TREATMENT-RESISTANT MIXED ANXIETY AND DEPRESSION: A GENUINE MENTAL ILLNESS OR AN EXPRESSION OF OVERLOOKED DISORDERS?

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ABSTRACT
Introduction: Depression is a leading cause of disability worldwide. Approximately 85% of patients with depression have significant symptoms of anxiety and demonstrate mixed symptoms of anxiety and depression. Up to 30% of patients treated for anxiety or major depressive disorder (MDD) are treatment-resistant. High prevalence rates of attention deficit hyperactivity disorder (ADHD) and personality disorders (PDs) in patients with major MDD and anxiety have been reported. In addition, the role of hormonal imbalance in the pathogenesis of anxiety and depression has been discussed and emphasized in the literature. Methods: This report describes a 34-year-old obese male with a diagnosis of treatment-resistant chronic mixed anxiety and depression, associated with recurrent self-harm, suicidal thoughts, and suicidal attempts. The patient received multiple antidepressants with neither subjective nor objective improvement. Given the chronicity and severity of his illness, the patient has been reassessed to explore the presence of other potentially treatable etiologic factors. Re-assessment included a clinical interviews, blood tests, vital signs, anthropometric characteristics, and self-rating questionnaires to assess for ADHD (ASRSv-1.1) and personality disorders (including borderline personality disorder (BSL-23)). Besides, the Hamilton rating scales for depression (HAM-D17) and anxiety (HAM-A) have been used to quantify the depression and anxiety symptoms severity. The patient has been treated with a combination of testosterone gel, methylphenidate, and iron supplement. The effect and side effects of the treatment were monitored during a follow-up period of 11 weeks. Results: Clinical and laboratory reassessment revealed severe degree of anxiety and depression on a background of clinically significant hypogonadism, ADHD- borderline personality disorder comorbidity, and anaemia. At week 11 of treatment, the patient achieved complete remission in all his signs and symptoms, including suicidal thoughts and self-harm behaviour. At the end of the follow-up period, the patient reported >95% improvement in his symptoms. Clinically significant and meaningful improvement in ADHD (complete remission) and borderline symptoms (91% reduction from baseline). Parallel to this improvement, HAM-D17 and HAM-A demonstrated reduction from baseline respectively -85% and -78%. The patient reported his full contentment with his treatment and improvement in his family life, social relationship and work. Conclusion: Treatment-resistant anxiety and depression are associated with severe physical and psychological symptoms associated with impairment of daily living skills and social functioning, and high suicidal risk. Successful management of this relentless mental health illness might be hampered by an underlying indiscernible physical and/or mental illness and, therefore, requires an integrated diagnostic approach to better understand other factors that manifest themselves in anxiety and depression and contribute to poor treatment response.

KEYWORDS mixed anxiety and depression, Hypogonadism, ADHD, Borderline personality disorder, Anaemia

Introduction

Up to 30% of patients treated for anxiety or major depressive disorder (MDD) are treatment-resistant [1-4]. Treatment-resistant depression (TRD) is usually associated with longer episodes of greater depression severity, higher suicide risk, obesity (BMI ≥30kg/m²), and sexual dysfunction [2, 5]. Despite its substantial burden on both patients and the community and the negative impact on patient’s quality of life, the currently prescribed antidepressants have limited treatment effectiveness [1, 2].

The presence of overlooked psychopathology such as underlying attention deficit hyperactivity disorder (ADHD) and personality disorders (PDs) and/or hormonal dysregulation might lead to misdiagnosis of an apparently treatment-refractory disease. It has been reported that up to 80% of adult patients with ADHD have at least one comorbid mental health illness [6]. The
commonest comorbidities associated with adult ADHD were found to be mood disorders, including major depressive disorder (38.3% to 53.8%), and anxiety disorders, including social phobia and generalized anxiety disorder 23.1% to 47.1% [7,8]. On the other hand, the rate of ADHD among patients diagnosed with anxiety disorders have been reported to be 27.9% [7]. Among patients diagnosed with TRD 34% have been reported to meet the diagnostic criteria for ADHD [6,9]. Furthermore, 18% of patients with adult ADHD and depression were reported to have comorbid personality disorders, including borderline personality disorder (BPD). In this regard, symptoms are usually more severe and treatment-resistant [6]. In addition, the role of hormonal dysregulation in the pathogenesis of treatment-resistant anxiety and depression has been addressed in a recent paper [1].

Overlooking underlying primary psychopathologies such as ADHD and BPD or hormonal imbalance may complicate the diagnosis, hamper appropriate treatment, prolong the suffering of the patient and impairment of his functions.

In this case report, we describe a 34-year-old male patient diagnosed with treatment-resistant chronic mixed anxiety and depression who demonstrated complete remission of his mental illness after treating overlooked ADHD- BPD comorbidity, anaemia and hypogonadism with oral methylphenidate, locally applied testosterone, and iron supplement combination therapy.

**Methods**

This report describes a 34-year-old obese male (Mr. LD) with an established diagnosis of treatment-resistant chronic mixed anxiety and depression associated with recurrent self-harm, suicidal thoughts, and suicidal attempts. Mr. LD is a non-smoker, non-alcoholic, compulsive overeater, obese, otherwise healthy man. Mr. LD received and used multiple psychotropic medications for several years with neither subjective nor objective improvement in his mental health illness. The psychotropic medications he received included duloxetine, venlafaxine, sertraline, mirtazapine, and citalopram. Over the past 2 years, Mr. LD received and used fluoxetine 60 mg a day and quetiapine 150 mg a day, again without any improvement in his mental health illness nor remission in his suicidal ideations or self-harm.

Given the chronicity and severity of his illness, the patient has been reassessed to explore the presence of other potentially modifiable underlying treatable etiopathology.

In addition to history taking and self-reported symptoms, clinical re-assessment included blood tests including full blood count and hormonal profile, vital signs, anthropometric characteristics, and self-rating questionnaires to assess for ADHD (ASRSv-1.1) [10] and personality disorders (including BPD (BSL-23)) [11]. Besides, 2 clinician-rated scales with well-established reliability, validity, and sensitivity, the Hamilton Rating Scales for Depression (HAM-D17) and anxiety (HAM-A), have been used to quantify the severity of Mr LD’s depression and anxiety symptoms (quoted from reference 1).

Adult ADHD Self-Report Scale (ASRS) is a self-rating scale based on the DSM-IV diagnostic criteria for ADHD. It consists of 18 questions (reflecting ADHD symptoms) scored on a 5-points Likert scale ranging from 0 (never) to very often [4]. The higher the score, the more frequent and the greater the severity of the symptoms [10]. The 18 questions are divided into 2 parts, part A (6 questions) and part B (12 questions). Scoring is based on the number of checkmarks in the darkly shaded boxes [10]. Four or more marks appearing in the darkly shaded boxes of part A indicate that symptoms are highly consistent with ADHD in adults [10]. Part B has no diagnostic value; however, the total score in this part might indicate the severity of the symptoms [12]. The validity and reliability of this screening tool have been widely addressed in the literature [12, 13]. ADHD symptoms, as listed in the ASRS questionnaire, can be subdivided into 2 subsets, 9 questions each: Inattention (IA) and Hyperactivity-Impulsivity (Hy-I). To quantify each subset of symptoms, the quantitative ranking of Yeh and associates [13] has been adopted. A sum score on either subscale (IA or Hy-I) of ≥24 means that ADHD is highly likely to be present; a score between 17–23 means ADHD is likely to be present; and 0–16 ADHD is unlikely to be present [13]. In this case report, these scores have also been used to reflect the change in the severity of both subscales, IA and Hy-I, during the course of treatment.

BSL-23 questionnaire has been designed to assess and monitor BPD symptoms severity [14]. The BSL-23 is a 23 items questionnaire based on BPD diagnostic criteria of the DSM-IV / DSM-5. Each item is rated on a 5-point Likert scale ranging from 0 = not at all to 4=very strong, making a total score between 0 and 92. The sum of all items score is then divided by 23 to give a mean score [14]. In this context, a cut-off value of 0.64 has been reported to discriminate between BPD patients and healthy controls. In addition, 6 grades of BPD severity based on the obtained mean score have been suggested: none or low:0–0.3; mild: 0.3–0.7; moderate: 0.7–1.7; high: 1.7–2.7; very high: 2.7–3.5; and extremely high: 3.5–4 [14].

The HAM-D17 is a 17-point scale with a total score range between 0 and 52. The score of 0-7 is normal, 8–16 reflects mild depression, 17–23 reflects moderate depression, and scores ≥ 24 indicate severe depression (quoted from reference 1). The HAM-A consists of 14 symptom-defined anxiety parameters with a total score between 0 and 56. A total score 0-7 indicates no or minimal anxiety, 8-14 mild anxiety, 15-23 indicates moderate anxiety, and ≥ 24 represent severe anxiety (quoted from reference 1). As previously indicated [1], although HAM-A may not discriminate between anxiety and depression, limiting its use in clinical trials, this does not negatively affect the data demonstrated in this case report. This is given the already established diagnosis of mixed anxiety and depression in this patient, which makes this scale suitable to use in this case report.

The results of clinical and laboratory information gathered during reassessment (Baseline data, BL) have been discussed with Mr. LD. After obtaining his approval on an outlined treatment plan, he was commenced on oral Methylphenidate (MPT), local testosterone (T) and iron supplement (I) combination therapy (MPT-T-I). In this regard, Mr. LD received MPT at a dose of 60 mg a day for 4.5 weeks, followed by 90 mg a day. Testosterone gel (2%) has been locally applied (as per manufacturer instruction) at dose of 60 mg a day and gradually increased up to 80 mg a day. After commencement of the combined treatment, Mr LD was followed up for 11 weeks to monitor the subjective and objective changes in his mental health illness. Meanwhile, Mr LD continued receiving fluoxetine and quetiapine before he reduced the dose of these psychotropic medications, on his initiative, at week 9 of the follow-up period.

During a follow-up period of 11 weeks, Mr. LD’s mental health status and the efficacy of treatment given have been monitored at 2-time points, 4.5 weeks (i.e., during week 5) and 11 weeks after commencement of treatment. This included reviewing clinical interviews, self-reported symptoms, self-reported questionnaires, and blood tests.
Figure 1: BL= baseline; W5 = week 5; W11= week 11. HAM-D17= Hamilton Rating Scale for Depression; HAM-A= Hamilton Rating Scale for anxiety. See text for interpretation of scores.

Figure 2: BL= baseline; W5 = week 5; W11= week 11. ASRS = Adult ADHD Self-Report Scale Symptom Checklist (A=part A and B=part B). See text for interpretation of scores.

Figure 3: BL= baseline; W5 = week 5; W11= week 11. BSL-23= Borderline Symptom List. Values multiplied by 10 for demonstration. ASRS-IA = Adult ADHD Self-Report Scale Symptom Checklist (inattention items). ASRS-Hy-I = Adult ADHD Self-Report Scale Symptom Checklist (Hyperactivity- impulsivity items). See text for interpretation of scores.

Results

At BL, Mr. LD reported feeling anxious and depressed the whole time despite the medications he was on for a long time. He reported that many of his symptoms started during the childhood-adolescence period. He was a hyperactive child and had reduced concentration and difficulty keeping his attention. When explored, he indicated that he can be very impulsive and feels regret after acting impulsively. He had a high degree of hypervigilance, emotional lability, and difficulty controlling his actions. This led to anger outbursts and aggression towards himself and others, including his spouse. In this regard, Mr LD had been admitted to the hospital on 2 separate occasions due to suicide attempts. In addition, he had been engaged in self-harm (cutting in his arms and legs). He indicated having social anxiety and difficulties in interpersonal relationships. He had difficulty planning or organizing activities, including his work and had neither motivation nor interest to engage himself in normal daily tasks nor social activities or hobbies. When asked, he mentioned that he has no libido and has suffered erectile dysfunctions for a long time. He mentioned that these symptoms are long-standing and are causing severe distress to him and his family.

General physical examination revealed obesity (BMI > 32.9 kg/m2) and left retractile atrophic testicle. Further, no physical abnormalities. Vital signs values were all within normal, blood pressure 135/82, pulse 84 bpm, and SpO2 98%.

The blood test results obtained at BL revealed clinically significant low total testosterone level, 6.8 nmol/L (reference range 9-29 nmol/L). Other hormonal parameters, including prolactin, LH, FSH and TSH and T4 serum levels, were all within normal range. The haematology report revealed anaemia with low haemoglobin (Hb) level 122 g/L (reference range: 130-180 g/L), reduced red blood cell count (RBC) 4.16×10¹²/L (reference range: 4.50-6.00 × 10¹²/L) and low Haematocrit (Hct) 0.36 L/L (reference range: 0.40-0.52). Clinical chemistry results indicated hypertriglyceridemia. No other clinically relevant findings have been encountered in the laboratory test results.

Analysis of the clinical data, including the clinical interview, physical examination and laboratory test results obtained from the BL information, indicated severe anxiety and depression. In addition, Mr LD met full DSM diagnostic criteria for ADHD and BPD. His clinical laboratory tests confirmed the presence of hypogonadism and anaemia.

Four and a half (4.5) weeks (i.e., during week 5) after receiving the MPT-T-I combined treatment Mr LD reported ca 90% improvement in his mental health problems mentioned above. However, at this stage, he reported 0% improvement in his sexual functions. At week 11, Mr LD reported more than 95% improvement in his mental health problems, including complete remissions in self-harm and suicidal thoughts and 100% improvement in his libido, sexual functions, and activity. Blood tests performed at week 6 revealed an increase in the total testosterone level to 38.5 nmol/L (i.e., 1.3 times above the upper limit normal level). Given this, the dose of topical testosterone has been reduced to 70 mg a day. In addition, the reduced RBC and low Hb and Hct observed at BL returned to the reference ranges (Hb 138 g/L, RBC 4.73 ×10¹²/L, and Hct 0.42 L/L). Parallel improvement in the severity of ADHD, BPD, anxiety, and depression has been observed, particularly at week 11. Regarding the ADHD severity score (part B of the ASRS), this showed an increase (compared to BL) during week 5, followed by a significant decrease at week 11. Similar changes have been noticed in the Hy-I score.
The HAM-D17, HAM-A, ASRS (part A and B), and BSL-23 scores obtained at baseline and during the course of treatment are shown in figures 1-3.

**Discussion**

This case report describes a 34-year-old male patient diagnosed with treatment-resistant chronic mixed anxiety and depression, associated with recurrent self-harm, and suicidal thoughts and attempts. Reassessment of his physical and mental health revealed two interesting observations. First, 4 overlooked disorders have been identified, hypogonadism, anaemia, ADHD, and BPD. These may have generated and sustained the clinical picture of anxiety and depression in this patient.

Prior to commencing him on MPT-T-I combined therapy, the patient has been receiving fluoxetine and quetiapine for 2 years without response. Complete remission in his signs and symptoms occurred within 11 weeks after starting MPT-T-I treatment. As been recently described (1), MPT-T treatment could have facilitated the antidepressant effect of the psychotropic medications the patient was already receiving. Nevertheless, this patient had clinical manifestations that met all diagnostic criteria for ADHD and BPD, in addition to hypotestosteronaemia and anaemia. Treatment of these underlying disorders was associated with parallel complete remission in his anxiety and depression. This suggests that the symptoms and signs of chronic mixed anxiety and depression in this patient are probably caused and sustained by the encountered underlying disorders.

From a clinical perspective, depression and anxiety are common comorbidities of ADHD and BPD. This might be due to the common neurobiological ground of these mental health disorders. The relationship between disturbance in dopamine, serotonin, and noradrenaline neurotransmission and the symptoms of depression and anxiety is well established in the literature. Dysfunction in these 3 monoaminergic systems is also implicated in the pathogenesis of ADHD and BPD. It is, therefore, conceivable that treatment of the monoaminergic systems dysfunction will lead to improvement in clinical manifestations generated from this dysfunction. Testosterone increases brain serotonin and dopamine release, reduces striatal dopamine turnover, and enhances hippocampal neurogenesis; aspects commonly disturbed in patients with anxiety and depressive disorders. Methylphenidate significantly increases dopamine and noradrenaline release and synaptic neurotransmission in the brain limbic and cortico-striatal systems. Therefore, treatment with both MPT and T not only improves ADHD and BPD symptoms, including attention deficit, hyperactivity, executive dysfunctions, and impulsivity but also improves anhedonia which is a core criterion in the diagnosis of TRD (see reference 1 for details).

The patient received an iron supplement because of the anaemia detected in his blood tests. In this regard, the impact of anaemia on mood and behaviour and the potential role of iron supplements and testosterone in this scenario are worth mentioning. The patient demonstrated low Hb level and decreased RBC. Haemoglobin is the iron-containing protein in the red blood cells that carry oxygen to tissues. Low haemoglobin level usually implies an absolute or relative deficiency in circulating iron level and might lead to disturbed brain functions. Low brain iron levels have been reported to disturb dopaminergic neurotransmission. Iron is a cofactor for tyrosine hydroxylase, which is necessary for dopamine production. In addition, iron deficiency has also been reported to reduce the activity of dopamine transporter and decrease the density of Dopamine D2 receptors in striatum, and prefrontal cortex [15, 16]. The changes could be clinically translated into inattentiveness, anhedonia, depression and deterioration in cognitive ability and executive functions [17,18]; features commonly encountered in ADHD, BPD, and anxiety and depression. In clinical studies, iron deficiency anaemia has also been linked to the generation of ADHD in children and adults [19, 20] and the severity of ADHD symptoms, particularly inattentiveness and distractibility [19]. Testosterone plays an important role in iron homeostasis. Testosterone administration is associated with increased erythropoietin secretion and a decrease in the level of iron regulatory peptide, hepcidin [21]. This results in increased systemic iron bioavailability and utilization (incorporation into blood cells) [22]. Taken all together, iron and testosterone therapy might have increased iron bioavailability and its systemic level and, therefore, enhanced the dopaminergic neurotransmission and improved the deficit in cognitive ability and executive functions in this patient.

Second, the MPT-T-I combined therapy resulted in parallel improvement in BPD and ADHD symptoms. This might be explained by clinical and neurobiological reasoning.

From a clinical point of view, ADHD and BPD commonly coexist. On the one hand, 24% of patients with combined type ADHD were reported to have BPD [23], and approximately one-third of patients with a lifetime history of ADHD have been reported to have BPD [24]. On the other hand, 59.9% of adult BPD patients scored above the cut-off value for ADHD on Wender Utah Rating Scale (WURS), after controlling for gender, antisocial personality disorders and axis I diagnose [23, 25]. Furthermore, both ADHD and BPD share core diagnostic criteria such as emotion dysregulation and impulsivity, including impulsive aggression. The overlap in these core symptoms led to the suggestion that both conditions could have common underlying pathologic mechanisms [23]. Therefore, it is conceivable that successful treatment of ADHD will lead to remission of at least the shared symptoms and signs.

Neurobiologically, dysfunction in the dopaminergic and noradrenergic neurotransmission are implicated in the pathogenesis of ADHD. Dysfunctions in these systems and the serotonergic system are linked to the generation of BPD symptoms, including deficits in cognitive and executive functions and emotional processing resulting in disinhibition and impulsivity, self-harm, and suicidal attempts [26, 27]. Impulsivity and aggressive behaviour have also been linked to lower serotonin activity [24]. In this regard, lower serotonin receptor 1A (5-HT1A) sensitivity and activity have been linked to BPD symptoms, including aggression and suicidal behaviour [26, 27].

The positive effect of MPT on the dopaminergic and noradrenergic systems has been discussed above and in a recent paper [1]. Testosterone enhances dopamine and serotonin release and neurotransmission modulates the activity of the 5HT1A receptor and increases its response to 5HT1A agonists [28]. Testosterone has also been reported to increase serotonin binding in the basal ganglia and amygdala, which are brain areas implicated in impulsivity [29, 30]. Similarly, the positive effect of testosterone on the limbic noradrenergic system has been addressed by Bektinieva and Viliannia kastratiski [31]. Castration in male rats was found to reduce noradrenaline in various regions of the brain, including the limbic system. The latter is involved in the regulation of emotion and control of impulsivity. This effect has been reversed after testosterone administration [31].
Taken all together, this might explain the parallel improvement in ADHD and BPD symptoms after treatment with MPT-T-I combined therapy.

Finally, the data in this report demonstrate an increase in the ASRS-part B score during week 5 (compared to BL). This reflects the increase in ADHD symptoms severity. The parallel increase in Hy-I score revealed the deteriorated domains (Hyperactivity and impulsivity). One or more of the following might explain the observed deterioration; [1] the increase in Hy-I score might indicate that the response to treatment effect on impulsivity/hyperactivity has a delayed onset of ≥ 5 weeks. Clinically significant effect of testosterone on serotonin expression has been observed after 1 month of testosterone administration to female-to-male transsexuals [29]; [2] this patient demonstrated superphysiologic serum testosterone level (defined as total serum testosterone of > 1000 ng/dl, i.e., >34.7 nmol/L [32]). In this context, serum testosterone levels within normal/ reference range have been reported to have a positive impact on impulsivity (see above). On the contrary, superphysiologic testosterone levels were found to be likely associated with impulsivity and hyperactivity [33, 34]); and / or [3] the dose of MPT (60 mg a day) given during the first 4.5 weeks have been less than proportional to the patient’s weight and age. Barkley et al. [35] reported a better response in hyperactivity with a higher dose of MPT in children with ADHD. From week 5 and onward, the patient received MPT at a dose of 90 mg a day, and complete remission was reported and observed at week 11.

Although the findings in this case report might open the avenue for further verifying clinical studies and eventually might lead to improvement in clinical practice and approach to patients with treatment-resistant chronic mixed anxiety and depression, this report has 2 main limitations. First, the serum ferritin and transferrin saturation levels which are sensitive laboratory indicators for iron deficiency anaemia, have not been assessed. Second, a separate assessment of impulsivity level by a valid instrument such as the Barratt Impulsiveness Scale has not been performed. Further studies need to take these limitations into consideration.

Funding
This work did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest
There are no conflicts of interest to declare by any of the authors of this study.

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