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EDITORIAL COMMENTARY

Hypothyroxinemia in Preterm Neonates: Not Always Hypothyroidism

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Thyroid physiology in preterm neonates is characterized by differences from that in the term counterpart. Challenges to interpretation of the results of newborn screening (NBS) for congenital hypothyroidism (CH) include: (a) low serum thyroxine (T4), which may mislead one to a diagnosis of CH, in T4 based NBS, and (b) falsely low TSH (or delayed rise of TSH, due to immaturity of the pituitary gland) which may lead to missed diagnosis of true CH in TSH based NBS. Besides the setting of NBS, thyroid function tests are performed for a variety of indications in the neonate; these results too may be subject to wrong interpretation.

The accompanying article in this issue of IJP therefore, is a timely opportunity to review these concepts [1]. There are multiple causes for the apparent low T4 (with normal TSH) in preterm neonates. The as-yet immature fetal thyroid abruptly becomes the only source of T4 after birth. The more preterm the baby is, the lower is the T4, as highlighted by Sharma et al. [1]. Hepatic production of thyroxine binding globulin (TBG) is suboptimal. Additionally, critical illnesses typical of the preterm neonate can depress thyroid function – a state known as "sick euthyroid syndrome". The term "euthyroid" is given because though total T4 is reduced due to a variety of transient alterations including peripheral thyroxine metabolism and TBG binding, free thyroxine (FT4), which is not affected by TBG and its binding, is most often normal (A caveat is that commonly available FT4 assays are not truly "free" T4 assays; only more expensive and time-consuming assays using equilibrium dialysis would measure FT4 accurately). Even in conditions of prematurity not associated with critical illness, FT4 by equilibrium dialysis is often normal, in contrast to total T4. Needless to say, whatever the assay, results should be interpreted against age related reference range of newborns, not the adult normal range (a case in point while reading the article by Sharma et al).

This apparent hypothyroxinemia of prematurity (THoP) is transient, recovering spontaneously by 6 to 8 wk of age. The question posed by the catchy title of the accompanying paper is regrettably not answered by their study, as only 7 hypothyroxinemic preterms survived to 7 wk; however, this fact is already well documented in literature. Long term studies have found no association of THoP with neurocognitive status of young adults [2]. The related burning question, as to whether THoP should be treated (albeit transiently for a few months or till review at 3 y of age) has already been examined in randomized controlled trials which found no long term benefit of treatment.

Current guidelines do not recommend treatment of THoP in the absence of elevated TSH [3], particularly keeping in mind the deleterious effects of overtreatment on neurocognition [4]. Also, due to the frequent finding of delayed TSH rise in preterms, guidelines recommend a "second screen" in TSH based NBS programs, at the age of 2 to 4 wk, so as not to miss true CH in preterms [3, 5]. Notwithstanding this, since the majority of CH so diagnosed (by elevated TSH only on the second screen) turn out to be mild / transient CH, pediatricians must exercise judgement as to whether their local logistic constraints will allow routine second screens for all preterms. Severe permanent CH in a term infant should never be missed by an overburdened system!

Compliance with Ethical Standards

Conflict of Interest None.

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References

1. Sharma JD, Nazir MFH, Khan AG, Hoque B. Does hypothyroxinemia of preterm neonates persist beyond 7 weeks of life? Indian J Pediatr. 2019. https://doi.org/10.1007/s12098-019-02935-2.

2. Hollanders JJ, Israëls J, Van der Pal SM, et al. No association between transient hypothyroxinemia of prematurity and neurodevelopmental outcome in young adulthood. J Clin Endocrinol Metab. 2015;100: 4648–53.
3. Léger J, Olivieri A, Donaldson M, et al, ESPE-PES-SLEP-JSPE-APEG-APPES-ISPAE, Congenital Hypothyroidism Consensus Conference Group. European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. J Clin Endocrinol Metab. 2014;99:363–84.
4. Bongers-Schokking JJ, Resing WCM, Oostdijk W, de Rijke YB, de Muinck Keizer-Shrama SMPF. Relation between early over and under treatment and behavioural problems in preadolescent children with congenital hypothyroidism. Horm Res Pediatr. 2018;90:247–56.
5. Desai MP, Sharma R, Riaz I, Sudhanshu S, Parikh R, Bhatia V. Newborn screening guidelines for congenital hypothyroidism in India: recommendations of the Indian Society for Pediatric and Adolescent Endocrinology - part I: screening and confirmation of diagnosis. Indian J Pediatr. 2018;85:440–7.