EDITORIAL

Prevention of Neurocognitive Impairment in Children Through Newborn Screening for Congenital Hypothyroidism

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Congenital hypothyroidism (CH) is probably the most important preventable cause of intellectual disability in children [1]. CH has been reported in approximately 1 in 1000 to 4000 births from various parts of the world [2]. Some developing countries, including Iran and India, have reported a higher incidence of CH [3,4].

Most newborn screening (NBS) programs use serum thyroid-stimulating hormone (TSH) as a primary test, and positive tests are confirmed by serum thyroxine (T4) levels. Infants with confirmed CH are started on treatment with levothyroxine (LT4) to achieve euthyroid state to prevent neurocognitive disabilities. TSH peaks in the first few days after birth and falls rapidly to 4-fold lower levels over the next few days. Mild increases in TSH over the recommended cut-off in NBS protocols for CH are often misclassified as normal. A significant number of these newborns may develop permanent primary hypothyroidism on follow-up. For this reason, many NBS programs order a second specimen in situations where the TSH concentration is mildly elevated between the cut-off and an upper limit of 40 or 50 mU/L [5,6]. A recent study noted that even in USA, many programs do not adjust TSH cut-offs according to the infant's age, and initial as well as repeat TSH measurements are performed outside the age for which the cut-offs were established [7].

NBS and early LT4 therapy have markedly reduced the prevalence of intellectual disability in children with CH from 8-28% to 1% or less [8]. Mild neurocognitive impairment is reported despite diagnosis and treatment of CH following NBS. These include reduced intelligence quotient (IQ), behavioral problems, attention deficits and subtle motor, language and visuospatial impairments [5,9-12]. These are attributed to negligible T4 availability before birth and postnatal factors, including delayed diagnosis, delayed initiation of treatment [13], later time to normalize thyroid function [14], both under and overtreatment with LT4 [9,15], and fewer follow-up clinic visits [16]. Parental education and problems in communicating with parents in rural settings are other important barriers.

The severity of CH, as defined by the levels of T4 and TSH at the time of diagnosis, is one of the most important risk factors for neurocognitive development in children with CH [10,11]. Intellectual impairment is more common with thyroid agenesis than other etiologies [13]. A role for prenatal hypothyroidism remains unconfirmed. The maternal T4 transferred by the placenta has a protective effect on the fetus, but cord T4 levels in newborns with CH are lower than normal controls [17]. The study by Rahmani, *et al*. [3], published in this issue of *Indian Pediatrics*, noted that the children with permanent CH have greater deficit in IQ compared to the children with transient CH, despite early detection and treatment unlike previous studies, which failed to note any such association [18].

It is possible to achieve a better outcome with earlier treatment and an initial high-dose of LT4, which rapidly normalizes thyroid function [19]. The European Society for Pediatric Endocrinology (ESPE) consensus guide-lines recommend that an initial LT4 dose of 10-15 µg/kg per day should be given as soon as possible and no later than 2 weeks after birth [6]. High-dose LT4 treatment may increase the free T4 levels to supraphysiologic levels with resultant temperament, attention, behavior and psychiatric problems later.

Better outcomes may be achieved with more frequent follow-up visits and testing than those recommended currently [20]. ESPE guidelines recommend that the first follow-up examination should take place 1-2 weeks after the start of LT4 treatment. Subsequent evaluation should take place every 2 weeks until a complete normalization of TSH concentration is reached; then every 1 to 3 months thereafter until the age of 12 months. Between the ages of 1 and 3 years, children should undergo frequent clinical and laboratory evaluations (every 2 to 4 months). Thereafter, evaluations should be carried out every 3 to 12 months until growth is completed [6]. Simple tools such as the Denver Developmental Screening Test (DDST) can be effectively used for neurodevelopmental screening at a younger age in children with CH on LT4 therapy [21].

We lag behind in our programs for NBS. NBS

programs in India are currently limited to a few states and union territories. The reported incidence of CH by NBS in India ranges from 1 in 1000 to 3100 [4]. Undiagnosed for months and years, many children with CH are being brought for evaluation with significant neurocognitive morbidity at a later age. The Indian Society for Pediatric and Adolescent Endocrinology had recently come out with locally relevant and cost-effective strategies for implementing NBS for CH (ISPAE, personal communication). This emphasizes the need for establishing NBS programs in all states of India. To achieve a better neurodevelopmental outcome, our NBS procedures should ensure that samples are collected and transported in time, age-specific cut-offs for TSH and T4 are defined, and results communicated to parents in time so that the affected newborns are brought to the treating team to confirm the diagnosis and start LT4 therapy within the first two weeks after birth. It is important to strengthen the surveillance system to ensure timely visits to the physician and efficient control of serum thyroid hormones levels to assure euthyroid state in children with CH. We have a long way to go!

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