

doi: 10.13241/j.cnki.pmb.2018.10.034

促甲状腺素受体抗体及白细胞介素-2、白细胞介素-6在Graves病¹³¹I治疗中的变化及临床意义*

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摘要 目的:研究促甲状腺素受体抗体(TRAb)及白细胞介素-2(IL-2)、白细胞介素-6(IL-6)在Graves病¹³¹I治疗中的变化并分析其临床意义。**方法:**选取2015年8月-2016年8月于我院接受¹³¹I治疗的Graves病患者112例为研究对象,按照第6个月的甲状腺功能检查结果的不同分为治愈组(n=54)、缓解组(n=21)和甲减组(n=37)。分别比较治疗前、治疗3个月、6个月后三组患者的甲状腺功能指标以及TRAb、IL-2、IL-6水平。**结果:**治疗前三组患者游离T3(FT3)、游离T4(FT4)、促甲状腺激素(TSH)水平比较差异无统计学意义(P>0.05),治疗3个月、6个月后三组患者FT3、FT4水平均明显低于治疗前,而TSH水平明显高于治疗前(P<0.05)。治疗3个月、6个月后甲减组FT3、FT4水平均明显低于治愈组、缓解组,治愈组又明显低于缓解组,TSH水平明显高于治愈组、缓解组,治愈组又明显高于缓解组(P<0.05)。治疗前三组患者TRAb、IL-2、IL-6水平比较差异无统计学意义(P>0.05)。治疗3个月后三组患者TRAb水平均明显高于治疗前(P<0.05),治疗6个月后治愈组与甲减组患者TRAb水平与治疗前比较无统计学差异(P>0.05),但缓解组患者TRAb水平高于甲减组,差异有统计学意义(P<0.05)。治疗3个月、6个月后,治愈组与甲减组患者IL-2、IL-6水平均低于治疗前,而缓解组高于甲减组,差异均有统计学意义(P<0.05)。**结论:**TRAb、IL-2、IL-6可作为评估Graves病¹³¹I治疗后的指标,通过检测三项指标治疗前后水平变化情况,从而为临床预后评估提供指导作用。

关键词:Graves病;碘放射性同位素;促甲状腺素受体抗体;白细胞介素-2;白细胞介素-6

中图分类号:R581.1 **文献标识码:**A **文章编号:**1673-6273(2018)10-1969-04

Changes and Clinical Significance of Thyrotropin Receptor Antibody, Interleukin-2 and Interleukin-6 in Treatment of Graves' Disease by ¹³¹I*

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ABSTRACT Objective: To study the changes of thyrotropin receptor antibody (TRAb) and interleukin-2 (IL-2) and interleukin-6 (IL-6) in the treatment of Graves' disease by ¹³¹I and to analyze its clinical significance. **Methods:** A total of 112 patients with Graves' disease, who were treated with ¹³¹I in Loudi Central Hospital of Hunan Province from August 2015 to August 2016, were selected as research subjects. According to the results of thyroid function examination at the 6th month, the patients were divided into cure group (n=54), remission group (n=21) and hypothyroidism group (n=37). The thyroid function indexes and the levels of TRAb, IL-2 and IL-6 were compared among the three groups before treatment, 3 months and 6 months after treatment. **Results:** There was no significant difference in the levels of free T3 (FT3), free T4 (FT4) and thyroid stimulating hormone (TSH) among the three groups before treatment (P>0.05). 3 months and 6 months after treatment, the levels of FT3, FT4 in the three groups were significantly lower than those before treatment, and the level of TSH was significantly higher than that before treatment (P<0.05). 3 months and 6 months after treatment, the levels of FT3, FT4 in hypothyroidism group were significantly lower than those in the cure group and the remission group, the cure group was significantly lower than the remission group, the TSH level was significantly higher than that in the cure group and the remission group, and the cure group was significantly higher than the remission group (P<0.05). There was no significant difference in the levels of TRAb, IL-2 and IL-6 among the three groups before treatment (P>0.05). 3 months after treatment, the level of TRAb in the three groups was significantly higher than that before treatment (P<0.05); 6 months after treatment, there was no significant difference in the level of TRAb between the cure group and the hypothyroidism group (P>0.05), however, the level of TRAb in the remission group was higher than that in the hypothyroidism group, and the difference was statistically significant (P<0.05). 3 months and 6 months after treatment, the levels of IL-2 and IL-6 in the cure group and the hypothyroidism group were lower than those before treatment, while the remission group were higher than the hypothyroidism group, and the differences were statistically significant (P<0.05). **Conclusion:** TRAb, IL-2 and IL-6 can be used as indicators for evaluating Graves' disease after treatment by ¹³¹I. It is possible to detect the levels of three indicators before and after treatment so as to provide guidance for clinical prognosis evaluation.

* 基金项目:湖南省自然科学基金项目(2013JJ6268)

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(收稿日期:2018-01-07 接受日期:2018-01-31)

Key words: Graves disease; Iodine radioisotope; Thyrotropin receptor antibody; Interleukin-2; Interleukin-6

Chinese Library Classification(CLC): R581.1 **Document code:** A

Article ID: 1673-6273(2018)10-1969-04

前言

Graves 病又称为毒性弥漫性甲状腺肿,具有引发甲状腺功能亢进的功能,约占所有甲状腺功能亢进疾病中的 85%^[1]。相关报道认为,Graves 病的发生与机体的免疫功能紊乱有关,属于一种自身免疫性疾病^[23]。Graves 病患者主要临床表现包括甲状腺弥漫性对称性肿大以及甲状腺相关眼病、皮肤病等,对患者的生命健康造成了极大的威胁^[45]。目前,临床上主要采用¹³¹I 治疗,该治疗方式属于“破坏性治疗”,主要是通过破坏部分甲状腺组织,以达到消除甲亢的目的^[67]。然而,¹³¹I 治疗 Graves 病可能引起甲减等并发症,如何对治疗情况和患者预后进行准确诊断一直都是临床医师重点关注的问题。促甲状腺素受体抗体(thyrotropin receptor antibody, TRAb)是由 B 淋巴细胞分泌的针对 FSH 的自身抗体,是 Graves 病发生、发展的重要因子^[8]。而白细胞介素-2(interleukin-2, IL-2)、白细胞介素-6(interleukin-6, IL-6)则是机体重要的炎症因子,与 Graves 病发生也有密切关系^[9]。三者可能对 Graves 病¹³¹I 治疗预后判断有一定价值。鉴于此,本文通过研究 TRAb 及 IL-2、IL-6 在 Graves 病¹³¹I 治疗中的变化并分析其临床意义,旨在明确上述三项指标对 Graves 病¹³¹I 治疗后的影响,现作以下报道。

1 资料与方法

1.1 一般资料

选取 2015 年 8 月-2016 年 8 月,于我院接受¹³¹I 治疗的 Graves 病患者 112 例为研究对象。纳入标准:(1)所有患者均符合 Graves 病诊断标准;(2)住院后接受¹³¹I 治疗;(3)临床病历资料完整;(4)患者均为首次发病。排除标准:(1)合并心、肝、肾等脏器功能严重障碍者;(2)正参与其他研究者;(3)合并恶性肿瘤疾病者;(4)伴有精神疾病或沟通障碍者;(5)治疗依从性较差者和随访丢失者。按照第 6 个月的甲状腺功能检查结果不同分为治愈组 54 例,缓解组 21 例,甲减组 37 例。其中治愈组男 21 例,女 33 例,年龄 21-55 岁,平均(38.24±10.52)岁。缓解组男 7 例,女 14 例,年龄 22-53 岁,平均(38.72±10.62)岁。甲减组男 15 例,女 22 例,年龄 23-56 岁,平均年龄(38.66±10.65)岁。三组性别、年龄比较差异无统计学意义($P>0.05$),说明组间存在可比性。三组患者均签署了知情同意书,我院伦理委员会已批准本次研究。

1.2 诊断标准及分组标准

1.2.1 Graves 病诊断标准^[10] (1)存在甲亢相关体征;(2)甲状腺功能以及抗体检查结果显示游离 T3(free T3, FT3)、游离 T4(free T4, FT4)、促甲状腺激素(thyroid stimulating hormone, TSH)降低;(3)存在高代谢症候群;(4)非甲状腺炎导致的一过性甲亢。其中 FT3、FT4、TSH 正常水平范围分别是 3.1-6.8 pmol/L、12-22 pmol/L、0.27-4.20 μU/mL。

1.2.2 分组标准^[11] 治愈组:经过治疗后甲亢症状、体征完全消失,FT3、FT4、TSH 恢复正常;缓解组:经过治疗后甲亢症状、

体征完全好转,FT3、FT4 较治疗前下降,TSH 仍偏低;甲减组:治疗后无或有甲减症状,FT3、FT4 降低,TSH 升高。

1.3 方法

1.3.1 ¹³¹I 治疗 根据经验公式予以相应的剂量^[9]:经验公式=每克甲状腺组织所需剂量×甲状腺重量/最高摄¹³¹I 率。

1.3.2 甲状腺功能检测 分别于治疗前、治疗 3 个月后、治疗 6 个月后采集患者清晨空腹静脉血 5 mL,采用罗氏 Cobas e601 型全自动电化学发光仪与专用配套试剂进行 FT3、FT4 以及 TSH 的检测,具体操作严格按照试剂盒说明书进行。

1.3.3 TRAb、IL-2 与 IL-6 水平测定 分别于治疗前、治疗 3 个月后、治疗 6 个月后采集患者清晨空腹静脉血 5 mL,以 3000 r/min 离心 10 min,取上层血清外送艾迪康实验室检测 TRAb 水平。采用放射免疫分析法检测血清 IL-2 与 IL-6 水平,具体操作严格按照试剂盒说明书进行,试剂盒购自北京华英生物科技有限公司。

1.4 观察指标

所有患者治疗后通过门诊复查等方式进行随访 6 个月,分别比较三组患者治疗前后甲状腺功能指标,包括 FT3、FT4、TSH,记录 TRAb、IL-2、IL-6 水平。

1.5 统计学方法

采用 SPSS 20.0 进行统计分析,计量资料以($\bar{x} \pm s$)表示,行 t 检验,多组间比较采用 F 检验,计数资料以率表示,采用卡方检验,检验标准设置为 $\alpha=0.05$ 。

2 结果

2.1 三组患者治疗前后甲状腺功能指标对比

治疗前三组患者 FT3、FT4、TSH 水平比较差异无统计学意义($P>0.05$),治疗 3 个月、6 个月后三组患者 FT3、FT4 水平均明显低于治疗前,而 TSH 水平明显高于治疗前($P<0.05$)。治疗 3 个月、6 个月后甲减组 FT3、FT4 水平均明显低于治愈组、缓解组,治愈组又明显低于缓解组,TSH 水平明显高于治愈组、缓解组,治愈组又明显高于缓解组($P<0.05$)。见表 1。

2.2 三组患者治疗前后 TRAb、IL-2、IL-6 水平对比

治疗前三组患者 TRAb、IL-2、IL-6 水平比较差异无统计学意义($P>0.05$)。治疗 3 个月后三组患者 TRAb 水平均明显高于治疗前,治疗 6 个月后治愈组与甲减组患者 TRAb 水平与治疗前比较无统计学差异($P>0.05$),但缓解组患者 TRAb 水平高于甲减组,差异有统计学意义($P<0.05$)。治疗 3 个月、6 个月后,治愈组与甲减组患者 IL-2、IL-6 水平均低于治疗前,而缓解组高于甲减组($P<0.05$)。见表 2。

3 讨论

近年来随着国人生活水平的不断提高以及饮食习惯的逐渐改变,Graves 病的发生率正呈逐年上升趋势,严重影响人们的身心健康^[1213]。目前临床上对于 Graves 病主要采用抗甲状腺药物治疗、手术治疗、介入栓塞治疗和¹³¹I 放射治疗等方法

表 1 三组患者治疗前后甲状腺功能指标对比($\bar{x} \pm s$)Table 1 Comparison of thyroid function index of three groups before and after treatment ($\bar{x} \pm s$)

Groups	n	FT3(pmol/L)			FT4(pmol/L)			TSH(μ U/mL)		
		Before treatment	3 months after treatment	6 months after treatment	Before treatment	3 months after treatment	6 months after treatment	Before treatment	3 months after treatment	6 months after treatment
Cure group	54	26.10 $\pm$ 12.92	7.49 $\pm$ 3.01 ^{*ab}	5.32 $\pm$ 1.20 ^{*ab}	58.28 $\pm$ 20.61	21.33 $\pm$ 3.50 ^{*ab}	17.80 $\pm$ 3.01 ^{*ab}	0.01 $\pm$ 0.00	1.09 $\pm$ 0.36 ^{*ab}	2.18 $\pm$ 0.44 ^{*ab}
Remission group	21	24.61 $\pm$ 14.52	16.62 $\pm$ 5.13 ^{*a}	13.28 $\pm$ 3.71 ^{*a}	57.12 $\pm$ 26.46	39.55 $\pm$ 10.31 ^{*a}	27.41 $\pm$ 2.58 ^{*a}	0.01 $\pm$ 0.00	0.18 $\pm$ 0.10 ^{*a}	0.20 $\pm$ 0.10 ^{*a}
Hypothyroidism group	37	27.41 $\pm$ 12.32	2.65 $\pm$ 2.12 [*]	2.51 $\pm$ 1.05 [*]	60.78 $\pm$ 22.77	8.16 $\pm$ 6.70 [*]	8.09 $\pm$ 4.31 [*]	0.01 $\pm$ 0.00	38.27 $\pm$ 33.44 [*]	44.02 $\pm$ 33.05 [*]
F		1.984	18.046	22.336	2.332	21.087	28.096	0.000	28.922	36.436
P		0.328	0.000	0.000	0.296	0.000	0.000	1.000	0.000	0.000

Note: compared with before treatment, ^{*}P<0.05; compared with hypothyroidism group, ^aP<0.05; compared with remission group, ^bP<0.05.

表 2 三组患者治疗前后 TRAb、IL-2、IL-6 水平对比($\bar{x} \pm s$)Table 2 Comparison of levels of TRAb, IL-2 and IL-6 of three groups before and after treatment ($\bar{x} \pm s$)

Groups	n	TRAb(U/L)			IL-2(pg/mL)			IL-6(pg/mL)		
		Before treatment	3 months after treatment	6 months after treatment	Before treatment	3 months after treatment	6 months after treatment	Before treatment	3 months after treatment	6 months after treatment
Cure group	54	70.14 $\pm$ 10.58	261.25 $\pm$ 45.39 ^{*ab}	68.73 $\pm$ 9.05 ^{ab}	44.22 $\pm$ 6.39	34.81 $\pm$ 7.25 [*]	32.66 $\pm$ 3.81 [*]	163.21 $\pm$ 28.36	138.01 $\pm$ 16.29 [*]	128.90 $\pm$ 17.91 [*]
Remission group	21	76.01 $\pm$ 16.47	403.41 $\pm$ 84.23 ^{*a}	285.68 $\pm$ 51.26 ^{*a}	45.81 $\pm$ 7.68	42.50 $\pm$ 10.57 ^a	36.72 $\pm$ 6.52 ^{*a}	165.32 $\pm$ 18.01	160.88 $\pm$ 8.94 ^a	155.43 $\pm$ 10.33 ^{*a}
Hypothyroidism group	37	72.40 $\pm$ 11.48	275.21 $\pm$ 44.27 [*]	74.85 $\pm$ 12.06	44.51 $\pm$ 6.09	35.12 $\pm$ 6.74 [*]	33.77 $\pm$ 5.18 [*]	161.84 $\pm$ 19.01	138.87 $\pm$ 24.11 [*]	131.14 $\pm$ 17.19 [*]
F		1.984	18.046	22.336	2.332	21.087	28.096	0.000	28.922	36.436
P		0.328	0.000	0.000	0.296	0.000	0.000	1.000	0.000	0.000

Note: compared with before treatment, ^{*}P<0.05; compared with hypothyroidism group, ^aP<0.05; compared with remission group, ^bP<0.05.

[14,15]。其中 ^{131}I 治疗因操作简单、费用较低以及适用范围较广、疗效确切等优势开始被越来越多的医生以及患者所关注[16,17]。然而,该治疗方式在治疗后发生甲状腺机能减退症的风险较高。因此,寻找一种有效对 ^{131}I 治疗预后予以评估的方式显得尤为重要。目前临床上主要通过甲状腺相关激素的检测来评估 ^{131}I 治疗 Graves 病的效果,这种方法虽然评估准确,但由于甲状腺细胞被破坏后,有大量的甲状腺激素释放到血液中,其代谢需要一定的时间,仅通过甲状腺相关激素评定存在一定局限性[18]。有研究报道显示[19,20],TRAb 是直接作用于甲状腺细胞膜上的 TSH 受体的抗体,与 Graves 病发生的密切相关。而炎症反应也是 Graves 病发生、发展的重要因素,其中 IL-2、IL-6 是炎症反应的重要因子。

本研究通过对我院收治的 Graves 病患者对照研究发现,治疗 3 个月、6 个月三组患者 FT3、FT4 水平均明显低于治疗前,而 TSH 水平明显高于治疗前($P<0.05$)。治疗 3 个月、6 个月后甲减组 FT3、FT4 水平均明显低于治愈组、缓解组,治愈组又明显低于缓解组,TSH 水平明显高于治愈组、缓解组,治愈组又明显高于缓解组($P<0.05$)。这与陈茹芬等人的研究报道相一致[21], ^{131}I 治疗 Graves 病可显著改善患者甲状腺功能,且随着临床

治疗效果的不断提高,患者甲状腺功能改善情况越明显。因此,在临床工作中可通过 FT3、FT4 以及 TSH 水平进行联合检测,从而有助于临床 Graves 病患者接受 ^{131}I 治疗后的预后评估。此外,治疗 3 个月后三组患者 TRAb 水平均明显高于治疗前,治疗 6 个月后治愈组与甲减组患者 TRAb 水平与治疗前比较无统计学差异($P>0.05$),但缓解组患者 TRAb 水平高于甲减组($P<0.05$)。治疗 3 个月、6 个月后,治愈组与甲减组患者 IL-2、IL-6 水平均低于治疗前,而缓解组高于甲减组($P<0.05$)。说明治疗后 TRAb 水平先呈上升趋势,随后呈下降趋势,并于治疗 6 个月下降至治疗前水平,而缓解组下降幅度相对较小,其中 TRAb 可与 TSH 受体相结合,且能激活之后的信号转导系统,促使甲状腺滤泡细胞增生以及甲状腺激素合成分泌的增多[22,23]。而 IL-2 具有激活 T 细胞,并刺激其进入细胞分裂周期的作用,同时可在一定程度上增强 T 细胞的杀伤能力,于体外可与多种细胞因子共同诱导细胞毒性 T 细胞的产生,并增强其活性,间接参与了免疫反应[24,25]。IL-6 主要是通过增强 T 细胞表达 IL-2 与 IL-2 受体,进一步参与自身免疫性疾病的发生、发展过程[26,27]。这提示了 Graves 病患者在经 ^{131}I 治疗后,TRAb 首先会出现短期的升高,继而逐渐下降。分析原因,作者认为在 ^{131}I 治

疗后 TSH 受体分子会自被破坏的甲状腺滤泡细胞中释放入血,从而导致自身免疫反应加重,进一步促使 TRAb 发生一过性增高^[28]。与此同时,在 ¹³¹I 治疗后患者免疫学异常可得到逐步纠正,但恢复期较长,大约在 6 个月之后。

综上所述,Graves 病患者经过 ¹³¹I 治疗后 TRAb、IL-2、IL-6 发生变化,不同预后患者 TRAb、IL-2、IL-6 水平不同,治疗 6 个月后治愈组与甲减组患者 TRAb、IL-2、IL-6 水平均显著低于缓解组,治愈组患者 TRAb 低于甲减组,可通过联合检测上述三项指标治疗前后水平变化情况,从而为临床预后评估提供参考依据。

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