Alterations in pituitary gland volume in Polycystic Ovary Syndrome: A structural magnetic resonance imaging study.

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Aims and objectives

Polycystic ovary syndrome (PCOS) is the most common female endocrinopathy, affecting 4-10% of the female population in their reproductive years [1]. It is a diverse and complex endocrine disorder with regards to clinical presentation and laboratory manifestations. The underlying defect in polycystic ovaries still remains unknown, however, there is a growing consensus that the key features are hyperandrogenism, hyperinsulinaemia and abnormal excessive serum luteinizing hormone (LH) concentrations [2].

PCOS is characterized by increased LH pulse amplitude and exaggerated LH responses to exogenous gonadotropin-releasing hormone (GnRH), whereas plasma follicle-stimulating hormone (FSH) levels are relatively low and the reason for hypersecretion of LH from the pituitary gland is not exactly known [1].

The pituitary gland is known to produce hormones such as LH and FSH, which control the activity of other endocrine glands. Moreover, based on previous Magnetic resonance imaging (MRI) studies, the pituitary gland is a dynamic organ that changes in response to different influencing factors, such as age or stress. Its volume increases in puberty, pregnancy or with the administration of exogenous estrogens [3-5].

MRI is currently the technique best suited to examine the pituitary gland because of its high spatial and contrast resolution [6-8]. In healthy adults, the normal size of the pituitary gland is approximately 5-10 mm in height, 10 mm in length, and 10-15 mm in width [9].

It is well established that dysfunctions, such as major depressive disorder [10,11], psychosis [4] or primary hypothyroidism [5] leading to elevated adrenocorticotrophic hormone (ACTH) or thyroid-stimulating hormone (TSH) levels are associated with an increased volume of the pituitary gland.

This study was initiated after we noted that some patients who had pituitary enlargement on their MRI scans had increased LH/FSH ratio. In the current study, we aimed to assess the impact of PCOS on pituitary gland volume as measured by MRI under the hypothesis that the endocrinologic changes in PCOS can lead to morphologic changes, namely, hypertrophy of the pituitary gland. Also we aimed to investigate the associations between pituitary volume, mean ovarian volume, age and hormonal parameters. To the best of our knowledge, this is the first study examining pituitary gland volume in patients with PCOS.
Methods and materials

Patients

This prospectively designed cross-sectional observational study was carried out between January 2014 and May 2014 at our university hospital. Informed consent was obtained from all included subjects, and the study protocol was approved by the local Ethical Committee. All women with PCOS were recruited from among those who visited the Department of Obstetrics and Gynecology of our university hospital. The diagnosis was based on the Rotterdam criteria [12].

The patient group consisted of 26 normal-weight women with PCOS and 31 age and BMI-matched normal-weight female volunteers with normal ovulating cycles (28 ± 2 days, blood progesterone levels >10 ng/ml in two consecutive cycles), no signs of hyperandrogenism, and normal ultrasonographic appearance of the ovaries.

Body mass index (BMI, kg/m$^2$) was calculated by dividing weight in kilograms (kg) by height in meters, squared (m$^2$) to assess obesity. The subjects with normal weight were included in the study because of the possible effect of obesity on HPA axis [13]. None of the women studied had any systematic disease that could possibly affect their reproductive physiology. Also, all the study population had a normal brain MRI as evaluated by a clinical neuroradiologist. Exclusion criteria for both groups were as follows: age <16 or >35 years, BMI < 18.5 kg/m$^2$ or >25 kg/m$^2$, galactorrhea, causes of increased pituitary volume such as pregnancy, administration of exogenous estrogens, hypothalamic and pituitary tumors, primary hypothyroidism, Addison's disease, psychosis and severe major depression.

MRI Data Acquisition

All subjects were scanned with a 1.5 Tesla Philips Intera MR unit (Philips Medical Systems, Amsterdam, The Netherlands) using a 3-D spoiled gradient echo sequence (T1-FFE) on the 2-5$^{th}$ day of their menstrual cycle. T1-weighted images were obtained in the coronal plane with 1.5 mm contiguous sections. Image parameters were as follows: matrix size, 574x574; field of view 20 cm, time-to-echo,4,5 ms; time to-repetition, 25 ms; flip angle, 12°. Additionally, a dual spin echo sequence was used to obtain T2-weighted images in the axial plane to determine unexpected structural lesions.

Image Analysis
Pituitary glands were manually traced on structural T1 sequence MRIs by one rater (EK) who was blinded to any identifying information such as the presence/absence of PCOS. Each pituitary gland was initially identified on the sagittal plane where anterior and posterior borders were marked and used to define the number of coronal slices containing the gland. Then, pituitary glands were traced in all coronal slices, where the pituitary gland could be visualized following clearly defined anatomical boundaries, i.e., diaphragma sellae, superiorly; the sphenoid sinus, inferiorly, and the cavernous sinuses, bilaterally (Fig.1) \[4,5,10,11\]. An average of 7.08 ± 1.05 slices were used. The infundibular stalk was excluded from the tracings, but the posterior pituitary was included \[4,5,10,11\].

Anatomical volume measurements of the pituitary gland were conducted on a DELL Precision Workstation. A segmentation process was performed in order to use images for 3D reconstruction. Collection of data and the segmentation process were performed using Mimics 10.1 software (Materialise, Leuven, Belgium). The segmentation process was converted to a 3D mesh model using an adapted marching cubes algorithm and the volume value was obtained (Fig.1) \[14\]. Intracranial volumes were also computed. Measurements were performed by two radiologist with segmentation experience (EU, MBA). The overall Pearson correlation for interobserver reliability, assessed on ten randomly selected images, was 0.95 and intrarater reliability, based on 10 scans measured twice by the same rater (EU) was 0.97. All these values are well within acceptable limits.

Serum hormone level measurements

Fasting blood samples were collected for measurements of serum levels of estradiol, FSH, LH, prolactin (PRL), free testosterone (Ftest) and total testosterone (Ttest), and dehydroepiandrosterone sulfate (DHEAS), on days 2-5 (early follicular phase) of the spontaneous menstrual cycle.

Transvaginal / pelvic Ultrasonography

Transvaginal / pelvic ultrasonography was also performed on the same day and the volume of each ovary and the number of follicles in each ovary were determined. Polycystic ovaries were diagnosed when ≥ 12 follicles with a diameter of 2-9 mm were present in one or both ovaries and/or when the ovarian volume was >10 cm³. Each ovary was measured in three dimensions and the volumes were calculated using the approximate formula for an ellipsoid: \(V = \frac{4}{3} \pi \times A \times B \times C \times 0.523\), where A is the longitudinal diameter, B is the anteroposterior diameter; and C is the transverse diameter of the ovary \[15\].

Statistical Analysis
Statistical analysis was performed using SPSS, version 19.0 (SPSS, Chicago, IL). Mann-Whitney U test was used for comparison of groups for variables that were inconsistent with a normal distribution. Independent student t-test was used for comparison of groups for variables that were consistent with a normal distribution. A multiple linear regression model was used for determination of the relation between pituitary volume and independent variables such as age, LH to FSH ratio and mean ovarian volume. As there were no differences in whole-brain volume (WBV) between first-episode subjects and controls ($P=0.3$), the main analyses of pituitary volume did not include this variable as a covariate. Pearson's Correlation Coefficient test was used for the comparisons of pituitary and ovarian volume alterations with age. Intraobserver and interobserver reliability was evaluated with use of the Pearson correlation coefficient. A $p$ value lower than 0.05 was accepted as statistically significant.
**Images for this section:**

**Fig. 1:** A-B. Each pituitary was manually traced on coronal slice of T1 sequence MRI. C. A segmentation process was performed in order to use images for 3D reconstruction and was converted to a 3D mesh model using an adapted marching cubes algorithm.

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Results

Baseline characteristics of patients with PCOS and controls are presented in Table 1. The patient group consisted of 26 normal-weight women with PCOS (age, 17-30 years; mean 25 ± 2.9, mean BMI 22.3 ± 2.7 kg/m$^2$) and 31 age and BMI-matched normal-weight female volunteers (age, 18-30 years; mean 22 ± 3.7 years, mean BMI 23.1 ± 1.7 kg/m$^2$).

Comparing parameters between groups

Serum LH, LH/FSH ratio, Ftest and DHEAS levels were significantly higher in the PCOS group ($P<0.05$). Patients with PCOS had a mean pituitary volume of 667.8 ± 55.7 mm$^3$, whereas healthy control subjects had a volume of 525.3 ± 77.8 mm$^3$. Statistical analysis showed pituitary volume to be significantly higher in patients with PCOS than in healthy control subjects ($P<0.001$) (Fig.2). There were no significant differences in intracranial volumes ($P=0.3$). Also mean ovarian volumes were significantly higher in the PCOS patients (9.4 ± 1.0) than in control subjects (8.7 ± 1.1), ($P=0.02$).

The correlations between PGV age and hormonal parameters

Pituitary gland volumes were significantly correlated with LH/FSH ratio in the whole sample ($R=0.39$, $P=0.002$) and also in the PCOS group ($R=0.37$, $P=0.04$). On the other hand, multiple linear regression model results showed that the LH/FSH ratio was the only predictor of pituitary volume ($P=0.047$). There were no correlations between PGV and estradiol, Ftest, Ttest and DHEAS levels.

Correlation analysis showed that in healthy control subjects, PGV was significantly lower in older individuals ($R= -0.24$, $P=0.05$), whereas patients with PCOS showed a trend toward increasing gland volume with age (coef.=-0.13, multiple linear regression model) but without reaching statistical significance ($P=0.08$) (Table 2) (Fig.3).

The correlations between PGV and ovarian volume in patients with PCOS

There was no significant correlation between PGV and mean ovarian volume in PCOS patients ($P>0.05$) (Table 2). PCOS patients showed a significant increase in ovarian volume with age ($R=0.67$, $P< 0.001$). Also, as mentioned above, patients with PCOS showed a trend toward increasing PGV with age but this was not statistically significant ($P=0.08$). To further investigate, the comparisons of pituitary and ovarian volume alterations with age were analyzed (Fig.4). There were no significant differences in
ovarian volume between PCOS patients who were younger than 18.2 years and healthy subjects, and also ovarian volume did not increase with age between 17 and 18.2 years. After 18.2 years, mean ovarian volume began to gradually increase, whereas PGV was significantly higher in the age range 17-18.2 in the PCOS group and showed a trend toward increasing with age. This analysis demonstrated that pituitary volume began to rise before ovarian volume increased.

**Table 1.** Baseline characteristics of patients with PCOS and controls

<table>
<thead>
<tr>
<th></th>
<th>CONTROL (n=31)</th>
<th>PCOS (n=26)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>25±2.9</td>
<td>22±3.7</td>
<td>0.5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pituitary volume</td>
<td>525.3±77.8</td>
<td>667.8±55.7</td>
<td>0.002*&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total brain volume</td>
<td>1131±83</td>
<td>1144±39</td>
<td>0.3</td>
</tr>
<tr>
<td>E2</td>
<td>44.2±38</td>
<td>40.3±19</td>
<td>0.8&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>DHEAS</td>
<td>250±100</td>
<td>317±135</td>
<td>0.03*&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>LH</td>
<td>4.8(2.5)</td>
<td>10.6(8.6)</td>
<td>0.004*&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>FSH</td>
<td>5.6±2.4</td>
<td>6.2±1.8</td>
<td>0.3&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>LH / FSH</td>
<td>0.7(0.4)</td>
<td>1.5(0.9)</td>
<td>0.001*&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Free Testosterone</td>
<td>0.9±0.4</td>
<td>2.9±2.2</td>
<td>0.006*&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total Testosterone</td>
<td>37±17</td>
<td>39±28</td>
<td>0.7&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean ovarian volume</td>
<td>8.7±1.1</td>
<td>9.4±1.0</td>
<td>0.02*&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

* Significant differences were signed (if p<0.05)

Values were given as mean±St. Deviation for normal distributed variables, median(IQR) for abnormal distributed variables.

<sup>a</sup> Independent sample t-test was used,  <sup>b</sup> Mann whitney-U test was used

**Table 2.** The relations between pituitary volume and age, LH / FSH ratio, mean ovarian volume in patients with PCOS

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>p value</th>
<th>95% CI for Coef.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower  Upper</td>
</tr>
</tbody>
</table>

Page 8 of 18
<table>
<thead>
<tr>
<th>Feature</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.13</td>
<td>0.08</td>
<td>-10.3</td>
<td>10.7</td>
</tr>
<tr>
<td>LH/FSH ratio</td>
<td>0.37</td>
<td>0.04</td>
<td>27.8</td>
<td>52.4</td>
</tr>
<tr>
<td>Mean ovarian volume</td>
<td>0.51</td>
<td>0.7</td>
<td>-32.3</td>
<td>42.6</td>
</tr>
</tbody>
</table>

Multiple linear regression model was used.
Fig. 3: Correlations of pituitary gland volumes with age. Pituitary gland volume was significantly lower in older individuals in healthy control subjects (R = -0.24, P=0.05), whereas patients with PCOS showed a trend toward increasing gland volume with age. (P=0.08).

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**Fig. 4:** Comparisons of pituitary and ovarian volume alterations with age. Note: Pituitary volume (1/100 in scale)

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Fig. 2: Pituitary gland volumes across groups. Pituitary volumes are significantly higher in patients with PCOS than in healthy control subjects (p< 0.00)

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Conclusion

The main findings of the present study are as follows: i) an increase in pituitary volume in PCOS patients compared with age and BMI matched healthy controls was noted. ii) PGV’s were positively correlated with LH levels in PCOS patients and also in the whole study population. iii) PCOS patients also showed a significant increase in ovarian volume with age. iv) A negative correlation between pituitary volume and age was noted in the healthy controls whereas patients with PCOS showed a trend toward increasing gland volume with age. v) Finally, we found that ovarian volumes began to gradually increase after 18.2 years of age. These data indicate that volume of the pituitary began to rise before the ovarian volume increased. All these findings were consistent with our previous hypothesis that increased LH levels in PCOS are associated with hypertrophy of the pituitary gland, which can be an issue in PCOS pathogenesis.

LH and FSH are produced in the pituitary gland, which we investigated in the present study by means of 1.5T MR imaging. Patients with PCOS have increased LH pulse frequency and amplitude, without the normal cyclic variation seen in healthy women, which is characterised by excessive secretion of LH but normal secretion of FSH [17].

The reason for increased secretion of LH from the pituitary gland in PCOS is not exactly known. The larger question is whether this alteration in LH secretion is due to an intrinsic defect of the hypothalamus or due to external factors such as disturbances in the negative feedback mechanism from the ovary. The increased LH pulse frequency may reflect an increase in GnRH release and the presence of a hypothalamic defect, whereas some authors have proposed that the rapid GnRH and LH frequency in PCOS simply reflects a lack of this luteal steroid feedback [1,17]. Moreover, the pattern is exacerbated by exogenous GnRH, which further gives rise to exaggerated secretion of LH and testosterone in women with PCOS [1]. In the present study, PGV’s were significantly larger in patients with PCOS compared to control subjects and were significantly correlated with LH / FSH ratio in the whole sample ($R = 0.39$, $p = 0.002$) and also in the PCOS group ($R = 0.37$, $p = 0.04$). Also, in our data, the LH to FSH ratio proved to be the only independent predictor of PGV in patients with PCOS. We therefore hypothesized that in patients with PCOS, high testosterone levels with elevated LH levels and hyper-responsiveness of LH to gonadotropin-releasing hormone are possible signs of a larger reserve of LH.

Although the pituitary gland is a small structure, its volume can be measured using MRI. Even though many studies could demonstrate that changes in pituitary gland dimensions predominantly affect the height of the gland [19], a direct volumetric approach by use of 2D or 3D MR images was used in more recent studies.

As mentioned above, physical hyperplasia of the pituitary gland occurs during puberty [3] and PGV decreases gradually with age after around the second decade in healthy females [3]. Our analysis showed that women with PCOS showed a trend to
increasing pituitary gland volume with increasing age, whereas control subjects showed a statistically significant decrease in volume. The latter finding is consistent with previous findings of a gradual decrease with age in adulthood [9]. Enlargement of the pituitary gland with age in PCOS may reflect an ongoing process of gland hypertrophy in the course of time and duration of the disease.

In the present study, there were no significant differences in ovarian volume between PCOS patients who were younger than 18.2 years and controls. The patients over that age had significantly larger ovaries, and volumes gradually increased with age. This analysis indicates that PGV could be increasing in early stages of the disease and chronic stimulation with LH may lead to an increase in ovarian volume in later stages of PCOS. Therefore, it is reasonable for us to speculate that the pituitary enlargement may be the initial imaging finding or a preceding factor for the ovarian volume increase in PCOS.

A possible limitation of our study, common to all studies examining pituitary volume by imaging methods, is the inclusion of the posterior lobe of the pituitary gland while tracing the boundaries of the gland. The posterior pituitary, which releases vasopressin and oxytocin, constitutes less than 20% of the total pituitary volume and also there are no known conditions associated with posterior pituitary enlargement, except tumours [4]. Thus, we believe that the changes in pituitary volume we have described are due to changes in the volume of the anterior pituitary rather than the posterior pituitary.

In conclusion, we have found that patients with PCOS have higher pituitary volumes than healthy individuals even at early ages, previously not reported, as well as a positive correlation of pituitary gland size and LH to FSH ratio. Therefore, the association between enlargement of the pituitary gland and PCOS should be kept in mind when pituitary hyperplasia is detected on MRI, before unwarranted interventions are initiated. We also conclude that the evaluation of pituitary enlargement may be useful in the early diagnosis of PCOS, even before ovarian volume alterations. However, further studies are needed to prove that pituitary enlargement may represent a forerunner of PCOS in peripubertal hyperandrogenaemia.
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