Complex Neurogenetic Overlap : GNAO1 disorder in Trisomy 21

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INTRODUCTION

GNAO1-related disorder is a rare genetic encephalopathy characterized by early-onset epilepsy, hyperkinetic movement disorder, and severe developmental impairment. The relationship between *GNAO1* and Trisomy 21 is not directly established in current medical literature. To our knowledge, this is the first reported case to demonstrate a *GNAO1*-related disorder co-occurring with Trisomy 21.

CASE PRESENTATION

A 4-year-old male with Trisomy 21 referred for autism evaluation due to severe developmental delays. He is nonverbal, non-ambulatory, unable to self-feed, and demonstrates mixed hypo and hypertonia. Despite intensive therapies, functional abilities remain at an estimated 7-8-month developmental level. His clinical course is further complicated by severe growth failure and seizure disorder. Initial laboratory evaluation, including complete blood count, comprehensive metabolic panel, thyroid function testing, and celiac screening, is unremarkable. Brain MRI demonstrates bilateral hippocampal abnormalities and a small-appearing pituitary gland, raising concerns for possible neuroendocrine involvement. Given severity of neurologic impairment and atypical features, whole exome sequencing was pursued which identified a likely pathogenic autosomal dominant variant in *GNAO1*. He is currently undergoing additional neurological and endocrine work up to further characterize the contribution of *GNAO1*-related disorder to his phenotype.

DISCUSSION

GNAO1 (*G protein subunit alpha O1*) encodes the Gαo protein, a key mediator of G-protein-coupled receptor (GPCR) signaling involved in neurotransmission and neurodevelopment. Gαo regulates intracellular signaling downstream of several neurotransmitter receptors, including dopamine, GABA, and acetylcholine receptors, which are critical for normal brain development and function. Disruption of Gαo signaling impairs neuronal communication and has been associated with developmental delay, epilepsy, hypotonia, and movement disorders. *GNAO1*-related disorder is typically caused by a de novo pathogenic variant and encompasses a broad phenotypic spectrum characterized by hyperkinetic movement disorders and/or epilepsy, frequently accompanied by developmental delay and intellectual disability. The diagnosis should be considered in individuals presenting during infancy with epilepsy, movement disorders, axial hypotonia, feeding difficulties, and mild-to-profound intellectual disability.[1,2]

In our patient, the severity of developmental impairment, seizure disorder, and growth failure was disproportionate to what would typically be expected in individuals with Trisomy 21 alone. The coexistence of Trisomy 21 and *GNAO1*-related disorder likely contributed to his unusually complex neurological phenotype. Furthermore, although pathogenic variants in *GNAO1* are classically associated with severe neurological manifestations such as drug-resistant epilepsy and involuntary movements, emerging evidence suggests that *GNAO1* may also represent a novel genetic cause of combined pituitary hormone deficiency (CPHD). This association is particularly relevant in our patient, whose neuroimaging demonstrated pituitary hypoplasia, providing a potential mechanistic explanation for his growth failure.[1,2,3]

Prevalence of Health Concerns in Trisomy 21 and *GNAO1*-related disorders

Clinical Feature	Trisomy 21 (T21)	*GNAO1*-related disorder	Patient with T21 and likely-pathogenic *GNAO1* variant
Developmental delay	Common	Common	Profound
Severe motor delay	Uncommon	Common	Non-ambulatory
Seizures	Uncommon	Common	+
Growth failure	Mild to moderate	Emerging association	Severe

CONCLUSION

Children with Down syndrome commonly experience developmental delays and have multiple medical comorbidities. However, profound neurologic impairment, refractory epilepsy, or severe growth failure that appears disproportionate to the expected phenotype should prompt evaluation for additional underlying etiologies. Recognition of a dual diagnosis has important implications for prognosis, clinical management, surveillance, and genetic counseling.

The coexistence of a pathogenic *GNAO1* variant and Trisomy 21 represents an exceptionally rare and complex clinical presentation. Further investigation of this patient and identification of additional individuals with both conditions will be important to better define the phenotypic spectrum and to clarify potential interactions between *GNAO1*-related disorders and Trisomy 21.

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