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Case Report

From depression to hypomania: antidepressant-triggered switching in a bipolar patient with phenotypic mitochondrial features

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ABSTRACT

Antidepressant-induced mania (AIM) is a recognized complication in bipolar disorder, particularly in patients with neurobiological vulnerabilities. Mitochondrial dysfunction, which impairs neuronal energy metabolism, has been implicated in both bipolar pathophysiology and antidepressant sensitivity. We report the case of a 25-year-old woman with bipolar disorder who presented with a two-month history of worsening depressive symptoms. Her medical history included exercise intolerance since adolescence, recurrent migraine headaches. Given her persistent low mood, sertraline was initiated. Within 10 days, she developed pressured speech, decreased need for sleep, and increased goal-directed activity, consistent with hypomania. The antidepressant was discontinued. She remains stable on lurasidone with maintenance ketamine infusions every 7 weeks. This case illustrates the potential role of mitochondrial dysfunction as a biological amplifier for polarity switching in bipolar disorder. Systemic features of mitochondrial impairment may warrant greater caution with antidepressant use, with emphasis on mood stabilizer-centered regimens and close monitoring for early signs of mood elevation.

Keywords: Bipolar disorder, Antidepressant induced mania, Mitochondria, Mitochondrial dysfunction

INTRODUCTION

Bipolar disorder is a heritable psychiatric condition that is characterized by diminishing episodes of mania and depression.[2,3] Research suggests that approximately 0.53% of the global population currently lives with bipolar disorder, with this condition commonly affecting individuals of working age.[4] During these episodes, patients typically experience symptoms such as decreased need for sleep, grandiosity, psychomotor agitation, distractibility, increased activity, and pressure of speech.[3] If an individual only exhibits a depressive episode, they cannot be diagnosed with bipolar disorder, which leaves the possibility of a manic or hypomanic episode. Bipolar disorder is currently one of the leading causes of disability due to its damaging effect on daily life, such as strained relationships, difficulty performing daily activities, or complications at work and/or school.[4]

Antidepressant-induced mania (AIM) is categorized by the observation that manic and hypomanic symptoms have the potential to emerge when patients with bipolar disorder are exposed to antidepressants, especially when they are not taking simultaneous mood stabilization medication.[1] Clinicians typically screen for AIM when treating patients

with unipolar depression, but little is known regarding which clinical factors can increase the risk of AIM.[1] AIM can substantially affect an individual's quality of life due to its effects on mood, behavior, and cognition, which can lead to increased cost of suffering and changing medications.

Mitochondria are known for their prominent role in ATP production as well as redox regulation, apoptosis, biosynthesis, and calcium signaling.[5] The majority of the cellular ATP is produced through oxidative phosphorylation (OXPHOS) and additionally plays a vital role in the regulation of reactive oxygen species (ROS).[5] In healthy cells, a balanced cycle of fusion and fission ensures mitochondrial stability. If these dynamics are significantly altered, it can result in altered mitochondrial localization and structure, leading to changes in cellular behavior and metabolic reprogramming.[5]

Mitochondrial dysfunction has the potential to affect multiple neurobiological processes, such as enhanced apoptosis and altered synapses, which can potentially have a profound effect on the progression of psychiatric disorders.[6] This could lead to the predisposition of mood disorders such as bipolar disorder.[6]

In the context of AIM, a hyperenergetic mitochondrial state or functional imbalance can predispose individuals with bipolar disorder to potentially develop mania when exposed to antidepressants. This can further dysregulate mitochondrial bioenergetics and promote increased cellular stress. Our case highlights the possible link between bipolar disorder and mitochondrial dysfunction, suggesting that such vulnerabilities may increase the likelihood of mood switching following antidepressant exposure.

CASE REPORT

A 25-year-old woman with a 4-year history of bipolar disorder presented with a 2-month history of worsening depressive symptoms, including persistent low mood, hypersomnia, anhedonia, and marked fatigue. She reported a gradual decline in stamina, requiring frequent rest periods and experiencing generalized muscle weakness.

Her past medical history was significant for exercise intolerance since adolescence, recurrent migraine headaches, hypotonic bladder with six urinary tract infections in the past six months, and an episode of acute respiratory distress following botulinum toxin injections for migraine prophylaxis at the Mayo Clinic, which required hospitalization. She also noted a maternal family history of fatigue, mood instability, and early-onset hearing loss.

On examination, she exhibited mild proximal muscle weakness (4/5) in the shoulders and hip flexors, without focal neurological deficits. Given her worsening depressive episode, sertraline 50 mg/day was initiated while continuing lurasidone. After 10 days, she developed pressured speech, decreased need for sleep, increased goal-directed activity, and excessive online spending, consistent with hypomania. Sertraline was discontinued, and she was then started on lurasidone 20 mg.

At follow-up, she remained stable on lurasidone and received maintenance ketamine infusions every 7 weeks for treatment-resistant depressive symptoms.

DISCUSSION

Although the pathophysiology of bipolar disorder remains relatively obscure, recently acknowledged factors include non-coding RNAs (ncRNAs).[7,8] Evidence suggests a strong correlation to genetic and epigenetic components.[9] Human studies have shown that variances in nerve growth factor (NGF), neurotrophin-3 (NT-3), brain-derived neurotrophic factor (BDNF), and neurotrophin-4 (NT-4) demonstrate neurotrophic signaling associated with decreased neuroplasticity.[9] Neuroimaging studies suggest that changes in regional activity, neuronal activity, functional connectivity, and bioenergetics correlated with bipolar disorder have expressed dendritic spine loss in the dorsolateral prefrontal cortex in post-mortem brain tissue of bipolar disorder patients.[9] Additional mechanisms include oxidative stress, immune-inflammatory imbalance, mitochondrial dysfunction, and weakened hypothalamic-pituitary-adrenal (HPA) axis.[9]

Antidepressants acutely raise monoaminergic levels, particularly serotonin, norepinephrine, and dopamine, and in the context of bipolar disorders, unstable mood regulation, this surge can overshoot into pathological elevation, precipitating mania.[11] Sensitization of mesolimbic dopamine signaling, especially increased D_2/D_3 receptor responsivity, has been proposed as a core switching mechanism, with antidepressants potentiating dopamine transmission and lowering the threshold for manic states.[12] Since then, multiple studies have examined the effects of antidepressants on depressive episodes in bipolar disorder, with some reporting an association between their use and a switch to mania or hypomania.[13-18] The degree of switch liability varies among antidepressant classes, with serotonin norepinephrine reuptake inhibitors such as venlafaxine carrying a higher risk and bupropion a lower one, reflecting differences in their activation of noradrenergic and dopaminergic pathways.[20]

Mitochondrial dysfunction, a well-documented feature of bipolar disorder, creates an energy production deficit. When antidepressants increase neuronal firing and synaptic activity, the mismatch between energy supply and demand, compounded by oxidative stress, can tip circuits into manic activation.[21] Elevated reactive oxygen species and impaired calcium buffering from such dysfunctional mitochondria introduce further instability into synaptic transmission, thereby magnifying the risk of mood destabilization under antidepressant challenge.[22] Over time, repeated switches may sensitize dopaminergic and

neuroplasticity pathways, progressively lowering the threshold for future antidepressant-triggered manic episodes in susceptible individuals.[12]

Mitochondrial dysfunction plays a vital role in the pathophysiology of various mood disorders and treatment response.[10] Mutations or polymorphisms in mitochondrial DNA (mtDNA) have been debatedly associated with glutamate-mediated excitotoxicity, calcium buffering deficiency, and differential response to treatment.[21] The overall framework of mitochondrial dysfunction stems from bioenergetics, which is gradually progressing to a broader relationship with the cellular environment.[25] Mitochondrial dysfunction in disease pathogenesis can have an effect on various processes, such as the citric acid (TCA) cycle and oxidative phosphorylation by reducing energy content.[19] These processes later interplay with glycolysis and lactic acid production.[19]

In mitochondrial impairment, the brain's energy reserves are already limited.[21] The introduction of antidepressants, particularly those with strong monoaminergic effects, increases synaptic activity and metabolic demand.[23] Inadequate mitochondrial capacity to meet these demands may destabilize prefrontal-limbic circuits, reducing inhibitory control over subcortical reward pathways and triggering pathological activation states.[24] This energy mismatch may act as a biological amplifier for polarity switching, explaining the heightened vulnerability to AIM in bipolar disorder patients with mitochondrial dysfunction.[23]

In this case, we want to highlight the need for increased clinical awareness when clinicians are prescribing antidepressants to patients with a previous history of bipolar disorder and are presenting with symptoms correlated to an underlying mitochondrial dysfunction. While the temporal relationship between antidepressant initiation and manic switching in this patient raises the possibility of an association, this observation does not necessarily imply causality and may represent a coincidental occurrence.

CONCLUSION

This case highlights how phenotypic features suggestive of mitochondrial dysfunction, such as exercise intolerance, migraines, and autonomic symptoms, may increase vulnerability to antidepressant induced mood switching in bipolar disorder. In patients presenting with these systemic clues, careful medication selection, emphasis on mood stabilizers over antidepressant monotherapy, and vigilant monitoring for early signs of mania are suggested. The potential relationship between mood instability and mitochondrial dysfunction may increase patient vulnerability to antidepressant induced mania, warranting the heightened necessity of close monitoring regarding early signs of heightened affect. Recognizing such patterns may not only prevent destabilizing episodes but also prompt further evaluation for underlying metabolic contributions to psychiatric illness. Further research is endorsed to better understand the characteristics of antidepressant induced mania related to an underlying mitochondrial dysfunction and to inform the development of early interventional strategies.

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