Investigation of hormonal profile in 19 patients with cluster headache

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Abstract

Introduction: Current evidences has shown hypothalamic dysfunction in cluster headache (CH). CH is so explosive that finding any relationship between this type of headache and different hormones could help to its better prevention and treatment.

Methods and Materials: This study was performed in Isfahan University of medical sciences from June 2006 to June 2007 among 131 CH patients. Data was obtained from 19 of these cases randomly.

Results: In our study we found statistically significant relation among cortisol, thyroid hormone (T3) and follicle stimulating hormone (FSH). Among 19 CH Patients, 11 cases had low FSH level (57.9%) and three cases (15.8%) had high values. One case (5.3%) had low serum T3 level. 52.6% (10cases) demonstrated low cortisol level. Other results for testosterone, T4, TSH and LH were not statistically significant.

Conclusion: The altered hormone level (cortisol, FSH, T3) is a further indication of permanent hypothalamic disturbance in cluster headache and might be a clue to prevent, or treat this severe headache by hormonal modification.

Abbreviations: CH cluster headache, FSH follicle stimulating hormone, LH luteinizing hormone, TSH thyroid stimulating hormone, T3 and T4 thyroid hormones.

Key words: cluster headache, hypothalamus dysfunction, gonadotropins, cortisol, thyroid hormones.

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Introduction
The etiology of cluster headache (CH) is still unknown, but the finding from neuroimaging studies\(^1,2\) as well as the effect of deep brain stimulation,\(^3\) have demonstrated the involvement of the hypothalamus, particularly in active headache periods.

The cyclic nature of CH and dysautonomic signs during attacks may suggest a dysfunction in the central nervous system related to rhythmic regulating centers.\(^4-12\) These patterns suggest that the body’s biological clock is involved. Human’s biological clock is in hypothalamus.

Current evidence points to the hypothalamic dysfunction with increased metabolic hyperactivity in the region of the suprachiasmatic nucleus as being important in the genesis of CH. The hypothalamus is at the crossroads of two major endocrine pathways: a horizontal retinohypothalampineal pathway entraining the pineal gland to day-night cycles, and the (anatomically) vertically oriented hypothalamic anterior pituitary axis, responsible for hormonal control.\(^13,14\) More recently, positron emission tomography (PET) and functional MRI studies have demonstrated that the ipsilateral posterior inferior hypothalamus is activated during CH attacks and is structurally asymmetric in CH patients.\(^1,2\) Thus, the posterior hypothalamic area was chosen first by Leone et al. as a target for stereotactic neurostimulation leading to a profound relief in the severity and frequency of attacks in chronic CH patients.\(^15,16\) For years it has been recognized that male cluster headache patients appear over masculinized. Addressing this issue, Sjaastad et al.\(^17\) and Polleri\(^18\) suggested that a peripheral hypersensitivity to circulating hormone may explain the “hyper”-masculinized features in patients with CH. Recent neuroendocrine and sleep studies now demonstrate an association between gonadotropin and corticotropin levels.\(^19\) Accumulated evidence suggests sympathetic dysfunction—embodied in the Horner sign so commonly seen in the cluster headache as a necessary ingredient in the inspection of the cluster headache. Sympathetic dysfunction is now thought to be associated with the hypercortisolism, hypotestosteronism, and lower-than-normal melatonin levels in the active cluster patients.\(^20\) CH is infrequent, but so explosive, recurring in rapid succession that many afflicted men have committed suicide;\(^21\) on the other hand this kind of survey has never been done before in our country, so it seems very important to find any physiological changes in these patients. By finding a definite relationship between CH and different hormones, we could prevent or treat this type of headache much better. According to this point of view, we decided to evaluate different hormones in cluster headache patients.
Methods and Materials
Subjects: In our previous study, 131 patients with definite cluster headache were selected randomly from patients who had gone to Alzahra hospital, Noor hospital and other neurologist offices, from June 2006 to June 2007. Using MRI, CT scan and blood sample studies, other diagnoses were excluded. Those selected had definite CH criteria on the basis of the International Classification of Headache Disorders. Patients with non-definite diagnosis or another diagnosis were not included in our study. All the cases were healthy and took no chronic medication. They were: 120: male, 11: female, 68.7%: 20-40 years old (mean age: 35-55 years: range: 18-63). 19 male cases were chosen randomly among these 131 patients.

Protocol:
All subjects were fasting from 8:00h, Venus blood samples were collected in the morning for testosterone, T3, T4, TSH, LH, FSH and cortisol in. One LH and one FSH level were missed during the measurement.

Assays:
All samples were analyzed at the laboratory of Khaje Nasir, huddling being done according to accredited, commercial methods. Data was determined by Radio Immuno Assay method. The company that produces the kits is Iran Kavoshyar associated with Immuno Tech company.

Statistics:
This study was performed in Isfahan University of Medical Sciences. Data was analyzed using SPSS for repeated measurement design. Normal values, upper and lower normal limits were estimated for each hormone by Npar-Test. The results were compared with P value of 0.05 by T-Test.

Results
Testosterone:
In our study 15.8% of patients had low and the same (3 cases), had high serum level and 68.4% (13 cases) had normal values, that according to P value of 0.278, was not statistically significant (0.278>0.05).

Cortisol:
10 cases (52.6%) had low cortisol levels. 9 cases (47.4%) had normal values. It was significant due to P value of 0.000 (0.000<0.05).
LH:
14 cases (73.7%) had normal values and 4 cases (21.1%) had low level LH. This result was not statistically significant too (0.287 > 0.05).

FSH:
11 (57.9%) cases showed low levels and 3 (15.8%) cases had high levels. 4 cases (21.1%) had normal level. These results were significant (0.046 < 0.05) (figure 2).

T3, TSH, T4:
17 cases (89.5%) had normal TSH values and 2 cases (10.5%) had high levels, that wasn’t significant due to p value of 0.175 (0.175 > 0.05). 18 cases (94.7%) and 9 cases (47.4%) had normal T3 and T4 levels. 1 case (5.3%) had low serum T3 level. 4 cases (21.1%) had low and 6 cases (31.6%) had high T4 levels. The results were significant for T3 but not significant for T4 (0.004 < 0.05, 0.899 > 0.05). (Figure 3)
Discussion

We could not find any significant relation between serum level of testosterone, LH, TSH, T4 and cluster headache. However, there were significant relations between other hormones (cortisol, T3, FSH). Low testosterone levels had been noted in patients with episodic and chronic CH as far back as three decades ago.\(^{(24-27)}\) Three of the 10 chronic CH patients in Nelson’s\(^{(25)}\) study had low testosterone levels, which he attributed to opioid analgesic use. Another study found low testosterone levels in episodic CH and not chronic CH; this was attributed to the disruption of REM sleep.\(^{(26)}\) The circadian changes in testosterone and cortisol secretion and morning luteinizing level were evaluated in nine CH patients in one survey, the results of which showed reduction of testosterone levels and increased cortisol concentration, but LH was similar in CH and control groups. It was suggested that stress accompanying the attack expectancy in the active phase is the mechanism behind the elevated plasma cortisol level.\(^{(28)}\) Accordingly Murialdo et al.\(^{(27)}\) examining testosterone, its metabolites, 17 B-estradiol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and luteinizing hormone–releasing hormone (LHRH) in episodic CH patients, chronic CH patients, and normal controls; they found decreased total and free testosterone only in chronic CH sufferers. LH peaks were lower in response to LHRH in this population, suggesting impairment in the pituitary-gonadal feedback loop. Others have suggested the same, attributing low testosterone levels and/or the development of CH to stress-induced alterations in the production of cortisol.\(^{(28,29,30)}\) Concomitant increased basal cortisol rates in the episodic CH patients confirmed the suspicion of a
hyperactive hypothalamic pituitary-adrenal axis. Our results were correlated with low cortisol levels in 10 cases (52.6%), but we should remind that our study wasn’t done in the active phase of headache and LH values weren’t significant just like the previous results, on the other hand, testosterone values weren’t significant statistically. In another mentioned study, nine cases demonstrated low or low-normal testosterone levels that were not related to our results. In several other investigations, the measurements demonstrated strong correlation between testosterone, cortisol, LH and chronic cluster headaches, the testosterone and LH levels were significantly depressed but cortisol concentration was increased.

Another survey demonstrated increased basal and peak FSH level in episodic and chronic CH groups. We showed 15.8% increased, 57.9% decreased and 21.1% normal FSH levels. Increased cortisol and reduced TSH response to TRH were the results of one article. Another study demonstrated statistically significant differences in T3 concentrations; it was reduced. We noted significant correlation between FSH, T3, and CH patients. 5.3% (one case) had low T3 level and others demonstrated normal T3 values, 2 cases (10.5%) had high TSH and the others demonstrated normal levels.

**Conclusion**
The altered hormonal levels (T3, cortisol, FSH) are a further indication of permanent hypothalamic disturbance in CH and might be a clue to prevent or treat this severe headache by hormonal modification.

**References**


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بررسی پروفایل هورمونی در 19 بیمار با سردرد کلاستر

کچیده
سابقه و هدف: یافته های اخیر مبنی بر اختلال عملکرد هیپوتالاموس در سردرد کلاستر می باشد. سردرد کلاستر یکی از شایع‌ترین بیماری‌های درمان نیروی نظامی و غیرنظامی است که کننده است. کننده است به صورت تصادفی ثبت شد. تحقیق به دو دسته تقسیم می‌گردد: سردرد کلاستر به دو دسته تقسیم می‌گردد: سردرد کلاستر و بیماری، سردرد کلاستر در دوره ای انجام شد. اطلاعات مربوطه از 19 بیمار کلاستر به صورت تصادفی ثبت شد. (تام بیماران در دوره سردرد کلاستر بوکند)

یافته ها: در این مطالعه رابطه معنی دار آماری بین سطوح سردمی کورتیزول، هورمون نیروی بدن و هورمون محرک فولیکولی (FSH) نماینده بهبودی در بین این 19 بیمار، 11 نفر (FSH 97%) و سه نفر داشتند. یک بیمار (FSH 15%) سطح بالای سردمی داشتند. کننده است در این بیماران داشتند. کننده است در این بیماران داشتند. کننده است در این بیماران داشتند. کننده است در این بیماران داشتند. کننده است در این بیماران داشتند. کننده است در این بیماران داشتند. کننده است در این بیماران داشتند. کننده است در این بیماران داشتند. کننده است در این بیماران داشتند. کننده است در این بیماران داشتند. کننده است در این بیماران داشتند. کننده است در این بیماران داشتند. کننده است در این بیماران داشتند. کننده است در این بیماران داشتند. کننده است در این بیماران داشتند.

نتیجه گیری: تغییرات سطح هورمون‌ها (FSH و T3 و T4) و هورمون‌های دیگری با نتیجه مناسبی یافت نشدند، درمان مناسبی ایجاد شد و ناتوان کننده امکان پذیر خواهد بود.

واژگان کلیدی: سردرد خوشه‌ای اختلال هیپوتالاموس، نستروسترون، کورتیزول، تیروتروپین