静止期轻度和中重度甲状腺相关眼病的眼表损害特征

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摘 要：【目的】分析静止期轻度和中重度甲状腺相关眼病(GO)患者眼表损害的临床特征。【方法】回顾性收集2017年4月至2019年4月于中山大学孙逸仙纪念医院内分泌与眼科诊断为静止期轻度及中重度GO的初诊患者资料，共192例192眼。其中，轻度患者121例121眼；中重度患者71例71眼。将患者分为角膜损害组和无角膜损害组，对眼表刺激征和泪膜破裂时间(TFBUT)、上睑缘瞳孔反射距离1(MRD1)、下睑缘瞳孔反射距离2(MRD2)、基础泪液分泌实验(Schirmer's test II)、眼球突出度等指标在两组之间的差异进行分析。【结果】本研究静止期轻度GO患者中角膜损害组表现异物感(21例，52.5%)和畏光(23例，57.5%)较无角膜损害组更常见(23例，28.4%；29例，35.8%)($P \leqslant 0.05$)；而静止期中重度GO两组之间没有差异。静止期轻度GO角膜损害组MRD15.1($S = 1.9$) mm，宽于无角膜损害组4.4($S = 1.5$)mm，($P \leqslant 0.05$)；静止期中重度GO角膜损害组TFBUT3.2($S = 2.3$)s，较无角膜损害组明显缩短6.2($S = 3.2$)s，($P \leqslant 0.05$)；同为角膜损害，轻度与中重度GO之间的症状和体征无明显差别。【结论】静止期轻度GO眼表损害患者更易出现异物感和畏光症状，眼表损害与MRD1增加相关；而中重度GO角膜损害患者症状与无角膜损害患者无差别，眼表损害与TFBUT缩短相关。

关键词：甲状腺相关眼病；静止期；眼表损害
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Characteristics of Ocular Surface Damage in Inactive Mild and Moderate-severe Graves' Orbitopathy

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Abstract: 【Objective】 To analyze characteristics of ocular surface damage in inactive mild and moderate-severe Graves' Orbitopathy (GO). 【Methods】 In this retrospective study, the clinical characteristics of GO patients at Sun Yat-sen Memorial Hospital between April 2017 and April 2019 were reviewed. Data were collected from 192 eyes of 192 cases. There were 121 eyes of 121 cases with mild GO, and 71 eyes of 71 cases with moderate-severe GO. All patients were divided into corneal-damage and non-corneal-damage groups. The ocular surface irritation, tear film breakup time (TFBUT), marginal reflex distance 1 (MRD1), marginal reflex distance 2 (MRD2), Schirmer's test Ⅱ, and proptosis of the two groups were compared. 【Results】 Grittiness (21 cases, 52.5%) and photophobia (23 cases, 57.5%) were higher, in corneal-damage group of inactive mild GO patients, compared with non-corneal-damage group (23 cases, 28.4%, 29 cases,

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35.8%, respectively) ($P \leq 0.05$); but there was no statistical difference in symptoms between the two groups of moderate-severe GO patients. There was statistical difference in increased MRD1 between corneal-damage group [5.1(S = 1.9) mm] and non-corneal-damagegroup [4.4(S = 1.5) mm] of inactive mild GO patients ($P \leq 0.05$). Besides, decreased TFBUT in moderate-severe corneal-damage GO patients was 3.2(S = 2.3) s, shorter than non-corneal-damage group [6.2(S = 3.2) s, ($P \leq 0.05$)]. In corneal-damage groups, there was no significant difference in symptoms and signs between mild and moderate-severe GO. 【Conclusions】 Grittinessand photophobia are common symptoms in patients with mild GO ocular surface damage, and MRD1 is related with ocular surface damage. There is no difference in symptom between corneal-damage group and non-corneal-damage group of moderate-severe GO patients, and TFBUT is related with ocular surface damage.

Key word: Graves′ orbitopathy; inactive; ocular surface damage

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甲状腺相关眼病(Graves′ orbitopathy, GO)是Graves病在眼部表现,属于自身免疫性疾病,其病理特征是眼眶淋巴细胞浸润以及水肿,导致眼外肌与眼眶脂肪的增厚与纤维化[1],进而表现为眼球突出、眼睑后退、重影、视力降低等不同程度的眼部病变。欧洲Graves眼病专家组(The European Group on Graves′ Orbitopathy, EUGOGO)根据上述表现的程度不同,分为轻度、中重度以及威胁视力3种严重程度的分类。同时,GO依据软组织的炎症表现,分为炎症活动期与炎症静止期。以往关于GO眼表损害[2-4]研究,主要针对活动期GO进行分析,然而,静止期患者也同样经受着眼表的不适。而由于静止期的眼表损害的研究较少,迄今为止,临床上对静止期GO的眼表损害特点尚不明确,EUGOGO组织对GO的诊疗指南中也没有提出针对性的治疗。因此,鉴于轻度和中重度GO的临床特点和严重程度不同,本研究期望通过对静止期轻度和中重度甲状腺相关眼病眼表损害的临床特征进行比较,探索有针对性而有效的治疗。

1 材料与方法

1.1 材料和方法

本研究为回顾性研究,收集2017年4月至2019年4月于中山大学孙逸仙纪念医院内分泌与眼科诊断为静止期轻度及中重度GO的初诊患者资料。随机抽取一眼作为研究对象;如双眼病情不一致,取较严重眼为研究对象,记录一般情况、症状、眼部检查结果。根据GO诊断依据Bartly诊断标准[5]诊断GO;并排除以下对眼表存在影响的情况:①影响眼表微环境药物使用史,如:治疗睑板腺疾病、边缘性睑缘炎、风湿性关节炎、抗抑郁等其他疾病的滴眼液、眼膏或全身性药物;②既往眼科手术史、眼眶放射治疗史;③角膜接触镜佩戴史;④倒睫;⑤其他眼表疾病如翼状胬肉等。以EUGOGO评价标准[6]对GO进行疾病严重程度分级:分为轻度、中重度和威胁视力GO;其中,本研究取轻度和中重度GO患者。以临床活动度评分(clinical activity score, CAS)[6-7]判断GO活动性,CAS≥3/7被认为炎症活动。本研究中患者均为静止期,即CAS<3/7。观察以下指标:裂隙灯检查角膜上皮染色、上睑缘瞳孔反射距离1(marginal reflex distance 1, MRD1)、下睑缘瞳孔反射距离2(marginal reflex distance 2, MRD2)、睑裂宽度(MRD1+MRD2)、基础泪液分泌实验(Schirmer′s test Ⅱ)、泪膜破裂时间(tear film breakup time, TFBUT)、眼球突出度等。本研究的实施严格遵照赫尔辛基宣言原则,并且本研究的协议通过中山大学孙逸仙纪念医院伦理委员会。本研究经本院伦理委员会审查批准并经患者知情同意。

1.2 统计学方法

本研究统计分析采用SPSS软件22.0(Statistical Package for Social Sciences; SPSS Inc. IBM, Armonk, NY)进行统计学分析。定量资料采用平均值和标准差进行统计描述,采用K-S检验(Kolmogorov-Smirnov Test)判断数据是否服从正态分布,若数据资料服从正态分布且方差齐,采用t检验进行组间比较统计学差异;若各组服从正态分布但方差不齐,则采用t'检验进行组间比较统计学差异;定性资料采用用频数和频率进行统计描述,定性资料的两组组间比较采用Pearson χ^2检验或Fisher确切概率法(Fisher′s exact probabilities)。

$P \leqslant 0.05$ 认为差别具有统计学意义。

2 结　果

2.1 一般临床资料以及角膜损害的发生率分析

本研究共收集静止期患者192例192眼，其中男性58例（30.2%），女性134例（69.8%），男女比例为1∶2.3，患者年龄41.1（S=13.9）岁（范围16～75）。其中，轻度患者121例121眼，中重度患者71例71眼，轻度患者年龄小于中重度患者。所有患者眼部CAS评分均低于3分，其中轻度GO患者CAS评分0.8（S = 0.8）分（范围0～2）；中重度GO患者CAS评分0.8（S = 0.7）分（范围0～2）。静止期GO角膜损害的发生率为34.4%（66例），其中轻度GO角膜损害的发生率为33.1%，与中重度角膜损害的发生率（36.6%）相似（表1）。

表1　静止期轻度和中重度GO患者一般情况

Table 1　Demographic characteristics of inactive mild and moderate-severe GO patients

［cases（%）/（cases：cases）/ mean ± SD（range）］

		Mild	Moderate-severe	χ^2/t	P
CAS/*n*	0	45（37.2）	25（35.2）	0.546	0.761
	1	50（41.3）	33（46.5）		
	2	26（21.5）	13（18.3）		
Male/Female（*n*）		31/90（1∶2.9）	27/44（1∶1.6）	3.268	0.071
Age/years		39.3 ± 13.4	44.5 ± 13.6	−2.566	0.011
Corneal damage/*n*		33.1%（40/121）	36.6%（26/71）	0.252	0.616

2.2 静止期轻度GO眼表损害的临床资料分析

静止期轻度GO的角膜损害组和无角膜损害组之间：①在症状方面均可出现异物感、畏光、流泪，并且多数发生率超过50%，在体征方面均有眼睑闭合不全、TFBUT缩短、眼球突出度增加，而Schirmer′s test Ⅱ和睑裂宽度并没有明显异常；②两组比较发现：在症状方面角膜损害患组出现的异物感、畏光，较无角膜损害组更常见（$P \leqslant 0.05$），在体征方面角膜损害组MRD1大于无角膜损害组（$P \leqslant 0.05$）；③静止期轻度GO CAS评分的不同组间具有统计学差异，其中2分组与0分组、1分组两两比较均有统计学差异（$\chi^2 = 4.355$，$P = 0.037$；$\chi^2 = 5.791$，$P = 0.016$），而0分组与1分组之间没有统计学差异（表2）。

2.3 静止期中重度GO眼表损害的临床资料分析

静止期中重度GO的角膜损害组和无角膜损害组之间：①在症状方面均可出现异物感、畏光、流泪，并且多数发生率接近50%，在体征方面均有眼睑闭合不全、TFBUT缩短、眼球突出度增加，而Schirmer′s test Ⅱ和睑裂宽度并没有明显异常；②两组比较发现：在症状方面各项指标无统计学差异，在体征方面角膜损害组TFBUT较无角膜损害组缩短（$P \leqslant 0.05$）；③静止期中重度度GO CAS评分的不同组间无统计学差异（表3）。

2.4 静止期GO轻度和中重度的眼表损害组临床资料比较及分析

本研究中，同为角膜损害组，静止期轻度与中重度GO之间的症状和体征无明显差异（表4）。

3 讨　论

3.1 静止期GO眼表损害的症状

既往研究多针对炎症期的GO患者眼表损害进行研究[2-4,8-10]，但静止期GO患者同样具有眼表不适的困苦，如异物感、流泪、畏光等，为此，本研究针对静止期患者的眼表损害进行初步分析。结果显示，在静止期轻度以及中重度患者中，仍约有1/3存在角膜损害；而无论是否有角膜损害，都会有眼表不适的症状。

静止期患者眼表损害的表现在眼表损害的症状方面，本研究结果显示，无论是否有角膜损害，静止期GO患者都会出现异物感、畏光、流泪等症状。其中在轻度患者中，角膜损害的患者异物感、畏光等的不适症状发生率高于无角膜损害的患者。而在中重度患者中，上述症状的发生率在角膜损害组与无角膜损害组之间无统计学差异。

表2 静止期轻度GO角膜损害组和非角膜损害组之间临床资料比较分析

Table 2 Comparison of clinical characteristics between corneal-damage and non- corneal-damage groups in inactive mild GO

[cases(%)or mean ± SD]

		Inactive mild GO			
		Corneal-damage(n = 40)	Non-corneal-damage(n = 81)	χ^2/t	P
CAS	0	13(32.5)	32(39.5)	6.556	0.038
	1	13(32.5)	37(45.7)		
	2	14(35.0)	12(14.8)		
Age/years		40.3 ± 14.3	38.5 ± 13.4	0.646	0.520
Male/Female(n)		9/31	22/59	0.305	0.581
Grittiness/n		21(52.5)	23(28.4)	6.724	0.010
Photophobia/n		23(57.5)	29(35.8)	5.144	0.023
Tearing/n		29(72.5)	44(54.3)	3.697	0.054
lagophthalmus/n		10(25.0)	14(17.3)	1.003	0.339
Bell's phenomenon(-)/n		2(5.0)	1(1.2)	-[1)]	0.254
TFBUT/s		3.7 ± 2.2	5.1 ± 3.5	-1.643	0.109
Schirmer's test Ⅱ/mm		7.1 ± 4.7	9.3 ± 7.2	-1.026	0.314
The width of palpebral fissure/mm		9.7 ± 2.9	9.4 ± 2.1	0.527	0.599
MRD1/mm		5.1 ± 1.9	4.4 ± 1.5	2.068	0.041
MRD2/mm		5.1 ± 0.9	5.3 ± 0.9	-1.279	0.204
Proptosis/mm		17.7 ± 2.8	17.5 ± 2.8	0.358	0.721

TFBUT: tear film breakup time; MRD1: marginal reflex distance 1; MRD2: marginal reflex distance 2. [1)]Fisher's exact probabilities

表3 静止期中重度GO角膜损害组和非角膜损害组之间临床资料比较分析

Table 3 Comparison of clinical characteristics between corneal-damage and non-corneal-damage groups in inactive moderate-severe GO

[cases(%)or mean ± SD]

		Inactive moderate-severe GO			
		Corneal-damage(n = 26)	Non-corneal-damage(n = 45)	χ^2/t	P
CAS	0	9(34.6)	16(35.6)	0.667	0.716
	1	11(42.3)	22(48.9)		
	2	6(23.1)	7(15.6)		
Age/years		44.7 ± 11.8	44.3 ± 14.6	0.093	0.926
Male/Female(n)		9/17	18/27	0.203	0.653
Grittiness/n		12(46.2)	19(42.2)	0.104	0.748
Photophobia/n		11(42.3)	23(51.1)	0.512	0.474
Tearing/n		18(69.2)	22(48.9)	2.772	0.078
lagophthalmus/n		9(34.6)	16(35.6)	0.006	1.000
Bell's phenomenon(-)/n		1(3.9)	2(4.4)	-[1)]	1.000
TFBUT/s		3.2 ± 2.3	6.2 ± 3.2	-2.406	0.031
Schirmer's test Ⅱ/mm		8.2 ± 3.3	8.8 ± 6.0	-0.237	0.819
The width of palpebral fissure/mm		10.0 ± 3.4	9.8 ± 2.3	0.264	0.792
MRD1/mm		5.3 ± 2.4	4.4 ± 2.1	1.684	0.097
MRD2/mm		5.1 ± 1.2	5.4 ± 1.0	-1.258	0.213
Proptosis/mm		18.8 ± 3.0	18.8 ± 3.6	0.006	0.996

TFBUT: tear film breakup time; MRD1: marginal reflex distance 1; MRD2: marginal reflex distance 2. [1)]Fisher's exact probabilities

表4　静止期GO轻度和中重度的角膜损害组临床资料比较及分析

Table 4　Comparison of clinical characteristics of corneal-damage groups between inactive mild GO and inactive moderate-severe GO

[cases(%)or mean ± SD]

		Corneal-damage group			
		Inactive mild GO(n = 40)	Inactive moderate-severe GO(n = 26)	χ^2/t	P
CAS	0	13(32.5)	9(34.6)		
	1	13(32.5)	11(42.3)	1.177	0.555
	2	14(35.0)	6(23.1)		
Age/years		40.3 ± 14.3	44.7 ± 11.8	−1.299	0.199
Male/Female(n)		9/31	9/17	1.166	0.397
Grittiness/n		21(52.5)	12(46.2)	0.254	0.801
Photophobia/n		23(57.5)	11(42.3)	1.456	0.314
Tearing/n		29(72.5)	18(69.2)	0.082	0.788
lagophthalmus/n		10(25.0)	9(34.6)	0.711	0.419
Bell's phenomenon(−)/n		2(5.0)	1(3.9)	−[1)]	1.000
TFBUT/s		3.7 ± 2.2	3.2 ± 2.3	0.626	0.536
Schirmer's test Ⅱ/mm		7.1 ± 4.7	8.2 ± 3.3	−0.766	0.451
The width of palpebral fissure/mm		9.7 ± 2.9	10.0 ± 3.4	−0.453	0.652
MRD1/mm		5.1 ± 1.9	5.3 ± 2.4	−0.502	0.618
MRD2/mm		5.1 ± 0.9	5.1 ± 1.2	0.098	0.922
Proptosis/mm		17.7 ± 2.8	18.8 ± 3.0	−1.562	0.123

TFBUT: tear film breakup time; MRD1: marginal reflex distance 1; MRD2: marginal reflex distance 2. [1)]Fisher's exact probabilities

3.2　静止期GO眼表损害的体征

引起GO眼表损害的原因包括睑裂增宽、突眼、上睑后退、上转受限以及无bell's征等[9,11-15]。进一步分析，本研究结果发现，在轻症GO患者中，虽然都存在着睑裂增宽、突眼等可以导致眼表损害的因素，但角膜损害组MRD1大于无角膜损害组，MRD1增宽提示在角膜损害组中上睑后退的程度比无角膜损害组更加严重，与以往研究[10]一致。因此，对于轻症GO，存在角膜损害的患者，需要采取减少上睑后退的措施治疗角膜损害，如采用手术方式行眼眶减压术、上睑后退矫正术、或肉毒杆菌毒素注射等。

在轻度和中重度GO患者中，角膜损害组与无角膜损害组的TFBUT均缩短，而中重度患者角膜损害组则较无角膜损害的TFBUT缩短更加明显；提示随着疾病严重程度增加，泪膜稳定性下降也越明显。

以往关于GO炎症期[2-4,8,16]和静止期[17-21]眼表损害的研究，主要针对Schirmer's test I进行分析，并且认为GO相关的炎症因子攻击泪腺，影响泪腺分泌功能；而副泪腺功能是维持基础的泪液分泌，且目前对GO患者的基础泪液分泌研究尚少，所以本研究针对基础分泌（即Schirmer's test Ⅱ）进行研究，探讨副泪腺的功能变化。虽然本研究静止期轻度和中重度GO的Schirmer's Test Ⅱ结果均未达到临床诊断异常标准，且轻度和中重度GO两组比较无明显差异，但是对比其他研究[22-26]中正常组Schirmer's Test Ⅱ结果均在(13-23)mm之间，本研究的结果明显缩短；提示静止期GO的副泪腺功能也可能受损。

本研究中患者虽然皆为静止期，但CAS评分并非为0，提示即使在静止期的患者中，仍会有轻度的眼部软组织的炎症存在。目前，尚没有静止期GO患者眼表炎症的分子生物学研究，但在活动期GO有关眼表损害的炎症因子的研究中，显示TSHR在泪腺中表达[2,27]、IL-6等炎症因子在泪腺和泪液[28-33]、球结膜中表达[19,29]，提示炎症因子也有可能表达于静止期GO的眼部组织中，并与眼表损害关，此有待进一步研究。

3.3　静止期GO眼表损害的治疗提示

2016年EUGOGO组织联合欧洲甲状腺协会发布的Graves眼病管理指南[34]上提出甲状腺相关

眼病全程进行眼表治疗,基础的治疗为采用不含防腐剂的人工泪液。同时指南议静止期中重度GO进行开眶治疗,该手术可以减轻眼球突出度和眼睑后退,还有降低眼内压、改善斜视,及当患者有视神经视网膜微血管循环障碍时还可以改善视力。但是开眶手术并未提及对眼表损害治疗的益处。

而本研究的结果显示,静止期GO眼表损害、特别是角膜损害也与眼部组织解剖学异常有关,如上睑后退等,提示静止期GO应当重视改善眼睑结构异常手术治疗。

3.4 结 论

眼表损害的表现众多,还包括球结膜病变等,而本研究仅针对静止期GO的角膜损害进行了临床分析,其他研究者[21,35]通过印迹细胞学以及共聚焦显微镜检查发现静止期GO患者的球结膜上皮也存在着细胞密度降低,球结膜上皮细胞鳞状化生的现象;静止期GO患者角膜神经退化、敏感性下降[3,36]。因此,在下一步的研究中,需要进一步从细胞及分子层面了解静止期GO的眼表损害特点。

综上所述,本研究的结果显示,静止期GO患者的眼表损害中存在着异物感、畏光等相关症状,而副泪腺功能异常、GO眼睑的病变则与眼表损害有关,因此提示,静止期GO眼表的损害除需要人工泪液治疗之外,尚需纠正GO的眼睑结构和功能异常等,既可以减少角膜损害,还可以改善容貌,减轻心理负担,提高生活质量。

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