



Rapid cycling bipolar disorder, pathogenesis to treatment: A case report and review

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In this paper, we discuss a case report along with literature review focusing on background information, pathogenesis, biomarkers and potential treatment options for Rapid Cycling Bipolar Disorder.

Keywords: Rapid cycling (RC), Bipolar Disorder (BD), Pathophysiology.

Introduction

Rapid Cycling Bipolar Disorder (RCBD) is a rare psychiatric disorder that is characterized by at least four affective episodes manic, hypomanic or major depressive during the past twelve months [1]. In patients, until age 36, mean duration has been documented to be 8 years [2]. It is very rare in unipolar patients but its prevalence is higher in Bipolar Disorder patients [1]. Major clinical factors and sleep-related factors have been proposed to play an extremely important role in the pathogenesis of this disorder, which includes subclinical hypothyroidism, anomalies in sleep-wake cycle and obesity [1, 3]. From a clinical standpoint, a classic presentation of the patient is female with main diagnosis of Bipolar Disorder type 2 with symptoms of depression along with cycles of depression, mania and euthymia [1]. In addition, these patients can also have other psychiatric comorbidities that include anxiety disorder and substance abuse history as well [1]. From the perspective of pathophysiology, multiple factors have been hypothesized that include genetic factors, thyroid dysfunction, menstrual disturbance, circadian rhythm disturbances and psychotropic medications [1]. In the following paper, we discuss a case report that demonstrates RCBD. Furthermore, we also elaborate on its pathophysiology, therapeutic targets along with molecular markers intertwined with neurophysiology that have been hypothesized to play an important role in the context of RCBD.

Methods

In addition to the case report demonstrated below, we performed a literature review of case reports, research publications, academic journals and review papers in order to gather adequate background information about RCBD. We specifically focused on articles: (1) that describe different hypothesis of mechanism of pathogenesis of RCBD, (2) documented RCBD and various medical & psychiatric co-morbidities (3) gender predisposition of RCBD along with possible blood markers that have been linked to RCBD and (4) possible potential treatment options.

Case Report

Patient is a 54-year-old divorced, unemployed Caucasian female with a history of bipolar disorder, Deep Vein Thrombosis (DVT), hypothyroidism, hypertension currently admitted to inpatient psychiatric facility for physical aggression at a group home. Prior to her admission, patient

allegedly got into a fight with the staff and other residents in her group home where she was found gathering knives from the kitchen. Patient was reported to have climbed onto a television stand and attempted to pull the television stating "I am Jesus Christ". At the time of admission, when asked about the events leading to her hospitalization, she stated, "False reports that I was throwing knives around. I took care of those ladies. They just don't like me". She felt that others at the group home were conspiring against her. Patient was reportedly punched in the face by another patient for trying to "baptize someone by pouring orange juice on them". On further interview, patient reports having trouble concentrating while reading, reports reduced sleep hours at night, increased energy, racing thoughts. She also reported a history of depressive symptoms such as poor concentration and feelings of hopelessness/ helplessness owing to the fact that she had a mental illness which led her to be suicidal and was admitted before 3 months.

Patient has a long psychiatric history dating back more than 30 years starting at the age of 19 when she was diagnosed with bipolar disorder and subsequently treated. Patient had 5 inpatient hospitalizations each during the prior two years and 4 inpatient hospitalizations 3 years prior when patient was found to be manic, hostile,

inappropriate, grandiose, tangential, delusional and other occasions melancholic, depressed attempting to kill herself along with one episode of hypomania. In between, these episodes patient was reportedly at "baseline" as per family and was behaving "normally". She also has one prior suicide attempt by trying to overdose on Xanax. In addition, patient also has multiple felony and misdemeanor charges. Patient denied use of alcohol, cannabis, cocaine, benzodiazepines and opioids but reported smoking 3 cigarettes/day for the last 5 years. Patient's mother had a history of mood disorder. Father was an alcoholic. No known family history of suicide. Patient reported being a "swimsuit model" while she was in her 20s and stated that her mental needs hindered her career since she needed frequent inpatient hospitalizations and had weight gain secondary to antipsychotic medications.

On physical examination, temperature 96.1°F, BP 120/77mmHg, HR 77 beats/min, RR 18 breaths/min. Patient was alert, awake and oriented x 3, appearing older than stated age, with fair grooming, maintaining intense eye contact. Speech was noted to be pressured at times with profanities. She was noted to have tremors and unsteady gait and orthostatic with systolic blood pressure dropping to 90s while standing. Mood was described as anxious. Affect was noted to be irritable, suspicious and paranoid at times. Thought process was disorganized. She denied suicidal ideations and auditory/visual hallucinations. Insight and Judgment were poor. Mini-Mental State Examination (MMSE) 29/30. Neurological examination showed unsteady gait. Reflexes, coordination and sensory system were within normal limits. Cranial nerves 1 through 12 were intact. Allergies to Sulfa, Zyprexa, Cogentin and Haldol were reported.

Laboratory findings were consistent with WBC 8.1, ANC 5.0, Clozapine Level 519, TSH 2.790 and Lithium level of 0.7 upon admission. EKG was read as normal sinus rhythm with QTC 400.

Patient was started on Depakote 1000 mg orally twice daily, Clozaril 325 mg orally at night, Lithium 300 mg orally twice daily and Ativan 0.5 mg orally three times daily. Orthostasis improved with administration of oral fluids and reducing the dose of Metoprolol. Regular monitoring of renal function, liver function and CBC was performed to monitor the side effects of the medications. Patient was noted to have a worsening creatinine of 2.03. Nephrology consulted and patient was noted to have chronic kidney disease stage 3 at baseline creatinine 1.3-1.5 secondary to lithium nephrotoxicity. Patient was further noted to have nephrogenic diabetes insipidus and hypertension. Consequently, lithium was discontinued. Due to worsening psychosis after discontinuation of Lithium, Depakote was increased to 500 mg orally twice daily and 1000 mg at night and Clozaril was increased to 350 mg orally at night and Fluphenazine 5 mg was added at night. We are considering an option of Electroconvulsive therapy (ECT) since the patient has shown suboptimal clinical improvement despite being on Clozaril. (Serum Clozapine level 855; therapeutic serum clozapine level 350-650).

Discussion

From the case above we, can see patient had minimum of 4 mood episodes in the past 12 month period which included mania, hypomania and depression symptoms along with partial remission for at least 2 months as per family which from DSM 5 criteria is diagnostic for RCBBD [4,5,6]. Multiple risk factors have been elucidated to play an important role in development of RCBBD which include female gender [7], previous suicide at- tempts, early age of onset, atypical depression symptoms and high antidepressant use [8,9,10], majority of which were present in the case report demonstrated above.

Even though the exact mechanism of pathogenesis is not known several extrapolations and hypothesis can be generated. From a neurobiological standpoint, imaging studies in humans have demonstrated atrophy in the ventral prefrontal cortex along with gray matter degeneration in orbital pre-frontal cortex, cingulate cortex and parahippocampus [11, 12]. In addition, many important bio-psycho-social factors have been hypothesized to be possible contributors to RCBBD that include history of family neglect, intra-familial conflicts and child abuse [13]. Many genetic factors that include low expression of COMT gene that codes for Catechol-O-Methyl Transferase gene [14] and *P2RX7* gene have been linked to RCBBD [15]. Furthermore, enzyme anomalies in arachidonic and prostaglandin pathway have been shown to play an important role in RCBBD; more specifically low expression of enzyme Prostaglandin D synthase (PTGDS), Prostaglandin D Synthase which converts Prostaglandin H₂ to Prostaglandin D₂ [16,17]. Age and gender adjusted analysis of mRNA expression of PTGDS in peripheral mononuclear cells has been shown to be significantly correlated to high incidence RCBBD

[16] Furthermore, BDNF (Brain Derived Neurotrophic Factor) has been shown to associated with chronic RCBBD, specifically in all three phases: euthymic, de- pression, manic/hypomanic phase [18]. Interestingly, patients with RCBBD Type 1, have been to have significant cell membrane alterations which leads to increase choline containing compounds like glycerophosphocholine and phosphocholine [19]. Finally, an interesting case report of Anti-AMPA receptor-mediated encephalitis in a Turner Syndrome patient who developed RCBBD has been documented [20].

Interestingly, many significant comorbid findings have been reported in RCBBD that includes anxiety disorder [21], hyper-homocystenemia which increases risk of recurrent strokes [22], obesity [23], high suicide risk [24], migraines [25] and high level of inflammatory markers like interleukin 6 and 18 which could potentially contribute to mania and hypomania [26]. Based on current hypothesis for depression [27], the enzyme IDO (Indolamine 2,3 Dioxygenase) seems to upregulated secondary to high interleukin production in patients. This leads to depletion of tryptophan which in turn decreases serotonin and increases quinolonic acid which potentially leads to increased NMDA receptor activation [27] and lead to depression (Figure 1). So it possible that interleukins 6 and 18 mentioned above could be further contributing to exacerbation of depression in RCBBD cases.

From a therapeutic standpoint, previous research has shown multiple drugs to effective. For instance, Lamotrigine has been known to increase the amount of euthymia in patients with RCBBD as compared to placebo [28, 29]. In addition Pramipexole has been shown to alleviate resistant depression in RCBBD patients [30]. Furthermore, continuation of lithium and ECT has been shown to stable the mood in patients with RCBBD [31]. In patients with co-morbid conditions like hypothyroidism, Levothyroxine augmentation therapy was shown to resolve RCBBD symptoms in patients [32]. Finally, Ketamine has also been shown to be extremely useful in RCBBD patients with active suicidal ideations [33].

Conclusion

Hereby, we have demonstrated a case report along with a literature review which focusing on background information, pathogenesis, biomarkers and potential treatment options for Rapid

Cycling Bipolar Disorder.

Conflicts of Interest: Authors have no conflicts of interest to disclose.

References

1. Apadimitriou G, Calabrese J, Dikeos D, Christodoulou G. Rapid cycling bipolar disorder: biology and pathogenesis. *Int J Neuropsychopharmacol*. 2005;8(2):281-92.
2. Koukopoulos A1, Sani G, Koukopoulos AE, Minnai GP, Girardi P, Pani L, et al. Duration and stability of the rapid-cycling course: a long-term personal follow-up of 109 patients. *J Affect Disord*. 2003; 73:75.
3. Buoli M, Dell'Osso B, Caldiroli A, Carnevali GS, Serati M, Suppes T, Ketter TA, Altamura AC. Obesity and obstetric complications are associated with rapid-cycling in Italian patients with bipolar disorder. *J Affect Disord*. 2017;208:278-83.
4. Amsterdam J, Lorenzo-Luaces L, Derubeis R. Comparison of treatment outcome using two definitions of rapid cycling in subjects with bipolar II disorder. *Bipolar Disord*. 2017;19(1):6-12.
5. Scott J, Grunze H, Meyer T, Nendick J, Watkins H, Ferrier N. Research report: A bipolar II cohort (ABC): The association of functional disability with gender and rapid cycling. *J Affect Disord*. 2015;185:204-8.
6. Carvalho A, Dimellis D, Gonda X, Vieta E, McIntyre R, Fountoulakis K. Rapid Cycling in Bipolar Disorder: A Systematic Review. *J Clin Psychiatry*. 2014;75(6):e578-86.
7. Erol A, Winham SJ, McElroy SL, Frye MA, Prieto ML, Cuellar-Barboza AB, et al. Sex differences in the risk of rapid cycling and other indicators of adverse illness course in patients with bipolar I and II disorder. *Bipolar Disord*. 2015;17(6):670-6.
8. Valentí M, Pacchiarotti I, Undurraga J, Bonnín CM, Popovic D, Goikolea JM, et al. Risk factors for rapid cycling in bipolar disorder. *Bipolar Disord*. 2015;17(5):549-59.
9. El-Mallakh RS, Vöhringer PA, Ostacher MM, Baldassano CF, Holtzman NS, Whitham EA, et al. Antidepressants worsen rapid-cycling course in bipolar depression: A STEP-BD randomized clinical trial. *J Affect Disord*. 2015;184:318-21.
10. Gigante AD, Barenboim IY, Dias RD, Toniolo RA, Mendonça T, Miranda-Scippa Â, et al. Psychiatric and clinical correlates of rapid cycling bipolar disorder: a cross-sectional study. *Rev Bras Psiquiatr*. 2016;38(4):270-4.
11. Narita K, Suda M, Takei Y, Aoyama Y, Majima T, Kameyama M, et al. Volume reduction of ventromedial prefrontal cortex in bipolar II patients with rapid cycling: a voxel-based morphometric study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35(2):439-45.
12. Blumberg HP, Krystal JH, Bansal R, Martin A, Dziura J, Durkin K, et al. Age, rapid-cycling, and pharmacotherapy effects on ventral prefrontal cortex in bipolar disorder: a cross-sectional study. *Biol Psychiatry*. 2006;59(7):611-8.
13. Agnew-Blais J, Danese A. Childhood maltreatment and unfavourable clinical outcomes in bipolar disorder: a systematic review and meta-analysis. *Lancet Psychiatry* 2016; 3:342.
14. Kirov G, Murphy KC, Arranz MJ, Jones I, McCandles F, Kunugi H, et al. Low activity allele of catechol-O-methyltransferase gene associated with rapid cycling bipolar disorder. *Mol Psychiatry*. 1998;3(4):342-5.
15. Backlund L, Lavebratt C, Frisén L, Nikamo P, Hukic Sudic D, Träskman-Benz L, et al. P2RX7: expression responds to sleep deprivation and associates with rapid cycling in bipolar disorder type 1. *PLoS One*. 2012;7(8):e43057.
16. Munkholm K, Kessing L, Vinberg M, Peijs L. Reduced mRNA expression of ptgds in peripheral blood mononuclear cells of rapid-cycling bipolar disorder patients compared with healthy control subjects. *Int J Neuropsychopharmacol*. 2015;18(5):1-9.
17. Gurvich A, Begemann M, Dahm L, Sargin D, Miskowiak K, Ehrenreich H. A role for prostaglandins in rapid cycling suggested by episode-specific gene expression shifts in peripheral blood mononuclear cells: a preliminary report. *Bipolar Disord*. 2014 Dec;16(8):881-8.
18. Munkholm K, Pedersen B, Kessing L, Vinberg M. Elevated levels of plasma brain derived

- neu-rotrophic factor in rapid cycling bipolar disorder patients. *Psychoneuroendocrinology*. 2014;47:199-211.
19. Cao B, Stanley JA, Passos IC, Mwangi B, Selvaraj S, Zunta-Soares GB, et al. Elevated Choline-Containing Compound Levels in Rapid Cycling Bipolar Disorder. *Neuropsychopharmacology*. 2017;42(11):2252-8.
 20. Quaranta G, Maremmanni A, Perugi G. Anti-AMPA-Receptor Encephalitis Presenting as a Rapid-Cycling Bipolar Disorder in a Young Woman with Turner Syndrome. *Case Rep Psychiatry*. 2015;2015:1-5.
 21. Castilla-Puentes R, Sala R, Ng B, Galvez J, Camacho A. Anxiety disorders and rapid cycling: data from a cohort of 8129 youths with bipolar disorder. *J Nerv Ment Dis*. 2013 Dec;201(12):1060-5.
 22. Awara M, Zahid S, Elnenaei M. Rapid cycling bipolar affective disorder and recurrent strokes secondary to high blood homocysteine. *J Ment Health*. 2014;23(5):276-9.
 23. Galvez JF, Bauer IE, Sanches M, Wu HE, Hamilton JE, Mwangi B, et al. Shared clinical associations between obesity and impulsivity in rapid cycling bipolar disorder: a systematic review. *J Affect Disord*. 2014;168:306-13.
 24. Garcia-Amador M, Colom F, Valenti M, Horga G, Vieta E. Research report: Suicide risk in rapid cycling bipolar patients. *J Affect Disord*. 2009;117:74-8.
 25. Gordon-Smith, K., Forty, L., Chan, C., Knott, S., Jones, I., Craddock, N., et al. Rapid cycling as a feature of bipolar disorder and comorbid migraine. *J Affect Disord*. 2015;175:320-4.
 26. Munkholm K, Weikop P, Kessing L, Vinberg M. Elevated levels of IL-6 and IL-18 in manic and hypomanic states in rapid cycling bipolar disorder patients. *Brain Behav Immun*. 2015 Jan;43:205-13.
 27. Steiner J, Walter M, Gos T, Guillemin GJ, Bernstein HG, Sarnyai Z, et al. Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus: evidence for an immune-modulated glutamatergic neurotransmission? *J Neuroinflammation*. 2011;8:94.
 28. Kemp DE, Gao K, Fein EB, Chan PK, Conroy C, Obral S, et al. Lamotrigine as add-on treatment to lithium and divalproex: lessons learned from a double-blind, placebo-controlled trial in rapid-cycling bipolar disorder. *Bipolar Disord*. 2012;14(7):780-9.
 29. Goldberg JF, Bowden CL, Calabrese JR, Ketter TA, Dann RS, Frye MA, et al. Six-month prospective life charting of mood symptoms with lamotrigine monotherapy versus placebo in rapid cycling bipolar disorder. *Biol Psychiatry*. 2008;63(1):125-30.
 30. Aditya H, Aditi S, Malvika R, Janardhanan C N, Suresh Bada M. Pramipexole in the treatment of refractory depression in a patient with rapid cycling bipolar disorder. *Indian J Psychol Med*. 2015;37(4):473-4.
 31. Huber J, Burke D. ECT and lithium in old age depression - Cause or treatment of rapid cycling? *Australas Psychiatry*. 2015;23(5):500-2.
 32. Chen P, Huang Y. Remission of classic rapid cycling bipolar disorder with levothyroxine augmentation therapy in a male patient having clinical hypothyroidism. *Neuropsychiatr Dis Treat*. 2015;11:339-42.
 33. Sampath H, Sharma I, Dutta S. Treatment of suicidal depression with ketamine in rapid cycling bipolar disorder. *Asia Pac Psychiatry*. 2016;8(1):98-101.