Review article

Screening for congenital hypothyroidism: A review of current practices and recommendations for developing countries

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Abstract:

Background: Congenital hypothyroidism (CH) is the commonest endocrine and most treatable cause of mental retardation. Laboratory diagnosis must be made soon after birth, and effective treatment initiated promptly to prevent irreversible brain damage. The advent of neonatal screening programs for congenital hypothyroidism has dramatically improved the prognosis for affected infants. The goal of newborn screening is to detect CH and begin treatment before the infant reaches one month of age. Newborn screening has been practiced for about four decades in most developed countries, while Asian and North African countries commenced implementation in recent years. It is yet to start in many developing countries, particularly in Africa.

Method: We searched multiple databases including PubMed and several published national and institutional guidelines to review the various screening methods, both laboratory and clinical; highlighting their strengths and drawbacks. We also described the processes involved and challenges in developing a screening programme.

Recommendation: The implementation of this screening programme in other developing countries including Nigeria is advocated.

Introduction

Congenital hypothyroidism (CH) is a condition of significant decrease in or absence of, thyroid function present at birth.[1, 2] It has a worldwide incidence of 1:3000 to 4000 infants, with a female preponderance of 2:1.[2-6] It is the commonest endocrine and most treatable cause of mental retardation and also manifests with severe growth retardation.[5-10] Thyroid hormone is critical for normal cerebral development in the early postnatal months; biochemical diagnosis must be made soon after birth, and effective treatment initiated promptly to prevent irreversible brain damage.[2, 3, 5, 6, 10]

Therefore early diagnosis and treatment of this condition cannot be over-emphasized. The advent of neonatal screening programs for detection of congenital hypothyroidism has dramatically improved the prognosis for affected infants. Early diagnosis and adequate treatment from the first weeks of life result in normal linear growth and intelligence comparable with that of unaffected siblings.[2, 8, 11] The goal of newborn screening is to detect CH and begin treatment before the infant reaches one month of age.[12]

Most children with CH who are correctly treated with thyroxine grow and develop normally in all respects with only minor problems except for babies who are severely hypothyroid at birth whose mothers also have hypothyroidism.[13-15] Even most of those with athyrosis and undetectable T4 levels at birth develop with normal intelligence. Few treatments in the

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practice of medicine provide as large a benefit for as small an effort.[4]

The introduction of screening for CH in Quebec about four decades ago revolutionized the prognosis of children with CH.[16] Among 800 children with CH reviewed from literature before screening was introduced, the mean IQ was less than 80.[17] Two hundred and fifty of these children (65% had IQ <85, 40% had IQ <70 and 25% IQ <55). The risk of retardation was greatest in the children with the least amount of functioning thyroid tissue, as indicated by their serum thyroxine (T4) and thyroid stimulating hormone (TSH) concentration, thyroid radionuclide imaging and delayed bone age. In 1981 the value of screening was further buttressed by the result of a prospective controlled study [18] which revealed that early treatment of infants in whom CH was detected by screening 3 to 6 days after birth was associated with normal mean IQ and normal distribution of individual IQ.

One of the first discoveries of the screening program is that the incidence of CH was higher than anticipated from the clinically determined incidence of 1: 6,300 in early 1980s. The reported [19] incidence based on screening ranged from 1; 3300 in Europe to 1: 5700 in Japan, in fact, some authors have reported incidence as high as 1:1,400-1:2,800, [20- 23] however the incidence in most areas is 1:4500. [19] Thus about 30% of infants diagnosed by newborn screening would not have been diagnosed clinically, until the infant was symptomatic with growth and mental impairment.[24]

Screening Methods.

Different newborn screening programs are being used in different parts of the world, each with its merits and demerits.[2,7,9,25] The available newborn screening methods for congenital hypothyroidism are:

(1) Primary TSH with backup T_4 measurements.
(2) Primary T_4 with backup TSH measurements.
(3) Combined TSH and T_4 measurements.

In addition to the above mentioned methods, congenital hypothyroidism can be evaluated clinically using neonatal hypothyroid index,[26] especially in the resource- poor countries where the above mentioned screening methods are not available. Other clinical scoring tools to screen hypothyroidism generally include; Billewicz diagnostic index and Zulewski's [27] clinical score for hypothyroidism. However, the choice of which to use is age dependent due to parameters being assessed. Billewicz diagnostic index utilizes 7 symptoms and 6 signs (diminished sweating, dry skin, cold intolerance, weight increase, constipation, hoarseness, deafness, slow movement, coarse skin, cold skin, periorbital puffiness, pulse rate and ankle jerk).[27] The score may range from +67 to -47, with a score of +25 or more suggestive of hypothyroidism, while a score of -30 excludes the disease.[27] Zulewski's scoring methods uses 7 symptoms and 5 signs, with one score given for each. [27] There is a total score of 12, and a score > 5 points defined hypothyroidism, while a sore of 0-2 points defined euthyroidism.[27]

However studies have shown that establishing a diagnosis of congenital hypothyroidism on clinical grounds at an early age is difficult and may be delayed because symptoms appear gradually,[2, 8, 28] this is because most infants with congenital hypothyroidism are asymptomatic at birth and less than 5% of infants with congenital hypothyroidism are detected clinically at birth, even if there is complete agenesis of the thyroid gland,[2, 6-8, 28] leading to the most severe outcome of congenital hypothyroidism, namely, mental retardation.[7] This

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situation is attributed to the passage of moderate amounts of maternal T_4 transplacentally and through breast milk, emphasizing the importance of screening programs in early detection of hypothyroid infants.[7,28]

Primary T_4 with backup TSH measurements – This program is being used by most North American countries;[9] T_4 measurement is followed by TSH measurement in filter paper specimens with low T_4 values. [2, 7, 9] This approach will detect infant with low T_4 values (low or low-normal T_4 with elevated TSH concentrations), and is also more sensitive in identifying infants with thyroxine-binding globulin deficiency or hypothalamic-pituitatry hypothyroidism which usually have low or low-normal T_4 with normal TSH and infants with hypothyroxinemia with delayed TSH elevation especially LBW and VLBW,[2,7,9] which could easily be missed using primary TSH screening program. The program also has the potential to identify infants with hyperthyroxinemia.[9] However, there may be a higher recall (false positive) rate especially those that report low T_4 using an absolute cutoff, otherwise the recall rate is almost the same with primary TSH.[2,7,9] The high frequency of false positives is mainly in low birth weight and premature babies.[7] The false positive screen create undue anxiety and stress on families, psychological harm in normal infants (i.e. by creating the 'vulnerable child') excess workload for staff.[5,9]

Primary TSH with T_4 backup measurements- most programs in Europe, Japan, Canada, Mexico, and the United States screen by TSH measurements supplemented by T_4 determination for infants with elevated TSH values.[7,9,25] Therefore, switching to a primary TSH screen for congenital hypothyroidism has been advised, as this will decrease the number of false positive results and still promote early and correct detection of congenital hypothyroidism followed with immediate treatment (i.e. increasing overall sensitivity and maintain specificity).[5,25,29,30]

Primary TSH method detects overt and compensated primary hypothyroidism and has shown to be more specific with less false positive rate, however, it misses secondary/tertiary hypothyroidism, TBG deficiency, and premature infants with very low body weight with delayed TSH surge.[7] Primary T_4 program has shown higher sensitivity than primary TSH program, [7, 25] however, the sensitivity with current TSH assay techniques has improved (enzyme-linked immunoassays, chemiluminescent assays, and fluoroimmunoassays)

The trend toward early discharge of mothers and infants before 48 hours presents a problem to primary –TSH program, because of physiological surge of TSH at birth which can increase the ratio of false positive TSH elevations.[7,25,30] Furthermore, when TSH is high (i.e. falsely high due to the above mentioned reason), the T_4 level in a newborn with congenital hypothyroidism may initially appear normal due to maternal hormone coverage prior to birth.[30] However, the new TSH assays have the advantages of using nonradioactive labels with greater sensitivity and better potential for separation between normal and abnormal concentrations. [9,25] Also the age-adjusted TSH cutoffs in a primary TSH screening approach in infants discharged after 24 hours of age, the recall rates of patients is lower with negligible false-negative test results.[25]

Combined TSH and T_4 measurements – This represents the ideal screening approach,[9,25] and will eliminate the limitations of both primary T_4 and primary TSH approaches, however, it is not cost effective. [7] Until T_4 and TSH determinations can be done practically for all infants, physicians should be aware of the potential limitations of each method of

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screening for congenital hypothyroidism. [9, 12, 25] Using combinations of the tests can lower the recall rate. [12]

North America and almost all the countries in Europe have well established newborn screening program for CH. The South American countries,[31, 32] Middle East, [33, 34] and the Asian countries [35, 36] have tried to follow suit with some of them having well established newborn screening program. Some North African countries are making considerable efforts to implement the screening program by aligning with some middle-east countries. It is sad however that the situation remains gloomy in sub-saharan African countries, Nigeria inclusive, where attention is riveted on donor-driven programmes to address HIV/AIDS, Tuberculosis and Malaria. [37]

Financial implications

In most cases where newborn screening is a national or local government mandate, a portion of the government health budget is allocated to support the programme. However, in some cases, national or local government budgets do not include funding for the screening of newborns and the programme is left to obtain funds through other means. Many developing programmes find that a fee is necessary when the programme is starting up in order to defray the expenses of testing. [12]

While some may view a newborn screening fee as unnecessary or too expensive, the fee charged is usually significantly less than the cost of most other pre-natal activities. Relative to other health care costs, newborn screening is considered inexpensive in most settings. In order to encourage screening, a plan should be developed to encourage prospective parents to save for it.[12] Altruistic organizations or local governments may also participate in programme financing in order to lower or eliminate costs. Alternatively, it may be of benefit to educate prospective parents on the value of screening, and they may budget for any fee that may be required. Ideally, no one should be refused screening because of their inability to pay, but this idealistic goal usually can be reached only after the programme is established and costs can be supplemented with some sort of government or insurance assistance. It is important for the newborn screening programme to develop local financing models and advocate for their use. [12]

This funding should cover screening laboratory costs, follow-up services (including education and counseling), computerization, advisory committee meetings, and quality assurance site visits to screening laboratories and birthing facilities.[12]

Screening for congenital hypothyroidism is cost-saving, with the averted costs of care exceeding the costs of providing screening and diagnostic services and treatment.[38] Family caregivers for children with disabling sequelae such as mental retardation are liable to miss days of work, or leave the workforce altogether.[39] In 2001, United States spent over $120 million on newborn screening in their 2001 fiscal year, with most states spending from $20 to $40 for each infant screened.[40]

In a cost-benefit analysis study of the Neonatal Screening Program Implementation for congenital hypothyroidism in Iran by Delavari *et al,*[8] they found out that the total cost of implementation of the neonatal screening program for identification of newborns suffering from CH during the first year was $ 2,000,000 compared with $32,240,000, the care costs, over 14 years, of number of mentally retarded individual that would have resulted from congenital hypothyroidism. Therefore, cost savings due to early diagnosis and proper metabolic control during the first year of implementation would be $30,240,000. [8]

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The ratio of the cost of care for the children to the cost of implementation of the screening program is about 1 to 16 and the ratio of the benefit (cost saving) to the implementation cost is 1 to 15.

Yarahmadi *et al* in 2008, also in Iran found out that newborn screening for congenital hypothyroidism has economical advantages and reduces capital expenditures and preserves normal IQ of the patients under treatment and prevents mental retardation and growth complications, and therefore the screening program is said to be cost effective.[11]

Legal considerations

Since newborn screening is intended to prevent catastrophic health consequences that can result from undetected and untreated conditions, cases that are detected late, either inside or outside of the screening system, have the potential for giving rise to lawsuits for negligence. Newborn screening is designed to detect all cases that exhibit biochemical abnormalities at the time of screening while keeping the number of 'false positive' cases as low as possible to reduce case detection costs, maintain physician confidence, and avoid the anxiety that accompanies retesting. [12] In order to minimize legal exposure, the system should have well defined, realistic procedures in place and ensure that they are performed accordingly. Wherever possible, documentation should exist that confirms that all policies and procedures have been followed.[12]

Components of the newborn screening programme

Newborn screening is not just a laboratory test. Over the past 40 years, newborn screening has evolved into a system that relies on smooth integration of the efforts of a number of individuals and processes. The critical points in the development of an infrastructure for the screening of newborns include the following:

Education - Education of professionals, policy makers, parents and the general public is one of the most essential components of any newborn screening programme.

Screening – laid down guideline should be followed to ensure good outcome especially; proper timing and specimen collection, transport, laboratory testing and reporting. This must be done under vigorous supervision

Early follow-up -Rapid recall and complete follow-up for all newborns must occur with positive screening test results. This includes abnormal test notification, tracking and confirmatory testing.

Diagnosis – Clinical and diagnostic serum tests are required on all newborns with positive screening test results.

Management - This includes counseling, immediate thyroxin replacement therapy, treatment monitoring, long term follow up, and carrying out other diagnostic tests.

Evaluation - Outcome monitoring, quality assurance throughout the system and periodic audits are necessary to evaluate every aspect of the newborn screening system. [12, 41, 42]

Challenges

The range of challenges to overcome in developing a newborn screening programme includes: [12]

• Creating a plan and vision for development, implementation and sustainability of the newborn screening programme.

• Organizing a group(s) of persons dedicated to the successful implementation of screening for newborns.

• Providing education to the medical community and gaining their support.

• Obtaining pilot data to validate the value of the screening programme.

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• Ensuring adequate resources for laboratory testing, including appropriate staff and training.

• Developing a central laboratory facility for screening.

• Providing necessary training for the adequate and appropriate collection of specimens.

• Providing for the logistics of the transport of specimens to the testing laboratory.

• Establishing a follow-up system for presumptive positive findings.

• Ensuring the availability of an adequate follow-up tracking system and of appropriate confirmatory testing.

• Developing a system for appropriate diagnosis and treatment.

• Developing and disseminating educational materials for the general public.

• Establishing a record keeping system (computerized if possible) for all newborns who are offered testing including: consent/dissent documentation, specimen date(s), testing outcomes, result notifications, information on confirmatory testing, and treatment.

• Considering and developing a comprehensive quality assurance programme for the system, including listings of quality indicators, procedures for monitoring, and monitoring results (along with a record of corrective actions).

• Providing external proficiency testing for the screening laboratory.

• Developing detailed operating manuals and flow diagrams for all parts of the system, including descriptions of procedures for quality assurance.

• Obtaining government and financial support for the programme, including inclusion in maternal benefits or other appropriate health insurance programmes.

• Developing and enacting an overall evaluation and improvement plan for the newborn screening system.[12]

Critical ingredients for programme sustainability

The critical ingredients required for the sustainability of a newborn screening programme include:

• Active public advocacy efforts directed at:

Experts, Media, Government and NGOs, Parents, Health practitioners;

• Integration in existing government infrastructure;

• Issuance of policies on newborn screening;

• Public–private partnerships

• Funding for newborn screening

• National coordination

• Evaluation and audit. [12]

Conclusion

The benefits of early diagnosis of congenital hypothy roidism and prompt treatment cannot be overemphasized. There is a great need for increasing the societal awareness of CH and its identification by newborn screening.

Universal routine neonatal screening for congenital hypothyroidism is feasible and should be adopted by all countries including developing nations.

Developing a sustainable programme for screening involves a multi-disciplinary approach.

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