International Symposium on Graves' Orbitopathy

The EUGOGO 20th Anniversary Meeting

Pisa (Italy), November 7th- 9th, 2019

Organizing Secretariat

A.I.C. Asti Incentives & Congressi

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EUropean Group On Graves' Orbitopathy

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DEI MEDICI CHIRURGHI
E DEGLI ODONTOIATRI
DELLA PROVINCIA DI PISA

SSN Servizio Sanitario della Toscana

IN SUPREMÆ DIGNITATIS 1343

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Dipartimento medicina clinica
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SCIENTIFIC PROGRAMME

Auditorium Ricci

Thursday, 7th November 2019

12.00 - 1.00 pm **Registration**

1.00 - 1.15 pm **Opening Ceremony**

1.20 - 1.30 pm **Tomb of Sarteano: the first GO painting in history**
Lelio Baldeschi (Brussels, BE), Maurizio Martinelli (Florence, IT)

1.30 - 1.50 pm **Mark Prummel memorial lecture**
Chairperson: Claudio Marcocci (Pisa, IT)
EUGOGO achievements over 20 years - *Wilmar Wiersinga (Amsterdam, NL)*

1.55 - 3.35 pm **Symposium 1: the immunopathogenesis of GO in 2019**
Chairpersons: Paul Banga (London, UK), Marvin Gershengorn (Bethesda, USA)

1.55 - 2.15 pm Genetics and epigenetics of GO - *Simon Pearce (Newcastle upon Tyne, UK)*

2.15 - 2.35 pm Role of fibrocytes in GO - *Terry Smith (Ann Arbor, USA)*

2.35 - 2.55 pm Teprotumumab - *Raymond Douglas (Los Angeles, USA)*

2.55 - 3.15 pm Overview of the immune response in GO - *Willem A. Dik (Rotterdam, NL)*

3.15 - 3.35 pm The microbioma in Graves' disease and GO - *Marian Ludgate (Cardiff, UK)*

3.35 - 3.55 pm Graves' disease and GO following immune reconstitution - *Ilaria Muller (Cardiff, UK)*

4.00 - 5.00 pm **Oral Presentations 1**
Chairpersons: Nicola Currò (Milan, IT), Michele Marinò (Pisa, IT)

Rapamycin effectively ameliorates collagen and lipid deposition of the Graves' ophthalmopathy in balb/c mice - *Yue Wang (Xi'an, China)*

Serum antibodies against the insulin-like growth factor-1 receptor (Igf-1r) in Graves' Orbitopathy do not stimulate fibroblast proliferation - *Giulia Lanzolla (Pisa, Italy)*

Efficacy of rituximab in patients with active moderate-severe Graves' Orbitopathy: outcome of different dose regimens - *Elisa Lazzaroni (Milan, Italy)*

Asymmetric Graves' Orbitopathy: a post-hoc analysis from the PREGO study *Grigorios Panagiotou (Newcastle upon Tyne, UK)*

Real-world use of non-echoplanar diffusion-weighted magnetic resonance imaging for detection, disease monitoring and clinical decision-making in Graves' Orbitopathy - *Claire Feeney (London, United Kingdom)*

Contrast sensitivity in Graves' Orbitopathy: what can we do?
Marta Pérez-Lopez (Valencia, E)

5.00 - 5.20 pm ***Coffee Break***

5.20 - 7.00 pm **Symposium 2: diagnostic issues on GO phenotypes**

Chairpersons: Christoph Hintschich (Munich, DE), Raymond Douglas (Los Angeles, USA)

5.20 - 5.40 pm Unilateral, hypothyroid and euthyroid GO - *Anja Eckstein (Essen, DE)*

5.40 - 6.00 pm Orbital volumetry and its significance - *Wilmar Wiersinga (Amsterdam, NL)*

6.00 - 6.20 pm IgG4-related disease, the inflammatory neophyte in the orbit *Isle Mombaerts (Leuven, BE)*

6.20 - 6.40 pm Differential diagnosis of GO: the importance of multidisciplinarity and specialized centers - *Lelio Baldeschi (Brussels, BE)*

6.40 - 7.00 pm Diagnostic criteria and management of optic neuropathy - *Antonella Boschi (Brussels, BE)*

7.05 - 7.25 pm **George von Arx memorial lecture**

Chairperson: Lelio Baldeschi (Brussels, BE)

The importance of the ophthalmologist and of the joint clinic in GO *Nicole Fichter (Olten, CH)*

7.25 - 8.00 pm ***Welcome Cocktail***

Friday, 8th November 2019

8.30 - 8.50 am **Aldo Pinchera memorial lecture**

Chairperson: Paolo Vitti (Pisa, IT)

Epidemiology and secular trends of GO - *Petros Perros (Newcastle upon Tyne, UK)*

8.55 - 9.55 am **Symposium 3: animal models of GD and GO**

Chairpersons: Gerd Krause (Berlin, DE), Marian Ludgate (Cardiff, UK)

8.55 - 9.15 am Epitope peptides derived from the TSH receptor as an effective treatment in a mouse model of Graves' disease and GO - *Martin Ungerer (Bavaria, DE)*

9.15 - 9.35 am The "English" model - *Paul Banga (London, UK)*

9.35 - 9.55 am The "German" model - *Utta Berchner-Pfannshmidt (Essen, DE)*

10.00 - 11.00 am **Oral Presentations 2**

Chairpersons: Katharina Ponto (Mainz, DE), Miloš Žarković (Belgrade, SRB)

Modulations of the gut microbiota in a mouse model of Graves' Orbitopathy impacted on induced disease characteristics - *Giulia Masetti (Cardiff, UK)*

Immunotherapy with fingolimod improves outcome of experimental Graves' disease and associated orbitopathy - *Svenja Plöhn (Essen, DE)*

Oral steroid prophylaxis for orbitopathy after radioiodine for Graves' disease: is it still a safe choice? - *Sara Rosetti (Varese, IT)*

The quiet white eyes paradox in Graves' Orbitopathy - *Nicole M. Iñiguez-Ariza (Rochester, USA)*

Efficacy and side effects of deep lateral orbital wall decompression including the orbital rim in patients with Graves' Orbitopathy - *Maren Horn (Göttingen, DE)*

Retinal, choroidal and optic disc analysis in patients with Graves' disease with or without orbitopathy - *Giamberto Casini (Pisa, IT)*

11.00 - 11.20 am ***Coffee Break***

11.20 - 12.40 am **Symposium 4: ophthalmological controversies and unmet needs**

Chairpersons: Kostadinos Boboridis (Thessanoliki, GR), Colin Dayan (Cardiff, UK)

11.20 - 11.40 am EUGOGO consensus on eye motility assessment - *Nicola Currò (Milan, IT)*

11.40 - 12.00 am Assessment of primary and secondary outcomes of immunosuppressive treatment of active GO - *Luigi Bartalena (Varese, IT)*

12.00 - 12.40 am DEBATE: Is CAS always a reliable tool to define GO activity?

***Pro**: Lucy Clarke (Newcastle upon Tyne, UK)*

***Cons**: Peter Dolman (Vancouver, CA)*

12.40 - 2.00 pm ***Lunch and Poster viewing (NO CME)***

2.00 - 3.20 pm **Symposium 5: from pathogenesis to medical treatment: focus on the TSH receptor**

Chairpersons: George Kahaly (Mainz, DE), Terry Smith (Ann Arbour, USA)

2.00 - 2.20 pm TSH receptor and signaling pathways - *Gerd Krause (Berlin, DE)*

2.20 - 2.40 pm TSH receptor and IgF-1 receptor interactions - *Marvin Gershengorn (Bethesda, USA)*

2.40 - 3.00 pm Small molecules antagonists as potential new agents for therapeutic targeting of the TSH receptor - *Susanne Neumann (Bethesda, USA)*

3.00 - 3.20 pm TSH receptor monoclonal blocking antibodies - *Jadwiga Furmaniak (Cardiff, UK)*

3.20 - 4.20 pm **Symposium 6** (Part 1): **old and novel treatment modalities**

Chairpersons: Nichole Fichter (Olten, CH), Mario Salvi (Milan, IT)

3.20 - 3.40 pm Intravenous glucocorticoids - *Claudio Marcocci (Pisa, IT)*

3.40 - 4.00 pm Selenium - *Michele Marinò (Pisa, IT)*

4.00 - 4.20 pm Mycophenolate (The MINGO Study) - *George Kahaly (Mainz, DE)*

4.20 - 4.40 pm ***Coffee Break***

4.40 - 5.40 pm **Symposium 6** (Part 2): **old and novel treatment modalities**

Chairpersons: Anja Eckstein (Essen, DE), Simon Pearce (Newcastle upon Tyne, UK)

4.40 - 5.00 pm Combined immunosuppression and radiotherapy (The CIRTED study) *Peter N. Taylor (Cardiff, UK)*

5.00 - 5.20 pm Rituximab and other B cell targeting options - *Mario Salvi (Milan, IT)*

5.20 - 5.40 pm Tocilizumab - *José V. Pérez Moreiras (Santiago de Compostela, E)*

5.45 - 6.15 pm **Interactive Discussion on Symposium 6**

Chairperson: Luigi Bartalena (Varese, IT)

5.45 - 5.50 pm Chairperson's summary

5.50 - 6.15 pm Interactive discussion

8.30 - 11.30 pm ***Network Dinner***

Saturday, 9th November 2019

8.30 - 9.50 am **Symposium 7: ophthalmic perspectives**

Chairpersons: Peter Dolman (Vancouver, CA), Marco Nardi (Pisa, IT)

8.30 - 8.50 am Orbital decompression: does the approach matter? A review of the literature *Christoph Hintschich (Munich, DE)*

8.50 - 9.10 am Outcome measures for strabismus surgery - *Branislav Stanković (Belgrade, SRB)*

9.10 - 9.30 am Treatment of eyelids and tear film alteration in GO - *Kostadinos Boboridis (Thessaloniki, GR)*

9.30 - 9.50 am Nanotechnology applied to Graves' Orbitopathy: a potential alternative to more invasive medical and surgical treatments - *Dion Paridaens (Rotterdam, NL)*

9.55 - 10.55 am **Oral Presentations 3**

Chairpersons: Göksun Ayvaz (Ankara, TR), Antonella Boschi (Brussels, BE)

Implication of miRs 199a-3p/5p in oxidative stress and angiogenesis in local and systemic effects of Graves' disease - *Julie Craps (Brussels, BE)*

New perspectives in microRNA utilization in Graves' Orbitopathy *Jacopo Manso (Padua, IT)*

Correlation between serum ANTI-TSH receptor autoantibodies and the severity of Graves' Orbitopathy - *Francesca Nicolì (Pisa, IT)*

Short tau inversion recovery sequence versus clinical activity score in graves' ophthalmopathy (GO) patients with recent-onset progressive diplopia *Kelvin Kam-lung Chong (Hong Kong, China)*

Morphological and functional evaluation of optic nerve retinal fibers in patients affected by Graves' Orbitopathy - *Simone Donati (Varese, IT)*

Retinal vessel metrics: a novel tool to non-invasively estimate intraorbital pressure in dysthyroid optic neuropathy - *Katharina Ponto (Mainz, DE)*

10.55 - 11.15 am ***Coffee Break***

11.15 - 12.15 am **Patient Forum**

Chairpersons: Dan Morris (Cardiff, UK), Petros Perros (Newcastle upon Tyne, UK)

11.15 - 11.35 am The quality of life in GO and the impact of GO in public health - *Katharina Ponto (Mainz, DE)*

11.35 - 11.55 am	My life with GO - *Janis Hickey (British Thyroid Foundation, UK)*
11.55 - 12.15 am	Implementing change for improving the care of patients with GO: the TEAMED paradigm - *Colin Dayan (Cardiff, UK)*
12.20 - 12.40 am	**Lecture** ***Chairperson: Wilmar Wiersinga (Amsterdam, NL)*** Quo vadis GO? - *Marius Stan (Rochester, USA)*
12.40 - 1.00 pm	**Closing Ceremony**

Patients' parallel session (NO CME)

Pacinotti room

8.30 - 9.30 am	**Overview of GO** ***Chairpersons: Claudio Marcocci (Pisa, IT), Gail Moore (Lakeland, USA)*** Each topic will be introduced by a related question formulated by a patient. Duration 15 minute (8 minutes presentations followed by 5 minutes discussions + final discussion)
8.30 - 8.45 am	Pathogenesis, Prevention and Natural History - *Mario Salvi (Milan, IT)* question formulated by: *Xenia Stephanie Dal Cin*
8.45 - 9.00 am	Clinical features and Diagnosis - *Angela Sframeli (Pisa, IT)* question formulated by: *Alessandra Maiello*
9.00 - 9.15 am	Quality of Life - *Nancy Patterson (Hendersonville, USA)* question formulated by: *Barbara Gianfrancesco*
9.15 - 9.30 am	Management - *Roberto Rocchi (Pisa, IT)* question formulated by: *Orietta Terminali*
9.35 - 10.40 am	**Question and Answer Session** ***Chairperson: Luigi Bartalena (Varese, IT)*** ***Panelists:*** *Nicole Fichter (Olten, CH), George Kahaly (Mainz, DE), Nicola Currò (Milan, IT), Michele Marinò (Pisa, IT), Mario Salvi (Milano, IT), Lelio Baldeschi (Brussels, IT)*
9.35 - 10.05 am	3 short talks (5 minutes each) on personal experiences given by 3 patients, each followed by a 5 minutes discussion *Carla Carletto* *Nicoletta Fontani* *Lara Visentin*
10.10 - 10.55 am	Open questions by the patients

FACULTY

Ayvaz Göksun (Ankara - TR)

Baldeschi Lelio (Bruxelles - BE)

Banga Paul (London - UK)

Bartalena Luigi (Varese - IT)

Berchner-Pfannshmidt Utta (Essen - D)

Boboridis Kostas (Thessaloniki - GR)

Boschi Antonella (Bruxelles - BE)

Clarke Lucy (Newcastle upon Tyne - UK)

Currò Nicola (Milan - IT)

Dayan Colin M. (Cardiff - UK)

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Dolman Peter (Vancouver - CA)

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Salvi Mario (Milan - IT)

Sframeli Angela (Pisa - IT)

Smith Terry (Ann Arbour - USA)

Stan Marius (Rochester - USA)

Stanković Branislav (Belgrade - SRB)

Taylor Peter N. (Cardiff - UK)

Ungerer Martin (Bavaria - DE)

Vitti Paolo (Pisa - IT)

Wiersinga Wilmar (Amsterdam - NL)

Žarković Miloš (Belgrade - SRB)

ORAL PRESENTATIONS

RAPAMYCIN EFFECTIVELY AMELIORATES COLLAGEN AND LIPID DEPOSITION OF GRAVES' OPHTHALMOPATHY IN BALB/C MICE

Meng Zhang[1], Yue Wang[1], Bingyin Shi[1]

1. Department of Endocrinology, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

Background

As the main extrathyroidal manifestation of Graves' disease (GD), the pathological features of Graves' Ophthalmopathy (GO) are de novo adipogenesis, hyaluronan synthesis and enlargement of extraocular muscles. Rapamycin is a macrolide immunosuppressant regulating cell growth, proliferation and survival, especially in T-cell lineage that have been confirmed crucial in the pathogenesis of GO. This study aimed to investigate the effects of rapamycin on GO in mouse models as well as the underlying mechanism.

Methods

Female BALB/c mice aged 8 weeks were randomly assigned into three groups: control, model and intervention. The animal model was established by intramuscular injection of Ad-TSHR289 for 9 times. The intervention was given by a diet containing rapamycin (14ppm) from the 11th week to the end of the study. Measurements including thyroid function tests, flow cytometry and histological examination were performed at the end of the study (the 34th week).

Results

Orbital histological examination showed the proportion of orbital collagen enlargement in the intervention group was significantly lower than that in the model group (4/16vs10/16, p=0.037). The area of the adipose tissue around the optic nerve in the intervention group also decreased compared to the model group (p=0.027). The proportion of increased TT4 in the intervention group was also decreased (p=0.023), consistent with the results of thyroid histological examination, while TRAb did not. Flow cytometry indicated that in the intervention group, the Treg cell ratios (Foxp3+CD4+/CD4+) and Th2 cell ratios (CD4+ IL-4 +/CD4+)were increased compared to the model group, while the Th17 cell ratios (CD4+ IL-17a +/CD4+) and the Th1 cell ratios (CD4+ IL-4 +/CD4+) show the opposite results.

Conclusions

This study for the first time showed that rapamycin could reduce the proportion of collagen and lipid deposition of Graves' Ophthalmopathy effectively, as well as the TT4 Levels. Moreover, rapamycin noticeably ameliorates the Th17/Treg and Th1/Th2 cell balance, which were broken in the model mice.

SERUM ANTIBODIES AGAINST THE INSULIN-LIKE GROWTH FACTOR-1 RECEPTOR (IGF-1R) IN GRAVES' ORBITOPATHY DO NOT STIMULATE FIBROBLAST PROLIFERATION

Giulia Lanzolla, Giovanna Rotondo Dottore, Ilaria Bucci, Claudio Marcocci, Michele Marinò

Department of Clinical and Experimental Medicine, Endocrinology Units, University of Pisa and University Hospital of Pisa, Via Paradisa 2, 56124, Pisa, Italy

Background

A role of the insulin-like growth factor-1 receptor (IGF-1R) in the pathogenesis of Graves' Orbitopathy (GO) has been proposed and anti-IGF-1R-antibodies (IGF-1R-Abs) have been detected in a minority of patients with Graves hyperthyroidism (GH), regardless of the presence of GO. However, the function and significance of these autoantibodies has not been established. The aim of the present study was to investigate the action of IGF-1R-Abs in terms of cell proliferation in orbital fibroblasts.

Methods

Primary cultures of orbital fibroblasts from patients with GO were established and challenged with purified IgGs obtained from sera taken from patients with GH, with or without GO, positive forIGF-1R-Abs. Cell proliferation was measured using a commercial assay. IgGs purified from IGF-1R-Abs-negative sera from patients with multinodular goiter were used as controls.

Results

Regardless of the concentration used and of the presence of absence of GO, serum IgGs from GH patients did not stimulate proliferation of orbital fibroblasts. This was case also for control IgGs.

Conclusions

Serum IGF-1R-Abs do not seem to have a functional, direct role in the pathogenesis of GO. The role of IgF-1R is more likely related to its interactions with the TSH receptor.

EFFICACY OF RITUXIMAB IN PATIENTS WITH ACTIVE MODERATE-SEVERE GRAVES' ORBITOPATHY: OUTCOME OF DIFFERENT DOSE REGIMENS

E. Lazzaroni, D. Covelli, I. Campi, G. Vannucchi, N. Currò, G. Pirola, C. Guastella, A. Dolci, M. Arosio, M. Salvi

Aim

We assessed the efficacy of different doses of rituximab (RTX) in patients with active, moderate-severe Graves' Orbitopathy (GO).

Methods

40 patients, 5 M/35 F; mean age (± SD) 58 ± 11 years; 21(53%) smokers. All patients received RTX: 14 patients (group 1) a single 100 mg dose; 15 patients (group 2) a single 500 mg dose, 11 Patients (Group 3) 2 doses of 1000 mg.

Results (1)

	Nr	Duration with no relapse	Duration with relapse	Patients' age (years)	Pat. with previous steroid therapy	Baseline CAS*	12 weeks CAS*	24 weeks CAS*
Group 1	14	11.3	2.2	56	7/14	4.5 ±1	2.1 ±1.6	*1.1 ±-0.8*
Group 2	15	8.9	2.5	57	2/15	4.3±1	1.3 ± 1.5	*0.1±1.1*
Group 3	11	14.3	4.5	63	2/11	4.4 ±1	1.8 ±1.3	*0.8±1.1*
ANOVA				n.s.	n.s.	n.s.	n.s.	***0.04***

*values are expressed as mean ±SD

Results (2)

- Serum TRAb levels were significantly reduced in the in the three groups at 24 weeks. At 12 weeks serum TRAb levels decreased significantly only in group 2
- 13/40 patients at baseline and 14/40 at 24 weeks were persistently hyperthyroid, despite the change in serum TRAb title throughout RTX therapy.
- 2 patients of group 1 (100 mg dose) developed optic neuropathy.
- 3 patients presented major adverse reaction after only 25-75 mg of RTX (acute cytokine release syndrome).

Conclusions

1) RTX inactivated GO in all patients, independently of the doses used.
2) Serum TRAb decreased at 24 weeks in all three groups of patients.
3) The use of low dose RTX does not seem to prevent adverse effects and the progression to optic neuropathy.

ASYMMETRIC GRAVES' ORBITOPATHY: A POST-HOC ANALYSIS FROM THE PREGO STUDY

Grigorios Panagiotou[1], Milos Žarković[2], Petros Perros P, on behalf of EUGOGO

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[2]Department of Endocrinology, School of Medicine, University of Belgrade, 11000 Belgrade, Serbia

Background

Asymmetry in Graves' Orbitopathy (GO) is common, but little is known about its aetiology. The aim of the present study was identify clinical characteristics that distinguish asymmetric, unilateral GO and symmetrical disease.

Methods

PREGO (doi: 10.1136/bjophthalmol-2015-306733) was an observational study of all new referrals of patients with GO to EUGOGO centres recruited prospectively during a 4-month period. The data from PREGO were analysed with a specific focus on asymmetry. Asymmetrical disease was defined as a difference of >2mm in proptosis between eyes.

Results

269 patients were initially recruited. Two subjects did not have data entered on proptosis and were excluded from our analyses. Patients were categorized as symmetrical (n=168, 82.3% female; mean age 46.6 ±13.7 years), asymmetrical (n=68, 62.1% female; mean age 50.3±14.4 years) and unilateral (n=33, 81.1% female; mean age 47.7±14.4 years). Between-group comparisons showed statistically significant differences in distribution of gender (p=0.005), country of origin (lowest unilateral France 2.7% versus highest Denmark 33.3%, p=0.009, clinical activity score (CAS) (symmetrical: 1.9±1.7; asymmetrical: 2.8±1.6; unilateral: 1.48±1.7) and Total Eye Score (TES) (symmetrical 5.4+4.4; asymmetrical 9.05+7.2; unilateral 3.4+2.1, p<0.05). No other significant differences were evident. Using Multinomial Logistic Regression Analysis, the asymmetrical group emerged as the most distinct and contained the lowest percentage of females, as well as highest CAS and TES (p<0.05 for all). Duration of symptoms of GO was also significantly shorter in asymmetric and unilateral disease than symmetric (symmetric (median in months and range) 10 (0-334); asymmetric 9 (1-552); unilateral 8 (1-156), p<0.05).

Conclusions

Male gender, increased CAS, short duration of GO and higher TES are predictive of asymmetry in GO. These findings warrant further investigation in longitudinal studies.

REAL-WORLD USE OF NON-ECHOPLANAR DIFFUSION-WEIGHTED MAGNETIC RESONANCE IMAGING FOR DETECTION, DISEASE MONITORING AND CLINICAL DECISION-MAKING IN GRAVES' ORBITOPATHY

Feeney C[1,2], Lingam RK[3], Lee V[1*], Rahman F[1], Nagendran S[1]

[1]*Eye Department, Central Middlesex Hospital, London, United Kingdom*

[2]*Imperial Centre for Endocrinology*

[3]*Department of Radiology, Northwick Park & Central Middlesex Hospital, London Northwest University Healthcare NHS Trust, United Kingdom*

Background

The Clinical Activity Score (CAS) is widely used to grade activity of Graves' Orbitopathy (GO) and guide treatment decisions but has a number of limitations. Non-echoplanar diffusion-weighted magnetic resonance imaging (non-EPI-DWI) of the extra-ocular muscles (EOMs) may be able to address some of the limitations posed by CAS and other imaging techniques but the correlation with CAS is unknown.

Methods

A retrospective observational study of 31/88 patients seen in a multidisciplinary GO clinic over a 5 year period who had at least one ophthalmic and endocrine assessment including CAS score and non-EPI-DWI Apparent Diffusion Coefficient (ADC) calculation. Spearman's rank correlation coefficient was used to determine the relationship between CAS and non-EPI-DWI. A Decision Tree was constructed to evaluate clinical decision-making and Receiver-Operator Curves (ROC) were generated for mild GO and dysthyroid optic neuropathy (DON).

Results

In total, 60 non-EPI-DWI scans (368 EOMs) were evaluated. There was a significant positive correlation between CAS and ADC ($rs=0.403$ CI 0.312-0.489, $P<0.0001$). ADC values were significantly higher in the CAS ≥3 group compared to the CAS <3 group, $P<0.0001$. Our Decision Tree identified a third 'intermediate' severity cohort where non-EPI-DWI was particularly useful in guiding clinical decisions. ADC performed well as a diagnostic test in predicting DON (AUC 0.974 95% CI 0.93-1.0).

Conclusions

Non-EPI-DWI correlates well with CAS in our patients and was a useful adjunct to CAS in making clinical decisions especially in patients with 'intermediate' severity GO and may also be useful in identifying patients at risk of DON.

CONTRAST SENSITIVITY IN GRAVES' ORBITOPATHY: WHAT CAN WE DO?

Marta Pérez-Lopez Md, PhD[1], Isabel Cid-Garcia[2], Santiago Montolio-Marzo[3], Carlos Sanchez Md, PhD[3]

1. Ophthalmology, Hospital Universitario La Fe Valencia

2. Fisabio Oftalmologia Medica

3. Endocrinology, Hospital General Valencia

Purpose

To measure contrast sensitivity (CS) in patients diagnosed with inactive Graves' Orbitopathy (GO) without optic neuropathy and to compare it with a control group of healthy subjects. We would also evaluate the effect of using specific filters in GO visual function.

Material and methods

28 patients diagnosed with inactive mild and moderate- to severe GO and full visual acuity (6/6) were recruited between January 2017 and January 2018. Contrast Sensitivity was measured in mesopic and scotopic conditions using FACT in all patients. Complete ophthalmological examination including epithelial thickness mapping (to asses ocular surface) using Optovue was performed in all patients. A control group of 15 healthy subjects underwent the same examinations.

Results

CS in all spatial frequencies was significantly reduced in inactive GO patients compared to controls in both mesopic ($p<0.001$ U Mann_Whitney) and scotopic condicions ($p<0.001$ U Mann_Whitney). If patients were divided by disease severity, CS was significantly reduced compared to controls in both mild GO ($p<0.001$ U Mann_Whitney) and moderate-to-severe GO ($p<0.001$ U Mann_Whitney). No significant differences were found between GO patients and controls in corneal epithelial thickness measured with RTVue100 (Optovue) ($p=0.286$ U Mann Whitney). The greatest decrease in CS in GO patients compared to controls occurred at highest spatial frequencies. Selective filters were offered to GO patients. All of the he ones who accepted to wear them, selected 400 nm filter with significant improvement in their visual function QL-GO score.

Conclusions

There is a significant reduction of CS in both mild and moderate-to-severe inactive GO patients compared to healthy subjects. It may be caused by a subtle damage to the optic nerve due to the increase in retroocular pressure that occurs in Graves´ orbital disease. Selective filters may be helpful in improving visual quality of GO patients.

MODULATIONS OF THE GUT MICROBIOTA IN A MOUSE MODEL OF GRAVES' ORBITOPATHY IMPACTED ON INDUCED DISEASE CHARACTERISTICS

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Background

We recently proposed a role for the gut microbiota in a hTSHR-induced mouse model of Graves' Orbitopathy (GO) and identified disease-associated taxa. To investigate further, we modified the gut microbiota of the female BALB/c mice using antibiotic (vancomycin), probiotic or human faecal material transfer (hFMT) prior to immunization.

Methods

Dams and subsequently their pups received vancomycin throughout the experiment. The hFMT comprised faeces (cultured, pooled, freeze-dried) from 6 GO patients. Pups were gavaged with probiotic LAB4, hFMT or autoclaved water (control); one day after birth, at weaning, before and in the middle of immunisations with TSHR-A subunit or βgal plasmids. Samples were obtained at sacrifice; blood, thyroid, lymph nodes and orbital contents assessed the induced GD/GO. DNA from intestinal contents was extracted for 16S rRNA gene sequencing.

Results

Vancomycin treatment significantly reduced gut microbiota richness and diversity compared with all other groups, Lab4 and hFMT had more subtle effects but sufficed for predicting the correct treatment with a per-class accuracy of >70%. Significant thyroid pathology (TSAB, elevated T4, hyperplastic thyroid) developed in 72% untreated TSHR-immunized (36% had moderate-to-severe disease) which increased to 82% in Lab4 and hFMT treated (73% and 55% moderate-to-severe respectively). In contrast only 50% of vancomycin treated had mild autoimmune hyperthyroidism. Regarding orbitopathy, 85% of untreated TSHR-immunized mice developed mild or moderate-to-severe disease. Lab4 or hFMT treated displayed clinical disease in 72% and 67% respectively but only 43% of vancomycin treated developed mild GO. In lymph nodes CD25+ Treg numbers were significantly lower/higher in antibiotic and probiotic treated animals respectively.

Conclusions

The manipulation strategies successfully modified the gut microbiota in the early-stage of life, with an impact on TSHR-induced disease. The reduced thyroid and orbital pathology, combined with diminished Tregs, in vancomycin treated mice support a role for the gut microbiota in promoting GO.

IMMUNOTHERAPY WITH FINGOLIMOD IMPROVES OUTCOME OF EXPERIMENTAL GRAVES' DISEASE AND ASSOCIATED ORBITOPATHY

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Graves' Orbitopathy (GO) occurs together with autoimmune hyperthyroidism and is caused by stimulating thyrotropin receptor (TSHR) autoantibodies and autoreactive T cells. While thyroid dysfunction can be efficiently treated in patients, current treatments for GO remain unsatisfactory. Sphingosine-1-phosphate (S1P) and receptors have been shown to be involved in orbital inflammation and tissue remodeling processes. Furthermore, our previous study revealed involvement of S1P in orbital T-cell recruitment. All together these in vitro studies suggest S1P receptor modulators as a treatment option for GO. We therefore explored both preventive and therapeutic treatment with fingolimod in a mouse model for autoimmune hyperthyroidism and associated GO induced by immunization with hTSHR A-subunit encoding plasmid. Preventive treatment during immunization inhibited the induction of stimulating TSHR autoantibodies and modulated peripheral blood CD3 T-cell subtypes. Splenic CD4, CD8 T cells and Treg numbers were decreased under preventive treatment. In animals undergoing therapeutic treatment after immunization, the blood and splenic T-cell numbers were declined while pathogenic autoantibodies levels remained stable. In result, the following signs of hyperthyroidism were reduced or even normalized in the treated animals: weight gain, elevation of body temperature, elevated serum T4 concentration and hypertrophic thyroid morphology accompanied by enlarged heart size and tachycardia. Moreover, examination of orbital tissue revealed significant amelioration of orbitopathy manifestations by reduction in orbital CD3 T-cell infiltration, adipogenesis and hyaluronan deposition. Our study discovers that S1P receptor modulators like fingolimod have the potential for early treatment of both autoimmune hyperthyroidism and associated GO, and allow the conclusion that T-cell autoimmunity is important for GO development.

ORAL STEROID PROPHYLAXIS FOR ORBITOPATHY AFTER RADIOIODINE FOR GRAVES' DISEASE: IS IT STILL A SAFE CHOICE?

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Background

Oral low-dose steroid prophylaxis is widely used to prevent the development or exacerbation of Graves' Orbitopathy (GO) after radioiodine (RAI) treatment for Graves' hyperthyroidism[1]. A 2017 US population based cohort study has recorded a high rate of steroid-related complication (fractures, sepsis, thromboembolism), even with a relatively short-term course (prednisone 20 mg/die for 30 days)[2]. Following this alarming results, we retrospectively re-evaluated the rate of steroid-related complications in our patients treated with steroid prophylaxis after RAI.

Methods

We retrospectively evaluated 210 patients with Graves' hyperthyroidism and mild or no GO submitted to RAI treatment and short-term low-dose steroid prophylaxis (starting mean dose: 0.3 mg/kg/die, mean treatment period: 35 days). We evaluated the patients at the time of RAI administration, six and twelve months after RAI, for fractures, sepsis and thromboembolism. Patients presenting any steroid-related complication in the medical history were excluded. Only patients with age between 18 and 64 years old were included in the complication analysis, like in the US cohort. We also evaluated GO with the Clinical Activity Score (CAS) at RAI, six and twelve months after RAI. GO was considered worse when CAS during follow-up was two points higher than CAS at the time of RAI treatment.

Results: As expected from the US paper, we did not record any cases of sepsis or thromboembolism. The rate of fracture is lower than expected (1 vs 3.51); the only fracture was related to a traumatic event. Six and twelve months after RAI treatment, 98.1% of the patients had stable/improved GO.

Conclusions

The routinely use of oral steroid prophylaxis for GO after RAI treatment is not associated with an increased risk of sepsis, thromboembolism and fractures. The use of low-dose prednisone for a short period is safe; we also confirm its effectiveness in preventing GO development/ progression after RAI.

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THE QUIET WHITE EYES PARADOX IN GRAVES' ORBITOPATHY

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Background

Graves' Orbitopathy (GO) is considered to start with an active inflammatory stage - active disease - followed by resolution of inflammation and progression to a fibrotic stage - inactive disease. The clinical activity score (CAS) is used in practice to distinguish these two phases. However, in our practice we have encountered cases that have not had at any point the elements of active disease and we aim to describe those patient here.

Methods

We conducted a retrospective chart review in order to identify all GO patients seen at our institution who throughout the course of their disease did not have any evidence for active GO, defined as CAS >2.

Results

20 individuals (16 females) met the inclusion criteria. Median age was 55 years. 25% (n=5) were active smokers and 50% (n=10) had a prior diagnosis of Graves' disease (GD) before referral. Median time between onset of GD and GO was 7 months (IQR 1- 45 months). 80% (n=16) were euthyroid at the time of GO onset (median TSH 1.7 mIU/L. The most common sign was diplopia, present in 95% (n=19) of patients. Proptosis was present in 60% (n=11). Interestingly the disease was unilateral in 30% of cases. Overall median CAS score was 0.5 (IQR 0-1). Severity wise, 85% (n=17) of patients were classified as moderate to severe while the rest had mild GO. Orbital decompression was required in only 2 cases while extraocular muscle surgery was performed in 14 cases.

Conclusions

There is a subgroup of patients that defies the GO paradigm and does not display the typical stage of active disease. This subgroup presents primarily with diplopia and proptosis and tends to be euthyroid more often that the overall GO population. Further evaluation of this group might identify useful insights into GO pathophysiology and help optimize therapeutic choices.

EFFICACY AND SIDE EFFECTS OF DEEP LATERAL ORBITAL WALL DECOMPRESSION INCLUDING THE ORBITAL RIM IN PATIENTS WITH GRAVES' ORBITOPATHY

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Background
Orbital decompression is an established surgical procedure for the treatment of exophthalmos in Graves' Orbitopathy. Aim of the study was to evaluate the efficacy and side effects of deep lateral orbital wall decompression including the orbital rim.

Methods
In this retrospective, non-comparative case series, all patients with Graves' Orbitopathy, who underwent lateral orbital wall decompression at the Eye Clinic of the University of Goettingen between 2008 and 2015, were analysed in terms of exophthalmos reduction, diplopia (Gorman score) and complications. The surgical technique involved the removal of the lateral orbital wall including the orbital rim combined with additional orbital fat resection via swinging eyelid approach.

Results
127 patients/195 interventions were included. Mean exophthalmos reduction was 4.0 ± 1.2 mm (range 1.5-7.5 mm). Preoperatively, 47 patients/77 orbits (37.0/39.5%) presented without diplopia. Postoperatively, 3 patients/3 orbits (6.4/3.9%) showed new- onset diplopia (2.4% of all patients, 1.5% of all orbits). Diplopia in primary gaze was noted in one of the 3 patients (0.8 % of all patients, 2.1% of patients without preoperative diplopia). Postoperative improvement of diplopia was noted in 19 patients/ 19 orbits (15.0 % of all patients, 23.8 % of patients with preoperative diplopia/9.7% of all 195 interventions,16.1% of cases with preexisting diplopia). No severe complications were seen, except for one case of postoperative bleeding, which was successfully managed surgically without any functional deficits. A visible scar formation was noted in 6 cases (3.1%), temporal hollowing in 3 cases (1.5%), oscillopsia when chewing in 3 cases (1.5%) and a de-insertion of the lateral canthal region in 2 cases (1 %).

Conclusions
Deep lateral orbital wall decompression, including the orbital rim, is an effective surgical technique to reduce exophthalmos in patients with Graves' Orbitopathy with a low risk of functional and aesthetic complications.

RETINAL, CHOROIDAL AND OPTIC DISC ANALYSIS IN PATIENTS WITH GRAVES' DISEASE WITH OR WITHOUT ORBITOPATHY

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Background
Graves' Orbitopathy (GO) is characterized by an inflammatory and proliferative process that involves all orbital structures including fat, muscles and optic nerves. To our knowledge no previous studies aimed to investigate retinal, choroidal and optic nerve changes in patients with GD with or without clinical signs of orbitopathy.

Methods
Optical coherence tomography and Heidelberg retinal tomography were performed in 40 patients with Graves' orbitopathy (GO), 40 subjects with Graves's disease with no sign of orbitopathy and 40 healthy controls. Degree of exophthalmos, ocular alignment, clinical activity score (CAS), choroidal thickness, retinal thickness, ganglion cell layer (GCL) thickness, disc area, cup area, rim area, cup/disc area ratio, linear cup/disc ratio, and mean peripapillary retinal nerve fiber layer thickness were analyzed.

Results
GO patients and healthy controls significantly differ regarding mean central retinal thickness (275±19 μm and 285±20 μm, P = 0.017); mean central GCL thickness (14.87±3.0 μm and 17.92±5.02 μm, P = 0.001) mean disc area (2.00±0.44 mm^2 and 1.72±0.37 mm^2, P = 0.003); mean cup area (0.53±0.52 mm^2 and 0.31±0.20 mm^2, P = 0.003); cup/disc area ratio (0.22±0.10 and 0.17±0.08, P = 0.010); linear cup/disc ratio (0.47±0.15 and 0.40±0.13 respectively, P = 0.011). No difference was found between patients without orbitopathy and healthy controls. There was no statistically significant relationship between retinal thickness, ganglion cell layer thickness, mean disc area, mean cup area, cup/disc area ratio, linear cup/disc ratio, CAS, exophthalmometric value and ocular alignment.

Conclusions
GO patients showed significant changes in foveal and GCL thickness, and optic nerve head morphology suggesting a possible influence of the orbital inflammatory process.

IMPLICATION OF MIRS 199a-3p/5p IN OXIDATIVE STRESS AND ANGIOGENESIS IN LOCAL AND SYSTEMIC EFFECTS OF GRAVES' DISEASE

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Graves' thyroiditis (GD) is characterized by hyperthyroidism and is often associated to ophthalmopathy (TAO). GD thyroids and adipose tissue present high oxidative stress (OS) and hypervascularization. miR199a-3p (3p) and miR199a-5p (5p) dysregulation has been linked with endothelial function, OS, angiogenesis and adipogenesis. Therefore, we aimed to measure 3p/5p expression in samples from GD patients and evaluate their potential impact on development of GD-clinical and systemic effects.

Plasma and thyroid samples were obtained from patients operated for multinodular goiters (controls) or GD. Orbital fat samples came from blepharoplasty or TAO. miRs expressions were evaluated following quantitative real-time PCR and in situ hybridization. To mimic GD, human primary thyrocytes were stimulated with IL-4. Microvascular endothelial cells were cultured in matrigel support in the presence of medium from non-treated or IL-4 treated (GD-conditioned medium) thyrocytes and their angiogenic effect was evaluated by tubes formation.

GD thyrocytes showed an increased of 4-hydroxynonenal, indicating a rise in lipid peroxidation, and increased catalase expression suggesting improved H2O2 detoxification. In GD thyroid samples, NADPH-oxidase-4 upregulation correlated with HIF-1α stabilization and upregulation of VEGF expression. GD-conditioned medium promoted tubes formation in 2D-endothelial cell culture. Interestingly, GD thyroids, GD plasma samples and TAO adipocytes showed a significant downregulation of 3p/5p. In GD orbital fat, we found that caveolin-1 and glucose transporter (Glut-4) were decreased, while VEGF and NADPH-oxidase-2 protein expression were significantly increased. HIF-1α and Deiodinase-3 were also upregulated. Noteworthy, VEGF, NADPH-oxidase-2, HIF-1α and Deiodinase-3 were identified as potential direct targets of miR199a in prediction databases.

In conclusion, we showed a dramatic reduction in miR199a-3p/5p expression in GD thyroid extracts and TAO fat. Taken together, our results are in agreement with a potential implication of these miRs as regulators of OS, angiogenesis and GD systemic manifestations. The causal relationship between miR dysregulation and protein expression is under evaluation.

NEW PERSPECTIVES IN MICRORNA UTILIZATION IN GRAVES' ORBITOPATHLY

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Background
Graves' Orbitopathy (GO) is an autoimmune disease of the eye and retro-ocular tissues. The principal treatments for active GO are based on intravenous glucocorticoids (GC-IV) possibly associated with ocular radiotherapy (RT). MicroRNAs are small single-stranded non-coding RNAs that play a role in the regulation of biological processes.

Methods
18 consecutive moderate to severe active GO patients were enrolled to undergo standard therapy (GC-IV ± RT). The exclusion criteria were age<18 years, hepatitis C or B, severe liver disease, uncontrolled hypertension, severe heart disease, pregnancy, uncontrolled diabetes mellitus. Each patient was clinically and instrumentally characterized before, during and after treatment. Plasma samples of 14 patients were collected at the beginning of therapy to evaluate expression of miR-21 and miR-146a, comparing them to a population of 19 healthy controls.

Results
A reduction in the clinical activity score ($p=0.0001$) and VISA-overall-severity score ($p<0.0001$) were observed at the end of therapy. The expression levels of circulating miR-146a and miR-21 at the beginning of therapy were respectively higher ($p=0.0043$) and not dissimilar compared to a healthy population. Higher circulating levels of miR-21 ($p=0.0071$) and miR-146a ($p=0.04$) before starting therapy were associated with the development of major side effects related to GC IV. Then, a cut-off of 0.18 for miR-21 ($p<0.0001$) and 22.82 for miR-146a ($p=0.044$) were identified.

Conclusions
We describe for the first time the expression levels of circulating miR-21 in GO; furthermore, circulating miR-146a results over-expressed in GO. Circulating miR-21 and miR-146a pave the way for their possible use as predictors of the development of adverse effects related to GC-IV in GO, emerging as a future possible tool in the decision-making process of precision-medicine.

CORRELATION BETWEEN SERUM ANTI-TSH RECEPTOR AUTOANTIBODIES AND THE SEVERITY OF GRAVES' ORBITOPATHY

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Background

Graves' Orbitopathy (GO) is the most common extrathyroidal manifestation of Graves' Disease (GD). A number of studies support the involvement of TSH receptor autoantibodies (TRAb) in the pathogenesis GO, and a correlation between GO features and TRAb has been reported, but not confirmed by all studies on the subject. Thus, we conducted a cross-sectional investigation to determine whether there is a correlation between TRAb levels and the clinical features of GO in the initial phase of the eye disease.

Methods

Forty-two consecutive patients with untreated GO (32 women and 10 men, age 48.5 ± 11.5 yr) with a GO lasting 6.7±3.6 months were included. All patients were under methimazole for Graves' hyperthyroidism. Patients who had undergone glucocorticoid or any other immunosuppressive treatments were excluded. All patients underwent an endocrinological and ophthalmological evaluation, the latter including: exophthalmometry, measurement of eyelid width, clinical activity score (CAS), visual acuity, assessment of diplopia, NOSPECS score and a modified NOSPECS score. TRAb levels were measured by an enzyme-linked immunosorbent assay (ELISA).

Results

There was no correlation between the levels of TRAb and exophthalmometry, CAS, eyelid width, visual acuity and diplopia. However, there was a statistically significant positive correlation between TRAb levels and the NOSPECS score (P=0.03) and between TRAb levels and the modified NOSPECS score (P=0.04).

Conclusions

The levels of TRAb in subjects with a recent-onset, untreated GO are directly correlated with the severity of the disease (the NOSPECS and the modified NOSPECS scores) confirming the role of autoimmunity against the TSH-receptor in the pathogenesis of GO.

SHORT TAU INVERSION RECOVERY SEQUENCE VERSUS CLINICAL ACTIVITY SCORE IN GRAVES' OPHTHALMOPATHY (GO) PATIENTS WITH RECENT-ONSET PROGRESSIVE DIPLOPIA

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Background
Majority of Graves' Ophthalmopathy (GO) patients in our population presented with recent-onset (<6 months) diplopia had low (<3/7) Clinical Activity Score(CAS) and lack basis for therapeutic intervention according to the EUGOGO recommendation. Magnetic Resonance Imaging (MRI) Short Tau Inversion Recovery (STIR) sequence objectively measures water content, which reflects tissue edema and underlying inflammation of extraocular muscles (EOM). We hypothesize that measuring MRI STIR EOM may be more useful than CAS to identify patients for immunosuppressive therapy.

Methods
Consecutive treatment-naive euthyroid patients with progressive GO and recent-onset (<6 months) diplopia (score >1) were evaluated by a single oculoplastic surgeon on 7-item CAS and semi-quantitative extraocular motility restriction (from 0 to -4). All patients underwent orbital MRI using the same machine and scan protocol. The brightest signal (STIR) and the largest area (T1-weighted non-contrast) coronal images of each rectus were manually segmented by two independent, masked and trained observers.

Results
Ninety patients (55 female) aged 38+/-14 years (20-75) with progressive diplopia were scanned. Mean CAS was low (1.6+/-1.4) while eighty patients (90%) were inactive by CAS (<3). Brightest STIR signal and largest T1W area, but not CAS, were significantly correlated to the EOM restriction (Pearson coefficient=0.25, 0.13; $p<0.001$, $p<0.02$ respectively). STIR signals significantly improved, along with diplopia and EOM restriction in patients with pretreatment low CAS (<3) on follow-up MRI 6-month after pulse steroid and orbital irradiation ($p<0.005$).

Conclusions
STIR signal is more sensitive than EOM area on MRI or CAS in assessing EOM inflammation and predicting response to combined immunosuppression especially for GO patients who are "cold-presenter".

MORPHOLOGICAL AND FUNCTIONAL EVALUATION OF OPTIC NERVE RETINAL FIBERS IN PATIENTS AFFECTED BY GRAVES' ORBITOPATHY

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Background

Graves' Orbitopathy (GO) presents different clinical features and may impact in different ways to visual function. Nowadays optic nerve head and peripapillary analysis by Optical Coherence Tomography (OCT) allows to evaluate early modifications or damages due to compressive optic neuropathy of any etiology.

The aims of our studies were to analyze morphological modifications of neural retinal layers in GO and their relation to disease stage and functional data.

Methods

A trasversal and prospective study have been performed.

Trasversal study: we evaluated 60 eyes in 30 patients affected by GO, with no clinical signs of optic nerve dysfunction. We divided patients into three groups: Group 1: low GO; Group 2: moderate-severe GO and Group 3: control cohort. Each patient underwent a complete ophthalmogical examination completed by OCT, VF and orthoptic visit. OCT evaluated retinal nerve fiber layer and ganglionar cells layer thickness (RNFL and GCL).

Prospective study: we evaluated six patients (eleven eyes) affected by a severe stage of the pathology. We studied morphological and functional data at baseline and at six months after steroid treatment.

Results

Considering observational study, mean RNFL values (μm) were respectively for Group 1, Group 2, Group 3: 89.40, 90, 93.02 ($p<0,05$ for Group 2 vs Group 3); mean GCL values (micron) were respectively: 80.11, 80.85, 84.03. We showed a diffuse reduction of RNFL thickness in all patients, with a significative correlation with the stage of the disease but no correlation with functional data. Moreover we found a significative correlation between GCL thickness and exophthalmos degree in all patients.

In the second study, we didn't find any significant difference between baseline and post treatment data in functional and morphological values. Mean RNFL (micron) respectively at baseline and at month 6 was: 90.63, 89.45 ($P=0.74$); mean GCL (micron) was respectively: 80.273, 79.909.

Conclusions

OCT examination may represent a new tool for diagnosis of optic nerve damage in Graves' Orbitopathy. In this direction, diagnostic and management criteria may be revised to treat the pathology on the early phase of neurological damage, to prevent severe visual sequelae.

Authors declares not financial interests on the matter of the research.

RETINAL VESSEL METRICS: A NOVEL TOOL TO NON-INVASIVELY ESTIMATE INTRAORBITAL PRESSURE IN DYSTHYROID OPTIC NEUROPATHY

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Background and Aims

Recognition of dysthyroid optic neuropathy (DON) requires sensitive diagnostic tools. In-vivo measurement of retinal vascular calibers may be used to non-invasively and indirectly estimate intraorbital pressure in Graves' Orbitopathy (GO) and especially in DON. We hypothesized to find larger retinal venules in patients with than in those without DON.

Methods

Fundus photographs from eyes of patients with GO were assessed using the 'retinal vessel analyzer' software (IMEDOS) to determine the central retinal arteriolar equivalent (CRAE) and the central retinal venular equivalent (CRVE).

Results

A total of 32 patients (46 orbits) with GO (n=24 female or 75%, median age 58 years; range: 24-83 years) were included in this prospective study. Reasons for decompression surgery in a total of 19 (46.3%) orbits were DON in 13 (68.4%) and cosmetic-esthetic rehabilitation in 6 (31.6%) orbits, respectively. A larger retinal venular equivalent (median: 151.21, range: 125.28-220.04) was measured in patients with DON than in those without (133.02, 82.56-239.97, p=0.007). After decompression surgery, the median CRVE decreased by 6.33 (range: -54.55 -7.89) in patients with versus 4.59 (-70.82 -61.64) without DON (p>0.05). No significant differences of the CRAE were found between patients with and without DON.

Conclusions

This study is the first to satisfactorily indicate that – as an indirect sign of elevated intraorbital pressure with impaired venous outflow – retinal venular equivalents are larger in patients with DON than in those without. The finding that enlarged venous calibers also seem to shrink after bony decompression surgery should be confirmed in larger prospective studies.

POSTERS
(NO CME)

Poster Index

PO 12 TRAB OF VARIABLE GRAVES' ORBITOPATHY PHENOTYPES ALWAYS STIMULATE CAMP PRODUCTION ON TSHR EXPRESSING HEK CELLS AND STIMULATION CAN BE DOWNREGULATED WITH TSHR ANTAGONISTS

Mareike Horstmann[1], Mareile Stöhr[1], Gerd Krause[2], Patrick Marcinkowski[2], Susanne Neumann[3], Marvin Gershengorn[3], Gina-Eva Görtz[1], Sebastian Hönes[4], Utta Berchner-Pfannschmidt[1], Anja Eckstein[1]
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PO 13 AWARENESS OF EUGOGO CONSENSUS STATEMENTS AND ITS PRACTICAL USAGE IN CROATIA: AN ONLINE, INTERNET-BASED SURVEY AMONGST ENDOCRINOLOGISTS, OPHTHALMOLOGISTS AND NUCLEAR MEDICINE SPECIALISTS

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PO 14 ANTI-NUCLEAR AUTOANTIBODIES IN GRAVES' ORBITOPATHY

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PO 15 CLINICAL CHARACTERISTICS OF DYSTHYROID OPTIC NEUROPATHY IN HONG KONG CHINESE PATIENTS: A SINGLE CENTRE EXPERIENCE

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PO 16 A SURVEY OF CURRENT PRACTICES BY BRITISH OCULOPLASTIC SURGERY SOCIETY AND RECOMMENDATIONS FOR DELIVERING A SUSTAINABLE MULTIDISCIPLINARY APPROACH TO GRAVES' ORBITOPATHY (GO) IN THE UNITED KINGDOM

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PO 17 REDESIGNING RUNDLE'S CURVE FOR DYSTHYROID OPTIC NEUROPATHY?

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PO 18 DEMOGRAPHICS OF GRAVES' ORBITOPATHY ACROSS THREE ADJACENT MULTI-DISCIPLINARY (MDT) CLINICS IN THE SAME CITY

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PO 26 REGIONAL HEALTH SERVICES RESEARCH AT A GERMAN MULTIDISCIPLINARY ORBITAL CENTER

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PO 37 SINGLE - CELL PROFILING OF CD4+ T LYMPHOCYTES FROM GRAVES' OPHTHALMOPATHY REVEALS A CYTOTOXIC SUBSET ASSOCIATED WITH INFLAMMATION AND FIBROSIS

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PO 38 A NINE YEAR AUDIT OF THE EDINBURGH JOINT THYROID EYE CLINIC

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PO 39 RIM - SPARING VERSUS RIM - REMOVAL TECHNIQUES IN DEEP LATERAL WALL ORBITAL DECOMPRESSION FOR GRAVES' ORBITOPATHY

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PO 40 EYELID LENGTHENING WITH ACELLULAR XENOGENIC DERMAL MATRIX AS A SPACER GRAFT TO TREAT EYELID RETRACTION RELATED TO THYROID ASSOCIATED OPHTHALMOPATHY

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PO 41 BOVINE ACELLULAR DERMAL MATRIX FOR LEVATOR LENGTHENING IN THYROID-RELATED UPPER - EYELID RETRACTION

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PATIENTS PERSPECTIVES ON LIVING WITH THYROID EYE DISEASE: FROM FEELINGS TO EFFECT ON ACTIVITIES

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Background

Thyroid eye disease (TED) can have significant impact on physical and psychosocial wellbeing, as well as being potentially disfiguring and/or sight-threatening. Understanding concerns and feelings of patients with TED is an integral aspect of healthcare practice for clinicians. We aimed to assess clinical perspectives and feelings that individuals associate with TED.

Methods

We designed an informative and educational day for patients with thyroid eye disease. An interactive anonymized session was created to evaluate life quality and explore feelings associated with TED. Responses were uploaded directly to the Cloud via a web-based platform.

Results

Eighteen adults completed the questionnaire. Words most commonly associated by individuals with TED were “pain” (30%) and “ugly” (17%). Other words associated included “debilitating” and “distressed”. The main concern patients had on their condition was “it getting worse”, followed by “sight” and “appearance”. Thyroid control & treatment was the lowest of concerns. Daily activities affecting most individuals were driving (41%) and their social life (35%), but also affected regular activities e.g. working (35%) and walking (18%).

Conclusions

Thyroid eye disease has significant impact on activities of daily living and feelings associated to aesthetic appearance and discomfort. Close attention needs to be paid to quality of life of patients with TED and to ensure they receive appropriate support.

SECOND LINE IMMUNOSUPPRESSION WITH MYCOPHENOLATE IN GRAVES' OPHTHALMOPATHY

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Background

Graves' Ophthalmopathy (GO) is a complex condition with the potential for significant visual disability. The EUGOGO consensus for first line treatment in active moderate/severe disease is 12 once weekly course of intravenous steroids (IVMP). Although this has good efficacy (improvement seen in up to 63%) sustaining the treatment response and avoiding relapse over the disease course has proven challenging. The MINGO study has shown promise for mycophenolate (MMF) as a second line agent.

Methods

Retrospective review of 21 patients with moderate to severe GO treated in an MDT thyroid eye clinic and started on MMF post IVMP. Data collection included reported symptoms, clinical findings and clinical activity score (CAS score) before and after treatment, side effects, adverse events and the need for re-treatment with steroids.

Results

Our analysis included 9 males and 12 females with a mean age of 53, 9 (43%) of whom had dysthyroid optic neuropathy. A mean reduction in the CAS score of 2.33 (range 0 to 6) was found following initiation of MMF ($p<0.0001$). Follow up duration ranged from 1 to 10 months and the dose of MMF ranged from 500mg to 2g daily.

Most patients reported improvement in pain with over 80% reporting an improvement in diplopia and a third showing improvement in periorbital swelling.

Only one patient required maintenance with concurrent oral prednisolone. One was refractory to MMF and was switched to ciclosporin. One discontinued due to muscle cramps, and another due to gastrointestinal side effects.

Conclusions

Our experience shows promise for the role of MMF as a second line agent. We have seen an encouraging improvement in disease activity with a safety profile comparable if not superior to steroids.

SINGLE CENTER EVALUATION OF STEROID THERAPY IN GRAVES' ORBITOPATHY: COMPARISON OF EFFICACY AND SAFETY OF TWO DIFFERENT PROTOCOLS - PARENTERAL VS COMBINED PARENTERAL AND ORAL

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Background

The most effective glucocorticoid (GC) treatment protocol for Graves' Orbitopathy (GO) with low relapse rate and less side effects is still to be defined. The aim of the present study was to evaluate efficacy, safety and outcome of parenteral vs. parenteral and oral GC protocols in euthyroid patients with untreated and active moderate to severe GO.

Methods

Total of 140 consecutive patients were treated with combined intravenous and oral GC (CombGC group, 66 patients, mean age 49±10 years), or only intravenous GC (IVGC group, 74 patients, mean age 51±11 years, p=ns). CombGC therapy included 500mg of methylprednisolone in 500ml of saline solution for two alternative days, followed by oral prednisone tapering dose repeated each month for the next 5 months (cumulative dose 10.2g). IVGC therapy included infusions of 500mg of methylprednisolone weekly for the first six weeks, followed by infusions of 250mg weekly for the remaining six weeks (cumulative dose 4.5g).

Results

The overall success of the treatment was 43/66 (65%) in CombGC group, and 37/73 (51%, p=0.071) in IVGC group. Improvement in CAS was similar in both goups (CombGC 83% vs. IVGC 81%, p=0.700). CombGC group was more efficious in all evaluated ocular measurements, but induced significantly more adverse events (74% vs. 38%, p<0.001). After 6 months, relapse of GO was observed in 10/37 (26%) in IVGC group, whereas none of patients in CombGC had relapse (p<0.001).

Conclusions

Our data suggest that CombGC therapy with high cumulative dose was more efficient with significantly less relapse rate, but with more induced side effects in comparison to IVGC therapy.

TARGETING THE NEONATAL FC RECEPTOR FOR THE TREATMENT OF MODERATE TO SEVERE ACTIVE GRAVES' OPHTHALMOPATHY

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Background
Graves' Ophthalmopathy (GO) or thyroid eye disease, is an autoimmune disease mediated by pathogenic IgG (pIgG) that target the thyroid stimulating hormone receptor (TSHR). IMVT-1401 is a fully human monoclonal antibody being developed for the treatment of GO and other autoimmune disorders. IMVT-1401 inhibits the binding of IgG to FcRn, resulting in rapid catabolism of IgG. Targeting the FcRn pathway has been shown to dramatically reduce circulating IgG, thus supporting its use in the treatment of auto-Ab mediated diseases, such as GO.

Methods
To fully investigate the potential benefit of IMVT-1401 in treating GO, two Phase 2 trials have been initiated as part of the ASCEND GO Program. A Phase 2a, open label study in approximately 8 participants was designed to investigate the safety, tolerability, and PK/ PD of subcutaneous (SC) administered IMVT-1401 in GO patients using an induction dosing regimen. The Phase 2b, double masked placebo-controlled study was designed to examine the effects of SC IMVT-1401 versus placebo on proptosis responder rate of IMVT-1401 in approximately 70 GO patients across 3 dose levels.

Anti-TSHR antibody serum levels have been shown to be directly associated with GO clinical features with high TSHR titers demonstrating a greater risk of severe disease course and outcome. In the Phase 2a study, the first 680 mg SC injection is expected to reduce total IgG 45-50%, with the second SC administration reducing IgG an additional 15-20%. Subsequent 340 mg SC doses would maintain this level of total IgG reduction.

Results
Both the Phase 2a and Phase 2b studies are ongoing with results expected by end-2019 and mid-2020, respectively.

Conclusions
Results from these studies will be used to demonstrate proof of concept for IMVT-1401 as the only anti-FcRn treatment for GO as well as to support the optimal dosing regimen to be used in Phase 3.

Study Supported by: Immunovant Sciences GmbH

GRAVES' ORBITOPATHY ASSOCIATED WITH MYASTHENIA GRAVIS: A CASE SERIES

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Background
The association of Graves' Orbitopathy (GO) and myasthenia gravis (MG) is possible, and important to recognize as their management differs and could interfer. We report a series of 7 patients with coexisting GO and MG.

Methods
We retrospectivaly identified 7 patients with concurrent MG and GO followed at a referral ophthalmological center between 2009 and 2019. We excluded 7 patients with ocular MG and Graves'Disease (GD) but without evidence of GO (among them 4 new diagnosis of MG) and 2 patients with GO which ocular symptoms were falsly attributed to MG.

Results
All 7patients had ocular manifestation due to MG (diplopia and/or ptosis), 5 patients had bulbar involvement. In 2 patients, MG was the initial presentation and GD occurred 17 and 24 years after MG. Three patients had simultaneous onset of MG, GD and GO. In 2 patients MG was discovered 2 and 3 years after GD, with one case of recurrent myasthenia crisis. 3 patients had underlying thymoma and 4 patients had antibodies to acetylcholine receptor (AChR-Ab). MG can be aggravated by thyroid dysfunction which was present at diagnosis of MG in 4/7 cases.

Treatment for active, moderate to severe GO is weekly administration of IV glucocorticoids pulses : 2/7 patients received this treatment. One patient was treated by cyclosporine for MG and IV steroids were well tolerated. The other-one experienced worsening of diplopia and onset of ptosis and generalized muscle weakness in all four extremities which were attributed to steroid-induced exacerbation of MG.

Conclusions
GO and ocular MG are distinct oculo muscular diseases with overlapping features. The diagnosis of this 2 diseases association is sometimes difficult. However it is very important due to its therapeutic consequences.

IMMUNE LANDSCAPE OF THE ORBITAL MICROENVIRONMENT IN THYROID-ASSOCIATED OPHTHALMOPATHY

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Background

Unique features of local immunity in thyroid-associated ophthalmopathy (TAO) may affect disease progression. This study aimed to investigate the association between the orbital immune microenvironment and TAO development.

Methods

TAO and control orbital connective tissues were collected. Single-cell sequencing examined orbital lymphocytic infiltrates. Multicolor flow cytometry explored the phenotypes of different cell subsets and in vitro models for cell functional studies. Coculture experiment and western blotting assay were used to determine underlying mechanism of the enhanced T helper 17 (Th17) cell pathway.

Results

The TAO orbital microenvironment was composed of natural killer cells, dendritic cells, macrophages, T cells, plasma cells, and $CD34^+$ orbital fibroblasts, but few B cells. Increases in $CD3^+CD8^-$ IL-17A-producing and RAR-related orphan receptor (ROR)γt-expressing T cells and in $CD3^+CD8^-$ IL-13-producing and GATA3-expressing T cells suggested Th17 and Th2 cell responses in TAO orbits. Increased interferon-γ (IFN-γ)-producing and $ROR\gamma t^+Tbet^+$ T cells indicated a Th1-like phenotype of orbital-infiltrating Th17 cells. Higher IL-23R and IL-1R expression and lower IL-21R expression were also observed on Th17 cells in TAO orbits. Multivariate analyses revealed that the Th17 pathway [IL-17A ($P = 0.001$), IFN-γ ($P = 0.009$), RORγt ($P = 0.003$), IL-23R ($P = 0.033$), IL-21R ($P = 0.019$)], and Th2 pathway [IL-13 ($P = 0.015$), GATA3 ($P = 0.012$)] were associated with TAO. IL-17A, IL-23R, and IL-1R correlated with clinical activity score and visual acuity. $CD34^+$ orbital fibroblasts exhibited distinct cell surface marker expression and promoted IL-23R and IL-1R expression on T cells to facilitate the Th17-cell phenotype through prostaglandin E2-EP2/EP4-cAMP signaling.

Conclusions

Our study addresses the importance of retroorbital immunity and suggests possible means of disrupting TAO pathogenesis.very important due to its therapeutic consequences.

A RETROSPECTIVE COHORT STUDY OF GRAVES' OPHTHALMOPATHY AT NATIONAL UNIVERSITY HOSPITAL, SINGAPORE

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Purpose

To present the clinical findings, demographic data and management of Graves' Ophthalmopathy (GO) in Singapore.

Methods

This is a retrospective cohort study of GO patients seen at the multidisciplinary TED clinic in National University Hospital, Singapore from January 1998 to October 2016.

Results

Severity: 71.3% of patients had mild GO, 20.7% had moderate GO and 8.0% had severe GO.1
Gender: 64% were female, 36% male. Smoking: 31%. Family history: 25%.
Ethnicity: 80% Chinese, 13% Malay and 4% Indian. Mean age was 39 years.
Autoimmune disorders 5%: Rheumatoid arthritis, myasthenia gravis, systemic lupus erythematosus, type 1 diabetes mellitus, keratoconjunctivitis sicca and ankylosing spondylitis.
Autoantibodies: TRAB was positive in 94% and TSI was positive in 91% of TED pts.
Graves' Disease management: Anti-thyroid drugs 72% with mean duration of 58months. Block-and- replace strategy was used in 17%. Radioactive iodine was done in 18%. Six percent underwent surgery which included total thyroidectomy (72%), subtotal thyroidectomy (17%) and hemithyroidectomy (8%).
Graves' Orbitopathy management: 65% of patients were conservatively managed. 16% had medical management (Prednisolone (N=17), IV Methylprednisolone (N= 24) and immunosuppressants: Azathioprine, Cyclosporine and Methotrexate (N= 20)). Nine percent of patients underwent rehabilitative surgery and/or decompressive surgery. Two patients underwent radiotherapy.

Table 1. Baseline characteristics of 306 patients.

Gender		Treatment Duration (months, mean ± SD)	58 ± 44
Male	109 (36%)	Thyroid status:	
Female	194 (64%)	Overt hyperthyroidism	77 (25)%
Race		Overt hypothyroidism	20 (7%)
Chinese	245 (80%)	Euthyroid	104 (34%)
Malay	40 (13%)	Subclinical hyperthyroidism	87 (28%)
Indian	13 (4%)	Subclinical hypothyroidism	16 (5%)
Others	8 (3%)	Graves' Disease Treatment	
Age at diagnosis of Graves' Disease (years, mean ± SD)	48 ± 16	Medical management with ATDs alone	222 (73%)
Other Autoimmune Comorbidities	15 (5%)	Block and replace	53 (17%)
Rheumatoid Arthritis	6	RAI	54 (18%)
Myasthenia Gravis	3	Surgery	36 (6%)
Type 1 Diabetes Mellitus	1		
Systemic Lupus Erythematosus	2		
Vitiligo	1		
Ankylosing Spondylitis	1		
Keratoconjunctivitis sicca	1		
Family history of thyroid disorder			
Positive	77 (25%)		
Smoking history			
Non smoker	210 (69%)		
Exposed to 2nd hand smoke	9 /210 (4%)		
Smoker	96 (31%)		
Active smoker	58 (60%)		
Previous smoker	38 (40%)		

Table 2. Management Modalities in the NUH TED Clinic

TED Intervention	N (%)
No active intervention/ observation	200 (65%)
Medical management alone	50 (16%)
Prednisolone	24 (8%)
IV Methylprednisolone	18
NUH High dose Protocol*	6
Modified EUGOGO#	20 (7%)
Immunosuppressants	14
Azathioprine	4
Methotrexate	1
Cyclosporine	
Surgery	26 (9%)
Rehabilitative &/or decompressive	
Radiotherapy	2 (1%)

Conclusions

South east-asia has a significant Graves' orbitopathy patient population with a proportionate multiracial prevalence. We presented the clinical profile of our TED clinic patients, most of whom had protracted course of disease and requiring prolonged course of anti-thyroid drugs. TSI may be considered in GO patients with TRAB-negative result. Mainstay of medical management of GO in our patients was cortico-steroids with good outcomes and patient acceptance.

NOVEL RADIOLOGIC SIGNS IN THYROID ORBITOPATHY

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Purpose

Thyroid orbitopathy is an autoimmune inflammatory disorder that affects the orbit and periorbital tissues. While the soft tissue signs (extraocular muscles, orbital fat involvement) are well recognized on imaging1, bony changes to the orbital walls and junctions are often overlooked. The purpose of this study was to document and study the remodeling and expansion of the orbital walls in long standing TED. We measured the angle of infero-medial orbital strut (AIOS) and degree of convexity/concavity of the medial wall (Angle of the Medial wall (AMW)) on CT scans of TED patients compared to a control group.

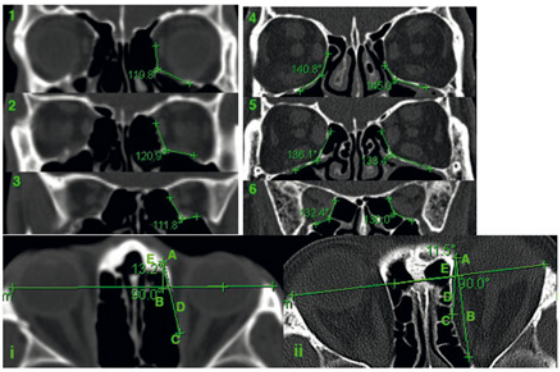
Methods

Computed tomography (CT) scans of 280 orbits of 140 TED patients and 70 orbits of 70 controls (patients with unilateral orbital fractures) were obtained.

AIOS is the angle between the planes of the medial wall and the orbital floor in coronal CT scans corresponding with the orbital strut. The AIOS was studied at three points:

1. Anteriorly (first cut behind the lacrimal sac)
2. Posteriorly (the last cut where the angle between orbital floor and medial wall can be reliably measured near the apex) &
3. Midway (halfway point between anterior and posterior).

   AMW was studied in the axial cut of the mid-orbit (the plane at which the lengths of the optic nerve, medial rectus and lateral rectus are all simultaneously best visualized). The degree of convexity/concavity of the medial wall of the orbit was measured.
4. Point 1 was defined as the nasal bone and start of the medial wall.
5. Line A: Line from Point 1 perpendicular to the inter-zygomatic line.
6. Point 2 is the maximum excursion of the medial wall from line A. Line B joins point 1 and 2. Angle C, the angle of the medial wall (AMW) bulge, is between lines A and B. It is positive if Point 2 is lateral to Line A and negative if medial to Line 2.



Results

	TED patients			Normals			
	No	Mean	SD	No	Mean	SD	P - value
AIOS Ant Average	140	141.64	8.03	70	140.10	8.11	0.243
AIOS Mid Average	140	138.60	9.67	70	132.76	11.77	< 0.001
AIOS Pos Average	140	144.86	9.64	70	137.28	8.54	< 0.001
Angle of medial wal bulge	140	7.98	5.02	68	8.89	4.80	0.211

The AIOS was found to be significantly larger in TED patients compared to controls at the middle and posterior sections. However, the medial angle bulge was smaller (less convex) on average in TED patients but this difference was not statistically significant.

Discussion

This study demonstrates bony changes from remodeling in TED from mechano-transduction, a key mechanism of remodeling of bone tissue[2]. This has been demonstrated in the skull from benign masses[3], raised intracranial pressure[4], and to the orbital apex in thyroid eye disease[5] with associated compressive optic neuropathy.

We hypothesize that in TED, an increased intraorbital soft tissue volume with resultant increase in intraorbital pressure induces bony remodeling of the floor, medial wall and the strut with radiological and possibly clinical consequences. In our study, an increased AIOS angle was observed in TED patients. This remodelling indirectly supports the theory of bony orbital volume expansion in TED[6].

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THE ROLE OF ORBITAL FIBROBLASTS IN THE IMMUNOPATHOLOGY OF GRAVES' ORBITOPATHY

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Graves' disease is an autoimmune thyroid disorder caused by autoantibodies against the thyrotropin stimulating hormone receptor (TSHR) leading to hyperthyroidism. Graves' orbitopathy (GO) is the main extra-throidal manifestation which is characterized by inflammation, remodeling of the orbital connective fat and muscle tissue. GO patients individually develop disease subtypes with either more adipogenesis leading to proptosis of the eyes or inflammation and fibrosis of the extraocular muscles (EOM) leading to squint of the respective eye. Inflammation and expansion of the retroocular tissue can cause hypoxia and the induction of hypoxia dependent pathways due to the limited space of the bony orbit. In this study we investigated whether cytokines such as TNF-α and INF-γ and hypoxic conditions influence HIF-1 action and induction of immunomodulatory markers. We isolated orbital fibroblasts (OF) from retrobulbar fat biopsies of GO patients and from murine orbital tissue of experimental GO model. To investigate the role of immunomodulatory factors we stimulated OFs with TNF-α and INF-γ under normoxic and hypoxic conditions. HIF-1α and p65 Levels were determined by western-blot analysis. Immunmodulatory markers like PD-L1, ICAM-1 and HLA-DR as well as receptors like TSHR and CD90 were analyzed by flow cytometry. We found increased HIF-1α levels in OFs from human and mice after TNF-α/INF-γ-stimulation under normoxia and also under hypoxia. In human OFs p65 expression is enhanced under hypoxia and further induced after TNF-α/INF-γ stimulation. In OFs from GO mice p65 tend to higher levels after TNF-α/INF-γ stimulation under normoxia and hypoxia. Likewise, immunmodulatory markers like PD-L1, ICAM-1, HLA-DR and the TSHR were strongly induced after treatment with TNF-α/INF-γ. CD90 was not stimulable after TNF-α/INF-γ stimulation. Our results indicate that cytokines induce inflammatory processes in the retrobulbar fat tissue of GO patients and orbital tissue of experimental GO mice.

FORNIX TRIAMCINOLONE INJECTION FOR THYROID ORBITOPATHY

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Purpose

In this pilot study we aimed to examine the association between eyelid fornices triamcinolone injections and clinical activity score in patients with active thyroid orbitopathy.

Methods

Adult patients aged 18 years or older, diagnosed with active thyroid orbitopathy and a clinical activity score ≥3 were recruited to this interventional prospective pilot study between 2010 and 2013. Three upper and lower fornices injections of triamcinolone acetate 20 mg (40 mg/ml) were administered at 4-week intervals. Each patient included was followed up for a period of 6 months. Clinical activity score was estimated at each monthly visit. Extraocular muscle thickness was measured by ultrasound examination at entrance and at the last visit.

Results

Eleven eyes of seven patients were included in our study. Initial clinical activity score was 3.81±1.80 and fell to 0.63±0.72 during a 6-month follow-up. There was a significant difference in clinical activity score between the baseline examination and the following visits (p-value< 0.005). Lid retraction was reduced by the treatment. Side effects included a transitory increase in intraocular pressure in one patient, which was controlled with topical medication.

Conclusions

In this pilot study a series of three separate triamcinolone fornix injections at 4-week intervals reduces the inflammatory effects of thyroid orbitopathy, as measured by clinical activity score. The treatment was simple, effective, and safe eliminating the side effects associated with systemic corticosteroid use.

OUTCOMES OF MODIFIED LATERAL WALL DECOMPRESSION TECHNIQUE FOR THYROID EYE DISEASE: RESULTS AND COMPLICATIONS OF A CASE SERIES

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Purpose

In this retrospective study we aimed to describe the outcomes of modified lateral orbital wall decompression technique for thyroid eye disease (TED), its safety and effectiveness.

Methods

File of consecutive lateral orbital wall decompressions by one surgeon done between January 2012 to January 2018 were reviewed. The purpose of the surgery was for functional and aesthetic rehabilitation of patients with TED. We analyzed the change in proptosis, diplopia and post-operative complications.

Results

250 lateral orbital wall decompression cases were analyzed. Mean and range of reduction in Exophthalmometry will be presented. A qualitative analysis of the change of appearance will be presented. There were no intraoperative complications. The most common postoperative complication was temporal numbness. Masticatory oscillopsia was uncommon and short-lived. There were no cases with new postoperative diplopia.

Conclusions

This modified technique of lateral orbital wall decompression is safe, and effective for mild to moderate proptosis. It carries a low complication rate and is effective in aesthetic and functional rehabilitation of TED patients with Proptosis.

TRAB OF VARIABLE GRAVES' ORBITOPATHY PHENOTYPES ALWAYS STIMULATE CAMP PRODUCTION ON TSHR EXPRESSING HEK CELLS AND STIMULATION CAN BE DOWNREGULATED WITH TSHR ANTAGONISTS

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Graves' orbitopathy (GO) can occur at different time points in relation to thyroid disease with variable TSHR antibody (TRAb) levels and GO severity. The aim of this study was to detect the stimulatory potential of TRAbs in these different patient groups in a TSH-overexpressing HEK cell-system and to investigate the response to small molecule antagonists (SMANTAGs) of TSH receptor (TSHR) signaling.

Methods

We selected 76 sera at 3 time points (3, 12, and 24 months after GO onset) out of the University Essen GO data- and biobank with the following thyroid phenotypes: remission/relapse of hyperthyroidism, GO after radioiodine therapy (RIT), after early thyroidectomy (TX) due to uncontrolled hyperthyroidism, with euthyroid GO (EuGO), and GO with Hashimoto-thyroiditis (HD). Most of the patients had severe GO, except 50% EuGO, HD and all remission patients with mild GO. TSHR autoantibodies were evaluated using human TSHR-transfected HEK-cells (cAMP in supernatants) and in a binding assay (Roche Elecsys - TBII). Additionally, the inhibitory potential of SMANTAGs for the TSHR - ANTAG3 (NCGC00242364, NIH, Bethesda USA) and S37a (Leibniz Institut, Berlin, Germany) was tested in sera of all groups.

Results

TRAB levels measured in the binding inhibition assay (TBII) differed considerably in the GO patient groups. As expected, patients after radioiodine therapy, with relapsing hyperthyroidism and after early thyroidectomy due to uncontrolled hyperthyroidism, showed highest TBII levels while patients with remission of hyperthyroidism, HD and EuGO have lower TBII levels. Despite rather low TBII-levels assessed in patients with EuGO, HD and remission considerable cAMP stimulatory activity in the cell-system was revealed. As expected, RJT, TX and relapse patients had also the highest stimulation in the cell-system. The tested SMANTAGs were efficient in all patient groups.

Discussion

Despite partly negative TBII-levels sera of all GO patient groups induced cAMP-production, especially in euthyroid GO patients, underlining the central pathophysiological role of TSHR in GO. Both tested SMANTAGs reduced the stimulatory activity of TRAbs at the TSHR independent of the associated thyroid condition in GO patients.

AWARENESS OF EUGOGO CONSENSUS STATEMENTS AND ITS PRACTICAL USAGE IN CROATIA: AN ONLINE, INTERNET-BASED SURVEY AMONGST ENDOCRINOLOGISTS, OPHTHALMOLOGISTS AND NUCLEAR MEDICINE SPECIALISTS

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Background

Although in 2008 and 2016 EUGOGO published consensus statement on the management of Graves' orbitopathy (GO) and is widespread ever since, the general perception and practical usage of the statement amongst Croatian clinicians dealing with GO is still unknown. The idea is to evaluate the awareness and practical usage of the EUGOGO consensus statements and to explore the attitudes towards the statements amongst Croatian endocrinologists ,ophthalmologist and nuclear medicine specialists. As well, the aim is to acquaint the colleagues with the EUGOGO group and its activities and to encourage them to apply proposed protocols in everyday practice.

Methods

An internet based, anonymous online survey will be conducted from July to October 2019. It will be sent by e-mail to 100 ophthalmologist, 100 endocrinologists and 100 nuclear medicine specialists in Croatia, members of national societies. The survey will contain questions regarding EUGOGO activities, namely assessment tools while diagnosing GO and questions regarding algorithms in clinical practice while treating GO. Also, general socio-demographic data (age, gender, work experience, facility, academic/educational status) will be collected.

Results

of the study will be presented at the 20th EUGOGO Anniversary meeting in Pisa

Discussion

The study could be considered as pilot one for the other EUGOGO sites. Collected data from all centres would probably point to the direction of further Society engagement regarding education and training of health professionals involved in the care of GO.

ANTI-NUCLEAR AUTOANTIBODIES IN GRAVES' ORBITOPATHY

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Background

The pathogenesis of Graves' Orbitopathy (GO) is believed to reflect autoimmunity against antigens expressed by the thyroid and orbital tissues, resulting in cell proliferation and release of glycosaminoglycans. Antinuclear antibodies (ANA) are frequently detected in patients with autoimmune thyroid diseases (ATD), including Graves' disease, with uncertain clinical significance. Other autoantibodies associated with systemic autoimmune diseases, including those against the extractable nuclear antigens, have been sporadically mentioned. Because GO affects primarily the connective tissue and non-organ-specific autoantibodies are considered markers of autoimmunity against connective tissue, we investigated whether there is a correlation between ANA and GO.

Methods

We measured serum ANA in 23 consecutive patients (19 women and 4 men; age 53.4±11.5 yr) with untreated GO. Patients underwent an endocrinological and ophthalmological evaluation. The overall degree of GO was classified through the NOSPECS score and a modification of the NOSPECS score.

Results

The prevalence of serum ANA was 15/23, namely 65.2%. There was no correlation between the prevalence of ANA and the duration of GO, the individual GO features (proptosis, clinical activity score, degree of diplopia and visual acuity), the NOSPECS score, and the modified NOSPECS score. Only the latter two variables, for unknown reasons, correlated inversely with ANA titer (P=0.04 for NOSPECS and P=0.05 for modified the NOSPECS score), but not with ANA pattern.

Discussion

Keeping into account the small sample size, our study suggest that GO patients may have a higher frequency of ANA compared with the general population (~18%), without a significant correlation with the activity or severity of the disease. Moreover, we found an unexpected inverse correlation between ANA titer and the severity of GO. Further perspective studies are needed to confirm these preliminary conclusions and understand their clinical significance.

CLINICAL CHARACTERISTICS OF DYSTHYROID OPTIC NEUROPATHY IN HONG KONG CHINESE PATIENTS: A SINGLE CENTRE EXPERIENCE

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Background

Dysthyroid optic neuropathy (DON) is a sight threatening manifestation of Graves' orbitopathy (GO), affecting 3-5% of GO patients. High dose intravenous methylprednisolone (IVMP) and, if failed, decompressive surgery are first line treatments. We aim to review treatment efficacy of DON and co-existing active GO.

Methods

10 patients with DON who presented to our unit from 2013 to 2019 were retrospectively reviewed. All patients had apical crowding on imaging, decreased visual acuity (<0.5) and impaired colour vision.

Results

10 patients were identified (6 male, 4 female, median age 59). All patients had active GO. 8 DON patients (80%) required decompressive surgery within 1 month of diagnosis despite IVMP (<= 1g/week). All eyes with DON required decompressive surgery ultimately. 3 patients developed DON after starting standard treatment of active GO. Among the 6 patients who developed bilateral DON, 5 were metachronous and contralateral DON developed despite IVMP +/- other second line treatments. 7 patients (70%) required orbital radiotherapy and at least one other immunomodulatory treatment, either for suboptimal response post-decompressive surgery / prevention of DON recurrence or persistently active GO despite IVMP.

Conclusions

Standard dose IVMP is ineffective as the first-line treatment of DON and it could not prevent the development of contralateral DON in patients with bilateral metachronous DON. Multiple treatment modalities were often required to inactivate GO in patients with DON. Further research in newer treatment approaches, e.g. upfront combination of immunomodulatory treatments or use of novel therapies (e.g. Teprotumumab, tocilizumab) may improve patient outcome.

A SURVEY OF CURRENT PRACTICES BY THE BRITISH OCULOPLASTIC SURGERY SOCIETY AND RECOMMENDATIONS FOR DELIVERING A SUSTAINABLE MULTIDISCIPLINARY APPROACH TO GRAVES' ORBITOPATHY (GO) IN THE UNITED KINGDOM

Vickie Lee, Parizad Avari, Ben Williams, Petros Perros, Colin Dayan

Background

The Amsterdam Declaration (2009) and the Royal College of Physicians (RCP, 2015) guidance and UK Thyroid Eye Disease Amsterdam Declaration Implementation Group (TEAMeD-5,2017) recommendations have the common goal of improving access to high quality care for thyroid eye disease (TED). Moderate/severe GO patients should have access to an appropriately skilled multidisciplinary clinic with combined Ophthalmology and Endocrinology expertise.

Methods

The British Oculoplastic Surgery Society(BOPSS) represents oculoplastic surgeons who usually lead GO care in the UK. A 2-stage survey of the full membership was conducted to ascertain current practice of existing resources to meet this recommendation. 41% (65/158) responded to Survey 1, and 28 (18%) respondents to Survey 2.

Results

Sixty percent (39/65) of respondents are working in a multidisciplinary thyroid eye clinic with co-location of an ophthalmologist and an endocrinologist. Care for GO appears not to be provided in a multidisciplinary context in up to 31%(20/65). Thirty five (54%) of the respondents rated their relationship with their endocrinology colleagues as good. Best practice guidelines recommend routine quality of life assessments but only 6/28(21%) of respondents use this modality in current practice. A few areas (6%,4/65) in the UK appear not to be using intravenous steroids. In many areas (25%16/65), second line immunosuppression is provided in a different Trust. Access to orbital decompression surgery appeared available in most parts of the country, though frequently in a different Trust (35%23/65).

Conclusions

This survey is a 'snapshot' of some aspects of current GO management in the UK and the findings suggest that there is scope for improvement. Our proposed standards have been endorsed by multi-disciplinary stakeholder societies.

REDESIGNING RUNDLE'S CURVE FOR DYSTHYROID OPTIC NEUROPATHY?

Ahmed ALNAHRAWY, Clare Chan, Soma Farag. Vickie Lee, Ahmad Aziz, Rajni Jain Claire Feeney, Vassiliki Bravis, Stephen Robinson, Karim Meeran

Purpose

Since 1945 Rundle's curve is use to describe the temporal activity and severity of thyroid eye disease (TED). However many patients' disease do not follow this model. Also Rundle did not incorporate the course of the endocrine disease. The study aims to explore the temporal relation of Dysthroid optic neuropathy (DON) and subsequent ocular treatment outcomes relative to the course of the endocrine disease to create a multidisciplinary perspective to improve predictive and diagnostic criteria for this syndrome.

Methods

A retrospective case note review of DON patients seen at three linked Thyroid MDT clinics. Parameters included patient demographics, clinical and radiological features, timeline and thyroid status and eye disease severity/activity, management and outcome.

Results

There were 17 DON patients (Male 4, Female 13),13 had bilateral disease. Medianage 44yrs (IQR 33-54). 10/17 (59%) had thyroid family history 82%(14) were euthyroid at DON diagnosis. Median time to DON diagnosis was 7 months (IQR1-38 months) with 10/17 presenting within 12 months of thyroid onset, 2 between 12-24 months and 5/17 presenting more than 24 months. 29% were smokers. 4 (24%) had diabetes. Presenting and final VA better than 6/12 in 8 and 15 patients. All received the EUGOGO DON Intravenous methylprednisolone protocol with 8 having urgent decompression and 8 having orbital radiotherapy. 13/17 had second line treatment with mycophenolate.

Conclusions

Presentation of DON can be insidious in euthyroid patients many years after onsetof thyroid disease. Orbital decompression is not curative but useful as adjunctive treatment in an emergency setting. Most patients require long term second line immunosuppression and/or radiotherapy to prevent relapse. Viligance is always essential to prevent visual loss.

DEMOGRAPHICS OF GRAVES' ORBITOPATHY ACROSS THREE ADJACENT MULTIDISCIPLINARY (MDT) CLINICS IN THE SAME CITY

Soma Farag, Claire Feeney, Vickie Lee, Ahmad Aziz, Rajni Jain, Vassiliki Bravis, Stephen Robinson, Karim Meeran

Purpose

There is increasing evidence that a multidisciplinary (MDT) approach optimises diagnosis and management in active Graves' Orbitopathy (GO) and is recommended by current TEAMeD-5 guidelines1. Here we aim to describe the clinical and endocrine characteristics of a large cohorts of patients with GO seen in 3 MDT clinics in London.

Methods

A retrospective patient-cohort study of 236 patients with suspected GO referred to these services between 2012-2019. Whole group correlations and subgroup analyses were analysed at baseline across several patient factors.

Results

Median patient age was 49.0 yrs, 77.5% were female, 23.3% Afro-Caribbean. 166 (70.3%) were on treatment for Graves' thyrotoxicosis, 25(10.6%) were hypothyroid at first clinic and 29 (12.3%) had normal thyroid function and on no treatment. Of 183 (77.5%) patient who had an autoantibody measurement, 80.5% had positive thyroid-stimulating hormone (TSH) antibody titre, with the median titre being 6.6IU/L (IQR:2.4-17.8, normal: <1.75IU/L). A positive correlation between Clinical Activity Score (CAS) and TSH antibody titre was found ($R = 0.30$, $p < 0.05$). There were 52/236 (22.0%) current smokers, all of whom received documented smoking cessation advice. 32.5% patients had a positive family history for thyroid disease, however significantly fewer patients with sight-threatening disease had a positive FH than those without ($p<0.05$). Patients with sightthreatening disease were significantly older than those without ($p = 0.0378$).

Conclusions

These results suggest that cases of sight-threatening disease were more prevalent in older populations and reported family history was not a predictor of disease activity. TSH R antibody demonstrated a positive correlation CAS but other factors influence the variance seen in CAS. Further biomarkers are warranted in this complex, costly and debilitating disease.

EXPLORING A POSSIBLE LINK BETWEEN GRAVES' ORBITOPATHY (GO) AND DIABETES

Soma Farag, Claire Feeney, Vickie Lee, Ahmad Aziz, Rajni Jain, Vassiliki Bravis, Stephen Robinson, Karim Meeran

Purpose

There are sporadic reports illustrating more severe GO and complications in those with diabetes mellitus (DM) and from local experience these patients have poorer outcomes as seen in other diseases, such as cardiovascular disease. However, the relationship between glycaemia and clinical activity/severity and disease course are not well described.

Methods

A multi-centre retrospective patient-cohort study of 236 patients referred to three GO multidisciplinary (MDT) clinics in London between 2012-2019. Patient characteristics were analysed to investigate group-wise differences and correlations between variables collected at baseline to help predict subsequent disease activity, with particular focus being placed on glycaemic control factors.

Results

Median age was 49.0 yrs (interquartile range: 36-57), 19.5% Asian, 77.5% female. Out of 236 patients, 14.0% had diabetes. The proportion with diabetes also increased with disease activity and severity, culminating in 23.5% in those with dysthyroid optic neuropathy (DON). The median HbA1c in the 131/236 patients who had a baseline HbA1c was 39 mmol/mol (IQR 36-43, NR <42 mmol/mol). For the whole group, there was a trend towards a positive correlation between HbA1c and CAS ($r = 0.1684$, $P = 0.05$). HbA1c was significantly higher in patients who had moderate-to-severe disease or DON compared to those with milder disease ($p= 0.0114$)

Conclusions

Our results show a higher prevalence of DM compared to the rest of the UK (6.0%) in our cohort with GO. However ethnicity variation, could influence our reported high prevalence. The relationship between HbA1c and disease severity requires further exploration but potentially is a modifiable risk factor that could influence outcome. It is important as therapies for GO e.g orbital radiotherapy and high-dose corticosteroids are relatively contraindicated in DM. Underlying mechanisms could include aberrant signaling of insulin-like growth factor-I receptor(IGFR-1), as well as low-grade systemic inflammation seen in both disease states.

OCCURRENCE OF GRAVES' HYPERTHYROIDISM AND GRAVES' ORBITOPATHY AFTER FINE NEEDLE ASPIRATION BIOPSY OF THYROID NODULES

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Background

Graves' Orbitopathy (GO) is believed to be the consequence of autoimmunity against antigens expressed by the thyroid and by orbital tissues. Massive release of thyroid antigens is associated with the appearance or deterioration of GO in patients with Graves' hyperthyroidism (GH), as it occurs following radioiodine treatment. In theory, a similar release of autoantigens may occur following a thyroid trauma or surgical manipulation. Here we report, a case of de-novo appearance of GH and GO after a fine-needle aspiration biopsy (FNAB) of thyroid nodules, possibly reflecting spreading of autoantigens and activation of the immune system against antigens shared by the thyroid and orbital tissues.

Case Report/Methods

An otherwise healthy, 48-year old woman, came to our observation for a multinodular non-toxic goiter. She had a familial history of thyroid autoimmunity (mother with autoimmune thyroiditis) and was a non-smoker. Her thyroid function was normal, with undetectable anti-thyroid autoantibodies, including anti-TSH receptor autoantibodies (TRAb). The thyroid was multinodular but normoechoic at ultrasound. She underwent FNAB of the dominant cold nodules, which were cytologically benign. Approximately 2 weeks later she complained with tachycardia, fatigue, insomnia, nervousness, increased sweating and weight loss (4 Kg in two months), as well as ocular symptoms. She underwent thyroid tests showing a thyrotoxicosis, undetectable anti-thyroglobulin (TgAb) and anti-thyroproxidase (TPOAb) antibodies, but detectable serum TRAb (20 U/L; NV ≤1.5). She underwent an ophthalmological evaluation suggesting the presence of a moderately severe GO.

Conclusions

The development of GH and GO after FNAB may reflect thyroid tissue damage with release of autoantigens and consequent autoimmunity in a predisposed individual. The simultaneous development of hyperthyroidism and GO is in keeping with the hypothesis that GH and GO are due to autoimmunity against antigens present both in thyroid and orbital tissues.

M2 MACROPHAGE POLARIZATION MEDIATES FIBROSIS IN ORBITAL FIBROBLASTS IN GRAVES' ORBITOPATHY

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Background

Fibrosis is the final and common pathological consequence of wound repair. In Graves' Orbitopathy (GO), fibrosis is one of the major pathological features in the orbit especially in the late stage of the disease. Many roles have been described of the M2 macrophage polarization in fibrotic diseases.

Methods

Orbital connective tissues were obtained from surgical waste in GO and healthy controls and were subjected to flow cytometry analysis and fibroblasts culture. Primary human macrophages were differentiated from CD14+ monocytes isolated from peripheral blood mononuclear cells (PBMCs) by MACS positive selection. The cells were treated with PMA and subsequently with LPS+IFN-γ to promote their polarization into M1 macrophages and IL-4+IL-13 to trigger the M2 phenotype. The culture medium of polarized macrophages was used as conditioned medium (CM) to co-culture with fibroblasts to study the effect of macrophages on the differentiation of fibroblasts. The expression fibrosis-related protein like fibronectin, α-SMA, collagen I and TIMP-1 in fibroblasts were analyzed by western blot.

Results

We reported the increased frequency of M1 macrophages in orbital tissue from patients with active GO (CAS>3) compared with inactive GO (CAS<3) and healthy controls. In addition, with the progression of the disease, there was a higher proportion of M2 macrophages in inactive GO. The results demonstrated that the expressions of fibronectin, α-SMA, collagen I and TIMP-1 in fibroblasts cultured in M2-CM were significantly increased.

Conclusions

Our study revealed that M1 macrophage infiltration is predominant in the early stage of disease while M2 macrophage plays an important role in the fibrosis of orbital tissue in the late stage of GO.

SURGICAL ORBITAL DECOMPRESSION IN GO: WHEN AND HOW? A CRITICAL REVIEW OF THE LITERATURE

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Background

According to the EUGOGO consensus statement on the management of Graves' orbitopathy (GO), surgical orbital decompression should be performed: I) as rescue treatment for active severe GO with Dysthyroid optic neuropathy (DON), refractory to IV glucocorticosteroids (IV GCs); II) as a rehabilitative care in moderate-to-severe and inactive GO, with the aim of reducing exophtalmos, decreasing in intraocular tension and relieving pain.

Methods

We conducted a literature review of MedLine publications, including prospective and retrospective studies as well as previous reviews, regarding results of surgical orbital decompression in GO.

Results

Management of active severe GO with DON or keratitis, is mainly based on one RCT that failed to show better results of surgery over IV GCs. However this study concerned a very small population and its results remains debatable. Two other RCTs compared different surgical techniques in rehabilitative decompressive surgery, suggesting a proportional efficiency to the extend of bony removal, but included also very small samples. All other data are concluded from retrospective studies with potential important bias.

Conclusions

Surgical management of GO still relies on weak evidences. Optimal timing of surgery in DON remains unknown and there is no proof that delayed surgery is not damageable. Moreover, the best decompressive technique during the rehabilitative phase is still uncertain. Further studies are needed to give more robust data and precise when and how surgical orbital decompression should be performed.

EXTRAOCULAR MUSCLE DYSFUNCTION CAUSED BY THREE CONCURRENT DISORDERS IN A PATIENT WITH GRAVES' ORBITOPATHY

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Background

In Graves' orbitopathy (GO) the extra-ocular muscle dysfunction is generally characterised by restrictive myopathy. Here we describe a patient with two additional possible causes of eye muscle abnormalities.

Case Report

A 53-year-old woman with metabolic syndrome presented inconstant diplopia, becoming constant after one month. She also developed right oculomotor nerve palsy; the orbits MRI showed thickened inferior and medial rectus muscles of the right eye. The following month she also developed right upper eyelid ptosis; antibodies to acetylcholine receptor (AChRAb) were slightly positive (0.80 nmol/l; nv<0.4), while antibodies to muscle-specific kinase were negative. A repeated orbits MRI showed increased thickening of inferior and medial rectus muscles of the right eye, suggestive for GO, thus she was treated for one month with iv methylprednisolone (total 2.5 g) followed by oral prednisone (total 500 mg), under metformin treatment to control metabolic adverse effects. She was then referred to our Centre; the eyes examination showed bilateral exophthalmos, eye movement impairment and no signs of activity except for conjunctival hyperaemia. We confirmed the presence of moderate GO and the thyroid investigation showed subclinical autoimmune hypothyroidism: thyroid-stimulating-hormone 5.73 mIU/L (0.28-4.30), free-thyroxine 12.1 ng/L (8.0-17.0), free-triiodothyronine 3.9 ng/L (2.0-5.0), anti-thyroglobulin antibodies 1811 KIU/L (<60), anti-thyrotropin-receptor antibodies 0.25 KIU/L (<0.55). Her right eyelid ptosis had worsened after steroids withdrawal: repeated AChRAb were clearly positive (3.5 pmol/ml; nv<0.5), thus she was diagnosed with concomitant myasthenia gravis and started pyridostigmine treatment, with significant improvement of eyelid ptosis.

Conclusions

All three ocular/orbital diseases presented by this clinical case can cause extra-ocular muscles dysfunction: GO, myasthenia gravis and right oculomotor nerve palsy. The origin of the oculomotor palsy is multifactorial; in this patient it could be secondary to metabolic syndrome or myasthenia gravis. We advise careful differential diagnosis in the presence of extra-ocular muscles dysfunction associated with eyelid ptosis.

EVALUATION OF THE INFLUENCE OF GENDER ON THE SEVERITY AND COURSE OF GRAVES' ORBITOPATHY

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Background

Severity and natural course of Graves' orbitopathy (GO) show wide individual differences and are influenced, among others, by thyroid situation and smoking habits. For optimal treatment, it is important to be able to predict the natural course of the disease as accurate as possible to counteract with anti-inflammatory and surgical treatment as much as needed and as little as possible. Therefore, we aimed to further elucidate the impact of Gender on GO.

Methods

We collected the clinical and demographic data of all patients of our tertiary referral center from January 2008 till May 2017 and analyzed it with descriptive statistics.

Results

In total, we evaluated the data of 4641 patients. Of these referred patients, 92% (n=4260) were diagnosed with GO. Most of these were women (83%). The mean age at onset of the disease was 41.8 years. Men were significantly older at onset compared to women (52.9 vs. 39.1; $p<0.0001$). About one third of patients were smokers in both gender groups. 2203 patients (52%) were treated with intravenous steroids. 1198 patients (28%) were treated with orbital irradiation. Orbital decompression had to be performed in 20% of patients (n=839). About 18% of patients had to undergo strabismus (n=795) and oculoplastic surgery. Men presented significantly more often with more severe forms of GO compared to women ($p<0.0001$) and were therefore treated significantly more often with surgery, steroids and irradiation.

Conclusions

Our retrospective analysis showed once more that women are more often afflicted by GO. In contrast, men seem to be more severely afflicted and in need of anti-inflammatory and surgical treatments. This might be due genetic and hormonal differences, as well as different approaches to the health system. Men seem to be more hesitant to seek medical help, which might be the reason for less frequent mild male GO cases in our specialized center cohort.

GRAVES' ORBITOPATHY IN CHILDREN AND ADOLESCENTS: THE VIENNA EXPERIENCE

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Purpose
To assess the demographics, risk factors, clinical features and treatment options for pediatric Graves' orbitopathy (GO) in our tertiary referral centre.

Methods
In our retrospective case series we analyzed the charts of all pediatric and adolescent patients (aged 18 years and younger) who presented at our GO clinic between January 2008 and December 2013.

Results
48 patients were identified; females to male ratio: (75.0% to 25.0%). Ethnicity: 83.0 % Caucasian, 4 8.0% Asian, 6.0% African and 2.0% was of Arabic descent. Mean age at presentation was 12.0 years (range 2.2-18.1). Positive family history was recorded in 17.0 % cases. Smoking: 33.0 % were active- and 17% passive smokers. Additional autoimmune disorder was present in 6.0%. Mild disease was observed in 49.0%, moderate in 40.0% and 11.0% developed severe pediatric GO. The most frequent ophthalmic symptom was exophthalmos (77%), lower eyelid retraction (75,0%) and upper eyelid retraction (52%). Conjuntival injection with sicca symptomatic was observed in 48.0%, pain (retrobulbar or on eye movement) occurred in 44.0%, followed by lid edema and/or erythem (38.0%). 4.0% developed acquired epiblepharon. Ocular motility involvement was noted in 38.0%; limitation of abduction in 27.0%, of elevation-deficit in 21.0%. Interestingly, in 6.0% of the cases symptomatic optic neuropathy was diagnosed. Management: besides lubrication, 75.0% was treated with anti-thyroid medication alone, 23.0 % received combination therapy with beta-blockers. Five patients required, however, iv methylprednisolone pulse therapy that resulted in prompt clinical improvement.

Conclusions
Although the course of pediatric Graves' orbitopathy is proved to be mild to moderate in most of our patients, severe, sight threatening GO - requiring immunosuppression - may occur at young age, as in our 5 patients over a period of five years.

REGIONAL HEALTH SERVICES RESEARCH AT A GERMAN MULTIDISCIPLINARY ORBITAL CENTER

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Background and Aims

Data on health services research in the field of Graves´ orbitopathy (GO) are sparse. Aim of this study was to assess the regional health services situation of patients with GO treated at a multidisciplinary joint thyroid-eye clinic in Germany.

Methods

We systematically assessed the medical records pertaining to clinical spectrum, access route, and medical specialty of the referring physician from patients who were treated within a period of five years at our EUGOGO tertiary referral Orphan expert center for GO.

Results

A total of 431 consecutive unselected subjects with GO (n=354 female, 82%; age (median): 40 years; range: 5-79 years) were included in the retrospective study. 148 (35%) and 123 (29%) patients were referred by family physicians and ophthalmologists, respectively. 135 (34.5%) had a mild, 256 (60.2%) a moderate-to-severe, and 22 (5.2%) had a sight-threatening GO. GO was clinically active in 173 (40.3 %) patients. 221 (51.3%) patients were untreated prior to referral, 48 (11.1%) had orbital surgery, and 126 (29.2%) had prior medical therapy for GO. An access route ≥ 50 km was associated with the co-existence of other autoimmune diseases (OR: 1.86; 95% confidence interval, CI: 1.02-3.39; p=0.044). These patients were already pre-treated (1.80; 0.95-3.43; p=0.072) and had a moderate-to-severe or a sight-threatening GO (1.78, 0.91-3.47; p=0.090). There was an association between an access route ≥ 100 km and a prior medical treatment, too (3.78, 1.18-12.05; p=0.025).

Conclusions

GO patients with a broad clinical spectrum are treated at our multidisciplinary orbital center. Especially patients with severe disease, additional autoimmune diseases and prior treatment accept long access routes.

ANALYSIS OF THE CLINICAL ACTIVITY SCORE (CAS) AT BASELINE IN A COHORT OF PATIENTS WITH MODERATE TO SEVERE GRAVES' ORBITOPATHY (GO)

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Objectives

Treatment of Graves' Orbitopathy (GO) with anti-inflammatory/immunosuppressive procedures is generally given to patients with an "active" disease, but not to those who have an inactive GO. GO activity, namely the extent of inflammation, is assessed by a standardized clinical activity score (CAS), including seven ocular signs/symptoms, two of which self-assessed. Being mostly a subjective assessment, CAS carries several limitations, as some of the items can be present also in normal subjects. In this regard, to our knowledge, the relative weight of each of the seven items, namely their sensitivity and specificity, has not been established. Therefore, in the present cross-sectional study, we analyzed the frequency of each CAS item in a large population of GO patients, in order to establish their sensitivity and specificity.

Methods

We studied 538 consecutive, untreated GO patients (146 men and 393 women,age: 51.06±10.3 yr, range 25-80 yr) scheduled to undergo orbital radiotherapy and/or glucocorticoid treatment. We evaluated the sensitivity and specificity of the 5 non-self-assessed CAS items based on their frequency in inactive (CAS <3) or active (CAS ⊠3) GO, as determinedby an atlas-based ophthalmological evaluation.

Results

The frequency of each of the 5 items is reported in the Table below. Eyelid swelling and conjunctival redness were the most sensitive (86 and 94.8 respectively), but less specific (25 and 53.8), items, whereas the remaining items (chemosis, eyelid erythema and caruncle swelling) appeared to be less sensitive (56.7, 61.8 and 39.5 respectively), but more specific (74.1, 94.5 and 94.5 respectively) for GO activity.

CAS	No.	Conjunctival redness	Eyelid swelling	Chemosis	Eyelid erythema	Caruncle swelling
1-2	108	50 (46.2%)	81 (75%)	28 (25,9%)	6 (5.5%)	6 (5.5%)
3-7	430	408 (94.8%)	370 (86%)	244 (56.7%)	266 (61.8%)	170 (39.5%)
Sensitivity		**94.8**	**86.0**	56.7	61.8	39.5
Specificity		53.8	25	**74.1**	**94.5**	**94.5**
Specificity/ Sensitivity ratio		0.56	0.29	1.30	1.52	2.39

Conclusions

Eyelid swelling and conjunctival redness are the most sensitive, but less specific, items within CAS. Chemosis, eyelid erythema and caruncle swelling are more specific, but less sensitive. Development of a semi-quantitative sub-scoring of each CAS item may help increasing the specificity and sensitivity of the various CAS items.

SUBPOPULATIONS OF T AND B CELLS INFILTRATING ORBITAL TISSUES IN GRAVES' ORBITOPATHY (GO) AND THEIR RELATION WITH GO ACTIVITY

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Background

Graves' orbitopathy (GO) is a disfiguring condition most commonly associated with Graves' hyperthyroidism. The pathogenesis of GO is believed to reflect an autoimmune aggression against antigens expressed both in thyrocytes and orbital fibroblasts. The immune mechanisms responsible for GO occurrence and persistence are known only in part. We recently reported a significant correlation between the activity of GO and the number of B and T cells infiltrating orbital tissues. The aim of the present investigation was to determine which lymphocytic subpopulations are involved in the immune aggression to orbital tissues.

Methods

We designed an observational, cohort study, aimed at evaluating the immunohistochemical phenotype of orbital lymphocytes and relate it with the activity of GO, assessed with the clinical activity score (CAS). The study population included 8 men and 12 women, all Caucasians (age: 46±13 yr), who underwent orbital decompression surgery. Orbital tissues samples were collected and subjected to histology and immunohistochemistry.

Results

As reported previously, by univariate analysis there was a significant correlation between CAS and both T (CD3-positive, P=0.008) and B lymphocytes (CD20-positive, P=0.002). CAS correlated also with T-helper (CD4-positive, P=0.01), T-suppressor (CD8-positive, P=0.02), B-memory (CD25-positive, P 0.01) and B-precursor cells (CD19-positive, P=0.04). No NK cells were found in the lymphocytic infiltrate. In a multiple linear regression model, as reported previously, CD3-positive (P=0.04) and CD-20-positive (P=0.004) cells maintained their effect on CAS when adjusted for smoking and GO duration, two additional variables that also correlated with CAS. This was the case also for CD4-positive cells (P=0.05), whereas the remaining lymphocytic subpopulations were no longer correlated with CAS.

Conclusions

In addition to the known correlation between total T and B lymphocytes infiltrating orbital tissues and the activity of GO, the present study shows a major role of T-helper cells, possibly enhancing our understanding of the relationship between GO immunological features and clinical expression.

HYPERTHYROIDISM IN TRANSGENIC MICE EXPRESSING HIGH LEVELS OF THE THYROID STIMULATING HUMAN MONOCLONAL AUTOANTIBODY M22

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Background

The thyroid stimulating human monoclonal autoantibody M22 is a powerful stimulator of the TSH receptor (TSHR) in vitro and in vivo. To study the effects of continuous TSHR stimulation in vivo a transgenic mouse line expressing M22 was produced.

Methods

Transgenic mice expressing M22 were produced using the C57Bl/6J strain and standard procedures. The presence of the M22 gene was confirmed by PCR and an initial transgenic line was established. Serum M22 IgG and total T4 levels were measured and thyroid specimens were assessed by histopathology examination.

Results

Concentrations of M22 IgG in the initial transgenic mice line ranged from 1.3 to 253 µg/mL. Total T4 concentrations in M22 expressing transgenic mice varied from normal to highly elevated levels (22 - 432 nmol/L; median 186 nmol/L). Follicular cell hyperplasia and/or hypertrophy was found in all thyroid specimens from animals (36-360 days old) presenting with different levels of M22 (2.8 – 109 µg/mL; n=9) in terminal samples These changes indicative of thyroid stimulation were observed in mice with either normal or elevated serum total T4 in terminal samples. In addition, follicular cell adenomas were seen in 3/9 mice. Thyroid histology of wild type mice was consistent with that of control mice of the same age and strain. Transgenic mice were selectively bred to isolate a sub-line of transgenic M22 mice which consistently expressed high M22 levels. 145/151 (96%) of animals in this sub-line had serum M22 concentrations between 80µg/mL and 371µg/mL (equivalent to approximately 9000 to 42000 U/L of Thyroid Stimulating Autoantibodies). All 151 mice in this sub-line had high total T4 levels (median 230 nmol/L compared to 56 nmol/L in control mice). Skin scratching was observed in the transgenic mice and was considered to be consistent with hyperthyroidism.

Conclusions

A hyperthyroid transgenic mouse model expressing high levels of M22 has been produced.

SURGICAL MANAGEMENT OF DYSTHYROID STRABISMUS THROUGH MUSCULAR WEAKENING PROCEDURES WITH ADJUSTABLE SUTURES

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Background

Autoimmune dysthyroidism may result in a form of restrictive strabismus characterized by a severe reduction of ocular motility and patient's quality of life. In case of diplopia not manageable with prisms and/or in case of abnormal head position (AHP) not tolerated by patient surgical treatment is the gold standard procedure.

Methods

In this perspective monocentric study we examined dysthyroid patients awaiting for surgical correction of ocular strabismus. All enrolled patients were subjected to muscular recession associated with adjustable sutures. Primary endpoints of this study were subjective diplopia (evaluated with Gorman Score), residual deviation (measured in prismatic diopters, PD), field of single binocular vision (evaluated with Sullivan Score) and patients' quality of life(evaluated with Go-Qol questionnaire).

Results

Forty-four patients (29 females and 15 males with a mean age of 56,09±8,72 years) have been enrolled in this study with one year follow-up. At baseline visit all patients presented constant diplopia (Gorman score = 1) with a total deviation of 36 PD in primary gaze (IQR 28-45), a 15 PD mean horizontal deviation (IQR 6-33) and a 16 PD mean vertical deviation (IQR 4-30). At one year after surgery only 2,27% of patients referred diplopia not manageable with prisms. Mean residual deviation was 3 PD (IQR 0-6) in primary gaze. Field of binocular single vision was 81±3% while Go-Qol improved from 15,71±18,85% at baseline to 95,71±8,57% at one year visit.

Conclusions

Muscular weakening with adjustable sutures represents a safe and an effective procedure for dysthyroid strabismus correction and usually determines a significant improvement in patients' quality of life.

PREDICTING POTENTIAL OF ASSAY TECHNOLOGIES FOR THE DETERMINATION OF TSH-RECEPTOR-AUTOANTIBODIES (TRAB) FOR THE COURSE OF HYPERTHYROIDISM AND GRAVES' ORBITOPATHY (GO)

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Background

Regarding the interaction between TSH-receptor autoantibodies (TRAb) and the onset and course of both hyperthyroidism and Graves' orbitopathy (GO) and additionally due to improvements of assay technology (using monoclonal antibody/bridge technology/cell-based bioassay) the primary objective of the study was to analyse the predicting potential of TRAb and thyroid stimulating antibody (TSAb) measurements with three different assays concerning the course of GO and GD.

Methods

For the investigation, a cohort of patients (n=254) with GO from the University Essen GO data- and biobank were consulted and sera at different timepoints were evaluated in two automated immunoassays; TRAb binding assay Elecsys®(Cobas,Roche) and TSI bridge assay (Immulite®,Siemens), whereas the bioactivity of the TSAb were measured in the cell-based bioassay (Thyretain®,Quidel). Patients were enrolled, if they were observed for GD 24 months after onset and at least 12 months after onset of GO. Patients were divided into remission or relapse group regarding the status of hyperthyroidism. Course of GO (mild/severe) was classified according the NOSPECS score after 12 months of onset of GO.

Results

Relapse but not remission could be prognosed according to antibody levels with all three assays 6, 12 and 18 months after the beginning of antithyroid drug treatment (ATD). Exemplary, we cite the Cut-off-values for relapse 6 months after the beginning of ATD: 11.3 IU/l (sensitivity 59%) measured by binding assay, 5.3 IU/l with bridge assay (sens.62%) and 687% by cell-based bioassay(sens.42%) with a specificity of 90%. Correspondingly to thyroid disease also only a severe course of GO could be predicted according to high levels exceeding: 11.4 IU/l (sens.42%) measured by Elecsys®, 5.5 IU/l(sens.50%) by Immulite® and 709%(sens.31%) by Thyretain® 6 months after GO onset.

Conclusions

In comparison to the results of the 2nd generation human TRAb assay about 50-60% of patients with poor prognoses of hyperthyroidism and GO can be identified with high TRAb or TSI-levels relatively independent of assay technology.

INTERLEUKINS AND TSH-RECEPTOR ANTIBODIES AS PREDICTORS OF FULL THERAPEUTIC RESPONSE TO GLUCOCORTICOIDS IN PATIENTS WITH GRAVES' ORBITOPATHY

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Background

Glucocorticoids (GCs) are the mainstay of treatment for active moderate-to-severe Graves' orbitopathy (GO) with response rate of 70-80%. Partial and non-responders to GCs often require additional therapy. TSH-receptor antibodies (TRAb) and different interleukins (IL) are involved in the pathogenesis of GO.
We aimed to assess the potential of TRAb, IL-6, IL-8 and IL-10 to predict full therapeutic response to GCs in GO patients.

Methods

Thirty-one patients (27 females), mean age 51.6, with active moderate-to-severe GO were enrolled. IL-6, IL-8, IL-10 and TRAb levels were measured at baseline. All patients underwent a 3-month course with systemic GCs. TRAb were evaluated again after the treatment. The overall therapeutic response was assessed using Bartalena's criteria. Full responders formed group 1 (n=13), partial and non-responders - group 2 (n=18).

Results

There was no significant difference between the two groups in terms of age, sex, duration of GO, smoking status, clinical activity score and baseline levels of IL-8 and IL-10. IL-6 was higher in group 1 (3.7 pg/ml vs 2.6 pg/ml, p=0.005) and correlated positively with IL-8 and IL-10 (p=0.023). TRAb levels at baseline and at the end of the therapy did not differ between the two groups (p>0.05). However, TRAb relative reduction was significantly higher in group 1 (65% vs 40%, p=0.004).

The receiver operating characteristic analysis showed that TRAb relative reduction>50% had 92% sensitivity and 71% specificity to predict full response to GCs, while IL-6>2.5 pg/ml - 92% and 61%, respectively.

Conclusions

IL-6>2.5 pg/ml and TRAb relative reduction>50% could early differentiate full responders to GCs from partial and non-responders.

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PHENOTYPES IN THYROID EYE DISEASE

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The pathophysiology of thyroid eye disease manifests clinically as different observable phenotype which can be used to manage patients' prognosis and treatment.

Purpose

To describe the clinical implications of a classification system of thyroid eye disease based on the phenotypic features (clinical and radiological) of the disease.

Methods

Clinical features, photographic and orbital imaging of thyroid eye disease patients were considered in relation to their natural history and treatment response in the experience of the author. Phenotypically distinct categories of patients were identified and described.

Results

At least six phenotypes of thyroid eye disease are observed: 1. Congestive (active inflammatory) 2. "White eye" expansion 3. "Hydraulic" apex 4. "White eye" apex 5. Cicatricial active and 6. Cicatricial passive.

Conclusion

The observable characteristics of thyroid eye disease are determined by the underlying pathophysiology of the disease. Thyroid eye disease is heterogeneous in its underlying pathogenesis, clinical manifestations, and response to medical and surgical treatment modalities. Several previous categorizations of the clinical appearance of thyroid eye disease exist, but they are dichotomous and under-represent the heterogeneity of the disease. We present clinical and radiological features of six different classes or phenotypes of TED and their response to different treatments.

THERAPY WITH HIGH-DOSE INTRAVENOUS METHYLPREDNISOLONE (IVMP) PULSES IN MODERATE-TO-SEVERE GRAVES' ORBITOPATHY IS ASSOCIATED WITH INCREASED HEART RATE

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Background

Influence of high dose intravenous methylprednisolone (IVMP) pulse therapy on heart rate variability still remains unknown. The aim of our study was to estimate whether treatment with IVMP pulses used in patients with active, moderate-to-severe Graves' orbitopathy (GO) is associated with adverse heart rate changes.

Methods

20 patients (14 women and 6 men) with diagnosis of active, moderate-to-severe GO on IVMP pulse therapy were included according to EUGOGO recommendations (6x500mg plus 6x250mg every week). Each IVMP infusion was administered at the same time interval (10-12 a.m.). All patients underwent 24-hour Holter ECG monitoring (HMECG). HMECG was performed for 3 consecutive days (24-h before and 48-h after) during 1st, 6th and 12th IVMP pulse.

Results

We found a significant increase in mean heart rate (HR) in day of IVMP administration in all pulses ($p<0.05$). Increased HR was not correlated with the presence of major cardiovascular adverse events. However, some patients reported recurrent palpitations after IVMP.

Conclusion

The study demonstrated for the first time effect of IVMP pulse therapy on increased heart rate. However, future researches are needed to provide greater insight into the mechanisms of this association.

EVALUATION OF EXTRAOCULAR MUSCLES IN PATIENTS WITH MODERATE-TO-SEVERE GRAVES' OPHTHALMOPATHY USING APPARENT DIFFUSION COEFFICIENT MEASURED BY MAGNETIC RESONANCE IMAGING BEFORE AND AFTER RADIATION THERAPY

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Background

Retrobulbar radiotherapy has been proven to have satisfactory anti-inflammatory in patients with Graves' ophthalmopathy (GO). This study aimed to characterize the inflammation of extraocular muscles(EOM) in moderate-to-severe GO patients using apparent diffusion coefficient (ADC) measured by magnetic resonance imaging (MRI) before and after radiation therapy and to correlate ADCs of extraocular muscles (EOM) with clinical activity.

Methods

ADCs of the superior rectus (SR), inferior rectus (IR), medial rectus (MR), lateral rectus (LR) muscles were measured with MRIin 52 eyes of 26 GO patients before and 3 months after orbital radiation therapy. 38 eyes of 20 healthy vonlunteers were included. Clinical activity scores were evaluated. ADC maps were reconstructed automatically by the commercially available software and was measured on coronal diffusion-weighted imaging(DWI) sequence and calculated in mm2/s.

Results

The mean ADCs of the extraocular muscles in patients with GO before treatment were 1.42±0.23 in SR, 1.37±0.23in IR, 1.41±0.21 in MR and 1.28±0.25 in LR. The mean ADCs after treatment were 1.27±0.18, 1.22±0.26, 1.30±0.22 and 1.15±0.21, respectively. There was a significant drop in ADC values of extraocular muscles after radiation therapy (all $P<0.001$). And the ADCs of TAO patients were significantly highly than those of healthy controls(1.08±0.19 in SR, 1.03±0.15in IR, 1.02±0.23 in MR and 0.97±0.13 in LR).There was a statistically significant correlation between the mean ADC of all 4 muscles measured and the clinical activity scores both before and after treatment (Before:$r=0.520$, $P<0.001$; After:$r=0.625$, $P<0.001$)

Conclusion

The ADC values of extraocular muscles may discriminate the activity of GO and monitor its treatment response as a quantitative indicator.

CLINICAL FINDINGS AND TREATMENT STRATEGIES IN THYROID ORBITOPATHY CASES ADMITTED TO A TERTIARY REFERENCE CENTER IN TURKEY

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Aim

The aim of this study is to evaluate the symptoms, clinical evaluation, follow-up and treatment results of our thyroid orbitopathy (TO) cases according to the parameters specified by the European Graves' Orbitopathy Group (EUGOGO).

Methods

The records of 410 patients (169 M, 241 F) who were followed up with the diagnosis of TO between January 2008 and December 2017 were retrospectively reviewed. Demographic characteristics, clinical findings, preferred treatment scheme, follow-up and treatment results were analyzed.

Results

The mean age of the patients was 42.5 ± 13.2 years. Time interval between the diagnosis of thyroid disease (TD), TO and admission to our clinic was 50.5 months and 27.4 months, respectively. In 7.6% of the cases, TD was diagnosed after the eye findings. Family history was positive in 28.2% and smoking history was positive in 55.8% of the patients. Clinically, unilateral TO was observed in 15.9% of the cases. Oral antithyroid therapy was given to 168 cases (41.0%), thyroidectomy was performed in 147 cases (35.9%) and radioactive iodine therapy was given in 37 cases (9%) in order to provide euthyroidism. The severity of TO was mild in 227 cases (55.4%, CAS: 0.9 ± 1.3), moderate-severe in 91 cases (22.2%, CAS: 2.4 ± 1.9) and vision-threatening disease in 92 cases (22.4%, CAS 3.5 ± 2.3). Valve retraction was the most common finding (333 cases, 81.2%) followed by proptosis (Hertel value> 20 mm), (289 cases, 70.5%) and soft tissue involvement (176 cases, 43.6%) in the first evaluation. For the treatment of TO; systemic steroid treatment was given in 126 cases (30.7%), orbital decompression surgery was performed in 53 cases (12.9%), valve surgery in 22 cases (5.4%), vision correction with strabismus surgery and / or prismatic glasses in 26 cases (6.3%), and external orbital radiotherapy in 9 cases (2.2%).

Conclusion

Use of standardized clinical evaluation parameters in the diagnosis, staging, follow-up and treatment of TO will increase success in the management of the disease.

SINGLE-CELL PROFILING OF CD4+ T LYMPHOCYTES FROM GRAVES' OPHTHALMOPATHY REVEALS A CYTOTOXIC SUBSET ASSOCIATED WITH INFLAMMATION AND FIBROSIS

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Background

CD4+ T cells are the predominant pathogenic factor in Graves' ophthalmopathy (GO), and novel immunosuppressive therapy targeting on pathogenic T subsets would be helpful in improving patients' life quality. However, the relationship between quantitative and qualitative differences in T cell subtypes of GO remains unknown.

Methods

We performed single-cell RNA sequencing of 96278 CD4+ T cells isolated from peripheral blood samples of three Graves' disease (GD) and six Graves' ophthalmopathy (GO) patients. CD4+ T cells were collected from GD patients prior to MMI therapy, and from GO patients before and after different therapeutic methods. Specifically, four of six GO patients received high-dose intravenously methylprednisolone therapy (IVMP), one GO patient received rapamycin monotherapy which 0.5 mg/day rapamycin at 13 o'clock every day, and the last GO patient received IVMP/rapamycin combination therapy.

Results

We show that significant heterogeneity exists in the CD4+ T cell population, and twenty CD4+T cell subtypes were identified, including different subpopulations in certain cell types, as well as marker genes underlying their heterogeneity. By comparing GO with GD samples, we demonstrate that GO contained a specific CD4+ T subtype with features of cytotoxicity and this subtype cells expressed high levels of GZMB, GNLY, NKG7,PRF1 and FGFBP2. Analysis of geneontology gene sets highlighted that Cell Adhesion, Cell Activation, Interferon Gamma Response, Cytotoxicity, Cell Chemotaxis and Hypoxia as the top enriched signature in GO specific CD4+ cytotoxic subset (CTL). Myc targets and MTORC1 signaling were also enriched in GO specific CD4+ CTL. The GO specific ligand–receptor interactions between CTL and th17-like subset mainly focused on chemotaxis (CCL20-CCR6, CXCR6-CXCL16), cell adhesion (TIGIT-PRR3, JAM2_JAM3) and immunomodulation (KLRF1-CLEC2B, TNFSF9-TNFRSF9). Different therapeutic methods showed distinct effect on gene signatures of CD4+ cytotoxic subset. IVMP therapy could reduce the expression of lymphocytes activation or interferon gamma response, however, it had little effect on cell adhesion and chemotaxis. Clinical remission of GO induced by IVMP/rapamycin combination therapy was associated with a significant reduction of cell activation, adhesion and chemotaxis.

Conclusion

CD4+ cytotoxicity T subtype expressing high levels of GZMB, GNLY, NKG7, PRF1 and FGFBP2 may act as a pathogenic cells in GO development, which result in tissue damage, inflammation and progressive fibrosis. On the other hand, the pathological process of GO not only consists of lymphocytes activation, but also cell adhesion and chemotaxis. Novel combination treatment precisely targeting on the pathogenic factors would significantly improve therapeutic effect.

A NINE YEAR AUDIT OF THE EDINBURGH JOINT THYROID EYE CLINIC

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Background

The European Group on Graves' Orbitopathy (EUGOGO) recommends that patients with thyroid eye disease be seen in joint thyroid eye clinics. However, there is limited published evidence confirming the benefits of joint clinics. In May 2010, a multidisciplinary thyroid eye clinic was set up in Lothian. This audit assesses the Lothian joint clinic to establish whether it has achieved any improvement in clinical outcomes. Comparison data is available for 12 months (2008-2009) just prior to setting up the joint clinic.

Methods

The joint clinic audit covers May 2010 to July 2019 and includes 439 patients with thyroid eye disease. Key outcomes include time from referral to first assessment, clinical activity score (CAS), TSH Receptor Antibody (TRAb) levels, smoking status, use of corticosteroids and selenium uptake.

Results

The median time from referral to first appointment was 42 days in 2008-2009 prior to the joint clinic being set up. This improved to 33 days for routine patients and 19 days for urgent referrals in 2018-2019. 126 new patients were seen over the last 3 years, 19 of whom required glucocorticoid therapy and/or rituximab for active disease (median TRAb 9.4 and median CAS 3 compared to TRAb 7.9 and CAS 1 for those who did not require glucocorticoid or immunosuppressant therapy). 95% of patients with active disease received glucocorticoids intravenously, compared to just 40% with active disease receiving iv methylprednisolone in 2008-9 (60% received oral prednisolone). Prior to setting up the joint clinic 15% of smokers quit, compared to a quit rate of 25% since the joint clinic was established.

Conclusion

The joint clinic's use of corticosteroids was effective and compliant with EUGOGO guidelines. Referral to clinic times have improved since the joint clinic was set up with increases in use of selenium and improved rates of smoking cessation.

RIM-SPARING VERSUS RIM-REMOVAL TECHNIQUES IN DEEP LATERAL WALL ORBITAL DECOMPRESSION FOR GRAVES' ORBITOPATHY

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Background

To compare the surgical outcomes of deep lateral orbital decompression using the rim-sparing technique versus the rim-removal technique in Graves' orbitopathy (GO).

Methods

A retrospective cohort study was performed on 75 orbits from 50 patients with GO. Proptosis, best corrected visual acuity (BCVA), intraocular pressure (IOP), upper and lower lid margin to reflex distances (MRD-1 and MRD-2, respectively), diplopia, ocular restriction and GO quality of life (GO-QOL) questionnaire were analyzed pre- and postoperatively.

Results

The average proptosis reductions ranged from 3.5-6.7 mm and from 3.6-6.7 mm with the rim-sparing and rim-removal techniques, respectively ($p > 0.05$). All orbits with dysthyroid optic neuropathy in the rim-sparing group and 87.5% of the orbits in the rim-removal group showed improved BCVA ($p = 0.321$). Reductions of IOP, MRD-1, and MRD-2 were observed with both techniques. Patients with the rim-sparing technique had greater improvements in the GO-QOL appearance score ($p = 0.043$).

Conclusion

The rim-sparing orbital decompression provides efficacious outcomes with greater improvements in patients' quality of life than the rim-removal technique. The rim-sparing technique should be considered as a preferable option because it preserves the integrity of the lateral vertical maxillary buttress and a bony protection for orbital contents.

BOVINE ACELLULAR DERMAL MATRIX FOR LEVATOR LENGTHENING IN THYROID-RELATED UPPER-EYELID RETRACTION

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Background

Eyelid retraction is the most common and often the first sign of thyroid eye disease (TED). Upper-eyelid retraction causes both functional and cosmetic problems. In order to correct the position of the upper eyelid, surgery is required. Many procedures have demonstrated good outcomes in mild and moderate cases; however, unpredictable results have been obtained in severe cases. Dryden introduced an upper-eyelid-lengthening procedure, which used scleral grafts, but outcomes were unsatisfactory. A new technique is introduced in this study as a reasonable alternative for TED-related severe upper-eyelid retraction correction.

Material and Methods

An innovative technique for levator lengthening using bovine acellular dermal matrix as a spacer graft is introduced for severe upper-eyelid retraction secondary to TED. Additionally, 2 modifications were introduced: the fibrous cords scattered on the surface of the levator aponeurosis were excised and the orbital fat pad anterior to the aponeurosis was dissected and sutured into the skin closure in a "skin-tarsus-fat-skin" fashion.

Results

The modified levator-lengthening surgery was performed on 32 eyelids in 26 patients consisting of 21 women and 5 men (mean age, 37.8 years; age range, 19-67 years). After corrective surgery, the average upper margin reflex distance was lowered from 7.7±0.85 mm to 3.3±0.43 mm. Eighteen cases (69%) had perfect results, while 6 cases (23%) had acceptable results.

Conclusion

A modified levator-lengthening procedure using bovine acellular dermal matrix as a spacer graft ameliorated both the symptoms and signs of severe upper-eyelid retraction secondary to TED. This procedure is a reasonable alternative for correction of TED-related severe upper-eyelid retraction.

EYELID LENGTHENING WITH ACELLULAR XENOGENIC DERMAL MATRIX AS A SPACER GRAFT TO TREAT EYELID RETRACTION RELATED TO THYROID ASSOCIATED OPHTHALMOPATHY

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Background

To use the acellular xenogenic dermal matrix (AXDM) as a graft in the eyelid lengthening surgery to treat upper and/or lower eyelid retraction (UER/LER) in patients with thyroid associated ophthalmopathy (TAO), and to evaluate the efficacy and safety.

Methods

This is a retrospective case series study. From January 2016 to December 2017, all the TAO patients who underwent the eyelid lengthening surgery with AXDM as a spacer graft were included in the study. The follow-up duration was at least 6 months. Eyelid height, ocular discomfort symptoms, and complications were recorded.

Results

54 patients (70 eyes) were included, consisting of 43 patients (56 eyes) with UER and 11 patients (14 eyes) with LER. At 6 months after surgery, all the patients acquired improvements for lagophthalmos, ocular discomfort, tearing, etc. In patients with UER, the MRD1 was lowered from 7.82±0.44mm to 3.66±0.55mm ($p<0.001$). The upper scleral show was lowered from 3.18±0.43mm to 0mm ($p<0.001$). In patients with LER, the MRD2 was lowered from 8.04±0.79mm to 5.46±0.58mm ($p<0.001$). The lower scleral show was lowered from 2.79±0.70mm to 0.29±0.51mm ($p<0.001$). In total, 74.1% of the patients acquired good outcomes, 20.4% acquired acceptable outcomes, and 5.5% had recurrence, and no significant difference was found among the patients with UER and LER ($p=0.369$, $p>0.05$). No other complications, such as infection, rejection, or dislocation were observed.

Conclusion

The eyelid lengthening surgery with AXDM as a graft can be a reasonable alternative for eyelid retraction in TAO patients, achieving both the functional and aesthetic improvements.

GENERAL INFO

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INFORMATION FOR PRESENTERS

Abstracts

For each accepted abstract, an author is expected to attend the congress and present the poster or oral communication. Abstracts for which no author has registered to attend the congress will not be included in the congress proceedings.

Slide Center

A slide center will be avaiable throughout the entire Congress for Speakers and Authors of oral communications. All speakers/authors are expected to produce a power point presentation. Presentations should be saved on a USB memory stick and delivered to the slide center. PCs at the slide center will be available to make changes to the presentations. The use of the speakers' own laptop for the presentation is not allowed.

Posters

All posters wil be on display for the duration of the Congress from 7th to 9th November. Each poster has been given a number and should be fixed to the board marked with the same number.

Set up time: 7th November from h.12.00 am.

Dismantle time: 9th November by h. 1.00 pm.

Presenters must therefore be available at their poster board during poster viewing on November 8th, in order to discuss their poster with interested viewers and reply to any question received. The Organiser are not responsible for loss of any posters that have note been removed by the end of the sessions.

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