THYROID EYE DISEASE: NEW PARADIGM OF DISEASE CLASSIFICATION

Introduction

Thyroid eye disease (TED) is an orbital inflammatory disease that is related to autoimmune thyroid conditions. It causes expansion and fibrosis of orbital fat, striated extraocular muscles and lacrimal gland. This orbital disorder significantly disrupts appearance, vision and quality-of-life, although it is self-limited. Managing TED requires identifying its clinical features and grade its severity and activity, translating into a few classifications. Accurate evaluation of the clinical features of TED is essential for early diagnosis, identification of high-risk disease, planning medical and surgical intervention and assessing response to therapy. This article illustrates and compares several TED classifications together with the new one proposed by Uddin et al.

Activity versus Severity in TED

An impression of the degree to which the body reacts to autoantigen is defined as an activity. Assessment of activity in TED includes an absence or presence of the symptoms and signs related to inflammation. The degree of activity can be inactive, moderately active or severely active. In contrast, severity signifies physical consequences of activity that persists despite control of activity.

TED Classification

Few systemic classifications of TED have been described and proposed by several authors. Nunery et al. defined a dichotomous Type I versus Type II classification based on the clinical features and CT scan findings. Type I of lipogenic variant manifests symmetrical proptosis with no signs of orbital inflammation. Type II is the restrictive myopathy type of orbitopathy and presents with diplopia and asymmetrical proptosis. The following are several classifications that are commonly used for TED classification.

NO-SPECS Classification by Dr Wegener (1977)

This classification is an acronym that represents the symptoms and signs related to TED. It grades the disease features in order of frequency of presentation. However, the descriptions are loosely defined. It is often based on only one variable. There is neither assessment for clinical activity nor a guide for management.

ABRIDGED CLASSIFICATION OF EYE CHANCES OF GRAVES' DISEASE[1]

Class*	Definition†
0	No physical signs or symptoms
1	Only signs, no symptoms (signs limited to upper eyelid retraction, stare, and eyelid lag)
2	Soft tissue involvement (symptoms and signs)
3	Proptosis
4	Extraocular muscle involvement
5	Corneal involvement
6	Sight loss (optic nerve involvement)

European Group on Graves' Orbitopathy (EUGOGO) by Dr Mauritz

This classification measures severity based on three categories which are mild, moderate to severe and sight threatening. Patients with eyelid retraction, mild proptosis and minimal muscle involvement are categorized as mild disease and treated conservatively. Whereas patients with moderate to severe disease are those with features of proptosis greater than 25 mm, inflammation or significant extraocular movement limitation that impairs daily function. This condition is often treated medically. For sight-threatening conditions, for example, compressive optic neuropathy and corneal ulceration, are often managed surgically.

Stage	Feature
Mild thyroid eye disease	Minor impact on activities of daily living Insufficient justification for immunosuppression or surgical treatment One or more of the following Minor lid retraction (<2 mm) Mild soft tissue involvement Proptosis<3 mm above normal for race and gender No or transient diplopia Corneal exposure responsive to lubricants
Moderate-to - severe thyroid eye disease	Impact on activities of daily living Justifies treatment (immunosuppression and/or surgical treatment) Two or more of the following Lid retraction 2 mm or more Moderate to severe soft tissue involvement Proptosis≥3 mm above normal for race and gender Diplopia (inconstant or constant)
Sight threatening thyroid eye disease	Compressive optic neuropathy Corneal ulceration

Clinical Activity Score (CAS)

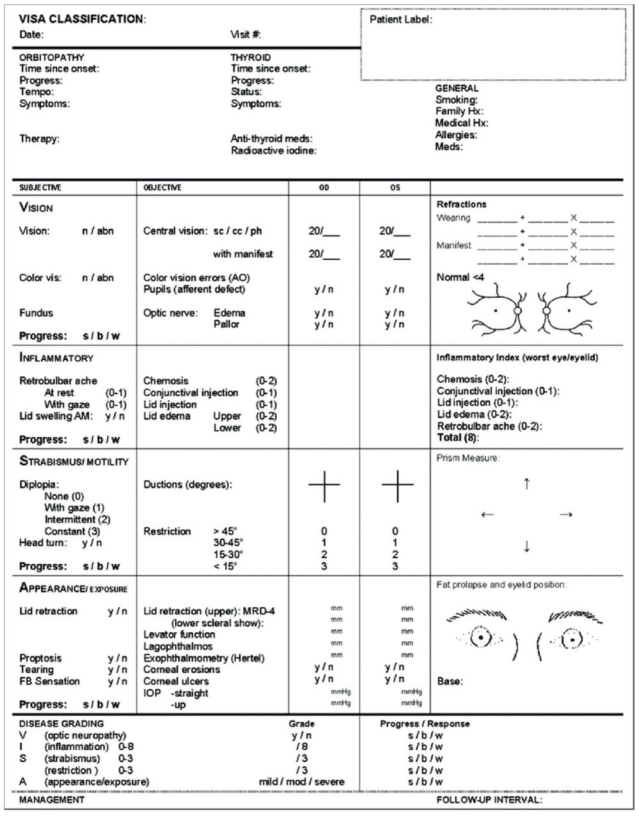
This classification is intended to identify the activity of TED. However, it does not correlate with the risk of developing significant complications such as diplopia or compressive optic neuropathy. The setback of CAS is that it does not reflect the equality of each clinical feature. For instance, one who had optic neuropathy would have a similar weightage to another person with eyelid erythema. It is a binary scale that only shows symptoms or signs but does not demonstrate disease progression or response to therapy.

	For initial CAS score items 1-7
1	Spontaneous orbital pain
2	Gaze evoked orbital pain
3	Eyelid swelling that is considered to be due to active GO
4	Eyelid erythema
5	Conjunctival redness considered due to active GO
6	Chemosis
7	Inflammation of caruncle or plica
	Follow-up after 1-3 months score items including 8-10
8	Increase of >2 mm proptosis
9	Decrease in uniocular ocular excursion in any one direction of >8 degrees
10	Decrease of acuity equivalent to 1 Snellen line

One point is given for the presence of each of the parameters assessed. The sum of all points define clinical activity: Active ophthalmopathy if score is >3/7 at first examination or >4/10 in successive examination. GO – Graves' orbitopathy

VISA by Dr Peter Dolman

The VISA four parameters determine the activity and severity of TED. This system requires a worsening of the inflammatory score of 2 or more as evidence of disease progression and activity with a maximum score of 20 to grade it. There is also additional information on risk factors such as smoking, family history of TED and other comorbidities (e.g. diabetes) included in the form.



Phenotypes of Thyroid Eye Disease by Dr Uddin JM et al. (2018)

Phenotype is an observable physical property of a disease. This encompasses the clinical and radiological appearances of the disease as well as its response to treatment. It was proposed by Dr Uddin et al. in ITEDS 2019 and published in OPRS ed 2018. The concept of phenotype in disease classification is still early in development and has been explored in chronic obstructive pulmonary disease (COPD). Phenotypes in COPD are associated with prognosis and with different responses to currently available therapies. Similarly, personalized treatment in TED -such as immunosuppression or decompression – can be based on the features of the disease, together with their severity and activity.

Summary of clinical features, imaging, and potential response to therapies in TED phenotypes

	Congestive (Active Inflammatory)	"White Eye" Expansion	"Hydraulic" Apex	"White Eye" Apex	Cicatricial Active	Cicatricial Passive
Timeline to presentation	Weeks/months	Late presentation	Late/posttreatment presentation	Late/posttreatment presentation	Early presentation with progression	Late/posttreatment presentation
Ocular surface	Moderate/severe injection and chemosis	Minimal injection and chemosis	Moderate/severe injection and chemosis with dilated episcleral vessels	Minimal injection and chemosis	Minimal injection and chemosis	No/minimal injection and chemosis
Extraocular movements	Moderate global limitation	Moderate global limitation	Moderate/marked global limitation	Moderate global limitation	Marked limitation	Moderate limitation
Resistance to retropulsion	Soft/moderate orbit	Soft/moderate orbit	Firm orbit	Moderate/firm orbit	Soft/moderate orbit	Soft/moderate orbit
Optic neuropathy	No	No	Yes	Yes	No	No
CT findings	Muscle and fat expansion	Fat expansion	Apical crowding with muscle expansion	Apical crowding	Single muscle expansion	Muscle expansion
Response to treatment	Responds to immunosuppression	Unknown response to immunosuppression	Good response to decompression; poor response to immunosuppression	Good response to decompression; partial response to immunosuppression	Possible response to local steroid	Poor response to treatment, likely inactive/fibrotic phase

TED, thyroid eye disease.

Comparison of All Classifications

The author made a comparison among those classifications and concluded the following:

NO SPECS	*EUGOGO*	*CAS*	*VISA*	*Phenotype of TED*
Class 0: ***N***o physical signs or symptoms Class 1: ***O***nly signs (eyelid retraction or eyelid lag) Class 2: ***S***oft tissue involvement (0: absent, a: minimal, b: moderate, c: marked) Class 3: ***P***roptosis (0: absent, a: minimal, b: moderate, c: marked) Class 4: ***E***xtraocular muscle signs (0: absent, a: limitation in extreme gaze, b: evident restriction, c: marked) Class 5: ***C***orneal involvement (0: absent, a: stippling, b: ulceration, c: clouding, necrosis, perforation) Class 6: ***S***ight loss (0: absent, a: vision 0.63-0.5, b: 0.4-0.1, c: 0.1-no light perception)	Mild: • < 2mm eyelid retraction • Mild soft-tissue involvement • < 3 mm exophthalmos (above normal for race & gender) • Transient or no diplopia • Corneal exposure responsive to lubricants Moderate-to-severe: • ≥ 2 mm eyelid retraction • Moderate or severe soft-tissue involvement • ≥ 3 mm exophthalmos (above normal for race & gender) • Inconstant or constant diplopia Sight-threatening (or very severe): • Dysthyroid optic neuropathy • Corneal breakdown	Pain: • Painful, oppressive feeling on or behind globe during the last 4 weeks • Pain on attempted up, side or downgaze during the past 4 weeks Redness: • Redness of the eyelid(s) • Diffuse redness of the conjunctiva, covering at least one quadrant Swelling: • Swelling of the eyelid(s) • Chemosis • Swollen caruncle • Increase by 2 mm or more in proptosis for the past 1-3 months Impaired function: • Decrease in eye movements in any direction of ≥ 5^0 for the past 1-3 months • Decrease in visual acuity ≥ 1 line on Snellen chart (pinhole) for the past 1-3 months	**V**ision: Subjective • Vision: n/ abn • Colour vision: n/ abn Objective • Central vision: sc/ cc/ ph • Colour vision error • Pupils (afferent defect): Y/N • Optic nerve: oedema (Y/N), pallor (Y/N) **I**nflammation: Subjective • Retrobulbar ache (none: 0, with gaze: 1, at rest: 2) • Lid swelling a.m: Y/N Objective • Chemosis: 0-2 • Conjunctival injection: 0-2 • Eyelid injection: 0-1 • Lid oedema: upper (0-1), lower (0-1) Total: 0-8 **S**trabismus: Subjective • Diplopia: (none: 0, gaze: 1, intermittent: 2, constant: 3) Objective: • Restriction: <15^0: 0, 15-30^0: 1, 30-45^0: 2, >45^0: 3 **A**ppearance: Subjective • Lid retraction: Y/N • Proptosis: Y/N • Tearing: Y/N • FB sensation: Y/N Disease Grading for each segment	6 Phenotypes of TED were identified based on the following features: • Timeline to presentation • Ocular surface • Extraocular movement • Resistance to retropulsion • Optic neuropathy • CT findings • Response to treatment Congestive (active inflammatory) Phenotype White Eye Expansion Phenotype Hydraulic Apex Phenotype White Apex Phenotype Cicatricial Active Phenotype Cicatricial Passive Phenotype

Features	*NO-SPEC Classification*	*EUGOGO*	*CAS*	*VISA*	*TED Phenotype*
Assessment	Symptoms and signs	Symptoms and signs	Symptoms and signs	Symptoms and signs (subjective and objective manner	Clinical, radiological of TED and treatment response
Grading System	Severity	Severity	Activity	Severity and Activity	Identifying of characteristics from 6 phenotypes TED
Advantages	• Simple and easy to remember	• Simple and easy to remember	• Simple and easy to remember • Not time-consuming • Provide guidance to management	• Both subjective and objective assessment of the disease activity and severity are taken into account • Inclusion of risk factors and morbidities	• Clinical and radiological features together with definitive management and prognosis
Disadvantages	• Difficult to assess disease response • No guidance to management	• Distinction between mild and moderate is imprecise and broad	• Binary scale • No correlation with the complications	• Much effort needed to fill up the form	• Need more established study to confirm with the clinical correlation and prognosis

Conclusion

The author concludes that the more recent classification has a promising way to guide ophthalmologists to manage patients with TED. It includes imaging and response to therapy that allow us to prognosticate the outcome of TED and personalized treatment. However, the concept of phenotype in disease classification especially for TED is still early in development. It requires a validated, larger scale study of patients with this disease. Perhaps in future, we could contribute to future research correlating the phenotypes with pathogenesis of TED.

References

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