

Screening for Congenital Hypothyroidism

Chin Shern Lau,¹ *MBBS, MRCP*, Roy Joseph,^{2,3} *MBBS, MMed Paeds, FRCPC*, Tar Choon Aw,^{1,4,5} *MMed Int Medicine, FRCPE, FRCPA*

Introduction

Congenital hypothyroidism (CHT) is a significant clinical problem with a reported incidence of 1 in 2,000 to 1 in 4,000.^{1,2} A large Chinese study undertaken from 2004–2016 using blood spot thyroid-stimulating hormone (TSH) for initial screening, followed by venous TSH and free thyroxine (fT4) at recall, detected up to 0.96% of CHT cases (4,220/437,342) with a positive predictive value of 4.8% (192 out of 4,039 successfully recalled infants), giving a CHT incidence of 1 in 2,278.³ The symptoms of CHT are subtle, not specific (e.g. increased somnolence, feeding difficulty and prolonged jaundice) and may be easily missed. Screening for CHT at birth is essential to prevent any missed diagnosis of CHT as the condition is eminently treatable. However, the window of opportunity to render treatment is narrow. Prompt treatment within 2–4 weeks to improve the infant's cognition is the goal of the screening programme.⁴

In the US, newborn screening began with phenylketonuria (PKU) in 1961 when a test for phenylalanine became available.⁵ Europe followed soon after. Samples were tested from dried blood spots collected from neonatal heel pricks 3–5 days after birth in Massachusetts.⁶ Notably, cord blood cannot be used for PKU screening.⁷ Babies have to be sufficiently exposed to dietary protein and blood collection 72–96 hours after birth is recommended.⁸ When assays for thyroid hormones became available, CHT was added to the newborn PKU screening programme in Quebec, Canada in 1974.⁹ Filter paper heel blood taken between 3 and 5 days of age was the sample of choice as it piggybacked on the PKU programme for economic and logistical convenience.⁹ Besides, it is not the usual practice in North American obstetrics to discharge patients within 24 hours after delivery.⁹ Early CHT screening comprised an initial thyroxine (T4) test with a follow-up T4¹⁰ and/

or TSH for those with low T4 values.¹ As thyroid assays improved, screening then commenced with TSH¹¹ followed by TSH and/or T4/fT4 at recall for those with high TSH results.¹

Newborn screening in Singapore started with cord blood glucose-6-phosphate dehydrogenase (G6PD) in 1965.¹² Kernicterus was a significant cause of neonatal hyperbilirubinaemia in the early 1960s and G6PD deficiency accounted for 44% of these cases.¹³ PKU screening is not done as PKU seems quite rare in Singapore and the majority of the newborns are discharged within 48 hours after birth.⁸ In fact, a study from Thailand reported a PKU incidence of 1 in 212,535¹⁴ in contrast to 1 in 12,500 in western countries.¹⁵ Newborn G6PD screening is not done in the US.¹⁶

In this issue of the *Annals*, the Growing Up in Singapore Towards healthy Outcomes (GUSTO) study on cord blood TSH is an important addition to the literature, as well as an update on local practice.¹⁷ In particular, new local data are now available on maternal factors influencing cord TSH. It is especially pertinent for local practitioners to be cognisant of the proper interpretation of cord TSH with respect to the mode of delivery and the assay method employed.

Causes of CHT

CHT can be permanent or transient, and due to primary, secondary or peripheral aetiologies.¹⁸ Primary hypothyroidism may be due to thyroid dysgenesis (e.g. ectopic thyroid) or dyshormonogenesis (e.g. sodium-iodide symporter defects). Secondary causes of hypothyroidism are uncommon and often central in nature; they include thyrotropin-releasing hormone deficiency or resistance. Peripheral causes are more remote and include conditions with resistance to thyroid hormones, or abnormalities of thyroid hormone transport.

¹ Department of Laboratory Medicine, Changi General Hospital, Singapore

² Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

³ Department of Neonatology, National University Health System, Singapore

⁴ Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

⁵ Pathology Academic Clinical Programme, Duke-NUS Medical School, Singapore

Address for Correspondence: Department of Laboratory Medicine, Changi General Hospital, 2 Simei Street 3, Singapore 529889.

Email: tarchoon@gmail.com

CHT may also be part of rare syndromes such as Pendred (metabolic alkalosis, sensorineural deafness, goitre and hypothyroidism), Bamforth-Lazarus, and Kocher-Deber-Semilange.¹ However, transient causes of CHT are also common, for example from maternal intake of antithyroid drugs or maternal iodine deficiency.

CHT screening in Singapore

CHT screening in Singapore started out on the back of the established cord screening for G6PD deficiency.⁸ Details of this CHT screening programme have been reviewed in previous issues of the *Annals*.^{8,19} In 1980, the initial screening strategy involved a primary cord serum TT4 and a supplemental TSH screen using an in-house radio-isotopic assay.¹⁹ When cases of CHT with cord T4 that was higher than the 10th centile cut-off value were found, this was changed to both TSH and TT4 in 1985 at the National University Hospital (NUH). In 1990, the Ministry of Health Singapore sponsored a trial of cord TSH and TT4 at NUH, Singapore General Hospital and Kandang Kerbau Maternity Hospital. CHT was identified in 10 out of 20,072 cases. This strategy was later shifted to primary cord blood TSH screening with supplemental cord TT4 when TSH >25mU/L as TSH was more critical for sensitivity while TT4 improved specificity. With the availability of reliable assays, fT4 has replaced TT4 as both have equivalent performance and are unaffected by any altered binding protein abnormalities.¹⁹ Since the 1990s, all newborns have been routinely screened for congenital hypothyroidism using cord blood TSH (>25mU/L) with or without supplemental TT4/fT4.¹⁹ Babies with TSH >25mU/L are recalled by day 3–4 for further evaluation. At 72–120 hours of age, the venous blood thyroid hormone levels of healthy term infants (n=130) are: fT4 24.8–46.8pmol/L, and TSH 30mU/L (97th percentile). Treatment can be instituted for CHT by the end of the first week. CHT screening rates are over 99.9% with recall rates of around 1%.⁸ The recall rate can be reduced to 0.7% when subjects with supplemental fT4 <18.3pmol/L (mean+1SD [standard deviation]) on abnormal cord TSH (>23mU/L) are retested versus 0.9% for those tested with TSH alone.¹⁹ Notably, newborn thyroid hormone concentrations are much higher than adult venous levels (TSH 0.4–4.0 and fT4 10.0–20.0pmol/L).²⁰

Thyroid hormone assays

Most modern TSH and fT4 assays are performed on automated analysers using chemiluminescent immunoassays (CLIAs). TSH assays are typically non-

competitive (sandwich) immunoassays, whereas fT4 assays are competitive immunoassays. Although the performance of such assays is good, there still remains much variability between different TSH and fT4 assays as the assays are not standardised. Some studies show that the coefficient of variation (CV) between different TSH immunoassays for control samples range from 6–20%.²¹ In another study comparing 13 fT4 and 14 TSH assays, fT4 biases ranged from -28–62% for concentrations <9pmol/L, and -21–12% for TSH concentrations >5mIU/L.²² As such, it is preferable that the same immunoassay platform is consistently used in the assessment of TSH and fT4.

Caveats in neonatal CHT screening

We highlight some pointers in the interpretation of results. Studies have shown that it is possible for cord TT4 and fT4 levels to be normal in CHT.¹⁹ This phenomenon may be due to a compensated response from an increased TSH, or from abnormalities in the peripheral thyroid hormone receptors. Furthermore, post-natal stress can lead to a temporary rise in TSH and fT4, which can remain elevated for up to 5 days.⁴ Thus, prompt early clamping of both ends of the cord will mitigate against sampling cord blood contaminated by stress-induced TSH surge in neonatal blood.

Some preterm neonates with CHT also display a delayed rise in TSH.²³ As such, a repeat blood test several days later in these cases may be prudent. A two-screen approach for CHT screening, particularly for low birth weight or premature neonates, has been recommended by the European Society for Paediatric Endocrinology.¹⁸ Others have called for the use of lower TSH cut-offs to improve the CHT screening among preterm infants. Some studies have shown that up to 31% of these infants with blood spot TSH values >8.0–10mU/L can have permanent CHT.²⁴ While lower TSH cut-offs can improve the detection of CHT in these infants, it will also result in a greater rate of false-positive and possible overtreatment with thyroxine.²⁵ As such, a judicious balance is required. Thus close collaboration between the obstetric and neonatal teams experienced in newborn and neonatal endocrinology is vital.

CHT still remains a commonly encountered neonatal disorder. Screening for CHT using TSH and supplemental fT4 remains an essential part of neonatal evaluation. The assays used today have excellent performance. However, physicians must keep in mind certain caveats especially in low-birth weight or preterm infants.

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