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Case Report

Bipolar Disorder in a Patient with VACTERL Syndrome: A Case Report

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Abstract

VACTERL association is a non-random constellation of congenital anomalies, typically involving at least three of the following systems: vertebral defects, anal atresia, cardiac malformations, tracheoesophageal fistula, renal anomalies, and limb abnormalities. While defined by structural defects, emerging evidence suggests increased rates of correlations with neurodevelopmental and psychiatric conditions. Bipolar disorder is a chronic mood disorder marked by recurrent episodes of mania or hypomania and depression, with pathophysiology involving fronto-limbic dysregulation, neurotransmitter imbalance, neuroinflammation, mitochondrial dysfunction, and impaired neuroplasticity. We report a case of Bipolar I Disorder in a 21-year-old man with VACTERL association (vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal fistula) and normal cognitive development. He presented with a two-week manic episode with psychotic features and responded well to lithium and olanzapine. To our knowledge, this is the first case reported a potential link between VACTERL association and a bipolar disorder. This case highlights the need for increased awareness of possible psychiatric comorbidities in patients with complex congenital anomalities and underscores the importance of incorporating neuropsychiatric screening into VACTERL patient care.

Keywords: ***VACTERL, Bipolar disorder, Neuropsychiatric comorbidity, Surgery, Case report.***

Introduction

VACTERL association refers to a clinically recognized grouping of congenital anomalies that include at least three of the following: vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal fistula or atresia, renal anomalies, and limb abnormalities [1]. The condition is believed to arise from abnormal mesodermal development during early embryogenesis, and the estimated incidence ranges between 1 in 10,000 and 40,000 live births [2]. Although VACTERL does not inherently include neurological abnormalities in its diagnostic criteria, emerging evidence suggests that, beyond its anatomical manifestations, a subset of patients may also experience increased rates of neurodevelopmental and psychiatric conditions such as Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), and Intellectual Disability (ID) [3].

Bipolar disorder is a chronic psychiatric condition characterized by recurrent episodes of mood disturbance, ranging

from periods of elevated or irritable mood (mania or hypomania) to episodes of depression [5]. According to the World Health Organization, approximately 1 in 150 adults, equivalent to about 0.53% of the global adult population, were living with bipolar disorder [7]. The disorder has a spectrum of subtypes, such as Bipolar type I, Bipolar type II, Cyclothymic Disorder and Other Specified/Unspecified Bipolar Disorders, and each with distinct patterns and severity of mood episodes [6]. Bipolar disorder type I is defined by the presence of at least one manic episode, which may alternate with episodes of depression. Manic episodes are characterized by abnormally elevated or irritable mood, increased energy or activity, and impaired functioning [4].

Although bipolar disorder has been discussed in both the general population and in individuals with neurodevelopmental disorders, such as ADHD [8] and ASD [9], its co-occurrence in patients with VACTERL association has not been previously reported. To our knowledge, this is the first documented case of bipolar disorder, specifically type I, in an individual with VACTERL syndrome. This case underscores the need for clinical vigilance regarding neuropsychiatric manifestations in patients with congenital syndromes traditionally regarded as involving only somatic anomalies. Furthermore, it raises the possibility of an underlying pathophysiological or organic basis for psychiatric symptoms of VACTERL that may be rooted in structural or developmental abnormalities.

Case presentation

Mr. A, a 21-year-old man with VACTERL association involving vertebral defects, anal atresia, cardiac anomalies, and tracheoesophageal fistula, presented with acute onset of mood and psychotic symptoms. Despite multiple surgical interventions during childhood, he had normal cognitive development and no prior neurological or psychiatric diagnoses. At presentation, he exhibited two weeks of elevated mood, decreased need for sleep, racing thoughts, distractibility, irritability, and increased goal-directed activity. He also demonstrated grandiose and paranoid delusions, disorganized behavior, and tangential thought processes. There was no evidence of substance use or medical conditions contributing to his symptoms. He was diagnosed with Bipolar I disorder and treated with lithium and olanzapine, which led to marked clinical improvement. To our knowledge, this represents the first reported case of Bipolar disorder in a patient with VACTERL syndrome, emphasizing the importance of psychiatric vigilance in syndromes traditionally viewed as purely somatic.

Discussion

The term VACTERL association was originally described by Quan and Smith in 1973[10]. It is diagnosed as a non-random constellation of congenital anomalies affecting at least 3 of the following organ systems: vertebral (V), anorectal (A), cardiac (C), tracheoesophageal (TE), renal (R), and limb (L) [2]. While the pathogenesis of VACTERL is not yet fully understood, genetic studies have implicated disruptions in key developmental signaling pathways such as Sonic Hedgehog (SHH) and Wingless related integration site (Wnt), which are critical in early embryogenesis [11]. Variants in genes such as SHH, GLI, ZIC3, FOXF1, HOXD13, and regulators like FGF8 and LPP have been associated with VACTERL phenotypes [12]. Additionally, dysfunction of primary cilia, which mediate SHH signaling, is frequently observed in VACTERL, with implicated genes such as IFT172, IFT57, and TTLL11. 12,13 Environmental factors such as maternal diabetes, folate deficiency, exposure to assisted reproductive technologies and teratogens may further modulate disease expression [11].

Beyond structural anomalies, emerging studies have highlighted increased risks of neurodevelopmental disorders in individuals with VACTERL, including ADHD, autism spectrum disorder (ASD), and intellectual disability (ID) [3]. These associations may reflect shared genetic susceptibilities or consequences of early-life medical interventions such as repeated surgeries and anesthesia exposure [14]. Notably, exposure to anesthesia during critical periods of brain development, common in the VACTERL population due to the need for multiple surgeries, has been linked in some studies to long-term cognitive and behavioral effects, including increased risks for ADHD and learning difficulties[15].

Cohort studies further support this elevated neurodevelopmental burden, especially among patients with additional anomalies or syndromic features [3]. More broadly, children with complex congenital anomalies, particularly of the cardiac and gastrointestinal systems, demonstrate higher prevalence of neuropsychiatric conditions such as ADHD, ASD, and mood disorders [16,17]. While links between congenital anomalies and psychiatric disorders such as bipolar disorder are rarely reported, such associations may be underrecognized or overlooked.

Bipolar disorder is characterized by recurrent episodes of mania and depression and is associated with complex alterations in the brain's limbic network, neurotransmitter signaling, and cellular mechanisms. One core pathological mechanism in bipolar disorder involves immune and inflammatory-mediated damage to white matter within limbic network connections, destabilizing neurotransmitter systems such as dopamine and serotonin. These disruptions contribute to phasic changes in intrinsic brain activity and imbalances between brain networks responsible for mood, cognition, and motor activity [18].

Additionally, mitochondrial dysfunction has been implicated in the pathophysiology of bipolar disorder, with abnormal mitochondrial morphology, impaired energy production, and increased oxidative stress observed in both human and animal studies [19]. Changes in neuroplasticity, especially in regions like the hippocampus, further underlie mood instability and cognitive deficits seen in bipolar disorder [20]. These molecular, cellular, and network-level abnormalities work synergistically and may be exacerbated by chronic stress, genetic susceptibility, and neuroimmune dysfunction [19].

Our case presents a unique co-occurrence of VACTERL association and Bipolar I Disorder (BD-I). To our knowledge, this appears to be the first reported case exploring a potential relationship between VACTERL and bipolar disorder. While the clear mechanism behind this correlation still needs to be further explored, it is plausible that early neurodevelopmental disruptions from congenital anomalies and/or repeated surgical interventions, chronic psychosocial burden and potential genetic susceptibilities may interact to confer long-term neuropsychiatric vulnerability, culminating in the emergence of bipolar disorder.

Conclusion

This case highlights a novel and potentially underrecognized intersection between VACTERL association and bipolar disorder, expanding the spectrum of possible neuropsychiatric sequelae in patients with complex congenital anomalies. Although causality cannot be established from a single case, the convergence of developmental pathway disruptions, neuroinflammatory processes, early-life surgical and psychosocial stressors, and possible shared

genetic susceptibilities underscores the need for heightened psychiatric vigilance in this population. As surgical outcomes and survival rates continue to improve, clinical focus needs to include monitoring long-term psychiatric and psychosocial outcomes. Early neurodevelopmental screening, psychiatric evaluation, and longitudinal follow-up should be considered in the comprehensive care of VACTERL patients. Also, it's important to note that, in VACTERL patients with cardiac and renal defects, antipsychotic management should be individualized, with a cardio-nephro-psychiatric collaborative approach, and incorporate regular cardiac and renal monitoring. Further studies and translational research are needed to clarify the neuropsychiatric correlations in this disease population and explore the possible structural or neurobiological molecular mechanisms that may bridge VACTERL and psychiatric disorders.

List of abbreviations

ADHD: Attention Deficit Hyperactivity Disorder
ASD: Autism Spectrum Disorder
ID: Intellectual Disability

Declarations

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Conflict of interest

None

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