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Does Early Identification of Central Congenital Hypothyroidism Result in Improved Outcomes?

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The case for detecting primary congenital hypothyroidism (CH) by measuring thyroid-stimulating hormone (TSH) on dried blood spots (DBSs) was made in the late 1970s and is now established practice in newborn screening (NBS) programs in developed countries (1). Detection of TSH is sufficient for the detection of infants at risk of primary CH, but screening for central CH requires both thyroxine (T4) and TSH measurement. The comprehensive screening protocol employed in the Netherlands since 1995 involves primary T4 testing and supplementary or "reflex" TSH testing in patients with the lowest quintile of T4 concentrations, along with thyroxine-binding globulin (TBG) measurement for the lowest 5% of T4 concentrations and calculation of the T4/TBG ratio (2). However, most countries offer a TSH-only screening service, particularly in the light of more sensitive TSH cut-offs. In the United States, a recent review showed that TSH-only screening was used in 22 of 51 screening jurisdictions, initial T4 measurement with reflex TSH screening if T4 <10th centile in 22, and combined T4 and TSH measurement in all newborn DBS in 9 jurisdictions (3).

Why has combined T4 and TSH screening not been adopted in other European countries and in only a minority of North American NBS programs? Arguments against T4 testing as a first-tier screen include the rarity of central CH, with isolated central CH even more rare, and the perception that central CH is generally less severe than primary CH and will usually be diagnosed due to the presence of other pituitary hormone deficiencies. However, although central CH is less common than primary CH, with an incidence of 1 in 16 000 to 1 in 30 000 in recent publications (4), it is similar in magnitude to that of many other disorders that are widely screened, such as phenylketonuria, congenital adrenal hyperplasia, and medium-chain acyl-CoA dehydrogenase deficiency. The argument that pituitary hormone deficiencies are usually diagnosed based on clinical symptoms is not supported by empirical evidence. The important questions are to what extent is central CH associated with adverse

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developmental outcomes similar to primary CH and is early, presymptomatic diagnosis associated with normalization or amelioration of outcomes.

In this issue of JCEM, Naafs et al. report an admirably rigorous analysis of outcomes data for a large screened central CH cohort (5). The authors found that in 35 children with isolated central CH detected by NBS in the Netherlands, IQ was similar to sibling controls, whereas 52 children with accompanying anterior pituitary hormone deficiencies had IQ scores on average 10 points lower than their sibling counterparts. The normalization of IQ in children with isolated central CH detected through NBS is regarded by Naafs et al. as the likely effect of early diagnosis and treatment. The authors suggest that the lower IQ scores in the children with accompanying anterior pituitary deficiencies may reflect more severe hypothyroidism (moderate to severe hypothyroidism in 69% of children with multiple pituitary hormone deficiencies vs 37% of those with isolated central CH) as well as the neurodevelopmental consequences of the non-thyroidal hormone deficits.

Evaluating the impact of early diagnosis and treatment in the children with multiple anterior pituitary hormone deficiencies from Naafs et al.'s study is a complex task. As the authors state, the contribution of hypoglycemia related to concomitant adrenocorticotropic hormone and growth hormone deficiency to the poorer outcome in this group is not known. Also, although children with disorders, such as septo-optic dysplasia, that may affect cognition independent of the endocrine deficit were excluded, most included patients had interrupted pituitary stalk syndrome, which is now considered to be at the mild end of the holoprosencephaly spectrum and could potentially be linked with cognitive impairment. Thus, while timely diagnosis in patients with multiple pituitary deficiency is desirable, clear evidence for screening benefit should be sought in the group with isolated central CH.

The patients with isolated central CH showed reduced visuospatial processing speed and more motor difficulties compared with sibling controls. This finding points to a prenatal and early postnatal effect on the brain, consistent with a significant degree of hypothyroidism. The authors also report low pretreatment free T4 values—from 5 to 10 pmol/L in 12 and <5 pmol/L in 1 of 35 patients with isolated central CH. Based on data from children with primary CH and similar free T4 concentrations, these values would be expected to result in cognitive deficits. Hence, the normal IQ seen in patients with isolated central CH compared with sibling controls suggests benefit from early diagnosis and treatment.

The authors are careful to emphasize that their findings cannot prove that NBS for central CH improves outcomes and that comparison data from late-treated children with central CH are needed to demonstrate this. How can the data from unscreened cohorts with central CH be gathered? Collecting outcome data in patients detected clinically is difficult and carries the risk of spectrum bias from selective clinical ascertainment or referral of more severely affected children. Retrospective screening using DBS in combination with systematic follow-up of identified children to collect outcomes data is an alternative strategy that yields unbiased, population-based estimates (6). This approach was first used in Sweden when 100 238 DBS collected for phenylketonuria screening from 1977 to 1978 were rescreened for TSH elevation 5 years later, and cognitive outcomes assessed for most children, along with thyroid hormone status and clinical data (7). Retrospective screening with systematic follow-

up has also been used to assess long-term outcomes of untreated or late-treated medium-chain acyl-CoA dehydrogenase deficiency (8).

The minimum sample size for retrospective screening studies varies with the incidence of the disorder being studied. Assuming a prevalence for central CH of 1 in 20 000, a retrospective DBS sample size of 1 200 000—equivalent to 2 years of births in the UK—would detect around 60 infants with central CH. To help justify such a large retrospective screening study, other treatable endocrine and metabolic disorders could be examined as well. Such an initiative would have cost, legal and ethical implications, but the collective benefits would be considerable.

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Abbreviations:

CH	congenital hypothyroidism
DBS	dried blood spot
NBS	newborn screening
T4	thyroxine
TBG	thyroxine-binding globulin
TSH	thyroid-stimulating hormone

References

1. 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. Horm Res Paediatr. 2014;81(2):80–103. [PubMed: 24662106]
2. Stroek K, Heijboer AC, Bouva MJ, et al. Critical evaluation of the newborn screening for congenital hypothyroidism in the Netherlands. Eur J Endocrinol. 2020;183(3):265–273. [PubMed: 32580148]
3. Kilberg MJ, Rasooly IR, LaFranchi SH, Bauer AJ, Hawkes CP. Newborn screening in the US May miss mild persistent hypothyroidism. J Pediatr. 2018;192:204–208. [PubMed: 29246344]

4. Persani L, Cangiano B, Bonomi M. The diagnosis and management of central hypothyroidism in 2018. Endocr Connect. 2019;8(2):R44–R54. [PubMed: 30645189]

5. Naafs JC, Marchal JP, Fliers E, et al. Cognitive and motor outcome in patients with early-detected central congenital hypothyroidism compared with sibling controls. J Clin Endocrinol Metal. 2021. Published online Month xx, 20xx. doi: .

6. Grosse SD. Assessing the evidence for clinical utility in newborn screening. In: Khoury MJ, Bedrosian SR, Gwinn M, eds. Human Genome Epidemiology: Building The Evidence For Using Genetic Information To Improve Health And Prevent Disease. 2nd ed. Oxford University Press; 2010:517–532.

7. Alm J, Hagenfeldt L, Larsson A, Lundberg K. Incidence of congenital hypothyroidism: retrospective study of neonatal laboratory screening versus clinical symptoms as indicators leading to diagnosis. Br Med J (Clin Res Ed). 1984;289(6453):1171–1175.

8. Pourfarzam M, Morris A, Appleton M, Craft A, Bartlett K. Neonatal screening for medium-chain acyl-CoA dehydrogenase deficiency. Lancet. 2001;358(9287):1063–1064. [PubMed: 11589939]