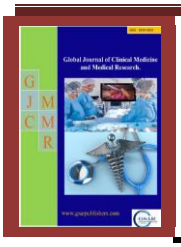

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Borderline Personality Disorder, A Psychological Illness OR Hyperandrogenic Disorder A Wider Insight into The Etiopathology, A Case Report

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Abstract

Introduction

Borderline personality disorder (BPD) is a chronic debilitating mental illness characterized by unstable interpersonal relationships, emotion dysregulation, marked impulsivity, recurrent non-suicidal self-injury (NSSI) and chronic suicidal behaviour. Psychotherapy is the cornerstone for BPD treatment. Nevertheless, approximately half of the BPD patients do not respond to psychotherapy.

Methods

This report describes a 29-year-old female patient diagnosed with posttraumatic stress disorder (PTSD) and chronic BPD with comorbid depression. Although PTSD was partially treated with psychotherapy, BPD core features remained active. Given the chronicity and severity of her illness, the patient had been reassessed to explore the presence of other potentially treatable etiologic factors. Reassessment included a clinical interview, blood tests, vital signs, anthropometric characteristics, and screening and monitoring tools to assess and quantify the severity of borderline core features and the presence of comorbidities. Due to the presence of masculine hair distribution, hirsutism was assessed by Ferriman-Gallwey Scale. The patient has been treated with a combination of spironolactone and metformin. The effect and side effects of treatment were monitored during a 10-week follow-up period.

Results*: Reassessment revealed active BPD core features with significant impulsiveness, moderate degree of anxiety and depression, and moderate to severe hirsutism on a background of hyperandrogenism. Four weeks post-treatment the patient achieved complete remission in all BPD core features including suicidal thoughts and self-harm behaviour. Besides, partial improvement in hirsutism was reported by the patient.*

Conclusion: *This case report demonstrates a state of hyperandrogenism as an underlying aetiologic factor for BPD core features in a young adult female. Treatment of hormonal dysregulation was associated with complete remission in all BPD core features and BPD comorbidities, anxiety and depression. This case report suggests the need for a wider holistic approach in the management of mental health disorders than that commonly adopted in current practice*

Key words: *Borderline personality disorder, Hyperandrogenism, Antiandrogens Treatment*

Introduction

BPD is a chronic debilitating mental illness with an estimated prevalence of about 10-12% in outpatient and 20-22% in inpatient psychiatric services (1,2). BPD key features include unstable interpersonal relationships, emotion dysregulation, marked impulsivity and high- risk behaviour, recurrent non-suicidal self-injury (NSSI) and chronic suicidal ideations and attempts. It has been reported that 65-90% of BPD patients engage in NSSI, 60-78% show suicidal behaviours, 73% will have approximately 3 suicide attempts in their lifetime, and up to 10% will die by suicide (1,3,4). Moreover, high prevalence of somatic morbidity (including endocrine, metabolic, respiratory, cardiovascular and infectious diseases) and

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mortality among patients with BPD has been reported (1). In this context, Leichsenring et al. (2024) (1) reported that 14% of BPD patients died by a non-suicide cause during a 24-year follow-up period.

BPD patients have been reported to have other psychiatric comorbidities such as anxiety disorders (88%), depression (71%-83%) and PTSD (25-58%) (1,2,5). The presence of such comorbidities may further worsen the clinical presentation, complicate the diagnosis and negatively affect treatment outcome. It has been reported that BPD-PTSD comorbidity (compared to either disorder alone) is associated with greater emotion dysregulation, higher rates of other Axis 1 disorders, and increased risk of suicide attempts and NSSI (6).

Treatment of BPD can be fraught with challenges. In this regard, no psychotropic medication has been proven to be effective in treatment of BPD core features (1,2) and psychotherapy remains the treatment of choice for BPD (1). Nevertheless, approximately half of the BPD patients do not respond to psychotherapy. Woodbridge et al. (2021) (7) reported failure of psychological treatment in 48.4% of BPD patients in the community mental health service who were followed up for a period of 12 months (7). In a more recent report, Leichsenring et al. (2024) (1) indicated that psychotherapy treatment for BPD has a medium effect size, between 0.50 and 0.65.

Dysfunction of serotonergic neurotransmission, particularly 5HT1A dysfunction, has been linked to BPD core features including emotional dysregulation, impulsivity, aggression, NSSI, and suicidal behaviour (8-14). Interestingly, some researchers reported similarity of the neurobiological effects of psychotherapy and conventional psychotropic medications in some mental health disorders including major depressive disorder (MDD) and BPD (8-10,15). Karlsson et al. (2010) (8) mentioned that molecular imaging studies demonstrated a widespread decrease in the density of serotonin 5-HT1A receptors in the brain of MDD patients. The authors reported a significant psychotherapy- induced increase in 5-HT1A receptor density and increased serotonin 5-HT1A receptor binding in multiple cortical regions. Lehtonen (2012) (9) reported psychotherapy- induced increase in serotonin binding in the brain of patients with typical depression. Similarly, Lai et al. (2007) (10) indicated that psychotherapy resulted in normalization of dysregulated frontal serotonergic neurotransmission in BPD patients. Given the suggested similar effect of psychotherapy and psychotropics on the serotonergic system, failure of psychotherapy might predict ineffectiveness of conventional psychotropics to treat BPD core features and therefore, could be an indication to apply a holistic approach to reveal a potentially overlooked cause for poor treatment response. This is in line with previous case reports (16,17) in which implementation of a holistic approach revealed testosterone dysregulation as an underlying aetiologic factor in male patients with anxiety, depression and borderline features. In this context, the influence of high testosterone levels on mood and behaviour in both animals and human has been reported in the literature. Agrawal et al. (2019) (18) reported that supraphysiological doses of testosterone increased impulsivity in gonadectomized rats via upregulation and hyperactivation of alpha-2A adrenergic receptors (α2AARs) specifically in the prefrontal cortex (PFC). In human, several studies (18-26) reported a relationship between high androgen level in women and depression and anxiety (common BPD comorbidities) and impulsivity, risky behaviour, emotional dysregulation, anger-related aggressive behaviour, impaired interpersonal relationship and suicidal behaviour (core features of BPD).

Spironolactone, a classic potassium-sparing diuretic drug, is a steroidal aldosterone antagonist that possesses an antiandrogen effect. Because of its antiandrogen effect spironolactone is commonly prescribed for patients with polycystic ovary syndrome (PCOS). Its antiandrogen effect is suggested to be due to one or more of the following mechanisms (27-30): lowering total testosterone level by a partial inhibition of the 17α-hydroxylase enzyme involved in the biosynthesis of testosterone. This mode of action was not supported by other investigators (27,28); competitive inhibition of the androgen receptors; increase in serum oestradiol; and oestradiol and progesterone receptor agonism.

Metformin, an antidiabetic medication, is also used to treat hyperandrogenism in women with PCOS. It has been reported that in women with PCOS treatment with metformin was associated with significant decrease in total testosterone level via a direct effect on ovarian androgen secretion (31), significant reduction in free testosterone level and significant increase in sex hormone binding globulin (SHBG) (32,33). In 2 more recent reports metformin administered to men with diabetes mellitus type 2 was associated with significant reduction in total and free testosterone levels (34,35). The testosterone- lowering effect of metformin has been reported to be more pronounced when combined with an antiandrogen (30). On a cellular level, metformin was found to downregulate androgen receptors (ARs) and counteract the testosterone-induced AR expression in human stromal cells (36).

This report describes a 29-year-old female patient with active BPD core features associated with partially treated PTSD and comorbid depression who demonstrated complete remission in all her BPD core features and depression and anxiety comorbidities after treating an overlooked hyperandrogenism with spironolactone- metformin combination. Although the use of antiandrogen treatment for hyperandrogenic features in female with PCOS, such as acne vulgaris and hirsutism, has been widely reported in the literature (30,37), to the best of my knowledge, no earlier studies have assessed the use of antiandrogens in the treatment of BPD core features and/or comorbidities. Therefore, this case report might open an avenue for a wider insight into the etiopathology and treatment strategies for borderline personality disorder.

Patient and method

Ms CA is a 29-year-old female. She is a light smoker and has no past nor current history of any illicit drug use nor alcohol abuse. She has no past or current history of relevant physical illnesses nor congenital disorders. Over the past several years

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she had been struggling with her mental health illness in terms of persistent signs and symptoms of depression and anxiety, significant impulsiveness, NSSI and chronic suicidal thoughts.

She has been under treatment and supervision of different mental health services across the Netherland. She has been given the following diagnoses: PTSD, BPD, and depressive disorder. Consequently, she received different psychotherapy treatment modalities including EMDR. In this regard, the patient indicated a positive effect of the EMDR on some aspects of her PTSD symptoms. Nevertheless, her borderline core features and the symptoms of comorbid depression did not resolve. She also received a short course of antipsychotics and other pharmacotherapy treatment including benzodiazepine. Her symptoms persisted, though.

On a physical level, the patient indicated that she has been struggling for years with excessive hair growth and acne. Her general practitioner referred her to a gynaecologist to exclude the presence of PCOS. In this regard, PCOS had been excluded and consequently she was prescribed oral contraceptives and topical treatment, however without relevant improvement.

Given the chronicity of her mental health symptoms, she had been reassessed to verify the nature of her mental illness and its underlying etiopathology. Re-assessment included a clinical interview, blood tests, vital signs (blood pressure and pulse rate), electrocardiogram (ECG), anthropometric characteristics, and several screening and monitoring tools. The latter included the Borderline Symptom List 23 (BSL-23), the Barratt Impulsiveness Scale (BIS-11), the Hamilton rating scales for depression (HAM-D17) and anxiety (HAM-A) and the hirsutism Ferriman-Gallwey Scale (HFGS).

BSL-23 questionnaire was purposed to assess the severity of the patient's BPD symptoms. The validity and reliability of this tool and the interpretation of obtained score has been previously addressed (16,17). The BIS-11 was purposed to verify and quantify the presence of trait impulsivity. Again, the validity and reliability of this screening- monitoring tool has been addressed in the literature (38, 39). BIS-11 is one of the most widely used instruments which assesses trait impulsivity (impulsiveness) as a multidimensional rather than a unidimensional construct (38). BIS-11 is a 30 item self-report questionnaire. Each item reflects impulsivity-related thoughts and behaviour in different situations and is rated on a 4-point Likert scale ranging from 1 (Rarely/Never) to 4 (Almost Always/Always). The total score ranges from 30 to 120 points. Higher scores indicate higher levels of impulsiveness. In this regard, total scores between 52 and 71 are reported to be within normal limits for impulsiveness while, a total score of 72 or more indicates high impulsiveness (38). Based on the concept that impulsiveness is a multidimensional construct (38), BIS also assesses 6 impulsivity domains or dimensions called first order factors. These include attention, cognitive instability, motor, perseverance, self-control and cognitive complexity.

The Hamilton rating scales for depression (HAM-D17) and anxiety (HAM-A) have been used to verify the presence and quantify the severity of depression and anxiety. The validity, usefulness, scoring and interpretation of the obtained results of these scales have also been previously mentioned (16,17). Due to masculine hair distribution (as described by the patient), assessment of hirsutism using the hirsutism Ferriman-Gallwey Scale (HFGS) has been used to quantify hirsutism. The validity and reliability of this tool have been widely addressed in the literature (40,41). In this regard, HFGS assesses the hair density in 11 different androgen dependent body sites (upper lip, chin, chest, upper abdomen, lower abdomen, 2 arms, 2 thighs, upper back and lower back). The density of terminal hair growth in each site is scored on a 5-point Likert scale ranging from 0 (no terminal hair) to 4 (extensive terminal hair growth). A total score, which is made by summing all sub scores, ranges from 0 to a maximum of 36. A total score of ≥ 8 indicates hirsutism, a score between 8 and 15 indicates mild hirsutism and a score > 15 indicates moderate– severe hirsutism and likely indicates the presence of androgen excess (40,41).

The following blood parameters have been assessed: complete blood picture, renal function tests, liver function tests, thyroid function tests, complete hormonal profile including oestradiol, progesterone, luteinizing hormone, follicle stimulating hormone, testosterone and SHBG, fasting blood glucose and HBA1c and vitamin profile. In order to assess the androgen status in this patient, the free testosterone level and Free Androgen index (FAI) were calculated. The free testosterone level which reflects the biologically active fraction of testosterone was calculated according to Vermeulen et al. (1999) (42). The FAI which mirrors the biologically active fraction of testosterone is calculated as the ratio of total testosterone to SHBG (expressed in the same unit). FAI is considered a useful indicator of hyperandrogenism in conditions such as PCOS and hirsutism, particularly when the total testosterone concentration is normal, but the SHBG is low (43).

Given the potential side effects of spironolactone including hyperkalaemia and hypotension, clinical side effects and blood pressure as well as renal functions and serum potassium were monitored. Clinical side effects were monitored at 7 time points, weeks 2, 3, 4, 5, 8, 9 and 10 after treatment commencement. All clinical reviews were performed face-to-face except for the last follow up review (at week 10). The latter was conducted over the phone at the request of the patient due to upper respiratory tract infection.

Blood pressure was monitored at the start of week 3 and week 4. Clinical questionnaires and monitoring tools were filled in and evaluated during week 8 follow up visit. Blood tests to assess serum potassium level and renal function tests were performed 1-, 4- and 9-weeks posttreatment. Other monitoring blood tests were performed at 4- and 9-weeks posttreatment.
The clinical and laboratory test results were compared to baseline (BL) data.

In terms of the blood samples, these were taken during the follicular phase in the morning (approximately 08:30 a.m.) of days 4 (BL sample), 10 (week 4 posttreatment sample) and 11

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(week 9 posttreatment sample) of the menstrual cycle. This was thought to minimize variability in hormone levels observed during different phases of menstrual cycle. BL blood tests were assessed in 2 different laboratories and the average was used.

Based on the obtained results (see below), the patient has been treated with a low dose of spironolactone and metformin.

Results

During the BL clinical interview, the patient reported the following symptoms: low mood, inability to control her own emotions, marked impulsive behaviour, irritability, disturbed social relations with frequent conflicts, sleep difficulties, long-standing recurrent suicidal thoughts and repeated NSSI. When asked, the patient indicated that she engages in NSSI to relieve her emotional pain and distress. According to the patient, her symptoms started around the age of 16 and have worsened over the past 5 years. In this regard, the patient mentioned that she had recurrent thoughts about assisted suicide (Euthanasia) to end her psychological suffering and that she discussed this with one of her treating psychologists.

On a physical level, the patient indicated that she has excessive hair growth (on face and body) and acne more intense on the back. When asked, she indicated having normal regular menstrual cycles.

BL assessment scales showed high grade features of BPD (BSL-23 score 2.65) and clinically significant impulsiveness (BIS-11 total score 72), moderate degree of anxiety (HAM-A score 16) and depression (HAM-D score 19) as well as moderate to severe hirsutism (HFGS score 16). BL physical assessments showed a blood pressure of 110/80 mmHg, a pulse rate of 67 bpm and a Body mass index (BMI) of 30. The obtained ECG showed a regular sinus rhythm with no abnormalities.

BL blood tests showed no clinically relevant findings except for low normal tetraiodothyronine (T4), severely reduced SHBG and high calculated free testosterone (CFT) and FAI. In this regard, serum levels of TSH and T4 levels were respectively 1.91 mE/L (reference: 0.27-4.20 mE/L) and 14.4 pmol/L (reference: 12-22 pmol/L). Regarding sex hormones profile, the average values for total testosterone, SHBG and CFT levels were respectively, 1.2 nmol/l (reference range 0.29-1.7 nmol/l), 7.3 nmol/l (reference range 32.4-128 nmol/l) and 0.039 nmol/l (reference range 0.003-0.033 nmol/l). The calculated FAI was 16.4% (reference range for women 7-10%). BL serum oestradiol level was within normal reference range (see below).

The obtained results including abnormal hormone profile has been explained to the patient. The patient was advised to maintain a healthy Lifestyle. In addition, different non-psychotropic treatment options have been discussed with the patient in details including the mechanism of action, potential side effects and post-treatment monitoring requirement. She clearly indicated her unwillingness to reuse any oral contraceptives to treat her condition. However, she confirmed her willingness to start treatment with spironolactone, metformin and levothyroxine. Given this, the patient was prescribed a low dose spironolactone (25mg once daily), metformin (500mg twice a day) and a low dose levothyroxine (50ug once daily). The latter was prescribed to improve thyroid function that is believed to improve SHBG profile. However, this did not seem to have any positive effect on the SHBG blood level.

At the start of week 3 posttreatment the patient indicated having no side effects. The obtained values for blood pressure and pulse rate were not significantly different from the BL values and were respectively 110/ 80 mmHg and 73 bpm.

Four weeks after commencing treatment the patient indicated complete remission in all her symptoms including impulsivity, emotion dysregulation, anxiety and depression, suicidal thoughts and NSSI. There were no clinical side effects observed or reported by the patient. The obtained blood pressure and pulse rate values were respectively 103/81 mmHg and 69 bpm.

At week 8 posttreatment, all clinical monitoring tools showed clinically relevant decline in the obtained scores compared with BL, **figures 1 and 2**.

Noteworthy is that, during week 8 follow up visit the patient indicated that this is her first time, since start of her mental illness, to realize that she has neither death wishes nor suicidal thoughts. Also, during the same visit (week 8) she reported improvement in her masculine hair distribution and near clearance of her acne. In concordance with the patient's verbal reporting, the HFGS score declined by approximately 25%, from 16 (moderate to severe hirsutism) at BL to 12 (mild hirsutism).

During the last follow up review (week 10 posttreatment) the patient confirmed the stable mental health status and the sustained complete remission of all BPD features and comorbid symptoms.

During the entire follow up period there were no clinically relevant changes either in serum potassium level or in renal function tests (serum creatinine and e-GFR) as compared to those obtained at BL. The values obtained at BL were as follows: serum potassium **(**4.3, reference: 3.5-5.1 mmol/l); serum creatinine (56, reference: 53-106 umol/L); and eGFR (> 90 ml/min/ 1.73 m2, reference > 90 ml/min/ 1.73m2). Values obtained at weeks 1, 4 and 9 assessment time points were 4.3, 4.4 and 4.2 mmol/L; 56, 67 and 69 umol/L; and > 90 ml/min/ 1.73m2 (at all 3 assessment time points, week 1, week 4 and week 9) respectively for serum potassium, serum creatinine and eGFR.

BL total testosterone level (1.2 mmol/l) declined to 0.6 nmol/l (-50%) at week 4 assessment time point. At week 9 the level albeit remained lower than BL increased slightly to 0.8 nmol/l.

Similarly, at week 4 post-treatment CFT levels declined by approximately 46% from BL to become 0.021 nmol/l. This value was slightly increased at week 9 to become 0.028 nmol/l which was still within reference range. Similar changes

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have been observed in the FAI. The values obtained at weeks 4 and 9 were respectively 10% and 11.8%.

Figure 3 demonstrates the results.
Serum oestradiol levels obtained at 3 time points during the follicular cycle (BL, week 4 and week 9) were respectively 184, 150 and 412 pmol/l. These values were within the reference interval (45,4- 854 pmol/ l) and was considered to reflect normal intraindividual variability of oestradiol levels during the follicular phase (44).

Discussion

This case report describes a 29-year-old-female patient diagnosed with BPD, PTSD and comorbid depression. Psychological treatment including EMDR could help resolution of a few of the PTSD symptoms. However, psychotherapy was ineffective to treat BPD core features and comorbid depression in this patient.

As mentioned before, reassessment of the patient revealed active BPD core features, moderate depression and anxiety and abnormal hyperandrogenic status reflected in elevated CFT and high FAI, despite the presence normal total testosterone level. In this regard, Al Kindi et. al (2012) (45) found that the diagnosis of hyperandrogenism in women was most obvious when using CFT or FAI than testosterone alone. In addition, the authors recommended including CFT and/or FAI in assessment of women with disorders related to clinical or biochemical hyperandrogenism.

Treatment with spironolactone and metformin combination was associated with complete remission of all BPD essential clinical features, including impulsiveness and suicidal behaviour. Parallel to this improvement, BSL-23, BIS-11, HAM-D17 and HAM-A monitoring tools all showed marked reduction in the posttreatment scores as compared to BL ones. Interestingly, the decline in the impulsiveness scale (BIS-11) score was more pronounced in attentional and motor impulsiveness domains, respectively -38% and -27%. This is in line with the suggestion that adults with suicidal behaviour tend to score higher on the BIS-11 motor or attentional subscales than those without (38).

The exact underlying pharmacodynamic mechanism responsible for complete symptoms remission in this patient remains to be elucidated. On one hand, symptoms remission is unlikely related to changes in serum oestradiol levels. This is because all obtained levels were within the reference range and therefore could reflect normal intraindividual variability in oestradiol as reported by Shultz et. al (2009) (44). On the other hand, there seem to be a medications-induced change in the androgen dynamics in this patient. These changes could be the result of direct or indirect effect of the pharmacological treatment. In this regard, decline in CFT and FAI could be, at least in part, responsible for symptoms remission. As noted before high testosterone level was reported to be associated with many of the BPD core features (18, 22- 26).

Neurobiologically, high testosterone levels might modulate emotions and behaviour through a number of mechanisms that involve prefrontal cortex and the amygdala.

High testosterone level causes upregulation and hyperactivation of α2AARs specifically in the PFC (18), a brain region that plays an important role in executive functions. Overactivation of α2AARs has been reported to impair PFC function (46). This in turn causes deficit in executive functions and impairment in cognitive regulation of emotions, 2 key elements in the psychopathogenesis of BPD (47,48). The amygdala which plays a pivotal role in processing emotion is under inhibitory control of the prefrontal cortex. It has been reported that excessive amygdala activation to negative emotion along with diminished frontal regulation of the amygdala responses are implicated in the pathogenesis of BPD (49,50). The amygdala is rich in androgen receptors and therefore has been considered to be a target for testosterone (51). Testosterone administration to women was found to increase amygdala responses to threat and fearful stimuli (51,52). In addition, Kogler et. al (2023) (53) reported that frontal cortex cognitive control over the amygdala is dependent on testosterone levels with a sex-dependent effect. In this regard, high testosterone levels in women were found to decrease coupling of the amygdala with cortical regions and consequently decrease the cognitive inhibition of an exaggerated amygdala response (53). Therefore, it is conceivable to assume that androgen reducing agents would be associated with remission of BPD symptoms via reduction in the biologically active fraction of circulating testosterone.

Another conceivable explanation for complete symptoms resolution could be the direct action of both spironolactone and metformin on the target receptors. As mentioned before, the suggested mode of action of spironolactone includes androgen receptor antagonism and oestradiol and progesterone receptor agonism. The effect of spironolactone on sex hormone receptors might have been augmented by metformin. The latter has been reported to induce downregulation of androgen receptors expression (36) and diminishes α 2 adrenoceptor activity in the prefrontal cortex (54).

Finally, hirsutism and acne in this patient might be explained by the elevated active testosterone fraction (free testosterone). However, a possible causative role played by androgen receptors hypersensitivity in this scenario cannot be ruled out. In this regard, some researchers have suggested that these symptoms are due to either androgen excess or increased sensitivity of androgen receptors regardless of androgen level (55).

Although spironolactone-metformin combination treatment was associated with complete remission in all mental health clinical symptoms, there was incomplete improvement in hirsutism (-25%) at week 8 follow up time point compared to BL. The incomplete remission of hirsutism might be reasoned by one or both of the following mechanisms: (1) spironolactone has a dose dependent direct peripheral effect on androgen receptors (competitive inhibition) (30,56) and therefore a low dose as given to this patient (25mg o.d.) would be expected to induce incomplete remission in hirsutism and/ or (2) the long hair follicles life cycle

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(approximately 6 months) which explains the delay in onset of action of most anti-hirsutism medications (57).

It is noteworthy to mention that despite the incomplete improvement in hirsutism and acne compared to baseline, the doses of both medications, spironolactone and metformin, were not increased at the request of the patient who was content with the complete remission in her BPD core features and comorbid anxiety and depression and did not want to escalate the dose.

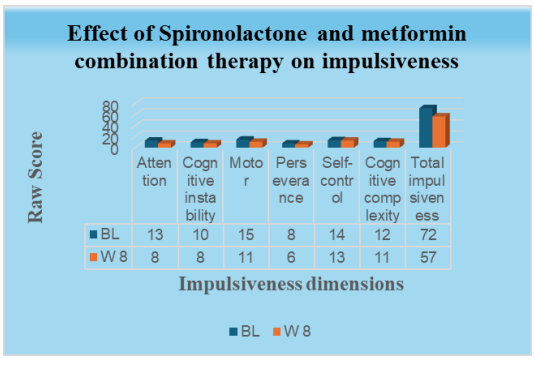
The main limitations of this report are: (1) the finding is in one subject (a case report); (2) the dose given was lower than those given to patients with PCOS- related hyperandrogenism (up to 100 mg a day for spironolactone and 1500 mg a day for metformin) (30); and (3) the short follow up period. This is particularly important given the slight increase observed in hormonal test results, viz. CFT and FAI at week 9 posttreatment and the incomplete improvement in hirsutism. Therefore, cohort studies with escalating doses and longer follow up period are warranted to evaluate and confirm the findings in this case report.

Conclusion

This case report demonstrates a disturbed hormonal profile as an underlying aetiologic factor for BPD core features in young adult female. Treatment of the hormonal dysregulation in this patient was associated with complete remission in all BPD core features including suicidal behaviour, and in comorbid anxiety and depression. In this context, this report is the 3rd case report that emphasizes the need for a wider holistic approach in the management of mental health disorders than that commonly adopted in current practice. This may not only reduce patient's suffering which could last for years compromising his/ her social and occupational functioning but also reduce the burden on the health care systems and other societal costs.

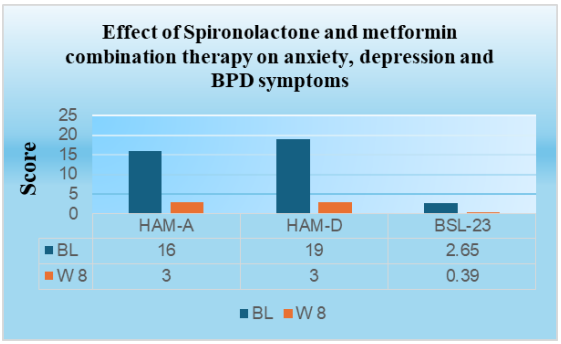
More studies with longer follow up periods are needed to confirm the finding in this report.

Figure 1.



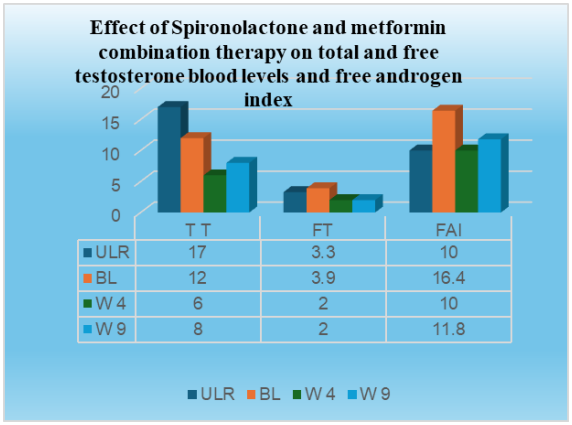
BL= baseline; W8= week 8

Figure 2.



BL= baseline; W8= week 8. HAM-A= Hamilton rating scale for anxiety; HAM-D17= Hamilton rating scale for depression; BSL-23= Borderline Symptom List 23.

Figure 3.



ULR= upper limit reference range; BL= baseline; W4 and W9 = week 4 and week 9.

TT= total testosterone, values are expressed in nmol/l and multiplied by 10 for demonstration. FT= calculated free testosterone, values are expressed in nmol/l and multiplied by 100 for demonstration. FAI= Free androgen index, expressed as %.

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