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Case Report

Integrated psychiatric management of Prader-Willi syndrome: a case report of disruptive mood dysregulation and ADHD

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ABSTRACT

Prader-Willi syndrome (PWS) is a genetic disorder characterized by behavioral disturbances such as temper outbursts, impulsivity, aggression, and self-injury. Due to symptom overlap, psychiatric comorbidities including ADHD, obsessive-compulsive behaviors, and disruptive mood disorders are frequently underdiagnosed. These symptoms typically emerge early in life and persist into adulthood, contributing to caregiver burden and functional impairment. Neuroimaging studies reveal abnormalities in brain regions associated with emotional regulation and social behavior, while epigenetic research points to altered methylation patterns in genes which may contribute to behavioral dysregulation. Despite the significant impact of these symptoms, pharmacological management lacks standardization and relies largely on case-based evidence, highlighting the need for detailed clinical documentation to guide individualized care. A 19-year-old male with PWS presented with food preoccupation, anxiety, mood swings, social challenges, and aggression. Multiple failed medication preceded the eventual diagnosis of disruptive mood dysregulation disorder (DMDD) and ADHD. A revised treatment plan led to marked clinical improvement in emotional regulation and functioning. This case illustrates the complexity of diagnosing and treating psychiatric comorbidities in PWS, where overlapping symptoms can obscure accurate assessment and delay appropriate intervention. The absence of standardized guidelines and limited empirical data reflect a critical need for focused research to refine diagnostic criteria and develop effective, evidence-based therapies. Greater understanding of the psychiatric profile of PWS is essential for improving outcomes and quality of life in this vulnerable population.

Keywords: Aggression, ADHD, Disruptive Behaviours, Prader-Willi-Syndrome

INTRODUCTION

Prader-Willi syndrome (PWS) is a complex neurodevelopmental disorder caused by the loss of paternally expressed genes on chromosome 15q11–q13. Clinically, it is characterized by hypotonia, hyperphagia, obesity, hypogonadism, and developmental delays.[1] Beyond its hallmark physical features, individuals with PWS often experience significant psychiatric and behavioral disturbances, which pose substantial challenges to care and long-term outcomes.

Behavioral dysregulation—including temper outbursts, aggression, impulsivity, and compulsive tendencies—is highly prevalent in individuals with PWS and often emerges in early childhood, persisting across the lifespan.[2,3] These behaviors frequently interfere with educational and social functioning and are among the leading causes of caregiver stress. Psychiatric comorbidities such as attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder, mood dysregulation, and obsessive-compulsive behaviors are also commonly observed.[4,5] Notably, ADHD symptoms, particularly inattention and impulsivity, may be underrecognized in this population due to overlapping features such as intellectual disability and compulsivity.[6] Aggressive and self-injurious behaviors further compound the burden of illness, underscoring the importance of targeted interventions.[7]

Recent neuroimaging studies have begun to shed light on the biological substrates underlying these behavioral manifestations. A study identified abnormal patterns of regional brain perfusion in individuals with PWS, particularly in areas implicated in emotion regulation and social processing.[8] These findings suggest a neurobiological basis for the behavioral symptoms observed in the syndrome and support the development of brain-based treatment approaches.

In parallel, epigenetic research has revealed potential biomarkers associated with behavioral dysregulation. Another study reported hypomethylation of the monoamine oxidase A (MAOA) gene promoter region in individuals with PWS who exhibited severe temper outbursts, pointing to the involvement of serotonergic and dopaminergic pathways in aggression and impulse control.[9] Such discoveries highlight the intricate interplay between genetic and epigenetic factors in shaping the behavioral phenotype of PWS.

Pharmacological management of these complex behaviors remains challenging. While various psychotropic agents, including antipsychotics, stimulants, and mood stabilizers, have been trialed with mixed outcomes, no consensus guidelines currently exist for the treatment of aggression or ADHD symptoms in PWS.[6] In this report, we describe the case of a child with PWS presenting with severe disruptive behaviors and comorbid ADHD, and we explore the clinical challenges and pharmacological strategies involved in his management.

CASE REPORT

A 19-year-old male with a confirmed diagnosis of Prader-Willi syndrome (PWS) presents for evaluation due to significant behavioral disturbances impacting his daily functioning. His clinical profile is marked by prominent obsessive behaviors, most notably a persistent preoccupation with food. He also exhibits heightened anxiety, frequent mood swings, and occasional episodes of physical aggression directed at others.

At school, he demonstrates notable social difficulties, including awkward interactions and engaging in inappropriate behaviors for his developmental age, such as nail biting. These challenges often result in emotional dysregulation and outbursts when he becomes frustrated or overwhelmed. He additionally reports experiencing social anxiety, low self-esteem, and feelings of hopelessness, particularly related to his awareness of being different from his peers.

The patient's psychiatric history is notable for multiple emergency department visits and one inpatient psychiatric hospitalization due to episodes of severe, unprovoked aggression. These incidents included physically assaultive behaviors such as hitting and biting others, as well as destructive actions like damaging furniture and property within the home. Due to the severity and persistence of these behaviors, he was enrolled in a specialized school for children with developmental and behavioral needs. He began receiving regular outpatient therapy to support emotional regulation and behavioral control.

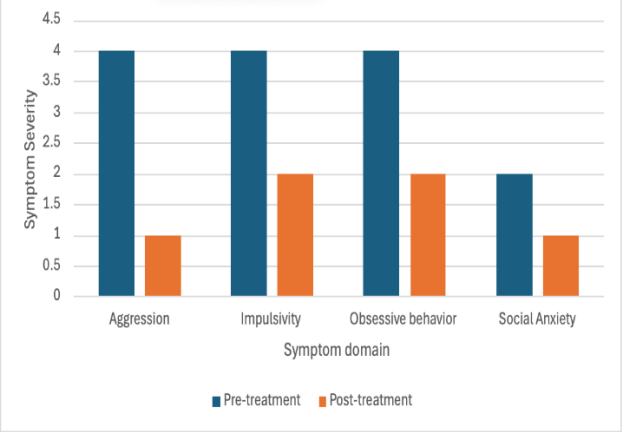

Figure 1: Effect of targeted therapy on psychiatric symptom severity in a patient with Prader-Willi syndrome (PWS).

Symptom severity across four domains—aggression, impulsivity, obsessive behavior, and social anxiety—was rated pre- and post-treatment using a clinical severity scale (range: 0–5). Following targeted pharmacological intervention, substantial reductions were observed in all symptom domains, most notably in aggression and impulsivity. This highlights the potential efficacy of individualized therapy in managing psychiatric comorbidities in PWS.

These behavioral challenges have been present since early adolescence and were initially attributed to his underlying intellectual disability. Prior pharmacologic interventions included trials of aripiprazole, risperidone, and sertraline, which were discontinued due to poor therapeutic response and concerns about side effects, including sedation and cognitive slowing. A comprehensive psychiatric re-evaluation was conducted in light of the ongoing mood instability and impulsive aggression. He was subsequently diagnosed with disruptive mood dysregulation disorder (DMDD) and attention-deficit/hyperactivity disorder (ADHD).

Following this updated diagnostic formulation, a new treatment regimen was initiated. A previously higher dose of valproic acid resulted in significant weight gain, necessitating a dose reduction (to 500 mg) and the adjunctive use of lamotrigine (100 mg) to maintain mood stability.

Additionally, Guanfacine 2 mg and Naltrexone 50 mg are used to help manage impulsivity and symptoms of ADHD. Since initiating this regimen, the patient has remained clinically stable, with a notable reduction in both frequency and severity of behavioral outbursts.

DISCUSSION

The behavioral challenges in PWS—particularly aggression, temper outbursts, impulsivity, and attention difficulties—can significantly impair quality of life and complicate care, often requiring targeted pharmacologic intervention. In this context, a number of medications have been explored for their efficacy and safety in ameliorating these symptoms.

Antipsychotics such as risperidone and aripiprazole have demonstrated effectiveness in managing aggression and behavioral disturbances in individuals with PWS. A study reported significant improvements in disruptive behaviors following risperidone treatment in a small cohort of PWS patients with relatively good tolerability.[10] Similarly, aripiprazole has been used in case reports to target aggression and obsessive-compulsive behaviors. Another study documented a notable reduction in aggressive outbursts and obsessive symptoms in a child with PWS treated with aripiprazole, without major side effects.[11] Selective serotonin reuptake inhibitors (SSRIs), especially sertraline, have shown promise in reducing emotional reactivity and temper outbursts. In a retrospective study, sertraline was associated with a decrease in irritability and frequency of outbursts, supporting the role of serotonergic dysregulation in PWS-related behavioral pathology.[9] SSRIs may also benefit comorbid anxiety and depressive symptoms, which frequently exacerbate behavioral instability.

Alpha-2 adrenergic agonists, particularly guanfacine extended-release (GXR), have been increasingly studied for their utility in addressing ADHD symptoms and associated aggression in PWS. A retrospective cohort study showed that GXR led to reductions in hyperactivity, impulsivity, and self-injurious behavior.[12] A more recent randomized, double-blind, placebo-controlled trial confirmed these findings, with significant improvements in aggression (as measured by the Modified Overt Aggression Scale) and ADHD symptoms, as well as reduced skin-picking.[13] Sedation was the most common side effect, but the medication was generally well tolerated.

Topiramate, an anticonvulsant with mood-stabilizing properties, has also emerged as a promising agent. Although its primary use in PWS has been for appetite suppression, the TOPRADER trial study observed secondary benefits regarding improved behavioral regulation. Given topiramate's GABAergic and glutamatergic modulation, its potential utility for aggression and impulsivity warrants further exploration.[14]

Though supported by limited evidence, other pharmacologic strategies have included fluoxetine and naltrexone. A case report described improvements in hyperphagic and aggressive behaviors with this combination in a patient with PWS.[15] Similarly, another study reported successful reduction of skin-picking—a self-injurious behavior closely linked to emotional dysregulation—in response to fluoxetine, suggesting serotonergic agents may have a broader role in managing impulsivity and behavioral compulsions.[16]

Interestingly, the neuropeptide oxytocin has also been investigated for calming effects in PWS. A randomized placebo-controlled trial found that oxytocin administration increased trust and reduced disruptive behaviors in PWS patients.[17,18]

Taken together, these findings underscore that behavioral disturbances in PWS, including aggression and ADHD-like symptoms, likely arise from complex neurobiological underpinnings, and while medications can be effective, their use must be tailored to the individual, considering side effect profiles and other comorbidities commonly observed as part of the syndrome.

CONCLUSION

This case underscores the heterogeneity of psychiatric manifestations in Prader-Willi syndrome, emphasizing the necessity for individualized treatment strategies. Given the broad variability in clinical profiles—including differences in behavioural presentation, comorbid diagnoses, and medication response—there is no one-size-fits-all approach to management. Instead, treatment must be carefully tailored to the unique needs based on a thorough diagnostic assessment. Further research is essential to characterize these diverse presentations better and to develop flexible, evidence-informed guidelines that support clinicians in delivering personalized, effective care for individuals with PWS.

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