Thyroid Scintigraphy Differentiates Subtypes Of Congenital Hypothyroidism

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**Key words:** Thyroid Gland, Hypothyroidism, Congenital Hypothyroidism, Scintigraphy, Neonatal Screening

Word Counts

Summary: 150 words

Main Text: 1196 words

# Summary

**Introduction**

UK screening for congenital hypothyroidism (CH) is based on dried blood spot Thyroid Stimulating Hormone (TSH). Scintigraphy may identify CH subtypes classified as dysplasia, gland in situ (GIS) and ectopia, but is not performed in all centres. We retrospectively investigated the role of scintigraphy to identify CH subtypes in a single tertiary centre cohort.

**Methods**

Babies screen positive for CH between 2007-2017 were studied (n=418 of 534,783). Scintigraphy outcomes were correlated with TSH and Levothyroxine dose. GIS patients were analysed for three year outcomes.

**Results**

303 patients started Levothyroxine. Scintigraphy demonstrated three subtypes: GIS (n=139, 46%) ectopia (n=84, 28%) and dysplasia (n=80, 26%). Three year follow up demonstrated permanence in 54% of 37 GIS cases.

**Discussion**

Thyroid scintigraphy differentiates subtypes of CH and suggests a higher than expected proportion of patients with GIS and ectopia. CH is permanent in half of those with GIS.

Introduction

Congenital Hypothyroidism (CH) results in inadequate production of thyroid hormone and if untreated can lead to intellectual disability. In the UK, CH is diagnosed by identifying high levels of Thyroid Stimulating Hormone (TSH) on newborn blood spot (BS) screening. Screening reduces the risk of intellectual disability from untreated CH1. The majority of CH is primary, arising from a small or absent gland (dysplasia/aplasia), ectopic gland (ectopia) or gland in situ (GIS) producing inadequate thyroid hormone.

Thyroid dysplasia/aplasia is considered to comprise the majority of cases of CH with only 15% of cases historically attributed to GIS1 despite recent studies showing a higher prevalence2. Very few cases of dysplasia are thought to have a genetic basis1 while GIS is more likely to be associated with an inherited dyshormonogenesis3. Although the terms dyshormonogenesis and GIS have been used interchangeably, GIS indicates a scintigraphy observation and does not imply the pathogenesis and genetic mechanisms underpinning dyshormonogenesis.

Evidence for imaging in CH is limited and many centres argue that it does not alter management1. Imaging is highlighted as desirable in the NHS Newborn BS Screening Programme CH Clinical Referral Guidelines (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\_data/file/753471/Congenital\_hypothyroidism\_lab\_guide.pdf) and is recommended by the European Society for Paediatric Endocrinology.

Scintigraphy can identify absent, eutopic and ectopic thyroid glandswith sensitivities of 96%, 92% and 100% respectively4. Thyroid ultrasound has a sensitivity of 10% for detecting an ectopic gland4. We investigated the performance of scintigraphy in differentiating subtypes of CH and have analysed three year outcomes of patients with GIS.

# Materials and Methods

From 2007 to 2017, 534783 newborns were screened by the Manchester Newborn Screening Laboratory. Newborns with a positive BS TSH screen were referred to the tertiary paediatric endocrinology service at the Royal Manchester Children’s Hospital for measurement of plasma free thyroxine (fT4) and TSH (pTSH) by venous sampling, typically at age 1-2 weeks (mode 12, median 14 days). Scintigraphy was routinely performed at this visit following venous sampling and before Levothyroxine (LT4) administration.

Electronic patient records were reviewed for pTSH, fT4, weight, initial dose of LT4 and original scintigraphy report. Scintigraphy was classified as normal/large (GIS), small/absent (dysplasia) or abnormal position (ectopia) by a consultant paediatric radiologist. The term GIS was based on qualitative assessment to differentiate a small from a normal or large thyroid gland without reference to the mechanism of disordered thyroid hormone production. In the absence of thyroid gene panel testing3, our study design did not support the determination of underlying pathophysiology.

Patients with GIS who were followed up by the tertiary centre had their notes reviewed for TFTs, dose of LT4 and result of trial off therapy (if performed) aged three years. CH was classified as permanent if LT4 was recommenced following a four week trial off treatment or if a trial was deemed inappropriate due to a large or increasing LT4 requirement. CH was classified as transient if therapy was discontinued following a trial off treatment.

Data were analysed using SPSS software. Non parametric tests assessed differences in continuous variables that were not normally distributed. Univariate analysis tested correlations between variables related to the diagnosis and management of CH.

# Results

418 newborns had a positive CH screen, of whom 326 underwent scintigraphy and 303 were subsequently started on LT4 (Fig 1). Scintigraphy revealed the following subgroups: GIS (n=139, 46%), ectopia (n=84, 28%) and dysplasia (n=80, 26%). Median (interquartile range (IQR)) BS TSH (mU/L) was lower in GIS [23.5 (28.0)] than in ectopia [106.0 (147.0)] and dysplasia [172.0 (183.0)] [p<0.001 for difference between groups] but non-discriminatory between dysplasia and ectopia [p=0.12] (Fig 2a). Median (IQR) pTSH (mU/L) was also lower in GIS [41.0 (95.5)] than in ectopia [264.5 (345.6)] and dysplasia [421 (656.1)] [p<0.001] (Fig 2b). Median (IQR) fT4 was higher in GIS [12.0 (9.5)] than ectopia [9.6 (8.9)] and dysplasia [4.0 (11.1)] [p<0.001] (Fig 2c). Initial median (IQR) LT4 doses (micrograms/day) were 25.0(12.5), 37.5(12.5) and 37.5(25.0) [p<0.001] respectively across the three subgroups.

In analysis of covariance, LT4 dose correlated independently with fT4 levels to discriminate GIS from ectopia [p=0.009, R2=0.40 for model], but not dysplasia from ectopia [p=0.22, R2=0.38]. This suggests that, independent of fT4 levels, the initial LT4 dose was at least partially influenced by scintigraphy phenotype.

Of the 139 patients classified as GIS by scintigraphy, 119 were over three years of age at the time of the study and therefore suitable for assessment of the permanence of hypothyroidism. Of these, 37 were followed up at our centre with available records for review. 20 (54%) were classified as permanent and 17 (46%) as transient. Within this subset the median (IQR) BS TSH at diagnosis was higher in those with permanent [66.5 (110.0)] than transient [22.5 (11.5)] [p=0.026] disease. The pTSH, fT4 and LT4 doses at diagnosis showed no significant differences between GIS subgroups at three years of age [p=0.19, 0.18 and 0.29 respectively].

# Discussion

Our data demonstrate that over an 11 year period at a large NBS centre, GIS was the commonest subtype of CH. This suggests a greater incidence of possible dyshormonogenesis than previous reports (10-15%)1. The incidence of ectopia (28%) was also higher than previous estimates1, reflecting the value of scintigraphy in altering commonly held paradigms about the aetiology of CH.

Although contradictory to current understanding, our findings are unlikely to reflect a local aberration as similar observations were noted from another large, UK tertiary centre2. It is possible that the high relative frequency of GIS could be partially due to a relatively lower cut off for BS TSH (8mU/L) used in our centre, resulting in a higher proportion of milder CH cases classified as GIS. In a subgroup of GIS patients, half were transient, suggesting that a proportion of true GIS CH may have been over-represented. However, resolution in later childhood does not preclude the diagnosis of CH nor exclude genetic causes such as those due to mutations in dual oxidase maturation factors 1 and 23. This study did not test for the possibility of iodine deficiency in newborns as a cause for CH with normal gland on scintigraphy.

Even after adjusting for resolution in some patients, the proportion with permanent forms of GIS remains relatively high, suggesting possible dyshormonogenesis and a genetic aetiology3. Genetic testing has been shown to offer prognostic value in distinguishing between transient and permanent hypothyroidism as well as predicting response to treatment5. Our study was not designed to investigate genetic aetiology in CH; such putative associations need to be tested in larger cohort studies.

In addition to a higher frequency of GIS CH, we also observed a higher frequency of thyroid ectopia1. It is likely that the lower frequency reported in previous studies reflects an absence of the use of scintigraphy leading to the mislabelling of thyroid ectopia as dysplasia/aplasia.

## Ethics:

As this was a retrospective audit of medical notes ethical approval was not required or sought.

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