The Key Role of Newborn Thyroid Scintigraphy With Isotopic Iodide (123I) in Defining and Managing Congenital Hypothyroidism

Edgar J. Schoen, MD*; Wesley Clapp, MD*; Trinh T. To, BS*; and Bruce H. Fireman, MA‡

ABSTRACT. Background. Thyroid imaging with isotopic iodide (123I) or technetium Tc 99m pertechnetate has been available for decades but is not routinely used in newborn infants diagnosed with congenital hypothyroidism (CH). Among clinicians who believe that presence, absence, or abnormal location of a thyroid does not alter management of CH, imaging is not advocated for anatomic diagnosis of CH.

Objective. To define the role of thyroid scintigraphy in diagnosing and managing newborn CH.

Methods. Retrospective review of 249 confirmed cases of CH seen at a large, group-model managed care organization during the 24-year period extending from September 1978 through December 2002. Neonatal thyroid scintigraphy was performed in 210 cases (86%); 123I was used in 143 cases (68%), and technetium Tc 99m pertechnetate was used in 67 cases (32%). To perform scintigraphy with 123I, 30 to 50 μCi (1.11–1.85 × 106 Bq) of 123I was administered orally; an uptake image was taken in 3 to 6 hours; and, if necessary, another image was taken in 24 hours. For technetium, 0.5 to 1 mCi (1.85–3.7 × 106 Bq) of technetium Tc 99m pertechnetate was administered intravenously with imaging 20 minutes later. Thyroid dysplasia was defined as an absent or ectopic gland requiring lifetime therapy and eutopic thyroid as a normal-appearing thyroid gland in the proper location but possibly malfunctioning and requiring therapy. Scintigraphy interpreter bias due to lack of objective standards. We cannot estimate the true prevalence of transient CH because not all physicians give children with CH a trial off therapy at 2 to 3 years old, even if a eutopic thyroid is shown by 123I scintigraphy. Because therapy with L-thyroxine is simple and inexpensive and the outcome of untreated CH can be devastating, some parents may still not have sufficient sensitivity.

Results. Of the 210 infants with CH receiving scintigraphy, 90 (43%) had eutopic (normal-appearing) thyroid diagnosed, and 120 (57%) had ectopic or absent gland (25% eutopic, 32% absent) diagnosed. Of these 210 infants, ethnicity was known in 198; of these, 76 (38%) were Latino/Hispanic, and 122 (62%) of the infants were non-Latino/non-Hispanic. Prevalence of CH differed between ethnic groups in our population of >700 000 newborn infants; total prevalence of CH was 1 per 3139. Prevalence of CH in Latino/Hispanic infants was highest at 1 per 1750 infants (1:1357 females, 1:2463 males). Prevalence of CH in non-Latino/non-Hispanic infants was 1 per 4648 infants (1:3500 females, 1:6914 males). Given that the total Kaiser Permanente infant population was ~19% Latino/Hispanic, the percentage of Latino/Hispanic infants with CH was significantly higher than expected. Dysplastic thyroid was more common in Latino/Hispanic females (69%) than in non-Latino/non-Hispanic females (52%). The female-to-male ratio of patients with CH was 1.9:1. Among the 210 infants with CH, normal thyroid was diagnosed more by 123I scintigraphy (49% of cases) than by scintigraphy using technetium Tc 99m pertechnetate (31% of cases). Use of technetium Tc 99m pertechnetate could have diagnosed dysplastic thyroid in some cases that would be considered eutopic had 123I been used. Eight familial cases of CH were identified.

Comments. CH, a heterogeneous disorder with prevalence influenced by familial, ethnic, and gender factors, is more common in Latino/Hispanic females. When present, a eutopic thyroid is more likely to be detected by 123I scintigraphy; this method is therefore preferred over scintigraphy using technetium Tc 99m pertechnetate for optimal management of CH. Parents can then be counseled on either the certainty of lifetime therapy (for dysplastic thyroid) or the possibility of later discontinuing therapy (for eutopic thyroid, because CH may be transient in these children). If the dysplastic thyroid gland is not present, a eutopic thyroid is more likely to be detected by 123I scintigraphy. Because therapy with LT₄ is simple and inexpensive and the outcome of untreated CH can be devastating, some parents and physicians are reluctant to discontinue treatment in children with CH, even when scans show a eutopic thyroid. Additionally, the clinical information contained in our database was not detailed enough to enable us to discover all cases of CH in which thyroxine therapy was discontinued. Because the study began in 1978 (>25 years ago), some patients were unavailable for long-term follow-up.

From the *Department of Genetics, Kaiser Permanente Medical Center, and Kaiser Permanente Northern California Perinatal Screening Program, Oakland, California; and the ‡Division of Research, Kaiser Permanente Northern California Region, Oakland, California. Accepted for publication Aug 16, 2004. doi:10.1542/peds.2004-0803

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Reprint requests to (E.J.S.) Department of Genetics, Kaiser Permanente Medical Center, 280 W MacArthur Blvd, Oakland, CA 94611. E-mail: edgar.schoen@kp.org

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In addition to allowing a more rational clinical approach to CH, $^{123}$I thyroid scintigraphy may help define underlying genetic factors and mechanisms of thyroid development and differentiation. This study’s findings, that prevalence of CH and of thyroid dysplasia differed between genders and among racial/ethnic groups, seem to support a genetic basis for CH. Our results confirm previously published reports from the State of California Department of Health Services, Genetic Disease Branch and other studies describing multiple genetic abnormalities associated with CH.

Conclusions. Despite data limitations, we believe that neonatal diagnosis of CH represents perhaps the greatest success of newborn screening programs. Initial laboratory diagnosis is simple and sufficiently accurate; treatment is simple, inexpensive, and effective. Severe mental retardation and growth failure can be prevented.

Considering today’s rapid advances in understanding the basic mechanisms of thyroid embryogenesis and gene abnormalities, thyroid scintigraphy may provide insight into clinical and genetic correlates in CH. Pediatrics 2004;114:e683–e688. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-0803; hypothyroidism/congenital, iodide; KP, Kaiser Permanente; TSH, thyrotropin.

METHODS

Kaiser Permanente (KP) is a group model managed care organization with a current membership of 3.2 million in its Northern California region. Since 1978, KP has routinely screened newborn infants for CH as part of the mandatory California State Department of Health Services newborn screening program under the Genetic Disease Branch.

Initial screening, laboratory confirmation, and clinical management were performed through the KP Regional Newborn Screening Program. The KP Northern California Institutional Review Board approved the study. Laboratory testing by the KP Regional Laboratory was performed using equipment, reagents, and methodology supplied by the California Genetic Disease Branch. In the period from September 1, 1978, to December 31, 2002, 700 013 infants born at KP were screened, of which 223 (1:3139) were confirmed cases of CH (repeat blood thyrotrpin [TSH] value ≥ 25 μU/mL). Twenty-six additional infants with CH who were born elsewhere were transferred to KP, bringing the total cases of confirmed CH to 249. Of these 249 cases, 210 (84%) had neonatal thyroid scintigraphy, 143 (68%) by using $^{123}$I and 67 (32%) by using technetium Tc 99m pertechnetate.

To perform scintigraphy with $^{123}$I, 30 to 50 μCi ([1.11–1.85] × 10$^6$ Bq) of $^{123}$I was administered orally; an uptake image was taken in 3 to 6 hours; and, if necessary, another image was taken in 24 hours. For technetium imaging, 0.5 to 1 mCi ([1.85–3.7] × 10$^6$ Bq) of technetium Tc 99m pertechnetate was administered intravenously, and an image was taken 20 minutes later. Thyroid dysplasia was defined as an absent or ectopic gland requiring lifetime therapy, and eutopic thyroid was defined as a normal-appearing thyroid gland in the proper location but possibly nonfunctioning and thus also requiring therapy. No clinical differences existed between the cohort scanned with $^{123}$I and that in which technetium Tc 99m pertechnetate was used. We encourage nuclear medicine departments within KP to use $^{123}$I because thyroid cells alone are responsible for $^{123}$I uptake but a variety of tissues take up technetium Tc 99m pertechnetate. However, in 32% of cases, technetium Tc 99m pertechnetate was used because (1) $^{123}$I was unavailable at the time of the scan (for example, on a weekend); (2) technetium Tc 99m pertechnetate was more readily available; (3) technetium Tc 99m pertechnetate was preferred by the nuclear medicine physician; or (4) some other decision by the individual nuclear medicine department was made that was unrelated to clinical criteria.

Methods of statistical analysis included the $\chi^2$ and Fisher’s exact test (when frequency in at least 1 cell was <6). A $P$ value of <.05 was considered significant. SAS version 8.2 (SAS Institute, Cary, NC) was used to perform all statistical analyses.

RESULTS

Of the 210 infants with CH who received scintigraphy (Table 1), 90 (43%) had a normal-appearing (eutopic) thyroid gland, and 120 (57%) had a dys-

| TABLE 1. Characteristics of 210 Infants With Neonatal CH |
|-----------------|-----------------|-----------------|
| CH | Eutopic Thyroid, $N$ (%) of Infants | Dysplastic* Thyroid |
| Scan type | | |
| $^{123}$I | 143 (68) | 69 (48) | 74 (52) |
| Technetium | 67 (32) | 21 (31) | 46 (69) |
| Groups | | | |
| Latino/Hispanic† | 76 (38) | 25 (33) | 51 (67) |
| Non-Hispanic† | 122 (62) | 59 (48) | 63 (52) |
| Latino/Hispanic female† | 49 (38) | 15 (31) | 34 (69) |
| Non-Hispanic females | 81 (62) | 42 (52) | 39 (48) |
| Total cases | 210 (100) | 90 (43) | 120 (57) |

Scintigraphy results data are expressed as number (% of cases). *Dysplastic includes absent and ectopic thyroid (32% absent, 25% ectopic).* †Race/ethnicity was not known for 12 cases. No statistical difference existed between the female-to-male ratio overall (1:9.1), for Latino/Hispanic infants (1:8.1), or for non-Latino/non-Hispanic infants (2:0.1).

ABBREVIATIONS. CH, congenital hypothyroidism; $^{123}$I, isotopic iodide; KP, Kaiser Permanente; TSH, thyrotropin.
plastic thyroid (absent, 32%; ectopic, 25%). Ethnicity was known in 198 of the 210 infants with CH, and marked differences in prevalence existed between groups. Of the 210 infants with CH, 76 (38%) were Latino/Hispanic, and 122 (62%) of the infants were non-Latino/non-Hispanic. The KP infant population is ~19% Latino/Hispanic; therefore, the percentage of Latino/Hispanic infants with CH was significantly higher than expected (P < .0001). More females than males had CH. Overall prevalence of CH in this cohort of >700,000 newborns was 1 per 3139 newborns. However, prevalence of CH in Latino/Hispanic infants was highest at 1 per 1750 newborns (1:1357 females, 1:2463 males). Prevalence of CH in non-Latino/non-Hispanic infants was 1 per 4648 newborns (1:3500 females, 1:6914 males). Female Latino/Hispanic infants, the group with the highest prevalence of CH, had dysplastic glands more often than did non-Latino/non-Hispanic females (P = .02).

In our 210 cases of CH, scintigraphy using 123I statistically more often showed eutopic thyroid (48%) than did scintigraphy using technetium Tc 99m pertechnetate (31%) (P = .02). These results suggested that use of technetium Tc 99m pertechnetate led to the diagnosis of dysplastic thyroid in some cases that may have been considered eutopic had 123I been used.

Infants with athyrosis had the highest initial confirmed mean TSH level (255 μIU/mL; range: 67–701 μIU/mL); infants with eutopic thyroid had the lowest mean level (174 μIU/mL; range: 31–594 μIU/mL); and infants with ectopic thyroid had an intermediate mean level (225 μIU/mL; range: 32–743 μIU/mL). However, a large, overlapping range existed; initial TSH levels were higher in some infants with CH and eutopic thyroid than in some infants with athyrosis.

Table 2 summarizes results of 8 cases in 4 families, each having 2 siblings with CH. In 1 Latino/Hispanic family, twin boys both had CH, but their scintigraphy results were discordant: 1 twin scanned with technetium Tc 99m pertechnetate was diagnosed as athyrotic; the other, scanned with 123I, had a eutopic thyroid.

Table 3 summarizes data of 17 children in whom L-thyroxine treatment was never started or was started and later discontinued (transient CH). The number of transient cases is probably underestimated, partly because our database was not capable of tracking and identifying all cases in which thyroid treatment was later discontinued. Because hypothyroidism in newborn infants can be transient, the decision to treat immediately or to wait and retest is based on the physician’s clinical experience and judgment. In 8 of the 9 children with transient CH who received a scan, scintigraphy showed a eutopic thyroid as expected; however, in 1 transient CH case scanned with technetium Tc 99m pertechnetate, ectopic thyroid was diagnosed.

**DISCUSSION**

We believe that newborn thyroid scintigraphy, preferably using 123I, is an integral part of the optimal management of CH. Thyroid scintigraphy using 123I gives the clinician maximal information on the anatomic status of the thyroid. Parents can then be counseled on the certainty of lifetime therapy (for children who have a dysplastic thyroid) or the possibility of later discontinuing therapy (for children who have a eutopic thyroid, because CH may be transient in these cases). If the thyroid gland is absent or ectopic (usually a small sublingual gland), the parents can be told that the infant will need lifetime thyroid therapy. If the thyroid gland is present in the normal position (eutopic), the child may not need permanent treatment if the condition is transient as demonstrated by controlled withdrawal of thyroid at an older age. Parents rightly expect this maximal clinical and laboratory information in the immediate newborn period.

In addition to allowing a more rational clinical approach to CH, 123I thyroid scintigraphy may help define underlying genetic factors and mechanisms of dyshormonogenesis. None of the familial or nonfamilial cases of CH (with eutopic thyroid) had a palpable goiter, although the thyroid might have enlarged if L-thyroxine treatment had not begun in the neonatal period.

**Genetic Basis for CH**

Our study found a difference in prevalence of CH and thyroid dysplasia between genders and among racial/ethnic groups, data that seem to support a genetic basis for CH. Of the 210 infants with CH who received scans, Latino/Hispanic females had the highest prevalence of CH and dysplastic thyroid glands, results that confirm published reports from the California Genetic Disease Branch. In a report of 1300 cases of CH identified from among 5 million infants screened in California, Lorey and Cunningham found CH prevalence of 1:1900 in Latino/Hispanic females compared with 1:3100 in non-Hispanic white females and 1:11 000 in African American/black females; the female-to-male ratio was 2:1 in non-Latino/non-Hispanic white infants and 3:1 in Latino/Hispanic infants. Our overall prev-

**TABLE 2.** Characteristics of 8 Infants With CH in 4 Families

<table>
<thead>
<tr>
<th>Family</th>
<th>Case</th>
<th>Gender</th>
<th>Race/Ethnicity</th>
<th>Scan type</th>
<th>Scan results</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>F</td>
<td>Latino/Hispanic</td>
<td>123I</td>
<td>Athyrotic</td>
</tr>
<tr>
<td>B</td>
<td>2</td>
<td>F</td>
<td>Latino/Hispanic</td>
<td>123I</td>
<td>Athyrotic</td>
</tr>
<tr>
<td>C</td>
<td>1</td>
<td>M</td>
<td>Non-Hispanic white</td>
<td>Technetium</td>
<td>Eutopic</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>M</td>
<td>Non-Hispanic white</td>
<td>123I</td>
<td>Eutopic</td>
</tr>
<tr>
<td>D (twins)</td>
<td>1</td>
<td>F</td>
<td>Non-Hispanic white</td>
<td>Technetium</td>
<td>Eutopic</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>F</td>
<td>Non-Hispanic white</td>
<td>123I</td>
<td>Eutopic</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>M</td>
<td>Latino/Hispanic</td>
<td>Technetium</td>
<td>Athyrotic</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>M</td>
<td>Latino/Hispanic</td>
<td>Technetium</td>
<td>Eutopic</td>
</tr>
</tbody>
</table>
ence rate (1:3159) and the prevalence among our non-Latino/non-Hispanic females were similar to prevalence reported for California. Among Latino/Hispanic females, the prevalence rate in our study (1:1357) was higher than that reported for California (1:1900). These and other differences in prevalence rates may partially be explained by population differences. The characteristics of KP members in California are similar to those of the entire population of California except for underrepresentation of the lower socioeconomic groups in the general California population, because they have lower rates of employment than the KP membership.

In infants with CH, the anatomic status of the thyroid (as determined by neonatal scintigraphy) may help to clarify genetic factors in thyroid development and differentiation. Recent studies have described multiple genetic abnormalities associated with CH. In a study of DNA from patients with permanent and transient CH, Moreno et al. analyzed mutation in the genes for thyroid oxidase 1 (THOX1) and 2 (THOX2) and found that biallelic inactivating mutations in the THOX2 gene were associated with permanent CH and that monoallelic mutations were associated with transient CH. Sunthornthepvarakul et al. described 3 siblings with CH that was associated with mutations in the thyrotropin receptor gene; and after finding a similar case, Biebermann et al. concluded that mutation of this gene may be the cause of a substantial number of cases of CH. These discoveries are recent; future studies will probably add evidence of genetic mechanisms in CH.

Comparing Radioisotopes

We prefer using 123I for thyroid scintigraphy. Nuclear medicine departments may be reluctant to use 123I because it is more expensive than technetium Tc 99m pertechnetate and must be ordered specially, whereas technetium Tc 99m pertechnetate is routinely stocked by nuclear medicine departments and is thus more easily available than 123I. Another difference is that 123I is taken up only by the thyroid, whereas technetium Tc 99m pertechnetate is taken up by many tissues, including salivary glands. During scintigraphy, technetium Tc 99m pertechnetate may be insufficiently concentrated by the thyroid; alternatively, the image may be obscured or distorted by uptake of technetium Tc 99m pertechnetate in surrounding tissues, thus giving the false impression of an ectopic thyroid when a eutopic gland is actually present.

We believe that results of scintigraphy using technetium Tc 99m pertechnetate are valid only for findings of eutopic or absent thyroid gland. In our series, for example, the percentage of athyrotic cases diagnosed using either 123I (29%) or technetium Tc 99m pertechnetate (34%) scans was similar to the 35% prevalence of athyrosis diagnosed solely by technetium Tc 99m pertechnetate scan in 199 cases of CH in an Australian study. However, we found that fewer cases of ectopic thyroid were diagnosed by 123I (22%) than by technetium Tc 99m pertechnetate (31%) scan; the Australian study had an even higher prevalence of ectopic thyroid when technetium Tc 99m pertechnetate was used (53%). This lack of specificity of technetium Tc 99m pertechnetate may explain the low prevalence of ectopic thyroid (12%) described by Connely et al. as well as other reported results of technetium Tc 99m pertechnetate scintigraphy in patients with CH.

The ratio of ectopic/eutopic thyroid in our series was 0.44:1 as diagnosed using 123I scans and 1:0:1 using technetium Tc 99m pertechnetate. In the Australian series, which used only technetium Tc 99m pertechnetate, the ratio was 4.4:1, ~9 times that of our 123I findings (P < .001), and >4 times that of our scans using technetium Tc 99m pertechnetate (P < .01). Although the low prevalence of ectopic thyroid (12%) in the Australian series could partly be explained by the lack of uptake specificity for technetium Tc 99m pertechnetate, the difference in relation to our findings (31% ectopic thyroid prevalence diagnosed using technetium Tc 99m pertechnetate) is more difficult to explain. Demographic factors could be a possible influence; we found a higher prevalence of dysplastic glands in Latino/Hispanic females. The only reference to ethnic or racial difference in the Australian study was the finding of lower prevalence of dysplasia in Middle Eastern patients.

Another possible source of discrepancy could be reader bias: a strong subjective factor exists in new-

### Table 3. Type and Results of Scintigraphy and Clinical Management in 17 Cases of Transient CH With Hyperthyrotropinemia

<table>
<thead>
<tr>
<th>Scan Type</th>
<th>Scan Results</th>
<th>N</th>
<th>Initial TSH range, µIU/mL*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No scan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment†</td>
<td></td>
<td>6</td>
<td>49–153</td>
</tr>
<tr>
<td>Treatment discontinued‡</td>
<td></td>
<td>2</td>
<td>135–144</td>
</tr>
<tr>
<td>Scan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td></td>
<td>4</td>
<td>22–149</td>
</tr>
<tr>
<td>Treatment discontinued‡</td>
<td></td>
<td>5</td>
<td>31–137</td>
</tr>
</tbody>
</table>

* TSH level >25 µIU/mL yielded a diagnosis of hyperthyrotropinemia, and the initial TSH value was confirmed by subsequent testing.
† Patients received no treatment, because the physician suspected hypothyroidism was transient.
‡ Treatment was discontinued when subsequent serum TSH testing showed values within normal limits for patients receiving a very low dose of thyroxine.

NA indicates not applicable; technetium, technetium Tc 99m pertechnetate.

For more information, please refer to the original source.
born scintigram interpretation because objective standards are lacking. Thyroid scintigrams are generally ordered only when laboratory test results suggest CH. If the prevalent view is that eutopic thyroid glands are rare in cases of CH, as is believed in Australia, the interpreter might hesitate to diagnose eutopic thyroid. Because we have found that eutopic thyroid is common in CH,6,12 our nuclear medicine physicians might be more willing to diagnose eutopic thyroid. Increased use of 123I and development of more objective standards for interpreting newborn thyroid scintigrams could help clarify the issue of reader bias.

The possibility of technetium Tc 99m pertechnetate scans misdiagnosing dysplasia in a normal gland had clinical implications in 2 of our cases. The twins with CH both received scans using technetium Tc 99m pertechnetate: 1 boy was diagnosed with athyrosis, and the other boy had a eutopic thyroid. This discordance is possible, but we find it unlikely in our study because scintigraphy results were concordant between siblings in the 3 other sets of siblings with CH. A eutopic thyroid was found in 8 of the 9 cases of transient CH; technetium Tc 99m pertechnetate scintigraphy was used to diagnose the single case of ectopic thyroid, and this patient remained euthyroid after L-thyroxine therapy was discontinued. Although a normal level of hormone production from an ectopic thyroid is conceivable, we believe that a more logical explanation here is that scintigraphy using technetium Tc 99m pertechnetate misdiagnosed a eutopic thyroid as being ectopic.

Study Limitations

Our finding of 17 cases of transient CH with hypothyrotropinemia among 249 cases of CH is misleadingly low. Unfortunately, we cannot estimate the true prevalence of transient CH, because not all physicians give children with CH a trial off therapy at 2 to 3 years old, even if a eutopic thyroid is shown by 123I scintigraphy. Because therapy with L-thyroxine is simple and inexpensive and the outcome of untreated CH can be devastating, some parents and physicians are reluctant to discontinue treatment in children with CH even when scans show a eutopic thyroid. In addition, the clinical information contained in our database was not sufficiently detailed to discover all cases of CH in which thyroxine therapy was discontinued. Because the study began in 1978 (>25 years ago), some patients were unavailable for long-term follow-up. Twenty three of the children in our study were <3 years old and may have been considered too young for a trial off therapy; a few of the eutopic patients in this group may later be found to have transient CH. Despite these data limitations, we believe that most children who have CH diagnosed during neonatal screening and confirmed by repeat testing (including children with a eutopic thyroid) will probably require thyroxine treatment permanently or at least throughout childhood.

We did not use ultrasonography for thyroid imaging. This technique was not available in the early years of our study, and we have concern that even with improved technology, the sensitivity of ultrasoundography is still not sufficient. As with use of technetium Tc 99m pertechnetate, if ultrasonography shows a eutopic thyroid, the diagnosis is validated, but we would have concerns about diagnosing ectopia or athyrosis ultrasonographically. Improved technology and comparative studies may validate the use of thyroid ultrasonography in the future.

Conclusions

Neonatal diagnosis of CH represents perhaps the greatest success of newborn screening programs. Prevalence of CH is high (~1:3100 overall) and is highest in Latino/Hispanic females (1:1357); initial laboratory diagnosis is straightforward and accurate; and treatment is simple, inexpensive, and effective. Moreover, neonatal diagnosis of CH can help prevent severe mental retardation and growth failure.123I neonatal thyroid scintigraphy is a safe and clinically important procedure which maximizes the information available for accurately counseling patients about CH and its optimal treatment, and 123I scintigraphy should be performed in all cases of CH. Because our findings indicate that scintigraphy using technetium Tc 99m pertechnetate is valid only in the case of eutopic or absent thyroid, use of this technique may lead to an erroneous and clinically misleading finding of ectopic thyroid; 123I scintigraphy should therefore be preferred. In addition, considering today’s rapid advances in understanding the basic mechanisms of thyroid embryogenesis and gene abnormalities, thyroid scintigraphy may provide insight into clinical and genetic correlates in CH.

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REFERENCES


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