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Familial Background of Complex Diseases in PCOS Probands of South Indian Population

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ABSTRACT

Polycystic Ovary Syndrome (PCOS) is a common reproductive health problem associated with long term complications. It is a condition of high clinical heterogeneity with familial clustering, however, the mode of inheritance is still controversial. A number of candidate genes have been implicated in susceptibility to PCOS, suggesting a strong role of genetic factor in the aetiopathogenesis of PCOS. The aim of the present study was to determine possible association between PCOS and family history of complex genetic diseases such as PCOS, Menstrual disturbance, type II Diabetes and Cardiovascular diseases. A total of 432 individuals comprising of 206 patients and 226 controls were involved in the present study. Clinical information, anthropometric measurements and three generation pedigree data with respect to CD was collected through proforma. Twenty five percent of PCOS probands exhibited clinical hyperandrogenism in the form of hirsutism, acne, premature pubarche and alopecia. Eighteen percent showed acanthosis, a marker for insulin resistance. Twenty percent of the patients were under the category of amenorrhea; while remaining 75% of cases were either with primary/secondary infertility. The anthropometric analysis revealed higher BMI and W/H ratio in the patient group compared to the controls. A high frequency of PCOS women exhibited the prevalence of complex diseases in their families compared to the control families (60 vs. 20%; $p < 0.05$). It is suggested that complex diseases provide significant genetic background for the susceptibility to develop this multifactorial disorder in a section of patients.

Key words: Polycystic ovary syndrome, diabetes, cardiovascular disease, familial incidence, complex diseases

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a major cause of female infertility and the most common endocrinological disorders that affects 4 to 12% of women of reproductive age worldwide. (Legro *et al.*, 1998; Gonzalez *et al.*, 2003; Knochenhauer *et al.*, 1998). It is a complex disorder with clinical features changing throughout the life span (Balen and Dunger, 1995; Elting *et al.*, 2000). It may start from adolescence to postmenopausal age and is characterized by hyperandrogenism, polycystic ovaries on ultrasound scan and chronic anovulation along with insulin resistance, hyperinsulinemia, abdominal obesity and dyslipidemia as frequent metabolic traits. This predisposes

the individual to serious long term consequences such as type 2 diabetes, endometrial hyperplasia, hypertension, thyroid dysfunction and cardiovascular disease. The signs and symptoms of hyperandrogenism include hirsutism, acanthosis nigricans, obesity, pelvis mass, virilization, acne, increased sebaceous activity and alopecia (Ovalle and Azziz, 2002; Legro, 2003; Hardiman *et al.*, 2003; Sharma *et al.*, 2008).

Genetic, biochemical, immunological factors and environment are implicated in the aetiopathogenesis of PCOS. This disease does not show clear Mendelian inheritance however, familial clustering is observed (Carmina *et al.*, 1997; Ferriman and Purdie, 1979; Lunde *et al.*, 1989; Stewart *et al.*, 2006). It is suggested that hyperandrogenic environment and lifestyle factors in early childhood mediate the effect of predisposing the individuals for the development of PCOS in later life (Vincent *et al.*, 2007). Understanding of PCOS is hampered due to low fecundity, absence of male phenotype, animal model and differences in diagnostic criteria (Pasquali and Casimirri, 1993; Gambineri *et al.*, 2002).

Studies with respect to familial background of diabetes, cardiovascular disorders, menstrual disturbance or PCOS in the families of PCOS subjects have been reported. However, Moini and Eslami (2009) in Iranian population has observed clustering of complex diseases in the families of PCOS patients. The present study is the first one dealing with the assessment of frequency of complex disease's in Indian population.

MATERIALS AND METHODS

A total of 432 individuals comprising of 206 patients and 226 controls were involved in the present study. Patients were selected based on Rotterdam criteria proposed by Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2004). Informed consent and permission was obtained for experimentation with human subjects from the local health authorities (ethical committee, Osmania University). Controls were included in the present study to observe the relative frequency/family history of complex diseases in general population and for comparative analysis with that of total patients. The inclusion criteria for controls was healthy, age matched, ultrasound scanned normal fertile women with minimum two kids to rule out polycystic ovaries and infertility. None of them had signs or symptoms of hyperandrogenism, menstrual dysfunction or history of 1° or 2° infertility. Information with respect to anthropometric measures, history of menstruation, hirsutism, alopecia, incidence of PCOS, MD, Db and CVD in 1° (parents and/or sibs) and 2° relatives of the subjects was collected by using a proforma. Markers for obesity and abdominal obesity were measured by calculating Body Mass Index (BMI) and Waist Hip Ratio (WHR), respectively. Hirsutism score was made by Ferriman-Gallway (FG) scoring system and a score of ≥ 7 was used to determine hirsutism (Ferriman and Gallway, 1961).

Statistical analysis: Statistical comparisons between the means were done by performing test of proportion the z-test; Odd's Ratio (OR) with 95% Confidence Interval (CI) in the two study groups were also calculated. All the values were expressed as Mean \pm SD. Two-tailed p values less than 0.05 were considered significant. The SPSS package (16th version) was used to perform statistical analysis.

RESULTS

The data analysis of 432 individuals involved in the present study (206 patients and 226 controls) revealed the presence of clinical hyperandrogenism in 22% of probands in the form of hirsutism, acne, premature pubarche and alopecia. Eighteen percent of individuals showed acanthosis, a marker for insulin resistance. When infertility was taken into consideration 25% of the patients were unmarried and were under the category of amenorrhea, however, more than 75% of cases were with primary/secondary infertility (Fig. 1).

A perusal of Table 1 showed that the marker of obesity, BMI was significantly different between the patients and controls ($p < 0.05$). Nearly 60% of PCOS probands are obese having $BMI > 25 \text{ kg m}^{-2}$. The W/H ratio of patients group was also significantly higher than the controls ($p < 0.05$). However, age at menarche did not differ significantly between the patient and control groups.

When information collected was assessed regarding the presence/absence of complex disease(s) through a questionnaire during interview from the study subjects, a total of 4138 individuals belonging to the families of 206 PCOS probands and 226 controls were obtained. This included 2246 (1081 males and 1165 females) individuals from families of PCOS probands (excluding proband) and 1892 (878 males and 1014 females) from the families of control subjects. The result suggests that gene pool of proband's families possess clustering of susceptibility genes for complex diseases that may influence the occurrence PCOS in interaction with environment (Fig. 2).

In order to investigate what percentage of probands has the background of either Db/CVD/MD/PCOS, further analysis in both patients and controls was carried out with respect to family history of complex diseases. The results may suggest the involvement of genes associated with diabetes and cardiovascular disorders play a role in predisposing the woman to develop PCOS (Table 2).

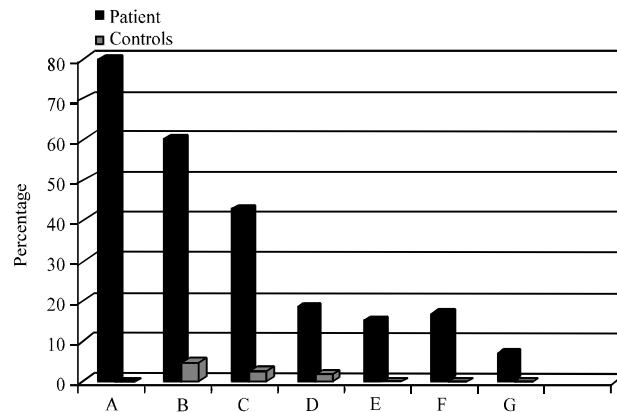


Fig. 1: Clinical characteristics of PCOS probands and control group. A: Infertility, B: Obesity, C: Hirsutism, D: Acne, E: Alopecia, F: Acanthosis, G: Premature pubarche

Table 1: Subject characteristics of total patients and control group

Characteristics	Total controls N = 185	Total patients N = 200	p-value
Age (years)	24.26±4.96	24.14±4.05	NS
BMI (kg m^{-2})	22.90±4.22	25.83±5.40	0.0001
W/H ratio	0.77±0.05	0.80±0.06	0.0009
AAM	12.41±0.89	12.30±1.36	NS

AAM: Age at maturity, BMI: Body mass index, NS: Not significant

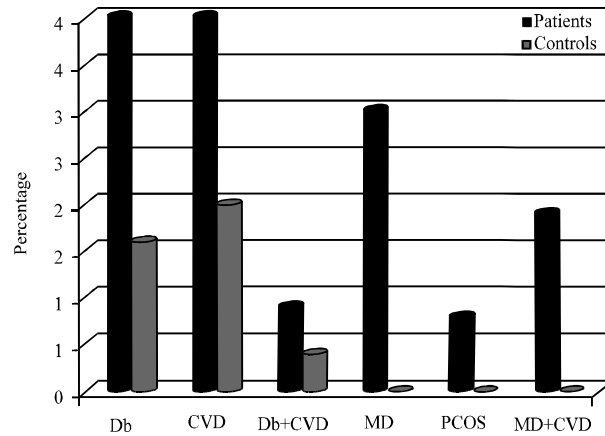


Fig. 2: Familial incidence of complex diseases in PCOS probands and the control subjects

Table 2: Incidence of family history of complex diseases (PCOS, MD, Db and CVD) in women with PCOS and without PCOS

Variables	Controls% (N)	Patients% (N)	p-value at 5% LOS
Families with PCOS background	0 (0)	7 (15)	0.0001
Families with MD background	0 (2)	16 (32)	0.0001
Families with Db	8 (18)	12 (25)	0.1970
Families with CVD	7 (16)	15 (30)	0.0180
Families with Db+CVD	5 (12)	18 (38)	0.0001
Families with history PCOS/MD/Db/CVD	20 (46)	68 (140)	0.0001
Families with no history of complex diseases	80 (180)	32 (66)	0.0001
Total patients	206	
Total controls	226	-----	

DISCUSSION

PCOS is a common and complex disorder that might result from the interaction of susceptible and protective genes under the influence of environmental factors (Weiss and Terwilliger, 2000). A number of candidate genes have been implicated in susceptibility to PCOS, suggesting a strong role of genetic factor in the aetiopathogenesis of PCOS (Balen, 2004). The success in resolving the underlying heterogeneity in any complex disorder depends on segregation of patients into homogenous groups based on some acceptable criteria.

In view of reported incidence of CD in the first degree relatives of PCOS patients, we have compared the incidence of PCOS, MD, Db and CVD in the parents, sibs and other relatives of PCOS probands (Hunter *et al.*, 2007; Cheang *et al.*, 2008; Peppard *et al.*, 2001; Talbott *et al.*, 2007). The present study appears to be the first report on this aspect where analysis was carried out on the assumption of inheritance of certain allele combinations by PCOS probands from their parents (affected from Db/CVD and MD) that may predispose the individual to PCOS. The percentage of relatives with Db and CVD in patient was significantly higher in the patient group than the control (1 vs. 0.4%). There was complete absence of history of MD and PCOS in the control group which was 3 and 1% in the patient group (<0.05). Eighteen percent of PCOS probands had parents with both Db and CVD compared to controls where it was 5% with such parental combinations. These results are supportive of our assumption that gene pool of proband's families possess clustering of susceptibility genes for complex diseases and certain combinations may influence additively/synergistically in predisposing the individuals to develop PCOS in interaction with environment.

Further, it was observed that 32% of PCOS probands had no history of CD neither in the parents nor in the second degree relatives. However, most of this section of patients had fallen under the category of elevated BMI and W/H ratio suggesting of the importance of obesity genes (Pasquali and Casimirri, 1993; Gambineri *et al.*, 2002; Hartz *et al.*, 1979) and environmental component (Escobar-Morreale *et al.*, 2005; Crosignani and Nicolosi, 2001) in susceptibility to PCOS. Increased degree of hyperandrogenism has been reported previously in PCOS women (Park *et al.*, 2001). In the light of lack of strongly associated candidate gene(s) for PCOS, familial history of CD to be the most informative risk factor for the development PCOS. However, further study with large data may be required to confirm these observations for resolving genetic heterogeneity associated with this disorder for molecular studies. Based on the present results, we predict that the incidence of PCOS is likely to be high in future in view of increasing prevalence of complex diseases like Db, CVD, MD, obesity etc.

In conclusion, subjects with the familial history of complex diseases are at high risk of developing PCOS and related complications, if left untreated. Hence awareness and early diagnosis contribute to better management with lifestyle modifications and early intervention, in turn reducing the burden of infertility, obesity, diabetes and cardiovascular disorders.

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