Journal of Clinical Neuroscience xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Case study

Changes in hormones of the hypothalamic-pituitary-gonadal axis in migraine patients

Wei Li, Xiaojun Diao, Chunfu Chen *, Congcong Li, Yingbo Zhang, Yingying Li

Department of Neurology, Shandong Provincial Hospital Affiliated to Shandong University, 324 Jingwu Road, Jinan, Shandong 250021, China

ARTICLE INFO

Article history:
Received 24 March 2017
Accepted 14 November 2017
Available online xxxx

Keywords:
Migraine
Estrogen
Testosterone
Progesterone
Prolactin
FSH
LH
GnRH

ABSTRACT

The incidence of migraine is higher in women than in men. Abnormality of the hypothalamus-pituitary-gonadal (HPG) axis is believed to be implicated in the pathogenesis of migraine. The aim of this study was to detect serum hormone levels in the HPG axis of migraineurs and analyze the relationship between the hormone levels and migraine-related clinical characteristics. One hundred and nineteen migraineurs were enrolled. Serum FSH, LH, estradiol, progesterone, testosterone, prolactin and GnRH was detected. Pain intensity and migraine-related disability were evaluated using the visual analogue scale (VAS) and the Migraine Disability Assessment questionnaire (MIDAS). The relationships between sex hormone levels and the VAS score and the MIDAS score were also examined. Progesterone levels in male migraineurs were lower than those in healthy controls ($P < .01$). In female patients, in the follicular phase, testosterone levels were lower than in healthy controls ($P < .01$). In the luteal phase, estrogen and testosterone levels ($P < .05$) were lower than in healthy controls. Progesterone and testosterone levels ($P < .01$) were lower than in healthy controls in the postmenopausal phase. In male patients, estrogen levels were negatively associated with the MIDAS score ($r = -0.602$). In female patients, in the follicular phase, estrogen levels were positively correlated with headache duration and VAS score ($r = 0.374$, $r = 0.331$, respectively) and negatively related with MIDAS score ($r = -0.334$). In the luteal phase, estrogen and progesterone levels were negatively correlated with the MIDAS score ($r = -0.772$, $r = -0.464$, respectively). The levels of HPG axis hormones were abnormal in migraineurs and were associated with migraine-related clinical characteristics.

1. Introduction

Migraine is a common primary headache, and the incidence of migraine was reported to be higher in women (12.8%) than in man (5.9%) in China [1]. However, the pathophysiological mechanisms of migraine are not yet fully understood. In recent years, a large number of researchers have shown that evident gender differences exist among migraineurs in terms of epidemiology, clinical characteristics, brain structure and function. Maleki et al. [2] found that female migraineurs had thicker posterior insula and precuneus cortices compared with male migraineurs and healthy controls of both sexes using high-field magnetic resonance imaging. Further use of functional magnetic resonance imaging (fMRI) revealed that the cerebral amygdala and the hippocampus were more sensitive to nociceptive stimulation in female migraineurs than in male patients.

Among all the factors involved in gender differences, sex hormones may be the most impotent. An abnormality of the HPG axis is believed to be implicated in the pathogenesis of migraine. Hormonal fluctuations in women may alter the trigger point for migraine. Estrogen may play an excitatory role in the brain neuronal system, whereas progesterone has an opposite effect [3]. Migraine attacks occurring during menstruation were more painful, longer lasting and more disabling [4,5]. Women may experience relief of migraine-associated symptoms during pregnancy and the postmenopausal period. Pregnancy may have a role in protection against migraine attacks. Migraine was less prevalent in nulliparous pregnant women compared with all nonpregnant

Abbreviations: CGRP, calcitonin gene related peptide; E2, Estrogen; FP, follicular phase; GABA, gamma-aminobutyric acid; HPG, hypothalamus-pituitary-gonadal; LH, luteinizing hormone; NO, nitric oxide; PRG, Progesterone; To, Testosterone; VAS, visual analogue scale; CSD, cortical spreading depression; fMRI, functional magnetic resonance imaging; FSH, follicle stimulating hormone; GnRH, gonadotropin-releasing hormone; LP, luteal phase; MIDAS, Migraine Disability Assessment questionnaire; PMP, postmenopausal phase; PRL, prolactin; TTH, tension-type headache.

* Corresponding author.
E-mail address: chencf301@163.com (C. Chen).

https://doi.org/10.1016/j.jocn.2017.11.011
0967-5868/

women and nulliparous nonpregnant women [6]. However, Frederick et al. [7] found that migraine and headache-related disability were prevalent conditions among pregnant women. Testosterone may have a protective effect against migraine, whereas prolactin was a risk factor for migraine [8,9].

The objective of this study was to detect serum levels of HPG axis hormones in migraineurs and analyze the relationships between these hormone levels and migraine-related clinical characteristics.

2. Materials and methods

2.1. Subjects

One hundred and nineteen migraineurs and 42 patients with tension-type headache were enrolled from the Out-patient Clinic of Shandong Provincial Hospital between Nov 2014 and May 2015. Thirty age- (±3 years) and sex-matched healthy control subjects were chosen from the Examination Center of Shandong Provincial Hospital.

The inclusion criteria were as follows. (1) Migraine and tension-type headache were confirmed according to the International Classification of Headache Disorders 2nd Edition, ICHD-Ⅱ [10]. (2) Headache duration was more than six months and the patients were between 13 and 65 years of age. (3) Menstrual migraine was divided into pure menstrual migraine and menstrually related migraine based on the International Headache Society criteria. Hereditary migraine refers to first-degree relatives of patients with migraine. The exclusion criteria included hypothalamus-pituitary endocrine diseases and internal medicine diseases, intracranial mass lesions, taking hormonal drugs within three months (including oral contraceptives), taking painkillers or traditional Chinese medicines within 2 weeks, regular medication for headache, pregnancy and lactation, and secondary headaches caused by hemorrhage or infection as confirmed by CT or MRI.

Basic information and migraine-related symptoms were recorded for each patient. Pain intensity and headache-related disability were evaluated using the visual analogue scale (VAS) and the Migraine Disability Assessment questionnaire (MIDAS), respectively. This research was approved by the ethics committee of the unit, and all subjects signed an informed consent form.

Blood samples were collected at 8–9 o'clock in the morning after fasting for 12 h. Each blood sample was centrifuged at 3000 rpm for 20 min and then poured into an Eppendorf tube. Samples were stored at −20 °C for the study. Serum FSH, LH, estradiol, progesterone, testosterone, prolactin content were evaluated using a chemiluminescence assay kit (Roche Cobas E601, Basel, Switzerland). Serum GnRH was detected using an enzyme-linked immunosorbent assay (ELISA) kit (Beijing Branch Surplus Technology Company, China).

2.2. Statistical analysis

Statistical analysis was performed using SPSS software version 19.0. A Shapiro-Wilk test was used as the normality test. Analysis of variance was used for comparison among three groups and the Student-Newman-Keuls (SNK) test was used for between-group comparisons when the data were normally distributed, otherwise a rank test was performed. Count data were analyzed using a chi-squared test among groups. Pearson correlation analysis was used if the data had a normal distribution, otherwise Spearman correlation analysis was performed. $P < .05$ was taken to represent statistical significance.

3. Results

There was no significant difference in gender or age composition among the three groups ($P > .05$; Table 1.1). Migraine-related symptoms are shown in Table 1.2.

The levels of prolactin ($\chi^2 = 6.714$, $P = .035$) and GnRH ($F = 19.606$, $P < .001$) were higher in male migraineurs than in healthy controls. Progesterone levels ($F = 5.931$, $P = .005$) were lower in male patients than in healthy controls (Table 2.1). In the follicular phase, testosterone levels were significantly lower in female migraineurs than in healthy controls ($Z = -2.886$, $P = .004$), and levels of prolactin ($\chi^2 = 9.348$, $P = .009$) and GnRH ($\chi^2 = 14.692$, $P = .001$) were significantly higher in patients with migraine and TTH than in healthy controls (Table 2.2). In the luteal phase, levels of estrogen ($t = -2.162$, $P = .041$) and testosterone ($t = -2.628$, $P = .015$) were lower than in healthy controls, and levels of prolactin ($Z = 2.038$, $P = .042$) and GnRH ($t = 2.902$, $P = .039$) were significantly higher than in healthy controls (Table 2.3). In the postmenopausal phase, levels of progesterone ($F = 11.515$, $P < .001$) and testosterone ($\chi^2 = 11.974$, $P = .003$) were significantly lower than in TTH patients and healthy controls, prolactin levels ($\chi^2 = 6.653$, $P = .036$) were significantly higher than in healthy controls, and GnRH levels ($\chi^2 = 8.381$, $P = .015$) were significantly higher than in healthy controls, but lower than in patients with TTH (Table 2.4).

The levels of FSH ($r = 0.474$) and LH ($r = 0.502$) in male migraineurs were positively related with the headache course, whereas progesterone levels were negatively correlated with the headache course ($r = -0.399$). In the follicular phase, FSH levels in female migraineurs were positively related with the headache course ($r = 0.325$) (Table 3.1). Estrogen levels in the follicular phase were positively correlated with headache duration ($r = 0.374$) (Table 3.2). Estrogen levels in the postmenopausal phase were negatively correlated with headache frequency ($r = -0.674$) (Table 3.3).

In the follicular phase, estrogen levels in female migraineurs were positively correlated with VAS scores ($r = 0.331$) (Table 4). Estrogen levels in male migraineurs were negatively associated with MIDAS scores ($r = -0.602$). The levels of estrogen in female migraineurs in the follicular phase were negatively correlated with MIDAS scores ($r = -0.334$). In the luteal phase, levels of estrogen ($r = -0.772$) and progesterone ($r = -0.464$) were negatively correlated with MIDAS scores, whereas levels of FSH ($r = 0.631$) and LH ($r = 0.713$) were positively related with MIDAS scores. The levels of progesterone ($r = -0.768$) and testosterone ($r = -0.889$) in the postmenopausal phase were negatively correlated with MIDAS scores (Table 5, Figs. 1–7).

Table 1.1
General information for patients.

Group	Migraine (n = 119)	TTH (n = 42)	Controls (n = 30)
Male	30	10	5
Age (years)	13–58	18–49	15–54
mean ± SD	32.37 ± 14.49	32.50 ± 9.36	34.80 ± 15.16
Female in RP	72	26	20
Female in FP	52	18	15
Female in LP	20	8	5
Age (years)	13–54	18–49	16–51
mean ± SD	33.74 ± 11.00	35.15 ± 10.25	32.65 ± 10.61
Female in PMP	17	6	5
Age (years)	45–61	48–55	48–60
mean ± SD	53.24 ± 4.29	50.67 ± 3.39	53.60 + 4.51

Note: RP, reproductive period; FP, follicular phase; LP, luteal phase; PMP, postmenopausal phase. $P > .05$.

Please cite this article in press as: Li W et al. Changes in hormones of the hypothalamic-pituitary-gonadal axis in migraine patients. J Clin Neurosci (2018), https://doi.org/10.1016/j.jocn.2017.11.011