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Thyroid ectopy — diagnostic and therapeutic challenges before and in the era of TSH neonatal screening

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Abstract

Despite the fact that TSH screening in newborns is currently conducted in most developed countries, patients with thyroid ectopy born before the procedure was introduced or those in whom the screening failed to establish diagnosis, might still appear.

In this paper we revise the current state of knowledge regarding the clinical presentation, diagnosis, and treatment of patients with thyroid ectopy. As an example, we report diagnostic and therapeutic difficulties in our three patients with thyroid ectopy remaining undiagnosed and untreated during early childhood. Introduction of neonatal screening for congenital hypothyroidism does not guarantee that all patients with thyroid ectopy will be correctly diagnosed and properly treated, due to the possibility of falsely negative results of TSH screening or lack of compliance from parents. Visualisation of an ectopic thyroid on ultrasound examination may be challenging for unexperienced sonographers; muscles in the thyroid bed may be misdiagnosed as heterogeneous and hypoechogenic thyroid gland with features suggesting autoimmune thyroid disease. Thyroid scintiscan is crucial for confirmation of the diagnosis of thyroid ectopy. In conclusion, hypothyroidism due to thyroid developmental anomaly should be taken into consideration in cases of hypothyroidism and normal thyroid autoantibodies in a patient at any age. **(Endokrynol Pol 2017; 68 (6): 708–714)**

Key words: *thyroid dysgenesis, thyroid ectopy, congenital hypothyroidism screening, thyroid ultrasonography, scintigraphy*

Introduction

Thyroid ectopy is a developmental anomaly defined as the presence of thyroid tissue in a localisation different from the typical one in the lower part of the neck. It is a consequence of arrested migration of thyroid primordium during embryogenesis on its way from the floor of the primitive pharynx to its final destination [1]. In 50–90% of cases of thyroid ectopy the process is stopped at the very beginning, which results in the final location of the thyroid in the lingual area [2, 3].

The aetiology in the majority of patients is unknown, but genetic factors are mentioned among potential causes. Mutations in thyroid transcription factors (*TTF-1*, *TTF-2*, *PAX8*) account for at least some of the patients with thyroid ectopy, and concern mostly syndromic cases, i.e. brain-lung-thyroid syndrome [4].

The prevalence of ectopic thyroid is estimated at the level of 1 per 100,000–300,000 in the population [1], and 1 per 2500–8000 patients with thyroid disease [5, 6]. In another study, the populational incidence of a lingual thyroid was estimated at 1 per 3000–10,000 [7]. However, it might be seriously underestimated because autopsy studies indicate that ectopic thyroid tissue may be visualised even in 10% of the population [8]. Taking into account the data from large cohort series, the vast majority of thyroid ectopies (61–88%) were diagnosed in females [1, 2, 9].

Hormonal function of an ectopic thyroid due to the lack of any possibility of growth expansion is usually insufficient to cover the full demand for thyroid hormones, and over 60% of patients with ectopic thyroid present with hypothyroidism [1]. Ectopic thyroid is usually smaller than eutopic gland and the high rate of hypothyroidism may be explained by the lesser amount of functionally active thyroid tissue. However, immaturity of the gland and functional deficiency are also mentioned as potential causes. The hormonal status of the patients is largely differentiated, from euthyroidism, through subclinical and overt acquired hypothyroidism, up to severe congenital hypothyroidism detected on neonatal screening [10]. Thyroid ectopy is mentioned as the underlying cause in 30–45% of patients diagnosed with congenital hypothyroidism [11]. On the other hand, due to the presence of remnant thyroid tissue and preserved hormonal function, thyroid ectopy is also the most frequent cause of false negative results of TSH neonatal screening [12]. The presence of a small amount of functionally active thyroid tissue may be responsible for the delayed rise in TSH; therefore,

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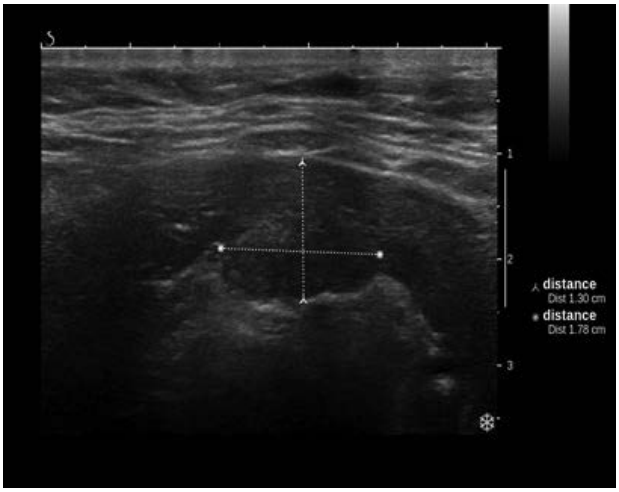

Figure 1. *Ultrasound examination of the upper part of the neck in a Patient 1. A hypoechogenic mass in the lingual area of size 1.3 × 1.78 cm was visualised. No thyroid tissue was present in the typical localisation in the lower part of the neck. Suspicion of lingual ectopic thyroid was made*

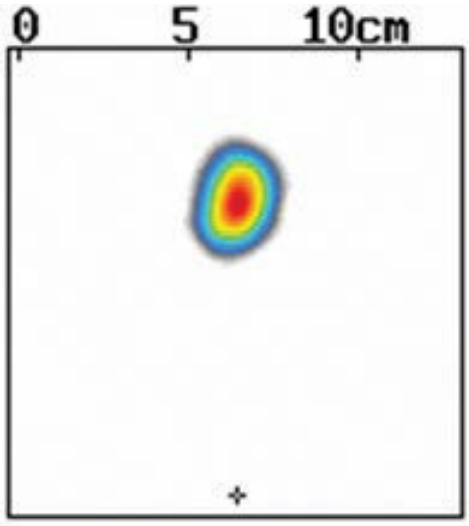

Figure 2. *I-131 scintiscan of the upper part of the neck performed in Patient 1 demonstrated unifocal uptake of the tracer in the lingual area. No radioisotope uptake was present in the lower part of the neck. Diagnosis of thyroid ectopy was confirmed*

the patient might remain misdiagnosed until the hypothyroidism becomes clinically apparent.

In the era of screening examinations for congenital hypothyroidism performed in the neonates, most patients with thyroid ectopy are detected at birth. However, despite the fact that TSH neonatal screening is currently conducted in most developed countries, patients born before the procedure was introduced, or those in whom the screening failed to establish diagnosis, might still appear [13].

In this paper the diagnostic and therapeutic difficulties in patients with thyroid ectopy are discussed based on the example of our three patients, who remained undiagnosed and untreated until the sixth year of age (Patient 2) or adulthood (Patient 1 and 3).

Examples of patients

Patient 1 was born in 1980 (before the introduction of TSH neonatal screening). She completed vocational school and had two children. Her height was 157 cm (lower compared to parents). At the age of 34 years she was diagnosed due to heart arrhythmia. Her TSH was 7.53 μIU/ml (normal 0.27–4.20), accompanied by normal free thyroid hormones and anti-thyroid autoantibodies. On ultrasound examination, no thyroid tissue was visualised in the lower part of the neck. However, when the probe was placed in the upper part of the neck, a hypoechogenic lesion corresponding to the lingual thyroid was visualised (Figure 1). Inside the gland, small focal lesions of mixed echogenicity and size 7 × 4 × 6 mm, 7 × 3 × 6 mm and 8 × 6 × 9 mm, as well as an isoechogenic one 5 × 4 × 5 mm, were demonstrated. The diagnosis of ectopic lingual thyroid was confirmed by thyroid scintiscan (Figure 2). Due to subclinical hypothyroidism, L-thyroxine at the dose of 50 μg/75 μg alternately was introduced. Currently the patient is asymptomatic and remains clinically and biochemically euthyroid. She does not present local compressive symptoms.

Patient 2 was born in 1991 (before the introduction of TSH neonatal screening). At the age of six years she was diagnosed due to short stature during periodic examinations. Her TSH was about 100 μIU/ml (normal 0.27–4.20) accompanied by decreased free thyroid hormones. Levothyroxine was prescribed. At the age of 26 years, on ultrasound examination no thyroid tissue was visualised on the neck. Her thyroglobulin level was 4.91 ng/ml (normal 3.5–77.0). On thyroid Tc-99m scintiscan small focus of tracer uptake was visualised at the base of the tongue (Figure 3). She received secondary education. Menarche occurred at the age of 11 years, and her menstrual cycles are regular. Her height is 160 cm, weight 48 kg. The patient does not present features of congenital hypothyroidism and she does not complain of local discomfort of the neck.

Patient 3 was born in 1995 (TSH neonatal screening had already been introduced in Poland). At the age of 17 years she had TSH measured during screening laboratory tests at school and she was diagnosed with hypothyroidism. Her TSH was 15.02 μIU/ml (normal 0.27–4.2). Her anti-thyroid autoantibodies and free thyroid hormones were within the lower normal ranges. Initially on ultrasound examination she was described to have normally located bilobed thyroid gland of heterogeneous and decreased echogenicity. She was eventually diagnosed with subclinical

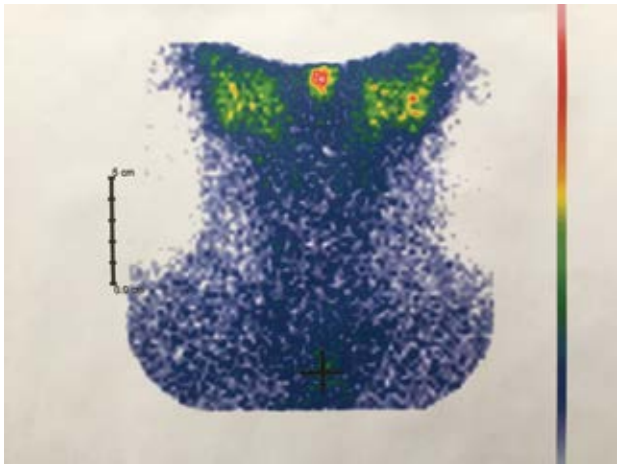

Figure 3. *Tc-99m scintiscan revealed a small foci of tracer uptake at the base of the tongue, corresponding to the ectopic lingual thyroid*

hypothyroidism due to Hashimoto's thyroiditis, and L-thyroxine was prescribed. At the age of 19 years she was admitted to our department for diagnostics of oligomenorrhoea. She had already been taking 75 μg of L-thyroxine and was clinically and biochemically euthyroid. On thyroid examination, lack of thyroid tissue in the lower part of the neck was noticed (Figure 4A). Ultrasound examination of the upper part of the neck revealed the presence of a large partially cystic lesion corresponding presumably to an ectopic thyroid (Figure 4B). The diagnosis of bifocal lingual and sublingual ectopic thyroid was made on the basis of neck scintiscan (Figure 5). Her height was 169 cm, weight 52 kg. She is a student of nursery. Her phenotype is not suggestive of congenital hypothyroidism, and she does not present local compressive symptoms. Of note, retrospective analysis of the result of her TSH neonatal screening revealed that at birth she was diagnosed with congenital hypothyroidism (first TSH screening assessment 140 μIU/ml, second assessment 61 μIU/ml). After birth, her hospitalisation was prolonged due to severe jaundice. Her parents were immediately informed of the results and the need to broaden the diagnostic procedures and introduce L-thyroxine treatment as well as potential consequences of waiver. However, they did not give consent for further diagnostics and therapy.

Discussion

Our three patients are women and presented with lingual (Patient 1 and Patient 2) and bifocal lingual and sublingual thyroid ectopy (Patient 3). Lingual thyroid is reported to occur 4–7-fold more often in women than in men [14, 15]. One of the largest cohort of patients with thyroid ectopy was reported by Yoon et al., where about 47% of cases were patients with lingual thyroid, a further 35% constituted subjects with sublingual location, and 14% had combined type [1]. Other frequent locations besides sublingual (defined as an area between geniohyoid and mylohyoid muscles) are submandibular, supra- or subhyoid, and prelaryngeal [16]. One of the very rare locations is intralaryngeal [17], or intratracheal [1]. Although most ectopic thyroids are located on the embryonic descent path, in 1–3% of cases an ectopic thyroid in the lateral part of the neck is described [18, 19]. The presence of the thyroid tissue on the lateral wall is explained with a theory of benign lymphatic transport, but requires differentiation between ectopic thyroid and metastasis of thyroid cancer, which might be the first sign of occult thyroid cancer. Differential diagnosis should also include a submandibular tumour, branchial cleft cyst, carotid body tumour, and lymphadenopathy of

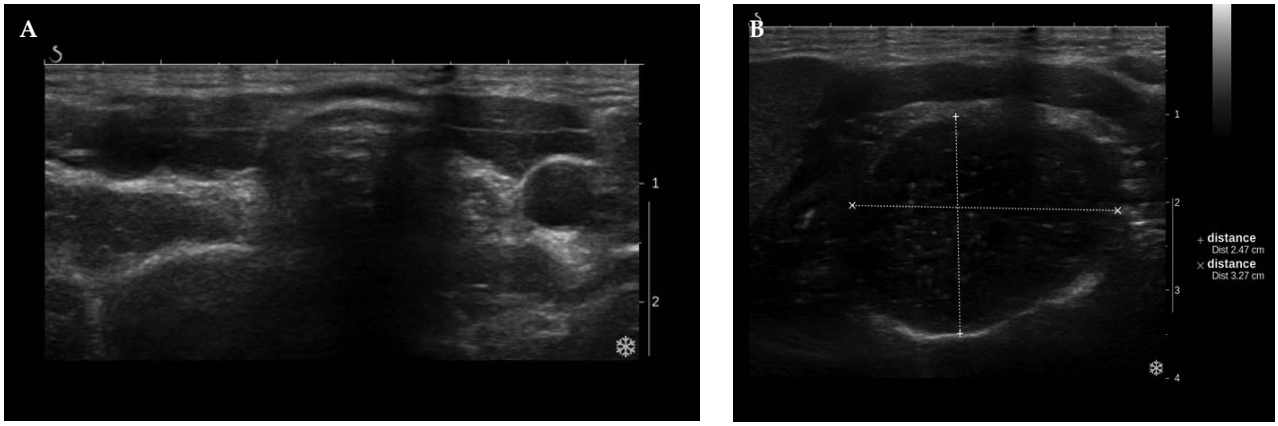

Figure 4A. *Ultrasound examination of the lower part of the neck (Patient 3). No thyroid tissue in typical localisation. Sterno-thyroid and sterno-hyoid muscles in the thyroid bed were previously misdiagnosed as thyroid of decreased and heterogeneous echogenicity typical for autoimmune thyroid disease.* **B.** *Ultrasound examination of the upper part of the neck in Patient 3. A mass of size 2.47 × 3.27 cm presenting cystic degeneration was visualised. Sublingual thyroid was suspected*

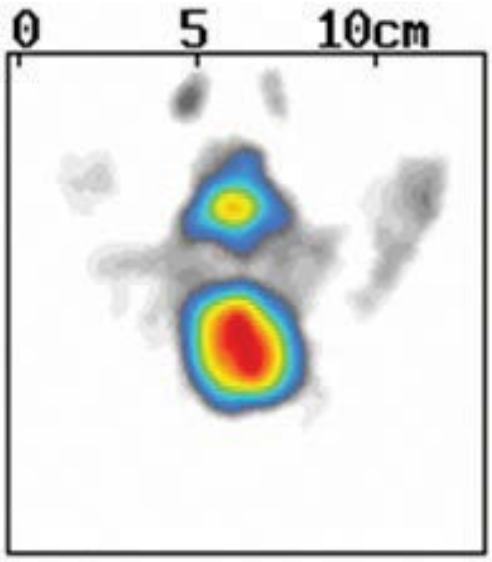

Figure 5. *Tc-99m scintiscan of the upper part of the neck performed in Patient 3 demonstrates bifocal uptake of the tracer in the double lingual and sublingual thyroid. No radioisotope uptake was present in the lower part of the neck. Diagnosis of thyroid ectopy was confirmed*

various aetiologies [20, 21]. Some of the localisations of ectopic thyroid, like intracranial, retrosternal, tracheal, oesophageal, pericardial, retroperitoneal, or pelvic, cannot be explained only by arrested migration of thyroid primordium during embryogenesis [1, 22]. In a minority of subjects, as is the case in our Patient 3, dual thyroid ectopy is diagnosed [23, 24], and such patients constitute only about 5% of cases of thyroid ectopy [16]. One patient with triple ectopia was also reported [25]. Rarely, ectopic thyroid may be accompanied by other thyroid developmental anomalies, i.e. thyroglossal duct cyst [26], or thyroid hemiagenesis [27, 28] as well as concomitant extra-thyroidal anomalies in the form of pyriform sinus fistula or cervical ectopic thymus [29]. However, no accompanying developmental anomalies were diagnosed in our patients.

Regular TSH neonatal screening was introduced in Poland in May 1994 [30]. Hence, Patient 1 and 2 were not screened for congenital hypothyroidism at birth. Patient 3 underwent screening, and congenital hypothyroidism was diagnosed. However, due to lack of parental consent for diagnostics and therapy, she remained untreated until almost adulthood.

Symptoms of ectopic thyroid may be a consequence of its localisation or might be associated with thyroid hypofunction. The age at diagnosis ranges from birth up to 85 years [1, 2]. In the cohort by Gopal et al. the mean age at diagnosis was 14.3 years [9]. One of our patients was diagnosed at the age of 34 years, another one at the age of 6, and the third one was initially diagnosed at birth, but the diagnosis was not confirmed until 17 years of age. In the neonatal period, thyroid ectopy might present as acute respiratory distress, stridor, and poor feeding [31]. An important and often reported clinical manifestation of an ectopic thyroid may be growth restriction, present in 10 out of 49 patients in a Korean cohort [1], and noticeable in two of our patients. One of the clinical manifestations of a lingual thyroid in children might be sleep apnoea [32]. In such cases, nasendoscopy might be useful in diagnosis. If the thyroid dysfunction is not present or is subclinical, and local symptoms are not evident, patients may stay undiagnosed until adulthood [33], as in our two patients. Prolonged TSH overstimulation might lead to thyroid tissue hyperplasia or nodular goitre development (as in one of our patients), which might result in the gradual development of compressive symptoms or even the presence of a palpable tumour of the tongue. Although about half of the patients may be asymptomatic, often local symptoms occur, i.e. sensation of a foreign body, dysphagia, dyspnoea, dysphonia with stomatolalia, snoring, haemoptysis, nasal twang, or upper airway obstruction [34, 35]. However, none of our patients presented with local symptoms. Such symptoms might not be present unless the pathological or physiological situation leading to an increase in the demand for thyroid hormones occurs, i.e. severe disease, pubertal period, pregnancy [36], or lithium therapy, which leads to an increase in TSH concentration and stimulates the thyroid for enlargement [37, 38]. A case of a male patient with an ectopic thyroid causing sleep apnoea was also described. What is interesting, the lingual thyroid was incidentally discovered during intubation procedure [39].

Patients with thyroid ectopy may present with either of the thyroid pathologies found in orthotopic thyroid, i.e. nodular goitre [40], Hashimoto's thyroiditis [41], or Graves' disease [42]. The incidence of differentiated thyroid cancer in lingual thyroid and thyroglossal duct cyst is estimated at approximately 1% of affected patients [43]. The most common types of thyroid cancer arising from an ectopic thyroid are follicular and classic variant of papillary thyroid carcinoma (PTC) [44, 45]. In a series described by Santangelo, one out of 28 patients undergoing thyroid surgery due to ectopic thyroid were histopathologically diagnosed with PTC [46]. However, a case of medullary thyroid cancer deriving from an ectopic thyroid was also described [47]. One of our patients presented with nodular goitre and subclinical hypothyroidism. In the third patient, subclinical thyroid dysfunction was the only detected accompanying pathology, while our second patient was diagnosed with overt hypothyroidism at the age of six years.

The diagnosis of perilingual ectopy is usually suspected on the basis of thyroid ultrasonography that

demonstrates lack of thyroid tissue in an eutopic localisation, but it may reveal ectopic gland when a probe is placed in the submandibular region. It is important that such an examination is performed by an experienced sonographer. Otherwise, muscles in the thyroid bed might be falsely diagnosed as a thyroid gland presenting features of thyroid autoimmune disease. The diagnosis ought to be confirmed by thyroid scintiscan, with I-131 being superior to Tc-99m [48]. SPECT might be of great value in better visualisation of the area of increased tracer uptake detected on scintiscan [49]. Recently the usefulness of hybrid single-photon emission computed tomography/computed tomography imaging using either 123-I or 99-Tc was reported [50]. Fiaschetti et al. described an ectopic thyroid visualised incidentally during MRI of the neck, performed due to pain in the neck [51]. An incidental detection of a lingual mass is an indication to perform scintiscan in order to confirm the presence of functional thyroid tissue. Asymptomatic lingual thyroid may also be an incidental finding detected in a whole body scintiscan performed during diagnostics following total thyroidectomy due to thyroid cancer [52].

Detection of an ectopic thyroid should also imply the need for assessment of the thyroid function. The majority (as much as 83%) of patients are subclinically or overtly hypothyroid [9]. The therapy of accompanying thyroid dysfunction in the case of an ectopic thyroid is adequate L-thyroxine replacement, not different from the management of primary hypothyroidism in patients with orthotopic thyroid. In asymptomatic cases, observation seems to be sufficient. Follow-up of the patients managed conservatively ought to include thyroid function monitoring and thyroid imaging to detect morphological changes (nodules, malignant transformation). In our three patients, the decision on conservative management in the form of L-thyroxine therapy and periodic ultrasound assessment was made. In patients with obstructive symptoms but accompanied by hypothyroidism, introduction of L-thyroxine therapy may result in decrease in TSH level and therefore reduction of the size of ectopic gland, providing significant resolution of symptoms, and thus preclude the patient from the need for surgical procedure [31]. Patients presenting local compressive symptoms despite normalisation of TSH level or with suspicion of neoplastic transformation require surgical intervention followed by life-long L-thyroxine substitution [15]. Surgery may also be a life-saving procedure if an ectopic thyroid presents with acute symptoms like bleeding or airway obstruction [53]. Nonetheless, thyroid ectopy is not a frequent diagnosis on surgical wards because patients with ectopic thyroid constitute less than 1% of patients undergoing thyroid surgery [46]. Resection may be performed through the transoral, transhyoid, or lateral pharyngectomy approach [34]. During the surgical procedure, ectopic thyroid might be a source of complications, i.e. it may cause problematic intubation or pose an increased risk of perioperative haemorrhage. Bianco et al. suggested that arteriography before surgical removal of ectopic thyroid is performed, which might be useful in determining the presence of potential accompanying vascular abnormalities, thereby facilitating the procedure [54]. Another option is transposition of a lingual thyroid to the submandibular region, which was reported in a 52-year-old patient presenting with progressive obstructive symptoms. A 12-month follow-up allowed assurance that the transplanted tissue was still functionally active. Thus, the authors suggested that such a procedure may be an alternative for removal of the gland, which results in a need for life-long L-thyroxine substitution [55]. Two more cases of lingual thyroid transpositioning from extraoral and transoral approach were described by Wu et al. The longest follow-up period reached 16 years, and the transplant survived and allowed the patient to maintain euthyroidism without the need for L-thyroxine supplementation [56]. A successful therapy with radioiodine I-131 was described in several cases of ectopy in patients presenting obstructive symptoms, which might be an alternative for surgery [50]. Temporary L-thyroxine withdrawal and low iodine diet should be applied a few months beforehand to increase the efficacy of such therapy. El-Shafie et al. reported successful therapy of large submandibular ectopic thyroid of size 8 × 6 cm with radioiodine at the dose of 976 MBq. The therapy resulted in hypothyroidism, which occurred three months after therapy [57]. However, ablative radioiodine therapy is reserved for patients in whom malignancy is not suspected, it may require administration of high doses of radioisotope, and it remains controversial in the young. Radiofrequency ablation has been also reported as a potential treatment modality of ectopic thyroid [58].

Conclusions

In spite of the introduction of TSH neonatal screening, in certain patients thyroid ectopy still remains a diagnostic and therapeutic challenge. Despite ongoing neonatal screening for congenital hypothyroidism, some patients with thyroid ectopy born before introduction of TSH screening may still remain undiagnosed. Introduction of the screening procedure does not guarantee that all patients with thyroid ectopy will be correctly diagnosed and properly treated due to the possibility of false negative results of TSH screening or lack of compliance from parents. Hypothyroidism due to thyroid developmental

anomaly should be taken into consideration in a patient with hypothyroidism and normal thyroid autoantibodies. Visualisation of an ectopic thyroid on ultrasound examination may be challenging for unexperienced sonographers; muscles in the thyroid bed may be misdiagnosed as heterogeneous and hypoechogenic thyroid gland with features suggesting autoimmune thyroid disease. Thyroid scintiscan is crucial for confirmation of the diagnosis of thyroid ectopy.

Highlights

1. Introduction of TSH neonatal screening revolutionised the diagnosis and prognosis of patients with congenital hypothyroidism. However, neonatal screening does not guarantee that all patients with thyroid ectopy will be correctly diagnosed and properly treated due to the possibility of falsely negative result of TSH screening or lack of compliance from parents.
2. Thyroid ultrasound examination is of crucial importance in establishing the aetiology of detected hypothyroidism. However, visualisation of an ectopic thyroid on ultrasound examination may be challenging for unexperienced sonographers; muscles in the thyroid bed may be misdiagnosed as heterogeneous and hypoechogenic thyroid gland with features suggesting autoimmune thyroid disease.

Conflict of interest

Authors declare that they have no conflict of interest regarding this publication.

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