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Predictive value of technetium-99m sodium pertechnetate thyroid scintigraphy in determining the permanence of congenital hypothyroidism

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ABSTRACT

Objectives: We aim to investigate the predictive value of [^{99m}Tc] pertechnetate thyroid scintigraphy in determining the permanence of congenital hypothyroidism (CH).

Material and Methods: A retrospective analysis of [^{99m}Tc] pertechnetate thyroid scans performed for evaluation of CH at the Nuclear Medicine Unit of a hospital in Hong Kong between January 1, 2008, and December 31, 2018, was conducted. Scintigraphic findings and parameters at diagnosis, including thyroid stimulating hormone (TSH), free thyroxine (fT4), gender, and gestational age, were reviewed. The need for lifelong thyroxine replacement therapy was reviewed.

Results: The study included 85 subjects, with 74 (87.1%) presenting with eutopic thyroid and 11 (12.9%) showing thyroid dysgenesis. Patients with scintigraphic evidence of thyroid dysgenesis required permanent thyroid hormone replacement therapy. Among the patients with eutopic thyroid, a higher TSH level was associated with the need for lifelong thyroid hormone replacement therapy (cutoff TSH value 18.72 mIU/L, sensitivity 77.3% and specificity 53.8%). Gender, gestational age, and fT4 did not show significant differences between the transient and permanent CH groups in patients with eutopic thyroid.

Conclusion: Scintigraphic findings of thyroid dysgenesis indicate a high prevalence of permanent CH. In patients with eutopic thyroid, higher TSH levels predict the requirement for lifelong thyroid hormone replacement therapy. These results provide insights into the prediction of CH and aid in individualized treatment decisions for patients with CH.

Keywords: Technetium-99m pertechnetate, Thyroid scintigraphy, Congenital hypothyroidism, Pediatric nuclear medicine

INTRODUCTION

Congenital hypothyroidism (CH) is the most common congenital endocrine disorder, affecting both pre-term and term infants with an incidence of 1:2404 in Hong Kong.[1] Early diagnosis of primary CH and timely thyroxine replacement therapy for neonates with confirmed CH have been proven effective to avoid intellectual disability. Technetium-99m (^{99m}Tc) sodium pertechnetate thyroid scintigraphy is a recommended imaging technique for evaluating the location of

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functioning thyroid tissue. It can also help determine the cause of CH, such as dyshormonogenesis, ectopia, or athyreosis. The latest consensus guidelines endorsed by the European Society for Pediatric Endocrinology and the European Society for Endocrinology recommend the use of imaging to differentiate CH into its subtype at the time of diagnosis,[2] in addition to biochemical tests and ultrasonography of the neck.[3,4] At our center, [^{99m}Tc] pertechnetate thyroid scans are performed for newborns with biochemically confirmed CH before starting thyroid hormone replacement therapy. We aim to investigate the predictive value of [^{99m}Tc] pertechnetate thyroid scintigraphy for the permanence of CH.

MATERIAL AND METHODS

Case enrolment

We retrospectively analyzed [^{99m}Tc] pertechnetate thyroid scintigraphy performed for evaluation of CH at the Nuclear Medicine Unit of a hospital in Hong Kong between January 1, 2008, and December 31, 2018. Electronic patient records and radiology information systems were used for data retrieval. The study included patients with confirmed primary CH who were subsequently placed on thyroxine replacement therapy. Exclusion criteria are as follows: (1) non-elevated thyroid-stimulating hormone (TSH) before the scintigraphy, (2) on thyroxine replacement therapy before the thyroid scintigraphy, (3) hypothyroidism explained by maternal diseases, (4) hypothyroidism explained by antibodies or medications, and (5) patients lost to follow-up within 3 years after the thyroid scintigraphy.

Procedure and acquisition of thyroid scintigraphy

Patients with CH did not require any special preparation. Intravenous injection of [^{99m}Tc] pertechnetate at a dose of 5.6 MBq/kg (minimum dose of 7.4 MBq) was administered. Anterior planar view of the neck for thyroid scintigraphy was obtained 15–20 min after radiopharmaceutical injection, using a pinhole collimator with a 15% window centered at 140 KeV and a collimator matrix of 128 × 128. If the functioning thyroid tissue was not visualized in the neck, additional images covering the thorax and lateral images covering the skull base and thorax were acquired using a pinhole collimator and low-energy high-resolution collimator.

Analysis of thyroid scintigraphy

Two nuclear medicine physicians with at least 5 years of experience in molecular imaging evaluated the [^{99m}Tc] pertechnetate thyroid scintigraphy using the viewer (Xeleris version 4.1 Functional Imaging Workstation, GE Healthcare, US). Thyroid eutopia was defined as the visualization of bilateral thyroid activity in the anatomical thyroid bed [example in Figure 1a], and thyroid dysgenesis encompassed thyroid ectopia, hemiagenesis, and athyreosis [examples in Figure 1b-f].

Clinical and biochemical parameters and clinical outcome

Clinical and biochemical parameters, including gender, gestational age, TSH, and free thyroxine (fT4) levels within 1 week of birth and before starting thyroid hormone replacement, were reviewed. All included patients had a minimum follow-up of 3 years in the pediatric department. After 3 years, patients underwent a trial of withholding of levothyroxine, with TSH levels monitored. Those with normalized TSH levels after levothyroxine withdrawal were classified as having transient CH. Those with elevated TSH requiring resumption of levothyroxine after withholding the drug and those requiring levothyroxine to maintain normal TSH level due to athyreosis, without a trial of withholding hormone replacement, were classified as having permanent CH. Patients' information was collected from electronic patient records and the radiology information system.

Statistical analysis

The descriptive statistics of the patients were reported according to their frequencies or their median. Data were tested with the Kolmogorov–Smirnov test for normality. Comparative analyses were conducted between the thyroid eutopia group and thyroid dysgenesis group based on the scintigraphic findings, and further subgroup analyses were done in the thyroid eutopia group. The Chi-square test or Fisher exact test was used to compare categorical variables. An independent t-test or Mann–Witney U-test was used to compare the continuous parameters. A receiver-operating characteristic (ROC) curve was generated to determine the optimal cutoff TSH level for predicting the permanence of CH. The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) Statistics (IBM SPSS Statistics for Macintosh, Version 29.0.1.0. Armonk, NY: IBM Corp). All hypothesis tests were two-sided with $P < 0.05$ considered statistically significant.

Ethical standards

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Research Ethics Committee (Kowloon Central/Kowloon East Cluster) of the Hospital Authority, Hong Kong (Reference number: KC/KE-21-0213/ER-1). Informed consents were waived.

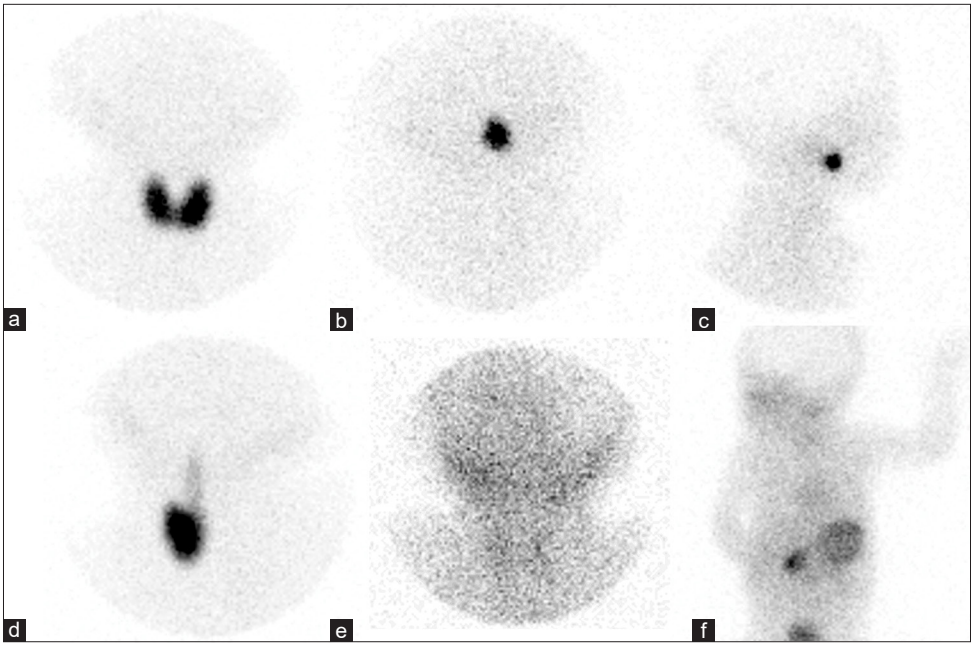

Figure 1: (a) [^{99m}Tc] pertechnetate thyroid scan showed marked bilateral thyroid lobe activity in the neck. This suggested thyroid eutopia. (b and c) [99mTc] pertechnetate thyroid scan showed a marked focal activity in the sublingual region, while there was no activity in the anatomical thyroid bed. This suggested thyroid dysgenesis (thyroid ectopia). (d) [^{99m}Tc] pertechnetate thyroid scan showed an absent left thyroid lobe, as evidenced by ultrasonography. This suggested thyroid dysgenesis (hemiagenesis). There was tubular activity in the upper to mid-neck, persistent after drinking water (images not shown), likely representing thyroglossal duct. (e and f) [^{99m}Tc] pertechnetate thyroid scan showed no thyroid activity in the neck and the absence of thyroid tissue was confirmed with ultrasonography. This suggested thyroid dysgenesis (athyreosis).

RESULTS

Patients' characteristics

During the study period, a total of 85 patients with [^{99m}Tc] pertechnetate thyroid scans performed were included in this study after reviewing the cases. Among them, 42 were female (49.4%) and 43 were male (50.6%). The [^{99m}Tc] pertechnetate thyroid scans revealed that 74 patients (87.1%) had thyroid eutopia, 9 patients (10.6%) had thyroid ectopia, 1 patient (1.2%) had thyroid hemiagenesis, and 1 patient (1.2%) had athyreosis. Cases of hemiagenesis and athyreosis were confirmed through neck ultrasonography. Examples of scintigraphic images are shown in Figure 1. During the follow-up period, 52 patients (61.2%) were successfully weaned off thyroxine replacement after at least 3 years of treatment, whereas 33 patients (38.8%) required lifelong thyroxine replacement due to persistently elevated TSH levels after a trial of withholding levothyroxine. Table 1 provides an overview of patient demographics, gestational age, TSH and fT4 levels before thyroxine replacement therapy, scintigraphic patterns, and the permanence of CH.

Comparison between thyroid eutopia group and thyroid dysgenesis group

Based on the scintigraphic findings, patients were divided into two groups: the thyroid eutopia group (visualization of a bilobed thyroid in the anatomical thyroid bed) and the thyroid dysgenesis group (including cases of eutopia, hemiagenesis, and athyreosis). In all patients with thyroid dysgenesis, permanent thyroid hormone replacement was required. A comparison between the two groups revealed a significant association between thyroid dysgenesis and permanent CH ($P < 0.001$). In addition, patients with thyroid dysgenesis had higher TSH levels (161.0 mIU/L vs. 23.5 mIU/L, $P < 0.001$) and lower fT4 levels (10.7 pmol/L vs. 15.9 pmol/L, $P = 0.021$). Furthermore, a significant association was found between female gender and thyroid dysgenesis ($P = 0.021$). However, no significant association was observed with gestational age. Table 2 provides detailed information on these comparisons.

Subgroup analysis of scintigraphic thyroid eutopia

Among patients with thyroid eutopia on the scintigraphy, 52 patients (70.3%) presented with transient CH, whereas

Table 1: Patient demographics, gestational age, TSH, and fT4 level before thyroxine replacement therapy, scintigraphic patterns, and clinical outcome (permanence of CH).

Number of patients	**85 (%)**
Gender	
Female	42 (49.4)
Male	43 (50.6)
Gestational age	
<38 weeks	19 (22.4)
≥38 weeks	66 (77.6)
TSH level (mIU/L)	27.1
fT4 (pmol/L)	15.2
Scintigraphic findings	
Thyroid eutopia	74 (87.1)
Thyroid ectopia	9 (10.6)
Thyroid hemiagenesis	1 (1.2)
Athyreosis	1 (1.2)
Clinical outcome	
Transient CH	52 (61.2)
Permanent CH	33 (38.8)

CH: Congenital hypothyroidism, TSH: Thyroid-stimulating hormone, fT4: Free thyroxine

Table 2: Comparison between thyroid eutopia group and thyroid dysgenesis group.

	Thyroid eutopia	**Thyroid dysgenesis**	***P*-value**
Number of patients	74	11	
Gender			***P*=0.021**
Female	33	9	
Male	41	2	
Gestational age			*P*=0.442
<38 weeks	18	1	
≥38 weeks	56	10	
TSH level (mIU/L)	23.5	161.0	***P*<0.001**
fT4 (pmol/L)	15.9	10.7	***P*=0.021**
Clinical outcome			***P*<0.001**
Transient CH	52	0	
Permanent CH	22	11	

Bold indicates statistically significant results (*P*<0.05). CH: Congenital hypothyroidism, TSH: Thyroid-stimulating hormone, fT4: Free thyroxine

22 patients (29.7%) had permanent CH. Patients with permanent CH exhibited significantly higher TSH levels (31.9 mIU/L vs. 17.9 mIU/L, $P = 0.011$). Gender, gestational age, and fT4 levels were not significantly associated with permanent CH ($P = 0.354$, $P = 0.163$, and $P = 0.969$, respectively). Subgroup analyses of the thyroid eutopia group are presented in Table 3. A ROC curve analysis [Figure 2] was conducted to determine the optimal cutoff value of TSH level for predicting the permanence of CH in patients with thyroid eutopia on [^{99m}Tc] pertechnetate thyroid scintigraphy. The area under the curve (AUC) was found to be 0.688 (95% confidence interval: 0.566–0.811, $P = 0.003$). With a cutoff value of TSH level 18.72 mIU/L, it showed a sensitivity of 77.3% and specificity of 53.8% to predict permanent CH in patients in thyroid eutopia group.

Table 3: Subgroup analysis of thyroid eutopia group.

	Transient CH	**Permanent CH**	***P*-value**
Number of patients	52	22	
Gender			*P*=0.354
Female	25	8	
Male	27	14	
Gestational age			*P*=0.163
<38 weeks	15	3	
≥38 weeks	37	19	
TSH level (mIU/L)	17.9	31.9	***P*=0.011**
fT4 (pmol/L)	15.9	16.1	*P*=0.969

Bold indicates statistically significant results (P<0.05). CH: Congenital hypothyroidism, TSH: Thyroid-stimulating hormone, fT4: Free thyroxine

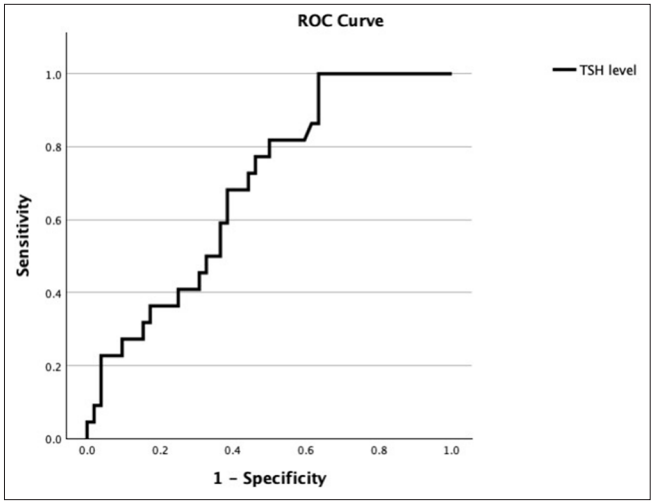

Figure 2: A receiver operating characteristic (ROC) curve analysis to determine the optimal cutoff value of thyroid stimulating hormone (TSH) level for predicting the permanence of congenital hypothyroidism in patients with thyroid eutopia on [^{99m}Tc] pertechnetate thyroid scintigraphy. The area under the curve (AUC) was found to be 0.688 (95% confidence interval: 0.566–0.811, *P*=0.003), with a cutoff TSH level of 18.72 mIU/L, showing sensitivity of 77.3% and specificity of 53.8%.

DISCUSSION

CH is a relatively common endocrine disorder characterized by deficient thyroid hormone production in newborns.[5,6] It is crucial to detect and treat CH early to prevent adverse outcomes, especially intellectual disability, as thyroid hormones play a vital role in normal growth, brain development, and metabolism.[6] Transient CH refers to a temporary impairment in thyroid hormone production that

resolves spontaneously over time. The etiology of transient CH can vary and includes conditions such as prematurity, iodine deficiency or exposure, maternal antibodies or intakes of antithyroid medications, loss of function mutations, and hepatic hemangiomas.[7] On the other hand, permanent CH refers to a lifelong insufficiency of thyroid hormone production. Permanent CH can result from various etiologies, including thyroid dysgenesis, such as aplasia or hypoplasia of the thyroid gland, or genetic defects affecting thyroid hormone synthesis or iodine transport.[6] Newborn screening programs have been instrumental in the early detection of CH, typically through measuring TSH levels from umbilical cord blood. Elevated TSH levels prompt further diagnostic evaluation, including serum T4 measurement and imaging.[8] The cutoff values of TSH to diagnose CH generally range from 10 to 20 mIU/L in different countries,[2] but as low as 5.5 mIU/L is taken in Turkey.[9] In our center, patients with persistently elevated TSH level higher than 6 mIU/L will be investigated and treated with levothyroxine, compatible with the consensus guidelines.[2]

Ultrasonography of the neck and thyroid scintigraphy with [^{99m}Tc] pertechnetate or [^{123}I]iodine is considered the standard imaging techniques for investigating the etiology of CH, with thyroid scintigraphy being recommended particularly when thyroid dysgenesis is suspected.[8] In this study, we aimed to investigate the predictive value of [^{99m}Tc] pertechnetate thyroid scintigraphy in patients with primary CH, specifically in predicting the clinical outcome as transient CH or permanent CH. The results demonstrated that thyroid scintigraphy is a useful tool for evaluating the etiology of CH.

Our findings showed that patients with thyroid dysgenesis, including ectopic thyroid glands, hemiagenesis, and athyreosis, required permanent thyroid hormone replacement therapy. In contrast, patients with scintigraphic evidence of a normal bilobed thyroid in the anatomical thyroid bed (eutopia) could be further stratified based on their TSH levels. A cutoff TSH level of 18.72 mIU/L was found to predict the need for lifelong thyroid hormone replacement therapy with a sensitivity of 77.3% and specificity of 53.8%. However, gender, gestational age, and fT4 levels did not show significant differences between the transient and permanent thyroxine replacement groups in patients with eutopic thyroid.

Most of the patients in our study presented with eutopic thyroid, and a significant proportion of them (70.3%) were successfully weaned off levothyroxine, indicating transient CH. Among the patients requiring permanent thyroid hormone replacement therapy, a subset showed eutopic thyroid (66.7%), whereas others had thyroid dysgenesis (33.3%). These findings differ from previous literature, which reported a higher percentage, up to 85%, of thyroid dysgenesis among patients with permanent CH and a lower percentage of transient CH (10%) among all patients diagnosed with CH.[10] This discrepancy may be attributed to our center's management approach, which treats patients with persistent mild CH (TSH >6 mIU/L) by following consensus guidelines and administers levothyroxine with monitoring of TSH level, conventionally for 3 years to prevent mental retardation associated with CH,[2] and as a result, our study may include more patients with eutopic thyroid and transient CH in comparison with previous studies.

This research confirmed previous findings that thyroid dysgenesis is more common in females and is associated with higher TSH levels and lower fT4 levels compared to eutopic thyroid cases.[4,11,12] However, we did not consider levothyroxine dosages in our analysis, which shows the predictive value for the permanence of CH in previous studies,[9,13] as our primary aim was to investigate the association between scintigraphic findings at diagnosis and the permanence of CH.

There were limitations to our study. First, it was a single-center retrospective study, which may limit the generalizability of the findings. In addition, the study primarily included Chinese subjects and the applicability of the results to other populations and ethnicities may be limited. Moreover, our sample size is not large, probably explained by the fact that a number of patients had lost follow-up in our hospital within 3 years.

CONCLUSION

Our study highlights the value of [^{99m}Tc] pertechnetate thyroid scintigraphy in evaluating the etiology of CH. The scintigraphic findings can help differentiate between thyroid dysgenesis and eutopic thyroid and predict the need for permanent thyroid hormone replacement therapy. These results provide insights into the clinical outcome prediction of CH with thyroid scintigraphy, and it can aid in individualized treatment decisions for patients with CH. Further studies involving larger and more diverse populations are warranted to validate these findings and explore additional factors that may influence the clinical outcomes of CH.

Ethical approval

The research/study was approved by the Institutional Review Board at the Research Ethics Committee (Kowloon Central/Kowloon East Cluster) of the Hospital Authority, Hong Kong, number KC/KE-21-0213/ER-1, dated November 2, 2021.

Declaration of patient consent

Informed consents were waived by the Research Ethics Committee because of the retrospective nature of this study and no personal data included.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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