TSH on the day of isotope scan (or nearest available day) is shown.

recently, with several publications showing the value of thyroid ultrasonography in neonates with congenital hypothyroidism.[16–19] For example, additional phenotypic abnormalities in infants with thyroid dysgenesis have been shown, including cysts along the normal pathway of the thyroglossal duct and cysts or thymic tissue in the empty thyroid area.[17 20] Normative data for thyroid ultrasonography in newborns have been published by two groups in Germany and Belgium,[21 22] and we have determined normative ranges for thyroid volume in 100 (49 male) healthy term infants from Glasgow.[23]

In theory, thyroid ultrasound would not be able to identify a lingual gland, but Ueda *et al*[24] have carried this out

successfully using two basic scanning positions: the midline sagittal and posterior coronal views of the floor of the mouth. However, colour Doppler ultrasonography has recently been shown to be superior to both grey-scale ultrasound and magnetic resonance imaging scanning for detecting ectopic thyroid tissue and may be a useful diagnostic tool.[25]

Our objective was to carry out thyroid ultrasound scanning on babies with increased TSH level on Guthrie card screening or venous samples and compare the findings with those on isotope scanning to assess the strengths and weaknesses of each diagnostic modality.

METHODS

Patients

After receiving approval from the Yorkhill Ethics Committee (Yorkhill, Glasgow, UK), all West of Scotland paediatricians were informed of the study. The responsible paediatrician was then invited to allow individual patients to participate in the study at the time of referral by the screening laboratory. Thyroxine treatment was started without delay (unless increase in TSH level was mild), and irrespective of when the scans could be carried out (see later).

Parents were asked to bring their infant for dual scanning in the Diagnostic Imaging Department of the Royal Hospital for Sick Children, Glasgow, UK. When intravenous cannula was inserted for administration of an isotope tracer, venous blood was obtained for thyroid function tests. Scans were carried out as early as possible, ideally within 7 days of starting treatment.

Babies with increased TSH level associated with extreme prematurity, sickness or congenital malformation were excluded from the study.

Ultrasound scanning

All infants were scanned by a paediatric radiologist (either SM or ACM) using an ACUSON 128XP 10 System (Acuson, Mountain View, California, USA) or an ATL 5000 HDI system (Bothwell, WA, California, USA). Transverse and longitudinal sections of the thyroid gland were performed using a linear 7.5 MHz probe or CL15-7 MHz probe with prewarmed coupling gel. The precise anatomical location of the thyroid was determined (transversely inferior to the thyroid cartilage and medial to the common carotid artery and jugular vein); then measurements of the maximum length of the gland from the sagittal images of both thyroid lobes were recorded. The maximum transverse diameter and the maximum depth of each lobe were measured from the transverse images. The thyroid volume was calculated using the formula for a prolate ellipsoid:

$$\text{Thyroid volume} = \text{length} \times \text{breadth} \times \text{depth} \times \pi/6.$$

Thyroid volumes were compared with normative data for the newborn.[23] The echogenicity of the thyroid was routinely assessed by comparison with the adjacent neck muscles as the thyroid gland is usually slightly hyperechoic, whereas fat is much more echogenic.[26] The sonographers were not blinded to the isotope findings by design; however, the isotope reports were not available at the time of ultrasound scanning, as both scans were carried out on the same day.

Isotope scanning

Isotope scanning was carried out with a pinhole collimator after an intravenous injection of 10–20 MBq 99m-technetium pertechnetate. An initial antero-posterior scan was performed before the placement of a marker (cobalt pen) in the sternal notch. Lateral and antero-posterior scans (including the abdomen) were then obtained. The normally sited thyroid gland lies posterior to the marker on the lateral scan. The level of radioisotope uptake by the thyroid was compared with the uptake by the salivary glands and stomach. The scans were interpreted by one of the paediatric radiologists (SM or ACM) in all but five cases.

Biochemistry

Babies were reviewed by their local paediatrician, and venous blood for total T4/free T4 (fT4) and TSH was obtained to confirm the diagnosis. Infants were started on thyroxine treatment at a median or mean (range) dose of 50 or 40.4 (12.5–50) μg/day.

On the day of scanning, venous blood was drawn for TSH and fT4. These were measured using the DPC Immulite 2000 (Diagnostic Products Corporation, California, USA).

The diagnosis of congenital hypothyroidism was made for each patient using all the information available (initial biochemistry, TSH at the time of isotope scan or duration of thyroxine treatment, family history and dual scanning results). Two clinicians (RJP and MDCD) reviewed the clinical, biochemical and radiological data in each case and agreed on a final aetiological diagnosis of congenital hypothyroidism.

Statistical considerations

In view of the small numbers, no formal statistics were applied, and a descriptive analysis was carried out.

RESULTS

Patient, maternal and screening data

During the study period, 76 infants (53 female) had an increased TSH level on Guthrie card screening. Table 1 summarises the clinical details of the infants (n = 40) included in the study (29 female). Of the remaining 36 infants, 15 had a single scan performed (ultrasound or isotope) and 21 had no imaging. The final diagnosis of the single scanned group is as follows: definite congenital hypothyroidism in 6, transient increased TSH level in 4 and uncertain status in 5 (4 with Down's syndrome). The final diagnosis of the unscanned group: definite congenital diagnosis in 6, transient increased TSH level in 9 and status uncertain in 6 (3 with Down's syndrome).

All but three children were Caucasian; these infants were of Pakistani, Indian and Afghani origin. Two infants (one with dyshormonogenesis and one with uncertain diagnosis with gland in situ) had affected elder siblings who did not

Table 2 Clinical data according to aetiological group

Diagnosis	No (male)	Guthrie TSH (mU/l)	Age at scans (days)	Day of thyroxine*	TSH at scans (mU/l)
Athyreosis	11 (3)	258 (146–447)	16.5 (14–27)†	7 (4–15)	47.2 (2.8–204)
Ectopia	12 (3)	144 (41–465)	16 (13–49)	5.5 (0–15)	48 (5.8–35)
Hypoplasia	8 (0)	66 (23–255)	19 (15–243)	7 (0–12)	7.7 (1–71.9)
Dyshormono genesis	5 (2)	49 (16–300)	17 (17–83)	7 (0–8)	37 (5–68)

TSH, thyroid stimulating hormone.
Median (range) for each category is shown.
*The duration of thyroxine (interval between age at treatment and age at scanning) is shown in column 5.
†Except one infant who had scans at 15 months, having started treatment on day 11.

Table 3 Comparison of ultrasound and isotope scan findings

	Ultrasound						
Isotope	**Normal**	**Large**	**Small**	**Absent**	**Ectopic**	**Abnormal shape**	**Hemi-agenesis**
Normal uptake	2	3	1		1		1
Increased		1					
Absent	**2**		**3**	11			**1**
Ectopic				11			
Abnormal shape						1	1
Decreased			1				

Bold values indicate discordant scans.

undergo dual scanning and are not included in the study. Median (range) gestational age and birth weight was 40 (31.7–42) weeks and 3.2 (1.95–4.68) kg, respectively. Three were preterm and six were low birthweight (<2500 g) infants. Twenty five infants were of appropriate size, 13 were small and 2 were large for gestational age. Apart from one male infant with congenital dislocation of the hip, no congenital anomalies were present in this group.

In the group of infants small for gestational age two mothers had a history of substance misuse and were hepatitis C positive; one mother had epilepsy treated with lamotrigine and another had pre-existing insulin-dependent diabetes mellitus. In the group that was appropriate for gestational age one mother received thyroxine for autoimmune thyroid disease and another received heparin for a previous deep venous thrombosis.

For all infants the median (range) age at Guthrie screening was 6 (4–13) days; at notification 11 (8–33) days; and at start of treatment (excluding three patients who did not start thyroxine) 11 (8–207) days. These data are consistent with a recent audit of the Scottish screening programme.[5] The median (range) age at dual scanning was 17 days (12 days–15 months). The median (mean) interval between starting thyroxine treatment and undergoing scanning was 7 (17.3) days, with a range of 0–446 days.

Scanning data

Tables 1 and 2 show the scan results for individual babies and aetiological groups, respectively. Thirty infants had increased TSH level >50 mU/l on Guthrie card screening and underwent dual scanning at a median age of 17 days. Ten infants with mild increase in TSH level (15–50 mU/l) were scanned later at a median age of 39 days. A variety of abnormalities were found on scanning the group with mild increase in TSH level: ectopia (n = 2), goitre (n = 3), left hemi-agenesis (n = 1) and hypoplasia (n = 2). One infant had a thyroid gland in situ of small volume (0.63 cf 0.7–3.3 ml) on ultrasound, but with prominence of the isthmus, and a normal isotope scan. Her increase in TSH level resolved at 2 years of age and was attributed to transient isolated hyperthyrotropinaemia. The one remaining infant, born at 32 weeks, had a normal-sized thyroid gland in situ on ultrasound and isotope scanning.

The agreed final diagnosis was athyreosis (n = 11), ectopia (n = 12), hypoplasia (n = 8), dyshormonogenesis (n = 5), transient hypothyroidism (n = 2; associated with prematurity in 1 case and maternal blocking antibodies in the other), transient hyperthyrotropinaemia (n = 1) and uncertain status with gland in situ (n = 1).

The infants tolerated the dual scanning well, with no adverse events recorded other than extravasation of radioisotope in one patient.

Isotope versus ultrasound scanning results

Table 3 compares isotope and ultrasound scan findings. Table 4 compares the duration of thyroxine treatment (ie, interval between age at treatment and age at scanning), initial dose of thyroxine and TSH at the time of scanning between groups with concordant or discordant scan results.

DISCUSSION

Isotope scanning, as expected, proved to be superior to ultrasonography in the detection of ectopic thyroid tissue, with a sensitivity of 91.7%. We were thus unable to reproduce Ueda *et al*'s[24] 100% success rate in showing the lingual thyroid on ultrasound scanning, as only one ectopic thyroid in our series was detected on ultrasonography (9.1%).

Although isotope scanning was superior in detecting ectopic thyroid tissue, ultrasound scanning detected the presence of thyroid tissue, which was not otherwise visualised in 6 (15%) of our 40 patients. The most common reason for this was the presumed suppression of TSH by thyroxine treatment. Other causes included the transfer of maternal blocking auto-antibodies, cystic degeneration and a postulated TSH receptor defect. Ultrasound scanning can therefore help to identify those neonates with TSH receptor blocking antibody or inactivating TSH receptor defect or with an iodine-trapping defect.

Also, we were able to show abnormalities in thyroid volume on ultrasonography that were not appreciable on isotope scanning. In cases with a normal isotope scan (n = 4), ultrasound provided evidence of goitre (n = 3) and hypoplasia (n = 1). In these cases ultrasound provided informative data to help determine aetiology. The superiority of ultrasound in determining thyroid volume has been shown previously by van Isselt *et al*[27] in adults with Graves' disease. Ultrasound scanning was shown to be more accurate than both planar scintigraphy and single-photon emission tomography for determining thyroid volume (using magnetic resonance imaging as the gold standard).[27]

Our series highlights the value of performing dual scans in infants with persistent mild increased TSH level. We found a morphological abnormality of the thyroid gland in 8 of 10 infants, in whom the increase in TSH level may otherwise have been attributed to isolated hyperthyrotropinaemia of infancy.

We have attributed non-uptake of radioisotope to thyroxine treatment with subsequent TSH suppression in three patients, and this raises a question about the timing of scanning. It is clearly important to start treatment without delay in infants with marked increase in TSH level (>50 mU/l) but early scans are more important for those infants who have only a modest increase in TSH levels on Guthrie card screening and are likely to have lower TSH at the time of screening. We have been unable to find reports of a specific TSH cut-off level required for adequate isotope uptake; for cancer screening a value of >30 mU/l is usually sought.[28] We were able to see uptake on scans with TSH values as low as 5.3 mU/l. We would recommend taking a blood sample for TSH measurement on the day of scanning to accurately interpret the scan findings. We suggest that isotope scanning be performed within 5 days rather than 7 days of starting thyroxine treatment.

Table 4 Comparison of clinical data between groups with concordant or discordant scans

Scans	No (male)	Guthrie TSH (mU/l)	Age at scans (days)	Day of T4	Initial T4 dose (mcg/day)	TSH at scan (mU/l)
Concordant	34 (9)	156 (16–465)	17 (13–456)	6 (0–446)	50 (0–50)	35.3 (5.3–354)
Discordant	6 (2)	80 (33–120)	17.5 (16–20)	8 (7–12)	43.8 (25–50)	2.2 ((1–71.9)

T4, thyroxine; TSH, thyroid stimulating hormone.
Median (range) for each category is shown.

What is already known on this topic

- Isotope scanning is the gold standard in imaging infants with congenital hypothyroidism.
- Ultrasound scanning can show a thyroid gland in situ and may also identify ectopic tissue.

What this study adds

- Ultrasound scanning can detect non-functioning thyroid tissue not visualised with isotope scanning. It can also show abnormalities in volume and morphology, which cannot be fully appreciated on two-dimensional isotope scans.
- Dual scanning is valuable in all children with increased thyroid stimulating hormone (TSH) level, especially in those with (persistent) mild increased TSH levels, as morphological abnormalities are common.
- Scans should be performed as early as possible after notification (preferably within 5 days). A blood sample for TSH measurement on the day of scanning is recommended to accurately interpret the scan results.

Although thyroglobulin could be a useful adjunct in the evaluation of infants with increased TSH levels, we did not consistently measure thyroglobulin in this group of patients.

We are currently establishing normative data in neonates and now include thyroglobulin in the routine evaluation of infants referred with increased TSH levels.

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