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Thyroid Eye Disease (TED) – Evolution of CAS with Time in a tertiary care setup.

Ophthalmology

KEYWORDS: Thyroid Eye Disease, TED, CAS, Rundle's curve

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ABSTRACT

Background and Objectives: Our study was undertaken to chart the evolution of thyroid eye disease (TED) by following thee Clinical Activity Score (CAS) over a period of one year in a tertiary hospital. While the Rundle's curve described the natural progression of the disease, our study looks at disease activity over time in patients undergoing treatment appropriate to the stage of disease presentation.

Material and Methods: A prospective, observational study was conducted at the out - patient department of the ophthalmology department of a tertiary level care hospital on 30 cases of both sexes. All willing and co-operative patients of thyroid disorder as per clinical & hormonal evaluation were considered for enrollment in the study, except those having other ocular co-morbidities (surgery, glaucoma, uveitis, keratopathy, complicated cataract, trauma). The study was conducted for a period of one and a half years(from 2011 to 2013), where each patient was followed up for a period of one year, with 3 visits of 0, 6 and 12 months for each patient. All patients underwent routine ophthalmological examination along with special stress on TED signs. Changes in CAS was evaluated over a period of one year. All patients were treated for the underlying thyroid disorder in the endocrine department of the tertiary care institute, as per their routine protocol.

Results: Out of the 26 patients who completed follow-ups, at first visit average CAS <4 was 80%, =4 was 11.5% and > 4 was 7.5%, which evolved in the third visit as <4 about 77%, =4 about 23% and >4 was 0%. A curve was plotted mapping average CAS as per duration of disease and its evolution over one year.

Conclusion: TED having a chronic course shows a unique trend with newer and better modalities of hormonal control, with a peak of CAS being maximum in the second year of the disease after diagnosis. More data and studies are needed to convey the exact change in the trend of active TED with evolution.

Manuscript:

Introduction:

Thyroid eye disease is a broad term used to include a battery of manifestations seen in the eyes, in patients with diseases of the thyroid gland. The most common being denoted as "Grave's Disease" (made famous by Grave), denoting an autoimmune disorder of the thyroid gland resulting in hyperthyroidism, although Parry described the goitrous enlargement of thyroid with exopthalmos almost ten years earlier. [1]

Most treatment modalities are aimed at modifying the spontaneous course of diseases, which implies the understanding and the knowledge of the natural history of a given pathological condition. In TED this is especially important as timing of anti-inflammatory or immunosuppressive or even surgical intervention is critical for preventing permanent sight/ cosmetic compromising sequelae. [2,3,4,5]

Further most of studies have reported on the natural evolution of TED [2,3,4,5], (references) but considering the advances in its treatment, this natural curve is nearly always altered in a tertiary care setup for referred patients. To the best of our knowledge, no study has tried to chart the evolution of TED in such a scenario. [5]

Eye manifestations have been classified by Werner as NO SPECS, the mnemonic "NO" implying non-infiltrative from "SPECS"- meaning infiltrative, each class, as one progresses includes the class before itself. There have been several others since then, including Mourit's denoting disease severity and for disease progression. It is designed based on the well known signs of inflammation by Celsus and Galen: Pain, Redness, Heat, Tumour and Function Loss. This was later modified into the Clinical Activity Score (CAS), which is widely used now. [6,7,8]

Our study aims to chart the progression of TED by its clinical co-relation using CAS scoring over a period of one year (for each patient), demonstrating the spectrum of changes in a graphical manner.

Considering the time since Rundle made famous his curve showing clinical activity with time, many changes have occurred in the endocrinal and ophthalmic management of TED. Also, a tertiary care setup demonstrates slightly altered activity due to the referral patterns of patients after treatment elsewhere.

The simplistic curve demonstrated here ensures a better understanding of TED evolution. It also demonstrates the useful nature of CAS for standardising measurements and care for TED patients.

Subjects and Methods:

The study was initiated after the clearance from the ethics committee of the institute. A prospective, observational study was conducted at the out - patient department of the ophthalmology department of a tertiary level care hospital on 30 cases of both sexes.

The study was conducted for a period of one and a half years(from 2011 to 2013), where each patient was followed up for a period of one year, with 3 visits of 0, 6 and 12 months for each patient. The number of patients lost to follow up was 4; hence the final analysis has been

conducted only on 26 patients.

All patients of Thyroid disorder as per clinical & hormonal evaluation were considered for enrolment in the study. Patients less than 20 years, prior ocular ailment/ surgery, unco-operative patients and those without any ocular complaints were excluded from the study.

Methods

The ophthalmic evaluation after written informed consent, which was carried out for each patient included recording of relevant ocular and medical history, recording of best corrected visual acuity, examination of the pupillary reaction and slit lamp evaluation of the anterior segment, along with grading of cataract. The intraocular pressure was recorded in three gazes. Exophthalmometry, squint evaluation, diplopia charting and perimetry were done, if the case so demanded.

All patients were graded as per the CAS (Clinical Activity Score), as per the chart in Annexure A. All patients were treated for the underlying thyroid disorder in the endocrine department of a tertiary care institute, as per their routine protocol. Those with optic neuropathy, with CAS of > 4 were given systemic steroids after due investigations. Most other patients with non-severe TED were given only symptomatic treatment. Relevant investigations in the form of hormonal levels were sent via the endocrinology department, including T3, T4 and TSH assays.

Each patient was followed up for a period of one year, with a total of three visits at 0, 6 and 12 months.

Statistical Analysis:

At the end of the study, the collected data was tabulated and descriptive statistics were used. The evolution of various ocular manifestation of TED was analysed after calculation of CAS and average CAS for all patients as per their duration of disease. This was charted graphically.

Results:

Nearly 87% of the patients remained in follow-up. In the present study there was a female preponderance, with 73.03 % being female patients with TED. Majority of patients belonged to 41 – 50 years age group overall, but in males the age group 31-40 years had preponderance.

The mean age of the thyroid patients presenting for ophthalmic complaints was 45.38 years for males & 45.39 years for females with a standard deviation of +/- 15.26 years and +/- 10.83 years respectively. The overall mean age is 45.38 years.

The CAS for each patient was calculated and tabulated as per evolution over each visit.

Table 1 10–Clinical Activity Score (CAS) in patients with TED

Clinical Activity Score	No. of patients first visit	No. of patients second visit	No. of patients third visit
< 4	21 (80.77%)	20 (76.82%)	20 (76.82%)
= 4	03 (11.54%)	04 (15.39%)	06 (23.08%)
> 4	02 (7.69%)	02 (7.69%)	00 (0%)

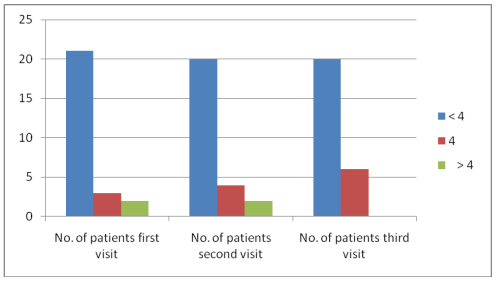


Chart 1 8: Clinical Activity Score (CAS) in patients with TED

*Bar diagram denotes number of cases, not percentages.

CAS score has been tabulated and presented as a bar diagram, showing the demarcation at <4, =4, >4 as this alters the management. Although different centers have used a different cut off for change of management, the endocrine department and the ophthalmology department at our institute have chosen the same for change of management.

At first visit CAS <4 was seen in 80% of patients which changed to 76% by third visit.

At first visit CAS =4 was seen in only 11% of patients which changed to 23% by third visit.

At first visit CAS >4 was seen in 7.69% of patients which changed to 0% by third visit.

None of these were found to be significantly altered after applying chi square test, as p value for each group was > 0.05.

Table 2 11- Evolution of disease as per CAS, in accordance with time duration for each patient

Patient	CAS as first visit (Time duration of disease)	CAS at second visit (Time duration of disease)	CAS at third visit (Time duration of disease)
1.	1	5	3
2.	2	2	1
3.	2	3	3
4.	0	3	4
5.	0	0	0
6.	3	3	2
7.	2	2	1
8.	1	0	0
9.	4	5	4
10.	0	1	2
11.	1	0	0
12.	1	0	0
13.	0	2	4
14.	0	0	0
15.	5	4	3
16.	2	4	4
17.	4	3	1
18.	2	4	3
19.	1	0	1
20.	0	2	3
21.	2	2	2
22.	0	1	4
23.	2	4	4
24.	1	0	0
25.	4	3	2
26.	6	3	1

This table shows the evolution of disease activity as calibrated by CAS value for each patient.

None of these changes were found to be significant on applying chi square test (p value for each being greater than 0.05).

The graph below shows the charting in line format for each patient, showing the change in CAS value.

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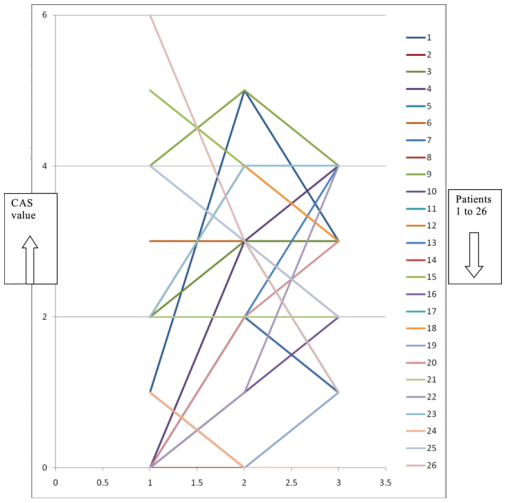


Chart 2: Evolution of disease as per CAS, in accordance with time duration

Graph showing evolution of disease activity according to CAS scale over a period of one year for all 26 patients analyzed.

The division of the data was done into larger groups according to age, in order to chart a continuous curve.

The following curve was obtained after rearranging the data…

Table 3 - Evolution of TED as per CAS, classifying the illness according to thyroid disease duration.

Duration of Thyroid illness*	First Visit – Avg CAS Score	Second Visit – Avg CAS Score	Third Visit – Avg CAS Score
0 - < 1.5 y	1.5	1.57	0.92
1.5 y – < 3 y	1.53	2.08	1.9
3 y – < 5 y	1.92	1.5	0.93
> 5 y	1.6	1	1.25

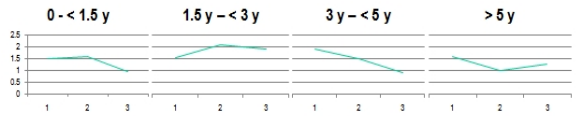


Chart 3 10: Curve showing Average CAS as per age groups, at each visit.

This graph portrays the evolution of TED over a period of 0 to >5 years as documented in our study, taking into account the average CAS scoring on the Y axis at the corresponding visit, 1,2 and 3rd on the X axis, in accordance with of the duration of Thyroid illness as covered by the table above.

Discussion:

There are many methods of classifying TED, but there are very few studies demonstrating a clear methodology for its evolution since Rundle and his curve were demonstrated. Our study tries to show how the newer methods of classification and newer modalities of treatment at a tertiary care setup have altered the evolution of the curve of TED. Study documenting the evolution of various signs of TED in the Indian scenario, especially in a tertiary care centre, has not been reported so far to the best of our knowledge.

It was found in our study that patients presented for ophthalmic evaluation most commonly within 6 months to 1 year, about 20% of cases along with the duration 2 y to 2.5 y which also constituted about 20%, of having systemic thyroid illness.

The mean duration of thyroid illness at which ophthalmic evaluation was sought is 2.29 years of thyroid illness, with a standard deviation of 2.81 years.

This is similar to the finding of Rundle, from which has been formulated the Rundle's curve. It also denotes the active phase to be from 6 mths to 18 mths, during which the patient usually presents to the ophthalmologist. [9,10,11]

The evolution as per CAS was found to be …

At first visit CAS <4 was seen in 83.33% patients which increased to 93.33%.

At first visit CAS =4 was seen in 10% patients which decreased to 3.33%.

At first visit CAS >4 was seen in 6.67% patients which decreased to 3.33%.

Studies that have been done generally try to document the relation between CAS and the eventual prognosis, especially when the cut off of 4 is applied. Mourits and co-workers conducted a study predicting the outcome of either radiotherapy or oral prednisone treatment in patients with moderately severe TED [12,13]. They found…

"a significantly higher CAS in the 22 responders than in the 21 non responders: using a cut-off point of 4, CAS could accurately predict the outcome of therapy, since 12 of 15 patients with CAS of 4 (80%) had a favorable outcome of treatment. Itshould, however, be pointed out that 10 of 22 responders (45%) had a CAS of 4 or less. Thus, it would appear that, while a high CAS is usually predictive of a good response to treatment, a low CAS does not necessarily rule out a possible favorable outcome of therapy."

Similar report was also given by Luigi Bartalena, Aldo pinchera & Claudio Marcocci. [14]

By calculating the average CAS and co-relating to the duration of TED and its evolution, we charted a curve (chart 3). This graph portrays the evolution of TED over a period of 0 to >5 years as documented in our study, taking into account the average CAS scoring on the Y axis at the corresponding visit, 1,2 and 3rd on the X axis, in accordance with of the duration of Thyroid illness.

This curve shows the general TED activity (Y axis) as it evolves over a period of 5 years, as per the duration (X axis) of Thyroid disease, tabulated by CAS value.

This can be compared to Rundle's curve, in which he has plotted time duration on x axis and on the y-axis, he depicted exophthalmometry readings, the range of ocular elevation and the position of the upper eyelid relative to the corneoscleral limbus.

All 3 clinical features in approximately 18 months reached a "static at a level of incomplete recovery" in Rundle's words. He further commentates…

[The graph] is an attempt to sketch diagrammatically the behavior of the principal ocular changes during the dynamic phase of protrusion and recession. They are ideal and theoretical curves in the sense that relatively few patients have been, or could be followed through the complete cycle [11].

As can be seen our own curve does not follow such a stabilization of disease activity, which co-relates with Rundle's own interpretation.

This is further confirmed in recent studies which have tried to emulate Rundle's finding with a larger number of patients. They found the maximum disease activity from 13 – 24 months of disease onset. [14]

However our disease peak activity duration was found to be 18 - 36 months. This may indicate the underlying changes due to patients undergoing prior and simultaneous treatment with the endocrine department in a tertiary care setup.

Summary and Conclusions:

The conclusions of our study are :-

- As found by our study TED is most commonly presented in the age group of 31-50 years, with the mean age for the detection of TED in women being 45.38 years, that in males is 45.39 years, with a standard deviation of 15.26 years and 10.83 years respectively.

- In our study, the percentage of females was 69%, while that of males was 31%. TED was found to be nearly two and a half times more common in females.

- At first visit CAS <4 was seen in 80% patients which changed to 76% at third visit.

At first visit CAS =4 was seen in 11% patients which changed to 23% at third visit.

At first visit CAS >4 was seen in 7.69% patients which changed to 0% at third visit.

The cut off of 4 has been used to predict the outcome for good prognosis.

- The curve of disease activity with time is slightly different from that described originally by Rundle, as our tertiary setup does not follow natural disease progression. The peak of disease activity occurred from 18 - 36 months, slightly later than that fond in natural disease progression studied earlier.

- Limitations of our study are mainly due to lack of a larger sample size. There are further lacunae due to lack of standardization in treating TED, both by ophthalmologists and endocrinologists.

Annexures:

A.

CAS:

Proposed classification system to assess diseaseactivity in Graves' oplthalmopathy

Category	Symptom / Sign	Score
Painful	Painful/ Oppressive feeling on or behind the globe.	I
	Pain on attempted up, side, or down gaze	I
Redness	Redness of the eyelid(s)	I
	Diffuse redness of the conjunctiva	I
Swelling	Chemosis,	I
	Swollen caruncule	I
	Oedema of the eyelid(s)	I
	Increase of proptosis of 2 mm or more during a period between Iand 3 months	I
Impairedf unction	Decrease in visual acuity of 1 or more lines on the Snellen chart(using a pinhole) during a period between 1 and 3 months	I
	Decrease of eye movements in any direction equal to or more than5 degrees during a period of time between 1 and 3 months.	I
Total		10

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