RESCUE OF NEUROLOGICAL DEVELOPMENT IN CONGENITAL HYPOTHYRODISM: WE SHOULD LEAVE NO STONE UNTURNED

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Key words: congenital hypothyroidism, Thyroid dysgenesis, cognitive function, IQ, MRI

CONFLICT OF INTEREST

LP declares no conflict of interest related to the content of this commentary.

FUNDING

No funding associated with this commentary.

Congenital Hypothyroidism (CH) affects 4-5 out of 10,000 live newborns around the globe and represents the major cause of preventable intellectual disability. In fact, the early detection of newborns at risk of CH and the timely start of thyroxine replacement therapy optimize the neurodevelopmental outcome of the affected children, with a virtual disappearance of CH-related intellectual disability—defined as an IQ <70. For these reasons, neonatal CH screening is considered a milestone accomplishment of preventive medicine whose establishment since about 40 years in high-income countries led to positive socio-economical paybacks and paramount benefits for the affected patients and their families.

In this issue of the JCEM, the article by the group of Dr Maghnie is reporting on neurocognitive function and brain white matter microstructure evaluation by 3Tesla-MRI in 39 children at the age of 9.5 years that had been diagnosed with CH based on an apparently accurate neonatal screening program, using low TSH cutoffs for diagnosis (1). When compared with a cohort of 39 controls enrolled through a screening program in the schools of the same Region, children with CH scored lower than controls on accurate and comprehensive cognitive tests. While minor intellectual functional limitations or hearing/attention deficits can be expected in CH children despite adequate protocols for screening and treatment (2,3), the results here reported are surprising in entity (IQ score ranging 71-84 was found in 28.6% and <70 in 10.7% of permanent CH) and because clinical and cognitive determinations were uniquely found to correlate with white matter microstructure alterations in children with permanent CH. As far as CH management is concerned, the Authors report a quite high variability in the age of thyroxine start (15.32±7.93 days) and average TSHs always above the normal range at all ages (5.3-6-4 mU/L), including when cognitive tests were administered (6.98±4.68 mU/L). Therefore, a considerable number of CH patients likely received suboptimal thyroxine replacement at all time points despite the reported satisfactory adherence to treatment.

These data indicate that the neurodevelopmental rescue of CH should not be taken for granted even in the era of newborn screening, and thyroxine undertreatment should be prevented by any mean as outlined in the recent update of the guidelines by an expert task force of the European Reference

Network on Rare Endocrine Conditions (ENDO-ERN) (2). The main recommendations for strict follow-up and timely adjustments of thyroxine therapy in the children with CH are here summarized:

- thyroxine replacement should be started as early as possible (not later than 2 weeks) to obtain a rapid normalization of circulating TSH ideally before the third week of extrauterine life. Therefore, high doses of thyroxine (10-15 μg/kg per day) should be given to all newborns with free or total T4 levels below the normal range; lower doses (5-10 μg/kg per day) can be given to newborns with free T4 within the normal range, thus reducing the risk of overtreatment;
- thyroxine should be given at a daily dose to maintain TSH within the reference range, this may generally require targeting free T4 at the upper limit of normal;
- to be accurate in the therapeutic intervention, reference centers should then establish reference ranges of TSH and free T4 appropriate for age of the children and monitor the therapeutic target probably more frequently than what it is usually done (i.e. 1 week after the start and then every 2 weeks until normalization of the parameters, and monthly thereafter till 12 months of age, less frequent assessments can be scheduled afterwards);
- parents (and later on the children themselves) should be instructed to optimize the compliance to the prescribed thyroxine replacement;
- If abnormal free T4 or TSH values are found, or if compliance is questioned, the evaluation frequency should be increased, and when changes on thyroxine dose are introduced a supplementary check after 4-6 weeks should be advised.

An additional interesting issue raised by this Italian study (1) is the finding of lower cognitive scores in CH children born to mothers with autoimmune thyroiditis and in those with a family history of thyroid disease. These deficits may reflect prenatal brain damage due to thyroid hormone insufficiency in utero, not completely reverted by postnatal treatment. Even though transplacental supply of maternal T4 may protect the fetal brain from severe neurological impairment, this may not be sufficient to protect from severe fetal hypothyroidism (4) and this risk may therefore be more pronounced in mothers with thyroid dysfunction (5).

This points to a defective control of thyroid diseases in mothers during pregnancy reinforcing the recommendation of a pre-conceptional check of thyroid function in all women with a personal or familial history of thyroid disease and the need of a timely adjustment of thyroxine therapy during the first weeks of gestation (2,5).

The association of familiarity for thyroid diseases may also indicate a role of the underlying inheritable genetic defects. On one hand, some of the genes known to be involved in the CH pathogenesis may directly influence neurodevelopment, cognitive and/or hearing outcomes, eg *NKX2-1*, *SLC26A4* (2,6). In addition, an unexplained type of tissue resistance to thyroxine treatment had been also reported in some CH patients (7). Finally, lower IQs had been reported in the siblings of CH patients (8) pointing to the possible role of other still unknown heritable or environmental factors in the determination of an intellectual functional limitation of CH patients.

All these findings indicate we should leave no stone unturned in the management of CH children and in this research field. We certainly need further studies aiming to understand the mechanisms underlying CH pathogenesis and how thyroid hormone action can be optimized in utero and during early postnatal life to improve the neurodevelopmental outcome of CH children and give them a full potential to compete in our demanding societies.

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