Pertechnetate Scintigraphy in Primary Congenital Hypothyroidism

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Primary congenital hypothyroidism (PCH) is currently detected effectively by heel-stick screening. When elevated thyrotropin (TSH) and/or decreased T4 are found in the blood of neonates, they are recalled, values are confirmed in venous blood and thyroxine replacement therapy (TRT) is immediately instituted, thus cretinism or severe retardation is prevented. However, in a significant percentage of neonates with abnormal blood levels of T4 or TSH, the disorder is transient. To help determine the exact cause of PCH and the possibility of transient PCH, pinhole thyroid imaging is performed 30 min after an intravenous injection of 18.5 MBq (500 μCi) ^{99m}Tc-pertechnetate (TcPT). Patients with a nonvisualized gland or patients with images suggesting dyshormonogenesis are reevaluated at age 3–4 y to exclude transient PCH. **Methods:** To define the role of TcPT imaging in determining the exact etiology of PCH and the possibility of its being transient, we reviewed data from 103 neonates with PCH who had scintigraphy in our laboratory between 1970 and 1996 and we correlated the results with clinical outcome. **Results:** Four patterns of thyroid scintigrams were recognized and these determined patient classification: (a) normal in 7 patients with false-positive heel-stick screening but normal venous blood hormone levels; (b) hypoplasia-ectopia in 32 patients requiring lifelong TRT; (c) nonvisualization in 35 patients—32 with agenesis requiring lifelong TRT and 3 with fetal thyroid suppression by maternal antibodies whose TRT was discontinued at a later age; and (d) dyshormonogenesis (markedly increased TcPT concentration) in 29 patients—25 with permanent PCH requiring lifelong TRT and 4 with transient PCH in whom TRT was discontinued. Of the 25 patients with dyshormonogenesis, 12 belonged to five families with two or three siblings having the same disorder. **Conclusion:** TcPT thyroid scintigraphy in the neonate with PCH provides a more specific diagnosis, is useful for selecting patients for re-evaluation to uncover transient PCH and discontinue TRT and defines dyshormonogenesis, which is familial and requires genetic counseling. It is also cost-effective.

Key Words: congenital hypothyroidism; transient congenital hypothyroidism; familial congenital hypothyroidism; thyroid scintigraphy; agenesis of thyroid; dyshormonogenesis; ectopic thyroid

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Thyroid scintigraphy with ^{99m}Tc-pertechnetate ($^{99m}TcO_4Na$ or TcPT) is used in clinical practice for evaluating the anatomy and the function (trapping mechanism) of the thyroid gland in adults and children (*1,2*). In the neonatal period, the main indication for thyroid imaging is the evaluation of neonates with blood levels of T4 and thyrotropin (TSH) consistent with primary congenital hypothyroidism (PCH), a serious disorder of variable etiology (Table 1). If congenital hypothyroidism remains untreated in early infancy, the end result is cretinism (retarded mental and physical development) (*1–4*). Recognition of PCH on a clinical basis at birth is usually not possible. However, neonatal screening programs using heel-stick blood for measurements of T4 and/or TSH provide an accurate, effective and efficient way of diagnosing this congenital problem. Infants with low T4 and/or high TSH in the heel-stick blood are recalled and the diagnosis is confirmed by venous blood hormone measurements. Thyroxine replacement therapy (TRT) is promptly prescribed when indicated and prevents severe mental retardation. With an incidence of congenital hypothyroidism of 1 per 2500–5000 live births, the screening program has proven to be cost-effective (*3,5–7*).

The initial treatment in every case of PCH is prompt TRT to prevent developmental retardation; however, lifelong therapy may not be needed in all patients. It has been well established that in some cases transient rather than permanent hypothyroidism is present and such cases need to be identified to allow safe discontinuation of TRT at a later time (*8–10*). Transient congenital hypothyroidism, in most parts of the world, appears to be associated with either fetal thyroid suppression by maternal antibodies (*10*) or mild dyshormonogenesis (*11*). However, there may be additional causes of transient congenital hypothyroidism in areas with iodine deficiency, where it has been reported with an incidence as high as 25% (*12*). In both maternal antibody suppression and some cases of mild dyshormonogenesis, spontaneous recovery of thyroid function is known to occur (*10,11*). In addition, in dyshormonogenesis, which may be familial and occasionally associated with hearing disorders, genetic counseling is indicated (*3*). However, at birth, the exact cause of congenital hypothyroidism cannot be determined by either clinical evaluation or blood levels of

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TABLE 1
Etiology, Laboratory Findings and Scintigraphy in Congenital Hypothyroidism

Diagnosis	Heel stick T4	Heel stick TSH	TcPT thyroid scintigraphy
Primary (all cases)	<4–6*	>20†	Variable
Agenesis			Nonvisualization
Maternal antibodies			Nonvisualization
Ectopic-rudimentary			Small ectopic
Dyshormonogenesis			Large hyperactive
Maternal ^{131}I therapy			Nonvisualization hypoactive
Endemic goiter			Large hypoactive
Pendred syndrome			Large hyperactive
Miscellaneous			Variable
Secondary (all cases)	<4	<0.01	Nonvisualization hypoactive
Hypopituitarism			Nonvisualization hypoactive
Hypothalamic cause			Nonvisualization hypoactive
End organ (all cases)	Normal	Normal	Normal

*μg/L or 51–77 nmol/L.
†μU/L or mU/L in international units.
TcPT = ^{99m}Tc-pertechnetate; TSH = thyrotropin.

TSH and T4, therefore transient hypothyroidism cannot be recognized, although maternal antibody suppression may be suspected from maternal history (thyroid diseases, goiters, use of thyroxine).

It has been the practice at Jackson Memorial Hospital, University of Miami, Miami, Florida, and other centers to include TcPT thyroid gland scintigraphy in the evaluation of suspected hypothyroid neonates. The scan cannot diagnose transient hypothyroidism but it can help identify the two subgroups among whom it is prevalent, that is, a nonfunctioning gland and dyshormonogenesis. In children of these groups after the critical period for brain damage has passed, at age 3–4 y, thyroxine is carefully and briefly withdrawn in an effort to evaluate whether the neonatal hypothyroidism in each patient was transient or permanent and to determine the need for lifelong therapy.

We retrospectively evaluated the role of TcPT thyroid scintigraphy in (a) determining the exact cause of PCH, (b) classifying neonates with PCH into patients with permanent defect and patients with potential transient hypothyroidism and (c) uncovering familial PCH (dyshormonogenesis).

MATERIALS AND METHODS

Screening neonates by heel stick for PCH was mandated by law in Florida in 1969. In the 25-y period of screening (1970–1996), 103 neonates (30 male, 73 female) were referred to our center because of abnormal heel-stick T4 and TSH blood levels (T4 < 6 μg/dL, TSH > 20 μU/L). The recalled neonates were evaluated and were treated as outpatients. After history, clinical examination and venous blood sampling for confirmatory hormonal measurements, the neonates were referred to the Nuclear Medicine Laboratory for thyroid scintigraphy.

Imaging was performed 30 min after the intravenous injection of 18.5 MBq (500 μCi) TcPT. The neonate was immobilized without sedation in anterior projection, with the neck in extension by means of a support under the back of the chest and shoulders. The extended head was supported and was held in place manually, usually by the parent. Thus, the anterior neck was most accessible for imaging. Pinhole (0.25 in. [6.4 mm] diameter) scintigraphy was performed by obtaining two anterior images of the neck and, subsequently, a lateral view. The first anterior view was a close-up and the second was a more distant view, including the neck, the face and the chest in the field of view. Typically, each view was acquired for a 5-min period, or 100,000 counts, whichever came first.

Four characteristic patterns of the thyroid scan were recognized: normal, nonvisualization, ectopic-hypoplastic and dyshormonogenesis. The findings were reported immediately to the referring endocrinologist.

Based on results of TcPT scintigraphy available to the endocrinologist, families of patients with dyshormonogenesis were offered genetic counseling and mothers of patients with nonvisualization were tested for antithyroid antibodies, depending on maternal history of thyroid-associated problems.

TRT was usually prescribed at the first visit in the endocrine clinic and the first dose was given to the neonate after venous blood was drawn for confirmation. Scintigraphy was usually performed the same day before treatment or the next day after the initiation of treatment, but occasionally therapy was begun on Friday and scanning was performed on Monday, if TSH was very elevated and immediate treatment was indicated.

The patients were followed up in the endocrine clinic at frequent intervals for evaluation of their growth and development. Measurements of venous blood levels of T4 and TSH were made and therapy was adjusted to achieve optimal blood levels of both hormones (TSH < 10 mU/L originally and <5 mU/L as age increases and T4 ≥ 10 ng/dL and between 7 and 12 ng/dL as age increases).

It is believed that thyroxine should not be withheld before 3 y of age because of the extreme importance of thyroid hormone in brain development in the first few years of life. After this critical period, an effort was made to identify transient hypothyroidism caused by maternal inhibitory antibody suppression or transient mild dyshormonogenesis. In cases of high maternal antibody suppression of neonatal thyroid activity, the dose of thyroid replacement usually did not require an increase over several months and was gradually tapered. Sonographic evidence of thyroid tissue in these infants was helpful in determining whether to taper replacement therapy. In patients at approximately 3 y old with a neonatal TcPT scan pattern of nonvisualization (without high maternal inhibitor antibody) or dyshormonogenesis, thyroxine replacement was withheld for 20 d and the T4 and TSH levels were then remeasured. If they remained physiologic, thyroxine replacement was not reinstituted, and patients continued to have thyroid hormonal profiles determined intermittently over the next 6 mo to 1 y. However, when abnormal T4 or TSH values were obtained, indicating persistent hypothyroidism (agenesis or persistent dyshormonogenesis), thyroxine was reinstituted.

For the purpose of this article, patient records were reviewed and laboratory, scintigraphic and follow-up data were recorded on the basis of the final diagnosis.

RESULTS

Among the 103 neonates (age 1–4 wk) recalled because of abnormal heel-stick test, four patterns of thyroid TcPT imaging were observed: (a) normal thyroid gland, (b) nonvisualization of functioning thyroid tissue, (c) hypoplastic and ectopic thyroid gland and (d) dyshormonogenesis (Table 2).

1. Normal thyroid gland (Fig. 1) (normal size, shape, location and intensity of TcPT accumulation). This was found in 7 patients with, apparently, false-positive heel-stick results; these patients had venous blood hormone level measurements that were found to be normal. Therapy was not required and was not prescribed for these patients and their follow-up was uneventful.
2. Hypoplasia-ectopia (Fig. 2) (small focus, or two foci, of low-level TcPT accumulation cephalad to the thyroid cartilage). There were 32 patients in this group requiring immediate and lifelong thyroxine treatment, because hypothyroidism was considered permanent and the suppression of the ectopic gland also appeared necessary.
3. Nonvisualization of the thyroid gland (Fig. 3). This pattern was found in 35 patients who were immediately placed on TRT. They were, however, followed and treated as discussed earlier with a re-evaluation at age 3–4 y by withdrawal of replacement therapy to establish a final diagnosis. Agenesis was present in 32 of the patients requiring lifelong TRT and fetal thyroid suppression by maternal antibodies was present in 3 of them in whom the T4 and TSH levels eventually became normal. In 2 of these 3 patients, therapy was not reinstituted and they remain euthyroid; in the third patient, therapy was again required 2 y later (permanent damage of the gland).
4. Dyshormonogenesis (Fig. 4) (normal shape but with markedly increased size and intensity of TcPT accumulation). There were 29 patients in this group requiring immediate thyroxine therapy. Families also received genetic counseling. Further follow-up of these patients resulted in finding 4 patients in whom transient dyshormonogenesis was found after thyroxine withdrawal, and replacement therapy was not reinstituted. They remain euthyroid. In the remaining 25 children with dyshormonogenesis, hypothyroidism did not resolve and they were continued on lifelong replacement therapy. Among these 25 children, there were siblings with the same anomaly in five families (two patients in each one of three families and three patients in each one of two families). One case of hearing defect was found.

TABLE 2
Findings and Diagnosis in 103 Neonate Patients with Low T4 and High TSH by Heel Stick

Final diagnosis	n	TcPT neonatal thyroid	T4 therapy
Normal	7	Normal	Not instituted
Hypoplasia-ectopia	32	Small hypoactive ectopic	Lifelong
Agenesis	32	Nonvisualization	Lifelong
Maternal antibody suppression	3	Nonvisualization	Discontinued age 3–4 y
Dyshormonogenesis			
Permanent hypothyroidism	25	Large hyperactive	Lifelong
Transient hypothyroidism (immaturity)	4	Large hyperactive	Discontinued age 3–4 y
Total	103		

TSH = thyrotropin; TcPT = ^{99m}Tc-pertechnetate.

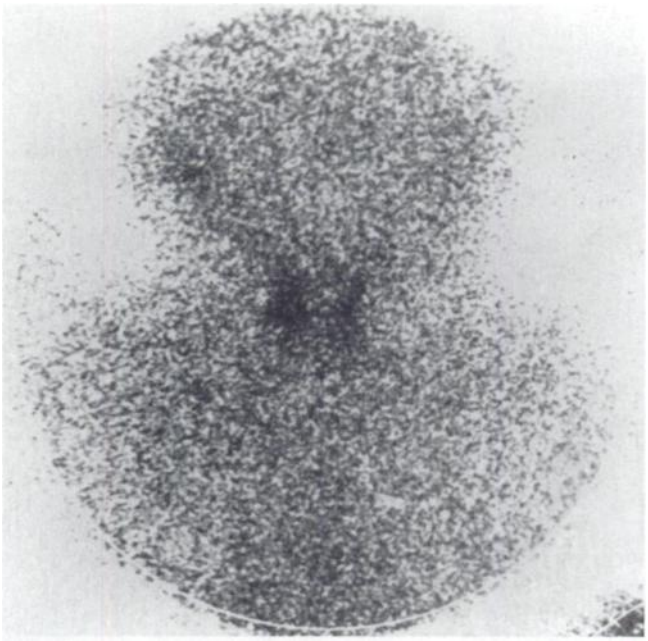

FIGURE 1. Normal neonatal thyroid scan with TcPT. This patient had at 24-h false-positive abnormal heel-stick T4 and TSH values, 7.7 μg/dL and 225 mU/L, respectively, but in subsequent venous blood evaluation 12 d after birth, values were normal (11.2 μg/dL and 5.7 mU/L, respectively). No therapy was needed.

It is interesting to note that, among the 103 patients with congenital hypothyroidism included in this analysis, there were 20 patients (of 28 studied) with various speech defects, randomly distributed among the three groups (7 dyshormonogenesis, 8 agenesis, 5 hypoplasia-ectopia).

DISCUSSION

Thyroid scintigraphy provided images supporting a diagnosis of congenital hypothyroidism in 96 of 103 neonates and was compatible with the exclusion of the disorder by normal repeated (venous blood) hormone levels in the remaining 7 patients. Furthermore, the scan allowed classifi-

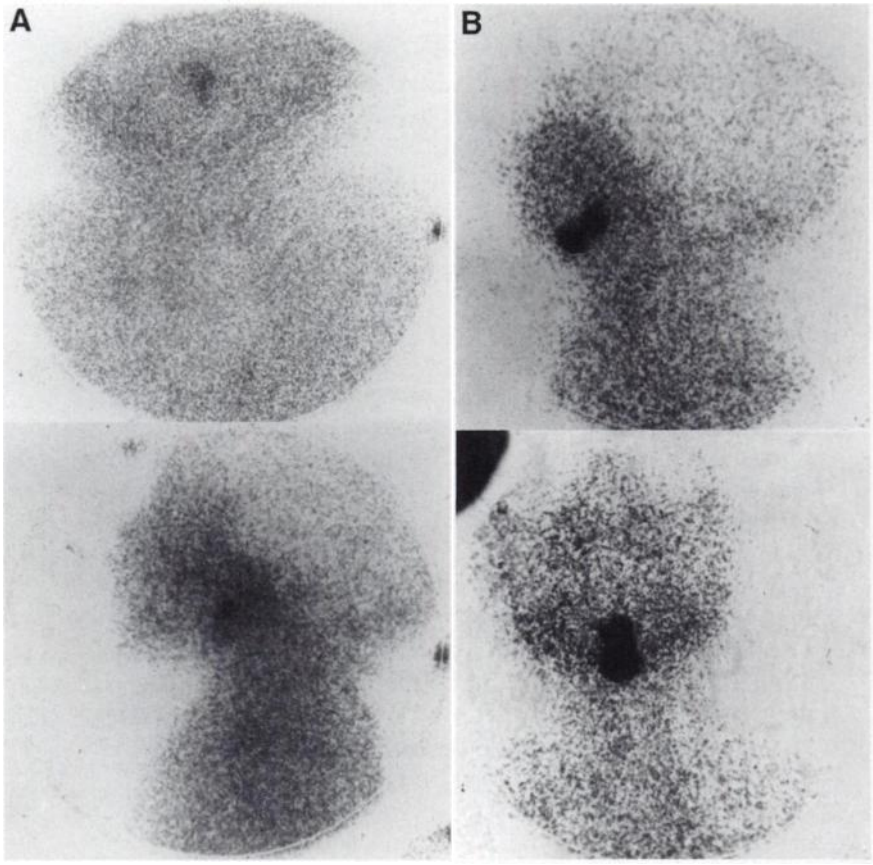

FIGURE 2. (A) Ectopic-rudimentary thyroid with TcPT. T4 (A, top) and TSH (A, bottom) at 24 h were 4.3 μg/dL and 500 mU/L, respectively, and remained abnormal at 14 d (2.1 μg/dL and 613 mU/L, respectively). (B) Bilobar ectopic hypoplastic gland. T4 (B, top) and TSH (B, bottom) at 48 h were 5.4 μg/dL and 413 mU/L, respectively, and remained abnormal at 15 d (8.1 μg/dL and 129 mU/L, respectively). Patients with such scans require lifelong T4 replacement therapy.

cation of the patients with true congenital hypothyroidism into a subgroup of 32 patients who required lifelong TRT (hypoplasia-ectopia) without re-evaluation and a subgroup of 64 patients who needed re-evaluation after withdrawal of treatment at age 3–4 y (nonvisualization, dyshormonogenesis). As a result, only 64 of 96 patients were re-evaluated at age 3–4 y and unnecessary treatment was discontinued in 3 patients who recovered from maternal antibody suppression of their thyroid gland and in 4 others with transient dyshormonogenesis. The scan was also useful in counseling parents of infants with dyshormonogenesis on the genetic nature of the problem.

TcPT thyroid scan is easy to perform (some expertise in venipuncture is required), inexpensive, fairly well tolerated and uniformly diagnostic. No complications have been reported. The use of TcPT allows fast (1 h) imaging without the need for prescheduling patients because TcPT is always available in the hospital.

Instead of TcPT, some centers prefer to use ^{123}INa, which is a more physiologic agent that addresses the global function of the thyroid gland and is orally administered (*11,13,14*). However, ^{123}INa is more expensive than TcPT, is not always available and requires a few hours of waiting between oral administration and imaging. Furthermore, dyshormonogenesis may not be promptly diagnosed with ^{123}INa (as it is with TcPT), because iodine scintigraphy may show variable activity, depending on timing of imaging, and requires repeated imaging with the perchlorate discharge technique to indicate this diagnosis. The radiation exposure with each agent is within acceptable limits (*11,13,14*).

The diameter of the pinhole insert is not critical because the goal is to visualize the gland and to determine its size, activity and location and not to detect focal disease. Therefore, any size insert is acceptable. An insert with a narrow diameter may be preferable, but then the time of imaging will be longer.

Nonvisualization of the gland, in addition to agenesis or maternal antibody suppression, may rarely be due to destruction of the infant's gland by ^{131}INa used during pregnancy for maternal therapy of thyroid carcinoma or hyperthyroidism. However, such a cause of congenital hypothyroidism was excluded by history in this group of patients. Secondary or tertiary hypothyroidism (low TSH or TRH) may also result in nonvisualization of the thyroid; but in all of our patients, TSH was elevated, therefore such patients were not included. All patients with ectopia had associated hypoplasia, which is the result of patient selection (low T4 and high TSH). Several children from the same general population not included in this analysis were found, incidentally, to have lingual or sublingual thyroid glands on physical examination and were euthyroid, but TSH concentration was often elevated. Finally, enlarged hyperactive glands are present not only in dyshormonogenesis but also in thyrotoxicosis (maternal Graves' disease), but in this situation T4 should be high, which was not the case in this population. Perchlorate discharge test was performed in 2 of the patients

with dyshormonogenesis and it was positive, but neither patient had a biopsy performed to histologically confirm the diagnosis.

Considering the cause of transient PCH, it is understood that maternal antibodies suppress the function of the gland, which later recovers once the antibodies are catabolized (*10*). It has been postulated that transient dyshormonogenesis is due to immaturity of the iodine organification mechanism, which later normalizes (*15*).

With the expected availability of recombinant human TSH, testing for recovery of the gland will be easier and safer. Indeed, without discontinuing TRT, thyroid imaging with ^{123}INa performed after TSH injection will indicate if a gland is present orthotopically with acceptable size and uptake, which will allow for safe discontinuation of exogenous thyroxine.

CONCLUSION

In our experience, in the neonate with suspected primary congenital hypothyroidism on the basis of screening (heel-stick blood levels of T4 or TSH abnormal), thyroid scintigraphy with TcPT is a useful adjunct diagnostic procedure that allows the best evaluation of the cause of the syndrome at this age. It is fast, easy, inexpensive, well tolerated and accurate. It helps confirm normal glands in patients with false-positive screening and it is especially important in differentiating the three subgroups of patients with PCH: hypoplasia-ectopia, nonvisualization and dyshormonogenesis. It identifies those patients who do not need to be evaluated for transient hypothyroidism and who should be given lifelong replacement therapy (31% with hypoplastic ectopic thyroid) and indicates those patients who need re-evaluation (62%, with nonvisualization or dyshormonogenesis). Among the latter subgroup of patients are patients with transient hypothyroidism who may not need lifelong TRT (7% of the total in this series). The cost of the lifelong TRT in 7% of the population ($11 per month × 80 y × 7 = $73,920) is much more costly than the onetime TcPT scanning of the group ($150 × 100 = $15,000). However, the psychological benefit to the children and families who are relieved of the concern about the disorder is invaluable.

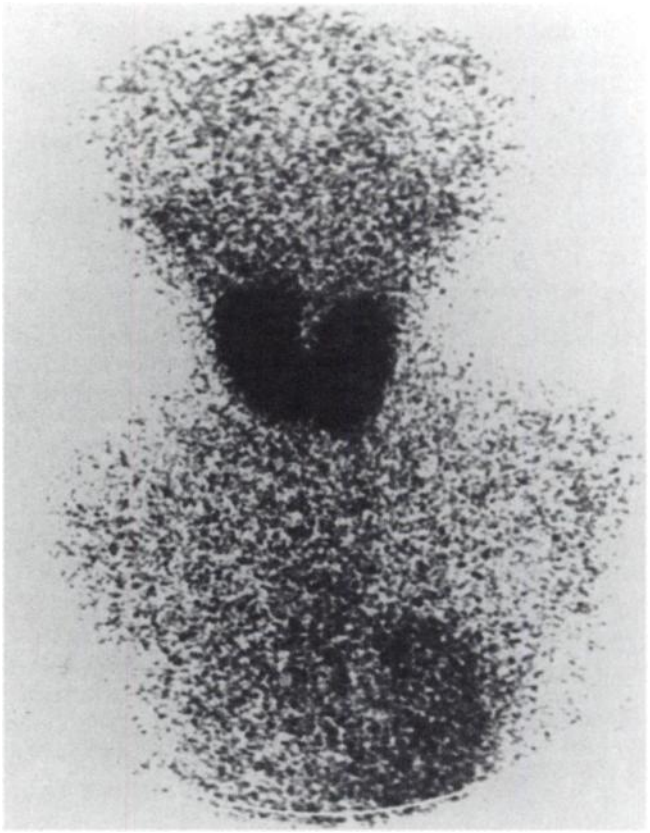

FIGURE 4. Dyshormonogenesis with TcPT. In this patient, T4 and TSH values at birth were 3.2 µg/dL and 375 mU/L; 13 d later, T4 was undetectable and TSH was greater than 100. The scan cannot differentiate permanent dyshormonogenesis from immaturity (transient hypothyroidism).

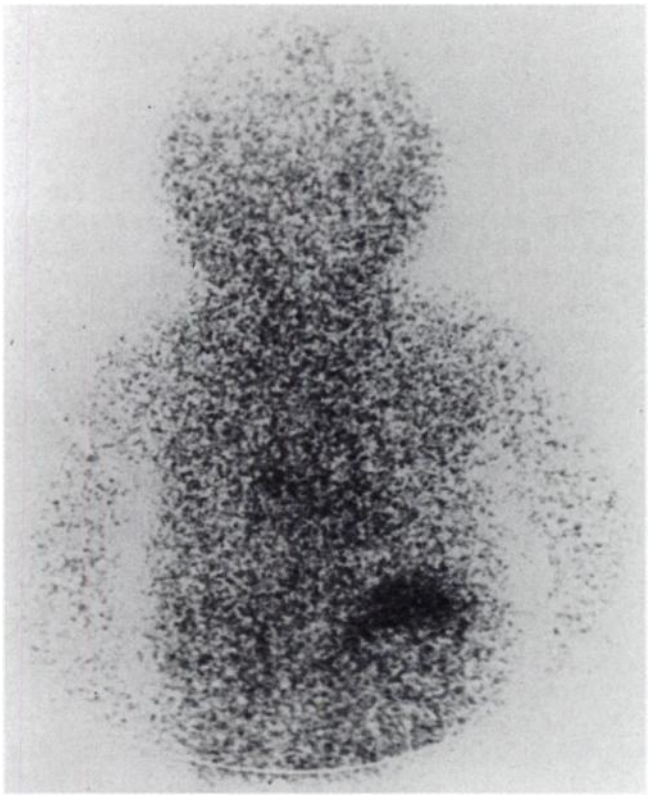

FIGURE 3. Nonvisualization of thyroid tissue with TcPT. Clinical and laboratory presentation is similar to Figure 2. T4 and TSH at birth were 5.8 µg/dL and 500 mU/L, respectively; 12 d later, T4 was undetectable and TSH was 616 mU/L. This neonatal patient may have agenesis or maternal antibody thyroid suppression or gland may have been destroyed by maternal ^{131}I therapy.

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