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Brain Diffusion Changes in Polycystic Ovary Syndrome

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Polycystic ovary syndrome (PCOS) is the most frequent endocrine disorder in women of reproductive age, affecting 4%-10% of the population. It is a complex disorder classically characterized by chronic oligo- or anovulation, polycystic ovaries, and hyperandrogenism. It is also associated with a number of comorbid conditions, including type 2 diabetes, cardiovascular disease, dyslipidemia, obesity, infertility, and breast and endometrial cancer [1,2]. In addition, psychiatric disorders are observed more often in PCOS patients than in the general population, particularly depressive, anxiety, and eating disorders [3–6]. According to previous reports, approximately 57% of PCOS patients have at least 1 psychiatric disorder [4,5].

To date, the exact etiology for increased risk of mood disorders in PCOS patients remains unknown and it has been generally suggested that the clinical and physical manifestations of PCOS, such as obesity, hirsutism, acne, or infertility, were thought to be the causes of considerable emotional distress in PCOS women [3–6]. This point of view may be partially true, however, we suggest that it is necessary to investigate the role of the central nervous system to establish a clear causal relationship between PCOS and mood disorders.

It has been shown that the brain regions involved in mood regulation are the anterior cingulate cortex, the orbitofrontal cortex, and the dorsolateral prefrontal cortex [7]. Also, the thalamus has a critical role in the modulation of cognition and emotion [8]. In addition, specific brain regions suggested to be related to hunger and satiety are the dorsomedial and dorsolateral frontal, orbitofrontal, anterior cingulate, middle temporal, visual, and insular cortexes; thalamus; amygdala; hypothalamus; hippocampal gyrus; midbrain; corpus striatum; and cerebellum [9].

Although a complete understanding of the underlying pathophysiology of PCOS is still lacking, it has been evidenced that many of the comorbidities are related to hyperandrogenism and continuous unopposed hyperestrogenism (hyperestrogenic state) in PCOS [2,10]. However, to date, the long-term effect of high levels of these hormones on brain have not been fully investigated. On the other hand, there is evidence for functional links between testosterone and the prefrontal cortex and amygdala in the regulation of social emotional behavior [11,12]. Also, a strong correlation was found between depressive symptoms and serum androgen levels [13,14].

Diffusion-weighted imaging (DWI), a well-established magnetic resonance imaging (MRI) sequence, provides important information on microstructural characteristics of tissues by detecting the microscopic movement of water molecules within the extracellular space [15]. DWI can distinguish cytotoxic edema from vasogenic edema, and thus is commonly used to diagnose early cerebral ischemia in clinical practice. DWI yields qualitative information, whereas apparent diffusion coefficient (ADC) values calculated from DWI data are quantitative measurements of the diffusion of water molecules that may be altered in pathologic conditions [16].

Given that psychiatric disorders are commonly associated with PCOS and the possible effects of high levels of androgens and unopposed estrogens on brain, we aimed to

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address the question whether there were brain diffusion changes in women with PCOS. Also we aimed to investigate possible relationships between hormonal parameters and ADC values. To the best of our knowledge, the our study is the first that investigate brain DWI findings in PCOS patients.

Materials and Methods

Study Population

This retrospectively designed study was performed in accordance with the Helsinki Declaration, and it was approved by the local Ethical Committee before data collection. The medical records of 658 subjects diagnosed with PCOS presenting to the Department of Obstetrics and Gynecology of our hospital between January 2008 and January 2015 were systematically reviewed from our hospital database. The diagnoses of patients with PCOS were based on the Rotterdam criteria [17]. Among these, PCOS patients who had also undergone brain MRI were searched from database. From the records, 20 PCOS patients who had brain MRI were included in the present study. The serum levels of estradiol, progesterone, prolactin, luteinizing hormone, follicle-stimulating hormone, total and free testosterone of PCOS patients were recorded. Subsequently, control subjects were selected from the subjects who had undergone brain MRI. The volunteers who met all the inclusion and exclusion criteria were invited to undergo gynecologic examination and pelvic sonographic examination. Finally 35 control subjects who had normal ovulating cycles, normal sonographic appearance of the ovaries, and no signs of hyperandrogenism were included in the study. Body mass index (BMI) (kg/m^2) was calculated to assess obesity. The subjects with normal weight were included in the study because of the possible effect of obesity on brain diffusion [9]. Also, all the study population had a normal brain MRI as evaluated by a clinical neuroradiologist. Exclusion criteria for both groups were as follows: <16 or >35 years of age; BMI >30 kg/m^2; or causes of hormonal imbalance such as pregnancy, breast-feeding, administration of exogenous estrogens, oral contraceptives, antiandrogens, or corticosteroids.

MRI Acquisition

All subjects were scanned with a 1.5-T Philips Intera MR unit (Philips Medical Systems, Amsterdam, the Netherlands) using standard head coil. The MRI examination consisted of spin echo images including axial and sagittal T1-weighted images (repetition time [TR] = 550 ms, echo time [TE] = 15 ms), axial T2-weighted images (TR = 3550 ms, TE = 115 ms), and fluid-attenuated inversion recovery images (TR = 9000 ms, TE = 105 ms, inversion time = 2500 ms). The sequences also included the following parameters: field of view = 230 × 230 mm^2, matrix size = 256 × 256 mm^2 , slice thickness = 5 mm, and number of slices = 20. DWI was performed with echo-planar imaging. The parameters were the following: TR = 4000 ms, TE = 10 ms, matrix size = 128 × 128 mm^2, slice thickness = 5 mm, field of view = 230 × 230 mm^2, number of acquisitions = 2, slice orientation = axial plane, number of slices = 20, scan time = 28 seconds. Diffusion gradients were applied separately in 3 orthogonal directions to generate 3 sets of DWI (x, y, and z axes). Diffusion-weighted images were displayed on a workstation for post-processing, including reconstruction of the ADC maps.

ADC Data Analysis

Circular regions of interest (ROIs) were placed in axial slices by 2 experienced neuroradiologist on predefined anatomic areas (dorsolateral and dorsomedial frontal, orbitofrontal, middle temporal, visual, and cingulate cortexes; midbrain; amygdala; cerebellum; hippocampal gyrus; hypothalamus; thalamus; corpus striatum; and insula) and ADC values were directly calculated from automatically generated ADC maps (Figure 1). The selection was based on literatures suggesting that those regions are related to depression, emotion, cognition, hunger, and satiety [7−9]. The ROIs were placed in the cerebrospinal fluid (CSF) at the midventricular level of each subject, which revealed a mean ADC of $2.96 \pm 0.39 \times 10^{-3}$ mm^2/s. We excluded all ADC pixel values that were $>2.0 \times 10^{-3}$ mm^2/s (corresponding to mean CSF ADC − 2 Standart Deviation) to avoid CSF contamination [18]. The ROIs were approximately 10 mm^2 in the midbrain, hippocampal gyrus, hypothalamus, amygdala, middle temporal cortex, insula, and thalamus; 20-30 mm^2 in the occipital, orbitofrontal, cingulate, dorsomedial, and dorsolateral cortexes; and 40 mm^2 in the corpus striatum and cerebellum. Partial volume effects emerging from CSF were also minimized by inspecting the slices below and above the region and using small ROIs in work areas. Similar ROI sizes were used for an individually selected region in all the study population. ROI analysis was blinded to the hypotheses of the study, clinical data and group assignment of the subjects. The overall Pearson correlation for interrater reliability assessed on 8 randomly selected images was 0.98 and intrarater reliability, and based on 8 scans measured twice by the same rater was 0.99. All these values were well within acceptable limits.

Statistical Analysis

Statistical analysis was performed using SPSS version 19.0 (IBM, Armonk, NY). Because the values were identified as normal distribution, an independent sample *t* test was used to evaluate differences between PCOS patients and control subjects. Pearson's correlation coefficient was used to determine relationship between variables of groups. A *P* value lower than .05 was considered statistically significant.