Diagnostic and Predictive Value of Ultrasound and Isotope Thyroid Scanning, Alone and in Combination, in Infants Referred with Thyroid-Stimulating Hormone Elevation on Newborn Screening

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Objective To determine the diagnostic and predictive value of ultrasound and radioisotope scans of the thyroid, alone and in combination, during a single visit after initial referral by the screening laboratory with thyroid-stimulating hormone (TSH) elevation.

Study design Retrospective blind review of ultrasound and radioisotope images followed by final diagnosis based on clinical features, biochemistry, imaging, and molecular genetic study.

Results Infants (n = 97; 61 female) with median birthweight 3.38 kg (range 2.04-4.86) and gestation 40 weeks (range 33-42), underwent successful dual thyroid ultrasound and technetium-99m pertechnetate radioisotope scan in a single center. Combined scanning at the initial visit resulted in a correct final diagnosis in 79 of 97 (81%) cases. One patient was misdiagnosed initially as having athyreosis as the result of delayed radioisotope scan and the diagnosis of ectopia made later on diagnostic challenge. The specificity/sensitivity for radioisotope scan and for ultrasound was as follows: 100%/97% and 100%/55% for ectopia (n = 39); 81%/100% and 54%/100% for athyreosis (n = 18); and 89%/90% and 80%/95% for dyshormonogenesis (n = 20). Neither modality, alone or in combination, predicted final diagnosis in eutopic glands due to hypoplasia (n = 4), transient TSH elevation (n = 12), and status still uncertain (n = 4).

Conclusion More than 80% of newborn infants with TSH elevation can be diagnosed correctly on initial imaging with combined radioisotope scan and ultrasound. Ultrasound cannot reliably detect thyroid ectopia. Radioisotope scan, especially if performed late, may show no uptake despite the presence of a eutopic gland. *(J Pediatr 2014;164:846-54)*.

Approximately 30 infants born in Scotland each year are referred by the Newborn Screening Laboratory with elevated thyroid-stimulating hormone (TSH) levels on newborn screening. Approximately two-thirds of these are found to have definite congenital hypothyroidism (CH).[1]

Clinical assessment and pretreatment venous thyroid function tests alone provide sufficient information to manage CH initially because they will identify compensated and decompensated CH[2] and thus direct appropriate treatment to the infant in question,[3] preventing neurodevelopmental impairment in severe cases.[4] However, the long-term management of the patient with CH and family is enhanced by establishing a precise diagnosis to show beyond doubt whether the child has true, permanent CH requiring lifelong treatment; provide a guide to L-thyroxine (T4) dosing[3]; allow accurate genetic counseling; and to target genetic investigations, particularly for enzymatic disorders[5] and TSH receptor gene defects.[6]

Thyroid imaging with ultrasound,[7] radioisotope scan,[8] and adjunctive measurement of serum thyroglobulin (Tg)[9] of infants with TSH elevation during the newborn period are of proven value in establishing the causes of CH. Since 1997, we have provided a service that offers both radioisotope scan and ultrasound scanning to infants born within the West of Scotland who are referred by the newborn screening laboratory with TSH elevation.[10] From 2004, we have refined this service and combined dual scanning with measurement of serum Tg from pretreatment venipuncture samples to aid diagnosis and classification of infants with raised TSH levels on newborn screening. The purpose of this paper is to detail the diagnostic and predictive value of both imaging modalities in our center between 2004 and 2011.

CH	Congenital hypothyroidism
FS	Functional sensitivity
fT4	Free thyroxine
T4	Thyroxine
Tg	Thyroglobulin
TPO	Thyroid peroxidase
TSH	Thyroid-stimulating hormone

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Methods

Since the inception of screening for primary CH in Scotland in 1979, a database has been kept of all infants referred by the Newborn Screening Laboratory as described previously.[1,2] The responsible clinician is asked to complete data for referred patients, with periodic updates. Information recorded includes birthweight and gestation, family history of thyroid disease, whether the child was unwell at the time of screening, signs of hypothyroidism, presence of goiter, and the presence of additional congenital malformations as well as initial biochemistry. The Glasgow West Research Ethics Committee approved the data extraction for audit and re-evaluation. Parents gave informed consent for data storage and for later anonymized data analysis and presentation.

We identified all patients, mostly from the West of Scotland, undergoing successful combined or dual scanning at our unit from January 2004 to December 2011 inclusive. Almost all had been seen initially by their local pediatric services after referral by the Newborn Screening Laboratory and had started thyroxine therapy unless venous TSH elevation was mild (<20 mU/L) with normal levels of free thyroxine (fT4).

Dry blood spot screening ("Guthrie") samples were tested for TSH levels by immunoassay AutoDELFIA Neonatal hTSH (PerkinElmer Life Sciences, Wallac Oy, Turku, Finland; functional sensitivity [FS] <2 mU/L) in the National Newborn Screening Laboratory. The cut-off TSH value for initial referral by the Newborn Screening laboratory was ≥25 mU/L, a repeat sample being requested for values between 8.0 and 24.9 mU/L, and referral if the repeat TSH value was ≥8 mU/L.

Venous TSH was measured using IMMULITE 2000 (Siemens, Wales, United Kingdom), FS 0.03 mU/L, pediatric reference range 0.3-5.5 mU/L and fT4 using IMMULITE 2000 (Siemens), FS 3.8 pmol/L, pediatric reference range 9-26 pmol/l. Serum Tg levels were measured using IMMULITE 2000 (Siemens), FS 2 μg/L. In the absence of a robust published reference range for infants, a pragmatic range of 9-150 μg/L was used, based on available data with reference ranges 17-160,[9] 28.5-198.4,[11] and 34-700 μg/L.[12] Tg antibodies were measured by IMMULITE 2000 (Siemens), taking values of >8 IU/mL as positive[10]; TSH receptor autoantibodies were measured by a radioimmunoassay (THYBIA; DiaSorin, Sallugia, Italy, analytical sensitivity 2.4 U/L, FS 8 U/L), calibrated with Medical Research Council standard B for Long-acting Thyroid Stimulator 65/122 and the World Health Organization standard 90/672 for thyroid-stimulating antibody. Thyroid peroxidase (TPO) antibodies were measured by 2-step immunoassay (ARCHITECT i2000 [Abbott Laboratories, Abbott Park, Illinois], analytical sensitivity 0.16 IU/L, FS 0.5 IU/L, standardized against Medical Research Council reference preparation).

Molecular genetic analysis was carried out in selected cases, and especially when imaging showed a eutopic thyroid gland. All samples were sent to the University of Mainz in Germany until 2011; since then, analysis for TSH receptor, TPO, and Tg has been available in Glasgow, with samples being sent to Germany for further study if required.

Protocol for Radioisotope Scan and Ultrasound

Combined radioisotope scan and ultrasound was carried out before day 10 of treatment where possible, to avoid poor uptake of radioisotope due to TSH suppression.[10] On the day of thyroid imaging, an intravenous cannula was inserted to facilitate application of isotopic label and to take venous blood for fT4 and TSH to assist interpretation of the radioisotope images. Radioisotope scan was carried out according to Society of Nuclear Medicine and Molecular Imaging guidelines[13] using technetium-99m pertechnetate with a high-resolution pinhole collimator (either Siemens Symbia; Siemens Medical Solutions, Hoffman Estates, Illinois, or Phillips Axis, Phillips Medical Systems, Surrey, United Kingdom). Before the intravenous administration of 10-16 MBq of tracer, the infant was fed in an attempt to induce calm and hence minimize movement artifacts, and also to diminish salivary gland activity. Fifteen minutes after injection, anteroposterior and lateral scans were obtained from head to abdomen, together with scans that included a cobalt marker to localize the sternal notch. Visible uptake in gastric, salivary, and bladder mucosa indicated adequate isotope application. The presence and position of uptake, size, symmetry, homogeneity, and avidity of tracer absorption were recorded. Ultrasound was used to determine thyroid tissue shape, echogenicity, homogeneity, echostructure, and the appearance of cysts or abnormal hyperechoic structures. Doppler imaging was used to investigate vascularity of structures and to highlight suspected lingual ectopic thyroid tissue.[14]

Gland volume was calculated as described by Perry et al,[15] enabling us to describe the thyroid tissue as enlarged, normal, or hypoplastic compared with local normative data for newborns (1.63 mL, SD 0.37). From 2004 to March 2008, ultrasound imaging was undertaken using a Philips/ATL 5000 HDI system (Bothell, Washington). Thereafter, the Philips iU22 (Koninklijke Philips Electronics N.V., Eindhoven, The Netherlands) featuring a 7- to 15-MHz hockey stick transducer with coupling gel was used. From 2008 onwards, the sublingual area was interrogated more closely with a view to identifying hypervascularized tissue that could be ectopic thyroid.

In 2008 one of the authors (D.N.) spent 3 months in the unit as part of a clinical fellowship. During this time D.N., J.J., and M.D. devised an information booklet for parents and attended all infants undergoing imaging. From 2008 onwards, it became our policy for J.J. or a clinician to attend and thus facilitate all scans.

Clinical images were retrieved from either E-Film or Picture Archiving and Communications System (Kodak Carestream; Carestream Health, Hemel Hempstead, United Kingdom). Laboratory results, clinical data, and original descriptions of ultrasound and radioisotope scans were