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Case Report

High dose Levothyroxine in combination with transcranial magnetic stimulation for the treatment of severe resistant subthreshold rapid cycling bipolar disorder; A case report

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Abstract

Bipolar Disorder (BD) is a common psychiatric condition. There is an overall agreement across treatment guidelines of BD type I and BD type II however, there is far less certainty regarding the treatment of subthreshold presentations including Rapid Cycling Bipolar Disorder. We present a patient with treatment-resistant rapid cycling Bipolar Disorder type I who deteriorated on Ketamine treatment but reached full remission with repetitive Transcranial magnetic stimulation, High Dose Levothyroxine, Lurasidone and Lithium Carbonate. This case highlights the previously demonstrated safety and effectiveness of the combined protocol of High Dose Levothyroxine and Transcranial Magnetic Stimulation for this population.

Introduction

Bipolar Spectrum Disorder (BSD) is a common and disabling condition with significant morbidity and mortality. It includes Bipolar I, II and subthreshold bipolar disorders. The understanding of BD has been evolving over the years with changes to the definition and criteria for classification. BD NOS/Subthreshold type is the most common presentation [1] and is seen in BP I and BP II as in this case. Rapid Cycling Bipolar Disorder (RCBD) is associated with a more malignant course and is difficult to treat. Cycling can be rapid over weeks, ultrarapid over days, or even ultradian with changes of polarity within a day, which may well be the subthreshold presentation by definition [2].

Alongside the evolvement of understanding of the BSD, treatment guidelines have been changed. Whereas there is an overall agreement across guidelines regarding the treatment of BD I and BD II, there is far less certainty regarding subthreshold presentations. Existing treatment for BD I and II is less effective and would require an average of 3.8 medications [3]. High-Dose Levothyroxine (HDT) in combination with repetitive Transcranial Magnetic Stimulation (rTMS) is shown to be well tolerated in BD in doses of 150 mcg to 1000 mcg [4]. Given the influence of genetic factors in both BD and circulating thyroid hormone (TH), it could be hypothesized that there might be common genetic factors that could explain both the effectiveness of HDT and the lack of expected side effects in BD [4]. The present authors have reported data on 20 remitted bipolar spectrum patients [5] all of whom showed mutations of DiO1, DiO2, and or SLCO1C1 Thyroid hormone protein transporters. Furthermore, of fifty-five patients reported by the present authors [4] who have received genetic testing at the start or early stages of treatment with combined HDT and rTMS, Fifty-two patients with complete data were identified as having similar genetic mutations. These mutations are associated with the availability of thyroid hormones in the

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brain and the periphery [4]. The physiological mechanism associated with the potential effectiveness of the combination of HDT and rTMS is not known. It might be associated with intracellular changes with mitochon Dr. iogenesis and increased cerebral blood flow and oxygen utilization, associated with the combination of the effect of each of the treatment components [6]. Neuroplasticity, which is associated with stable remission is enhanced by rTMS [7] and it is mitochon Dr. is dependent [8] and the thyroid hormones exert a profound impact on mitochon Dr. ia [9].

Case report

Here we present a case of a 43-year-old single male, highly functional sportsman, with a 20-year history of BD type 1 presenting with a 2-year history of severe rapid cycling subthreshold symptoms, who achieved remission on HDT combined with Lurasidone, Lithium Carbonate and rTMS, treated in a private outpatient center in London since 2019.

He presented with a history of three manic episodes, two with cannabis use and one after prescribed ketamine use, as well as hypomanic episodes lasting more than 4 days. He presented for treatment with alternating mixed and depressive subthreshold periods of less than 2 weeks duration, falling short of the ICD 11 diagnosis of a depressive or mixed episode. The patient recognized this pattern retrospectively during the assessment by AZ and stated that depression with a flight of ideas/ agitation was never enquired about by any Psychiatrist. The depressive subthreshold symptoms lasted at most 3 days and mixed phases lasted at most 2 days - 3 days. Over the course of the illness, he suffered from severe suicidality and was unable to function and work for 20 years. Various psychotropic medications (citalopram, fluoxetine, venlafaxine, sodium valproate, aripiprazole, paliperidone, risperidone, quetiapine, lithium and lamotrigine) were tried over the years by his previous treating teams which were either ineffective or intolerable due to side effects or both. There has been a period of approximately 1.5 years of relative mood stability (2015-2016) reported by the previous treating psychiatrist and at that time, he was not on any medication. This was followed by an episode of severe depression with suicidal ideation. He was subsequently deemed treatment-resistant and treated on intravenous ketamine at a research center in the UK. The first ketamine infusion was given in 2017 which consisted of two doses of 35 mg each infusion. After the second infusion, he experienced a severe manic episode with psychosis requiring hospital admission for three months. He was not on any other medications when he was treated with ketamine infusion. He was then switched to oral ketamine 200 mg combined with lithium 800 mg and quetiapine 25 mg which also proved ineffective. See Table 1 for a summary.

In March 2019, he was assessed by AZ at the private outpatient service. He was diagnosed with treatment-resistant RCBD with alternating subthreshold phases of mixed (depression with a flight of ideas), alternating with simple depressive phases and agitated depression with or without a flight of ideas. There were too many changes of polarity to be counted and in fact, there were no episodes per se. Given the past history, a diagnosis of BD type I was given, rather than that of Dr..ug (cannabis, ketamine) induced BD. He presented with intense distress, hopelessness, poor sleep and high suicidality. The Becks Depression Inventory (BDI) score was high at 59 (cut off point for severe depression is 29) and Sheehan's Disability Score (SDS) was 10/10 for each domain (a score equal to or greater than 7 suggests severe or very severe impairment) [10]. The patient was smoking occasionally, did not consume alcohol or caffeine, and was not using recreational Dr..ugs. There was no family history of mental illness. His mother had thyrotoxicosis during pregnancy and the wider family had a positive history of thyroid disorder. The authors routinely do genetic testing for DiO1, DiO2 and SLCO1C1 protein transporter protein of thyroid hormones. These genetic mutations indicate poor thyroid activation and transport either peripherally (leading to few side effects), or centrally explaining the pathology of these patients' mood disorders [7]. Over 90% of patients showed Single Nucleotide Polymorphisms (SNPs) in the coding for the above enzymes and/or protein transporter [7]. Two papers of 20 patients and 55 patients respectively published by the authors highlighted the potential role of thyroid and genetic tests and concluded that patients who do well on HDL have a high fT4:fT3 ratio and a DIO1 and/or DIO2 mutation (evidence level 2B) [4,5]. Therefore, assessing TH and genetic profiles helps improve the effectiveness and tolerability of treatment [7,8,4]. Genetic testing showed polymorphism of both DiO1 and DiO2 genes suggesting mutations affecting the thyroid activation genes in this patient. ECG and ECHO were normal. With consent, he was commenced on a treatment regime of High Dose Levothyroxine (HDT) and repetitive Transcranial magnetic stimulation (rTMS) under cover of lithium carbonate 800 mg yielding a blood level of 0.8 mmol/L. He was systematically monitored by a team consisting of a psychiatrist, endocrinologist and cardiologist.

Table 1: Treatment history prior to commencing rTMS and HDL.

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In addition to HDT and rTMS and lithium he was prescribed quetiapine 25 mg for sleep management. Lithium was of no benefit prior to Levothyroxine and the decision to continue lithium was taken because of the previous episodes of mania prophylactically. Levothyroxine was started at 50 mcg and increased up to 800mcg over a period of 7 months, whereas the highest dose quoted in Maudsley guidelines is 400 mcg [11]. Symptom improvement was noted from 3 months into treatment and remission (BDI = 4 and SDS = 0/10) was achieved at 7 months. At the start of rTMS treatment, the patient received seven weeks of 5 days a week right side 1Hz (35 sessions), followed by six weeks of once weekly maintenance of the same protocol (6 sessions), followed by two weeks of 5 days a week of the same protocol (10 sessions), followed by 7 months of one day a week maintenance of rTMS (30 sessions). This is more than what is considered to be a "course of treatment" for depressive disorder although this condition presented with resistant subthreshold bipolar symptoms, for which there are no treatments in the literature with rTMS or indeed any other treatment to our knowledge apart from the author's 2 cohort studies [5,12]. Quetiapine XR 300 mgs added to mood stabilizers failed to induce remission in these cases [13]. There are no data to support Lurasidone in subthreshold bipolar disorder, and only one case report to our knowledge supports its use in rapid cycling [14].

Continuation of rTMS was decided to achieve remission and not just improvement, due to the high suicidal risk. Remission was attained at 7 months on Levothyroxine 800 mcg, Lurasidone 74 mg, and Lithium 800 mg (0.8 mmol) and weekly rTMS maintenance. The patient discontinued Lurasidone 6 months after being in remission due to side effects, without relapse. He then decided to discontinue Lithium, 12 months after remission without informing the treating team. He continued to remain well. For 2.5 years since the initiation of treatment, the patient remained in full remission, with the SDS score at 0, with no side effects and is highly functional. In the last year of remission, he was only on Levothyroxine 200 mcg. See Table 2 for a summary. Of late, about 6 weeks ago and as we were writing the paper the patient traveled to France and deliberately stayed awake for 24 hours to work on a document which triggered a manic state. This responded quickly with full remission and no sequelae to 4 mg of Risperidone in an inpatient facility to full remission with no residual symptoms after 7 days. The patient discontinued risperidone and Lithium carbonate was recommenced at 800 mg with a blood level of 0.8 mmol/l and Levothyroxine was increased to 400 mcg. The patient remains well.

Conclusion

Bipolar Disorder (BD) is a common and disabling condition with significant morbidity and mortality. Whereas there is an overall agreement across guidelines regarding the treatment of BD I and BD II, there is far less certainty regarding the treatment of subthreshold presentations including RCBD. This patient with rapid cycling subthreshold symptoms BD I was treatment-resistant and deteriorated substantially on ketamine treatment. He reached full remission which was maintained for 2.5 years on HDT and rTMS. He not only recovered from his illness but resumed a fully productive functional social life. Noncompliance with lithium, lifestyle management and reduced HDT dose resulted in a brief lapse which responded very quickly to treatment with no sequelae. This case raises questions about the complexity of diagnosing BD, reiterates the serious challenges posed by subthreshold presentations, and highlights the risk associated with the use of ketamine

Table 2: Treatment progress.

Timeline	Levothyroxine	Other Psychotropic medications	rTMS	Response
Apr 2019	50 mcg titrated by 50 mcg weekly	lithium 800 mg (0.93) quetiapine 25 mg	5 days a week	
May 2019	350 mcg	lithium 1000 mg (0.93) quetiapine stopped due to sedation	5 days a week	
June 2019	700 mcg	lithium 1000 mg lurasidone 34 mg added due to depression	5 days a week	
July 2019	750 mcg	lithium 1000 mg lurasidone 74 mg	Weekly maintenance	Improvement noted
Aug 2019	800 mcg	lithium 1000 mg reduced to 800 mg due to tremors lurasidone 74 mg	Weekly maintenance	Improvement sustained Sleep improved Mild tremors
Sep 2021	800 mcg	lithium 800 mg lurasidone 74 mg	5 days a week for 2 weeks	Improvement noted
Oct 2019	800 mcg	lithium 800 mg (tremors abated) Lurasidone 74 mg	Monthly maintenance	Remission
Mar 2021	800 mcg	lithium 800 mg lurasidone stopped	Monthly maintenance	Remission
Aug 2021	600 mcg	lithium 800 mg	Stopped	Remission BDI 4 ; Sheehan 0
Oct 2021	200 mcg	Stopped lithium	None	Remission maintained
Oct 2022	200 mcg	None		Relapse with symptoms of mania for 7 days following travel and poor sleep.
Dec 2022	400 mcg	Commenced on Lithium Carbonate 800 mg, and risperidone 4 mg but the patient has stopped risperidone.		Remission

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as an antidepressant in this population. Furthermore, adds to the existing literature on the safety and effectiveness of HDT [15-17] and the combined HDT and rTMS treatment for this population [4,12].

Conflicts of interest

Andy Zamar is the founder and owner of The London Psychiatry Centre which holds a pending patent for the combined use of High Dose Levothyroxine and rTMS. Ashma Mohamed is a psychiatry trainee and has no conflict of interest to declare. Christos Kouimtsidis provides clinical sessions at the London Psychiatry Centre. He has no other conflict of Interest.

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