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Transient congenital hypothyroidism in Tunisia : A descriptive retrospective study

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ABSTRACT

Background : Congenital hypothyroidism (CH) is the most common preventable causes of intellectual disability. About 71% of babies worldwide are born in areas without establish newborn screening program; our country is one of those who have not yet established this program. The purpose of this study was to determine risk factors of transient CH compared to permanent CH and its etiologies.

Methods : Retrospective study in the pediatric and neonatology department of Mongi Slim Hospital was conducted between January 1999 and December 2018. All neonates and infants followed for CH were included in this study; cases of central CH were not included in this work; patients lost to follow-up were excluded from this study.

Results : A total of 53 patients were diagnosed with CH, of whom 43 patients (81%) were diagnosed with permanent CH and 10 (19%) with transient hypothyroidism. Prematurity was higher in the transient group (p = 0.05), whereas consanguinity was more frequent in infants with permanent CH (p = 0.034). Transient CH was associated with lower initial TSH levels than permanent hypothyroidism (p = 0.04). Infants who received lower L-thyroxine doses were likely to have transient CH, and it was statistically significant, as shown in table 2. We also found that time to normalize thyroid function is shorter in the transient group. The reported etiologies of transient CH were similar to that recorded in other studies.

Conclusion : The preliminary data from our study revealed that prematurity, low initial mean TSH levels, low mean L-thyroxine dose and short time to notmalize thyroid function are predictive of transient CH.

Keywords : congenital hypothyroidism, transient, permanent, L-thyroxine.

INTRODUCTION

Congenital hypothyroidism (CH) is the most common preventable causes of intellectual disability (1). About 71% of babies worldwide are born in areas without establish newborn screening (NBS) program, despite the existence of screening over 50 years (2). Our country is one of those who have not yet established NBS program. The need of thyroid hormone supplementation can be permanent or transient (3). Infants with transient CH have deficiency with thyroid hormone which is temporary and improve to normal thyroid hormone levels usually in few months (4). Permanent dysfunction mainly results from mal-development, absence or ectopic thyroid gland; whereas the underlying causes of transient functional impairment are less clear (5). The purpose of this study was to determine risk factors of transient CH compared to permanent CH and its etiologies.

METHODS

Retrospective study in the pediatric and neonatology department of Mongi Slim Hospital of Tunisia was conducted between January 1999 and December 2018. All neonates and infants followed for CH were included in this study. In the absence of NBS program, the diagnosis of CH have been retained if the symptoms started before the age of 6 months or if the diagnosis was made systematically when there are risk factors. Cases of central CH were not included in this work. Patients lost to follow up were excluded from this study. Patient data was collected: demographic characteristics, clinical manifestations, laboratory data, imaging results and follow-up. A first sample (TSH and FT4) was obtained as soon as the diagnosis was suspected. A second sample is performed at least in the week, if the first assessment was pathological according to pediatric reference intervals for thyroid hormone levels reported by Kapelari et al (6). TSH and FT4 values were interpreted according to the gestational term and postnatal age. Treatment was initiated immediately if the second assessment was pathological. All patients had thyroid ultrasound and in those aged over 3 years scintigraphy was performed. Follow-up visits were regular and included

anthropometric assessment, clinical examination, TSH/FT4 levels, skeletal age determination using Greulich-Pyle standard and neuro-developmental status. Discontinuation of replacement treatment was tried between 24 and 36 months of age when transient CH was suspected. After 4 weeks of discontinuation of thyroxin treatment, TSH/FT4 levels were checked to ensure normal thyroid function; those patients with normal test results were considered to be transient case. Yet, they must be followed closely and monitored for hypothyroidism signs and symptoms. Patients proved to have permanent hypothyroidism continued levothyroxine therapy and the dose was adjusted according to clinical and laboratory follow-up.
Statistical study was conducted using median for quantitative variables and percentage for qualitative variables. Comparison between groups was done using Mann Whinney test for quantitative variables, chi square test and Fisher's exact test for qualitative variables. P values equal to or less than 0.05 were considered statistically significant.

RESULTS

A total of 53 patients were diagnosed with congenital hypothyroidism during the study period. 39 (77%) of whom were diagnosed in the neonatal period. The median age of diagnosis was 44 +/- 6 days (IQ: 3 – 180) and the male to female ratio was 1.26. Parental consanguinity was present among 40% of all cases. 43 (81%) were determined to have permanent CH and the remaining ten patients (19%) were diagnosed with transient CH. The median age of diagnosis in the transient group was 17 days (5 – 30 days). The demographic characteristics and perinatal data of the patients with permanent and transient CH are presented in table 1.

Tableau 1 : Demogarphic characteristics of neonates with permanent and transient CH.

	Transient CH N = 10	Permanent CH N = 43	P value
Sex ratio (M/F)	1	1.26	0.5
Weight (g)	2665 ± 781.6	3012 ± 654.5	0.2
Intrauterine growth restriction	8 (80%)	35 (81%)	0.6
Prematurity*	5 (50%)	8 (18%)	0.05
Consanguinity*	1 (10%)	20 (46%)	0.034
history of thyroidism in mother	3 (30%)	7 (16%)	0.3

CH: congenital hypothyroidism
M: male F: female
p < 0.05

We found that prematurity was higher in the transient group, whereas, consanguinity was more frequent in infants with permanent CH. Laboratory findings, treatment and follow-up data are presented in table 2.

Tableau 2 : Laboratory findings and treatment in neonates with permanent and transient CH.

		Transient CH N = 10	Permanent CH N = 43	P value
Mean TSH level at first measurement (µUI/ml)*		10.98 ± 3.961	78.63 ± 145.687	0.04
TSH level at first measurement < 20 (µUI/ml)*		10 (100%)	21 (48%)	0.003
Mean FT4 level at first measurement (pmol/l)		6.5 ± 2.279	7.9 ± 5.872	0.2
FT4 level at first measurement < 5 (pmol/l)		2 (20%)	19 (44%)	0.2
Mean daily dose of Levothyroxin (µg/Kg/j)*	First year *	1.80 ± 0.240	4.92 ± 1.649	<0.001
	Second year *	1.30 ± 0.149	3.62 ± 1.299	<0.001
	Third year *	1.05 ± 0.233	2.71 ± 0.940	<0.001
Time to normal thyroid function (days) *		19.50 ± 4.743	50.15 ± 36.467	<0.001

CH: congenital hypothyroidism
TSH: thyroid stimulating hormone
FT4: free thyroxine
p < 0.05

The first sample TSH levels were significantly lower in transient cases than permanent cases. Infants who received lower L-thyroxine doses were likely to have transient CH, and it was statistically significant, as shown in table 2. We also found that time to normalize thyroid function is shorter in the transient group.
In all patients with transient CH, thyroid ultrasound, scintigraphy and bone maturation measurements were performed. Thyroid ultrasound showed heterogeneous goiter in one patient, and it was a normal thyroid gland in all the others. Scintigraphy findings were a low uptake of radioactive in two patients. Only one case of delay bone maturation at the first evaluation was reported. The reported etiologies of transient CH were fetal iodine exposure in 2 cases (a mother have been treated with radioactive iodine for papillary thyroid carcinoma, the other mother had a CT scan of the chest with contrast during pregnancy), transient hypothyroxinemia of prematurity (THOP) was retained in one patient, intrauterine exposure to antithyroid drugs was observed in one case , it was related to the transplacental passage of maternal immunoglobulin G (Ig G) that contains antibodies to the TSH receptor (TRAb) in one patient; however, no cause of transient CH was identified in the other five patients.

DISCUSSION

The incidence of transient CH has seen a marked increase in recent years, which justifies a systematic reassessment after the age of 3 years under hormonal

treatment, of all CH with in situ thyroid gland (3, 7).
In our study, the incidence of transient CH was 19% of cases of CH and 27% of cases of CH with in situ thyroid gland. In the study of Ordookhani el al, of a 35 neonates with primary CH, 25 (71.4%) had permanent CH, 6 (7%) had transient CH and 4 cases were unclassified (8). In a study conducted in Egypt by Bekhit et al, of the 248 patients diagnosed with CH, 204 (82.3%) patients were diagnosed to have permanent CH and 44 (17.7%) patient were diagnosed to have transient CH (9). Incidence of transient CH was 28% in United States as reported by Korzeniewski et al (10) and Mitchell et al (11). In our study, the male to female ratio was 1.26 in all cases of CH and 1 in cases with transient CH.
The male to female ratio was 1.2 and 1.4 in permanent and transient CH respectively, as reported by Bekhit et al (9); however, other studies reported higher incidence among females compared to males (8, 12). The rate of parental consanguinity among patients diagnosed with permanent CH was higher than those with transient CH in our study; these same data were also observed by Ordookhani et al (8), but do not agree with the findings of Bekhit et al (9). Preterm babies are more susceptible to transient hypothyroidism, and the incidence of THOP increases with decreasing gestational age (13). In addition, according to some reports, prematurity is a risk factor for transient CH (14, 15).
In our population, prematurity was a predictive factor of transient form of CH. However, we did not observe a significant correlation between intrauterine growth restriction and the transient nature of CH. These data do not agree with those in the literature; in addition, a study conducted by Korzeniewski et al et al, concluded that the odds of treatment cessation at follow-up were significantly elevated in nonwhite children, those born low birth weight and those admitted to the NICU after birth (10). In our study, the mean TSH levels before treatment were significantly lower in the patients with transient CH than in those with permanent CH.
This finding has been also reported by Hashemipour et al (3) in a study from Iran, by Nair et al (16) in a study from India and by Bekhit et al (9) from Egypt. However, in the study by Silva et al in Brazil (17), carried out to assess the characteristics and etiologies of congenital transient hypothyroidism, the TSH initial levels were not relevant to determine whether the thyroid dysfunction was transient or permanent. We noted that the mean T4 levels before starting treatment was not significantly different among patients with permanent or transient CH, the same findings are observed in studies from Iran (3) and Egypt (9); whereas, initial T4 levels were correlate with the etiology of CH as shown by Kempers et al (18). According to our data, the mean dose of levothyroxin was much higher among patients with permanent CH than those with transient CH. These findings were in accordance with other studies (6, 19). Diagnosis of transient hypothyroidism is important to avoid lifelong unnecessary therapy with its possible side effects. According to the current guidelines, majority of preterm infants in whom hypothyroidism is most likely transient are treated 3 years.
We know also that transient CH should be treated since there are severe long term consequences for untreated infants with long term morbidities (5), another study showed that infants who are likely to have transient CH, might be re-evaluated at 12 or 24 months rather than 3 years of age (6). Finally, specific guidelines for the diagnosis, treatment and follow-up for transient hypothyroidism are critically needed (5). The preliminary data from our study revealed that the incidences of CH as well as the transient form were similar to worldwide reports.
The etiologies behind the cases of transient CH remained undetermined in half of our patients. Several causes, including environmental, geographic (households consuming iodized salt), genetic or ethnic factors could provide more explanation. Through our results, we concluded that transient CH was associated with prematurity and that low initial TSH levels are predictive of transient form of CH. Moreover, we concluded that infants with CH requiring lower L-thyroxin doses are likely to have transient CH. In the other side, consanguinity is predictive of permanent CH.

CONCLUSION

In view of our results, we recommended that reevaluation of thyroid function should be performed in infants with factors suggesting a transient form of CH, namely prematurity and low initial TSH levels.
Infants who required low doses of L-thyroxin are also considered to have a transient form of CH. Ideally, the reassessment should be done at the age of 3 years to avoid possible neurocognitive impairments. Further studies are needed to present a rational approach to identifying patients with transient CH.

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