Consensus

Graves' disease in children

La maladie de Basedow chez l'enfant

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Abstract

R1 The diagnosis of Graves' disease in children is based on detecting a suppression of serum TSH concentrations and the presence of anti-TSH receptor antibodies. 1/+++. **R2** Thyroid ultrasound is unnecessary for diagnosis, but can be useful for assessing the size and homogeneity of the goiter. 2/+. **R3**. Thyroid scintigraphy is not required for the diagnosis of Graves' disease. 1/+++. **R4**. The measurement of T4L and T3L levels is not necessary for the diagnosis of Graves' disease in children but can be useful for the management and assessment of prognosis. 1/++. **R5**. In the absence of TSH receptor autoantibodies, the possibility of genetically inherited hyperthyroidism must be considered. 1/++. **R6**. Drug therapy is the primary line of treatment for children and consists of imidazole, carbimazole or thiamazole, with an initial dosage of 0.4 to 0.8 mg/kg/day (0.3 to 0.6 mg/kg/day for thiamazole) depending on the initial severity, up to maximum of 30 mg. 1/++. **R7**. Propylthiouracil is contraindicated for children with Grave's disease. 1/+++. **R8**. Before starting treatment, it may be useful to perform a CBC in order to assess the degree of neutropenia caused by hyperthyroidism. It is not necessary to perform systematic CBCs during follow-up. 2/+. **R9**. An emergency CBC should be performed if symptoms include fever or angina. If neutrophil counts are <1000/mm^3, synthetic antithyroid therapy should be discontinued or decreased and may be permanently contraindicated in severe (<500) and persistent neutropenia. Otherwise treatment may be resumed. 1/++. **R10**. Transaminases levels should be measured before initiating treatment. Systematic monitoring of liver function is not consensually validated. 2/+. **R11**. In cases of jaundice, digestive disorders or pruritus, measuring liver enzymes (AST, ALT), total and conjugated bilirubin and alkaline phosphatases is indicated. 1/++. **R12**. Patients and parents should be informed of the possible side effects of antithyroid agents. 1/+. **R13**. Therapeutic education of parents and children is important in ensuring the best possible treatment compliance. 2/++. **R14**. Given the specificities involved in the treatment of Graves' disease in children, medical care should be provided by a specialist accustomed to treating endocrinopathies in pediatric patients. 2/+. **R15**. Depending on patient age, the severity of the disease at diagnosis and the persistence of anti-TSH receptor antibodies, the initial course of treatment must take place over an extended period of 3 to 6 years. **R16**. The anticipated success rates of medical treatment (50% of patients in remission following several years of treatment) should be explained to the family and the child. The possibility that radical treatment may be required in case of failure or intolerance of medical treatment should also be discussed. 1/++. **R17**. In females with Graves' disease, it is important to explain that they must undergo an assessment by an endocrinologist before planning future pregnancies, from the start of pregnancy and during the course of pregnancy. This is true in all female patients, even those in remission after medical treatment, or those who have undergone radical treatment. **R18**. Indications for a radical treatment can arise in cases of: 1/+: contraindication to antithyroid agents; poorly controlled hyperthyroidism due to lack of compliance; relapse despite prolonged medical treatment; a request made by the family and child for personal reasons. **R19**. Surgery is the radical method of treatment used in children under 5 years of age, or in cases of very large, nodular, or compressive goiters. 2/++. **R20**. The surgeon's experience in dealing with thyroidectomies in children is likely to be the most significant determining factor in limiting the morbidity of the procedure (alongside any collaboration between a pediatric surgeon and an adult surgeon). 1/++. **R21** When radical treatment is indicated, I-131 treatment may be discussed after 5 years (but more often after puberty), if the goiter is not too large. Experience from monitoring Graves' disease in North American children is reassuring. 1/++.

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Résumé

R1. Le diagnostic de maladie de Basedow chez l'enfant repose sur la mise en évidence d'une suppression des concentrations sériques de la TSH ainsi que la présence d'anticorps anti récepteur TSH. 1/+++. **R2.** L'échographie thyroïdienne n'est pas nécessaire pour le diagnostic, mais utile pour apprécier le volume et le caractère homogène du goitre. 2/+. **R3.** La scintigraphie thyroïdienne est inutile pour le diagnostic de maladie de Basedow. 1/+++. **R4.** La mesure de la T4L et de la T3L ne sont pas nécessaires pour le diagnostic de la maladie de Basedow de l'enfant, mais utiles pour la prise en charge et l'appréciation de son pronostic. 1/++. **R5.** En l'absence d'anticorps anti récepteur TSH, les causes génétiques d'hyperthyroïdie doivent être évoquées chez l'enfant. 1/++. **R6.** Le traitement médicamenteux est le traitement de première ligne chez l'enfant, et repose sur les imidazolés, carbimazole ou thiamazole, posologie initiale 0,4 à 0,8 mg/kg/j (0,3 à 0,6 mg/kg/j pour le thiamazole) en fonction de la sévérité initiale, sans dépasser 30 mg. 1/++. **R7.** Le propylthiouracile n'est pas indiqué dans la maladie de Basedow de l'enfant. 1/+++. **R8.** Il est utile d'effectuer une NFS avant l'initiation du traitement, afin d'apprécier le degré de neutropénie due à l'hyperthyroïdie. Il est inutile d'effectuer des NFS systématiques durant le suivi. 2/+. **R9.** En cas de fièvre ou d'angine, une NFS doit être demandée en urgence. Si la numération des polynucléaires neutrophiles est < 1000/mm³ le traitement par antithyroïdiens de synthèse est arrêté ou diminué et peut être définitivement contre indiqué en cas de neutropénie sévère (<500) et persistante. Dans le cas contraire, le traitement peut être repris. 1/++. **R10.** Il est utile de mesurer les transaminases avant l'instauration du traitement. La surveillance systématique de la fonction hépatique n'est pas consensuelle. 2/+. **R11.** S'il existe un ictère, des troubles digestifs, un prurit, la mesure des enzymes hépatiques (ASAT, ALAT), de la bilirubine totale et conjuguée, des phosphatases alcalines, est indiquée. 1/++. **R12.** Les patients et parents doivent être informés des effets secondaires possibles des ATS. 1/+. **R13.**L'éducation thérapeutique des parents et des enfants est importante, pour assurer la meilleure observance possible 2/++. **R14.** Compte tenu des spécificités du traitement de l'enfant, la surveillance doit être assurée par un spécialiste habitué à la prise en charge des endocrinopathies de l'enfant. 2/+. **R15.** La cure initiale de traitement par les ATS chez l'enfant nécessite une durée prolongée comprise entre 3 et 6 ans en fonction de l'âge, de la sévérité de la maladie au diagnostic, de la persistance d'anticorps anti récepteur TSH. 2/++. **R16.** Les taux de succès attendus du traitement médical (50 % de rémission après plusieurs années de traitement) doivent être expliqués à la famille et à l'enfant, et la possibilité d'un traitement radical, en cas d'échec ou d'intolérance au traitement médical, doit être abordée. 1/++. **R17.** Chez la fille avec maladie de Basedow, il est important d'expliquer l'importance d'une évaluation par un endocrinologue au moment des grossesses futures, dès le début de la grossesse, et dans tous les cas, même devant une maladie de Basedow en rémission après traitement médical ou ayant bénéficié d'un traitement radical. **R18**. L'indication d'un traitement radical peut se poser en cas : 1/+ : contre-indication aux ATS ; en cas d'hyperthyroïdie mal contrôlée par manque de compliance ; après rechute malgré un traitement médical prolongé ; à la demande de la famille et de l'enfant pour raisons personnelles. **R19.** La chirurgie est le traitement radical à proposer chez l'enfant de moins de 5 ans ou en cas de goitre très volumineux, nodulaire ou compressif. 2/++. **R20.** Pour limiter la morbidité du geste, l'expérience du chirurgien en matière de thyroïdectomie chez l'enfant est probablement le facteur le plus déterminant. (ainsi que la collaboration éventuelle du chirurgien pédiatre et du chirurgien adulte). 1/++. **R21**. Lorsque le traitement radical est indiqué, l'I-131 peut être discuté chez l'enfant après 5 ans (mais plus souvent après la puberté), si le goitre n'est pas trop volumineux. L'expérience nord-américaine du suivi de ces enfants est rassurante. 1/++.

1. Epidemiology

Hyperthyroidism is a rare and severe disease in children. The disease is much rarer than in adults, with children accounting for approximately 1–5% of cases diagnosed in all age groups [1]. Hyperthyroidism in children is primarily linked to Graves' disease (99% of cases). The disease can occur at any age with a peak in prevalence during adolescence. Nevertheless, it can also occur in very young children under 5 years of age (about 10% of cases) [2]. As in all thyroid pathology and in adults, there is a strong predominance of cases in females.

Graves' disease is more common in children with other autoimmune diseases (linked mainly to Type 1 Diabetes, Turner's syndrome, Down Syndrome, DiGeorge Syndrome) and in children with a family history of autoimmune thyroid disease. Inherited forms account for 15 to 20% of cases (1st degree) [2–7].

As with Hashimoto's disease, the epidemiology of Graves' disease in children is poorly understood and has primarily been studied in northern Europe [8–10] and China [11]. The precise incidence of the disease in children is currently estimated to be on the rise. In Northern Europe, the rate of incidence is 0.1 per 100,000 person-years in young children and 3 per 100,000 person-years in adolescents [9]. In Hong Kong, a rate of up to 14 per 100,000 person-years has been reported, irrespective of observed differences in iodine intake. In the USA, a prevalence of 1 per 10,000 has been reported [12]. Recent data from administrative databases in France indicates that the incidence of the disease is 4.8 per 100,000 in subjects under the age of 15 [13].

2. Clinical and biological presentation

The majority of pediatric patients with Graves' disease display classic signs of hyperthyroidism. The first objective signs may include constant tachycardia, goiters, diarrhea or increased appetite with or without weight loss. However, initial signs are mostly non-specific, such as asthenia, sleep disorders, thermophobia, irritability, emotionality, tremors, palpitations and behavioral disorders accompanied by decreased academic performance.

Diagnosis of the disease is therefore likely to be delayed, with several specialist consultations required before diagnosis.

Goiters are present at diagnosis in more than half of cases and are firm and homogeneous, hyper-vascularized and of variable size [14].

Eye damage is not uncommon in children but occurs less frequently than in adults and is also less severe in its appearance, which may take the form of retraction of the upper eyelid, glare, palpebral edema and mild inflammation. Exophthalmos is rare and oculomotor damage and optic neuropathy are very uncommon [15].

The initial clinical presentation is often severe (>3/4 of cases), especially if the child is young, pre-pubescent and/or non-Caucasian.

Specific symptoms observed in children include:

- cardiac problems manifesting as badly tolerated tachycardia, , hypertension; systolic murmurs due to mitral insufficiency caused by mitral prolapse, [16] which requires an echocardiogram;
- accelerated growth rate with increasing bone maturation, in case of late diagnosis;
- neurological problems with abnormal involuntary spastic movements [17], rarely chorea or pseudomyopathy chorea or pseudo myopathy [18];
- behavioral problems: hyperactivity, concentration disorders, change in behavior and drop-off in academic performance [19];
- neuropsychiatric problems including anxiety and depression, agitation, opposition, aggressiveness or even confusion [19];
- bone problems, (as in adults) such as a decrease in bone mineralization (usually cortical bone) and which is corrected with hyperthyroidism treatment – [20] and, more unusually, pathological fractures or vertebral compression [21].

As in adults, hyperthyroidism may predominate on T3 levels, either initially or during evolution [22]. These forms account for 13% of pediatric patients. They are more common in younger children and are more severe in their clinical presentation, with higher levels of anti-TSH R antibodies at diagnosis. Treatment requires significantly higher doses of antithyroid agents for several months or possibly years [22]. This highlights the importance of free T3 dosage in patients with undetectable serum TSH concentrations. Furthermore, the long term outcomes (particularly the remission rate under drug therapy) are poorly understood.

> The clinical presentation of Graves' disease in children is often severe, especially in young children. The symptoms are not very specific and/or are misinterpreted. They include drops in academic performance, behavioral or personality disorders, tachycardia and increased growth velocity.

> **R1**
> **The diagnosis of Graves' disease in children is based on detecting a suppression of serum TSH concentrations and the presence of anti-TSH receptor antibodies. 1/+++.**

> **R2**
> **Thyroid ultrasound is unnecessary for diagnosis but can be useful for assessing the size and homogeneity of the goiter. 2/+.**

> **R3. Thyroid scintigraphy is unnecessary for the diagnosis of Graves' disease. 1/+++.**

> **R4. The measurement of T4L and T3L levels is not required for the diagnosis of Graves' disease in children but can be useful for the management and assessment of prognosis. 1/++.**

3. Differential diagnoses

In view of the high sensitivity of antibodies, differential diagnoses of Graves' disease should be considered in the absence of TSH receptor antibodies in children with hyperthyroidism:

- genetic causes of hyperthyroidism: activating germline mutations of the *TSH R* gene often appear early on as familial or de novo forms at clinical onset (but not always in the neonatal period). They can often lead to a simple goiter or a multinodular goiter. [23]. McCune-Albright syndrome (MCA) may cause hyperthyroidism in children, with an estimated frequency of 10% (appearing as homogeneous or multinodular goiters, or a toxic adenoma) [24]. Resistance to thyroid hormones caused by mutation of the beta receptor gene (elevated *T4L* and *T3L* and detectable *TSH*) can be considered a genetic cause;
- toxic adenomas are rare in children, with less than a hundred cases reported in the literature in children and adolescents. Hyperthyroidism predominates over T3, there are no autoantibodies and adenomas are extinctive to I-123 scintigraphy. This may result from a genetic cause, such as somatic or germinal TSH R activating mutations, or McCune-Albright syndrome. Treatment requires surgical intervention. Papillary thyroid cancers have been reported in 11% of extinctive adenomas in children (versus 5–6% in adults) [25];

- hashitoxicosis is a stage in hyperthyroidism found in Hashimoto's disease. The hyperthyroid phase is shorter than in Graves' disease (1 to 6 months) and is present in 5% of children with thyroiditis [26]. In most cases, there are no TSH receptor autoantibodies present, but there are anti-TPO antibodies (as in Graves' disease). However, there are forms of the disease that transition from thyroiditis to Graves' disease, or in the opposite direction (less than 5% of cases) [27];
- De Quervain's subacute thyroiditis is rare in children. It causes thyroid pain and acute release of thyroid hormones due to probable post-viral inflammation with no thyroid autoantibodies present [28];
- further causes of non-autoimmune hyperthyroidism in children are very rare and have been reported primarily in clinical cases such as iodine-induced hyperthyroidism, as a side effect of cervical radiotherapy, thyrotoxicosis factitial and pituitary adenoma secreting TSH;
- False hyperthyroidism can also be added to these causes. It can occur as a result of measurement errors in children receiving biotin (for example as an adjuvant treatment for metabolic diseases). In such cases the patient does not in fact have hyperthyroidism, but the use of streptavidin/biotin in some measurement kits can give a false clinical picture of biological autoimmune hyperthyroidism (high T4L and T3L, low TSH, and detection of anti TSH receptor antibodies).. Laboratory findings may indicate hyperthyroidism caused by Graves' disease, in contrast to the clinical picture indicating otherwise [29].

> **R5. In the absence of TSH receptor autoantibodies, the possibility of genetically inherited hyperthyroidism must be considered. 1/++**.

4. Drug therapy

Drug therapy is the first-line treatment for Graves' disease in children. It can result in the disease being completely cured, but it often has to be administered over a prolonged period. The initial treatment period required is by its nature longer than in adults, and depends on the initial severity of the disease and other specific criteria. The efficacy and tolerability of drugs should be monitored throughout the duration of treatment.

The only treatments prescribed for children are derivatives of imidazole, carbimazole or thiamazole. Due to the greater (though still low) frequency of hepatotoxicity occurring in children, propylthiouracil is contraindicated for children [30,31].

4.1. Course of treatment

The initial dosage of carbimazole or thiamazole is 0.4 to 0.8 mg/kg/d (0.3 to 0.6 mg/kg for thiamazole), up to a limit of 30 mg/d. Moderate doses of 0.4 mg/kg are suitable for moderate symptomatology (free T4 <50 pmoL/L), while 0.8 mg/kg is suitable for severe forms, corresponding to hyperthyroidism with severe clinical expression (T4L > 70 pmol/L).

Treatment usually leads to euthyroidism within a few weeks (generally 2 to 6 weeks). Monitoring of drug tolerance and biological thyroid balance (free T4, free T3, and TSH) is usually required after 2 weeks, after 1 month, and on a monthly basis thereafter, until normalization of TSH (because the effect of treatment on T4L and T3L is not equivalent, and some types of Graves' disease predominately affect T3). When TSH is normalized, clinical and biological monitoring (only TSH) can take place on a quarterly basis.

Treatment is administered in 1 to 2 doses per day. Administration in 1 dose per day may result in better patient compliance [32]. TSH can be suppressed for several weeks, even if clinical and biological euthyroidism (assessed on the basis of T4L and T3L) has been achieved. When normal function of the thyroid is achieved, treatment can be gradually reduced by 30–50% to a minimum effective maintenance dose that usually amounts to between 5 and 15 mg/d in children [33]. Maintaining high doses of antithyroid agents combined with levothyroxine ("block and replace"), is not recommended; it has no benefit (particularly in relation to the risk of relapse) and could be linked to an increase in the frequency of side effects of antithyroid agents [34].

If the symptoms are severe (tachycardia) or are poorly tolerated, additional treatment with beta-blockers (atenolol 1 to 2 mg/kg in 1 dose, or propranolol 1 to 2 mg/kg in 2 to 3 doses), during the first 2–4 weeks of treatment with antithyroid agents may be proposed until the normalization of thyroid hormones is achieved.

4.2. Side effects

Agranulocytosis (even rarer: pancytopenia) complications occur very rarely (0.2%) [35]. Systematic monitoring of CBCs is not consensusally validated. Hyperthyroidism itself may be responsible for mild neutropenia or for a moderate rise in transaminases. Liver damage is rare.

Minor side effects such as urticaria, arthralgia and rashes occur frequently in children, in 5–25% of cases. These are transient side effects, with the majority of patients being able to continue treatment.

Imidazoles have been linked to the presence of ANCA (anti-neutrophil cytoplasmic antibodies) [36]. The presence of ANCA can occur at any time during the course of treatment, while the majority of side effects occur during the first 3 to 6 months.

> **R6. Drug therapy is the primary line of treatment for children and consists of imidazole, carbimazole or thiamazole, with an initial dosage of 0.4 to 0.8 mg/kg/day (0.3 to 0.6 mg/kg/day for thiamazole) depending on the initial severity, up to maximum of 30 mg. 1/++**.

R7. Propylthiouracil is contraindicated for children with Grave's disease. 1/+++.

R8. Before starting treatment, it may be useful to perform a CBC in order to assess the degree of neutropenia caused by hyperthyroidism. It is not necessary to perform systematic CBCs during follow-up. 2/+.

R9. An emergency CBC should be performed if symptoms include fever or angina. If neutrophil counts are <1000/mm^3, synthetic antithyroid therapy should be discontinued or decreased and may be permanently contraindicated in severe (<500) and persistent neutropenia. Otherwise treatment may be resumed. 1/++.

R10. Transaminases levels should be measured before initiating treatment. Systematic monitoring of liver function is not consensually validated. 2/+.

R11. In cases of jaundice, digestive disorders or pruritus, measuring liver enzymes (ASAT, ALAT), total and conjugated bilirubin and alkaline phosphatases is indicated. 1/++.

R12. Patients and parents should be informed of the possible side effects of antithyroid agents. 1/+.

R13. Therapeutic education of parents and children is important in ensuring the best possible treatment compliance. 2/++.

R14. Given the specificities involved in the treatment of Graves' disease in children, medical care should be provided by a specialist accustomed to treating endocrinopathies in pediatric patients. 2/+.

4.3. Treatment duration, relapse risk factors, long term outcomes

The remission rate following 2 years of treatment is around 30% in children vs 40–60% in adults, meaning the relapse rate is generally higher in children. Studies in children have shown that age (early age), goiter size (large goiter), the initial severity of the disease (based on serum T4l concentrations and anti-TSH receptor autoantibody levels at diagnosis and during progression), the time required to achieve euthyroidism and the duration of initial medical treatment were all factors predictive of relapse in Graves' disease [37–46].

In the French multicenter prospective study, the risk of disease relapse after an initial 2-year course of antithyroid agents was higher in patients of non-Caucasian ethnic origin, in the very young and also in those with severe symptomatology at diagnosis, as indicated by elevated serum levels of anti-TSH receptor autoantibodies and T4l [41]. The benefits of prolonged treatment with antithyroid agents were demonstrated in the same cohort of this pediatric population [42] and proved that a longer duration of treatment was associated with a higher remission rate. Results showed a remission rate of 50% after 8 years of treatment, comprising several sequential courses of treatment. In the long term, forms of the disease that were initially more moderate and linked to other autoimmune conditions were associated with an increased rate of remission. These results indicate the value of prolonged antithyroid agent treatment in children and adolescents if no undesirable side effects are experienced by the patient [42,47]. This has also been shown more recently in a retrospective study of a cohort of 1138 patients [45].

The predictive factors for remission of Graves' disease in children are summarized in Table 1 below.

Therefore, the prevailing current hypothesis is that remission of Graves' disease is linked to achieving euthyroidism rather than the immunosuppressive action of antithyroid agents [48]. Hyperthyroidism can strengthen autoimmune mechanisms that trigger increased production of anti-TSH R autoantibodies, which in turn leads to more severe hyperthyroidism.

Following restoration of euthyroidism, disease remission can gradually be achieved through prolonged periods of treatment

Table 1
Predictive factors of remission of Graves' disease in children.

Negative	Positive
Biochemical severity	Other associated autoimmune pathologies
Young age	Adolescence
Large goiter	Prolonged treatment period (>2 years)
Non-Caucasian subjects	
Insufficient compliance with treatment	

using antithyroid agents. This is why an initial prolonged treatment period is now preferred, rather than the 2-year repeated courses of treatment that were suggested previously [42,47]. Nevertheless, the proper management of this disease remains a controversial issue in pediatric endocrinology and the optimal duration of medical treatment to induce remission of the disease is still to be determined more accurately, depending on the age of the patient at onset and the severity of the disease.

> **R15. Depending on patient age, the severity of the disease at diagnosis and the persistence of anti-TSH receptor antibodies, the initial course of treatment must take place over an extended period of 3 to 6 years**.

> **R16. The anticipated success rates of medical treatment (50% of patients in remission following several years of treatment) should be explained to the family and the child. The possibility that radical treatment may be required in case of failure or intolerance of medical treatment should also be discussed. 1/++**.

4.4. Long term outcomes

Long term outcomes depend on the potential remission of the disease and the type of treatment used. In addition, some patients may also develop secondary autoimmune hypothyroidism. Long term follow-up care is required, especially in young girls and before any future pregnancies, due to the risk of fetal and neonatal hyperthyroidism induced by persistent high levels of stimulating TSH receptor antibodies. The management of these levels is essential for ensuring a healthy pregnancy, the health of the fetus and newborn and its developmental prognosis.

> **R17. In females with Graves' disease, it is important to explain that they must undergo an assessment by an endocrinologist before planning future pregnancies, from the start of pregnancy and during the course of pregnancy. This is true in all female patients, even those in remission after medical treatment, or those who have undergone radical treatment.**.

Negative impacts of the disease in terms of quality of life in adults include implications for mental health and energy levels [48]. These negative aspects do not seem to be related to the status of patients' thyroid hormones during the follow-up period or to the nature of the treatment (medical or radical). These aspects are yet to be assessed in children suffering from the disease; however, it seems there is a need for prolonged follow-up care both to monitor thyroid function and to diagnose and manage the possible psychological or emotional consequences of the disease.

5. Radical treatment

> **R18. Indications for a radical treatment can arise in cases of:**
>
> - **Contraindication to antithyroid agents;**
> - **Poorly controlled hyperthyroidism due to lack of compliance;**
> - **Relapse despite prolonged medical treatment;**
> - **A request made by the family and child for personal reasons;**
> - **1/+.**

Secondary hypothyroidism induced by radical treatment requires a monitored and well-coordinated replacement treatment plan in the form of levothyroxine. Patients prescribed levothyroxine should adhere to treatment recommendations and their therapeutic education throughout their lives; this is particularly important for children and adolescents because of the impact the treatment may have on growth and puberty. This also applies to young women in order to prevent risks to the course and outcome of pregnancy and, subsequently, to the child's development (compliance and blood control). This must be fully explained to the family at the outset.

5.1. Surgery

Where radical treatment is required, surgery is the treatment of choice in children under 5 years of age (radioactive iodine is contraindicated). Surgery is required if the goiter is very

large (>80 g) or is causing compression (16%), if thyrotoxicosis is severe and accompanied by neurological symptoms, if the patient is suffering from severe thyroid eye disease, or in cases where conventional iodine treatment is contraindicated [14,49].

Alternatively, in other circumstances surgery is an option together with I-131 treatment.

In order to reduce the risk of recurrence, surgery should remove the entirety or the majority of the thyroid [50]. In cases of partial or subtotal thyroidectomies, the risk of recurrence is estimated to be 10–15%. The patient must be in euthyroidism at the time of surgery and Lugol administration for 10 days prior to the operation will optimize conditions for the surgical procedure by limiting the vascularization of the thyroid..

Thyroidectomy complications recorded in children are the same as in adults (hypoparathyroidism, lesion of the recurrent laryngeal nerve, scars). However, the relative frequencies of complications are typically higher than in adults, and in inverse proportion to the child's age [51]. Few studies have been reported, and they show a rate of complications of 10 to 20%: (11% in adolescents and up to 22% in children under 6 years, mostly transient hypoparathyroidism and recurrent laryngeal nerve paralysis [52].

Severe complications (hematoma, infection, recurrent laryngeal nerve paralysis and permanent hypoparathyroidism) are rarer. When surgery is performed by a trained surgeon in a specialist multidisciplinary center, incidence rates in children are almost identical to those in adults [53].

> **R19 Surgery is the radical method of treatment used in children under 5 years of age, or in cases of very large, nodular, or compressive goiters. 2/++**.

> **R20. The surgeon's experience in dealing with thyroidectomies in children is likely to be the most significant determining factor in limiting the morbidity of the procedure. (alongside any collaboration between a pediatric surgeon and an adult surgeon). 1/++**.

5.2. Radioactive iodine treatment

Radioactive iodine treatment is increasingly used in Europe in preference to surgery. However, it continues to be prescribed less often in children and adolescents in France. By contrast, in North America the treatment is offered earlier, after only 1 to 2 years of medical treatment with antithyroid agents.

It is contraindicated:

- expressly in children under 5 years of age (due to the sensitivity of tissues to radiation);

- in relative terms for pre-pubescent children;
- for large goiters over 80 g in mass.

The objective of treatment with radioactive iodine is to use an ablative dose to achieve hypothyroidism (but never euthyroidism) given the risk of secondary thyroid cancer. This is especially important in children due to the particular sensitivity of the thyroid gland to radiation.

As in adults, two methods can be used [54], but there are no comparative pediatric studies between them:

- a fixed dose of no more than 10 to 15 mCi;
- a dose calculated in relation to the volume of the goiter and to a fixation rate of approximately 150 to 200 μCi/g of thyroid tissue.

5.2.1. Early side effects
- Local pain possible in the week following treatment (less than 10%);
- unlike in adults, given the extremely rare nature of severe thyroid eye disease, preventive corticosteroid therapy is not systematic.

5.2.2. Long term risks

There are few studies on the long term outcomes of children treated with I-131 therapy. The theoretical risk of secondary cancer remains unresolved, particularly in young children whose total body exposure for the same dose is higher than that of older subjects. Read's study [55,56], covering 36 years of follow-up of a cohort of 116 patients under 20 years of age, concluded that there was no increased risk of cancer in this population; however, this sample size is small and studies of larger cohorts of children are essential before definitive conclusions can be drawn, particularly in pre-pubescent children.

Therefore, radioactive iodine treatment currently appears to be an effective and safe second-line treatment in children and an alternative to surgery.

> **R21. When radical treatment is indicated, I-131 treatment may be discussed after 5 years (but more often after puberty), if the goiter is not too large. Experience from monitoring Graves' disease in North American children is reassuring. 1/++**.

Disclosure of interest

The authors declare that they have no competing interest.

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