Etiologic discussion and clinical relevance of thyroid ultrasonography in subclinical hypothyroidism. A retrospective study in 1845 patients

Discussion étiologique et intérêt clinique de l’échographie thyroïdienne dans l’hypothyroïdie infraclinique. Étude rétrospective de 1845 cas

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Résumé

Position du problème. – L’hypothyroïdie infraclinique de l’adulte est principalement due à une thyroïdite auto-immune. En l’absence de goître ou de thyroïde ferme à la palpation, la recherche des anticorps antithyroïdiens permet de préciser le diagnostic étiologique. Que les anticorps antithyroïdiens soient détectés ou non, quel pourrait être l’intérêt clinique de l’échographie thyroïdienne au cours de cette affection ? Méthodes. – Nous avons étudié 1845 cas d’hypothyroïdie infraclinique de l’adulte dépistés sur des signes évocateurs d’hypothyroïdie ou d’une pathologie thyroïdienne. Tous ces patients ont eu une recherche des anticorps antithyroïdiens et une exploration échographique du corps thyroïde. Localisation. – Étude rétrospective multicentrique. Résultats. – La thyroïdite chronique auto-immune a été affirmée chez 70% des patients. Les anticorps antithyroïdiens n’ont pas été décelés dans 30% des cas. Chez tous les patients, l’échographie thyroïdienne a permis de mesurer le volume thyroïdien, de détecter des nodules non palpables et d’en permettre ainsi l’examen cytologique. Chez les patients sans anticorps antithyroïdiens décelables, l’examen échographique a permis d’évoquer une thyroïdite auto-immune dans 31% des cas. Inversement, l’échographie thyroïdienne n’a pas été contributive chez les patients sans nodules et chez lesquels l’échostructure thyroïdienne était normale. La stratégie du traitement hormonal thyroïdien n’est pas influencée par les données échographiques. Sur l’ensemble des patients, l’examen cytologique a permis de dépister dix cas de suspicion de cancer (4%). La chirurgie a permis de confirmer le diagnostic de cancer neuf fois sur dix. L’échographie avait montré des aspects suspects dans six cas sur dix. Conclusion. – Dans l’hypothyroïdie infraclinique, l’échographie thyroïdienne n’est pas nécessaire pour le diagnostic de thyroïdite auto-immune, mais elle est utile lorsque la palpation thyroïdienne est anormale et elle permet la détection de nodules non palpables. Chez les patients sans anticorps antithyroïdiens décelables, l’échographie thyroïdienne a permis de d’évoquer le diagnostic de thyroïdite auto-immune dans certains cas.

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Abstract

Background. – Acquired subclinical hypothyroidism in adulthood is mainly due to autoimmune thyroiditis. In the absence of a goiter or a palpable firm thyroid, measurement of thyroid antibodies can improve the diagnosis. Whether thyroid antibodies are detected or not, what might be the clinical relevance of ultrasonography in this setting? Methods. – We studied 1845 cases of subclinical hypothyroidism in adults recruited for symptoms indicative of hypothyroidism or thyroid pathology. All patients were screened for thyroid antibodies and underwent an ultrasonographic thyroid examination. Localisation. – Multicentric retrospective study. Results. – Chronic autoimmune thyroiditis was confirmed in 70% of patients. Thyroid antibodies were undetectable in 30% of patients. In all patients, thyroid ultrasonography facilitated measurement of the thyroid volume and detection of non-palpable nodules and therefore allowed biopsy. In patients negative for thyroid antibodies, ultrasonography suggested autoimmune thyroiditis in 31% of cases. Ultrasonography did not contribute to diagnosis in a large number of patients without nodules and in case of normal echostructure. The strategy of thyroid hormone replacement therapy was not influenced by ultrasonographic data. Thyroid biopsies detected smears suspected to be cancerous in 10 patients (4%). Cancer was confirmed in nine patients after surgery. Ultrasonography displayed suspicious aspects in six patients.

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Acquired hypothyroidism in adulthood is mainly due to autoimmune thyroiditis [1]. Diagnosis usually involves patients with subclinical hypothyroidism who are positive for thyroid antibodies [2].

Etiologic diagnosis is more difficult in patients lacking palpable thyroid abnormalities and negative for thyroid antibodies.

The aim of the present study was to evaluate the use of ultrasonography to improve in etiologic diagnosis and determine usefulness for making therapeutic decision in a large number of patients with subclinical hypothyroidism.

1. Studied subjects and methods

We retrospectively studied 1845 patients (1730 women, 115 men), 18–80 years old, with subclinical hypothyroidism. These patients were previously recruited by general practitioners for symptoms indicative of hypothyroidism or thyroid pathology (i.e. goiter and/or nodules, tiredness, weight gain, hair loss, mood troubles). These patients were referred to three Endocrinology centers from 1995 to 2005, where the lab tests were controlled.

The diagnosis for subclinical hypothyroidism was based on serum thyrotropin concentrations of 4–20 µU/mL, and a serum free thyroxine concentration greater than 9 pmol/L [3,4]. Serum thyrotropin concentrations were measured by a third generation immunoenzymatic assay (functional sensitivity lower than 0.02 µU/mL) (Access Sanofi Pasteur, Chiron ACS, Centaur Bayer). Serum concentrations of free thyroxine were measured by a chemoluminescent assay.

The stoutness of patients was calculated using the body-mass index (BMI) in which the weight in kilograms is divided by the square of the size in meters [5]. The body-surface area (BSA) was calculated with the formula [6]:

\[
BSA \left( m^2 \right) = \left( \frac{\text{weight (kg)}}{725} \right)^{0.425} \times \left( \frac{\text{size (cm)}}{71.8} \right)^{0.725} \times 10^{-4}
\]

Thyroid ultrasound examinations were performed in all patients by nine experienced radiologists. Each scan was interpreted by a single radiologist for the purpose of this retrospective study. High frequency linear array transducers were used in each case (greater than or equal to 7.5 MHz).

The volume of each thyroid lobe was calculated with the formula [7]:

\[
\text{volume} = \text{length (cm)} \times \text{width (cm)} \times \text{thickness (cm)} \times 0.52
\]

The thyroid volume (TV) was the sum of the volume of each lobe without considering the isthmus volume.

A goiter was defined by a TV greater than 18 cm³ in women and greater than 20 cm³ in men [8,9]. Thyroid atrophy was defined by a TV less than or equal to 6 cm³ in both sexes [10].

The ultrasonographic thyroid examination identified two echostructural aspects:

- normal appearance of the parenchyma;
- typical aspects of chronic thyroiditis associated with a total hypoechogenicity of the parenchyma versus the prethyroid muscles, blurred and battered contours of the lobes, disseminated and more echogenic longitudinal streaks, and the possible presence of pseudo-nodules. The sonographic aspect was occasionally less typical or incomplete with only heterogeneity and/or hypoechogenicity of the parenchyma [11].

The palpable nodules were assessed by fine-needle biopsy. Ultrasonically guided biopsy was proposed for the assessment of non-palpable nodules when the nodule diameter was greater than 1 cm [12]. The pseudo-nodules in chronic thyroiditis were not assessed. The calliper of the needles for biopsies was 23 to 27 G and biopsies were performed without aspiration.

Antibodies against thyroperoxidase (TPOAb) were identified by immunochemoluminescence. Antibodies against thyroglobulin (TGA) were identified by sandwich immunochemoluminescence or passive hemagglutination only in patients negative for TPOAb. Antibodies against thyrotropin receptor (TRAb) were determined by radioimmunoassay only in some patients.

Patients were divided into the two following groups:

- AI+ (positive thyroid autoimmunity) including patients of both sexes with a thyroid autoimmune disease (elevated TPOAb or TGA, above normal range);
- AI− (negative thyroid autoimmunity) including patients of both sexes without evidence of thyroid autoimmune disease (TPOAb or TGA undetected or within normal values).

We excluded patients previously treated with thyroid hormones and patients with the following conditions:

- previous neck or chest radiotherapy;
- previous Graves’ disease;
- previous treatment with antithyroid drugs;
- previous thyroid surgery;
- progression of subacute thyroiditis;
- previous lithium or interferon or other cytokines therapies;
- iodine or radioiodine therapy;
- nephrotic syndrome;
Subclinical hypothyroidism in 1845 patients. Auxology according to the sex.

<table>
<thead>
<tr>
<th>No of patients</th>
<th>AI+ women</th>
<th>AI− women</th>
<th>AI+ men</th>
<th>AI− men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>48.5 ± 13.3</td>
<td>48.6 ± 14.8</td>
<td>52.6 ± 14.7</td>
<td>56.3 ± 17.8</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>25.26 ± 6.09</td>
<td>26.39 ± 5.85</td>
<td>27.69 ± 4.21</td>
<td>29.19 ± 5.34</td>
</tr>
<tr>
<td>Body-surface area (m²)</td>
<td>1.69 ± 0.26</td>
<td>1.73 ± 0.17</td>
<td>2.01 ± 0.15</td>
<td>2.01 ± 0.21</td>
</tr>
<tr>
<td>Thyrotropin (mIU/mL)</td>
<td>7.25 ± 3.22</td>
<td>6.18 ± 2.42</td>
<td>7.36 ± 3.46</td>
<td>7.22 ± 3.58</td>
</tr>
<tr>
<td>Free thyroxine (pmol/L)</td>
<td>12.23 ± 2.29</td>
<td>12.80 ± 2.32</td>
<td>12.49 ± 2.60</td>
<td>13.33 ± 2.54</td>
</tr>
<tr>
<td>Thyroid volumes (cm³)</td>
<td>10.85 ± 6.86***</td>
<td>7.48 ± 4.97</td>
<td>15.42 ± 19.78***</td>
<td>9.56 ± 8.36</td>
</tr>
</tbody>
</table>

Mean plasma thyrotropin and free thyroxine values. Mean thyroid volumes.

Valeurs moyennes des TSH plasmatiques, des thyroxinémies libres et des volumes thyroïdiens.

Plus-values are means ± S.D. Comparisons between the two mean values were made separately for each sex groups (*P<0.05, ***P<0.001).

AI+ women: aged 19–80 years/detected thyroid autoimmunity.
AI− women: aged 19–80 years/undetected thyroid autoimmunity.
AI+ men: aged 19–80 years/detected thyroid autoimmunity.
AI− men: aged 19–80 years/undetected thyroid autoimmunity.

- Turner’s syndrome;
- Down’s syndrome;

The screening under very exceptional conditions of subclinical hypothyroidism (i.e. genetic defects) was not conducted.

Statistical results are expressed as means plus or minus one standard deviation (S.D.). The comparison between two mean values with a significant difference (P<0.05) was based on the Z score calculation and the use of Fisher and Yates table of Z scores. The comparison between two observed rates, subject to the general problem of linking between two qualitative characters, depended upon the χ² test and the use of the Fisher and Yates χ² table.

2. Results

Among the 1845 patients included in this study, 1285 (69.6%) possessed immune features of autoimmune thyroiditis and 560 (30.4%) had no evidence of thyroid autoimmunity according to the described criteria. Among the 1285 patients with autoimmune thyroiditis, 1203 (93.6%) were TPOAb positive and 82 (6.4%) were TGAAb positive.

TRAb was detected in five patients of the 72 who underwent this measurement and undetected in 67 patients. These five patients were also positive for the other autoimmunity markers and belonged to the AI+ group.

The clinical and biological characteristics of all patients are detailed in Table 1 (AI+ and AI− patients were divided into two subgroups according to their sex). No significant difference of BMI or BSA appeared in any group. The AI+ patients had slightly higher mean serum thyrotropin concentrations than AI− patients. The difference was not significant.

The thyroid biometry and the ultrasonographic aspects of patients from both groups are detailed in Table 2. Among AI− patients, 31% showed indications of autoimmune disease in their ultrasounds (versus 76% among AI+ patients) and 69% produced normal ultrasounds, irrespective of the TV (versus 24% among AI+ patients). The differences in rates between the two groups were highly significant.

Table 3
Subclinical hypothyroidism in 1845 patients.

<table>
<thead>
<tr>
<th>AI+ patients</th>
<th>AI− patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>1285</td>
</tr>
<tr>
<td>Patients who underwent fine-needle biopsy (%) (N)</td>
<td>16 (211)</td>
</tr>
<tr>
<td>Benign smears with signs of chronic lymphocytic thyroiditis (%) (N)</td>
<td>66 (139)</td>
</tr>
<tr>
<td>Benign smears without signs of chronic lymphocytic thyroiditis (%) (N)</td>
<td>29 (62)</td>
</tr>
<tr>
<td>Smears suspected to be cancerous (%) (N)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Undetermined smears (%) (N)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Prevalence of nodular pathology and cytological diagnosis of thyroid lesions.

Étude de la biométrie et de l’échostructure thyroïdiennes.

All results are percentages followed by the corresponding number of patients (**P<0.001).

AI+ patients: men and women aged 19–80 years/detected thyroid autoimmunity.
AI− patients: men and women aged 19–80 years/undetected thyroid autoimmunity.
The prevalence of thyroid nodules and the outcomes of cytological investigations in both groups are detailed in Table 3. Among AI− patients who underwent fine-needle biopsies, 23% had smears of chronic lymphocytic thyroiditis.

Among all patients biopsied, 10 had smears suspected to be cancerous: six had a palpable nodule (only in AI+ group) and four had a non-palpable nodule (two in each group). Among these 10 patients, six had suspect ultrasonographic appearance (hypoechogeticity, blurred contours). The frequency of smears suspected to be cancerous between the two groups was similar. Nine of these 10 patients had a thyroid cancer confirmed after surgery.

3. Discussion

3.1. Sex ratio in subclinical hypothyroidism

In our study, we noticed a 9/1 female prevalence among patients presenting with clinical troubles. This disparity in sex ratio might be explained by a decreased tendency for males to seek medical attention after teenage years. A centre de recherche, d’étude et de documentation en économie de la santé (CREDES) investigation published in 2000 showed that in France 18% of a general practitioner’s clientele is composed of 20-year-old males versus 33% females of the same age [13]. The tendency to seek medical attention for 20–60-year-old men was significantly lower than in women of the same age. It is not until the age of 68 that the rate of attendance for males matches that of females. Men are probably less likely to seek medical care for moderate symptoms.

3.2. TV and ultrasound aspect

In this study, the TV differences were not explained by BMI or BSA variations. The mean thyrotropin concentrations were greater among patients with positive autoimmunity markers, significantly so in women. This might be linked to the increased mean TV in AI+ patients [14].

In patients with subclinical hypothyroidism, we observed a significant proportion of normal TV values. This could be logical at the early stage of hypothyroidism.

We noticed many thyroid atrophies in subclinical hypothyroidism, usually among patients negative for the autoimmunity markers. Generally, it is reported that thyroid atrophy is a progression of the chronic autoimmune thyroiditis [1]. Conversely, thyroid atrophy might be present in patients of our study at the time of the diagnosis of subclinical hypothyroidism.

Thyroid atrophy triggers a primitive myxedema, an uncommon thyroid pathology characterized by negative tests for TPOAb and/or TGAb and positive tests for TRAb, indicating an autoimmune origin [15]. In our study, TRAb were undetected when searched for in some patients with thyroid atrophy. This might suggest a pathological entity distinct from primitive myxedema.

Thyroid biometric data and ultrasonographic signs of subclinical hypothyroidism have not been systematically reported in previous studies. In the present study, almost 75% of AI− patients had the sonographic characteristics of autoimmune thyroiditis. The percentage of normal thyroid echostructure was conversely greater (almost 70%) among patients with undetected autoimmunity. These conditions do not trigger an advanced thyroid autoimmune disease. The improvement of ultrasonography apparatuses from 1995 to 2005 has no impact on TV measurements. Conversely, this improvement might display more thyroiditis aspects.

In our study, 30% of patients had at least one thyroid nodule detected by palpation or ultrasonography. The cytological investigation of the nodules with diameter greater than 1 cm (16% of all patients) has been shown to accurately confirm lymphocytic thyroiditis, and we detected 10 cases with lesions suspected to be cancerous. The incidence of smears suspected to be cancerous is similar to previous published data [16]. Four of these thyroid cancers were observed by ultrasonography and two of them had a suspicious appearance. We only noticed one case of false positive after surgery. That points out the interest of cytological investigation of the nodules.

The incidence of undetermined smears is similar to recent published data [17,18].

3.3. Etiologic discussion

Hypothyroidism is the consequence of an autoimmune disease in patients positive for thyroid antibodies. Ultrasonography is not required for the diagnosis of autoimmune thyroiditis but it is useful in patients with abnormal thyroid palpation and it allows the detection of non-palpable thyroid nodules.

The diagnosis of autoimmune thyroiditis is more difficult in patients negative for the thyroid antibodies.

It is accepted that the echostructural aspects of chronic autoimmune thyroiditis are specific [12]. This may indicate that the diagnosis of chronic autoimmune thyroiditis is likely in patients with typical echostructural aspects and negative for thyroid antibodies (one third of AI− patients in our study).

In the present study, 21 patients negative for thyroid antibodies underwent a cytological investigation of nodules which lead to the diagnosis of lymphocytic thyroiditis. This point emphasizes the benefit of a fine-needle biopsy of thyroid nodules to assert a thyroid autoimmune disease in patients negative for thyroid antibodies. Baker et al. reported an observation of Hashimoto’s thyroiditis negative for thyroid antibodies in serum (thyroid antibodies were determined by hemagglutination and immunoenzymatic assays) and characterized by the presence of the antibodies in the thyroid [19]. The lymphocytic thyroiditis was confirmed by cytological and histological studies. In that casestudy published in 1988, an ultrasonographic examination would have possibly detected typical features of autoimmune thyroiditis.

Moreover, our medical practice has revealed that thyroid antibodies may be detected several years after the beginning of the autoimmune disease. An autoimmune mechanism should not be excluded in patients with undetected thyroid antibodies.

Finally, all known thyroid antibodies are not measured in current practice. The routine typing of all thyroid antibodies
will better define the etiology of subclinical hypothyroidism for patients in whom antibodies cannot be detected at the present time. The pathophysiological involvement of these antibodies remains controversial [20].

Therefore, the ultrasonography examination leads to detection of non-palpable nodules and allows fine-needle guided biopsies. Moreover, ultrasonography may detect autoimmune thyroiditis appearance in patients negative for thyroid antibodies.

The etiology of subclinical hypothyroidism is uncertain in patients with a normal thyroid echostructure and negative antibodies for thyroid antibodies (70% of patients with a normal thyroid echostructure in this study). We have previously mentioned that patients with other etiologic conditions of acquired hypothyroidism have been excluded from the study, except for those conditions related to iodine deficiency and the toxic effects of smoking and other pollutants which lead to goiters but not thyroid atrophies [21,22].

Our data confirm that there is an autoimmune origin of subclinical hypothyroidism in a large number of patients. Conversely, 20% of subclinical hypothyroidism patients (369/1845) had no obvious etiology when negative for thyroid antibodies, particularly in situations of thyroid atrophy or normal TV or normal echostructure. These data focus on the usefulness of the ultrasonography examination to improve the etiology work-up of subclinical hypothyroidism even in patients negative for thyroid antibodies. Ultrasonography is also helpful for the detection of non-palpable nodules and occult cancers. However, the strategy of thyroid hormone replacement therapy is not influenced by ultrasonography data.

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References