Mini Review

Congenital hypothyroidism: Screening dilemma

Meena P. Desai

Hon. Consultant, B.J. Wadia Hospital for Children and Institute of Child Health and Research Centre – Endocrinology Division, Parel, and Hon. Pediatrician, Sir Hurkisondas Nurrotumdas Hospital and Research Centre, Raja Rammohan Roy Road, Mumbai, India

ABSTRACT

Primary sporadic congenital hypothyroidism (CH) is the most common cause of hypothyroidism infancy early childhood in iodine sufficient region. Screening for neonatal CH began in 1970s. The rationale and reason for neonatal screening for CH (NSCH) are well established. It is mandatory in most developed countries along with the screen for metabolic disorder. The possibility of measuring TSH and thyroid hormones in cord blood paved the way for newborn screening (NS) for CH. Worldwide it is estimated that 25% of the live born population of 130 million babies undergo NSCH. Klein *et al.,* by 1972 had shown improved CNS prognosis in CH treated by age 3 months. NSCH has largely eradicated the severe irreversible neurodevelopmental damage and reversed the chances of growth failure in infancy and early childhood.

Key Words: Congenital hypothyroidism, neonatal screening

Primary sporadic congenital hypothyroidism (CH) is the most common cause of hypothyroidism infancy early childhood in iodine sufficient region. Screening for neonatal CH began in 1970s. The rationale and reason for neonatal screening for CH (NSCH) are well established. It is mandatory in most developed countries along with the screen for metabolic disorder. The possibility of measuring TSH and thyroid hormones in cord blood paved the way for newborn screening (NS) for CH. Worldwide it is estimated that 25% of the live born population of 130 million babies undergo NSCH. Klein *et al.,* by 1972 had shown improved CNS prognosis in CH treated by age 3 months. NSCH has largely eradicated the severe irreversible neurodevelopmental damage and reversed the chances of growth failure in infancy and early childhood.

Neonatal screening for CH was introduced in 1974 by using newborn heel prick filter paper (FP) blood sample, a technique pioneered by Guthrie in 1963. NSCH has been universally accepted as an essential part of screening for various metabolic disorders. It is successfully implemented in most developed countries, and has proven to be one of the most cost effective screening programs in the field of preventive medicine and public health. The cost benefit ratio is 10:1 along with tremendous clinical impact. There has been a progressive increase in coverage, technological performance, shortened turn around time, early reconfirmation of diagnosis, initiation of treatment, consensus on the dose (10 to 15 μg/kg) to be used, periodic follow-up, and ultimate outcome.

Screening procedures in newborns have to take into account the complex interaction between feto-maternal and placental unit. Though fetal endocrine system functions largely independently of that of the mother, maternal endocrine disorders can influence the fetus adversely. The dilemmas in screening for congenital hypothyroidism (CH) can relate to maternal thyroid status, fetal factors like gestational age and maturity of the fetal H-P-T axis, perinatal intranatal factor (use of iodine application during delivery) and mode of delivery. These can also relate to environmental and nutritional factors or technical and laboratory errors in neonatal blood sampling.

The incidence of primary hypothyroidism varies from

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.104027

Corresponding Author: Dr. Meena P. Desai, Hon. Consultant, B.J. Wadia Hospital for Children and Institute of Child Health and Research Centre – Endocrinology Division, Parel, Mumbai, India. E-mail: drmeenadesai@gmail.com

1 in 1000 to 1 in 3500 live births depending on iodine sufficiency, laboratory methods, screening practice (changes in test cut offs) demographic, geographic, racial/ethnic and other unknown factors. The incidence is higher in Hispanics and South Asians ((1:2000) and in India, and lower in American Africans (1:32000). Religious customs like consanguinity also alter the incidence.

Majority of screening programs use filter paper TSH or T4 collected by heel prick, followed by back up TSH in the lowest 10 to 20 % or use both, on days 2/3 to 5 after birth, when the TSH and T4 levels have normalized following the initial surge in TSH which occurs within 30 min of birth and in T4 within the first 24 h. In some programs, a second sample is collected for TSH and T4 between 2-6 weeks of life. This helps to identify newborn with later rise in TSH. Screening earlier than this (unless placental side of cord blood is used) increases the number of false positives. In most screening programs, false positive to confirmed CH case ratio is 2 to 3:1. Errors in screening procedure can occur hence reconfirmation is required within one or 2 weeks of birth or earlier. About 5% of CH may be missed on screening irrespective of the methodology used, due to specimen handling errors, problems with testing or data analysis or immaturity of the H-P axis with a delayed rise in TSH. While interpreting the screening result all these factors must be borne in mind. Elevated TSH or subnormal T4 based on the screening cut off values indicates primary hypothyroidism. Problems arise when borderline values are obtained. Unusual instances of initial normal screening report in newborns with CH are documented. There are advantages and disadvantages of both TSH and T4 screening. Transient hypothyroxinemia of prematurity more often seen in newborns < 34 weeks is a problem to reckon with. T4 supplementation in this group of babies is still under survey. Aside from human errors, truly normal screening values have been noted in infants who developed severe hypothyroidism during infancy for reasons which are not known. Interestingly, monozygotic twins, genetically discordant for thyroid dysgenesis with normal screening values in the affected twin because of subtle intermixing of blood of the normal twin fetus are reported. Dopamine infusion also leads to false elevation of plasma TSH therefore, repeat determination may be necessary.

Thyroid Dysgenesis which is the most common cause of CH involves 2/3 (66%) of those with permanent CH, and dyshormonogenesis about 15 to 20 %. 'Thyroid Dysgenesis' includes number of abnormalities of thyroid development due to faulty embryogenesis varying from aplasia/agenesis, hypoplasia and ectopia, grouped together. The spectrum of thyroid deficiency in thyroid dysgenesis varies. The severity of dyshormonogenesis due to biosynthetic defects also varies. Newborns with hypoplastic or ectopic thyroid gland or dyshormonogenesis may be missed on initial screening as thyroid hormone deficiency, biochemical and clinical may become evident later. Hence, in spite of initial screen showing normal TSH or T4, if patients have suggestive clinical findings in infancy or early childhood, diagnosis of CH should be considered. Transcription factors play an important role in thyroid embryogenesis. Thyroid dysgenesis is usually sporadic (mechanism?) with F:M ratio of 2:1, but 2 to 3% are familial with mutation of homeobox genes TTF1, (NKF 2.1) TTF2 (FOXE1) or PAX8. Recently mutation of transcription factor GL153 is described with a rare syndrome of neonatal diabetes and congenital glaucoma along with CH. Hence, neonates with these problems should be checked for CH. Higher incidence of CH in patients with chromosomal disorders like Down syndrome is known. Non-thyroid congenital anomalies–cardiac, CNS, musculoskeletal, digestive, urological, cleft palate and eye anomalies are noted in 8 to 10% of infants with CH. This has practical implications. First degree relatives of infants with CH have increased prevalence of thyroglossal duct cysts, a pyramidal thyroid lobe, thyroid hemiagenesis, and ectopic thyroid anomalies. These findings are compatible with autosomal dominant mode of inheritance with low penetrance up to 21%. All the observations listed above support the possibility of genetic predisposition in some patients with CH.

Thyroid dysgenesis is the etiologic factor in most infants with permanent CH detected on screening with varying spectrum of severity of thyroid deficiency. Near normal T3 in face of low T4 suggests presence of some residual thyroid tissue, which can be confirmed by thyroid scan. Measurable level of thyroglobulin (TG) also favors presence of some amount of functioning thyroid tissue. A thyroid infant has no circulating TG.

Maternal thyroid disorders can affect the fetus and the newborns. Rarely thyroid dysgenesis in association with maternal autoimmune thyroiditis is documented. It could be coincidental, but has been documented in subsequent sibships also. Maternal ingestion of antithyroid drugs, goitrogens, or other factors difficult deliveries can cause transient hyperthyrotropinemia in the newborn. They need careful follow up. Dyshormonogenesis can lead to presence of goiter at birth along with abnormal biochemical thyroid profile at birth. Thyroid resistance syndrome usually do not manifest at birth. In fetus and newborns of mothers with thyrotoxicosis based on the transfer of thyrotropin receptor blocking or stimulating antibodies a transient state of hypo or hyperthyroidism may occur. This will lead to subnormal or elevated T4 levels in the newborn. Transfer

of maternal antithyroid drugs across the placenta can also lead to TSH elevation with transient hypothyroidism in the newborn. Neonatal hyperthyroidism occurs in 1 to 2% of the offspring of thyrotoxic mothers with active or inactive disease.

Evaluation of infants with positive screening report for CH needs prompt clinical and laboratory evaluation based on the threshold for cut off values. Less than 5% of newborns can be diagnosed clinically before screening reports and 15 to 20% of CH may develop suggestive clinical symptoms and signs during the first few weeks. In neonatal period (2-6 weeks) T4 < 6.5 μg/dl, FT4 < 0.8 ng/dl and TSH > 10 mU/L – suggest CH. With proven CH 90% have TSH > 50 mU/L, 75 % have low T4 and FT4 as mentioned above. Up to 20 % with CH may have T4 and FT4 in normal range of 6.5 to 13 μg/dl and 0.8 to 1.9 ng/dl respectively, but with elevated TSH > 30 mU/L. They need further testing on follow-up. Near normal T3 in face of low T4 or measurable TG favors the presence of some residual tissue. Further confirmation can be obtained by imaging studies. A primary TSH strategy will miss the central (pituitary/hypothalamic) CH, which is uncommon (1 in 60,000), TBG deficiency and hyperthyroxinemia because of maternal thyroid stimulating immunoglobulin (TSI) transfer. Primary T4/back up TSH program will miss compensated hypothyroidism, which may be due to ectopic thyroid or dyshormonogenesis. In central hypothyroidism (pituitary or hypothalamic) subnormal thyroid response to TSH or TSH response to TRH are helpful in locating the site of the disorder. Study of other pituitary hormones will be helpful. Hypothalamic TRH deficiency is more likely. TBG deficiency is asymptomatic and T4 is subnormal on screening. These infants do not need any treatment. TBG deficiency may be inherited. Infants with atypical congenital hypothyroidism with delayed thyrotropin rise and are also missed on screening as their thyrotropin and T4 levels on initially screen are normal. T4/TBG ratio or free T4 helps confirm the diagnosis.

Based on the screening results imaging studies may be undertaken. There is occasionally discordance between USG and radionuclide scintigraphy (RS) in some infants which can be misleading. The nature of non-thyroidal tissue in thyroid fossa seen on USG is unknown (Thymus remnants of ultimobranchial bodies). Presence of heterogeneous tissue in the thyroid fossa on USG may be a diagnostic trap in infants with proven thyroid ectopia on Isotope Scan (RS). RS will not be helpful in patients with TSH receptor defect, iodide trapping defect or TRAB block by maternal thyroid binding antibody (TBA). In this situation USG may be helpful.

Many avenues for early detection in the newborn and eradication of postnatal problems due to undiagnosed CH in newborns exist today. In countries like ours the problems for non-implementation of screening do not relate to lack of scientific or technical know-how but are related to socioeconomic and population burden. Neonatal screening for congenital hypothyroidism needs to be introduced in this country which has significantly high incidence of CH to prevent future morbidity from mental and physical handicaps.

References

1. Peter F. Thyroid dysfunction in the offspring of mothers with autoimmune thyroid disease (commentary) Acta Paediatr 2005;94:1008-10.
2. Fisher DA, Nelson JC, Carlton EI, Wilcox RB. Maturation of human hypothalamic pituitary-thyroid function and control. Thyroid 2000;10:229-34.
3. Fisher DA. Thyroid function and dysfunction in premature infants. Pediatr Endocrinol Rev 2007;4:317-28.
4. LaFranchi SH. Increasing incidence of congenital hypothyroidism: Some answers, more questions. J Clin Endocrinol Metab 2011;96:2395-7.
5. Fisher DA. Disorders of the thyroid in the newborn and infants. In: Sperling MA, editor. 2nd ed. Pediatric Endocrinology. Philadelphia: WB Saunders; 2008. p. 161-86.
6. Delange F. Neonatal Screening for congenital hypothyroidism: Results and perspectives. Horm Res 1997;48:51-61.
7. Peter F, Muzsnah A. Congenital Disorders of the Thyroid: Hypo/Hyperthyroidism Pediatr Clin N Am 2011;58:1099-115.
8. Marks AG, LaFranchi SH. Assessing Thyroid Function in Infants and Children in Thyroid Function Testing. In: Brent GA, editor. Germany: Springer Science + Business Media LLC; 2010.
9. American Academy of Pediatrics. Rose Sr, Section on Endocrinology and Committee on Genetics, American Thyroid Associatin; Brown RS, Public Health Committee, Lawson Wilkins Pediatric Endocirne Society. Update of Newborn Screening and therapy for congenital hypothyroidism pediatrics 2006;117;2290-2303.

Cite this article as: Desai MP. Congenital hypothyroidism: Screening dilemma. Indian J Endocr Metab 2012;16:S153-5.

Source of Support: Nil, **Conflict of Interest:** None declared