Congenital Hypothyroidism: Role of Nuclear Medicine

Isabelle Keller-Petrot, Juliane Leger, Aline Sergent-Alaoui, Claire de Labriolle-Vaylet

Congenital hypothyroidism

Role of Nuclear Medicine

Isabelle Keller-Petrot[1] MD, Juliane Leger[2,3,4] MD, PhD, Aline Sergent-Alaoui[1] MD, and Claire de Labriolle-Vaylet[1,5] MD, PhD.

[1] : Service de Médecine Nucléaire Pédiatrique, Hôpital d'Enfants Armand Trousseau, F-75012 Paris, France

[2] Service d'Endocrinologie Diabétologie Pédiatrique, Centre de Référence des Maladies Endocriniennes Rares de la Croissance, Assistance Publique-Hôpitaux de Paris, Hôpital Robert Debré, F-75019 Paris, France

[3] : Université Paris Diderot, Sorbonne Paris Cité, F-75019 Paris, France

[4] : Institut National de la Santé et de la Recherche Médicale (Inserm), Unité 1141, DHU Protect, F-75019 Paris, France.

[5] : UPMC Univ Paris 06, Biophysique, F-75005 Paris, France

Corresponding author :

Claire de Labriolle-Vaylet, Service de Médecine Nucléaire, Hôpital d'Enfants Armand Trousseau, 26 rue du Dr Arnold Netter, F-75012, Paris, France

E-mail: claire.vaylet@aphp.fr

Fax: +33 144736198

Phone: +33 144736180 or +33603543190

Summary

Thyroid scintigraphy holds a key place in the etiologic workup of neonatal hypothyroidism. Routine screening for this disorder in maternity hospitals in industrialized countries, for nearly 40 years, has permitted early treatment and thereby helped to prevent its physical and mental complications. Neonatal hypothyroidism affects about 1 in 3000 births. The most common causes are abnormal thyroid gland development and defective hormone synthesis by an eutopic thyroid gland. The incidence of the latter has risen in recent years, for reasons that remain unclear.

A thorough etiologic work-up helps to determine the disease type. Current guidelines recommend thyroid imaging by means of ultrasound and scintigraphy. Ultrasound should be done by a practitioner trained to examine the cervical region of newborns, as the thyroid is very small and must be distinguished from the particular aspect of the "thyroid empty lodge". Ultrasound lacks sensitivity for detecting small ectopic glands but is the gold standard for measuring thyroid dimensions. Scintigraphy provides an etiologic diagnosis in most cases. The two isotopes used in this setting are technetium-99m and iodine-123. The latter gives more contrast and allows the perchlorate discharge test to be performed in order to detect abnormal iodide organification in the neonate with an eutopic thyroid. If scintigraphy cannot be performed during the neonatal period, a postponed procedure can be achieved after 3 years of age. Close cooperation between the nuclear medicine physician and the pediatric endocrinologist is crucial for timely and optimized scintigraphy.

(End of the summary)

What is the role of nuclear medicine in the management of neonatal hypothyroidism? The following article examines the utility of thyroid scintigraphy in patient management at this age, and also how to perform and interpret the scans.

Diagnosis of congenital hypothyroidism

Congenital hypothyroidism is associated with inadequate thyroid hormone concentrations at birth. The deficiency is usually of peripheral origin, with elevated plasma TSH levels, which distinguishes it from congenital hypothyroidism of central origin, a much rarer disorder generally accompanied by global hypopituitarism. Hypothyroidism is one of the most frequent congenital endocrine disorders. Because clinical signs in the neonatal period are non specific, diagnosis and treatment used to be delayed, resulting in markedly defective physical and cognitive development. In most industrialized countries, systematic neonatal screening was implemented in the late 1970s, usually on day 3 of life, using the dried blood spot method. The screening modalities now vary from country to country (1, 2). When the TSH concentration in a dried blood spot exceeds an established alert threshold (the detection limit is generally between 10 and 20 mIU/L, depending on the country), the parents are informed and the child is referred for diagnostic confirmation and L-thyroxin replacement therapy. Treatment started during the neonatal period markedly improves these children's physical and intellectual development (3, 4).

Optimal management will include therapeutic education, for both the parents and the child, stressing the importance of regular treatment and the criteria used to judge treatment

balance. Regular medical evaluation of thyroid function is necessary, with L-thyroxin dose adjustment if required, as well as regular assessment of the child's physical and mental development, particularly when the CH is initially severe (3). French cohort studies on the outcome of CH patients show that school performance is broadly comparable to that of healthy controls, with the same average age of graduation when treatment is well conducted (5). However, despite treatment, these children tend to be more overweight, to have more hearing or visual disorders in adulthood, and to be less well socially integrated, especially when the CH is initially severe (6).

Routine neonatal screening has transformed the prognosis of this disease, which is a major scientific and human success story. Screening has also been shown to be cost-effective (7) but, unfortunately, it is not yet performed in every country. One limitation is that TSH-based screening, used in the majority of countries, cannot identify rare forms of central (pituitary) hypothyroidism, contrary to T4 assay.

Etiologies

The most common cause of CH is thyroid dysgenesis, that is to say defective thyroid development. In most such cases, the thyroid tissue is present in the form of a nodule located between the base of the tongue and the base of the neck, following failed physiological migration of the thyroid bud during embryogenesis (ectopia). Slightly less frequently, there is a complete lack of thyroid tissue (athyreosis). More rarely, atrophic thyroid tissue is found in the thyroid lodge (hypoplasia or hemithyroidism) (8).

The other cause of CH is abnormal hormone production (dyshormonogenesis) (9, 10). In this case the thyroid is present, in the normal position (eutopic thyroid), with or without goitre, but it is non functional. Dyshormonogenesis is due to mutations in genes involved in thyroid hormone synthesis. These mutations can affect iodide uptake by the sodium/iodide symporter (NIS), passive iodide transport (*PDS* or Pendrin), iodide organification (*TPO, DUOX2, DUOXA2*), thyroglobulin synthesis, or iodide recycling (8, 11, 12).

When the thyroid is present, without hypoplasia, CH may be either permanent or transient (in 30% of cases) (9, 13). The most frequent causes of transient CH are iodine deficiency or iodine overload in the mother, placental transfer of blocking antibodies or antithyroid drugs (in case of maternal thyroid disease), and some genetic defects (e.g. compound heterozygous *DUOX2* gene mutations) (14-16). At birth, when history taking does not point towards a specific cause, it is often difficult to predict the permanent or transient nature of CH. Treatment with L-thyroxine must thus be started rapidly, and the situation reassessed at a later date (3, 17-19).

Incidence

The incidence of CH varies by country and iodine status. There is also an ethnic component. Thus, within the state of California, the incidence is higher in Indian populations (1/1200 births), followed by Hispanics (1/1600 births), Chinese and Vietnamese (1/2380 births), non-Hispanic Caucasians (1/3533 births) and African-Americans (1/11 000 births) (20).

The distribution of the different etiologies also varies widely according to the country and diagnostic method (21). In France, patients are included in a national registry. During the

period 1982-2012, 6622 cases of CH were diagnosed among 23 669 598 newborns tested nationwide, for an incidence of 1/3574 births. Dysgenesis was present in 71% of cases, while the thyroid was present in the remaining 29%. The French database confirms that the incidence of CH is rising by about 5% per year, as reported in other countries (22). This increase has received no clear explanation; it is not linked to a lowering of the alert threshold, contrary to some suggestions (23-26).

Importance of early etiologic diagnosis

It is very important to determine the etiology of CH at the time of diagnosis, even though initial treatment is always the same. Indeed, parents are very upset to discover their child has a congenital disease. When the thyroid gland is in place, they hope their child will be among the 30% in whom the hypothyroidism is transient. Visual confirmation of athyreosis or ectopia helps them come to terms with the need for lifelong daily treatment. Parents also raise questions about the risk of recurrence in subsequent pregnancies. Accurate etiologic diagnosis provides the answer: dysgenesis is mainly sporadic (27); familial forms represent only 2% of cases (28); and dyshormonogenesis often has a genetic component with autosomal recessive transmission in most cases (11, 12).

What imaging modalities for initial assessment of neonatal CH?

The Rome consensus conference, held under the auspices of the European Society of Paediatric Endocrinology (ESPE) and attended by representatives of Pediatric Endocrinology

societies around the world, resulted in the publication of *Consensus Guidelines on Screening, Diagnosis and Management of Congenital Hypothyroidism* in 2014 (3).

At the time of initial diagnosis, recommended examinations include radiography of the knees plus thyroid ultrasound and scintigraphy (29). Absent femoral and tibial epiphyseal nuclei reflect the severity of intrauterine hypothyroidism, which is a major determinant of the subsequent prognosis (5,6,30). The advantages of combining ultrasound and scintigraphy for thyroid exploration are that both high-resolution morphological (ultrasound) and functional (scintigraphy) information is obtained. Each technique compensates for the limitations of the other (21,31,32).

Thyroid ultrasound examination is delicate in the neonatal period, as the normal thyroid is very small, with a volume generally between 0.5 and 4 ml (33). However, ultrasound can reveal the presence of the thyroid gland, with or without goitre. The different forms of dysgenesis are distinguished by analysis of the thyroid lodge first and then the thyroglossal duct. Normal thyroid tissue is more echogenic than muscle and less echogenic than fat. Detection of an empty thyroid lodge can be complicated by the presence of small hyperechoic structures either side of the trachea, thymic tissue (hypoechoic), or cysts located in the thyroid lodge (29, 34). These artefacts can be identified by an experienced practitioner but, even with the use of color Doppler, ultrasound is informative in only 1 in 3 newborns with thyroid ectopia (35), which is only visible if the thyroid tissue is organized into a sufficiently large nodule. The strengths of ultrasound include detection of a normally located thyroid gland, the unique ability to accurately measure thyroid volume, and the ability to "correct" scintigraphic false-negatives.

Scintigraphy remains the gold standard for the workup of CH, particularly when seeking a developmental abnormality (ectopia or athyreosis). Iodine-123 or technetium-99m uptake by thyroid cells enables them to be located, provided the exam is done before or during the first week of replacement therapy. Beyond this window, especially if the initial TSH is moderately high, radioactive iodine uptake by thyroid tissue, which is under the control of TSH, may be almost zero.

When etiologic studies are not performed at birth, scintigraphy should be done after the age of 3 years, when treatment interruption no longer poses a risk (the critical period of neurocognitive development has passed) (3). Some authors recommend the use of recombinant TSH to avoid hormone withdrawal (36).

Thyroid scintigraphy in CH newborns: practical considerations

Organisation of the scintigraphy appointment

Scintigraphy should never be allowed to delay treatment initiation. The fact that scintigraphy must be done less than a week after the beginning of L-thyroxine therapy means that good coordination between the pediatric endocrinologist and nuclear medicine department is crucial. The request for scintigraphy must be made to the Nuclear Medicine department as soon as the endocrinologist has seen the family to initiate treatment. The Nuclear Medicine department then has a few working days to do the scan, which must be considered a priority.

Choice of isotope

Technetium-99m and iodine-123 are both captured by sodium/iodide symporters (NIS) located at the basal pole of thyroid cells, and both isotopes are suitable for imaging. Technetium is cheaper and therefore preferred in many countries, but the image is of lower quality than with iodine-123 (37): the signal-to-noise ratio is low, and the image only reflects NIS expression. Iodine-123 gives a higher signal-to-noise ratio due to the organification process; contrast is better and poorly functional thyroid tissue such as small ectopias can be visualized (8). Iodine-123 has the added advantage of allowing a perchlorate discharge test when the thyroid is present (8,38).

Radiopharmaceutical administration

The chosen radiopharmaceutical is injected intravenously, at an activity of 0.03 mCi (1.1 MBq) for iodine-123 or 0.11 to 0.22 mCi (4-8 MBq) for Tc-99m-pertechnetate. Pain can be minimized by breast or bottle feeding, or by using a pacifier dipped in 30% glucose. Iodine-123 can be administered orally if the intravenous route is unavailable. The disadvantages of oral administration are a higher risk of contamination with saliva or vomit.

Image acquisition

The images are acquired after 15 minutes with Tc99m or after 1 hour with I-123. Restraints used at this early age must be gentle. It is not easy to keep the head in extension if the child is not asleep. One solution is to use a mattress specially designed to restrain newborns (Fig. 1). Anterior acquisitions of the trunk are made for 5 min, with a LEHR collimator and a 128 x 128 matrix. Given the small size of newborns, the whole body is displayed on a single field. Complementary acquisitions (pinhole or profile) depend on the results of the anterior image.

Interpretation

When the thyroid is present, the two lobes are visualized at the base of the neck. The salivary glands and stomach secrete the isotope because their cells express the iodide (and Tc99m) transporter (NIS). The bladder is also visible because the radiopharmaceuticals are eliminated in urine (Fig. 2). The two lobes appear symmetric in the normal thyroid. The apparent size of the scintigraphic image depends primarily on the intensity of tracer uptake.

In case of hypoplasia, the thyroid is located in its lodge but has an abnormal, asymmetric morphology which is more visible on images obtained with a pinhole collimator: atrophy of one lobe may be seen (Fig. 3), or hemiagenesis, most frequently on the left (21). Tracer uptake is often low in this case, and sonographic findings usefully complement the scintigraphic results.

In case of ectopia, a circular focus of tracer accumulation is seen, and the lateral view confirms its position, usually at the base of the tongue (Figure 4). This small focus can be difficult to distinguish from salivary activity when Tc99m is used (38). Rinsing the mouth by making the neonate drink can avoid this source of error. Dual ectopia is infrequent. Not all ectopias are diagnosed in the neonatal period, because in rare cases hormone production is sufficient for the child to be euthyroid at birth (39).

When the thyroid is not visible on the scintigraphic image acquired 1 hour after IV injection, later acquisitions must be done (3 hours post-infusion with I-123) before diagnosing athyreosis (Fig. 5). Ultrasound findings can reveal rare false-negative scintigraphic results by showing the thyroid in its lodge whereas no isotope uptake is visible. The main avoidable cause of such false-negatives is scintigraphic examination after more than 7 days of replacement therapy, especially when the initial TSH is not very high. Maternal anti-TSH receptor blocking antibodies, in a context of maternal autoimmune thyroid disease, can also

prevent tracer uptake despite the presence of the thyroid gland (40). Neonatal CH is transient is such cases. In addition, very rare neonates with an intact thyroid are deficient in sodium/iodide symporters (NIS) (41). The lack of salivary and gastric tracer activity should point to this cause of negative thyroid uptake. Palpation and ultrasound reveal the presence of a goitre. Finally, inactivating mutations of the TSH receptor gene (27, 42) can lead to little or no tracer uptake (8) even if the gland is present and normal-sized or hypoplastic.

With Tc99m, the examination is considered complete once the acquisitions have been made. CH neonates with an normal thyroid are considered to have dyshormonogenesis, but their organification status cannot be determined in countries where iodine-123 is unavailable.

When iodine-123 uptake reveals an eutopic thyroid, without hypoplasia, the perchlorate discharge test is indicated.

The perchlorate discharge test

In normal conditions, iodide captured at the basal pole by sodium/iodide symporters (NIS) is quickly transported to the apical pole of thyreocytes, where it is fixed (organified) to thyroglobulin tyrosine residues, leaving no free iodide in the thyreocyte. By contrast, iodide accumulates in the thyreocytes if organification is defective. In this case, sodium perchlorate, which is also captured by thyroid cells but not organified, will compete with iodide and chase it out of the cells.

The effect of sodium perchlorate (Irenat^{R}, Bayer) is evaluated by measuring thyroid activity before and 1 hour after its administration. The dosage for a newborn is 90 mg (0.3 ml).

In the normal neonate, perchlorate does not alter thyroid activity and the test is therefore negative. In contrast, thyroid activity is reduced when organification is defective, and the

test is then positive. The change in activity is measured as the ratio between the difference in the activity of the thyroid ROI (corrected for background noise) before and after perchlorate, and the initial activity (also corrected for background noise). For accurate measurement of thyroid activity, the images must be acquired in identical geometric conditions, particularly the distance between the child's neck and the collimator. Subtraction of the background noise on each image is crucial, because 123-I recirculation increases the background noise. The background noise ROI, identical in size to the thyroid ROI, is placed in the right lung field to avoid radiation emitted by the thyroid and stomach. A sample calculation is shown in Figure 6. A change of 10% is considered significant (43). It can reach 98% in children with no iodide organification (fig. 7).

Defective organification is usually permanent, being due to a defect in a gene involved in organification (the TPO and DUOX2/DUOXA2 genes in >70% of cases) (21,44). It can also transient, however, following iodine overload due to polyvindione disinfection prior to maternal surgery (e.g. cesarean) (21). Some organification disorders, especially those related to DUOX2/DUOXA2 gene defects, may also be transient. Re-evaluation of thyroid function is thus recommended in all forms of hypothyroidism associated with an eutopic thyroid gland. In a French study of 71 CH neonates with a positive perchlorate test, CH was transient in 11 cases. Only one of the 11 children had a discharge test showing a change exceeding 90% (45).

The perchlorate test is normal in case of impaired thyroglobulin synthesis or secretion (46).

The pediatric nuclear medicine department of Armand Trousseau Children's Hospital in Paris studied 182 consecutive newborns referred for CH between 2005 and 2008 (47). The thyroid was eutopic in 43% of cases (77 children), who therefore underwent the perchlorate test.

The result was positive in 42/77 cases (55%), with more than a 70% reduction in thyroid activity in 13/77 cases (17%). These children with severe organification disorders, like those with athyreosis (21% of children in our study), have some of the most severe forms of CH. These children require close medical monitoring and very fine dose adjustment.

Dosimetry in neonatal thyroid scintigraphy

When Tc99m-pertechnetate is used, its activity is 0.16 mCi (6 MBq). An activity of 0.03 mCi (1.1 MBq) of iodine-123 is sufficient, although the Paediatric Dosage Card recommends a minimum of 0.08 mCi (3 MBq) (48). In these conditions, the effective dose is 0.12 rems (1.2 mSv) with Tc99m and 0.36 rems (3.6 mSv) with I-123. This effective dose (the same as natural background radiation in many countries) is probably on the high side (8), being based on the assumption of an eutopic thyroid fixing 30% of the injected activity. It is not valid in case of athyrosis or scarce ectopic thyroid tissue. When the thyroid is in place, uptake is low in case of hypoplasia. Perchlorate administration reduces the activity already fixed by the thyroid, if the test is positive. The activity does not decline if the test is negative but subsequent 123-I uptake by the thyroid decreases, due to competition between perchlorate and iodide (creating a break in the uptake curve). To our knowledge, there are no published "real-life" dosimetry data for neonatal thyroid scintigraphy.

CONCLUSION

Thyroid scintigraphy is relatively simple in a neonate with congenital hypothyroidism and makes a useful diagnostic contribution. In practice, it requires close collaboration between

the pediatric endocrinologist and nuclear physician. The former is convinced of the importance of scintigraphy for his or her patient, and wants it to be done rapidly. The latter should make it a priority, in order to make sure it is done before replacement therapy normalizes the serum TSH. Scintigraphic examination is more thorough with iodine-123, which is the only isotope compatible with the perchlorate discharge test. The choice of iodine-123 is all the more logical because the proportion of CH neonates with an intact thyroid gland is increasing.

Acknowledgments

The authors acknowledge the nuclear medicine staff of Hôpital Trousseau who expertly acquired images, and Pr E Hindié, MD, PhD, for his support.

REFERENCES

1. Ford G, LaFranchi SH: Screening for congenital hypothyroidism: a worldwide view of strategies. Best Pract Res Clin Endocrinol Metab 2014; 28:175-187

2. Rapaport R: Congenital hypothyroidism: an evolving common clinical conundrum. J Clin Endocrinol Metab 2010; 95:4223-4225 (editorial)

3. Léger J, Olivieri A, Donaldson M, et al: European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. J Clin Endocrinol Metab 2014; 99:363-384

4. Albert BB, Heather N, Derraik JG, et al: Neurodevelopmental and body composition outcomes in children with congenital hypothyroidism treated with high-dose initial replacement and close monitoring. J Clin Endocrinol Metab 2013; 98:3663-3670

5. Léger J, Larroque B, Norton J: Influence of severity of congenital hypothyroidism and adequacy of treatment on school achievement in young adolescents: a population-based cohort study. Acta Paediatr 2001; 90:1249-1256

6. Léger J, Ecosse E, Roussey M, et al: Subtle health impairment and socioeducational attainment in young adult patients with congenital hypothyroidism diagnosed by neonatal screening: a longitudinal population-based cohort study. J Clin Endocrinol Metab 2011; 96:1771-17 82

7. Geelhoed EA, Lewis B, Hounsome D, et al: Economic evaluation of neonatal screening for phenylketonuria and congenital hypothyroidism. J Paediatr Child Health 2005; 41:575-579

8. Clerc J: Imaging the thyroid in children. Best Pract Res Clin Endocrinol Metab 2014; 28:203-220

9. Gaudino R, Garel C, Czernichow P, et al: Proportion of various types of thyroid disorders among newborns with congenital hypothyroidism and normally located gland: a regional cohort study. Clin Endocrinol (Oxf) 2005; 62:444-448

10. Léger J: Congenital hypothyroidism: a clinical update of long-term outcome in young adults. Eur J Endocrinol 2015; 172:R67-R77

11. Park SM, Chatterjee VK: Genetics of congenital hypothyroidism. J Med Genet 2005; 42:379-389

12. Grasberger H, Refetoff S: Genetic causes of congenital hypothyroidism due to dyshormonogenesis. Curr Opin Pediatr 2011; 23:421-428

13. Eugster EA, LeMay D, Zerin JM, et al: Definitive diagnosis in children with congenital hypothyroidism. J Pediatr 2004; 144:643-647

14. LaFranchi SH: Approach to the diagnosis and treatment of neonatal hypothyroidism. J Clin Endocrinol Metab 2011; 96:2959-2967

15. Thomas Jde V, Collett-Solberg PF: Perinatal goiter with increased iodine uptake and hypothyroidism due to excess maternal iodine ingestion. Horm Res 2009; 72:344-347

16. Moreno JC, Bikker H, Kempers MJ, et al: Inactivating mutations in the gene for thyroid oxidase 2 (THOX2) and congenital hypothyroidism. N Engl J Med 2002; 347:95-102

17. Rabbiosi S, Vigone MC, Cortinovis F, et al: Congenital hypothyroidism with eutopic thyroid gland: analysis of clinical and biochemical features at diagnosis and after re-evaluation. J Clin Endocrinol Metab 2013; 98:1395-402

18. Vigone MC, Caiulo S, Di Frenna M, et al: Evolution of thyroid function in preterm infants detected by screening for congenital hypothyroidism. J Pediatr 2014; 164:1296-1302

19. LaFranchi SH: Screening preterm infants for congenital hypothyroidism: better the second time around. J Pediatr 2014; 164:1259-1261 (editorial)

20. Hinton CF, Harris KB, Borgfeld L, et al: Trends in incidence rates of congenital hypothyroidism related to select demographic factors: data from the United States, California, Massachusetts, New York, and Texas. Pediatrics 2010; 125 (suppl 2):S37-47

21. Clerc J, Monpeyssen H, Chevalier A, et al: Scintigraphic imaging of paediatric thyroid dysfunction. Horm Res 2008; 70:1-13

22. Barry Y, Bonaldi C, Goulet V, et al: Increased incidence of congenital hypothyroidism in France from 1982 to 2012: a nationwide multicenter analysis. Ann Epidemiol 2016; 26:100-105.e1-4

23. Deladoëy J, Ruel J, Giguère Y, et al: Is the incidence of congenital hypothyroidism really increasing? A 20-year retrospective population-based study in Québec. J Clin Endocrinol Metab 2011; 96:2422-2429

24. LaFranchi SH: Increasing incidence of congenital hypothyroidism: some answers, more questions. J Clin Endocrinol Metab 2011; 96:2395-2397 (editorial)

25. Corbetta C, Weber G, Cortinovis F, et al: A 7-year experience with low blood TSH cutoff levels for neonatal screening reveals an unsuspected frequency of congenital hypothyroidism (CH). Clin Endocrinol (Oxf) 2009; 71:739-745

26. Mengreli C, Kanaka-Gantenbein C, Girginoudis P, et al: Screening for congenital hypothyroidism: the significance of threshold limit in false-negative results. J Clin Endocrinol Metab 2010; 95:4283-4290

27. Szinnai G: Genetics of normal and abnormal thyroid development in humans. Best Pract Res Clin Endocrinol Metab 2014; 28:133-150

28. Castanet M, Lyonnet S, Bonaïti-Pellié C, et al: Familial forms of thyroid dysgenesis among infants with congenital hypothyroidism. N Engl J Med 2000; 343:441-442

29. Garel C, Léger J: Thyroid imaging in children. Endocr Dev 2007; 10:43-61

30. Wasniewska M, De Luca F, Cassio A, et al: In congenital hypothyroidism bone maturation at birth may be a predictive factor of psychomotor development during the first Year of life irrespective of other variables related to treatment. Eur J Endocrinol 2003; 149:1-6

31. Bubuteishvili L, Garel C, Czernichow P, et al: Thyroid abnormalities by ultrasonography in neonates with congenital hypothyroidism. J Pediatr 2003; 143:759-764

32. Perry RJ, Maroo S, Maclennan AC, et al: Combined ultrasound and isotope scanning is more informative in the diagnosis of congenital hypothyroidism than single scanning. Arch Dis Child 2006; 91:972-976

33. Tas F, Bulut S, Egilmez H, et al: Normal thyroid volume by ultrasonography in healthy children. Ann Trop Paediatr 2002; 22:375-379

34. Garel G, de Labriolle-Vaylet C, Léger J: Echographie et scintigraphie de la thyroïde chez le fœtus et le nouveau-né, in Medecine Sciences Lavoisier Publications: Imagerie de la thyroïde et des parathyroïdes. Paris, 2011

35. Marinovic D, Garel C, Czernichow P, et al: Ultrasonographic assessment of the ectopic thyroid tissue in children with congenital hypothyroidism. Pediatr Radiol 2004; 34:109-113

36. Fugazzola L, Persani L, Vannucchi G, et al: Thyroid scintigraphy and perchlorate test after recombinant human TSH: a new tool for the differential diagnosis of congenital hypothyroidism during infancy. Eur J Nucl Med Mol Imaging 2007; 34:1498-1503

37. Rose SR, Brown RS, et al: Update of newborn screening and therapy for congenital hypothyroidism. Pediatrics 2006; 117:2290-2303

38. Schoen EJ, Clapp W, To TT, et al: The key role of newborn thyroid scintigraphy with isotopic iodide (123I) in defining and managing congenital hypothyroidism. Pediatrics 2004; 114:683-688

39. Vercellino L, Alaoui NI, Faugeron I, et al: Lingual thyroid imaging with ^{123}I SPECT/CT. Eur J Nucl Med Mol Imaging 2011; 38:1173

40. Brown RS, Bellisario RL, Botero D, et al: Incidence of transient congenital hypothyroidism due to maternal thyrotropin receptor-blocking antibodies in over one million babies. J Clin Endocrinol Metab 1996; 81:1147-1151

41. Szinnai G, Kosugi S, Derrien C, et al: Extending the clinical heterogeneity of iodide transport defect (ITD): a novel mutation R124H of the sodium/iodide symporter gene and review of genotype-phenotype correlations in ITD. J Clin Endocrinol Metab 2006; 91:1199-1204

42. Cassio A, Nicoletti A, Rizzello A, et al: Current loss-of-function mutations in the thyrotropin receptor gene: when to investigate, clinical effects, and treatment. J Clin Res Pediatr Endocrinol 2013; 5 (suppl 1):29-39

43. Clerc J: Apport de la Médecine Nucléaire au diagnostic des hypothyroïdies congénitales et de l'enfant. Med Nucl 2002; 26:442-454

44. Medeiros-Neto G, Billerbeck A, Wajchenberg B, et al: Defective organification of iodide causing hereditary goitrous hypothyroidism. Thyroid 1993; 3:143-159

45. Cavarzere P, Castanet M, Polak M, et al: Clinical description of infants with congenital hypothyroidism and iodide organification defects. Horm Res 2008; 70:240-248

46. Medeiros-Neto G, Targovnik HM, Vassart G: Defective thyroglobulin synthesis and secretion causing goiter and hypothyroidism. Endocr Rev 1993; 14:165-183

47. Ismaili-Alaoui N, Mouzoune S, Sergent Alaoui A, et al: Scintigraphy for neonatal hypothyroidism: why 123-iodine should be preferred to Pertechnetate. Eur J Nucl Med Mol Imaging 2011; 38(suppl2), S190

48. Lassmann M, Biassoni L, Monsieurs M, et al: The new EANM paediatric dosage card: additional notes with respect to F-18. Eur J Nucl Med Mol Imaging 2008; 35:1666-1668

Figures

Figure 1: contention mattress for newborns. The child's head is maintained on both sides.

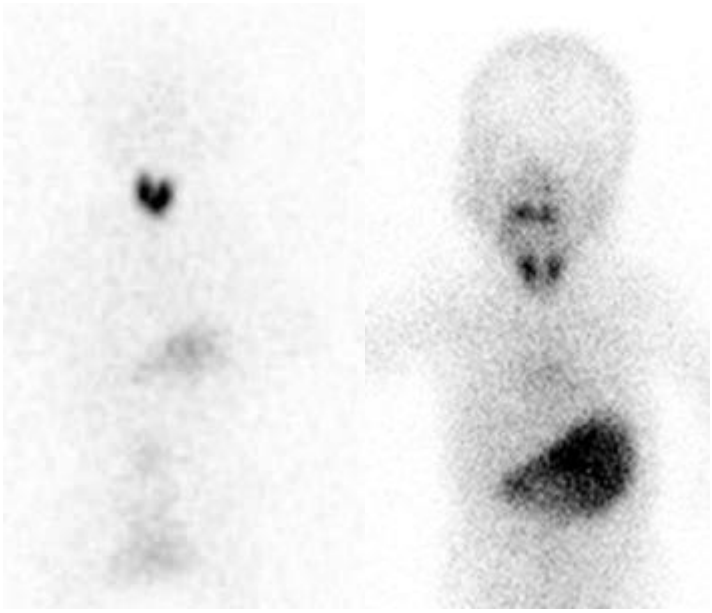

Figure 2: Scintigraphic aspect of the intact thyroid. Left: after iodine-123 injection; right: after injection of 6 MBq of Tc99m (courtesy of Dr I Roca). With the latter isotope, salivary activity present in the mouth can mask a small ectopic gland, and the acquisition should be repeated after giving the child a drink if the thyroid is not initially visible.

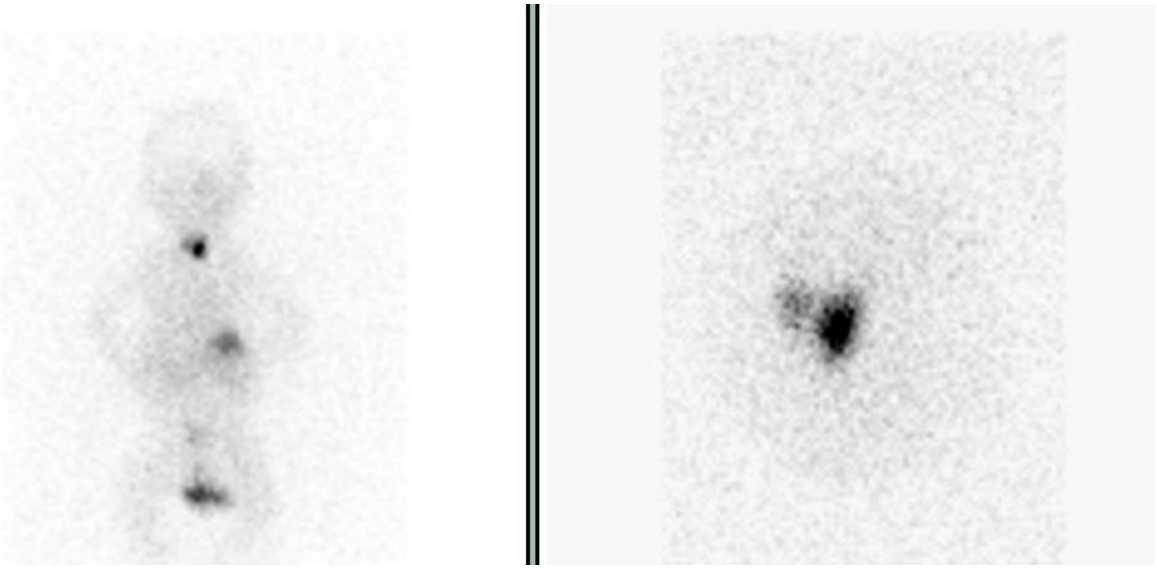

Figure 3: Hypoplasia. Anterior view (left) and pinhole magnification (right): the thyroid is in place but the right lobe is hypoplastic.

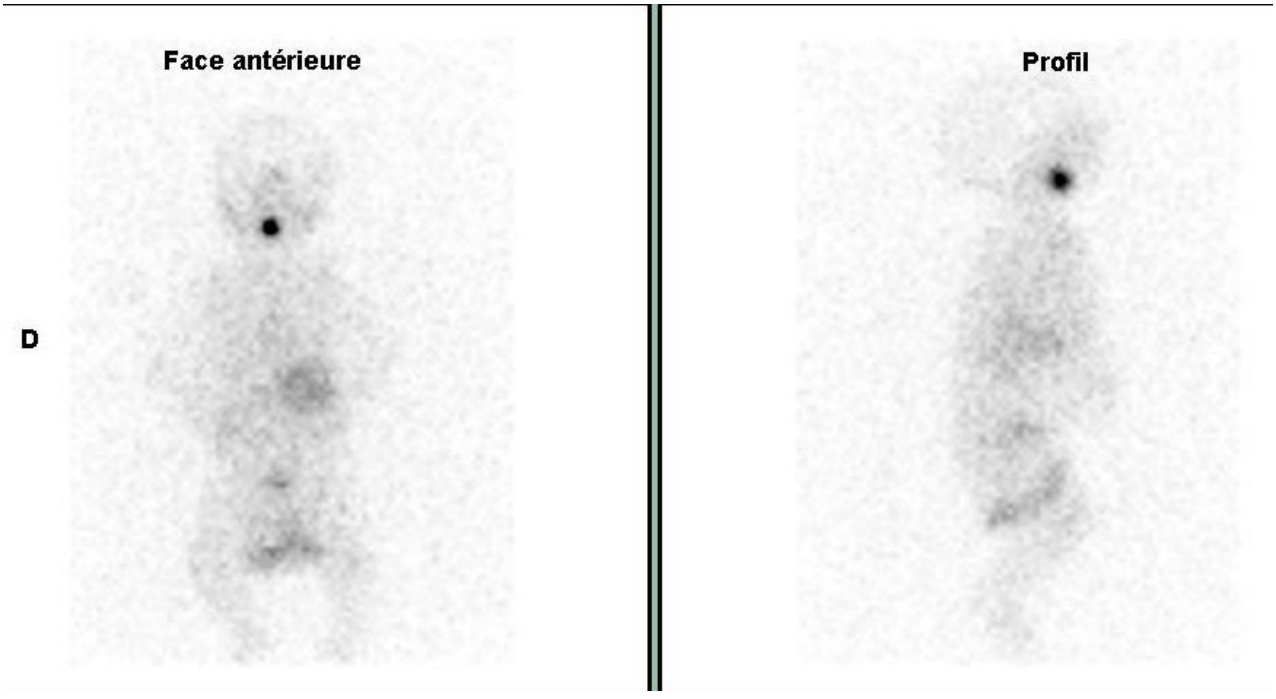

Figure 4: Ectopia. Front and profile views: the ectopic gland is located at the base of the tongue.

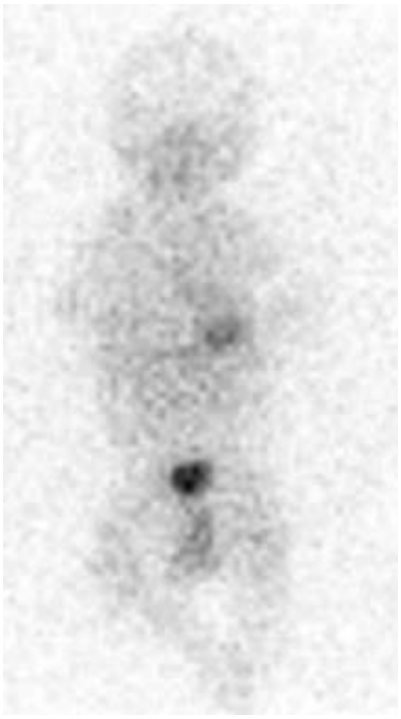

Figure 5: Athyreosis. Image acquired 3 hours after IV injection of iodine-123. Note the gastric activity and urinary activity (in the diaper).

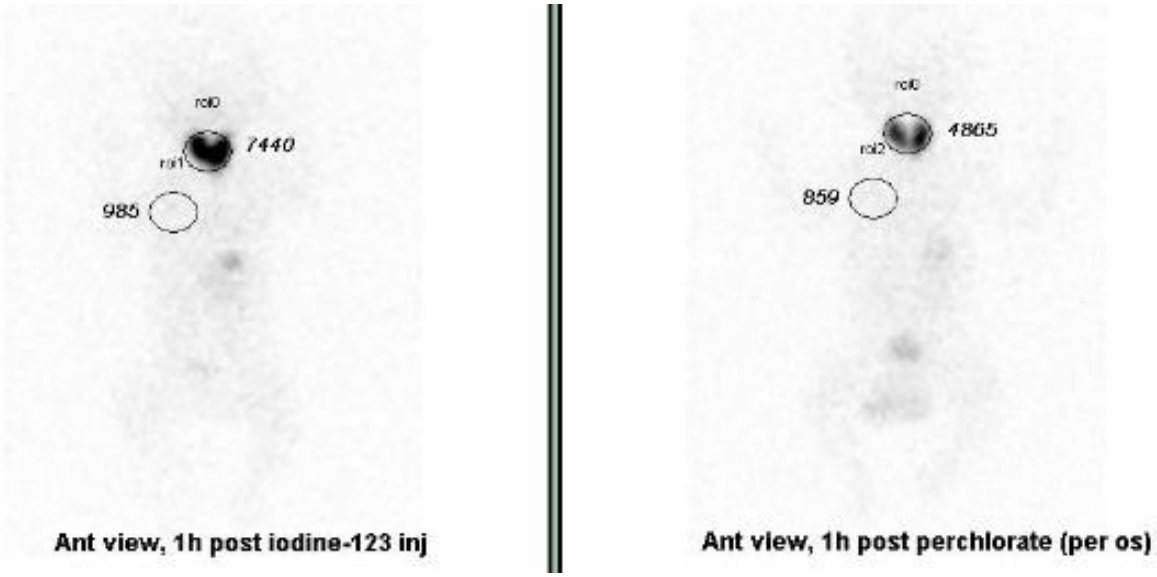

Figure 6: Perchlorate discharge test: calculating the change in thyroid activity.

Thyroid activity before perchlorate (left): 7440 - 985 = 6455;
Thyroid activity after perchlorate (right): 4865 - 859 = 4006

Change: -38%. This reveals moderately defective organification.

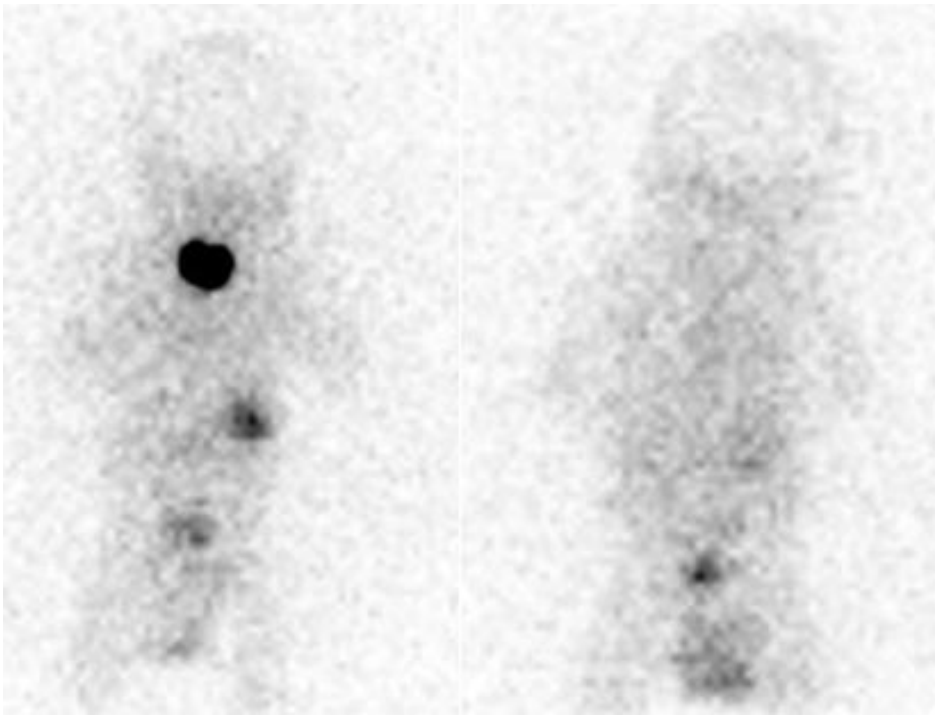

Figure 7: Completely defective organification (TSH at diagnosis was 487 mIU/L): high initial thyroid activity (left) disappears after perchlorate administration (right).