

Review Article on Congenital Hypothyroidism and Newborn Screening Program in Africa; the Present Situation and the Way Forward

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Abstract

Congenital hypothyroidism (CH) is a condition that affects infants from birth (congenital) and results from partial or complete loss of thyroid function (hypothyroidism). CH has existed since antiquity, as exemplified by goitrous dwarfs in 400 BC in South America, writing about goiter from ancient Rome in the first century and descriptions of mental retardation and goitrous hypothyroidism in a lecture and subsequent publication by Paracelsus in the sixteenth century [1]. Non goitrous sporadic CH was not described until the beginning of the industrial revolution by Thomas Curling in 1850. By the end of the nineteenth century, thyroid extract were observed to effectively treat patients with CH, however not until the 1970s was it possible for mental retardation caused by CH to be virtually eradicated by early treatment as a result of early diagnosis through newborn screening [2]. During the second half of the twentieth century, various enzymatic defects in hormonogenesis were shown to be responsible for CH [3]. Immune mediated mechanism have also been proposed to cause thyroid dysgenesis, but a causal relationship has not been proven [4,5]. In the 1990s mutations in the extracellular domain of Thyrotropin (TSH) receptor in the β sub unit of TSH and the transcription factors that regulate thyroid embryogenesis have been found to be rare cause of CH [6-10]. The suffering and heavy social and economic burden caused by congenital hypothyroidism prompted many countries to institute a formalized screening programme directed at newborns, just as a vaccination programme has become an integral part of child health care. In African countries however, this type of formalized service has not yet been established. Yet most African countries have crude birth rates (Nigeria-39.9, Kenya-39.2, south Africa-22.3 and Egypt-24.2) above the average (20.3 births per 1,000population) for the entire world, for African countries, the implementation of a universal neonatal screening programme will bring about a considerable improvement in child health care.

Introduction

Congenital hypothyroidism (CH) is a condition that affects infants from birth (congenital) and results from partial or complete loss of thyroid function (hypothyroidism). CH has existed since antiquity, as exemplified by goitrous dwarfs in 400 BC in South America, writing about goiter from ancient Rome in the first century and descriptions of mental retardation and goitrous hypothyroidism in a lecture and subsequent publication by Paracelsus in the sixteenth century [1]. Non goitrous sporadic CH was not described until the beginning of the industrial revolution by Thomas Curling in 1850. By the end of the nineteenth century, thyroid extract were observed to effectively treat patients with CH, however not until the 1970s was it possible for mental retardation caused by CH to be virtually eradicated by early treatment as a result of early diagnosis through newborn screening [2]. During the second half of the twentieth century, various enzymatic defects in hormonogenesis were shown to be responsible for CH [3]. Immune mediated mechanism have also been proposed to cause thyroid dysgenesis, but a causal relationship has not been proven [4,5]. In the 1990s mutations in the extracellular domain of Thyrotropin (TSH) receptor in the β sub unit of TSH and the transcription factors that regulate thyroid embryogenesis have been found to be rare cause of CH [6-10]. The suffering and heavy social and economic burden caused by congenital hypothyroidism prompted many countries to institute a formalized screening programme directed at newborns, just as a vaccination programme has become an integral part of child health care. In African countries however, this type of formalized service has not yet been established. Yet most African countries have crude birth rates (Nigeria-39.9, Kenya-39.2, south Africa-22.3 and Egypt-24.2) above the average (20.3 births per 1,000population) for the entire world,

for African countries, the implementation of a universal neonatal screening programme will bring about a considerable improvement in child health care.

Classification

CH may be primary or central and permanent or transient. The commonest cause of CH world wide is iodine deficiency [11,12], which is now being tackled by iodine supplementation. In iodine sufficient region regions, the most common cause is thyroid Dysgenesis; which include agenesis of the thyroid gland (absence of thyroid tissue), ectopic thyroid (abnormal located thyroid), hypoplastic thyroid (normal located thyroid but small and with decreased funtion), athyreosis (agenesis) accounts for 20% to 30% Of cases of dysgenetic thyroid [13]. All these can be distinguished by radionuclide scan with ¹²³I-Iodide or ^{99m}Tc-pertechnetate, recently some endocrinologist favour the use of ultrasonography to identify infants with eutopic thyroid gland as oppose to those with ectopic and athyreosis. Where there is no iodine deficiency, thyroid dysgenesis account for 80 to 85 percent of cases of

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CH. Mutation of PAX8, TTF-1, and FOXE1 have been recognized to be associated with dysgenesis.

Dyshormonogenesis refers to a heterogeneous group of (inborn errors) genetic defects associated with biosynthetic steps in thyroid hormone synthesis accounting for 10% to 15% of cases of CH. Most of them are inherited in an autosomal recessive manner, which means that the risk of recurrence is put at 25% for subsequent pregnancies. Thyroid peroxidase (TPO) deficiency is the commonest in this etiologic group, in a recent study TPO gene mutations were found in 25% of patients with CH and eutopic gland [14]. The genetic mutations implicated in dyshormonogenesis are DUOX2, TPO, Tg, NIS, THOX-2. Central causes of congenital hypothyroidism are very rare it may be due to TSH receptor (TSHR) defect; autosomal dominantly inherited [15]. Gene mutations implicated are TRH receptor, or beta-TSH, and (PROP) PIT-1), another rare cause is pendred's syndrome this result from mutation of the gene encoding for pendrin, a protein which is involved in the presentation of iodide to TPO for organification. Affected patients present with sensorineural deafness. Goiter is a common feature but may only be noted in childhood [16].

Transient CH; infant factors include exposure to iodine containing antiseptics and intravenous contrast agents [17]. Mother with grave's disease may have transplacental passage of medications (methimazole, propylthiouracil), TSH blocking antibodies [18,19] and maternal iodine deficiency may contribute to this form of CH. It is often difficult to distinguish newborns with transient CH from those with permanent CH, maternal TSH antibodies may be in the newborn's circulation for several weeks to months [20].

Central CH; TRH or TSH deficiencies are uncommon cause of CH. The patients typically have low or normal TSH and low T4. They don't have goiter and abnormalities of other hypothalamic-pituitary hormone are possible in some individual, deficiencies of GH and prolactin may be observed and it is often related to mutation in pituitary transcription factors PROP1 and PIT1 [21].

Clinical Manifestation

Only 5 to 10% of affected newborns have clinical signs or symptoms at or soon after birth, so most infants presenting for evaluation of an abnormal newborn screening result will appear healthy and have few or no specific signs or symptoms which may lead the physician to suspect thyroid disorder [22]. A baby presenting with severe CH lasting more than 4 to 6 weeks may present with poor feeding, constipation, lethargy or excessive sleeping and hoarse cry. The physical examination may reveal failure to thrive, large anterior and post fontanelles, dry skin, jaundice (usually prolonged), mottling, umbilical hernia, macroglossia and coarsening of the facies. A goiter may be present. The only sure way to catch the significant number of babies who will not have clinical symptom or sign of CH at birth is by screening every newborn at or soon after birth.

Newborn Screening

Some diseases are better prevented than treated when the damage is already done; CH is one of such [23]. Absence or reduced levels of thyroid hormone which is the hallmark of CH can be detected by testing the infant's blood. This is one of the situations where physicians rely on blood analysis for diagnosis. Early detection and prompt intervention of developmental disorders with consequent prevention of mental

retardation is among the most widely supported public health goal [24,25]. Screening programs were developed to achieve such aims.

The introduction of screening for CH in Quebec 34 years ago revolutionized the prognosis of children with CH [26]. Among 800 children with CH collected from literature before screening was introduced, the mean IQ was less than 80 [27]. 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 delay bone age. Newborn screening was introduced to prevent brain damage cause by CH through earlier treatment. In 1981 the value of screening was further buttressed by the result of a prospective controlled study [22] 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.

North America and almost all the countries in Europe have well established newborn screening program for CH and other metabolic diseases, in which capillary blood is collected on filter papers soon after birth and analyze for TSH or T4 [28]. Measurement of free T4 is the ideal and this actually has been done by a few screening programs in Japan [29]. Depending on which side of the major divide a program measures either of TSH or T4. Each of this method has its own drawback. Both programs may be fraught with human error with a number of infants missed with CH, however with years of experience and automation, this is now quite small [30] 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 [31] incidence based on screening ranged from 1: 3300 in Europe to 1: 5700 in Japan, with incidence in most areas being 1:4500. Thus about 30% of infants diagnosed by newborn screening would not have been diagnosed clinically, until the infant would have been old and brain damaged [32].

The South American countries [33,34], Middle East [35,36], and the Asian countries [37,38] have tried to follow suite with some of them having well established newborn screening program, some others are latching on to this noble course. It is imperative to know that north Africa is making effort to move in the right direction and have align with middle eastern countries who's newborn are benefiting from newborn screening [39]. However, it is sad to know that very few countries in sub-Saharan Africa have what seem to "look like" newborn screening [40-43]. To the best knowledge of the authors of this review article no well establish newborn screening program exist in sub Saharan Africa and probably in Africa has a whole. Presently there is a global fight against what is consider "the big three" (tuberculosis, HIV/AIDs and malaria) Africa being a beneficiary of foreign aids in million of dollars every year. Newborn screening and prompt treatment prevents mental retardation in children it also has been shown to save in treatment and home and institutionalized care in those with CH. It has been shown that the cost of screening varied from \$0.7 to \$1.60 per infant depending on which costs were included in the estimate in Iran [44], however in South African, it cost about 30R per infant [45]. More over The "costly screening" is likely to be affordable when newborn screening is universally accessible in sub Saharan Africa, obeying the law of demand and supply. Foreign aids should be extended in making newborn

screening a world wide program because of its cost-effective benefit. Every parent wants his/her child to have a better and fulfilling life, can a mentally retarded child achieve this? Every child has the right to life and a good quality of it. Even though established newborn screening is just now not available in sub-Saharan Africa, informing pregnant women about CH during antenatal care and newborn screening should be a knee jerk response for physicians (obstetricians and neonatologist) involve in their management with emphasis on its cost effective benefit, this is a form of provider initiated counseling and testing which is a laudable public health program.

Recommendations

Increase societal awareness of CH and its identification by newborn screening.

Health care providers should inform all pregnant mothers during antenatal visit about CH, newborn screening and its cost effective benefit.

Newborn screening should be mandatory and ultimately made free by legislation, just the way it is for birth registration and immunization.

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