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Case Report

10th Case Worldwide: A Case Study of Li-Ghorbani-Weisz-Hubshman Syndrome in a 4-Year-Old Boy

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Abstract

This case report details a 4-year-old boy presenting with speech delay, hyperactivity, and impulsivity, alongside minimal autism spectrum disorder (ASD) traits. Born full-term without complications and part of a twin pair, the patient exhibited developmental delays, particularly in speech, progressing to basic words by 3 years and 9 months. Physical examination revealed broad eyebrows, cognitive impairment, and epicanthus, with genetic testing identifying a variant of uncertain significance (VUS) in the KAT8 gene, raising suspicion of Li-Ghorbani-Weisz-Hubshman Syndrome (LIGOWS). Management included occupational therapy (OT), speech therapy (ST), and risperidone, resulting in gradual improvements in hyperactivity and impulsivity. Genetic testing confirmed LIGOWS, with MRI findings corroborating the diagnosis. This case underscores the importance of comprehensive diagnostic and management approaches for rare genetic syndromes.

Case Report

The patient, a 4-year-old boy, presented with concerns of speech delay, hyperactivity, and impulsivity, along with minimal autism spectrum disorder traits. He is a full-term infant, born without complications, and is part of a twin pair, with his brother being Twin B. Developmentally, the patient began walking at 11 months but experienced delayed speech until the age of 3 years and 9 months when he began uttering basic words like "Mama" and "Dada." Despite a smooth pregnancy and delivery, and no reported consanguinity between parents, the patient's developmental progress was hindered by delayed speech and hyperactivity. He demonstrated good eye contact, response to his name, and knowledge of body parts, albeit with limitations in color and number recognition.

Physical examination revealed broad eyebrows, cognitive impairment, and epicanthus. His weight is 19 kg (95th percentile), and his height is 111 cm (95th percentile). Genetic testing revealed a variant of uncertain significance in the KAT8 gene, raising suspicion of Li-Ghorbani-Weisz-Hubshman Syndrome.

Management involved a multidisciplinary approach, including OT and ST from the age of 2 years, alongside pharmacological intervention with risperidone due to hyperactivity and impulsivity. Despite gradual dose

escalation of risperidone to 1 ml TID, the patient continued to exhibit impulsivity, prompting further dose adjustments. Genetic testing confirmed the diagnosis of LIGOWS syndrome, revealing a mutation in the KAT8 gene (c.267 C>G p.(Phe86Leu)). Imaging studies corroborated abnormal MRI findings indicative of LIGOWS, including a thin corpus callosum, nodular heterotopia, and enlarged ventricles.

The patient's response to treatment, closely monitored through regular follow-up appointments, showed improvement in hyperactivity and impulsivity, albeit with ongoing speech difficulties and developmental delays. Ongoing genetic counseling for the family is advised, alongside continued multidisciplinary management to optimize developmental outcomes. The patient's case underscores the complexity of neurodevelopmental disorders and highlights the importance of a comprehensive diagnostic and management approach for individuals with rare genetic syndromes like LIGOWS. Notably, the patient represents the 10th reported case worldwide.

Discussion

Li-Ghorbani-Weisz-Hubshman Syndrome is a very rare neurodevelopmental disorder with limited data available. It is characterized by developmental delay, mild to moderate intellectual impairment, including speech and language development delay, and dysmorphic features. Seizures may also manifest in some cases. Individuals with LIGOWS often exhibit behavioral abnormalities such as hyperactivity, impulsivity, and difficulties with numbers and abstract concepts. Neuroimaging studies play a critical role in assessing structural brain abnormalities associated with this disease, providing insights into the underlying neuroanatomical changes. Imaging typically reveals abnormalities such as enlarged ventricles, a thin corpus callosum, decreased white matter volume, and nodular heterotopia in the gray matter, indicating abnormal cortical development.

Beyond the core features of developmental delay and intellectual impairment, a spectrum of behavioral issues might be seen in some individuals with LIGOWS that can vary widely in severity and impact. These may include difficulties in social interaction, sensory processing disorders, and challenges with adaptive functioning. The variability in clinical presentation underscores the heterogeneous nature of the syndrome, complicating both diagnosis and management.

The genetic basis of LIGOWS involves mutations in the KAT8 gene, with reported variants affecting its

function. The KAT8 gene encodes for a lysine acetyltransferase involved in histone modification and gene regulation, crucial for neurodevelopmental processes.

Our patient, a 4-year-old boy, presents with delayed speech and language development, hyperactivity, and impulsivity, aligning with the clinical spectrum of LIGOWS. His developmental milestones, such as delayed speech until 3 years and 9 months, and cognitive impairment are consistent with the typical features of the syndrome. Physical examination revealed broad eyebrows and epicanthus, which are mild dysmorphic features commonly seen in LIGOWS patients. His genetic testing identified a VUS in the KAT8 gene, suggesting a potential link to the syndrome.

A total of 9 patients have been reported, 8 of them diagnosed with an autosomal dominant inheritance while the ninth patient exhibited a possible rare autosomal recessive inheritance with complete penetrance. Our patient is the 10th diagnosed patient worldwide and has a heterozygous missense mutation in the KAT8 gene inherited in an autosomal dominant pattern.

Management of LIGOWS involves a multidisciplinary approach including speech therapy, occupational therapy, and potentially pharmacological interventions for behavioral symptoms. Regular follow-up and genetic counseling are crucial to monitor developmental progress, adjust therapies, and assess familial implications of the genetic variant. Targeted testing of family members is recommended to determine the inheritance pattern.

Characteristic	Details
Age range	2 to 18 years
Developmental features	Global developmental delay, early walking difficulties, fine motor delay, impaired intellectual development, language delay
Cognitive impairment	Mild to moderate IQ (in 2 patients), difficulties with numbers or money value, ADHD in 1 patient, autism in some patients
Seizures	Five patients had seizures, one had a single febrile seizure
Brain imaging	Abnormalities in 5 patients: enlarged ventricles, decreased white matter, thin corpus callosum, subependymal gray matter heterotropia, possible polymicrogryia in 1 patient
Dysmorphic features	Non specific and variable, includes hypotelorism, telecanthus, epicanthal fold, up slanted palpebral fissures, fullness of upper lids, estropia, low set or dysplastic ears, high or depressed nasal bridge, full lips, downturned corners of mouth, open mouth, fifth finger clinodactyly, overlapping toes
Vision problems	Few had vision problems mostly hyperpropia
Genetic mutations	De novo heterozygous missense mutations in the KAT8 gene, identified by exome sequencing and confirmed by SANGER sequencing
Functional studies	Mutations expressed at normal levels, impaired acetylation of histone 4 lysine 16, mutations could promote expression of MSL proteins similar to wildtype

References

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