To Rhona, Hannah, Douglas, Alice, Kathleen and Euan for being a great family, and especially to Fiona for her support during this and many other projects (LK)

To Indrani and Ishani (AB)

Problem Solving in Endocrinology and Metabolism

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Abbreviations

17-OHP 17-hydroxyprogesterone
ACTH adrenocorticotrophic hormone
ADH antidiuretic hormone
AECA anti-endothelial cell antibodies
AIDS acquired immune deficiency syndrome
AIT amiodarone-induced thyrotoxicosis
AITD autoimmune thyroid disease
ALD adrenoleukodystrophy
AMI acute myocardial infarction
AMP adenosine monophosphate
ANCA antineutrophil cytoplasmic antibody
anti-TPO antithyroid peroxidase
APA aldosterone-producing adenoma
APS autoimmune polyendocrine deficiency syndromes
autoimmune polyglandular syndromes
adrenergic postprandial syndrome
AQP2 aquaporin-2
ARR ratio of plasma aldosterone to plasma renin
ATP adenosine triphosphate
AVP arginine vasopressin
BAH bilateral adrenal hyperplasia
BMD bone mineral density
BMI body mass index
BMR basal metabolic rate
CAH congenital adrenal hyperplasia
CBZ carbimazole
CC clomiphene citrate
CEE conjugated equine oestrogen
CI confidence interval
CRH corticotrophin-releasing hormone
CT computed tomography
CTLA-4 cytotoxic T lymphocyte antigen
DA dopamine agonist
DDAVP 1-desamino-8-d-arginine vasopressin
DHEA dehydro-3-epiandrosterone
DHEAS DHEA sulphate
DI deiodinase
DIT diiodothyronine
DITPA 3, 5-diiodothyropropionic acid
DOC deoxycorticosterone
DST dexamethasone suppression test
ECG electrocardiogram
ED erectile dysfunction
EDTA ethylenediamintetraacetic acid
EPHESUS Eplerenone Neurohormonal Efficacy and Survival Study
FAI free androgen index
FNAC fine needle aspiration cytology
FSH follicle-stimulating hormone
GFR glomerular filtration rate
GH growth hormone
GLP glucagon-like peptide
GMP guanosine monophosphate
GnRH gonadotrophin-releasing hormone
GTP guanosine triphosphate
hCG human chorionic gonadotrophin
HIV human immunodeficiency virus
HLA human leucocyte antigen
HPA hypothalamic–pituitary–adrenal axis
HRT hormone replacement therapy
HU Hounsfield Unit
ICSI intracytoplasmic sperm injection
IGF insulin-like growth factor
IPSS inferior petrosal sinus sampling
ITU intensive therapy unit
JNC7 Joint National Committee 7
LH luteinizing hormone
LOD laparoscopic ovarian drilling
MDT multidisciplinary team
MEN multiple endocrine neoplasia
MIBG ^{123}I-metaiodobenzylguandine
MIVAT minimally invasive video-assisted thyroidectomy

MMAS Massachusetts Male Aging Study
MMI methimazole
MNG multinodular goitre
MORE Multiple Outcomes of Raloxifene Evaluation
MRI magnetic resonance imaging
NAION non-arteritic ischaemic optic neuropathy
NANC non-adrenergic non cholinergic [neurones]
NEFA non-esterified fatty acid
NHANES National Health and Nutrition Examination Study
NS non-significant
oGTT oral glucose tolerance test
OR odds ratio
PADAM partial androgen deficiency in ageing men
PCOS polycystic ovarian syndrome
PDE-5 phosphodiesterase-5 inhibitor
PKA protein kinase A
POF premature ovarian failure
PPAR-γ peroxisome proliferator-activated receptor-γ
PPTD post-partum thyroid disturbance
PSV peak systolic velocity
PTH parathyroid hormone
PTHrP parathyroid-related protein
PTU propylthiouracil
RALES Randomised Aldactone Evaluation Study
RR relative risk
SAGH subclinical autonomous glucocorticoid hypersecretion
SAME Syndrome of apparent mineralocorticoid excess
SCA silent corticotroph adenomas
SCC side chain cleavage
SERM selective oestrogen receptor modulator
SERPINA serine protease inhibitor superfamily member A7
SES sick euthyroid syndrome
SHBG sex hormone-binding globulin
SIADH syndrome of inappropriate ADH secretion
SMR standard mortality ratio
SPECT single photon emission computed tomography
SST Short synacthen test
T_3 triiodothryronine
T_4 thyroxine
TBG thyroxine-binding globulin
TBI traumatic brain injury
TBII TSH receptor antibodies (TSH binding inhibitory immunoglobulins)
TED thyroid eye disease
TNF tumour necrosis factor
TPO thyroid peroxidase
TRAB TSH receptor antibody
TRH thyrotrophin-releasing hormone
TSH thyroid-stimulating hormone
TTR transthyretin
UFC urine free cortisol
VLCFA very low chain fatty acids
VMA vanillylmandelic acid
WHI Women's Health Initiative

Thyroid

PROBLEM

01 Graves' Disease

Case History

A previously fit 32-year-old woman notices tremor and heat intolerance. She has lost one and a half stones (9.5 kg) in weight over the past 6 months. You note signs of hyperthyroidism and a diffuse goitre. Her mother is treated for hypothyroidism. The patient smokes 20 cigarettes per day. She and her husband want to start a family in the foreseeable future.

How should she be investigated?

Does she require a thyroid scan?

What is the preferred first line of treatment?

If she has a child, how likely is the child to be affected by Graves' disease?

Background

Thyrotoxicosis occurs in 2% of women and 0.2% of men. In younger people, Graves' disease is by far the commonest diagnosis, with peak onset at 20–40 years. Treatment is with drugs, radioactive iodine or surgery. Thionamide drugs are generally the first line of therapy in young women.[1,2] They have been used for over 50 years. They are safe and well tolerated. Up to 10% of patients experience mild side effects including urticaria, skin rash, joint pain, altered taste and nausea. These do not usually necessitate stopping the drug. The most serious side effect is agranulocytosis which occurs in less than 0.4%. Patients should always be warned to report skin rash, sore throat or any other untoward side effect, and this warning should be recorded in their notes. If side effects are reported, full blood count and differential should be requested urgently and consideration should be given to stopping the drug.

There are three thionamide drugs—carbimazole (CBZ), methimazole (MMI), and propylthiouracil (PTU). They are similar in their clinical effect. There have been no substantial head-to-head studies comparing them. CBZ is the most commonly used drug in the UK, whereas MMI is used in the USA and in many European countries. PTU is usually used as second line treatment. It has a shorter duration of action and therefore is best given in divided doses. PTU may have free radical scavenging activity, and it is not the drug of first choice before or after radioactive iodine because it may diminish the effectiveness of the latter. Skin rashes may be commoner with MMI—reported rate in trials was 7% for CBZ compared with 12% for MMI.[2] PTU is the drug of choice in acute severe thyrotoxicosis as it decreases conversion of T_4 to T_3.

In practice, duration of antithyroid treatment does not appear to be critical. Endocrinologists have all encountered patients who stop taking their drugs after a few months and do not relapse and others who relapse even after prolonged treatment. There is consensus that patients should be treated for at least 6 months, and certainly until serum thyrotropin (TSH) is no longer suppressed and levels of TSH receptor antibodies (TBII) have decreased. Longer treatment may lead to decrease in goitre size, and thus lower risk of relapse. Evidence slightly favours longer than 6 months' treatment; common practice is between 12 and 18 months, and there is no evidence to favour longer treatment.

Most endocrinologists commence patients on high dose and gradually decrease to maintenance dose according to response. Block and replace regimens were based on the hypothesis that antithyroid drugs had immune-modulating and antioxidant properties, and thus may modify the natural history of the disease. Exposure to higher doses of the drug for longer necessitates concurrent thyroid hormone treatment. The two regimens have been compared in 12 studies involving a total of over 1700 patients. The compliance with follow-up varied in these studies. On an intention-to-treat basis, and with follow-up greater than 2 years, relapse rate is just over 50% with either regimen. Higher dose of drug increases risk of side effects. There was no difference in the incidence of agranulocytosis. However, skin rashes were more common in block and replace studies—10% for block and replace vs. 5% for titration (odds ratio [OR] 2.62; 95% confidence interval [CI] 1.20 to 5.75). More people withdrew because of side effects in the block and replace groups.

Treatment with thyroxine following antithyroid drugs was hypothesized to decrease autoantigen exposure and thus lower relapse rate. Three studies have combined thyroxine and low-dose antithyroid drug after initial stabilization with antithyroid drug. No difference in relapse rate was found. In three further studies, antithyroid drug was followed by

a period of thyroxine treatment. In these studies relapse rate was 31% in the thyroxine-treated patients and 29% in those treated with placebo (not significant).

Thyrotoxicosis may temporarily worsen after ^{131}I because of a combination of radiation-induced thyroiditis and increased TBII. Severe exacerbation occurs in less than 1%. Antithyroid drugs are frequently used prior to ^{131}I to achieve more rapid symptom control. There is no real proof that pre-treatment with antithyroid drugs prevents exacerbation of thyrotoxicosis after treatment, but the increase in TBII is less marked, and exacerbations may thus be less severe.[3] Resumption of antithyroid drugs after radioactive iodine achieves symptom control but does not alter the outcome.[4] Antithyroid drugs are generally stopped 4–10 days before therapy and resumed 7 days after.

Genetics of Graves' disease

Graves' disease results from interaction between genetic and environmental factors. Up to 60% of patients have family history of autoimmune thyroid disease (AITD). About a third of first-degree relatives will develop, or have developed, AITD, and around half will be positive for autoantibodies. Concordance rates are higher for monozygotic twins than for dizygotic twins. Genetic influences are thought to account for up 80% of the susceptibility to Graves' disease.[5]

The human leucocyte antigen (HLA) complex located at chromosome 6p21 has three classes of antigen:

- class I—HLA-A, B and C
- class II—HLA DP, DQ and DR
- class III—complement, tumour necrosis factor (TNF)-α, heat shock protein-70 and other immune regulatory genes.

This is a highly polymorphic region of the genome, conferring susceptibility to a range of diseases. HLA-DR3 is the most useful marker. Among patients with Graves' disease 40–50% are HLA-DR3 positive, compared with 15–30% of the general population. Recent studies have identified associations with other HLA alleles, most notably DQA1*0501. HLA is probably important in all ethnic groups, but the precise associations in non-Caucasians differ from the above. Cytotoxic T lymphocyte antigen-4 (CTLA-4), located at chromosome 2q33, is a costimulatory molecule involved in interaction between T lymphocytes and antigen-presenting cells. At least four polymorphisms have been identified and confer susceptibility to autoimmune endocrine disease.[6] Together, HLA antigens and CTLA-4 confer around half the susceptibility to Graves'. Other candidate genes include immune regulatory genes, such as the vitamin D receptor, TSH receptor and thyroglobulin.

Recent Developments

1. Wang *et al.*[7] have shown that the A/G polymorphism at position 40 in exon 1 of CTLA-4 may be a marker for relapse after antithyroid drug therapy. Early identification of patients liable to relapse may allow us to target definitive treatment early.
2. The Nurses' Health Study[8] followed 115 109 women aged 25–42 over 12 years. The incident diagnosis of Graves' was 4.6 per 1000. Smoking was a risk factor (hazard ratio

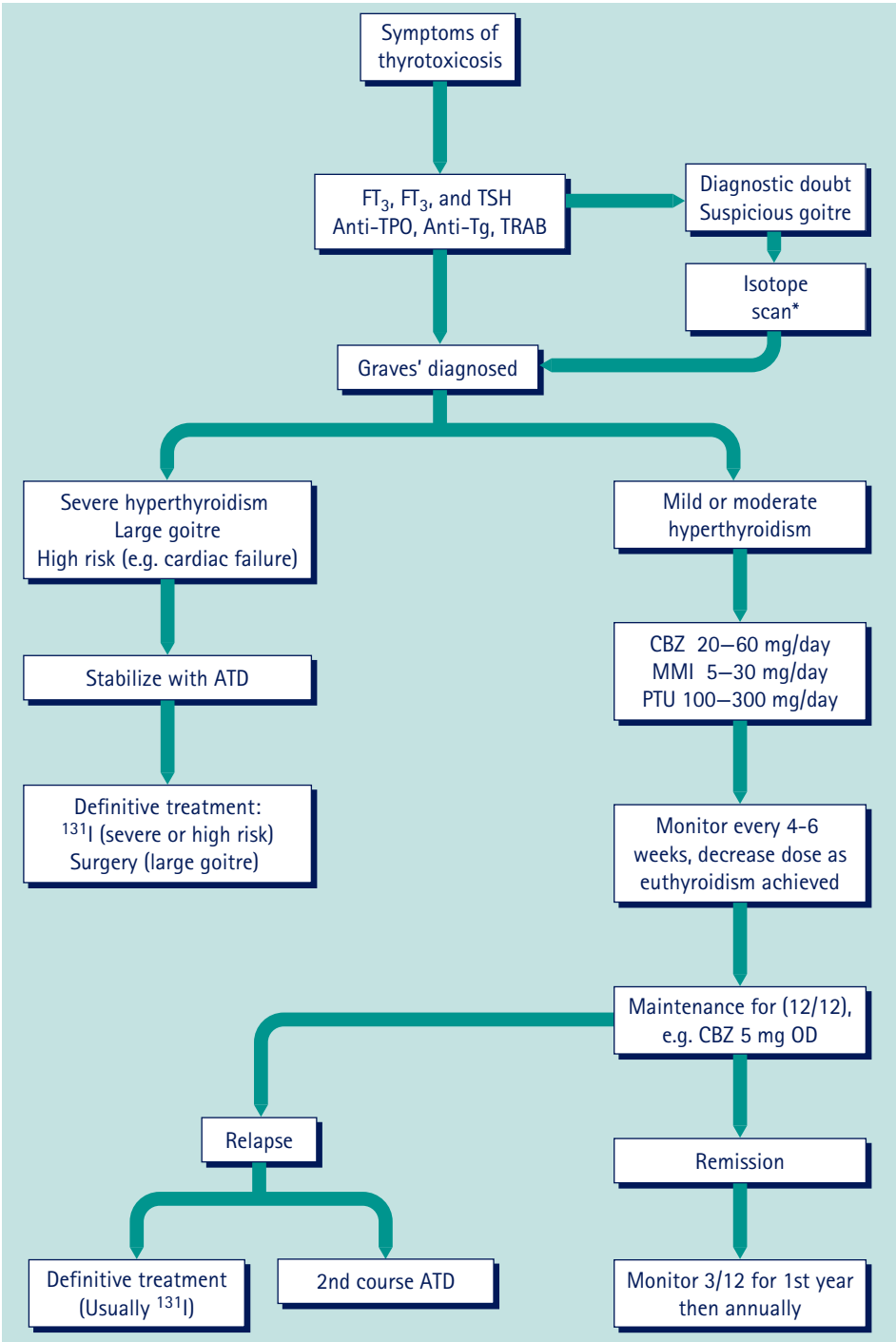

Fig. 1.1 Use of antithyroid drugs. *Scan with technetium-99m pertechnetate or iodide. ATD = antithyroid drugs; CBZ = carbimazole; MMI = methimazole; PTU = propylthiouracil; Tg = thyroglobulin; TPO = thyroid peroxidase; TRAB = TSH receptor antibodies.

1.93). Obesity was associated with lower risk of Graves'—hazard ratio for individuals with body mass index (BMI) greater than 30 kg/m^2 was 0.68 (95% CI 0.49 to 0.92).

3 Colour Doppler sonography may be useful in diagnosis of thyroid disorders. This is a safe, non-invasive technique to assess blood flow in the thyroid arteries. Results correlate highly with thyroid volume and function. In a preliminary study,[9] thyroid blood flow at baseline was highly correlated with outcome after 14 months of antithyroid drug therapy. Relapse could be predicted with a sensitivity of 71% and specificity of 100%.

Conclusions

Initial investigations should include thyroid hormone, TSH and thyroid antibodies, including TBII. Full blood count and liver tests should be requested at baseline and at intervals in patients taking antithyroid drugs (Figure 1.1). Thyroid scanning is not routinely warranted unless there is doubt about the diagnosis. Antithyroid drug treatment is usually the first line treatment. Radioactive iodine has been increasingly used in recent years. There is no evidence of teratogenicity. Obviously, it is absolutely contraindicated during pregnancy and most endocrinologists would avoid its use within 6–12 months of conception. The above patient should not be overly concerned about the implications of the disease for her children although, if female, they will inherit a roughly one in three lifetime chance of developing AITD.

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