Etiology of Congenital Hypothyroidism Revealed by Newborn Screening

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Abstract

The number of studied patents was 100 constituting of 61 (60.4%) females and 40 (39.6%) were males. Females were more commonly effected than males.Agenesis as a subcategory of dysgenesis was the most common diagnosed (43.3%) followed by ectopic (26.66%), then lingual (13.3%) following by hypoplasia (11. 6%), while the least common diagnosed were aplasia (3.3%).Incidence among years of follow up, showed slight increase and decrease with no steady increasing or decreasing pattern in both dysgenesis and dyshormonogenesisMost of neonates were asymptomatic during the neonatal period and in their first visit in the outpatient, which makes hypothyroidism in the new born period is almost always overlooked, and delayed diagnosis leads to severe outcome.So absence of symptoms and signs, makes screening, scintigraphy and thyroscan main tools of diagnosis.Screening is the ideal primary, easy, cost effective method of detection of congenital hypothyroidism, whatever permanent or transient.Ultrasound and scintigraphy were tools of etiological diagnosis of the disease. However sensitivity and specificity of U/S compared with scintigraphy in diagnosis is low, U/S failed to diagnose high percentage of ectopic cases and non functioning thyroid gland, only detecting anatomy of thyroid.

Keyword: U/S, Hypothyroidism, CH, GSU, SSCP

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List of Abbreviations

C	
CAMP	Cyclic Adenosine Monophospate
CDU	Color Doppler Ultrasonography
CH	Congenital Hypothyroidism
CH- C	Congenital Hypothyroidism – Central
CH-T	Congenital Hypothyroidism – Thyroidal
CT	Computed Tomography – Thyroidal
CT	Computed Tomography
CNS	Central Nervous System
D	
Dehal 1	Gene
DIT	Diiodo tyrosine
DNA	Deribonucleic Acid
Duox2	Dual Oxidase 2
E	
ECG	Electrocardiogram
F	
Foxe 1	Gene
FT4	Free Tetraiodothyronine
G	
GSU	Gray – Scale Ultrasonography
H	
HHEX	Gene
I	
I	Iodide

IgG	Immunoglobulin G
IID	Iodide Transport Defect
IV dose	Intravenouse dose
L	
LBW	Low Birth weight
L-T (4)	Levothyroxine
M	
MIT	Monoiodotyrosine
MRI	Magnetic Resonance imaging
M RNA	Messenger Ribo nucleic acid
N	
n	Number
NICUS	Neonatal Intensive Care Units
NIS	Sodium Iodide Symporter
NKX 2-5	Gene
P	
PAX8	Paired homeobox-8 (Gene)
PET	Positron emission tomography
PD dose	Oral dose
R	
R52P	Gene
RAIU	Radioiodide uptake
RI	Radionucleide Imaging
RIUT	Radioiodide uptake
RI	Radionucleide Imaging
RIUT	Radioiodide Uptake

RH TSH	Thyrogen
S	
SD	Standard Deviation
SSCP	Single Strand comformational polymorphism
T	
T3	Triiodo thyronine
T4	Tetraiodothyronine
TBG	Thyroid Binding Globulin
TBPA	Thyroid binding prealbumin
TC- 99m	Technetium – pertechnetate
TD	Thyroid Dysgenesis
TG	Thyroglobulin
THS	Thyroid Stimulating Hormone
TSH-R	Thyroid – stimulating Hormone receptors
TTF 1	Thyroid Transcription factor 1
TTF2	Thyroid Transcription Factor 2
T25	Diiodothyronine Sulfate
U	
UK	United Kingdom
US	Ultrasonography
V	
VLBW	Very Low Birth Weight
123 I	Iodine 123
131 I	Iodine 131

Introduction

Congenital hypothyroidism (CH), a condition of thyroid hormone deficiency present at birth, is the most frequent endocrine disorder in neonates***(Gruters et al., 2011; La Franchi et al.,2011).***

CH is classified into permanent and transient forms, which in turn can be divided into primary, secondary, or peripheral etiologies. Thyroid dysgenesis accounts for 85% of permanent, primary CH, while inborn errors of thyroid hormone biosynthesis (dyshormonogeneses) account for 10-15% of cases***(Rastogi et al., 2010).***

Thyroid dysgenesis occurs sporadically in most cases but is occasionally familial because of mutations or deletions of genes (*PAX8, TTF1,TTF2*) that are involved in fetal thyroid formation. Thyroid dysgenesis ranges in severity from thyroid aplasia or hypoplasia to functional ectopic thyroid tissue. Approximately 40-60% of infants with thyroid gland dysgenesis have some functioning tissue***.(Hardy et al., 2004)***

Most neonates born with CH have normal appearance and no detectable physical signs; hypothyroidism in the newborn period is almost always overlooked and delayed ***(Buyukgebiz et al., 2006).***

Untreated congenital hypothyroidism in early infancy results in profound growth failure and disrupted development of the CNS, leading to developmental cognitive delay (cretinism)***(Sbrocchi et al., 2008)***, as the developing brain has a critical dependence on thyroid hormone for the first 2-3 yr of life ***(La Franchi et al., 2011).***

The diagnosis in industrialized countries is usually made with population-based newborn screening that measures thyroid-stimulating

hormone (TSH) or TSH and total thyroxine (T(4)) in dried blood spots in the first 3 days of life***(Gruters et al., 2007).***

Neurodevelopmental outcome is inversely related to the age of diagnosis and treatment. Infants detected through newborn screening programs and started on l-T(4) in the first few weeks of life have a normal or near-normal neurodevelopmental outcome***(La Franchi et al.,2011).*** Further diagnostic studies, such as radionuclide uptake and scan and ultrasonography, may be performed to determine the underlying cause of hypothyroidism. The developing brain has a critical dependence on thyroid hormone for the first two to three years of life; thus, monitoring occurs at more frequent intervals than in older children and adults. Serum free T(4) and TSH should be checked at intervals frequent enough to ensure timely adjustment of l-T(4) dosing and to keep serum free T(4) and TSH levels in target ranges. Given the success of early detection and treatment of neonates with CH, a public health mandate should be to develop similar programs for the 75% of babies worldwide who are born in areas without newborn screening programs***(La Franchi et al., 2011).***

The goal of treatment of CH is to avoid disturbed mental development, and initial treatment can be adjusted to physiological conditions. To match the higher thyroid hormone concentrations in the first weeks of life, substitution with l-thyroxine should aim to achieve serum T(4)/free T(4) levels in the upper half of the normal age-related reference range. Some newborns and infants will have persistently high TSH levels despite normalized T(4)/ free T(4) serum concentrations ***(Gruters et al., 2007).***

Aim Of Work

The present work aims at describing hormonal and scintigraphic results of infants with CH subjected to newborn thyroid screening programs, and receiving therapy in several districts in Egypt.

OBJECTIVES

The objectives of this study is to

-Report prevalence of different aetiological categories of congenital hypothyroidism in the studied sample.

-Describe clinical manifestations among different diagnostic categories of congenital hypothyroidism.

-Match between results of thyroid scan and ultrasound in the studied sample .

-Discuss doses of L-thyroxine in control of patients with congenital hypothyroidism with different aetiologies.

Chapter 1
Anatomy , Development And Physiology Of Thyroid Gland

The **thyroid gland** or simply, the **thyroid** in vertebrate anatomy, is one of the largest endocrine glands. The thyroid gland is found in the neck, below (inferior to) the thyroid cartilage (which forms the laryngeal prominence, or "Adam's apple"). The isthmus (the bridge between the two lobes of the thyroid) is located inferior to the cricoid cartilage***(Kamath et al., 2010)***.

The thyroid gets its name from the Greek word for "shield", due to the shape of the related thyroid cartilage. The most common problems of the thyroid gland consist of an overactive thyroid gland, referred to as hyperthyroidism, and an underactive thyroid gland, referred to as hypothyroidism***(Kamath et al., 2010).***

Anatomy

The thyroid gland is a butterfly-shaped organ and is composed of two cone-like lobes or wings, lobus dexter (right lobe) and lobus sinister (left lobe), connected via the isthmus. The organ is situated on the anterior side of the neck, lying against and around the larynx and trachea, reaching posteriorly the oesophagus and carotid sheath. It starts cranially at the oblique line on the thyroid cartilage (just below the laryngeal prominence, or 'Adam's Apple'), and extends inferiorly to approximately the fifth or sixth tracheal ring. It is difficult to demarcate the gland's upper and lower border with vertebral levels because it moves position in relation to these during swallowing***(Kupper et al., 2008).***

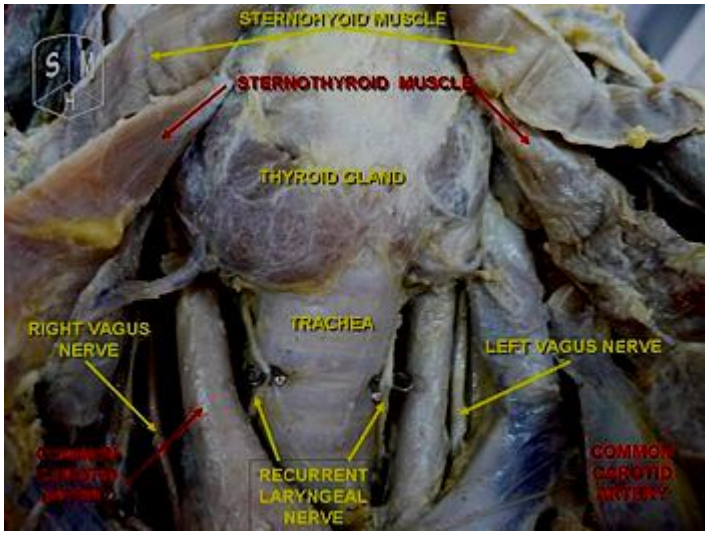

Fig (1) : Anatomy of thyroid gland.

The thyroid gland is covered by a fibrous sheath, the *capsula glandulae thyroidea*, composed of an internal and external layer. The external layer is anteriorly continuous with the *lamina pretrachealis fasciae cervicalis* and posteriorolaterally continuous with the carotid sheath. The gland is covered anteriorly with infrahyoid muscles and laterally with the sternocleidomastoid muscle also known as sternomastoid muscle. On the posterior side, the gland is fixed to the cricoid and tracheal cartilage and cricopharyngeus muscle by a thickening of the fascia to form the posterior suspensory ligament of Berry. The thyroid gland's firm attachment to the underlying trachea is the reason behind its movement with swallowing. In variable extent, Lalouette's Pyramid, a pyramidal extension of the thyroid lobe, is present at the most anterior side of the lobe. In this region, the recurrent laryngeal nerve and the inferior thyroid artery pass next to or in the ligament and tubercle***(Berbel et al., 2010).***

Between the two layers of the capsule and on the posterior side of the lobes, there are on each side two parathyroid glands.