Polycystic Ovarian Syndrome Diagnosis in a Patient Undergoing Treatment for Bipolar Affective Disorder at Mbale Regional Referral Hospital, Uganda: A Case Report

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BACKGROUND: The association between bipolar affective disorder (BAD) and polycystic ovarian syndrome (PCOS) is elucidated in medical literature. However, what is inconclusive is whether one causes the other and/or the neuroleptics such as sodium valproate could cause PCOS as a side effect. However, to the best of our knowledge, there is a dearth of such case reports in our setting. We therefore report a case of this nature in our setting with the aim of further reemphasizing the likely comorbidity and the need for collaborative multidisciplinary approach during management of such patients.

CASE REPORT: We present a case of 34 years old, parity 0+1, human immune virus seronegative, a known patient of bipolar affective disorder (BAD) for 18 years. She was initially started on chlorpromazine and carbamazepine that she used for 13 years and later switched to sodium valproate and sertraline daily due to side effects of chlorpromazine in 2014. She presented with 6 years history of abnormal uterine bleeding and dysmenorrhea for 2 months. A diagnosis of PCOS was made based on history and confirmed by laboratory and radiological investigations.

CONCLUSIONS: Physicians need be aware of the likely comorbidity or sequel and the need for multidisciplinary engagement.

Key words: Bipolar affective disorder; polycystic ovarian syndrome; sertraline; sodium Valproate; Mbale; Uganda.

INTRODUCTION

Polycystic ovary syndrome (PCOS) also known as Stein and Leventhal syndrome, is the most common endocrine disorder in reproductive aged women, with a prevalence estimated to be between 5% and 15%, depending on the diagnostic criteria one uses (DA., 2005; Lauritsen MP, 2014). It was first described by Stein and Leventhal as a syndrome of oligoamenorrhea and polycystic ovaries, additional clinical signs such as hirsutism, acne, and obesity have continued to define the syndrome (Barbieri RL, 1983; Irving F. Stein, 1935).

Since the 1990 National Institutes of Health-sponsored conference on polycystic ovary syndrome (PCOS), it has become appreciated that PCOS is a syndrome rather than a single clinical entity and thus encompasses an array of signs and symptoms. The 2003 Rotterdam consensus workshop concluded that PCOS is a syndrome that may include menstrual irregularities, signs of androgen excess, and obesity. Moreover, according to the Rotterdam criteria, diagnosis of PCOS requires the presence of at least two of the following three findings: hyperandrogenism, ovulatory dysfunction, and polycystic ovaries (Group, 2004). Therefore, clinically diagnosing a woman as having PCOS implies an increased risk for infertility, dysfunctional uterine bleeding, endometrial carcinoma, obesity, type 2 diabetes mellitus (DM), dyslipidaemia, hypertension, and possibly cardiovascular disease (CVD) - all that have wide implications both economically and socially (Ricardo Azziz, 2009).

The relationship between mental disorders and PCOS parasite is not a straightforward one. Symptoms that are associated with the syndrome itself such as acne, hirsutism, scalp hair loss, menstrual disorders with infertility and obesity are normally distressing enough and have been associated with impaired quality of life.

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Moreover, several studies (Aaron et al 2016, Gökhan Açma et al. 2013, Mallon et al. 1999, Sonino et al. 1993; Susanne et al. 2012) have demonstrated need for the physicians to put into consideration emotional assessment in patients diagnosed with PCOS. (Aaron J. Dawes, 2016; Gökhan Açma, 2013; Mallon E, 1999 ; N. Sonino, 1993; Susanne M. Veltman-Verhulst, 2012). Further still, pharmacological agents used to manage mental disorders have also been implicated as predisposing factors to PCOS (McIntyre RS, 2003; O'Donovan C, 2002; Okanović M, 2016 ; Rasgon NL, 2005).

**Case presentation:** We present a case of 34 years old, parity 0+1, seronegative for Human Immune Virus (HIV), laboratory assistant by profession who presented to Gynaecology outpatient clinic of Mbale regional referral hospital in Eastern Uganda, East Africa in October 2019 with 6years history of abnormal uterine bleeding and dysmenorrhea for 2 months 4years history of intermenstrual bleeding and Painful menstrual periods for 2 months.

**History of presenting complaints**

She had generally been well till about 16 years prior to the date of presentation. Her initial symptoms were those of elated mood with associated flight of ideas. She was brought to our Psychiatry department and a diagnosis of bipolar affective disorder (BAD) was made. She was consequently started on Chlorpromazine (she could not remember the dose) and 400mg of carbamazepine (400mg). She reports to have been on and off these drugs till 2014 when she was switched to sodium valproate 125mg 12hrly for 5 months. She reportedly had no complaints about her menses but later became amenorrhoeic for 6 months and then started to have monthly bleeding characterized by menorrhagia and dysmenorrhea.

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She reported that over the 10 years period, she had gained excess weight, especially over her belly and trunk but no history suggestive of hyperprolactinaemia or thyroid disease. Family and social history were unremarkable.

**Examination**

She was in a fair general condition, well kept, looked overweight but had no features suggestive of androgenism.

**Body Mass Index (BMI) = 86/(1.65)^2 Kg/m^2 =31.62 Kg/m^2**

(Obesity) with a pannus especially central Obesity and a waist circumference of 91cm.

**System examinations:** revealed normal findings.

**INVESTIGATIONS AND RESULTS**

- Transvaginal ultrasound scan October
  - The ovaries are enlarged and have more than 12 follicles each measuring up to 6mm in diameter
  - Right ovary = 13.2cm^3
  - Left ovary = 26.09cm^3
  - The uterus appeared normal
  - Endometrium = 8mm thick
  - No mass seen in the pelvis
- Small cysts on the cervix (5mm) noted.
- Urinalysis: Leukocytes = trace, Protein = Nil, Glucose = Nil, Pus cells +, Microscopy: Motile rods noted

Random blood sugar = 3.9 mmol/l

**Table 1: Hormonal assays done**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luteinizing Hormone</td>
<td>24.5 IU/L</td>
</tr>
<tr>
<td>Follicle Stimulating Hormone(FSH)</td>
<td>2.0 IU/L</td>
</tr>
<tr>
<td>Estradiol</td>
<td>24.49pg/ml</td>
</tr>
</tbody>
</table>

LH: FSH=12.25

**Note:** Biochemical hyperandrogenism test was not done because these are out-of-pocket services and client could not afford.

**Diagnosis:** P0+1, Known patient of BAD on treatment with Polycystic Ovarian Syndrome (PCOS)? Endometrial hyperplasia and Urinary tract infection

**Treatment:** She was managed on tablets of Metformin 500mg once a day, Tabs MEFTAL – ASPAS (Mefanamic acid 250mg+Diclofenac 10mg) 500mg 8hrly, Caps progesterone 400mg once a day for 10days. Tabs cefuroxime 500mg 12hrly for 5 days and supportive management that included scheduled exercise (aerobics) and avoiding sedentary lifestyle. We subsequently engaged the nutrition unit to provide the diet lessons and continued management with colleagues in psychiatry.
DISCUSSION

According to Androgen Excess Polycystic Ovarian Syndrome Society Task Force (AE-PCOS-S TF), Polycystic Ovarian Syndrome (PCOS), also known as Stein and Leventhal syndrome, should be defined by the presence of hyperandrogenism (clinical and/or biochemical), ovarian dysfunction (oligo-anovulation and/or polycystic ovariies), and the exclusion of related disorders. It is the most common endocrine disorder in reproductive aged women, with a prevalence estimated to be between 5% and 15%, depending on the diagnostic criteria applied (DA., 2005; Lauritsen MP, 2014). First described by Stein and Leventhal as a syndrome of oligoamenorrhea and polycystic ovaries, additional clinical signs such as hirsutism, acne, and obesity have continued to define the syndrome (Barbieri RL, 1983; Irving F. Stein, 1935). However, according to Ricardo et al, 2009, there may be forms of PCOS without overt evidence of hyperandrogenism (Ricardo Aziz, 2009). In our case we were not able to demonstrate evidence of biochemical hyperandrogenism because of financial constraints.

Although the pathogenesis of PCOS remains elusive, there is an accepted view that it seems to arise as a complex trait that results from the interaction of diverse genetic and environmental factors that usually first become evident at puberty. Moreover, according to Ehrmann et al, 2016, PCOS can be understood through a two-hit hypothesis: the first being a congenitally programmed predisposition and the second hit hypothesis being due to exposure to environmental stimulants (Ehrmann, 2016). Vink et al, 2006, in their study further pointed to the familial and genetic factors to PCOS with resemblance in monzygotic twin sisters compared to dizygotic twins as evidenced by tetrachoric correlation and trivariate genetic analysis of oligoamenorrhea, acne, and hirsutism confirmed familial component (J. M. Vink, 2006). However the pathogenesis of PCOS has been linked to altered luteinizing hormone (LH) action, insulin resistance, and possibly hyperandrogenism (A J Jakimiuk 2001; Konstantinos Dafopoulos 1, 2009; Seija Korhonen, 2001). According to Catherine Marin DeUgarte et al, 2005, the underlying insulin resistance up regulates hyperandrogenism by suppressing synthesis of sex hormone–binding globulin (SHBG) and increasing adrenal and ovarian synthesis of androgens, thereby increasing androgen levels, which eventually lead to irregular menses and physical manifestations of hyperandrogenism (Catherine Marin DeUgarte, 2005).

Furthermore, relationship between PCOS and BAD either as a comorbidity or sequel has been elucidated. Whereas endocrine disturbances could account for distressing symptoms and signs of PCOS and thus predispose one to BAD, Richard et al, 1998, demonstrated that nearly 50% of sisters of women with PCOS are hyperandrogenism (Richard S. Legro, 1998), while Liu et al, 2014, showed that brothers of such women also had alterations in gonadotropin and steroidogenic hormone secretion (D.M. Liu, 2014). These two studies suggest that PCOS has a genetic predisposition. Furthermore, shared familial factors between PCOS and psychiatric disorders may exist, including a common genetic predisposition, as well as shared psychosocial factors in childhood.

PCOS’ relationship with psychiatric disorders seems to begin at the maternal-fetal interface and even beyond. Children of mothers that suffer from PCOS are also at risk of psychiatric disorders. Thomas et al, 2018, in their study further emphasized the hit1 and hit2 hypotheses of PCOS as put forth by Carolyn et al, 2016, and Ehrmann et al, 2016. (Carolyn E Cesta, 2016; Ehrmann, 2016)

Hum et al, 2015 demonstrated that maternal androgen excess are thought to predispose to anxiety in the children of mothers with PCOS as demonstrated in a study involving rodent models in whom prenatal androgen exposure resulted in increased anxiety-like behavior in offspring, mediated via androgen receptor activation in the amygdala and accompanied by changes in serotonergic and beta-aminobutyric acid genes in the amygdala and hippocampus (Hu M, 2015). Brain development is influenced significantly by exposure to androgens during early gestation. Female rhesus monkeys exposed in utero to androgens show increased male-type behavior (Hines, 2008) whereas both attention deficit hyperactive disorder (ADHD) and autism spectrum disorder (ASD) are more likely to be diagnosed in males than females (Baron-Cohen, 2011; Rucklidge, 2010).

That notwithstanding, a study in Iowa by Kerchner et al, 2009 showed that those diagnosed with major depressive disorder and other depressive syndromes, anxiety syndromes, and binge eating disorder, PCOS was a significant risk in this population. (Kerchner A, 2009). Moreover, Jiang-Hsui Hung et al, 2014, in Taiwan, Fatemeh et al, 2013 in Veli e asr hospital and Arshad et al, 2015 in Kashmir underpin a significant relationship between psychiatry disorders (including but not limited to BAD) and PCOS (Fatemeh Davari-Tanha, 2013; Jiang-Hsui Hung 2014). In this case although efforts were made to inquire about the other family members, no one seemed to have the psychiatric or reproductive problems. It is possible that the patient did not have a full history about all the family members.

Moreover, associations between BAD pharmacological agents and PCOS have been noted. Isojärvi et al, 1993, reported the association of sodium valproate and PCOS (J I Isojärvi 1, 1993) and in vitro studies demonstrated that valproate stimulated androgen biosynthesis in human theca cells at doses that represented therapeutic levels in the treatment of epilepsy or bipolar disorder by increased levels of dehydroepiandrosterone (DHEA), androstenedione, and 17α-OH-progesterone, and decreased levels of progesterone (Velen L Nelson-DeGrave 2004). Furthermore, McIntyre et al, 2003, the patients with bipolar
affective disorders treated with sodium valproate were more likely to be obese with higher leptin levels, have menstrual irregularities, raised follicular phase androgen concentrations compared to those managed with Lithium (McIntyre RS, 2003). These findings have been emphasized by other researches that have concluded that sodium valproate may also increase the risk of menstrual disorders, infertility and other associated symptoms of polycystic ovarian syndrome (O’Donovan C, 2002; Okanović M, 2016). Rasgon et al, 2005, in their study they found higher rates of menstrual disturbances in women with bipolar disorder and these in most cases, preceded its diagnosis and treatment. They thus concluded that valproate may contribute an additional risk rather than the mere cause (Rasgon NL, 2005). Furthermore, another study showed new-onset PCOS features (oligoamenorrhoea and hyperandrogenism) developed in 10% of women taking valproate within one year of its initiation, compared to 1% of non-valproate users (Hadine Joffe 2006). In another study, Morrell et al, 2008, demonstrated that PCOS was likely to develop in those in whom valproate was started in a young population (below 40yrs of age) (Martha J Morrell 2008). This patient was on sodium valproate 5 years prior to onset of the PCOS symptoms. However, it must be made clear that although sodium valproate increases the risk of PCOS as has been reported in the above studies, this case cannot be used to report it as a cause. Moreover, the prevalence of PCOS in women with BAD, independent of psychiatric treatments was similar to that seen in the general population (Hadine Joffe 2006). This notwithstanding, studies by Bilo et al, 1988, and Bauer et al, 2000, did not demonstrate association between valproate and PCOS (J Bauer 2000; L Bilo 1988). This patient started neuroleptics before 40yrs of age, and had never been married.

CONCLUSION

This single case cannot be used to conclude that BAD or pharmacological management of it, predisposes to PCOS. It is however, plausible that women with bipolar disorder may also have neuroendocrine dysregulation because of the psychiatric illness, which increases their susceptibility to developing PCOS in the context of other potential risk factors. Moreover, from the literature, it is paramount that for patients presenting with features of PCOS or BAD, family and social history are important in addition to pharmacotherapy history. Attending physicians should further look out for and or consult colleagues in order to rule out coexistence or likely manifestation of the other at a later time during follow up. Obstetrics and Gynaecology physicians in Uganda should be aware of the various metabolic and psychiatric disorders that could affect patients diagnosed with PCOS. Therefore, referral to or management of PCOS clients in consultation with psychiatry physician and or clinical psychologist and a dietician should be prioritized.

ABBREVIATIONS

ADHD - attention deficit hyperactive disorder
ASD - autism spectrum disorder
BAD - bipolar affective disorder
CVS - cardiovascular system
DM - diabetes mellitus
LH - luteinizing hormone
PCOS - polycystic ovarian syndrome
SHBG - sex hormone–binding globulin

DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analyzed for this case report.

Ethics approval and consent to participate

Informed consent was obtained from the patient included in the study.

Conflict of interest

We declare no conflict of interest.

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