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PATOLOGÍA TIROIDEA

Graves' disease in the young – where are we going?

Enfermedad de Graves en los jóvenes: ¿hacia dónde vamos?

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Introduction

In the 1940's Wilfred Sheldon - one of the first doctors to focus exclusively on the care of paediatric patients in the UK - described the management of 'Exopthalmic goitre' in his textbook 'diseases of infancy and childhood'[1]. In this book he describes the management of Exopthalmic goitre (Graves' disease) as bed rest and ensuring the child consumes a nutritious diet with iodine under the care of a skilled nursing team. More severe cases could be treated with X-ray exposure with partial thyroidectomy considered in children when a trial of the above measures had not worked. 80 years have now elapsed and it can be argued that little has changed with the components of management described then being similar to those in use today. Care by a highly skilled health professional team is important if one is to reduce the likelihood of a thyrotoxic crisis; a nutritious diet is still under scrutiny as a means of improving outcome with interest in nutrients such as selenium; iodine is still used as an antithyroid drug when preparing patients for surgery or indeed as a component of longer-term treatment; radioactivity and surgery remain key treatment modalities. Novel approaches to management are required if children are to enter adulthood without being on thyroxine replacement for life.

Graves' disease presentation

The clinical features of a young person presenting with Graves' disease are extremely varied with behavioural, gastrointestinal as well as cardiovascular symptoms and signs resulting in referral to a range of different specialty teams. When the diagnosis is made it sometimes becomes clear that patients have been thyrotoxic for many months or even years. Not all patients lose weight and not all have a prominent goitre. Abnormal neurodevelopmental or a deterioration in school performance are striking features in some children[2,3]. Subtle eye signs are frequently present in young people but severe Graves' orbitopathy are relatively uncommon.

The pathological biochemical and immunological 'signature' of Graves' disease is the presence of elevated thyroid hormone concentrations, notably Free T3, a suppressed thyroid stimulating hormone concentration (TSH) and the presence of stimulating antibodies to the TSH receptor (TSHR), usually measured as thyroid receptor antibodies (TRAb). Graves' disease in the young is different to adults with different underlying genetic predisposition[4] and more profound biochemical disturbance at the time of diagnosis. Medical management is more challenging as discussed below.

Management summary

Initial therapy will usually involve the thionamide antithyroid drugs (ATDs) carbimazole (CBZ) or methimazole (MMZ). Beta blockade may be appropriate in more severe, symptomatic cases in the first weeks post-diagnosis. Propylthiouracil (PTU) should be avoided in the young because of the risk of liver failure [5]. Patients need thyroid function monitoring regularly in the initial phase but the frequency between appointments can be increased when patients are clinically and biochemically euthyroid. Unfortunately, remission rates after a course of ATD are lower in young people and yet there is an increased likelihood of CBZ side-effects when compared to adult patients.

When ATD is stopped then patients who relapse usually do so in the first 12 months.

ETA guidance

In 2022 the European thyroid association (ETA) published guidelines aimed at providing a more detailed framework for those managing young people with GD. A key reason for age-specific guidelines is the fact that the benefits versus risks of each treatment modality are different in the young[6]. A small, selected number of learning points, linked to the guideline content, are detailed below.

Antithyroid drug

The ETA guidance highlights the following issues:

1. At baseline one should make sure that the young person does indeed have Graves' disease. Measuring Free T3 can help because Graves' disease is characterised by free T3 excess and an elevated FT4. Marginal FT3 increase in the context of an elevated FT4 is more typical of Hashimoto's thyroiditis.

2. A suppressed or unrecordable TSH, marked Free T3 increase and an elevated TRAb titre is diagnostic of GD.

3. Measuring a full blood count (including a neutrophil count) and liver function tests before CBZ/MMZ is commenced is important because a relatively low WCC and raised ALT can be a consequence of thyroid hormone excess rather than thionamide treatment.

4. A dose titration approach to ATD administration should be used in most patients because of the reduced risk of adverse events with what is usually a lower dose of drug[7]. Another advantage of dose titration of antithyroid drug treatment (not specifically mentioned in the ETA guidance) is that the CBZ dose used to maintain euthyroidism will reflect disease activity and as such provides a signal regarding disease status.

5. The risk of substantial weight gain observed in some patients needs to be discussed with families at an early stage[8].

6. Ideally treat patients for at least 3 years before considering stopping ATD and only do so if the TRAb titre has normalised.

Patients who relapse and become thyrotoxic again when medication is stopped have the option of returning to ATD treatment or opting for definitive treatment with surgery or radioiodine RAI).

Surgery

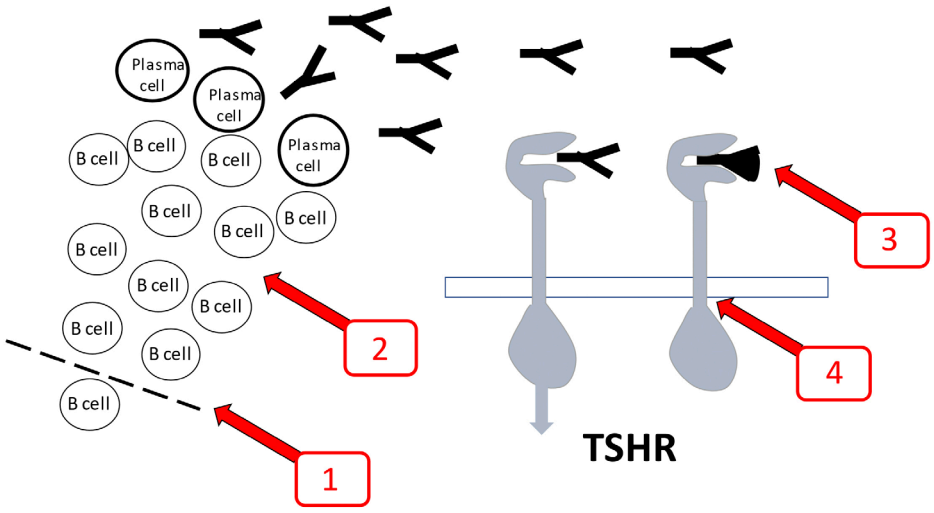
Much has been written about the importance of surgical expertise and many surgeons who undertake thyroid surgery on a weekly basis will be based in primarily in adult services rather than paediatric services. ETA guidance highlights the fact that complications such as long-term hypoparathyroidism and persistent voice change are very uncommon (less than 1% of patients) in skilled hands. Total thyroidectomy is the operation of choice and patients will therefore require long-term thyroid hormone replacement. Paediatric patients who might benefit from thyroidectomy include younger patients who have developed ATD side-effects and patients with a large goitre who fail to remit after a course of ATD.

Radioiodine

Advocates of radioiodine (RAI) therapy highlight the excellent short-term safety record of this treatment modality. The ETA guideline suggests that RAI should be avoided in the under-fives and only used as a last resort in the 5-10 year old age group. RAI is deemed to be appropriate therapy in children older than 10 years of age. The key disadvantages of RAI treatment include the initial 2 weeks when close contact with other people is to be avoided and the fact that hypothyroidism is not instantaneous. Concerns about the impact of RAI exposure on long-term cancer risk may be a concern for families and are hard to quantify accurately. Whilst the increase in cancer risk is likely to be relatively small it cannot be ignored completely when discussing RAI therapy with patients. The scope for a 15 year old patient with GD to develop cancer related to ionising radiation is likely to be greater than a 75 year old – in part because of the increased life-expectancy post-treatment. The ETA guideline recommends that the RAI dose be calculated based upon the thyroid gland weight or on the basis of an uptake scan rather than a 'fixed-dose' approach.

Quality of life

Quality of life in young people with GD is, perhaps not surprisingly, reduced when compared to healthy young people[9]. Adult studies have shown that quality of life in people on long-term thyroid hormone replacement following thyroidectomy or RAI is also suboptimal and reduced when compared to treatment with antithyroid drug. Whilst directing a young person towards surgery may be seen as management failure, it is worth noting that young people do not regret this course of action and many feel that they should have taken this route sooner[9]. Strategies to increase long term remission with fewer patients requiring long term thyroid hormone replacement are, nevertheless, an exciting prospect.



Legends
1. Blocking B cell activation or proliferation
2. B cell depletion
3. TSHR blocking antibodies
4. Targeting TSH receptor function

Figure I. Novel therapeutic avenues in Graves' hyperthyroidism.

Novel approaches to management (Figure 1)

Novel therapeutic strategies in GD aim to prevent the generation of pathogenic TRAb antibodies, the subsequent interaction between TRAb and the TSH receptor or to prevent downstream signalling following antibody-binding. Strategies to prevent plasma cell antibody generation might involve preventing B cells from being activated in the first place or targeting the B cell or plasma cell at a later stage of development. The strategies below do not represent a comprehensive list of novel approaches explored in recent years but provide a flavour of some of the investigations conducted in this disease area.

TSHR immunotherapy

Desensitising the immune response to a particular antigen has shown some promise in type 1 diabetes[10] and is a potential strategy in other autoimmune diseases such as GD. In a phase I study, a TSHR peptide preparation was administered by subcutaneous injection every 2 weeks for 18 weeks to patients with newly presenting, mild Graves' disease[11]. The peptide preparation contained two synthetic peptides that were closely related to sections of the TSHR. The biochemistry improved in 7 of 10 patients with little in the way of side-effects apart from local reactions at the site of peptide administration. There was a significant correlation between changes in free T3 concentrations and changes in TRAb (both thyroid binding inhibitory immunoglobulin, TBII and thyroid stimulating antibody, TSAb). Phase II studies will hopefully follow. A key advantage of this strategy is that side effects are likely to be minimal and in particular it should not alter the ability of the immune system to respond to pathogens.

Targeting the B cell

Disrupting B cell activation or proliferation

The anti-CD40 monoclonal antibody, Iscalimab targets the CD40–CD154 co-stimulatory pathway, resulting in attenuation of the B cell activation signal. In a recent study 15 adult patients with untreated GD were given five doses of intravenous Iscalimab over a 12-week period[12]. During the 24-week follow-up period TRAb concentrations fell in all patients and 7 (47%) developed normal free triiodothyronine (FT3) and FT4 levels, without a need for additional ATD during this period. All treatment-related side-effects were mild or moderate and resolved by the end of the trial. Two patients with GO whose hyperthyroidism responded to Iscalimab had an improvement in their eye symptoms and signs. Unfortunately, after the 24-week follow-up period, 4 of the 7 patients deemed responders relapsed and 3 of these patients then required low dose ATD medication.

Blocking B cell activation

B cell activating factor (BAFF) is a member of the tumour necrosis factor (TNF) family of cytokines and has a key role in the activation, differentiation and survival of B cells. The BAFF monoclonal antibody, belimumab, antagonises the activity of BAFF and prevents B cell proliferation and antibody generation. Patients with GD have increased thyroidal expression of BAFF and so this signalling pathway is a logical target for agents such as biologics[13]. Belimumab treatment is currently under investigation in a randomised controlled trial (RCT) recruiting GD patients with orbitopathy (EudraCT 2015-002127-26).

B cell depletion

Monoclonal antibodies that deplete B cells or plasma cells can theoretically alter disease course by impacting on B cell numbers and associated antibody production. B cell modulation of T cell function is an important consideration in this context because there are potential mechanisms whereby the impact of a monoclonal on antibody production leads to a long-lasting alteration in lymphocyte behaviour.

Rituximab (RTX) was originally reported to have efficacy in controlling rheumatoid arthritis (RA) and it has been used in other disorders such as myasthenia gravis (MG), haemolytic anaemia and systemic lupus erythematosus. RTX has been used extensively in young people. Several groups have investigated the use of RTX in Graves' hyperthyroidism with Fassi et al[14] reporting a prospective study of 20 patients with Graves' disease where they compared short-term MMZ treatment with or without RTX. The team demonstrated some efficacy with sustained remission in the RTX group (4/10 patients) after a mean of 23 months follow-up. RTX appeared to be most effective in those with low TRAb levels[14]. A recent single arm proof of concept trial showed that a single dose of RTX improved remission rates in 27 young people, aged 12-20 years old with GD. 48% of patients were in remission one year following a 12-month course of ATD. This contrasts with a figure of 20 to 30% usually seen after a 3-year course of ATD. The combination of RTX and ATD was well-tolerated with no serious side-effects linked to treatment[15]. Thus, RTX showed a clear signal of efficacy in modulating the natural history of Graves' disease in children.

Targeting the TSHR - blocking antibodies and small molecule TSHR antagonists

A logical goal when tackling the impact of the pathogenic antibodies in GD, TRAb, is to target the TSHR. A monoclonal TSHR-blocking antibody (K1-70) has been given on compassionate grounds to a patient whose metastatic follicular thyroid cancer was being driven by TRAb antibodies associated with co-existing GO[16]. The response in terms of thyroid stimulating activity in the serum was profound with benefits in terms of cancer progression and eye disease. There is an ongoing phase 1 trial (NCT02904330) of K1-70 in treatment naïve Graves' patients.

A number of small molecule agonists and antagonists have been developed and have the potential to directly stimulate or inhibit TSHR signaling[17,18]. These compounds have been studied *in vitro* and *in vivo* with experiments suggesting that, as an example, TSH-stimulated cAMP production can be reduced. One of the concerns with these agents is their specificity because there is the potential to impact on signalling of other G-protein coupled receptors such as the follicle stimulating hormone receptor (FSHR) and lutenising hormone/chorionic gonadotropin receptors (LH/CGRs). These compounds are expected to be active orally and because of their precise targeting to the TSHR may be suitable for long-term administration. None of these compounds have been trialled in man yet.

Outstanding questions

Standard treatment with ATD as well as other therapies including immunomodulators can affect the levels of the pathogenic antibodies (TRAb). What is not clear is the extent to which immunomodulation has the potential to improve remission rate in the long-term. One might expect that, for example, following B cell depletion repopulation of the B cell lineage will result in relapse but the fact that some people remit following standard treatment with thionamide medication and the fact that altering B cell numbers can alter T-cell behaviour provides the prospect that longer term tolerance can occur.

When a young person with GD is considering treatment options in future there will hopefully be additional therapies besides MMZ or CBZ that can impact on antibody production and improve long-term remission rates whilst at the same time leaving the ability of the immune system to tackle infection intact.

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