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CASE REPORT

Valproic Acid As An Effective Treatment For Self-Injurious Behavior In A Patient With Wolf-Hirschhorn Syndrome: A Case Report

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Abstract

Wolf-Hirschhorn Syndrome (WHS) is a neurodevelopmental disorder (NDD) characterized by a microdeletion, often accompanied by maladaptive behaviors. First-line treatment typically includes antipsychotics; however, their efficacy varies, and alternative options remain limited. This case report aims to demonstrate the effectiveness of valproic acid monotherapy in managing maladaptive behaviors in a patient with WHS presenting with self-injurious behavior. A 10-year 4-month-old female patient with WHS exhibited intense self-injurious behaviors. When her demands were not met, she would bang her head against the wall with significant force, risking severe traumatic injury, and bite her hand. She had previously received sufficient dosage and durations of aripiprazole and risperidone treatments without benefit. Valproic acid was initiated at a dose of 400 mg/day in divided doses. After the first month of treatment, the patient ceased the behavior of banging her head. Additionally, the behavior of biting her hand significantly decreased. The Aberrant Behavior Checklist (ABC) score, initially assessed at 51 points, decreased to 28 points after the first month of treatment. The decrease in the ABC score was particularly marked in the subscales of irritability and social withdrawal. This outcome suggests that in patients diagnosed with neurodevelopmental disorders (NDD) where antipsychotics have failed, valproic acid as a mood stabilizer may be beneficial as monotherapy in reducing self-injurious behavior.

Key words: Neurodevelopmental Disorders, Self-Injurious Behavior, Valproic Acid, Wolf-Hirschhorn Syndrome, 4p Deletion

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INTRODUCTION

Wolf-Hirschhorn Syndrome (WHS) is a neurodevelopmental disorder (NDD) characterized by multiple congenital anomalies and intellectual disability. Its prevalence is estimated to range between 1 in 50,000 and 1 in 20,000 live births, with a higher occurrence in females, approximately at a 2:1 ratio. This condition results from a partial deletion in the distal segment of the short arm of chromosome 4 (4p16.3). The critical region for WHS includes the two key loci currently recognized as WHSCR1 and WHSCR2 (1). The syndrome is typically diagnosed in infancy or early childhood based on distinctive craniofacial features, growth retardation, intellectual disability, and confirmatory genetic testing. However, studies are being conducted on prenatal diagnostic methods. (2). Prognostic outcomes vary depending on the size of the deletion and associated complications. While many individuals experience significant developmental delays, early intervention and supportive therapies can improve quality of life (1).

The deletion of WHSCR2 region is essential for the manifestation of key characteristics associated with WHS, including "Greek warrior helmet" appearance, growth deficiency, global developmental delay, feeding difficulties, intellectual disability, seizures, and maladaptive behaviors such as self-injurious behavior (SIB). Seizures are a hallmark feature of WHS, occurring in approximately 50-100% of affected individuals (3). These seizures often emerge within the first two years of life and can be challenging to manage due to their refractory nature (1). When maladaptive behavior in NDD becomes challenging, behavioral therapies serve as the first-line treatment. However, when behavioral therapies fail, patients should be supported with pharmacotherapy. The evidence supporting pharmacological treatments for SIBs remains limited and primarily based on lower levels of evidence. There is a critical need for well-structured studies to guide clinical decision-making. The limited available evidence for the use of common pharmacologic agents, such as second-generation antipsychotics, and less common agents, such as clonidine, n-acetylcysteine, riluzole, naltrexone, and topical anesthetics, is reviewed. Most research has been conducted in autism spectrum disorder (ASD) populations, with findings often extrapolated to other NDDs. These limitations may influence treatment outcomes, though the potential risks of pharmacotherapy remain relevant. (4). Limited research exists on the efficacy of mood stabilizers in treating NDD-related maladaptive behavior (5). Herein, we present a case where mood stabilizers effectively mitigated SIB in a WHS patient after unsuccessful trials with two antipsychotics.

CASE REPORT

We present the case of a 10-year-old female with WHS, brought to our child and adolescent psychiatry outpatient clinic due to SIB. Born to a G4P3 mother following a consanguineous marriage, the patient exhibited developmental delays from the prenatal period. The birth occurred via cesarean section at 36 weeks due to recurrent indications. The patient had a history of incubator care for one month and was breastfed for four months. Hypotonia and microcephaly were noted at birth. She started walking at 2 with the help of physical therapy and produced her first word at 2 years old. Early interventions included physical therapy, occupational therapy, special education, and speech-language therapy. The patient had no clinical history of seizures. She has been undergoing neurology follow-ups every six months, and her most recent EEG, performed at the age of eight, revealed no deterioration or pathological findings. The patient, who is currently attending a special education school, receives shadow teacher support and is in the first grade despite being 10 years old. Nevertheless, she is still struggling with early literacy skills—reflecting her moderate intellectual disability and developmental delay. At presentation, the patient was 110 cm tall (z score = -4.30) and weighed 13 kg (z score = -5.19).

The patient's self-injurious behaviors began three years ago, including self-biting and head-hitting, which were triggered by familial comings and goings, unmet desires, and emotional distress. Prior to that, from the age of three, she exhibited delayed speech and, when unable to express herself, would cry and scream. Additionally, since that time, she has continued to suck her thumb as a self-regulation mechanism. While head-hitting behavior predominantly occurred at home, self-biting when frustrated was also observed in social settings outside the home. However, she generally attempted to establish adaptive social interactions unless confronted with an undesired situation.

The patient's first psychiatric consultation occurred two years ago, at the age of eight, due to concerns regarding

SIB. Initially, risperidone treatment was started at 0.25 mg/day and titrated up to 1.5 mg/day. However, after four months of treatment, the patient did not benefit from dose escalation and experienced daytime drowsiness as a side effect. As a result, risperidone was discontinued, and aripiprazole was initiated at 1 mL/day. The aripiprazole dose was gradually increased to 4 mL/day and maintained at this dose for six months. Although no significant side effects were observed, the treatment did not yield any clinical improvement.

The psychiatric evaluation was conducted through a comprehensive clinical interview with the patient's mother, as the patient had significant communication limitations. The assessment focused on developmental history, behavioral patterns, emotional regulation, and daily functioning. Direct observation of the patient was also performed, where her limited verbal skills, frustration tolerance, and self-injurious behaviors (such as head-banging and hand-biting) were noted. The patient's 16-year-old older sister and 14-year-old older brother were also invited to repeated interviews. During these assessments, both siblings were found to have normal mental capacity, and no psychopathology was detected in either of them. During examination, she could only use the words "mother, father, and sister" and expressed her needs by pointing. However, she actively sought social interaction and was receptive to social engagement. She had hair loss in the frontal area due to head-hitting (Figure 1).

She became frustrated quickly and started biting her right hand, which was swollen and injured. Given the failure of previous antipsychotic regimens, valproic acid was initiated at 400 mg/day in divided doses (as 200 mg/day in the morning and 200 mg/day in the evening) as monotherapy, along with behavioral suggestions to the mother. In addition to the clinical interview and observation, standardized measures were used, including the Aberrant Behavior Checklist (ABC) to quantify behavioral symptoms and assess treatment response. ABC score was 51 at baseline (Irritability: 22; Social withdrawal: 11; Stereotypic behavior: 0; Hyperactivity: 13; Inappropriate speech: 5). After one week, the valproic acid serum level was 82 mEq/L. After one month, head-hitting subsided markedly, and hand-biting frequency decreased. No adverse effects were reported and repeat ABC score was 28 (Irritability: 9; Social withdrawal: 4; Stereotypic behavior: 0; Hyperactivity: 11; Inappropriate speech: 4). The decrease in the ABC score was particularly marked in the subscales of irritability and social withdrawal.

DISCUSSION

SIB in NDDs presents a significant clinical challenge, often necessitating a multifaceted treatment approach. While behavioral interventions remain the first-line strategy for managing SIB, pharmacological treatment becomes crucial when behavioral therapies alone prove

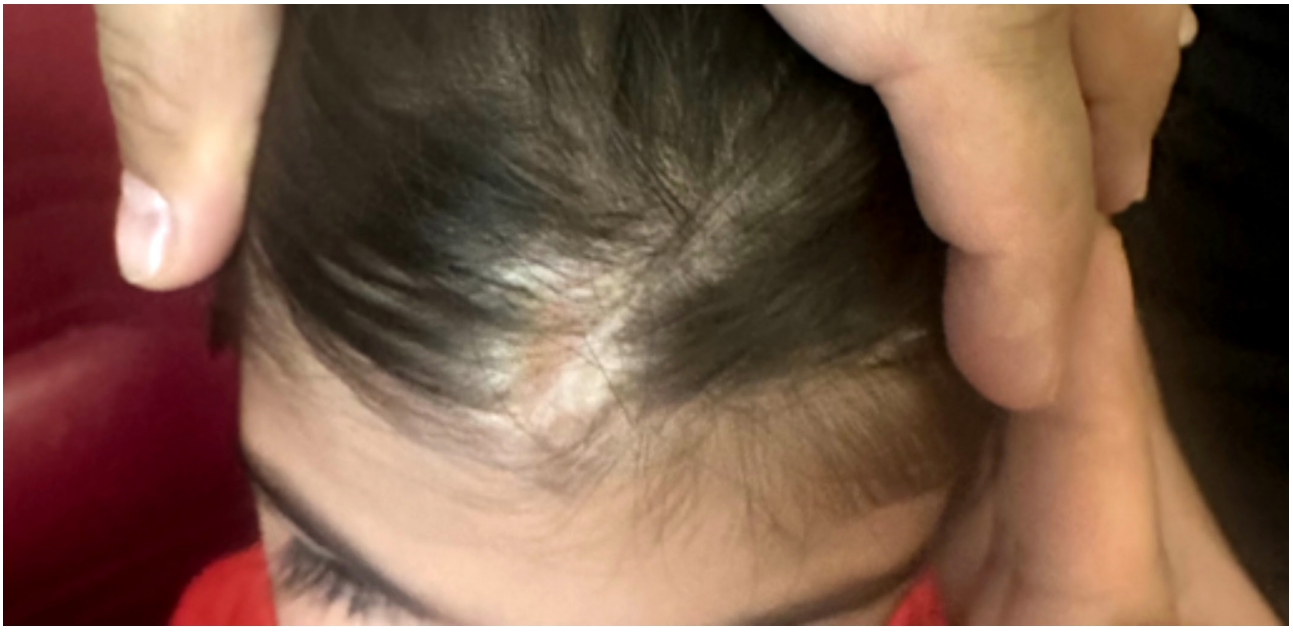

Figure 1: Hair loss on the frontal area

insufficient. WHS, a rare neurodevelopmental disorder characterized by intellectual disability, behavioral challenges, and frequent comorbidities such as epilepsy, is among the conditions where SIB is commonly observed.

Psychiatric comorbidities frequently associated with WHS include developmental delays, intellectual disability, receptive and expressive language deficits, and stereotypic behaviors, often coexisting with seizures (1). Although maladaptive behaviors are less commonly emphasized in WHS, they can significantly impact the quality of life. Among these, SIB is particularly concerning, as demonstrated by a study by McGill et al., in which 48% of patients with WHS exhibited self-injurious behaviors, with teeth grinding (86%), self-biting (43%), and head-hitting (38%) being the most prevalent (6). Given the clinical burden of SIB in WHS, exploring pharmacological interventions beyond traditional behavioral strategies is essential. This report highlights the therapeutic potential of mood stabilizers in addressing SIB in WHS, particularly in cases where first-line pharmacological agents, such as antipsychotics, have been ineffective or poorly tolerated.

From a pharmacological perspective, treatment options for SIB in NDDs remain limited. Second-generation antipsychotics, such as risperidone and aripiprazole, are often considered first-line pharmacotherapeutic agents due to their ability to reduce irritability and aggression (4). However, in this case, both risperidone and aripiprazole failed to provide clinical benefit, with risperidone causing intolerable daytime drowsiness. This outcome aligns with existing literature suggesting that while antipsychotics can be effective for certain behavioral symptoms in NDDs, their efficacy in reducing SIB specifically remains inconsistent (4). Furthermore, their use is often associated with significant side effects, limiting long-term adherence.

In this case, valproic acid was introduced as monotherapy following the unsuccessful trials with antipsychotics. Valproic acid, a widely used mood stabilizer, functions by enhancing gamma-aminobutyric acid (GABA) neurotransmission, stabilizing neuronal excitability, and regulating mood, which may contribute to its observed efficacy in reducing self-injurious behaviors (4). Its use in this patient resulted in significant improvement in SIB, as evidenced by the marked reduction in self-biting and head-hitting behaviors within one month of treatment. Notably, the ABC scores demonstrated substantial improvement in irritability and social withdrawal subscales, further supporting its efficacy.

Despite limited research on valproic acid for SIB in NDDs, evidence from ASD studies suggests its potential in reducing irritability and maladaptive behaviors. A randomized double-blind placebo-controlled study demonstrated that divalproex treatment, with minimum valproate blood level 50 μg/ml in children with ASD, led to a significant reduction in Clinical Global Impression (CGI) and ABC scores, highlighting its effectiveness in decreasing irritability and maladaptive behaviors (5). These findings suggest that mood stabilizers, including valproic acid, may serve as alternative treatment options when conventional pharmacotherapies, such as antipsychotics, prove ineffective or are poorly tolerated. This case further contributes to the growing body of evidence supporting the role of mood stabilizers in managing SIB in NDD populations.

Nevertheless, the limited evidence base for pharmacological treatment of SIB highlights the urgent need for well-designed, controlled studies to guide clinical decision-making. Future research should aim to evaluate the efficacy and safety of mood stabilizers, including valproic acid, across a broader spectrum of NDDs and behavioral presentations.

In conclusion, this case demonstrates that valproic acid may serve as an effective alternative for managing SIB in NDDs when antipsychotics are ineffective or poorly tolerated. While the findings are promising, clinicians should adopt a personalized treatment approach, carefully considering the patient's unique clinical profile and monitoring for potential side effects.

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Abbreviations list

ABC: Aberrant Behavior Checklist
ASD: Autism spectrum disorder
CGI: Clinical Global Impression
EEG: Electroencephalogram
GABA: Gamma-aminobutyric acid
NDD: Neurodevelopmental disorder
SIB: Self-injurious behavior
WHS: Wolf-Hirschhorn Syndrome

Ethics approval and consent to participate

Written informed consent was obtained from the patient's legal guardian for the publication of this report. All procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki.

Consent for publication

Written informed consent was obtained from the patient's legal guardian for the publication of this report.

Availability of data and materials

There is no data avaliable for this case report.

Competing interests

The data supporting this case report are stored both digitally and physically. Researchers interested in accessing the data may contact the corresponding author upon reasonable request.

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Authors' contributions

Idea/Concept: MU. Desıgn: MU. Control/Supervısıon MU, STH. Data Collectıon And/Or Processıng: MU. Analysıs And/Or Interpretatıon: MU. Lıterature Revıew: MU. Wrıtıng The Artıcle: MU. Crıtıcal Revıew: MU, STH, MFC. References And Fundıngs: MU. Materials: MU.

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