Introduction

Thyroid eye disease (TED) is an autoimmune inflammatory disease affecting the orbit and periocular tissues. Previous studies have reported age-adjusted annual incidence rates of 42/million for TED of all severity (10/million for moderate to severe disease),[1] and a prevalence of 0.25% within the developed world.[2,3] Although the natural history of TED remains unclear, it typically has a period of activity over 6 to 12 months followed by slow improvement over 2 to 3 years.[4] The disease may be disfiguring and has been shown to have a significant impact on physical and psychosocial wellbeing.[2,5-7] As cheap and safe interventions may prevent progression from mild to severe TED[8], there is an unmet need for early diagnosis, referral and treatment of these patients and these are key factors influencing patient outcome. For example, immunosuppressive therapies are most effective in the early active stages of TED and missing this window of opportunity is associated with worse outcomes.[8,9]

In 2009, a consensus group of world opinion leaders on TED proposed the "Amsterdam Declaration", that pledged to improve the care of patients with this condition.[10] The Amsterdam Declaration set out a number of 5-year targets aimed at referral timelines and treatment strategies. They included: to halve the time from presentation to diagnosis of TED, and from diagnosis of TED to referral to a centre of excellence; appropriate management of thyroid dysfunction including use of radioiodine; and, the implementation of vigorous anti-smoking measures in patients with or at risk of developing TED.[10]

The Thyroid Eye Disease Amsterdam Declaration Implementation Group UK (TEAMeD) was formed in 2010 in order to promote the objectives of the Amsterdam Declaration in the United Kingdom (UK). It comprises twelve representatives from key professional and patient-led stakeholders (including The Royal College of Ophthalmologists, the British Thyroid Association, the British Thyroid Foundation and the Thyroid Eye Disease Charitable Trust).[10,11] UK centres for the management of TED in the United Kingdom were invited to participate in an audit to provide baseline data in order to better define the Amsterdam 5-year targets and to highlight any major deficiencies in the current level of care provided for patients with TED in the United Kingdom.

Materials and methods

The National thyroid eye disease audit (UK) was a prospective non-randomised cross-sectional multicentre observational study. The seven hospital departments who responded to the survey were: Moorfields Eye Hospital, London; University Hospital Cardiff; Royal Devon and Exeter Hospital; Queen's Medical Centre, Nottingham; Queen Victoria Hospital, East Grinstead; Royal Hallamshire Hospital, Sheffield and Southampton General Hospital.

During a three-month period from 01 June to 31 August 2014, consecutive adult patients with TED who presented to the specialist eye clinics at participating tertiary eye centres for the first time were asked (along with their examining ophthalmologist), to complete a standardised questionnaire.

The questionnaire focused on the key 5-year targets of the Amsterdam Declaration and had six main domains: demographic information (age, gender); time from diagnosis to referral to a specialist centre; time from first symptoms to diagnosis; time from referral to review in tertiary centre; management of thyroid dysfunction; smoking; and thyroid eye disease classification (Appendix 1). Patients were identified as having “active” or “inactive” TED, based on the examiners’ overall clinical impression and the clinical activity score (CAS) (with a CAS of ≥3 being considered “active”).[12] The examining clinician interpreted the CAS in the context of the examination findings – for example, whether lid swelling was attributed to fat prolapse rather than eyelid oedema and after consideration of any clear history of a recent change in symptoms. This definition of active disease was the same as that employed by Perros *et al*.[15]

All patients underwent a comprehensive ophthalmological examination including best-corrected visual acuity obtained with a Snellen chart, slit lamp biomicroscopy, exophthalmometry, Ishihara colour testing and assessment of ocular motility. Eye signs were assessed according to established European Group on Graves’ Orbitopathy (EUGOGO) protocols.[13,14]

STATISTICAL ANALYSIS

Completed forms were collated and analysed using summary statistics only. The study protocol was approved by Moorfields Eye Hospital, the lead centre for the study. The study was performed in compliance with good clinical practice guidelines and in accordance with the principles of the Declaration of

Helsinki. Verbal consent was obtained from each patient after explanation of the purpose and process of the study.

Results

PATIENTS AND DEMOGRAPHICS

Ninety-one patients (77 females; 85%) entered the study at a mean age 47.8 years (SD14.1; median 48; range 19-80 years); the female:male ratio was 6:1. Fifteen questionnaires were returned without sufficient information to determine their specialist centre of origin and they were included in a group labelled 'Other' (Table 1).

DURATION OF SYMPTOMS

The median time was 2 months (range 0-204) between the first visit to any doctor with symptoms, until establishing a diagnosis of TED; the patient who waited 204 months for a diagnosis had inactive TED. The median time from diagnosis to initiating referral to a specialist eye clinic was 1.13 (range 0-72) months; it then took another median delay of 1 month (range 0-29) from the referral letter to actual review in a specialist eye clinic. Overall, the median time from first symptoms of thyroid eye disease to review in a specialist eye clinic was 7 months (range 0-600) (Figure 1).

MANAGEMENT OF THYROID DYSFUNCTION

The patient-reported management of thyroid dysfunction, including relapse of hyperthyroidism, was based on patients' testimony: that is, information the patients might have received from their doctor(s) prior to the specialist clinic appointment and/or their perception of recurrent symptoms of abnormal

thyroid function. (Appendix 1). At the first specialist clinic appointment, 11% (10/91) patients reported still being hyperthyroid, 27% (25/91) reported a recurrence or 'relapse' of hyperthyroidism, and 22% (20/91) reported being hypothyroid in the last 2 years. Patients took a median of 6 months to control their thyroid function (range 0-60 months), 54% patients did not know their current thyroid status, and at least one quarter of patients reported episodes of dysthyroidism since their diagnosis (27% hyperthyroid).

RADIOIODINE

Thirteen percent (12/91) patients received radio-iodine, 3 of whom had thyroid eye disease at the time; 2 of these 3 patients had active TED and received prophylactic systemic steroids.

Seven patients (all female) received radio-iodine whilst not having TED, but developed TED at a later date; their mean age at time of radio-iodine was 49 years, and all had a history of poor thyroid control (2 were still hyperthyroid, 3 didn't know their thyroid status, one had never been euthyroid and another took 10 months to become euthyroid). Four of the 7 had relapse of hyperthyroidism and 4/7 had been hypothyroid in last 2 years. Five out of 7 (71%) were smokers, of whom 4/5 (80%) had moderate to severe TED, whereas the 2 non-smokers had mild TED. The mean Clinical Activity Score (*CAS)* for these 7 patients was 2.5 (SD1.98, median 2, range 0-6), with 5/7 having "active" disease.

SMOKING AND PATIENT AWARENESS OF THE IMPACT OF SMOKING ON TED

Twenty-seven patients (30%) were current smokers and 28/91 (31%) were ex-smokers, but only 63% of the current smokers had been offered smoking cessation advice -- which was usually provided by the GP or the specialist eye clinic. Counselling and written information were the most common forms of help provided to encourage smoking cessation (Figure 2), with no clear difference in the modes of help provided across the different eye centres. Only one-third of patients (31%) were aware that smoking has an adverse effect on TED, although a quarter (26%) knew that treatments for TED (e.g. steroids/radiotherapy/surgery) are more effective in non-smokers or ex-smokers than current smokers. A fifth of patients (22%) knew a successful cure of thyrotoxicosis with anti-thyroid drugs was more likely in non-smokers, than in smokers (Table 2).

THYROID EYE DISEASE CLASSIFICATION

The mean CAS at presentation was 2/7 (SD 2.04; median 2; range 0-7) and 65% had “active” disease: 46% patients had sufficient swelling to warrant treatment. 54% had no diplopia, 23% had intermittent diplopia, 8% had inconstant diplopia and 29% had constant diplopia. Seven percent were deemed to have a ‘cornea at risk and 4% had optic neuropathy. In terms of disease severity, 43% patients had mild, 53% had moderate-to-severe, and 4% had sight-threatening disease (1 patient each at Moorfields, Nottingham and Sheffield) (Figure 3).

Discussion

Our patient population had a similar average age (48 years; SD 14 years) as that of a comparable study.[15] Our gender ratio (female:male - 6:1), whilst the same as that in a recent study,[16] was higher than the 3:1 reported by Perros *et al* in 2012.[15]

The importance of early diagnosis and management to prevent progression of TED has been well documented. For patients with mild TED, a 6-month course of oral selenium (100 □g twice daily) was shown to significantly improve quality of life, reduce ocular involvement, and slow progression of the disease.[17] Immunosuppressants such as systemic corticosteroids or orbital radiation) are only effective during the “active” phase of TED and so it is imperative that patients are identified and treated early, and the opportunity for effective intervention is not missed.[18]

In 2008, Sasim *et al*[19] found that 75% of patients with TED seen at a specialist eye centre had had the disease for over a year. Estcourt *et al*[9] reported that 33% of respondents waited more than 6 months from first consultation with any doctor to review at a specialist clinic; they also showed that patients treated at a specialist TED clinic were more likely to be satisfied with their ophthalmic treatment than those who did not attend a specialist clinic, and also that most UK patients with TED never reach specialist TED clinics or were referred too late. Their study also showed delays in diagnosis and referral of TED, limited access to specialist TED clinics and low patient satisfaction with treatment.[9]

Our study has shown a median of 2 months (range 0-204) between patients seeing their first physician for ophthalmic symptoms and the diagnosis of TED, this being a favourable result compared to the PREGO study[15] in which the median wait was 9 months (range 0-552) in 2012 and 16 months in 2000. Likewise, Estcourt *et al*[9] showed 26% of survey responders waited more than 12 months from first symptoms to diagnosis in the UK.

The median time from first TED symptoms to review in a specialist eye clinic was 7 (range 0-600) months (Figure 1), this comparing well with a European multi-centre study that reported a median of 9 months in 2012 from first TED symptoms to diagnosis, and then a further median of 6 months from diagnosis to first specialist clinic appointment.[15] Our study took place two years after the PREGO study[15] and our shorter timelines may be attributed to a general improvement in TED awareness and access to specialist treatment; alternatively, our results might suggest that the UK National Health Service (NHS) is performing better than European Healthcare systems in this regard.

Patients with uncontrolled thyroid function are more likely to develop TED and have more severe disease[20,21] and 54% of our patients did not know their current thyroid status: over half (54%) of patients were unsure of how long it took for their thyroid levels to become normal after diagnosis of thyroid eye disease, 18% were unaware of any relapses of hyperthyroidism, and 14% patients did not know if they had become hypothyroid in past 2 years. As current guidance recommends prompt achievement and maintenance of a euthyroid state in patients with newly diagnosed TED,[4,12] patients should be

encouraged to monitor their thyroid status and be informed of the association between uncontrolled thyroid levels and likelihood of more severe disease. This is in keeping with UK Government policy in which the NHS Outcomes Framework 2015/6 pledges improved support for people in managing their chronic disease.[22] Emphasis should be placed on achieving and maintaining normal thyroid levels, and such knowledge might promote improved compliance with medications and management of thyroid dysfunction. All doctors (General practitioners, Endocrinologists and Ophthalmologists) involved in care of patients with TED should keep them informed of their thyroid status and improved access of patients to their health records and test results may facilitate this; NHS England has declared that, by April 2016, online patient records should include test results accessible to the patient.[23]

RADIOIODINE AND STEROID PROPHYLAXIS

All patients in our study who received radioiodine for active TED were given prophylactic steroids,[10] but 7/12 (58%) patients having radioiodine developed TED only after the treatment. In line with earlier studies,[24] 5 of these 7 (71%) were smokers with poor thyroid control – that is, 4/7 had relapse of hyperthyroidism, and 4/7 had been hypothyroid in the preceding 2 years). These findings confirm the deleterious association of both smoking and thyroid dysfunction with TED: two key factors that have been consistently associated with worse outcomes.[24-28]

SMOKING AND PATIENT AWARENESS OF ITS IMPACT ON AUTOIMMUNE THYROTOXICOSIS AND TED

It is repeatedly reported that the proportion of smokers in cohorts with TED is higher than the general population,[15] and in our study, this was 30% current smokers, compared to 19% of the UK population.[29] The numbers were even higher in Europe with 40% current smokers reported by Perros *et al*[15] in their European-based prospective observational study of 269 new referrals with Graves' orbitopathy compared to 28% of the overall adult population. Europe has the highest prevalence of tobacco smoking in the world (28% vs. 21% world adult population).[30]

The association between smoking and TED is well-established: smoking has a dose-dependent association with severity of TED,[26] is associated with exacerbation of TED after radio-iodine therapy, and is an independent risk factor for a poor response to immunosuppression.[28] The exact mechanisms underlying this relationship are not yet clearly defined, although oxidants and free radicals contained in tobacco smoke are thought to increase oxidative stress.[31] Hyaluronic acid production and adipogenesis are stimulated by cigarette smoke in a dose-dependent manner.[32]

Our study suggests that not enough patients are being provided with advice about smoking cessation, or information about the impact of smoking on TED and control of thyroid function. Most patients were unaware that smoking increases the risk of worse TED, reduces the effectiveness of treatments for TED, and reduces the chance of being cured of hyperthyroidism. (Table 2). More than one-third (37%) of our current smokers had not been offered smoking cessation advice, and yet a quarter of patients who had been

smokers at the time of first thyroid diagnosis subsequently stopped; this latter figure is a higher than expected, as a meta-analysis of smoking cessation rates reporting only a 7% rate after intervention with nurse-led patient education.[33] This might suggest that educating patients about the impact of smoking on their disease can be effective in TED.[34]

Since smoking is such an important modifiable risk factor, it is imperative that all current smokers with thyroid gland disease are provided with smoking cessation support.[4,10] The 5-year target is: all patients seen in the specialist eye clinic should be provided with verbal information on the impact of smoking on TED and all current smokers should receive written information on smoking cessation. Patient-led organisations such as the British Thyroid Foundation[35] and the Thyroid Eye Disease Charitable Trust[36] play a major role in supporting patients with their disease and are an important source of disease-specific information. In accordance with NICE guidance, all current smokers in the UK should be offered a range of cessation strategies – for example, smoking cessation medications, cognitive behaviour therapy, acupuncture - by their General Practitioner as part of NHS Stop Smoking Services.[37]

TED CLASSIFICATION

At first ophthalmic assessment, our patients had more active and more severe disease than that reported by Perros *et al* in 2012 (active disease 65% vs. 36.8%; mild disease 43% vs. 60.5% respectively)[15] (Figure 3). This may be attributed to earlier diagnosis of TED in our study (median 2 vs. 9 months)

and this difference may be independent of smoking habits since more severe disease might be expected in Europe, where more patients smoke.[15,30]

LIMITATIONS AND FINDINGS OF THE STUDY

The study is limited by a lack of independent validation of patient responses to the questionnaire. Information about management of thyroid dysfunction was collected solely from the patient's testimony. The questionnaire did not include questions on past medical history including diabetic status, or current medication including anti-thyroid medication and selenium supplementation. As such, the history of thyroid status, treatment and current thyroid status were unverified from medical records. This limits conclusions that can be drawn about thyroid status at the time of specialist ophthalmic assessment and the incidence of relapse of thyrotoxicosis. Furthermore, since monotherapy with anti-thyroid drugs such as thiamazol may lead to poorly controlled thyroid levels, and given that the dose-response relationship of selenium levels may be non-linear in diabetics[38], in addition to concerns that high selenium levels may increase the risk of high grade prostate cancer[39], future studies in this area may benefit from collecting data on the type of thyroid medication used, selenium supplementation and diabetic status.

The study did not include the paediatric population and therefore cannot draw any conclusions as to the current level of care for children with thyroid eye disease in the United Kingdom. The authors would welcome future research in this patient demographic.

As a result of this study, we have gained a new insight into the current level of care of patients with TED in the United Kingdom, and this data provides a baseline against which the Amsterdam Declaration targets can be assessed in the future. The study has generally shown a consistent pattern of patient profiles, knowledge and management across the different recruiting centres, but patients would appear to be still waiting a long time not only from first symptoms to diagnosis, but also from diagnosis to ophthalmic assessment. The findings of this study support changes to practice particularly with respect to patient education and awareness of disease and the factors which influence its progression and prognosis, namely thyroid dysfunction and smoking. This is in line with the Amsterdam Declaration recommendation of vigorous anti-smoking measures.

In this study, we found complete adherence to the Amsterdam Declaration recommendation that all patients with thyroid eye disease undergoing radioiodine therapy should have prophylactic steroids to prevent worsening of their disease. The study has enabled greater definition of national 5-year targets based on the goals of the Amsterdam Declaration and this will facilitate planned future re-audit.

Conflict of interest

None registered.

Acknowledgements

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Titles and legends to figures

Table 1. To show the baseline characteristics and the distribution of the patients across the different specialist eye centres involved in the study. Key: MEH = Moorfields Eye Hospital, London; Notts = Nottingham University Hospitals NHS Trust; QVH = Queen Victoria Hospital, East Grinstead; Other = questionnaires of indeterminate origin (that is, returned without sufficient information to determine which tertiary centre they were from).

Figure 1. To show the median time (months) from first symptoms of thyroid eye disease to specialist eye clinic appointment. Key: MEH = Moorfields Eye Hospital, London; Notts = Nottingham University Hospitals NHS Trust; QVH = Queen Victoria Hospital, East Grinstead; Other = questionnaires of indeterminate origin (that is, returned without sufficient information to determine which tertiary centre they were from).

Figure 2. To show the frequency and range of smoking cessation support offered to patients. Key: CBT = Cognitive behavioural therapy; Written info = written information.

Figure 3. To show the distribution of TED disease activity and severity. Key CAS = Clinical activity score.

Table 2. To show the variation of patient awareness of the impact of smoking on thyroid eye disease, the efficacy of treatment of thyroid eye disease and Graves' disease across the different specialist eye clinics. Key: MEH = Moorfields Eye Hospital, London; Notts = Nottingham University Hospitals NHS Trust; QVH = Queen Victoria Hospital, East Grinstead; Other =

questionnaires of indeterminate origin (that is, returned without sufficient information to determine which tertiary centre they were from).

Appendix 1

Questionnaire: data collection proforma.

Appendix 2

Signatories of the Amsterdam Declaration

International Professional Organisations

Academia Ophthalmologica Europea

Academia Ophthalmologica Internationalis

American Thyroid Association

Asia-Oceania Thyroid Association

Asia Pacific Society of Ophthalmic Plastic and Reconstructive Surgery

Endocrine Society

European Association for Vision and Eye Research (EVER)

European Group on Graves' Orbitopathy

European Society of Endocrinology

European Society of Orbital Plastic Reconstructive Surgery

European Thyroid Association

Iberico-American Society of Ophthalmic Plastic and Orbital Surgery

International Thyroid Eye Disease Study Group

Latin-American Thyroid Society

World Society of Pediatric Ophthalmology and Strabismus (WSPOS)

International thyroid patient association

Thyroid Federation International

National professional organisations

All India Ophthalmological Society

American Association of Clinical Endocrinologists

Argentina Council of Ophthalmology (Consejo Argentino de Oftalmologia)

Argentina Society of Ophthalmology (SAO)

Belgian Endocrine Society

Belgian Thyroid Club

Bielschowsky-Gesellschaft fur Schielforschung und Neuroophthalmologie

British Oculoplastic Surgery Society

British Thyroid Association

Chinese Society of Ophthalmology

Cyprus Endocrine Society

Danish Thyroid Association

Dutch Endocrine Society

Finnish Endocrine Society

French Endocrine Society

French Society of Ophthalmic Plastic Reconstructive and Aesthetic Surgery

German Endocrine Society

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German Thyroid Board

German Society of Ophthalmology (Deutsche Ophthalmologische

Gesellschaft)

Hellenic Endocrine Society

Hellenic Society of Ophthalmic Plastic and Reconstructive Surgery

Irish Endocrine Society

Italian Association of Medical Endocrinologists (Associazione Medici Endocrinologi)

Italian Society of Endocrinology

Italian Society of Ophthalmic Plastic Surgery (Società Italiana di Chirurgia Oftalmoplastica, SICOP)

Italian Thyroid Association

Japan Thyroid Association

Japanese Society of Ophthalmology

Macedonian Endocrine Association

Oculoplastic Association of India

Ophthalmological Society of Portorico (Sociedad Puertorriqueña de Oftalmología)

Philippine Society of Ophthalmic Plastic and Reconstructive Surgery (PSOPRS)

Philippine Academy of Ophthalmology (PAO)

Polish Thyroid Society

Romanian Society for Endocrinology

Royal College of Ophthalmologists (UK)

Serbian Endocrine Society

Slovak Endocrine Society

Società Oftalmologica Italiana

Society for Endocrinology (UK)

South African Society of Oculoplastic Surgeons

Spanish Society of Ophthalmic Plastic and Orbital Surgery (Sociedad Espanola de Cirurgia Plastica Ocular y Orbitaria, SECPOO)

Swiss Endocrine and Diabetes Society (SGED/SSED)

Turkish Society for Endocrinology and Metabolism

National thyroid patient organisations

Association “Vivre sans Thyroïde”

British Thyroid Foundation

Finnish Thyroid Foundation

Georgian Union of Diabetes and Endocrine Associations (GUDEAS)

Italian Thyroid Patient Association

La Asociación Mexicana de Tiroides

Nederlandse Vereniging van Graves’ patienten

Norsk Thyreoideaforbund

Ohne Schilddruse leben e.V.

Schilddrusen-Liga Deutschland e.V.

Schildklierstichting Nederland (Thyroid Patients Organization of the Netherlands)

Svenska Sköldkörtel Föreningen.

The Australian Thyroid Foundation Ltd.

Thyroid Australia

Thyroid Eye Disease charitable trust (UK)

Thyreoidea Landsforeningen

Instituto da Tiroide

Japan Thyroid Foundation

Thyroid Foundation of Canada / La Fondation canadienne de la Thyroïde

Thyroid Foundation of St. Petersburg

United States of America Graves' Disease Foundation

Verein Schilddru sengruppe Schweiz