An algorithmic approach in the diagnosis and management of thyroid eye disease

Akshay G. Nair, Savari T. Desai

Thyroid eye disease (TED) or Graves ophthalmopathy is commonly associated with thyroid dysfunction and often causes a debilitating effect on the individual. Its presentations can result in misdiagnosis and often treatment is delayed in the initial acute inflammatory stages of the disease. The pathophysiology of this disease remains a complex process. The clinical examination, the activity and severity can help us decide the stage of the disease to help us formulate a management plan. The treatment strategy for TED is multi-pronged and consists of different modalities such as medical therapy, functional and cosmetic surgery and radiotherapy. Medical therapy ranges from supportive ocular surface protection and lubrication to potent immunosuppressive agents. Surgery, too can be vision-saving in severe dysthyroid optic neuropathy or exclusively cosmetic in cases of burnt-out orbitopathy. This review, discusses the examination, investigations of TED but essentially presents a step-by-step question based approach in the staging, diagnosis and management of thyroid eye disease.

Key words: Algorithmic, thyroid eye disease, rundles curve, steroid treatment, surgical decompression

Thyroid eye disease (TED) is an inflammatory orbital disease of autoimmune origin with the potential to cause severe functional, aesthetic and psychosocial effects.[1] Graves Disease (GD) is the most common autoimmune disease affecting the thyroid gland with the thyroid-stimulating hormone (TSH) receptor of thyrocyte being the target of the immune system. The most common extrathyroidal site of morbidity in GD is the eye.[2] Close to 10-20% of patients develop eye problems in the months before becoming thyrotoxic, about 10-15% present with current or previous hypothyroidism.[3]

The estimated incidence of TED in the general population is 16 females and three males per 100,000 person years.[6] Patients with Graves’ Ophthalmopathy (GO) are more likely to be women by a 2:1 ratio, following the usual predominance of autoimmunity in women.[2]

There is a female predilection for TED with the female to male ratio being reported to be 9.3:1 in patients with mild ophthalmopathy, 3.2:1 in those with moderate ophthalmopathy and 1.4:1 with severe ophthalmopathy.[2] These figures indicate an increasing proportion of male patients as the severity increases.

Treatment options for TED include oral and intravenous corticosteroids, immunosuppressive agents and orbital radiation. Surgically, lid procedures for cosmetic correction and orbital decompression to relieve pressure on the optic nerve are routinely performed in patients with TED. Recent trends in surgical management include fat decompression, extensive posterior sculpting of the lateral wall during decompression, direct approaches to the medial wall and endoscopic decompression techniques.[6] Thus, there are various treatment modalities, and choosing the right treatment depends on a variety of factors, such as the severity, the stage of the disease and the systemic status.

Through our knowledge of the pathogenesis of TED, treatment paradigms are expanding, but we are often left disillusioned, as there are apparently no effective means of preventing the disease or reliably altering its course. Excellent articles are available in the endocrinology, neuro-ophthalmology and thyroid domain journals, outlining the management of TED, which may not always be accessible to us. The aim of this article is to help a clinical practitioner decide whether a patient has TED or not, and if he does, what would be the further approach to diagnosis, and to finally decide upon the appropriate line of treatment for a patient with TED, based on a simplified guided algorithm and evidence based medicine. While examining a patient with suspected TED or established TED, the following questions may be used as a guide to ascertain the treatment protocol [Table 1].

Does the Patient Have Thyroid Eye Disease?

TED can present in a variety of ways. However, there are some features which are so specific to TED that there is usually little doubt about the diagnosis.[1,3] Upper lid retraction is the most common presentation and is seen in nearly 90-98% of patients.[7,8] The classic feature is the distinguishable contour of the retracted eyelid which shows a lateral flare and is almost pathognomonic for TED.[9] There is also lid lag, combined with...
the widened palpebral aperture, decreased blink rate and the increased rate of tear evaporation; all of which combined result in lacrimation, foreign body sensation and photophobia. Soft tissue swelling and inflammation, proptosis and restriction of movements are other classical features. [Figure 1: Clinical signs of TED]

The pathophysiology of TED includes infiltration of orbital fat, extraocular muscles, and the lacrimal gland by lymphocytes, the activation of orbital fibroblasts and deposition of glycosaminoglycans. This gradually leads to compression of the intraorbital contents resulting in disorders of the lid-corneal interface, exposure keratopathy, motility restriction and severe proptosis.[6] Hypertrophy of extra ocular muscles and enhanced adipogenesis, together with deposition of nonsulfated glycosaminoglycans and hyaluronate resulting in bulging of the eyelid sulci and orbital congestion, manifest as conjunctival chemosis, raised intraocular pressure. The eventual progression of this disease process leads to apical crowding within the orbit and subsequently resulting in dysthyroid optic neuropathy.[10]

TED can present unilaterally or bilaterally. At the same time it must be borne in mind that in bilateral cases, the disease can be asymmetrical, therefore presenting a diagnostic dilemma. Other differential diagnosis that may be considered are listed in Table 2.

**Which Investigations Should be Performed?**

A detailed history and a thorough clinical examination can never be substituted. Best corrected distance and near vision, color vision, exophthalmometry must be performed at every visit. However, clinical investigations aid in the diagnosis and monitoring the treatment of TED. In about 40% of patients with thyroid dysfunction, there is simultaneous onset of ocular and systemic symptoms.[11] Orbital inflammatory disease occurs in nearly 60% of the patients with hyperthyroidism and, of the patients presenting with clinical evidence of TED, 85% of them are biochemically hyperthyroid and 10% are found to be hypothyroid.[12] There is a small proportion of TED patients who maintain euthyroid status. In these patients, the presence of circulating serum antithyroid microsomal antibodies, antithyroglobulin antibodies or antithyroid stimulating hormone receptor antibodies may be found.[13] These group of patients who exhibit thyronormalcy are found to have less severe orbitopathy. It must also be remembered that the orbital signs may precede thyroid dysfunction, therefore underscoring the need to repeatedly checking the thyroid hormone levels and ensuring that a euthyroid state is maintained.

- **Photographic documentation at every visit is a must.** Often older patients are unable to express the exact duration of onset of eye disease and old and recent photos especially can help in identifying the approximate onset of the eye disease. The recommended views include the standard view, oblique view, worm’s eye view and bird’s eye view.[13] [Figure 2: Onset of TED by Photographic Documentation]
- **Biochemical Investigations:** Endocrine evaluation needs to be done by tests such as serum Triiodothyronine (T3), free thyroxine (T4), Serum TSH, thyrotropic receptor antibodies (TRAB). Serum TSH helps to establish the diagnosis of hyperthyroidism or hypothyroidism. TSH is high in hypothyroidism and low in hyperthyroidism. TRAB often acts a marker to assess response to antithyroid medication and is used by endocrinologists in determining the activity of the thyroid gland. However, while these test help us to identify the type of thyroid disease, to date, no single laboratory or imaging parameter is able to reliably predict response to treatment.[14]
- **Visual Function test:** Visual fields help in detecting early damage to the optic nerve that is seen as a result of apical crowding around the optic nerve. The changes on visual fields are reversible if the crowding is relieved early, either surgically or medically. Usually, the patterns of visual field loss vary, the most common being central, paracentral and/or inferior.[12]
- **Ultrasonography (USG):** USG B-scan is a useful imaging tool. However we do not use it a primary modality of imaging for TED. USG of the globe and the orbit can help in visualization of the tendinous insertions. This also helps to differentiate between active and inactive disease. By comparing the muscle thickness, ultrasound may help in confirming the diagnosis in unilateral cases. It also helps in differentiating associated diseases presenting with similar clinical features.
- **Orbital Imaging:** Imaging the orbit can be performed using either a computed tomography (CT) scan or an Magnetic resonance imaging (MRI) scan. However, CT is more sensitive than MRI in identifying enlarged extraocular muscles.[14] As a standard, 2 mm cuts should be requested for, along with coronal and axial slices. Typical radiological features seen in TED on CT are muscle belly enlargement that is classically described as ‘tendon sparing’, an increase in orbital fat volume, and crowding of the optic nerve at the orbital apex in severe

<table>
<thead>
<tr>
<th>Table 2: Differential diagnosis of eye signs that can present as TED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orbital Myositis</td>
</tr>
<tr>
<td>Non specific Orbital inflammatory disease (NSOID)</td>
</tr>
<tr>
<td>Allergic Conjunctivitis</td>
</tr>
<tr>
<td>Myaesthenia Gravis</td>
</tr>
<tr>
<td>Chronic Progressive External Ophthalmoplegia</td>
</tr>
<tr>
<td>Carotico cavernos fistula</td>
</tr>
<tr>
<td>Specific inflammatory orbitopathy</td>
</tr>
<tr>
<td>Orbital tumors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 1: Step by step algorithmic approach outline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the patient have Thyroid Eye Disease ?</td>
</tr>
<tr>
<td>What is the disease stage/phase?</td>
</tr>
<tr>
<td>What investigations should be performed?</td>
</tr>
<tr>
<td>What is clinical activity and severity and Mourits Clinical Score?</td>
</tr>
<tr>
<td>What risk factors does the patient have?</td>
</tr>
<tr>
<td>How do I manage the patient?</td>
</tr>
</tbody>
</table>
Orbital fat absorbs X-rays to a lesser degree than water; it is imaged in CT as a black, low-density area that contrasts with the higher-density image of extraocular muscles and the optic nerve. CT scans can help identify apical crowding and optic nerve stretch where a ‘taut’ nerve can be visualized. CT scans allow for better delineation of the bony orbit and therefore are invaluable in planning orbital decompression. [Figure 3a: Clinical Features of TED-CT scan Orbit].

The advantages of MRI include high quality orbital anatomic detail imaging obtained with surface coils and thin section scans. Also the T2 relaxation time is sensitive for demonstrating interstitial edema within recti eye muscles and edema in orbital fat. Furthermore, compared to CT, MRI is more sensitive to alteration in water content or hydrogen concentration processes. In the active phase, the extraocular muscles appear isointense in T1 weighted images and hyperintense in T2 weighted images; where as in the chronic phase, they appear hypointense on T2 images [Figure 3b: Clinical Features of TED-MRI Orbit].

What is Disease Stage/Phase?

Rundles Curve (Disease Stages): Rundle conceptualized two distinct phases for TED, which is graphically represented in his famous ‘Rundle’s curve’. Rundles curve aims to represent the natural course of TED. It is a fundamental concept in understanding and managing TED, and it determines choice of treatment. There is an initial active inflammatory phase which is characterized by periorbital erythema and edema, conjunctival chemosis, orbital inflammation and congestion, associated with upper lid retraction, proptosis, and occasionally diplopia. The inflammatory phase typically lasts for a period between 6 and 24 months and is followed by a quiet, minimally inflammatory chronic fibrotic phase which is associated with orbital fibrosis, glycosaminoglycan deposition and enlarged extraocular muscles. There are usually no active inflammatory episodes in this phase [Table 3: Features of Two Stages of Rundles Curve; Figure 4a and b: Two stages of Rundles Curve].
There have been various classification systems, which have been used to describe TED. In 1961, Werner devised the mnemonic NO SPECS (No signs and symptoms, Only signs, Soft tissue involvement, Proptosis, Extraocular muscle involvement, Corneal involvement, and Sight loss) to document disease severity. It, however, does not adequately identify patients in the active phase of disease. Subsequently, other classification and assessment systems were introduced such as the Vision, Inflammation, Strabismus, Appearance (VISA) system. Dolman and Rootman devised this classification system based on the International Thyroid Eye Disease (ITEDS) working group’s suggestion based on four disease endpoints that can be used in the office setting to record changes and to guide and assess therapy. Each of these headings have a subjective and measurable inputs which are repeated at every visit to compare and monitor the disease process.

The European Group on Graves’ Orbitopathy (EUGOGO) Atlas allows for recording the presence or absence of both symptoms and signs together with a comparative atlas to score the soft tissue signs. The main aim of these scoring systems is to assess inflammatory signs such that one can identify patients in the active phase who are most likely to respond to treatment.

What is Clinical Activity/Severity and Mourits Clinical Score?

As mentioned earlier, Rundle’s curve gives us a broad understanding of the likely chronology of events and the progression of the disease; that is the disease stage or level of activity. Activity implies the presence of inflammation and therefore the potential for change, either spontaneously or in response to immunomodulation.

The other concept that is relevant is the disease ‘severity’ which indicate how severe the disease is. The severity described the amount of inflammation present at any given time. Therefore, both the activity and severity must be considered for adequate description of TED.

Mourits et al., introduced the clinical activity system which was based on four of the five classical signs of inflammation (pain, redness, swelling and impaired function) and consists of ten items: two each under pain, redness and impaired function and four under swelling. One mark is given for each of the items that is present. The total sum of these points indicates the clinical activity score (CAS 0–10). The CAS system is useful in identifying if a patient has active disease or not. Since disease activity, and not disease duration, is the prime determinant of therapeutic outcome; CAS, reportedly has a high predictive value for the outcome of immunosuppressive treatment in GO.

What Risk Factors does the Patient Have?

• Smoking: There is ever-growing evidence which suggests that smoking adversely affects the development, progression, and management of TED. Graves’ disease patients who are smokers, have a five times higher risk of developing TED than those who do not. Furthermore, cessation of smoking reduces the risk of worsening of the orbitopathy, thereby increasing the chance of having a favorable response to medical treatment. Thus, smoking is the single most important modifiable risk factor in the management of TED. Cessation of smoking should be counselled aggressively.

• Diabetes: Kallman and Mourits have demonstrated that the prevalence of Insulin dependant diabetes mellitus (IDDM) in patients with GO is higher than in the normal population. Dysthyroid optic neuropathy occurs much more frequently...
in patients with Graves Orbitopathy and diabetes than in the total group of Graves orbitopathy patients and seems to have a worse visual prognosis.\cite{hence It is important to test for diabetes and monitor sugar levels.

- The risk and severity of ophthalmopathy in patients with Graves’ disease is also increased by factors such as advanced age, high stress levels, Hashimoto’s disease, among others.\cite{4,30}

How do I Manage the Patient?

As is abundantly clear from the discussion above, the management of any patient with TED depends precisely on the stage of the disease and the severity, which is determined by CAS. There are, however some ground rules for the management of TED, regardless of the stage and severity of the disease: Cessation of smoking.

1. Restore euthyroid status
2. Supportive symptomatic treatment

Euthyroidism therefore should be restored as rapidly as possible and maintained. The modality of treatment (anti-thyroid drugs, radioiodine, or thyroidectomy) is not as important as the final goal of euthyroidism.\cite{15} In case of radioactive iodine, it is important that the clinician works in collaboration with the endocrinologist as there may be transient worsening of the ophthalmopathy which can be controlled with steroids.\cite{31}

- Mild disease: In line with the EUGOGO consensus status, mild TED is said to be present when patient has one or more of the following\cite{15,24,30,Figure 5: Clinical Features of Mild Disease}:
  - Minor lid retraction (<2 mm).
  - Mild soft tissue involvement.
  - Exophthalmos less than 3 mm above normal for race and gender.
  - Transient or no diplopia.
  - Corneal exposure symptoms responsive to lubricants.

The CAS in mild disease is less than 4. Among patients with mild TED, progression to more severe disease, as reflected in a change in the CAS, occurs in about 15-25\%\textsuperscript{14}.

It has been reported that oral Selenium, an essential component of anti-oxidant enzymes, can slow progression of the disease in patients with mild GO.\cite{31-35}

Oral non-steroidal anti-inflammatory drugs may be considered in mild disease in order to reduce any amount of inflammation that may be present. A ‘no treatment’ policy may also be observed ensuring that the disease doesn’t progress and worsen.

- Moderate-severe non-sight threatening disease:
- Moderate-severe disease [Figure 6: Clinical Features of Moderate to Severe Disease] is classified as orbitopathy with sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive).\cite{15,24} In active disease, the mainstay of treatment is corticosteroids; however, the exact dosage, the duration of dosage and the route continue to be a controversy. It must be understood that the use of medical treatments in patients with active disease needs to take into account whether potential benefits outweigh the risks of side effects, bearing in mind that most patients will improve spontaneously with time.\cite{15}

Zang et al., have suggested a 12-week course of intravenous methylprednisolone (0.5 g as a single dose per week for 6 consecutive weeks followed by 0.25 g as single dose per week for 6 consecutive weeks, not to exceed a total of 8 g) for patients with active moderate-to-severe TED.\cite{EUGOGO performed a large multi-center, randomized, double-blind trial to access the efficacy and safety of three different cumulative doses (2.25, 4.98, and 7.47 g) of intravenous (IV) methylprednisolone over a 12-week period in patients with active moderate-to-severe TED. Their results suggested that the 7.47 g group had the greatest positive short-term response in terms of CAS. However, this benefit did not persist at 24 weeks and was in fact, associated with a slightly higher rate of adverse events compared with the lower doses.\cite{Current literature points to high-dose intravenous glucocorticoid pulses being effective for moderate to severe TED, with response rates of about 80% for parenteral treatment.\cite{Steroids are also used concurrently along with orbital radiotherapy to counter the transient inflammation that occurs at the onset of orbital radiotherapy (ORT).\cite{While discussing ORT, the typical ORT protocol for TED is a total of 20 Gy (or 2,000 rads) per orbit fractionated in 10 days (2 Gy/d) over a 2-week period. However, the exact duration, the fractionation and overall effectiveness of radiotherapy in TED is debated.\cite{In moderate to severe, non-sight threatening TED, if a worsening is seen; immediate institution of IV steroids and possible orbital decompression may be considered to rescue the optic nerve.

d. Severe or sight-threatening TED:

e. This can be as a result of severe proptosis and orbital fullness, which results in optic nerve stretch as well as apical crowding, resulting in dysthyroid optic neuropathy (DON) [Figure 7: Clinical Features of Severe Disease]. Surgical treatments may be used at two stages: either for sight-threatening disease when it is not controlled by medical treatments, or for restoring function and appearance during the inactive phase if that is desired by the patient.

The optimum treatment for optic neuropathy is high-dose systemic immunosuppression, with prompt surgical decompression performed when the response to medical treatment is inadequate. The commonly used protocol includes 500 mg daily for 3 consecutive days, then continue either with 250 mg weekly as required, or with slowly tapering course of oral prednisolone 0.7 mg/kg/day.\cite{In cases where an immediate and adequate response is not seen with medical management, surgical decompression...
of the posteromedial orbit should be considered which may result in rapid and beneficial effect on vision.[38] The main objective is to relieve the hydrostatic pressure at the orbital apex and, by doing so, reduce orbital congestion and improve vascular perfusion and axonal flow within the optic nerve and subsequently improve the optic nerve function.

The use of endoscopic surgery, balanced decompression and extended decompression are a few of the various, new techniques of bony and fat decompression that have evolved to accomplish the goal of reversing neuropathy while minimizing adverse effects. Because the outcomes of decompressive procedures have improved, the indications for surgery have expanded to include cosmetic cases.[6]

Summary

Acute TED is an emergency and is vision threatening. Corticosteroids form the mainstay of the treatment of active disease; intravenous being more effective than oral steroids. Recently various surgical approaches to the orbit have allowed for predictable outcomes. However, all these attempts aim at quelling the damage after the disease process has already been initiated. Future therapies will be aimed at preventing thyroid orbitopathy. Until such treatment is offered, such algorithmic approaches will guide clinicians and aid them in the treatment of TED.

References


Source of Support: Nil. Conflict of Interest: None declared.