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Treating patients not numbers: the benefit and burden of lowering TSH newborn screening cut-offs

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A century has passed since children affected by congenital hypothyroidism (CHT) were first treated successfully with thyroid extracts. At that time the diagnosis of severe 'sporadic' cretinism was based solely on clinical observation, long before measurement of thyroid hormone and thyroid stimulating hormone (TSH) was possible. Treatment success was evident with the dramatic clinical improvement in the growth and activity of these children.[1] However, the severe mental retardation failed to improve in those early cases, which led to the conclusion that thyroid hormone is critical for normal neuronal maturation within a critical time window early in life. The introduction of newborn screening for CHT – by measuring TSH or T4[2] – finally offered a normal mental outcome to children who otherwise would be severely mentally disabled. Actual studies in adult patients from those first screening programs show that early treatment results in a normal IQ in more than 90% of affected patients.[3 4] The treatment of CHT based on newborn screening is therefore one of the most successful achievements in paediatrics.

As always, such a success bears the risk of 'overdoing it', as the current discussion on TSH cut-offs points out. Stimulated by that early success and with the intention of further improving the programs, the TSH cut-off levels were lowered to facilitate the diagnosis of milder, previously 'missed' cases of CHT. Starting with 50 mU/l TSH as the cut-off in the early programs, which were able to identify severe cases of CHT, the current debate discusses a cut-off value as low as 5 mU/l.

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A new publication on this critical cut-off range was recently published in the *Archives of Disease in Childhood* by Korada *et al* from Newcastle, UK[5]. Applying a TSH cut-off of 6 mU/l (instead of the UK recommended 10 mU/l), the authors identified four additional children with a 'confirmed' increase in TSH of >6 mU/l and two children with CHT, while 63 additional children were identified as false-positive. The diagnosis of CHT was based solely on the fact that these children were subsequently treated with L-thyroxine during their follow-up. The two treated children had TSH levels below 50 mU/l (range 8.7–44.7) and serum free thyroxine (fT4) levels around 18 pmol/l, although those were determined at different ages (17–29 days) without providing an age-specific reference range for fT4. No off-treatment studies to confirm the diagnosis were reported. The authors conclude that the diagnosis of two additional cases justifies the lower TSH cut-off of 6 mU/l.

The study by Korada *et al* demonstrates the dilemma that screening children for CHT with a cut-off of 5–10 mU/l has been established in some programs before the following central questions have been answered:

(1) What is the definition – either clinical or laboratory – of the new, mild disease?
(2) What are the appropriate age related fT4/T4 levels in the newborn period to discriminate between mild hypothyreosis and normal children?
(3) What is the cognitive outcome of untreated children with a newborn TSH of 5–10 mU/l?

The assumption that newborns with elevated TSH are at risk for mental retardation is based on experience with very severe cases of CHT (very high TSH and low T4) in the prescreening era. The mild TSH elevations detected by a lowered TSH cut-off can be caused by different molecular variations that contribute to higher TSH levels without interfering with mental outcome or even with the T4 level. In addition, it has to be noted that even in the group of newborns identified with TSH levels of >50 mU/l, the question of whether all diagnosed children will benefit from treatment is not entirely clear. In a study from Sweden, newborn TSH levels were determined retrospectively in stored filter paper cards from a population based newborn cohort without TSH screening.[6] Reinvestigation at the age of 5 years revealed that half of the 31 children with a newborn TSH level of >40 mU/l were diagnosed based on their clinical symptoms, while the other half were either still undiagnosed with elevated TSH levels in the range of 6–83 mU/l (n=7) or were found to be have been euthyroid with a transient newborn TSH elevation (n=9). The seven cases with a clinically delayed diagnosis showed the expected poor cognitive outcome. However, in the group of undiagnosed children, IQ levels were surprisingly normal despite persistent elevated TSH levels over 5 years (mean TSH level 47 mU/l, range 6–83). These data highlight the suspicion that the natural course of mildly elevated TSH in children can result in a normal mental outcome.

Interestingly, a recent prospective study from the New England Screening Program including 500 newborn children[7] investigated the impact of different T4 levels within the normal range on cognitive outcome. The authors found no correlation between newborn T4 levels and cognitive outcome at the age of 5 years. Children with the lowest T4 levels were no less likely to have a high IQ compared with newborns with the highest T4 levels. This largest study to date on newborn thyroid function and cognitive outcome in healthy children refutes the assumption of a linear correlation between newborn thyroid hormone levels in the normal range and later mental development. Coming back to diagnosing mild TSH elevations as CHT, treatment can in fact be completely unnecessary or the decision can be postponed as long as the T4 values are within the normal range.

The next critical question is what are 'normal' serum T4 levels in newborn children?

T4 levels in the first days of life are more than double those in adults and decline very quickly in the first weeks to finally reach adult levels around the end of the first year. Published 'reference ranges' do not sufficiently reflect these dramatic changes within the first weeks of life. To use adult reference ranges is

even worse, because the lower T4/fT4 reference can be wrongly assessed as normal, lead to false-negative results and missed treatment. Even the most differentiated reference ranges[8] do not pay sufficient attention to the neonatal period.

Obviously the publication by Korada *et al* did not consider these central questions when recommending screening of mild CHT. However, the Newcastle data give us at least some insight into the consequences of lowering the TSH cut-off level to 6 mU/l. The authors pointed out the number of false-positive cases is two- to threefold greater compared to a higher TSH cut-off of 20 mU/l. We all know that every clinical intervention has side effects. The side effect of a screening program is the burden of false-positive results in terms of parental anxiety and depression. Families whose healthy newborns had a false-positive screening result showed long-lasting effects on the parental perception of the child's health, which was reflected in nearly doubled rates of hospitalisations in early childhood.[9]

Using such a low TSH cut-off touches the central idea of newborn screening because the target disease as well as the possible benefit of treatment is unknown. In 1971, Wilson and Jungner defined the 'principles of screening for diseases' which defined criteria to select suitable screening tasks. These were recently actualised by the American College of Medical Genetics[10] and applied to newborn screening for 60 different diseases. CHT fulfilled those criteria with the second highest score, but this does not apply to that group of thyroid function abnormalities which are indicated by TSH levels between 5 and 10 mU/l.

When considering newborn screening as a process with effects on the child and their family, the positive effects on the detected and treated patient must be balanced against the potential negative effects on the healthy child, their family and society as a whole. To estimate the burden of changed TSH cut-off levels, one must consider that several hundred million newborns are screened for CHT worldwide each year and a doubled false-positive rate brought about by lowering the TSH cut-off into the 5–10 mU/l range will disturb tens of thousands of families.

Probably the most important message for the paediatric community in this discussion is that there is an urgent need to generate new data on the natural course of newborns with mildly elevated TSH (5–20 mU/l) and that highly differentiated (by days or weeks of life) reference data on thyroid parameters might be key to identifying milder forms of neonatal thyroid dysfunction. To continue the successful story of treating children with CHT which started a century ago and to avoid "treatment of numbers (TSH values) instead of patients at risk" we need to have these data.

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