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卡马西平联合左甲状腺素对甲状腺功能减退症患者 血清 IGFBP-3、25(OH)D₃ 的影响 *

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摘要 目的:探讨卡马西平联合左甲状腺素对甲状腺功能减退症患者血清胰岛素样生长因子结合蛋白-3(IGFBP-3)、25羟维生素D₃(25(OH)D₃)的影响。**方法:**选择2017年5月~2018年6月本院接诊的103例甲状腺功能减退症患者进行研究,通过随机数表法分为观察组52例和对照组51例,对照组给予左甲状腺素口服治疗,观察组在对照组基础上联合卡马西平口服治疗,两组患者均连续治疗8周。比较两组临床疗效、治疗前后甲状腺功能、血清IGFBP-3和25(OH)D₃的变化情况及不良反应。**结果:**治疗后,观察组患者的临床疗效为94.23%,明显高于对照组患者的84.31%(P<0.05);观察组血清FT₃、TSH均明显比对照组低,FT₄明显高于对照组(P<0.05);两组患者治疗后IGFBP-3和25(OH)D₃的指标水平均高于治疗前,且观察组结果高于对照组(P<0.05);观察组不良反应总发生率为5.76%,低于对照组的13.73%,两组不良反应总发生率差异无统计学意义(P>0.05)。**结论:**卡马西平联合左甲状腺素对甲状腺功能减退症患者临床效果显著,可有效改善患者甲状腺功能,调节患者血清IGFBP-3和25(OH)D₃的表达水平,且不良反应少、安全性高,值得推广。

关键词:甲状腺功能减退症;卡马西平;左甲状腺素;胰岛素样生长因子结合蛋白-3;25羟维生素D₃;甲状腺素

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Efficacy of Carbamazepine Plus Levothyroxine on Serum IGFBP-3 and 25(OH)D₃ in Patients with Hypothyroidism*

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ABSTRACT Objective: To investigate clinical efficacy of carbamazepine plus levothyroxine on serum insulin-like growth factor binding protein-3 (IGFBP-3) and 25-hydroxyvitamin D₃ (25(OH)D₃) in patients with hypothyroidism. **Methods:** 103 patients with hypothyroidism admitted to our hospital from May 2017 to June 2018 were divided into the observation group (52 cases) and the control group (51 cases) by random number table method. The control group was given levothyroxine; and the observation group was combined with carbamazepine for oral treatment on the basis of the control group, and the patients in both groups were treated continuously for 8 weeks. Efficiency, thyroid function, serum IGFBP-3 and 25(OH)D₃ levels and adverse reactions were compared between the two groups before and after treatment. **Results:** After treatment, the clinical efficacy in the observation group was 94.23%, which was significantly higher than 84.31% in the control group (P<0.05); the serum FT₃ and TSH in the observation group were significantly lower than those in the control group, and FT₄ was significantly higher than that in the control group (P<0.05); after treatment, the levels of IGFBP-3 and 25(OH)D₃ in the two groups were higher than those before treatment, and the observation group were higher than the control group (P<0.05); the total incidence of adverse reactions in the observation group was 5.76%, which was lower than 13.73% in the control group, there was no significant difference between the two groups (P>0.05). **Conclusion:** The carbamazepine plus levothyroxine has a significant clinical efficiency on hypothyroidism. It can effectively improve the thyroid function of patients, regulate the expression level of IGFBP-3 and 25(OH)D₃ in patients' serum, with less adverse reactions and high safety. It is worthy of promotion.

Key words: Hypothyroidism; Carbamazepine; Levothyroxine; IGFBP-3; 25 hydroxyvitamin D₃; Thyroxine

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前言

甲状腺功能减退,是指血液当中甲状腺激素水平降低,或者甲状腺激素抵抗作用障碍出现的临床综合征^[1]。病因主要有

以下三个方面:^① 自身免疫性甲状腺疾病,比如自身免疫性甲状腺炎、桥本氏甲状腺炎、产后甲状腺炎等^[2,3];^② 由于甲状腺在手术过程中破坏过多而引起的甲减,另外碘过量也可以导致甲减;^③ 服用抗甲状腺药物,药物过量或者其他情况都有可能会

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出现甲状腺功能的衰退^[4,5]。

临幊上治疗该病的最常见药物左甲状腺素片，主要用于治疗先天性甲状腺功能减退、甲状腺切除术后的激素补充、单纯性甲状腺肿大以及慢性淋巴性甲状腺炎、甲状腺癌手术后的抑制治疗^[6]；卡马西平片是目前临幊上使用非常广泛的一种药物，主要作用是治疗癫痫病和缓解神经痛，其对症状性癫痫、部分性发作效果较好，对于三叉神经痛、枕神经痛、蝶腭神经痛等神经病理性疼痛止痛效果良好^[7,8]。该药能增强中枢神经系统中对去甲状腺激素的活性。但临幊上卡马西平联合左甲状腺素对该病的深入研究较少，因此，本文旨在探讨卡马西

平联合左甲状腺素对甲状腺功能减退症患者血清 IGFBP-3、25(OH)D₃ 的影响。

1 资料与方法

1.1 一般资料

选择本院 2017 年 5 月～2018 年 6 月收治的 103 例甲状腺功能减退症患者，通过随机数表法分为观察组 52 例和对照组 51 例，两组一般资料见表 1，组间比较差异无统计学意义 ($P > 0.05$)。

表 1 两组一般资料对比

Table 1 Comparison of general information between the two groups

Groups	Cases	Sex		Disease degree (case)			Age (year)	Course of disease (year)
		Man	Women	Light	Moderate	Severe		
The observation group	52	27(51.92)	25(48.08)	21(40.38)	25(48.08)	6(11.54)	55.47± 6.38	4.10± 1.24
The control group	51	28(54.90)	23(45.10)	19(37.25)	20(39.22)	12(23.53)	56.10± 6.40	4.09± 1.26

1.2 纳入排除标准

纳入标准：① 所有患者的病情均符合 Zielonka M 等^[9]在 2015 年《中央甲状腺功能减退症》的诊断标准：血清总 T₄、总 T₃、游离 T₃ 和游离 T₄ 的检查指标低于正常值；② 主要临床表现为：怕冷、少汗或无汗、颜面、眼睑浮肿、面色苍白、纳差、反应迟钝、记忆力减退等低代谢症状；③ 患者签署知情同意书。

排除标准：① 患者入院前接受过甲状腺相关的手术治疗；② 心、肝、肾等重要内脏器官功能性障碍；③ 免疫功能低下；④ 神经类疾病；⑤ 对研究药物卡马西平和左甲状腺素产生过敏反应。

1.3 方法

对照组患者给予口服左甲状腺素钠片（规格 50 μg*100 s/盒，厂家：Merck KGaA，国药准字 H20120405）治疗，左甲状腺素半衰期长，用法是：每日 1 次，空腹餐前半小时口服，初始剂量为 25～50 μg/d，且最高药物剂量不能超过 100 μg/d，替代治疗的左甲状腺素钠片剂量由患者的甲状腺功能减退的程度来决定。观察组患者给予口服卡马西平（规格 0.2 克，厂家：北京诺华制药有限公司，国药准字 H11022279）治疗，用法：初始剂量每次 100～200 mg，每天 1～2 次；逐渐增加剂量直至最佳疗效（通常为每次 400 mg，每天 2～3 次）。两组患者均连续治疗 8 周。

1.4 观察指标

临床疗效：比较两组临床疗效：临床疗效分为显效、有效、无效三类，评价标准参照欧洲内分泌学杂志修订的甲状腺功能标准方案进行评判^[10,11]；① 显效：治疗后患者临床症状，包括疲乏、记忆力减退、畏寒及病体特征明显得到明显改善，甲状腺功能得到明显的恢复；② 有效：治疗后，患者临床症状有所改善，

甲状腺功能得到一定的改善；③ 无效：对临床治疗没有反应，临床症状甚至有恶化的趋势；临床总有效率 = 显效率 + 有效率。

甲状腺功能：治疗前后抽取患者 10 mL 空腹静脉血，检测游离三碘甲状腺原氨酸 (FT₃)、游离甲状腺素 (FT₄)、促甲状腺激素 (TSH)。FT₃ 采用磁分离酶联免疫法进行检测，FT₄ 采用酶联免疫吸附法进行检测，TSH 采用电化学发光免疫法进行检测；所使用的试剂盒均由北京百奥莱科技有限公司提供。

血清 IGFBP-3 和 25(OH)D₃：治疗前后将待检的血清留取 5 mL，采用双抗体夹心法 ELISA 检测血清 IGFBP-3 和 25(OH)D₃ 的指标水平；所使用的试剂盒由北京百奥莱科技有限公司提供。

1.5 统计学方法

以 SPSS18.0 软件包处理，正态分布计量资料用 $(\bar{x} \pm s)$ 表示，组间比较使用独立样本 t 检验，组内比较使用配对样本 t 检验，计数资料以“率”表示，行 χ^2 检验， $P < 0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组临床疗效比较

观察组临床疗效明显高于对照组 ($P < 0.05$)，见表 2。

2.2 两组甲状腺功能比较

治疗前，两组血清 FT₃、TSH、FT₄ 比较无显著差异 ($P > 0.05$)；两组治疗后血清 FT₃、TSH、FT₄ 较治疗前均显著改善 ($P < 0.05$)，观察组血清 FT₃、TSH 均明显比对照组低，FT₄ 明显高于对照组 ($P < 0.05$)，见表 3。

表 2 两组临床疗效比较 [n(%)]

Table 2 Comparison of the clinical efficacy between two groups[n(%)]

Groups	Cases	Markedly effective	Valid	Invalid	Total efficiency
The observation group	52	37(71.16)	12(23.08)	3(5.76)	49(94.24)*
The control group	51	25(49.02)	18(35.29)	8(15.69)	43(84.31)

Note: Compared with the control group, * $P < 0.05$.

表 3 两组甲状腺功能比较($\bar{x} \pm s$)Table 3 Comparison of thyroid function between the two groups($\bar{x} \pm s$)

Groups	Cases	Time	FT ₃ (pmol/L)	TSH(mU/L)	FT ₄ (pmol/L)
The observation group	52	Before treatment	1.45± 0.53	26.90± 13.98	5.23± 1.60
		After treatment	3.03± 1.18*#	3.08± 1.15*#	10.71± 1.38*#
The control group	51	Before treatment	1.42± 0.67	26.85± 14.06	5.19± 1.57
		After treatment	4.55± 1.20*	6.39± 2.21*	6.79± 1.42*

Ps: Compared with before treatment, *P<0.05; compared with the control group, #P<0.05.

2.3 两组血清 IGFBP-3 和 25(OH)D₃ 的比较

治疗前,且观察组结果高于对照组(P<0.05),见表 4。

两组患者治疗后 IGFBP-3 和 25(OH)D₃ 的指标水平均高于表 4 两组血清 IGFBP-3 和 25(OH)D₃ 的比较($\bar{x} \pm s$)Table 4 Comparison of serum IGFBP-3 and 25(OH)D₃ between the two groups($\bar{x} \pm s$)

Groups	Cases	Time	IGFBP-3(μg/L)	25(OH)D ₃ (μmol/L)
The observation group	52	Before treatment	1.17± 0.33	43.64± 6.15
		After treatment	4.18± 0.56*#	71.45± 10.20*#
The control group	51	Before treatment	1.19± 0.31	43.59± 6.17
		After treatment	3.65± 0.42*	62.64± 9.71*

Ps: Compared with the before treatment, *P<0.05; compared with the control group, #P<0.05.

2.4 两组不良反应比较

观察组不良反应总发生率为 5.76%, 低于对照组的

13.73%, 两组不良反应总发生率比较差异无统计学意义 (P>

0.05), 见表 5。

表 5 两组不良反应比较[n(%)]

Table 5 Comparison of adverse reactions between the two groups[n(%)]

Groups	Cases	Headache	Hyperhidrosis	Arrhythmia	Total efficiency
The observation group	52	1(1.92)	1(1.92)	1(1.92)	3(5.76)*
The control group	51	2(3.92)	3(5.88)	2(3.92)	7(13.73)

Ps: Compared with the control group, *P<0.05.

3 讨论

甲状腺功能减退症是临幊上常见的内分泌系统疾病,主要是由于甲状腺激素合成、分泌减少所致,或其生理效应不足所诱发的机体代谢降低。患者的病理特征多表现为粘多糖堆积于组织及皮肤,造成粘液性水肿^[13,14]。相关流行病学统计甲状腺功能减退症的患病率为 0.8%~1.0%,且近年来还有着逐年增长的趋势,患者发病后临床症状多表现为以下六个方面:^①容易感到疲劳、畏冷、体重升高、记忆力日渐衰退、日间嗜睡、情绪低落、排便不畅、经期不调等,通过体检可表现为皮肤干燥、面色苍白,且眼睑、手部皮肤处呈浮肿状态,并有脱发、声音嘶哑等表现^[15,16];^②出现肌肉和关节的相关症状,表现为乏力或暂时性肌肉强直、痉挛等,且常感到肌肉疼痛等,部分肌肉甚至有进行性萎缩表现^[17,18];^③对心电系统有影响,主要是由于粘液性水肿,可对患者心肌功能产生不利影响,造成心室排血量降低、心动过缓等,加上心肌间质水肿等因素,可致患者出现非特异性纤维重症、心包积液增大、心室扩张等,若得不到及时的控制,极易进展成为冠心病^[19,20];^④对血液系统有影响,由于甲状腺激素水平的降低,容易导致机体血红蛋白合成障碍,影响肠道吸收铁功能,造成铁缺乏^[21];^⑤对消化系统有影响,患者可出现腹

胀、便秘、厌食等表现,病情严重的患者甚至发生麻痹性肠梗阻、黏液水肿巨结肠等^[22,23];^⑥对内分泌系统有影响,在女性患病人群中多表现为月经不调、月经过多甚至闭经等,长期性的甲状腺激素减退还可出现垂体增生、血清泌乳素增加等,对患者生活质量有着严重影响^[24]。因此对于甲减的临幊治疗应给予足够的重视。

左甲状腺素片是外源性的替代甲状腺素的一种药品,该药是人工合成的四碘甲状腺原氨酸,活性相当于生理甲状腺素,与自然分泌的甲状腺素相同,在外周器官中被转化为 T₃,然后通过与相应的受体结合,发挥其特定作用^[25]。主要用于甲状腺功能减退的替代治疗、治疗非毒性的甲状腺肿、甲状腺肿切除术后预防甲状腺肿复发、甲状腺功能亢进症的辅助治疗等。左甲状腺素钠片在人体内可以转变为三碘甲状腺氨酸,具有维持人体正常生长发育、促进代谢、增加产热的作用。过度的服用会造成患者心悸、心率异常、呕吐、腹泻、肌肉痉挛、体重下降等症状^[26,27]。卡马西平属于临幊常见的精神类药物,它的药理机制主要是降低神经元膜上的钠和钙的通透性,从而降低细胞的兴奋性,其主要作用有:^①广谱抗癫痫作用,对各类癫痫发作都有效,尤其对精神运动性发作效果最好^[28];^②治疗神经痛,如三叉神经痛、舌咽神经痛、外伤后神经痛、带状疱疹后神经痛、糖尿病

病及多发性硬化引起的周围神经痛,还可用于三叉神经痛缓解后的长期预防治疗;^① 预防或治疗狂躁性抑郁症;^② 抗心律失常,可治疗地高辛中毒所致心律失常;^③ 治疗酒精戒断综合征;^④ 治疗中枢性部分性尿崩症、不宁腿综合征、偏侧面肌痉挛等。近年来有研究发现,卡马西平能增强下丘脑释放促甲状腺激素,从而调节甲状腺分泌甲状腺激素^[29,30]。但目前关于卡马西平在甲状腺功能减退症的报道较少。

本研究结果显示,采用卡马西平联合左甲状腺素联合治疗的患者的临床疗效和甲状腺功能各指标水平,均明显高于单独使用左甲状腺素治疗的患者,通过分析是由于联合用药且可以促进机体对甲状腺细胞生长、甲状腺激素合成并且可调控分泌。卡马西平通过中枢神经系统对下丘脑产生调节作用,增加下丘脑分泌三肽激激素(TRH)的能力,从而进一步促进TSH的释放及合成等,而TRH神经元会受到神经系统其余部位的调节,将环境因素和TRH神经元之间相互联系,并和腺垂体连接,从而增加TRH的分泌,再加强TSH的释放能力,进一步减少T4、T3的表达,改善机体代谢消耗,帮助了甲状腺功能的修复^[31,32]。此外两组患者治疗后IGFBP-3和25(OH)D₃的指标水平均高于治疗前,且接受卡马西平联合左甲状腺素联合治疗的患者IGFBP-3和25(OH)D₃的指标水平均高于对照组,通过分析,IGFBP-3是人体内循环中较强的结合蛋白,能够与血清中游离的IGF-3受体相互结合,当服用卡马西平后,通过肠道吸收可以减少血清中游离的IGF-3受体的浓度,增强IGF-3受体的活性和表达,从而提高患者血清中IGF-3的水平^[33,34]。卡马西平可以从肠道和小肠上皮细胞间质直接吸收进入血液循环,更为有效地增加血液中25-羟基维生素D₃水平^[35]。与此同时,接受卡马西平联合左甲状腺素联合治疗的患者不良反应总发生率为5.76%明显低于对照组13.73%,显示联合用药并发症少,安全性高的特点。考虑参与该方案研究的样本量较少、住院治疗的时间较短等因素,因此对于该研究方案还有待联合多中心进一步长期的探讨。

综上所述,卡马西平联合左甲状腺素对甲状腺功能减退症患者临床效果显著,可有效改善患者甲状腺功能,调节患者血清IGFBP-3和25(OH)D₃的表达水平,且不良反应少、安全性高,值得推广。

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