Congenital Hypothyroidism in Children – A Cross-Sectional Study in a Tertiary Centre in Malaysia

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Abstract

Introduction. The causes of congenital hypothyroidism (CHT) are thyroid dysgenesis (TD), dyshormonogenesis (TDH) or transient hypothyroidism (TH).

Methodology. This is a cross-sectional study looking at data over a period of 16 years (2000-2016). Confirmed cases had thyroid scan at the age of 3-years-old and repeated TFT (after 6 weeks off medications). Relevant data was collected retrospectively.

Results. Forty (60% female) children with CHT were included in the study. Thirty (75%) children presented with high cord TSH. Nine (23%) presented after 2 weeks of life. Majority were diagnosed with TDH (42.5%) with TD and TH of 40% and 17.5% respectively. Median cord TSH of children with TD was significantly higher compared to TDH and TH (p=0.028 and p=0.001 respectively). L-thyroxine doses were not significantly different between TD, TDH and TH at diagnosis or at 3 years.

Conclusions. TDH is highly prevalent in our population. TD may present after 2 weeks of life. One in five children treated for CHT had TH. Differentiating TD, TDH and TH before initiating treatment remains a challenge in Malaysia. This study provides clinicians practical information needed to understand the possible aetiologies from a patient’s clinical presentation, biochemical markers and treatment regime. Reassessing TH cases may be warranted to prevent unnecessary treatment.

Key words: congenital hypothyroid, thyroid dysgenesis, thyroid dyshormonogenesis, transient hypothyroid, thyroxine, cord blood TSH

INTRODUCTION

Thyroid hormone is vital for the normal functioning of various organs in the body, including neural growth and transmission. This is especially important as studies have shown that there is a close association of thyroid hormone with foetal brain development.1 Congenital hypothyroidism (CHT) is the term used when the production of the thyroid hormones are inadequate or deficient in newborn babies. It is an important diagnosis to be made early to prevent mental retardation in children. Cord blood or early serum TSH screening has been widely used to detect CHT.2-3

Permanent or true congenital hypothyroidism is divided into thyroid dysgenesis (agenesis or ectopics) (TD) or thyroid dyshormonogenesis (TDH). Children with permanent congenital hypothyroidism require lifelong thyroxine replacement. There is an increasing recognition of transient hypothyroidism or subclinical hypothyroidism, which can be due to maternal thyroid disease, prematurity or iodine deficiency. These children are usually on temporary thyroxine replacement.

The prevalence of congenital hypothyroidism worldwide is around 1 in 4000 livebirths in USA, Canada and Western Europe.4 In our neighbouring country, Singapore,5 the prevalence was reported as 1 in 3000 live births. Local studies in Malaysia have reported the prevalence of CHT as between 1600 to 3500 per 100,000 live births.6,7 The prevalence of CHT in University Malaya Medical Centre (UMMC) was reported as 1 in 1515 term babies, slightly higher than previously reported Malaysian data.2

Data obtained from Leicester Royal Infirmary in UK,8 reported that congenital hypothyroidism is more prevalent in Asians compared to non-Asians, with the affected population of children mostly had thyroid dysgenesis (1 in 4000). Another study from the University of Montreal, Canada,9 found that for thyroid dysgenisis,
females were more affected compared to males. In Yazd, Central Iran, a larger population (54.5%) of children with transient hypothyroidism was reported compared to permanent hypothyroidism. However, the study population was small with only 22 children. In Malaysia, there is inadequate data to suggest distribution, however, a short report in 2009 showed thyroid dyshormonogenesis was much more prevalent than thyroid dysgenesis.

Initial presentation of children with CHT can be variable, with most being asymptomatic if detected early. Other symptoms include sleepiness, poor feeding, cold extremities, prolonged neonatal jaundice, lethargy, hypotonia, macroGLOSSIA, umbilical hernia, coarse facies and dry skin. Delayed bone maturation is shown through delayed closure of posterior fontanelle, large anterior fontanelle and wide sagittal suture. CHT if not treated will cause significant reduction in irreversible, permanent nervous system damage and a consequent developmental delay. Previous studies have shown that the first 4 to 6 weeks of life is a phase crucial for postnatal brain development and a delay in treatment for one week can cause a significant reduction of IQ (approximately 10 points) in children with CHT. This is why early detection and early treatment is so important. Meanwhile a study conducted by Albert BB et al., in New Zealand has shown that children with CHT even when treated early had delayed normalisation of the T4 values that may affect the child’s motor balance. This suggests the importance of early and aggressive treatment in this group of patients.

The Malaysian National CHT screening programme was initiated in October 1998. TSH levels are taken from cord blood due to logistics purposes. Babies with cord blood TSH more than 40 mIU/L is highly suspicious for CHT. Cord blood TSH between 20-40 mIU/L will also be recalled for a repeat test. Serum fT4 and TSH between day 3 and 5 would be done for confirmation. Abnormal TFT performed between day 3 and 5 are treated according to AAP 2006 guidelines. Those born prior to 2006 were treated according to AAP guidelines 1993. Babies with normal cord blood TSH but later found to have abnormal TFT levels (TSH >10 mIU/L with a relatively lower fT4 levels <15 pmol/L) were treated.

In developed countries, thyroid scans are done shortly after positive initial screening. However, in Malaysia, due to the limited availability of thyroid scans, babies suspected to have CHT were not subjected to thyroid scan at initiation of treatment, compared to some other centres in the world. Instead the scan is done at age 3 years. Babies who were started on treatment would have their levels monitored monthly for the first 6 months, then every 2 to 3 months until 2 years old and subsequently every 3 to 4 months until the age of 3 years. At that point, treatment would be stopped for 4-6 weeks before the children were sent for thyroid scan. TFT would also be taken just prior to the thyroid scan. Thyroid dysgenesis (TD) is diagnosed if the child has both abnormal thyroid scan and TFT at 3 years old. Children with abnormal TFT but have normal thyroid scan are considered to have thyroid dyshormonogenesis (TDH). Transient hypothyroidism (TH) children will have normal scan and normal TFT. Only those with TD or TDH will eventually need thyroxine for life.

This study aims to guide clinicians in developing countries with limited resources to understand the aetiologies and possible outcome based on patients’ clinical presentation. This includes timing of presentation, biochemical markers and treatment regimes.

**METHODOLOGY**

A cross-sectional study was conducted looking at data over 16 years from 2000-2016. This is to determine the prevalence, demographic profile, clinical and biochemical parameters of all CHT patients on follow-up at UMMC Paediatric Endocrinology clinic. UMMC is a tertiary referral centre in the urban population of Kuala Lumpur. Our study population were term babies born between year 2000 to year 2013 without any congenital anomaly or suspected syndrome. We identified CHT cases based on 3 sub-group diagnosis namely thyroid dysgenesis, dyshormonogenesis and transient hypothyroidism. These cases must have complete confirmatory diagnostic tests (re-testing TFT and thyroid scan) which was performed at 3 years old. We then collected data retrospectively from each case for analysis. All subjects were anonymised and potential identifiers removed. Relevant data was tabulated and analysed using SPSS software 22.0. This study was approved by the hospital ethics committee MREC No 2018913-6676.

Early presentation is defined as a patient presenting with either high cord blood TSH at screening or with symptoms before 2 weeks of life and late if presented after 2 weeks of life.

**STATISTICS**

Period prevalence was calculated based on the centre’s livebirth registry and confirmed CHT cases. Kruskal-Wallis test was performed to compare the three types of CHT and post hoc analysis was done to explore the differences. Fishers exact test for gender and ethnicity was also performed to reflect association between the groups.

**RESULTS**

Total number of livebirth from 2000-2013 was 72,652 in this centre. A total of 223 cases were suspected to have CHT. Only 40 cases met the inclusion criteria and were included in the analysis. These cases were confirmed to have congenital hypothyroidism (CHT). The calculated period prevalence in this study group is 0.055%. The most common type of CHT seen is thyroid dyshormonogenesis (n=17,42.5%), followed by thyroid dysgenesis (n=16,40%) and transient hypothyroidism (n=7,17.5%). Despite being the least common, about 1 out of 5 children with CHT had transient hypothyroidism and were treated with thyroxine for at least 3 years.

**Demographics**

We have found that CHT in our population has a female preponderance (60% p=0.019) (Table 1). This is especially true with thyroid dysgenesis (81.3% female) and transient hypothyroidism sub-groups (71.4% female) (Table 1). Apart from gender, ethnicity difference was equally significant across 3 major ethnicity group in Malaysia (p=0.027). Chinese ethnicity was the majority in this population (47.5%). However, comparing sub-groups, 50%
of the children who had thyroid dysgenesis were Malays, 70.6% of children with thyroid dysshormonogenesis were Chinese and 42.9% of those with transient hypothyroidism were Indians (Table 2).

### Table 1. The distribution by gender in different types of congenital hypothyroidism

| Types of CHT | Male | Female | Total |
|--------------|------|--------|-------|
| TD           | 3 (18.8%) | 13 (81.3%) | 16    |
| TDH          | 11 (64.7%) | 6 (35.3%) | 17    |
| TH           | 2 (28.6%) | 5 (71.4%) | 7     |
| Total        | 16    | 24     | 40    |

*p=0.019 *Fisher’s Exact test

### Timing of presentation

Among all the children with CHT (n=40), 31 (77.5%) of them presented early with high cord blood TSH or abnormal TSH above 10 mIU/L within first 2 weeks of life. The remaining 9 (22.5%) presented at or more than 2 weeks of life. Only 1 in 8 children with thyroid dysgenesis and thyroid dysshormonogenesis presented late. Majority of children (57%) with transient hypothyroidism presented late (Table 3).

### Table 2. The distribution by ethnicity in different types of congenital hypothyroidism

| Types of CHT | Malay | Chinese | Indian | Total |
|--------------|-------|--------|--------|-------|
| TD           | 8 (50%) | 5 (31.3%) | 3 (18.7%) | 16    |
| TDH          | 5 (28.6%) | 12 (70.6%) | 0 (0%) | 17    |
| TH           | 2 (28.6%) | 2 (28.6%) | 3 (42.9%) | 7     |
| Total        | 15    | 19     | 6      | 40    |

*p=0.027 *Fisher’s Exact test

### Clincical presentation

Clinically, children who presented early (n=31) were asymptomatic regardless of the type of CHT. Two cases of thyroid dysgenesis presented late. One had a missing record of cord blood TSH, however despite reminder, parents did not turn up for a repeat test and returned to their rural hometown for confinement. The second case had normal cord blood TSH. Both presented at much later stages with profound hypothyroidism (umbilical hernia, skin mottling, feeding difficulty and absent of femoral epiphyses). All late presenters from thyroid dysshormonogenesis group presented with mild symptoms of prolonged jaundice. It was more common for cases with transient hypothyroidism to present later with delayed TSH rise. Most were asymptomatic. One was incidentally found to have abnormal T4 levels during extensive workout for hypotonia and poor weight gain. She was treated with thyroxine when her T4 was persistently low (<15 pmol/L) despite normal TSH (6.33 mIU/L) (Table 3.1).

#### Biochemical levels

Median cord blood TSH level was observed to be higher in children with thyroid dysgenesis and dysshormonogenesis as compared to those with transient hypothyroidism. There was significant difference between the cord blood TSH level when compared to all sub-groups (p=0.01) (Table 4).

Post hoc analysis confirms statistically significant difference between levels in thyroid dysgenesis and thyroid dysshormonogenesis (p=0.028) and when compared between thyroid dysgenesis and transient hypothyroidism (p=0.001) (Table 4.1).

#### Dosing and treatment

At initiation of treatment, the mean starting dose of L-Thyroxine for thyroid dysgenesis, thyroid dysshormonogenesis and transient hypothyroidism were 11.83±3.88, 8.84±3.83 and 6.34±1.97 mcg/kg/day respectively. Although it appears to be different, Kruskal-Wallis test showed no significant difference between the three groups (p=0.614). Similarly at 3 years old, there were no statistical difference between the doses taken by the children comparing all groups (p=0.056). The mean L-thyroxine dose were 3.18±0.69, 2.56±0.79 and 1.91±0.82 mcg/kg/day for thyroid dysgenesis, thyroid dysshormonogenesis and transient hypothyroidism respectively (Table 5).
also showed a significantly higher incidence of congenital hypothyroidism in Asian families--1/1918 compared with 1/3391 in non-Asians. A study from the UK also showed predominance in Asian families to have CHT and females are more affected than males. In our study, the majority (42.5%) of our children with CHT had thyroid dyshormonogenesis. This is followed by thyroid dysgenesis (40%) and the remaining 17.5% transient hypothyroidism. We have demonstrated the ethnicity predisposition for CHT. This result also supports a paper published on New Zealand Asian births which had higher rates of dyshormonogenesis compared to New Zealand Europeans and consolidates our previous report where we found that the majority of our patients with congenital hypothyroidism are thyroid dyshormonogenesis.

Malaysia has a total population of 32.6 million, the majority are Malays (69%), followed by Chinese (22.8%) and Indians (6.9%). We found that distribution of CHT in our centre affects more Chinese (47.5%), followed by Malays (37.5%) and the Indians (15%). The Chinese population were found to be more predisposed to have thyroid dyshormonogenesis (70.6%), while the Malays (50%) had thyroid dysgenesis and Indian population tend to have transient hypothyroidism. This report supports another study by Lee et al., who reported 4 Malaysian-Chinese children with thyroid mutation genes (c.2268dup) related to thyroid dyshormonogenesis. Lee et al. also describes similar findings in 2 siblings with CHT who presented with goitre during late teenage years. Studies from California also showed increase prevalence of CHT in certain Chinese and Asian Indian ethnic groups.

One would anticipate a child with thyroid dysgenesis would not be able to produce thyroxine hence the high levels of cord TSH. We report 2 cases (12.5%) who presented late with profound symptoms. One child had no record of cord TSH. This was a missed case (inadequate cord blood sampling). Unfortunately, due to logistics issue, parents did not return child for a repeat sample at D3-5 despite reminder. This child presented with profound symptoms at 4 weeks old. The other child had a normal cord TSH which was unexpected. She presented much later with mild symptoms. In this study, we report 3 cases (17%) who presented with prolonged jaundice and had normal cord TSH with delayed TSH rise.

In thyroid dyshormonogenesis, the gland is normally formed but its function is abnormal, resulting in inadequate T4 and T3 levels, inducing an increase in TSH levels. Depending on the severity, cord TSH may not be as high and abnormal as thyroid dysgenesis. Some may have either normal or borderline raised levels and these children may present later with milder symptoms. In this study, we report 3 cases (17%) who presented with prolonged jaundice and had normal cord TSH with delayed TSH rise.

Majority of the children with transient hypothyroidism had delayed rise in TSH levels and their cord TSH are well within the normal range. These babies were recalled every 1-2 weeks to monitor their TSH levels. If the TSH remains abnormal according to AAP 2006 guidelines, we started them on low dose thyroxine replacement to prevent further rise in TSH levels. Three out of four late presenters were asymptomatic. The child who presented with hypotonia

University Malaya Medical Centre (UMMC) has been practicing neonatal screening for congenital hypothyroidism using cord blood TSH since the late 1980’s. Further confirmation by serum TFT would be then carried out on day 3 to 5 of life, at which treatment is instituted if the diagnosis was made. At the age of 3 years, all children treated for CHT were subjected to thyroid scan to confirm the cause of CHT. From diagnosis to 3 years old, these children were monitored closely and dosage adjustment was done according to laboratory tests, the TSH and T4 levels.

We report significant proportion in relation to gender. More females were found to have CHT (thyroid dysgenesis and transient hypothyroidism) in our population. However, for thyroid dyshormonogenesis, boys predominate. Although not widely reported, this trend was also seen in few research studies published on the demographics of population of children with congenital hypothyroidism, where female to male ratio is 2:1.4,15,19

In previous studies, Asians are shown to have much higher incidence of thyroid dyshormonogenesis. Screening in the North West health region of England

### Table 4. Median cord TSH values of different subgroups of CHT

| CHT Type | TD (n=16) | TH (n=7) | TDH (n=17) | p-value |
|----------|-----------|---------|------------|---------|
| Median Cord TSH (miu/L) | 109.80 | 21.30 | 28.64 | 0.01* |
| Maximum level (miu/L) | 595.00 | 28.00 | 167.00 | |
| Minimum level (miu/L) | 8.00 | 5.00 | 4.00 | |

*p-value calculated using Kruskal-Wallis test

### Table 4.1. Post Hoc analysis

| Comparison | p-value |
|------------|---------|
| Transient (TH) – Dysmorphogenesis (TDH) | 0.337 |
| Transient (TH) – Dysgenesis (TD) | 0.001* |
| Dysmorphogenesis (TDH) – Dysgenesis (TD) | 0.028 |

*p-value calculated using Kruskal-Wallis test

### Table 5. Mean dosage (initial dose and last dose) of L-Thyroxine/day of CHT, thyroid dyshormogenesis (TD), thyroid dyshormogenesis (TDH) and transient hypothyroidism (TH)

| Types of CHT | Starting thyroxine | Last dose thyroxine at 3-years-old |
|--------------|--------------------|-----------------------------------|
| TD n=16(40%) | Mean dose (mcg/kg/day) | 15 | 1 (94%) | 16 | 0 (100%) |
| TDH n=17(42.5%) | Mean dose (mcg/kg/day) | 11 | 6 (64%) | 17 | 0 (100%) |
| TH n=7(17.5%) | Mean dose (mcg/kg/day) | 2 | 5 (28%) | 6 | 1 (72%) |

*Significant at p=0.056

In thyroid dyshormonogenesis, the gland is normally formed but its function is abnormal, resulting in inadequate T4 and T3 levels, inducing an increase in TSH levels. Depending on the severity, cord TSH may not be as high and abnormal as thyroid dysgenesis. Some may have either normal or borderline raised levels and these children may present later with milder symptoms. In this study, we report 3 cases (17%) who presented with prolonged jaundice and had normal cord TSH with delayed TSH rise.

Majority of the children with transient hypothyroidism had delayed rise in TSH levels and their cord TSH are well within the normal range. These babies were recalled every 1-2 weeks to monitor their TSH levels. If the TSH remains abnormal according to AAP 2006 guidelines, we started them on low dose thyroxine replacement to prevent further rise in TSH levels. Three out of four late presenters were asymptomatic. The child who presented with hypotonia
and poor weight gain was extensively investigated and was found to have persistently abnormal T4 levels between the age of 8-9 months. The cause of hypothyroidism was not identified.

There are a few possibilities to the causes of transient hypothyroidism.30 Iodine deficiency is a condition to consider. Malaysian population is at high risk of iodine deficiency. Nazaimoon et al., has shown that up to 49% of children between 8-10 years old are iodine deficient.30 Another report from Sabah showed that iodine deficiency among pregnant and breastfeeding mothers in Malaysia is high.30 This is surprising as Sabah is known to have sufficient supply of seafood sources throughout different levels of society.

In Kuala Lumpur, although the hospital is situated in an urban location, the mean monthly household income is approximately RM 5000 (equivalent to USD 1200).31 This is high.30 This is surprising as Sabah is known to have sufficient supply of seafood sources throughout different levels of society.

We used the recommended guidelines of 10-15 mcg/kg at diagnosis and adjustment was made according to biochemical levels.15,32 Children with transient hypothyroidism were given a lower dose, which was found to be adequate enough to suppress the mildly elevated TSH. However, there was no statistical difference in the median TSH level. This data suggests that as clinicians, although one can easily suspect a case with thyroid dysgenesis, one should not assume or predict the diagnosis without proper diagnostic testing. In our centre and in Malaysia generally, the diagnostic test can only be done at the age of 2-3 years old after stopping thyroxine for 4-6 weeks.

At diagnosis, children with thyroid dysgenesis and dyshormonogenesis were relatively given higher doses as compared to children with transient hypothyroidism. We used the recommended guidelines of 10-15 mcg/kg at diagnosis and adjustment was made according to biochemical levels.15,32 Children with transient hypothyroidism were given a lower dose, which was found to be adequate enough to suppress the mildly elevated TSH. However, there was no statistical difference in the median TSH level. This suggests that clinicians are following general guidelines of treating CHT regardless of cord blood TSH levels. Further analysis on the titration of dosages and timing for TSH to normalise may give more insight to clinicians to treat CHT regardless of cord blood TSH levels. In our centre and in Malaysia generally, the diagnostic test can only be done at the age of 2-3 years old after stopping thyroxine for 4-6 weeks.

By the time these children were 3 years old, children with dysgenesis and dyshormonogenesis remained on slightly higher dose as compared to those with transient hypothyroidism. However, our data was not significant enough to suggest that children on lower doses would likely be transient. Titrating doses according to TSH trends were performed regularly. None had a trial of stopping thyroxine despite using lower doses due to fear of potential neurocognitive impairment.

The next question is whether stopping treatment earlier for children whom we suspect have transient hypothyroidism can be safely done. From this report, we do know that they usually present later, are mostly asymptomatic, and required relatively lower doses. JCEM 2014 guidelines suggests re-evaluation after stopping thyroxine preferably after 3 years of life, however earlier retesting may be possible in cases suspected with transient hypothyroidism. Bloods should be repeated after 2 weeks of stopping and monitored regularly.34

We would suggest clinicians, especially general paediatricians in Malaysia, to consider titrating further and stop thyroxine earlier (before 3 years old) in children suspected with transient hypothyroidism. This should be done under proper monitoring and guidance of an experienced paediatric endocrinologist.

CONCLUSION

The most common type of CHT seen were thyroid dyshormonogenesis followed by thyroid dysgenesis and transient hypothyroidism. Children with thyroid dysgenesis may present after 2 weeks of life. The most common type of CHT seen were thyroid dyshormonogenesis followed by thyroid dysgenesis and transient hypothyroidism. Children with thyroid dysgenesis may present after 2 weeks of life. One in 5 children who were treated for CHT had transient hypothyroidism. Given that the prevalence of transient hypothyroidism is common, clinicians may consider withholding or tapering off thyroxine earlier than 3 years old with careful assessment and diligent monitoring.

This study provides clinicians with practical information to understand the possible aetiologies of CHT from a patient’s clinical presentation, biochemical markers and treatment regime. Although genetic mutations for thyroid dysgenesis and dyshormonogenesis are available in some centres worldwide, funding and opportunity may not be sufficient for most centres in Malaysia to proceed with genetic diagnosis.

Statement of Authorship

All authors certify fulfillment of ICMJE authorship criteria.

Author Disclosure

The authors declare no conflict of interest.

Funding Source

None.

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