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MANAGEMENT OF BEHAVIORAL DISORDER IN LAMB-SHAFFER SYNDROME- A CASE REPORT

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ABSTRACT

Background: Lamb-Shaffer is a rare genetic syndrome with just 113 reported cases caused by SOX5 gene haploinsufficiency and disrupts the normal development of cartilage and the nervous system. It can cause an array of clinical features, including craniofacial abnormalities, intellectual disability, global developmental delay, ophthalmological abnormalities, and lesser-known behavioural disturbances. is a case report of ADHD and DMDD in Lamb-Shaffer syndrome, its presentation, and management. **Case Report:** A 7-year-old male patient presented to the clinic with hyperactivity and difficulty learning. He had a history of motor and language milestone delay, which led to genetic testing, and he was ultimately diagnosed with Lamb-Shaffer syndrome 2 years ago. The patient went to special needs school and had early access to physical, occupational, and speech therapies along with multiple trials of stimulant and non-stimulant medications, which led to adverse effects and failed to effectively help with behavioural and academic challenges. Neuropsychological assessment revealed significant cognitive impairment with a full-scale IQ of 57. The patient was ultimately diagnosed with disruptive mood dysregulation disorder (DMDD) and attention deficit hyperactivity disorder (ADHD), co-existing with Lamb-Shaffer syndrome. Treatment modifications included adjusting Viloxazine, introducing Clonidine, and planning to initiate Aripiprazole, alongside GeneSight genetic testing to optimize medication management. **Conclusion:** Management of Lamb-Shaffer is complex, especially with behavioural co-morbidities, and requires a multi-disciplinary approach. In our case, the patient failed multiple stimulant and non-stimulant medications, which prompts the importance of more longitudinal and long-term research for Lamb-Shaffer syndrome and behavioural co-morbidities and a need for individualized treatment.

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INTRODUCTION

Lamb-Shaffer syndrome is a rare genetic disorder with only 113 cases reported worldwide (1) characterized by the haploinsufficiency of the SOX5 gene (2). Mutations in SOX genes have been linked to various neurodevelopmental syndromes with overlapping clinical features. These mutations disrupt the normal function of proteins critical for regulating gene expression in brain structure, function, and behaviour.

Specifically, SOX5 mutations result in Lamb–Shaffer syndrome, and in most cases, it is caused by non-specific and sporadic mutations (3). SOX5 is an important member of the SOXD family of transcription factors, which play a crucial role in developing the Cartilage (4) and the Nervous System. It is believed to play an important role in the formation, differentiation, and migration of nerve cells in the brain (5). Recent studies have expanded the understanding of SOX5 mutations by identifying novel variants and their association with features such as craniofacial anomalies, including down slanting palpebral fissures, prominent philtrum ridges, open mouth appearance, upturned nose, bulbous nasal tip, frontal bossing and many others varying from patient to patient. It has also been associated with Intellectual disability, Global developmental delay, as well as prominent motor and language developmental delay (3,6). Less consistently associated features reported were hypotonia, strabismus, optic nerve atrophy, and renal, spine, and genital abnormalities (7). This wide array of phenotypic features seems to be explained by incomplete penetrance and variable expressivity (8). These disorders typically present early in childhood, with affected individuals experiencing delays in speech, motor skills, and social development. Neuropsychiatric manifestations such as hyperactivity and impulsivity can be present and may significantly impact the quality of life and daily functioning.

Cases with this genetic aberration have been described in the context of cytogenetics, intellectual disability, and ophthalmologic disorders. However, the literature on behavioural problems in these patients seems to be limited. This case describes the presentation and management of ADHD in a patient with Lamb-Shaffer syndrome.

CASE REPORT

A 7-year-old male presented to the clinic with symptoms of hyperactivity and difficulty in learning. His developmental history revealed that he was born via normal vaginal delivery at full term with perinatal period being uneventful and without any complications. Later on, his language and motor function milestones got severely delayed and were associated with increased drooling, poor muscle tone, and strabismus. He ultimately underwent genetic analysis, which led to the diagnosis of Lamb-Shaffer syndrome at age of 2 years. He also underwent surgery twice for strabismus at the age of 11 months and 5 years old.

His parents reported that he needed more help than other siblings in activities of daily living and suffered from inattention and hyperactivity, and it led to difficulties in education, for which he was put in special needs school. He was also started on Physical, Occupational, and speech therapies due to the timely diagnosis of his condition. The patient has poor frustration tolerance with unpredictable mood swings and outbursts. In the past, the patient responded poorly to Methylphenidate patch 15mg, leading to depressed mood and anxiety; Dexmethylphenidate 15 mg, which caused irritability; Amphetamine, which was not tolerated due to taste and irritability; and guanfacine being ineffective. The patient was currently taking Viloxazine 300mg daily but reported an unpredictable mood and poor focus on medication. The patient exhibits significant difficulties with sustained attention, impulse control, and task persistence, often displaying impatience and avoidance of challenging tasks. He also struggles with procrastination, poor time management, and poor organizational skills, leading to disruptive behaviours in the classroom and at home. Although previously observed, self-injurious behaviours like biting and hitting himself were currently absent. Neuropsychological testing performed by a skilled psychologist, revealed extremely low scores on verbal comprehension, visual-spatial comprehension, and fluid Reasoning and a very low score on working memory with a full-scale IQ of 57. Notably, there are no symptoms of social, generalized, or performance anxiety, nor any obsessive-compulsive, manic, or psychotic features. He interacts well with peers and has a group of friends, and there are no reports of bullying or abuse. The patient was diagnosed with disruptive mood dysregulation disorder and attention deficit hyperactivity disorder. For the treatment plan, it was decided to titrate Viloxazine to 200mg daily and start Clonidine liquid 0.1mg/ml 1ml daily, gradually titrating to 5ml daily. An option for starting Aripiprazole in future was also considered. GeneSight testing was conducted to better guide the treatment, and a follow-up appointment was set up.

DISCUSSION

Management of neurodevelopmental syndromes associated with SOX gene mutations involves a multifaceted approach, including genetic counselling, early intervention, and symptomatic treatment. Early developmental therapies crucial for optimizing functional outcomes and addressing developmental delays. Stimulants can be prescribed for ADHD, along with antipsychotics or antidepressants for managing irritability, aggression, or mood disorders. However, the failure rate of these medications in our case was high. This case showed similarity to previously reported cases in strabismus and global developmental delay, drooling, and hypotonia while also demonstrating features like selectivity and cognitive rigidity with clothing and eating habits. Particularly challenging was his emotional dysregulation, with frequent, unpredictable mood swings and disruptive outbursts impacting both educational and home environments. These behavioural manifestations, including significant inattentiveness, impulsivity, and hyperactivity, fulfilled DSM-V criteria for ADHD combined presentation and underscored the complexity of managing behavioural and emotional symptoms in patients with Lamb-Shaffer syndrome.

Furthermore, the patient's inadequate response to multiple pharmacological treatments highlights potential resistance and sensitivity to adverse effects of conventional medications in individuals with genetic neurodevelopmental syndromes. This led to the introduction of alternative medications like Clonidine and Aripiprazole, emphasizing the necessity of individualized medication regimens and regular follow-up. Whether the patient's specific mutation directly contributed to the medication resistance and behavioural complexity or other factors that influenced the response remains unclear. Hence, future research should focus on elucidating genotype-phenotype correlations and their effect on psychopharmacology in Lamb-Shaffer syndrome. This case also underlines the importance of neuropsychological assessments for guiding the efforts and effective management strategies aimed at improving the quality of life and developmental outcomes for these patients.

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Abbreviations

ADHD - Attention deficit hyperactivity disorder
DMDD - Disruptive Mood Dysregulation Disorder
DSM-V - Diagnostic and Statistical Manual of Mental Disorders Fifth Edition

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