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EDITORIAL

Screening T4 and TSH in Early Detection of Congenital Hypothyroidism in Newborns: What's the Dilemma?

Pemeriksaan T4 dan TSH dalam Deteksi Dini Hipotiroidisme Kongenital pada Bayi Baru Lahir: Apa Dilemanya?

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ABSTRACT

Untreated congenital hypothyroidism (CH) leads to intellectual disability. Newborn screening (NBS) for CH should be done on all infants. Prompt diagnosis by NBS leads to early and adequate treatment outcomes in very normal neurocognitive outcomes in adulthood. Newborn screening (NBS) for congenital hypothyroidism (CH) is one of the major achievements in preventive medicine. Most neonates born with CH have a normal appearance and no detectable physical signs. Blood spot thyroid stimulating hormone (TSH), thyroxine (T4), or both can be used for CH screening. The latter is more sensitive but not cost-effective, so screening by TSH or T4 is used in various programs worldwide. TSH screening is more specific in the diagnosis of CH. T4 screening is more sensitive in detecting newborns with rare hypothalamic-pituitary-hypothyroidism, but it's less specific with a high frequency of false positives especially in low birth weight and premature infants. NBS alone is not sufficient to prevent adverse outcomes from CH in a pediatric population. In addition to NBS, the management of CH requires timely confirmation of the diagnosis and accurate interpretation of thyroid function testing, effective treatment, and consistent follow-up. Doctors need to consider hypothyroidism in the face of clinical symptoms, even if NBS thyroid test results are normal. When clinical symptoms and signs of hypothyroidism appear (such as large posterior fontanelles, large tongue, umbilical hernia, prolonged jaundice, constipation, lethargy, and/or hypothermia), measurement of serum thyroid hormone and free thyroxine is indicated, regardless of NBS results. So all these babies should be treated as having CH during the first 3 years of life, taking into account the risk of mental retardation. Re-evaluation after 3 years is required in such patients.

Keywords: Neonatal screening; congenital hypothyroidism

ABSTRAK

Hipotiroidisme kongenital (CH) yang tidak diobati menyebabkan cacat intelektual. Skrining bayi baru lahir (NBS) untuk CH harus dilakukan pada semua bayi. Diagnosis yang cepat oleh NBS yang mengarah ke hasil pengobatan dini dan memadai dalam hasil neurokognitif yang sangat normal di masa dewasa. Skrining bayi baru lahir (NBS) untuk hipotiroidisme kongenital (CH) adalah salah satu pencapaian utama dalam pengobatan pencegahan. Kebanyakan neonatus yang lahir dengan CH memiliki penampilan normal dan tidak ada tanda-tanda fisik yang terdeteksi. Blood spot thyroid stimulating hormone (TSH) atau thyroxine (T4) atau keduanya dapat digunakan untuk skrining CH. Yang terakhir ini lebih sensitif tetapi tidak hemat biaya, sehingga skrining oleh TSH atau T4 digunakan dalam berbagai program di seluruh dunia. Skrining TSH terbukti lebih spesifik dalam diagnosis CH. Skrining T4 lebih sensitif dalam mendeteksi terutama bayi baru lahir dengan hipotalamus-hipofisis-hipotiroidisme langka, tetapi kurang spesifik dengan frekuensi tinggi positif palsu terutama pada berat lahir rendah dan bayi prematur. NBS saja tidak cukup untuk mencegah hasil yang merugikan dari CH pada populasi anak-anak. Selain NBS, manajemen CH memerlukan konfirmasi diagnosis yang tepat waktu, interpretasi yang akurat dari pengujian fungsi tiroid, pengobatan yang efektif, dan tindak lanjut yang konsisten. Dokter perlu mempertimbangkan hipotiroidisme dalam menghadapi gejala klinis, bahkan jika hasil tes tiroid NBS normal. Ketika gejala klinis dan tanda-tanda hipotiroidisme muncul (seperti fontanel posterior besar, lidah besar, hernia umbilikalis, penyakit kuning berkepanjangan, sembelit, lesu, dan / atau hipotermia), pengukuran hormon tiroid serum dan tiroksin bebas diindikasikan, terlepas dari hasil NBS. Sehingga semua bayi ini harus diperlakukan sebagai memiliki CH selama 3 tahun pertama kehidupan, dengan mempertimbangkan risiko keterbelakangan mental. Evaluasi ulang setelah 3 tahun diperlukan pada pasien tersebut.

Kata Kunci: Skrining neonatal; hipotiroidisme kongenital

Thyroid hormones play an important role in energy metabolism, growth, and nerve development. Specifically, thyroid hormone works to regulate neurogenesis, myelination, dendrite proliferation, and synapse formation during the fetal and post-natal period as well as regulating the development of the central nervous system.[1,2] Thyroid hormone is produced by the thyroid gland in response to stimulation by thyroid-stimulating hormone (TSH) produced by the anterior pituitary.

There are two active thyroid hormones, namely Thyroxine (T4) and Triiodothyronine (T3). The hormones T3 and T4 are secreted by the thyroid gland, and most of the circulating T3 comes from peripheral tissue deiodination of T4. The hormones T3 and T4 inhibit TSH secretion, by inhibiting TRH secretion either directly or indirectly. Additional factors that inhibit TSH release are glucocorticoids, somatostatin, and dopamine. Circulating T4 and T3 hormones will be tightly bound to serum proteins, including T4 binding globulin (TBG), and only a small portion of T4 (0.02%) and T3 (0.3%) is not bound, which is called free T4 and T3 free, both of which are biologically active.[3]

The condition of thyroid hormone deficiency detected at birth is called "congenital hypothyroidism" (CH). The condition must be diagnosed immediately because if there is a delay in diagnosis there will be a delay in treatment. So, it can cause irreversible neurological deficits and is one of the causes of intellectual disability, and this can be prevented if screening is carried out early. Before the advent of newborn screening programs, CH was one of the most common intellectual causes. Newborn screening (NBS) programs have successfully improved the diagnosis and treatment of CH and resulted in better neurodevelopmental outcomes.[1,4,5]

It is estimated that one-third of the hormone thyroxine (T4) from the mother will pass to the fetus during pregnancy. The maternal hormone T4, which has a half-life of six days, is metabolized and excreted by three or four weeks of age. If CH is not treated in the first few weeks or months of the baby's life, the symptoms will worsen and will cause problems with brain development. This is a very urgent condition and it is important to be screened, diagnosed for CH, and started CH treatment immediately after birth. The best way to prevent late diagnosis of CH is to conduct a large population screening of newborns.[6]

Newborn screening programs were established in many developed countries in the 1970s. Many studies have reported success in normalizing cognitive outcomes in children with severe primary CH. In addition, it can avoid lifelong care costs for children with intellectual disabilities. The estimated cost of neonatal screening is much less than the cost of diagnosing and treating CH at a later age.[3] Thyroid hormones play an important role in brain development and growth. All babies born in the United States, Canada, and other developed countries have a screening test to check thyroid function immediately after birth. Early detection and treatment of hypothyroidism can generally result in normal growth and development.[6]

The screening test is carried out by taking a blood specimen, and the most ideal is when the baby is 48 to 72 hours old. This is the average time it takes for a newborn's metabolism to adapt, stabilize, and adjust to the new environment after birth. However, in certain circumstances, blood sampling can still be tolerated between 24-48 hours. It is best not to take blood in the first 24 hours after birth because at that time TSH levels are still high, so it will give some false positive results. If in certain conditions mass screening must be carried out before 24 hours of age, then the T4 test is the best choice because it is relatively more stable during this period. Clinical and laboratory follow-up of children with CH is essential for appropriate management.[3,7,8]

The Newborn Screening program aims to detect all cases of the disease as early as possible, with an acceptable cost-benefit ratio, and to avoid false positive results. In recent years, more sensitive and automated methods (chemiluminescence, fluoro-immunoassay, etc.) have been used to determine TSH and T4 in dried blood spots.[9-15] These new methods have increased the sensitivity and specificity in detecting CH. However, despite the development of more accurate testing programs, approximately 5% of CH cases may still be missed in any screening program. The reasons could be the failure to collect samples, poor samples, and misinterpretation of samples or, as is the case for programs that only measure TSH, failure to detect babies with central CH10,[14-16.]

Neonatal screening for CH began to be carried out in 1974 using heel prick filter paper (FP) blood samples in newborn babies. This technique, which was pioneered by Guthrie in 1963, has been successfully applied in most developed countries and has proven to be one of the most cost-effective screenings in medicine in prevention and public health. The cost-benefit ratio is 10:1, apart from that it has an extraordinary positive clinical impact.[6,17,18] Because the orientation of CH screening is to detect primary hypothyroidism (permanent or transient) and following the recommendations of the American Thyroid Association, primary TSH examination is the most sensitive thyroid function test. Elevated TSH levels as a hormonal marker are accurate enough to be used for primary CH screening. The cut-off value is 20 mU/L (WHO) for suspected CH (presumptive classification). The Ministry of Health recommends laboratories with primary TSH

tests and TSH + FT4/T4 confirmation tests that have been accredited as implementing CH screening tests.

There are three possible TSH results, namely: (a) TSH level 20 mU/L. if the confirmation test results in a TSH level of less than 20 mU/L, then the results are considered normal and will be submitted to the specimen sender within 7 days; (b) TSH levels between >20-40 mU/L are TSH values that indicate doubtful results, so a resample is necessary. If the results of the re-take show a TSH level < 20 mU/L, then the result is considered normal. If the TSH level is > 20 mU/L, it is necessary to check serum TSH and FT4; (c) TSH level 40 mU/L If the examination results show such a value, it is necessary to carry out a confirmatory examination of serum TSH and FT4.[17]

Several things must be taken into consideration in screening procedures for newborn babies, such as the complex interaction between the feto-maternal unit and the placenta. Although the function of the fetal endocrine system is largely independent of the mother, maternal endocrine disorders can negatively affect the fetus. There is a dilemma in CH screening and this can be related to maternal thyroid status and fetal factors, such as gestational age, perinatal factors (use of iodine application during labor), and mode of delivery. It may also be related to environmental and nutritional factors or technical and laboratory errors in neonatal blood sampling. If an error occurs in the screening procedure, reconfirmation is required within one or two weeks of birth or if possible, sooner.

Approximately 5% of CH may be missed on screening regardless of the methodology used, due to specimen handling errors, problems with testing, or data analysis. When interpreting screening results. All these factors must be kept in mind.[17,18]

The development of sensitive tests to measure serum T4 and TSH using blood spots makes it possible to initiate newborn thyroid screening programs. Early diagnosis and treatment with adequate doses of L-T4 have saved affected children from a life of mental retardation. Before 1972, case detection was the only method of diagnosis. Unfortunately, the majority of CH babies in that era suffered from permanent neurological disorders. Currently, NBS allows diagnosis and treatment that can usually be achieved within 2 weeks after birth. Today, NBS for CH is accepted as a tool in the context of primary health care for infants such as breastfeeding, immunization, and oral rehydration.[9]

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