

**TRANSIENT CONGENITAL HYPOTHYROIDISM:
CUT OFF VALUE FOR DIAGNOSIS, MEDIAN TIME
FOR NORMALIZATION OF THYROID FUNCTION
AND FACTORS AFFECTING THE MEDIAN TIME**

DR. SITI HAZLINI ABDUL HAMID

**DISSERTATION SUBMITTED IN PARTIAL
FULFILLMENT OF THE REQUIREMENT FOR
THE DEGREE OF MASTER IN MEDICINE
(PAEDIATRICS)**



UNIVERSITI SAINS MALAYSIA

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CHAPTER I:

THE PRELIMINARIES

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LIST OF ABBREVIATIONS AND NOMENCLATURE

AAP:	American Academy of Paediatrics
AUC:	Area under curve
DUOX2:	Dual oxidase 2
FT4:	Free thyroxine
HR:	Hazard ratio
HUSM:	Hospital Universiti Sains Malaysia
IQR:	Interquartile range
JEPeM:	Jawatankuasa Etika Penyelidikan (Manusia)
ROC:	Receiver operating characteristic
SD:	Standard deviation
SGA:	Small for gestational age
TFT:	Thyroid function test
TSH:	Thyroid stimulating hormone
TSHR:	Thyroid stimulating hormone receptor

ABSTRAK

Hipotiroidisme kongenital sementara : nilai batasan bagi diagnosis, masa normalisasi fungsi tiroid dan factor-faktor yang mempengaruhinya

Objektif: melihat nilai batasan bagi diskriminasi awal di antara hipotiroidisme sementara dan kekal, untuk menentukan masa median untuk fungsi tiroid dinormalisasi selepas penamatan rawatan dalam kumpulan sementara dan faktor-faktor yang mempengaruhinya.

Kaedah: 55 kes hipotiroidisme kongenital dikenalpasti daripada tinjauan retrospektif rekod. 37 merupakan hipotiroidisme kekal dan 18 merupakan hipotiroidisme sementara. Nilai batasan optimum hormon yang merangsang tiroid (TSH) dan nilai tiroksin bebas (FT4) dianalisa menggunakan analisis ciri operasi penerima (ROC) untuk kedua-dua kumpulan. Analisis kemandirian Kaplan-Meier dijalankan untuk menganggarkan masa median untuk fungsi tiroid dinormalisasi dalam kumpulan hipotiroidisme. Bagi menentukan faktor-faktor yang memberi kesan terhadap masa median, ujian peringkat-log telah dijalankan.

Penemuan: Nilai permulaan batasan TSH bagi kumpulan hipotiroidisme sementara adalah 13.55 mIU/L dengan kawasan di bawah lekuk ROC 68.9% (sensitiviti 58.8 %, nilai spesifik 73.5%) dan nilai permulaan bebas T4 adalah 13.45 pmol/L dengan kawasan di bawah lekuk ROC 71 % (sensitiviti 70.6 %, nilai spesifik 64.7%). Median masa yang didapati adalah 8 minggu dan tiada faktor yang mempengaruhi secara signifikan yang dijumpai.

Kesimpulan: TSH permulaan hipotiroid sementara dalam kalangan kanak-kanak adalah lebih rendah berbanding hipotiroid kekal dan ianya mengambil masa selama dua bulan bagi fungsi tiroid dinormalisasikan semula.

Kata kunci: *hipotiroidisme kongenital sementara, masa median, nilai batasan*

ABSTRACT

Transient congenital hypothyroidism: cut off value for diagnosis, median time for normalization of thyroid function and factors affecting the median time

Purpose: To look into cut off value for earlier discrimination between transient and permanent hypothyroidism, to determine median time for thyroid function to normalize upon cessation of treatment in transient group and its affecting factors.

Method: 55 cases of congenital hypothyroidism were identified from retrospective record reviews. 37 cases were with permanent hypothyroidism and 18 cases were with transient hypothyroidism. The optimal cut off value of initial thyroid stimulating hormone (TSH) and free thyroxine (FT4) level were analyzed using receiver operating characteristics (ROC) curve analysis for both groups. Kaplan-Meier survival analysis was conducted to estimate median time for thyroid function to normalize within the transient hypothyroidism group. The log-rank test was used to determine factors affecting the median time.

Results: The cut off value for initial TSH within transient hypothyroidism group was 13.55 mIU/L with area under ROC curve of 68.9 % (sensitivity 58.8 %, specificity 73.5%) and the initial free T4 was 13.45 pmol/L with area under ROC curve of 71 % (sensitivity 70.6 %, specificity 64.7%). The median time obtained was about 8 weeks and there were no significant affecting factors identified.

Conclusion: Transient hypothyroid infants' initial TSH was lower compared to permanent group and it takes 2 months for thyroid function to normalized.

Keywords: *transient congenital hypothyroidism, median time, cut off value*

CHAPTER II:

THE TEXT

Section A:

Introduction

INTRODUCTION

Overview on congenital hypothyroidism

Congenital hypothyroidism is one of the most common known cause of preventable mental retardation, yet its detection at birth clinically is difficult ¹. As a continuum of this, screening programme was developed worldwide. Internationally, inaugural newborn screening for congenital hypothyroidism was published in 1993 by the American Academy of Pediatrics. Locally, the screening programme was started in Malaysia in October 1998. Local data showed that the incidence of congenital hypothyroidism is 1 in 3,914 ².

Screening programme identified not only permanent hypothyroidism, but also group of disorders which was unidentified before due to unapparent clinical course namely transient congenital hypothyroidism (elevated TSH, decreased FT4) and transient congenital hyperthyrotropinaemia (elevated TSH, normal FT4) ³.

There are various aetiologies for both permanent and transient congenital hypothyroidism ^{4,5}. Possible causes of permanent hypothyroidism are thyroid dysgenesis (agenesis, hypoplasia, ectopia), thyroid dyshormonogenesis, hypothalamic-pituitary hypothyroidism or generalised resistance to thyroid hormone. Transient hypothyroidism can either be primary, secondary or tertiary. Primary causes can either be due to endemic iodine deficiency, prenatal or postnatal iodine excess, maternal thyroid stimulating hormone receptor (TSHR) blocking antibodies, maternal antithyroid medications, dual oxidase 2 (DUOX 2) mutation or isolated hyperthyrotropinaemia (normal FT4, high TSH). Potential causes of secondary or tertiary

hypothyroidism are maternal hypothyroidism, prematurity, very low birth weight, drugs (examples are dopamine and steroids) and transient hypothyroxinaemia (low FT4, normal TSH).

Transient congenital hypothyroidism

Transient congenital hypothyroidism defines a group of disorders whereby reversion of thyroid function to normal level occur either spontaneously or later during follow up upon treatment withdrawal ^{4,6}. Transient hypothyroidism is relatively rare in North America (1 in 50 000) compared to iodine deficient areas of the world ¹. In areas of iodine deficient, the birth prevalence of transient primary hypothyroidism are variables ⁵.

The abnormal screening value may spontaneously reverted to normal level as soon as first confirmatory test ¹. The confirmatory test should be done as soon as possible but can only be taken after day three of life. This is to avoid TSH surge that occurs half an hour after birth to 72 hours of age ⁵. In the newborn whose mother is receiving antithyroid drugs, the thyroid function tends to normalize within 1 to 3 weeks without treatment.

If serial initial thyroid function showed elevation of TSH and low FT4, it renders the child to be started on treatment and to be reevaluate at the age of 3 ¹. Transient hypothyroidism is diagnosed if the thyroid function remains normal upon treatment withdrawal ^{4,6}. If TSH level elevated upon cessation of treatment, diagnosis of permanent hypothyroidism will be concluded ¹.

Timing for evaluation and cut off value

The advancement of medical care, better access, tendency of lower TSH value in screening of congenital hypothyroidism and an increase in the number of premature babies have contributed to a rise in the incidence of transient congenital hypothyroidism ^{4,7}. Though overall

improvement in screening programme and therapy have led to improvement of outcome ¹, this has indirectly place an impact on the cost and burden to the attending medical personnel. Hence, the timing for evaluation and the treatment decision making have to be seriously taken into consideration as missing out on early treatment may have a harmful effect.

When AAP 2006 guidelines defined transient hypothyroidism as a biochemical evidence of low T4 and elevated TSH which normalize on subsequent follow up at 1 to 2 months, this implies that transient cases can be diagnosed as early as 2 months old ^{1,8}. Supporting this was a Turkish study on transient hypothyroidism which found that 70% of studied subjects were diagnosed as transient hypothyroidism at a median age of 19 months ⁶. These subjects were successfully discontinued from treatment before the age of 3 as their TSH were suppressed despite on low dose of thyroxine. This is in contrary to the current guideline of evaluation at 3 years old, which may expose the child to unnecessary treatment and possible side effects of levothyroxine ^{4,7}.

Diagnosis of transient congenital hypothyroidism can be made earlier based on the trend of TSH and T4. The routine practice of evaluation at the age of 3 years old is due to the lacks of consensus of the definite thyroid function cut off value for earlier diagnosis of transient hypothyroidism. Following this, efforts has been made by various researchers looking into possible optimal cut off value of initial TSH and FT4 level to diagnosed transient hypothyroidism.

A recent study looking into factors associated with transient group found that lower dose of L-thyroxine at third year of treatment (2.76 microgram/kg) (p value < 0.001) and TSH level at 30.8 IU/L (p value 0.021) were significant prognostic indicators ⁹ in differentiating transient group from permanent hypothyroidism group. The same study outcome showed initial TSH cut

off value of 40.2 μ IU/mL (61.9% sensitivity and 64.7% specificity) with AUC of 0.636 were obtained within transient group. This was comparable to another study with initial TSH cut off value of 28.4 mIU/L (sensitivity, 80.6%; specificity, 52%) with AUC of 0.662 within the transient group ¹⁰. From these two studies, we can conclude that the range of optimal cut off value of initial TSH for transient hypothyroidism range from 28.4 to 40.2 mIU/L. Another study in UK support the fact that transient hypothyroidism group initial TSH level likely to be < 40 mIU/L. This study looked into level of capillary TSH as a prediction of venous free T4 as a guide to embark on treatment. They found that capillary TSH of \leq 40 mIU/L has low probability of having subnormal venous free T4 < 10 pmol/L ¹¹. From these findings, it reflects that the cut off value of initial TSH were lower in transient hypothyroidism.

Factors associated with transient hypothyroidism

Epidemiologically, it shows that the prevalence of congenital hypothyroidism differs based on cut off value used for thyroid function. Further epidemiological study on incidence showed that congenital hypothyroidism were affected by race and geographical area ^{1,7}. Incidence were higher in Hispanic (1:1559) and Asian infants (1:1016) compared to white (1:1815) and black infants (1:1902) ⁷. This reflected that genetic factor and iodine content differences by region as potential influencing factors.

Demographically, few studies were done to analyze potential factors affecting congenital hypothyroidism by demographic assessment. These include the familial, maternal, neonatal and environmental influences. Kanike et. al quoted from a New York study found that the incidence of congenital hypothyroidism was higher in older mothers (> 39 years old; 1:1328) than younger mothers (< 20 years old; 1:1703) ⁷. An Italian study outcome however showed the opposite. Maternal age (25 years old to > 40 years old) was not a significant determining factor in both

permanent and transient group ($p > 0.05$)¹². In the same study, the other familial factor such as parental education ($p=0.18$) was not a significant factor within transient hypothyroidism group. Regarding neonatal factors, Kanike et al. found prematurity was highly associated with transient hypothyroidism⁷. Mechanism related to relative deficiency of thyroid hormone in premature babies includes immature hypothalamus-pituitary axis and limitation to generate bioactive compound of thyroid hormone. This is exacerbated in sick preterm babies. Kara et al reported otherwise as the finding was devoid of discriminating parameters between transient hypothyroidism and permanent hypothyroidism. In this study, the p value was insignificant for gestational age less than 37 weeks ($p=0.31$). Other factors studied by Kara et. al such as birth weight around 3 kg ($p=0.08$), median age of detection ($p=0.94$) and age commencement of therapy ($p=0.82$) were not significant with p value > 0.05 for all the mentioned factors⁶. Another study concerning neonatal factor done in Italy showed that gender was not a significant determining factor for transient hypothyroidism, however potential significant factors identified within transient hypothyroidism group were low gestational age (OR=2.9, 95% CI 0.7-12) and intrauterine growth retardation (small for gestational age (SGA)) (OR=5.4, 95% CI 1.0-29.4)¹². While external factor such as advance maternal age might contribute to the risk of developing congenital hypothyroidism, patient's factors were far more important. These were prematurity and SGA.

Biochemically, consistent discriminating factor that is observe in many studies is higher value of initial TSH of above 40 IU/L in permanent group⁹⁻¹¹.

There were no recent studies done specifically looking into factors that might affect the time to normalization of thyroid function upon withdrawal of treatment in transient hypothyroidism.

An old study of case series by Delange et al. helped to estimate time for thyroid function to normalize after discontinuation of treatment at around 27 days¹³.

This study aims to look into the thyroid function cut off value for earlier stratification between transient hypothyroidism and permanent hypothyroidism. The study also will subsequently determine the median time for thyroid function to normalize once treatment was ceased in transient group and its prognostic factors.

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Section B:

Study protocol

Documents submitted for ethical approval

**Transient congenital hypothyroidism: cut off value for
diagnosis, median time for normalization of thyroid
function and factors affecting the median time**

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UNIVERSITI SAINS MALAYSIA

2018

Research title:

Transient congenital hypothyroidism: cut off value for diagnosis, median time for normalization of thyroid function and factors affecting the median time

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Introduction

Congenital hypothyroidism is one of the most common known cause of preventable mental retardation, yet detection at birth clinically is difficult ¹. As a continuum of this, screening programme was developed worldwide and started in Malaysia in October 1998 giving rise to local incidence of 1:3,914 ². Screening programme identified not only permanent hypothyroidism, but also group of disorders which were unidentified before due to unapparent clinical course namely transient congenital hypothyroidism (elevated TSH, decreased FT4) and transient congenital hyperthyrotropinaemia (elevated TSH,normal FT4) ³.

Problem statement & Study rationale

Designed guideline suggest trial to discontinue treatment at 3 years old to stratify them into either transient hypothyroidism or permanent hypothyroidism. Follow up studies done, looking into possible variables to differentiate these 2 groups earlier to avoid unnecessary prolong treatment, however no consensus achieve as yet ^{1,2,10}.

Research Question(s)

What is the pattern of thyroid function test among patients with congenital hypothyroidism and how can it help differentiate transient type?

Objective

General:

- To determine the thyroid function test cut off value for diagnosis of transient hypothyroidism.
- To study median time for thyroid function test normalization and its affecting factors among transient hypothyroidism patients.

Specific:

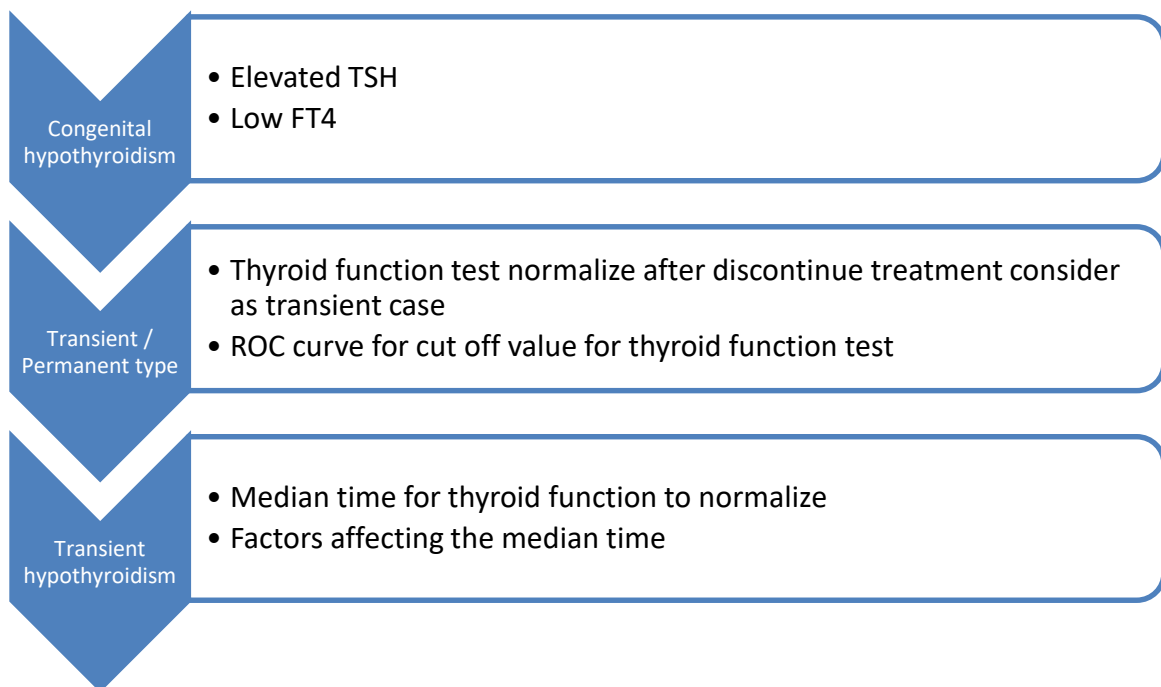
- To determine cut off level of TSH and FT4 to diagnose transient congenital hypothyroidism
- To determine the time for thyroid function test to normalize in the transient hypothyroidism group
- To study factors affecting time for thyroid function test to normalize

Literature review

Evidence suggests the possibility to diagnosed transient hypothyroidism earlier compared from the standard designed guideline at 3 years, however devoid of consensus of the definite thyroid function cut off value. A recent study looking into factors associated with transient group found that L-thyroxine dose at third year of treatment (p value < 0.001) and TSH level (p value 0.021) of significant prognostic indicators (Park et al., 2016) in differentiating transient from permanent hypothyroidism group. The same study outcome shows initial TSH cut off of 40.2 μ IU/mL (61.9% sensitivity and 64.7% specificity) with AUC of 0.636. This is comparable to another study with initial TSH cut off 28.4 mU/L (sensitivity, 80.6%; specificity, 52%) with AUC

of 0.662 (Cho et al., 2014). These reflect that as early as first thyroid function test can stratify the groups. Delange et al. cases help estimate time for thyroid function to normalize after discontinuation of treatment at around 27 days. This study aim to look into the thyroid function cut off value for earlier stratification between transient and permanent hypothyroidism, subsequently determine the median time for thyroid function to normalize in transient group and its prognostic factors.

Conceptual framework



Research design

Retrospective record review – based on search key 'Congenital hypothyroidism' through Hospital USM record office database, all related results case notes will be traced and review. This include tracing result through hospital online system if not available in the case notes.

Study area

- Paediatric Clinic Hospital USM
- Record office Hospital USM

Study population

- Reference population : All patients with congenital hypothyroidism on treatment
- Source population : Congenital hypothyroidism patients on treatment in Hospital USM

Subject criteria

Inclusion criteria:

- All patients diagnosed with congenital hypothyroidism and there are at least 2 thyroid function test result available
- On L-thyroxine

Exclusion criteria:

- Acquired form – late onset (detected later through antibody screening)
- No documented trial to off treatment before labeling as transient hypothyroidism

Sample size estimation

Objective	Sample size	Details
Determination of cut of value	n = 116 Adding 10% dropout, n = 128 Final, n = 128	Using formula of sample size for estimating accuracy index ¹⁴
Determination of median time for thyroid function test normalization and affecting factors	n = 19 Adding 10% dropout, n = 21 (each group) Final, n = 42	PS software, sample size for two survival time - power of 80%

Final, n = 128

For determination of cut of value, using the calculation of sample size for estimating

accuracy index found in sample size estimation in diagnostic test studies of biomedical

informatics, n = 116 (with addition of 10% dropout, n = 128). Related figures included in

this formula are $\alpha = 0.05$, estimated AUC (%) = 66.2 ¹⁰, desired precision = 10 and cases

ratio = 1.

For determination of median time for thyroid function test normalization and its affecting

factors, PS software sample size calculator for two survival time was used, with $\alpha =$

0.05, power = 0.8, A = 156, F = 24, m1 = 1, m2 = 2.5 and m = 1. All related figures are in

months for A, F, m1 and m2.

Sampling method and subject recruitment

List from record office, Hospital USM – **all related search record will be included in the**

study.

Research tool

Data collection sheet

Operational definition

- Congenital hypothyroidism (elevated TSH, decreased FT4) : congenital hypothyroidism can further be classify into permanent hypothyroidism (requiring lifelong treatment on L-thyroxine) and transient hypothyroidism
- Transient hypothyroidism – normal evaluation of thyroid function test after discontinue treatment
- Acquired form – late onset (detected later through antibody screening): refer to patient whom was initially diagnosed with congenital hypothyroidism with positive antibody upon screening, hence the diagnosis change to acquired hypothyroidism instead of congenital.
- If a patient diagnosed with transient hypothyroidism (normalization of thyroid function test) without trial to discontinue treatment, subject will be excluded.
- Incomplete record will be excluded

Data collection method

Retrospective record review

Study flowchart



Data analysis

Data will be entered and analysed using SPSS version 22. Descriptive statistics will be used to summarise the socio-demographic characteristics of subjects. Numerical data will be presented as mean (SD) or median (IQR) based on their normality distribution. Categorical data will be presented as frequency (percentage). ROC curve analysis will be done for estimation of accuracy index to determine cut off value of thyroid function test. To estimate median time

for thyroid function to normalize, Kaplan-Meier survival analysis will be done followed by multiple cox proportional hazard regression to determine the factors affecting the median time.

Expected result(s)

Table 1 : Demographic data

Characteristic	Transient hypothyroidism	Permanent hypothyroidism	<i>P</i> value
No of patients			
Sex, n (%)			
Female			
Male			
Birth weight (kg), n (%)			
< 2.5			
≥ 2.5			
Gestation (week), n (%)			
< 37			
≥ 37			
TFT, mean (SD)			
Serum TSH			
FT4			

Table 2 : Distribution of initial TSH

TSH value (mIU/L)	Transient hypothyroidism n (%)		Permanent hypothyroidism n (%)	
	Cord	Venous	Cord	Venous
≤ 5				
> 5 - 7				
> 7 - 9				
> 9				

Table 3 : Distribution of initial FT4 value

FT4 value (pmol/L)	Transient hypothyroidism n (%)		Permanent hypothyroidism n (%)	
	Cord	Venous	Cord	Venous
≤ 10				
> 10 – 15				
> 15 – 20				
> 20				

Note : For Table 2 and 3 will proceed with sensitivity and specificity testing to develop ROC curve

Table 4 : Median time for thyroid function test normalization in transient hypothyroidism

Interval after treatment discontinue	Number of patient with normal thyroid function (n)
1 month	
2 months	
3 months	
4 months	
5 months	
6 months	

Note : For Table 4, will proceed with Kaplan-Meier survival analysis

Table 5 : Factors affecting median time for thyroid function normalization in transient hypothyroidism

Variables	b (SE)	Adjusted HR (95 % CI)	Wald statistic	<i>p</i> value
Sex				
Female				
Male				
Birth weight (kg)				
< 2.5				
≥ 2.5				
Gestation (week)				
< 37				
≥ 37				
TFT				
Serum TSH				
FT4				

Note : For Table 5, will proceed with multiple cox proportional hazard regression

Gantt chart & milestone

Activity	2018							
	Jan	Feb	Mar	Apr	May	June	July	Aug
Data collection								
Data analysis								
Presentation & submission of report								
Report writing								
Project completion								
Submission								

Budget proposal [If applicable]:

Not applicable

Ethical consideration(s) [if applicable]:

1. Declaration of absence of conflict of interest

No potential conflict of interest

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