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Treatment of Graves' Disease in Children and Adolescents

Graves' disease (GD) is a rare disease in childhood and adolescence with only 1–5% of all patients being children. The incidence of juvenile GD ranges from 0.1 in young children to 3.0 in 100,000 in adolescents. Despite the numerous literature about therapy of GD in adults only a few investigations concerning children and adolescents were published in the last 15 years [1, 2]. Therefore, many differences and uncertainty in diagnosis and therapy were revealed by a European questionnaire study of the European Thyroid Association and the European Society of Pediatric Endocrinology [3]. The option of radioiodine treatment so far is not commonly accepted in Europe for children and adolescents. The report of Cheetham et al. [4] on their experience – although in a limited number of patients – demonstrates that radioiodine treatment is an appropriate alternative to surgical treatment in those patients who need definitive treatment. The fact that a second dose of radioiodine had to be administered in 4 of the 8 patients demonstrates that the optimal doses in children have to be assessed carefully, because the use of non-ablative doses should be viewed in the background of the Chernobyl experience indicating a high susceptibility of children for thyroid cancer, when exposed to ^{131}I in lower amounts than used therapeutically. The review of the results of any therapeutical option leads to the conclusion that – as for many rare diseases – evidence-based strategies for treatment are lacking and that the choices of therapy seem to be the result of tradition or personal opinions.

Antithyroid Drug Treatment

Most European investigators favor antithyroid drug treatment as the initial treatment of choice [4]. The doses, however, range considerably, but a consensus exists that doses above 0.5 mg/kg/day for methimazole or above 5 mg/kg/day of propylthiouracil should be avoided, because the frequency of side effects is dose dependent. Although in 95% of the patients no side effects of antithyroid drug treatment (ATD) were observed, serious and fatal side effects like liver toxicity leading to organ failure have been observed in single cases [5]. The reason for the choice of ATD as initial treatment is that in a substantial number of patients' GD is a self-limiting disease. Lippe et al. [1] have reported a remission rate of children and adolescents with GD of 25% every 2 years. These findings have resulted in the recommendation that, especially in younger children, ATD treatment should be administered for several years [6]. The results of a study in adult patients with GD, which have demonstrated a positive influence of a combined ATD and T4 treatment and continuation of T4 administration after ATD on long-term remission [7], are still controversial since so far they have not been confirmed by other studies [8, 9]. Usually, in children a combination of ATD and T4 is routine, since it avoids the development of hypothyroidism and enables less frequent monitoring.

A high risk for recurrence of GD in the first year after cessation of treatment and after previous relapses has been recognised. Therefore, it is necessary to question the sense of further ATD courses after recurrence. Only a few single cases are described where a second course of treat-

ment following relapse achieved complete remission [10, 11]. The most important problem limiting the success of ATD, as in any long-term therapy, is compliance. Regarding the recommendation of long-term ATD as the primary choice of treatment, it should also be taken into account that long-term quality of life assessments as well as follow-up investigations after ATD of GD in childhood and adolescence so far are lacking completely.

Subtotal and Total Thyroidectomy

In Europe subtotal or total thyroidectomy is the therapy of choice after a recurrence during or after ATD in children and adolescents with GD [4] and it has been discussed controversially also as the primary choice of treatment. Compared to adults the average period between diagnosis and thyroidectomy is significantly longer [12].

Information on intra- and postoperative complications and their long-term consequences is scarce. Postoperative hypoparathyroidism and recurrent nerve palsy seem to be less frequent (0.5–1.3%) compared to thyroidectomy in children because of thyroid cancer (7–20%) [13–15]. Depending on the surgical attempt of radicality, postoperative recurrence of hyperthyroidism is observed in a significant amount of patients (2–16%) [12]. Postoperative hypothyroidism, which occurs in up to 80% of the patients followed postoperatively, results in the need of lifelong thyroid hormone replacement therapy and lifelong monitoring of thyroid function. Especially in the young child noncompliance of thyroid hormone replacement will possibly lead to negative influences on mental development, growth and school achievement. Therefore, the beneficial effects of thyroidectomy have to be viewed critically against the problem of compliance and need for long-term monitoring of thyroid replacement therapy.

Radioiodine Treatment

Radioiodine therapy with ^{131}I has been employed successfully as definitive treatment for adults with GD for many years. For a long time the use of radioiodine treatment was restricted to patients past the reproductive age, but follow-up studies indicate that radioiodine treatment of thyrotoxicosis is not associated with decreased fertility or germ cell damage, birth defects or abnormal pregnancies [16]. In the United States, in children and adolescents radioiodine therapy has been generally selected as defini-

tive treatment after unsuccessful ATD, but it is also considered occasionally as the primary choice of treatment [17]. Many European pediatricians and pediatric endocrinologists are reluctant to use ^{131}I therapy [4], but in recent years also in the UK and the Netherlands radioiodine treatment has been offered to children and adolescents as primary choice or second-line therapy [19]. In a recent review on the experience in 587 American children aged between 1 and 18 years, no serious complications have been observed during a follow-up period of up to 23 years [18]. Therefore, radioiodine is considered as a safe and effective definitive therapy for GD in children and adolescents. Side effects include vomiting and radiation-induced thyroiditis as well as the development of thyroid nodules [18]. Recurrence of hyperthyroidism is observed in up to 50% of the patients, if insufficient doses of radioiodine are administered and retreatment was necessary. Permanent hypothyroidism occurred in 60–70% of the patients, leading to the same long-term problems as present after subtotal or total thyroidectomy. There is very limited experience with the radioiodine treatment of very young children. The Chernobyl experience has disclosed the fact that the younger the child is at exposure to radiation, the greater is the prevalence of thyroid carcinoma and it has raised concern that the young child may have an increased susceptibility for carcinogenicity of external irradiation and possibly also for ^{131}I [20].

Discussion

ATD fails to induce complete remission in a substantial amount of the patients with juvenile GD and a second or further course of ATD will fail in almost all patients, but prospective randomized trials using standardized ATD doses are lacking and the diagnosis of GD is not defined properly in many of the published studies. Since it has been estimated by Lippe et al. [1] that the remission rate of juvenile GD is 25% every 2 years regardless of the duration of previous therapy, and since 20–30% of the patients in the published series experienced complete long-term remission, it is still advisable to choose ATD as the first choice of treatment.

However, after the first recurrence, during or after ATD, definitive therapy should be approached. Since thyroidectomy has the disadvantages of hospitalization, surgical complications and postoperative hypothyroidism, there is now a tendency to advocate radioiodine as a choice of treatment also for children [18, 19]. In children

any form of treatment has to be considered in the background of a longer life expectancy, especially the relative risks of developing hypothyroidism, radiation oncogenesis and genetic damage. According to the North-American long-term follow-up data which have been published, radioiodine treatment in older children and adolescents seems to be safe and effective, but, like subtotal and total thyroidectomy, it will induce permanent hypothyroidism in a substantial amount of patients [18]. Although the relatively low risks and practicability of radioiodine treatment has favored this therapy for children and adults in the United States, the legal restrictions and the need of hospitalization makes it still less attractive for European countries. The unresolved concerns, which have been raised concerning radioiodine treatment of young chil-

dren [20], in whom GD is very rare, should restrict the radioiodine treatment so far to schoolchildren and adolescents. Further controlled investigations are necessary to improve the distinctive conditions of disease entity and ATD therapy in pediatric patients. Progress in the immunological understanding of the disease and of the genetic background of the disease will hopefully elucidate the pathogenesis and may give new ideas for a more successful and safe therapy. In the meantime, treatment strategies and follow-up studies have to be performed in order to optimize standard procedures. Therefore the European Society for Pediatric Endocrinology and the European Thyroid Association have launched a joint multicenter prospective, randomized study on the treatment of children and adolescents with GD.

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