

临床研究论著

89例垂体柄中断综合征患者垂体-甲状腺轴激素特点分析

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摘要: **目的** 分析垂体柄中断综合征 (pituitary stalk interruption syndrome, PSIS) 患者垂体-甲状腺轴激素特点。**方法** 回顾性分析解放军总医院自2000-2013年收治的89例PSIS患者垂体-甲状腺轴激素特点。**结果** 89例中71例(79.78%)发生中枢性甲减, 血清促甲状腺激素 (thyroid stimulating hormone, TSH) 为 (5.42 ± 3.67) mU/L; 18例甲状腺功能正常, TSH为 (3.66 ± 1.50) mU/L。中枢性甲减患者中29例(40.85%)TSH高于正常 [(8.79 ± 3.17) mU/L], 38例(53.53%) 在正常范围内 [(3.42 ± 1.30) mU/L], 4例(5.63%) 低于正常范围 [(0.02 ± 0.01) mU/L]; TSH升高组血清游离T4 (serum free T4, FT4) 较TSH正常组略低, 但差异无统计学意义 [(7.90 ± 1.38) pmol/L vs (8.08 ± 1.42) pmol/L, $P > 0.05$]。中枢性甲减伴TSH升高患者行甲状腺激素替代治疗后TSH降至正常 [(7.24 ± 0.98) mU/L vs (1.67 ± 1.51) mU/L]。PSIS患者TSH水平与垂体高度及垂体柄状态不相关 ($P > 0.05$)。**结论** PSIS所致中枢性甲减患者TSH升高比例更高, 升高幅度更大。PSIS患者TSH升高与垂体柄的状态及垂体前叶高度无关, 其原因可能为甲状腺激素的反馈抑制作用减弱致使垂体TSH细胞分泌了无生物活性的TSH。

关键词: 垂体柄中断综合征; 中枢性甲减; 促甲状腺激素

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Characteristics of pituitary-thyroid axis in patients with pituitary stalk interruption syndrome: An analysis of 89 cases

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Abstract: Objective To analyze the characteristics of thyrotrophic axis and the influencing factors in patients with pituitary stalk interruption syndrome (PSIS). **Methods** Clinical data about 89 patients with PSIS admitted to Chinese PLA General Hospital from 2000 to 2013 were retrospectively analyzed. **Results** Of the 89 patients, 71 patients (79.78%) were diagnosed with central hypothyroidism based on FT4 levels lower than 10.4 pmol/L with the TSH level of 5.42 ± 3.67 mU/L. The FT4 levels in the remaining 18 patients with no central hypothyroidism were close to the lower limit of reference range and the TSH was 3.66 ± 1.50 mU/L. Of the 71 central hypothyroidism patients, TSH level in 29 patients (40.85%) was higher than 5.5 mU/L with a mean \pm SD of 8.79 ± 3.17 mU/L, 38 patients (53.53%) was in the normal range with a mean \pm SD of 8.79 ± 3.17 mU/L and 4 patients (5.63%) was lower than the normal level with a mean \pm SD of 0.02 ± 0.01 mU/L. The FT4 levels of the higher TSH group were slightly higher than that of normal TSH group, but there was no differences in statistics (7.90 ± 1.38 pmol/L vs 8.08 ± 1.42 pmol/L, $P > 0.05$). Elevated TSH level in the PSIS patients with central hypothyroidism decreased to normal after hormone replacement therapy (7.24 ± 0.98 mU/L vs 1.67 ± 1.51 mU/L). TSH Level had no relationship with pituitary height and pituitary stalk ($P > 0.05$). **Conclusion** The ratio and amplitude of elevated TSH in PSIS induced central hypothyroidism patients are higher than that of the other causes of central hypothyroidism. The TSH level in PSIS patients is independent of the height of anterior pituitary and status of pituitary stalk, the possible reason is reduced thyroid hormone feedback inhibition stimulated the secretion of TSH with no biological activity.

Keywords: pituitary stalk interruption syndrome; central hypothyroidism; thyroid stimulating hormone

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垂体柄中断综合征 (pituitary stalk interruption syndrome, PSIS) 是指由于遗传因素导致垂体柄缺如合并垂体后叶异位, 下丘脑分泌的激素不能通过垂体柄输送到垂体所致的临床系列征候群^[1-2]。PSIS 可以表现为单纯生长激素缺乏, 也可以表

现为多种垂体前叶激素缺乏, 而垂体后叶激素正常^[3-4]。在临床工作中, 我们发现席汉综合征、垂体瘤等疾病导致中枢性甲减患者的促甲状腺激素(thyroid stimulating hormone, TSH)多在正常范围内, TSH升高的患者相对少见, 而PSIS所致中枢性甲减的患者TSH高于正常范围的比例明显高于其他类型中枢性甲减的患者, 有的患者TSH甚至超过10 mU/L, 易误诊为原发性甲减。随着对PSIS认识的增加, 关于该疾病临床和内分泌激素特征的总结报道也越来越多, 但关于垂体-甲状腺轴的激素特点及影响因素的探讨尚不深入^[5-6]。本研究通过分析89例PSIS患者垂体-甲状腺轴激素特点, 进一步提高临床医生对该疾病的认识。

对象和方法

1 对象 解放军总医院2000-2013年通过MRI影像学检查、垂体前叶功能评价以及临床特征相符的PSIS患者共89例。

2 方法 收集所有患者的临床特征。PSIS患者中血清FT4水平 < 10.4 pmol/L(正常范围 $10.4 \sim 24.3$ pmol/L)定义为PSIS相关性中枢性甲减。胰岛素样生长因子-1(insulin-like growth factor-1, IGF-1)和低血糖兴奋试验、吡啶斯的明兴奋试验、精氨酸兴奋试验评估垂体-生长激素轴功能; 睾酮、雌二醇基础值和促性腺激素释放激素(gonadotropin-releasing hormone, GnRH)兴奋试验评估垂体-性腺轴功能; 促肾上腺皮质激素(adrenocorticotrophic hormone, ACTH)、皮质醇基础值和低血糖兴奋试验评估垂体-肾上腺轴功能。垂体磁共振扫描+动态增强评估患者的垂体高度及垂体柄状态。垂体MRI显示垂体柄纤细或缺如、垂体前叶发育不良、垂体后叶高信号异位同时伴有一种或多种垂体前叶激素缺乏定义为PSIS。

3 统计学处理 所有数据均用SPSS17.0软件分析, 计量数据用 $\bar{x} \pm s$ 表示, 两组间比较采用 t 检验, 影响因素预测采用Logistic回归分析, $P < 0.05$ 为差异有统计学意义。

结果

1 一般资料 89例PSIS患者中男性79例, 女性10例, 平均年龄(20.46 ± 6.09)岁。多数患者因生长发育迟缓就诊, 平均身高(147.63 ± 16.31) cm, 平均体质量(45.46 ± 16.23) kg。所有患者均伴有生长激素缺乏; 促肾上腺皮质激素缺乏患者67例, 占75.28%; 促性腺激素缺乏患者77例, 占86.52%。

患者均为非近亲结婚, 足月分娩, 均无家族史。

2 PSIS患者垂体-甲状腺轴激素特点 89例PSIS患者中71例(79.78%)发生中枢性甲减, 18例(20.22%)甲状腺功能正常, 但FT4在正常低限。中枢性甲减患者的TSH均值高于甲状腺功能正常的患者($P < 0.05$)(表1)。中枢性甲减的PSIS患者中29例(40.85%)TSH高于正常范围, 38例(53.53%)TSH在正常范围内(平均水平高于正常中线值), 仅4例TSH水平低于正常。TSH升高组FT4较TSH正常组略低, 但差异无统计学意义($P > 0.05$)(表2)。中枢性甲减伴TSH升高患者行甲状腺激素替代治疗后TSH降至正常[(7.24 ± 0.98) mU/L vs (1.67 ± 1.51) mU/L]。见图1。

3 PSIS患者TSH水平相关因素分析 以TSH升高为因变量, 垂体前叶高度和垂体柄状态为自变量, 行Logistic回归分析, 结果未提示垂体前叶高度和垂体柄状态与TSH水平相关($P > 0.05$)。

表1 89例PSIS患者垂体-甲状腺轴激素特点
Tab.1 Characteristics of thyrotrophic axis in 89 PSIS patients ($\bar{x} \pm s$)

| | n (%) | FT4 (pmol/L) | TSH (mU/L) |
|-------|-----------|------------------|-------------------|
| FT4 ↓ | 71(79.78) | 7.90 ± 1.45 | 5.42 ± 3.67 |
| FT4 → | 18(20.22) | 12.38 ± 2.07 | $3.66 \pm 1.50^*$ |

* $P < 0.05$, vs FT4 ↓

表2 71例中枢性甲减PSIS患者垂体-甲状腺轴激素特点
Tab.2 Characteristics of thyrotrophic axis in 71 PSIS patients with central hypothyroidism ($\bar{x} \pm s$)

| | n (%) | TSH (mU/L) | FT4 (pmol/L) |
|-------|-----------|-----------------|-------------------|
| TSH ↑ | 29(40.85) | 8.79 ± 3.17 | 7.90 ± 1.38 |
| TSH → | 38(53.53) | 3.42 ± 1.30 | $8.08 \pm 1.42^*$ |
| TSH ↓ | 4(5.63) | 0.02 ± 0.01 | 6.15 ± 1.44 |

* $P > 0.05$, vs TSH ↑

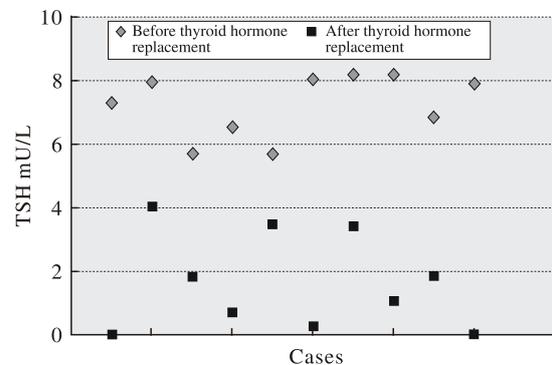


图1 中枢性甲减PSIS患者甲状腺激素替代前后TSH变化
Fig.1 Changes of TSH in PSIS patients with central hypothyroidism before and after thyroid hormone replacement

讨论

PSIS是近几年随着影像学技术的发展而被大

家逐渐认知的一种少见病,其典型影像学特征为垂体柄纤细或缺如,垂体前叶发育不良,垂体后叶异位。PSIS可以仅表现为生长激素缺乏,也可以表现为多种垂体前叶激素缺乏,而垂体后叶功能不受影响。郭清华等^[7]的报道显示,PSIS男性多发,多数患者为臀位产,主要就诊原因为生长迟缓和第二性征发育不良;伴有3种以上垂体前叶激素缺乏的患者高达92.7%,生长激素、促性腺激素、促肾上腺皮质激素、促甲状腺激素缺乏的比例分别为100%、95.8%、81.8%和76.3%,所有患者的垂体后叶功能均正常;垂体MRI显示平均垂体前叶高度为28 mm,垂体柄纤细或缺如。

中枢性甲减是由于下丘脑或垂体病变引起的促甲状腺激素释放激素(thyrotropin releasing hormone, TRH)或者TSH产生和分泌减少所致的甲减,中枢性甲减患者的TSH可以降低,也可以正常,甚至升高^[8-9]。Alexopoulou等^[10]曾报道大部分中枢性甲减患者的TSH在正常范围内,8%的患者TSH降低,8%的患者TSH升高,但升高的患者TSH绝对值一般不超过10 mU/L。本组PSIS所致中枢性甲减患者中TSH升高比例高达40.85%,且平均值为 (8.79 ± 3.17) mU/L,其升高的比例及幅度远大于前述文献报道的其他原因所致中枢性甲减,结合本组资料分析可能原因如下:1)垂体柄与垂体前叶发育状态:垂体TSH细胞分泌TSH受下丘脑所分泌TRH的影响,当垂体柄中断时,下丘脑分泌的TRH无法通过门脉系统到达垂体,刺激垂体TSH细胞分泌TSH,因此我们设想垂体柄的状态,垂体柄纤细还是完全中断会影响患者的TSH水平;垂体前叶是多种内分泌激素的起源部位,垂体发育欠佳时垂体前叶激素的分泌会受影响,TSH亦不例外^[11]。TRH兴奋试验有助于鉴别PSIS致中枢性甲减的病变来源于垂体柄还是垂体前叶^[10]。垂体性甲减时TSH对TRH刺激无反应,而下丘脑性甲减时TSH对TRH刺激反应正常。PSIS患者既有垂体柄中断又有垂体发育不良,两者中哪个更占优势目前尚不清楚,TRH兴奋试验有助于鉴别,但目前国内无TRH应用于临床,限制了该实验的开展,因此不能以此来鉴别病变来源。为此我们用Logistic回归分析评估TSH升高与垂体柄状态及垂体前叶高度之间的相关性。但本组资料Logistic回归分析结果显示,TSH升高与垂体柄状态及垂体前叶高径不相关。2)甲状腺激素的反馈抑制作用:TSH的分泌除受TRH的调控外,另外一个重要的调控因素就是甲状腺激素的负反馈作用。本组资料

显示,PSIS患者中甲减患者的TSH明显高于甲状腺功能正常的患者;在中枢性甲减的患者中40.85%的患者TSH升高,且TSH升高组FT4较TSH正常组略低,即在PSIS患者中FT4越低,TSH就越高,提示甲状腺激素对TSH的负反馈作用在TSH分泌中起了至关重要的作用。PSIS伴中枢性甲减的患者行甲状腺激素替代治疗后TSH均能降至正常范围,也验证了这一假设。3)无生物活性的TSH:伴TSH升高的中枢性甲减患者的甲减状态并未因TSH升高而得到相应改善,提示检测到血液中的部分TSH无生物活性,可能是因为甲状腺激素减少后,垂体TSH细胞代偿性地大量分泌TSH,因合成时间短、数量大,在TSH的合成过程中发生错误,导致无生物活性的TSH分泌至血液中。

综上所述,PSIS所致中枢性甲减患者TSH升高的比例及幅度均大于文献报道的其他原因所致中枢性甲减。PSIS患者TSH的升高与垂体柄的状态及垂体前叶高度无关,其可能原因为甲状腺激素的反馈抑制作用减弱而致使垂体TSH细胞分泌了无生物活性的TSH。

参考文献

- 1 Vijayanand P, Mahadevan S, Reddy N, et al. Pituitary stalk interruption syndrome (PSIS) [J]. *Indian J Pediatr*, 2007, 74 (9): 874-875.
- 2 Barbeau C, Jouret B, Gallegos D, et al. Pituitary stalk transection syndrome [J]. *Arch Pediatr*, 1998, 5 (3): 274-279.
- 3 Ioachimescu AG, Hamrahian AH, Stevens M, et al. The pituitary stalk transection syndrome: multifaceted presentation in adulthood [J]. *Pituitary*, 2012, 15 (3): 405-411.
- 4 Den Ouden DT, Kroon M, Hoogland PH, et al. A 43-year-old male with untreated panhypopituitarism due to absence of the pituitary stalk: From dwarf to giant [J]. *J Clin Endocrinol Metab*, 2002, 87 (12): 5430-5434.
- 5 郭清华, 陆菊明, 窦京涛, 等. 垂体柄中断综合征五例分析并文献复习 [J]. *中华内分泌代谢杂志*, 2008, 24 (5): 480-482.
- 6 Pham LL, Lemaire P, Harroche A, et al. Pituitary stalk interruption syndrome in 53 postpubertal patients: factors influencing the heterogeneity of its presentation [J]. *PLoS One*, 2013, 8 (1): e53189.
- 7 Guo QH, Yang Y, Mu YM, et al. Pituitary stalk interruption syndrome in Chinese People: clinical characteristic analysis of 55 cases [J]. *PLoS One*, 2013, 8 (1): 1-9.
- 8 Muthukrishnan J, Harikumar KV, Verma A, et al. Central hypothyroidism [J]. *Indian J Pediatr*, 2010, 77 (1): 94-96.
- 9 Yamada M, Mori M. Mechanisms related to the pathophysiology and management of central hypothyroidism [J]. *Nat Clin Pract Endocrinol Metab*, 2008, 4 (12): 683-694.
- 10 Alexopoulou O, Beguin C, De Nayer P, et al. Clinical and hormonal characteristics of central hypothyroidism at diagnosis and during follow-up in adult patients [J]. *Eur J Endocrinol*, 2004, 150 (1): 1-8.
- 11 Eisenberg MC, Santini F, Marsili AA, et al. TSH regulation dynamics in central and extreme primary hypothyroidism [J]. *Thyroid*, 2010, 20 (11): 1215-1228.