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Biotinidase Deficiency and Aplasia Cutis Congenita With Ecterodactyly Syndrome (ACCES) in A Case of Moya Moya Disease: A Missing Link

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Abstract

Biotinidase Deficiency (BD) is an uncommon autosomal recessive disorder resulting from mutations in the BTD gene, which causes dysfunction in biotin recycling and disturbances in energy metabolism, oxidative stress, and blood-brain barrier integrity. This condition elevates the risk of neurovascular incidents, including strokes. The loss of function of the UBA2 gene, due to various mutations, leads to Aplasia Cutis Congenita with Ectrodactyly (ACCES) syndrome, an autosomal dominant disorder characterized by highly variable expressivity. ACCES syndrome typically manifests with scalp defects and, less commonly, ectrodactyly, in addition to other subtle skeletal anomalies, early growth deficiency, and neurodevelopmental delays.

This case report examines a 6-year-old child who exhibited an acute stroke and notable dysmorphic characteristics, emphasizing a rare correlation between Biotinidase Deficiency and ACCES syndrome, which presumably facilitated the onset of Moya Moya Disease (MMD), an uncommon progressive cerebrovascular condition. The case indicates that the interplay of neurovascular stress from both BD and ACCES may elevate the risk of stroke and MMD in impacted individuals. This highlights the significance of identifying concurrent genetic disorders that may result in serious neurovascular complications.

Keywords: Biotinidase, Aplasia cutis congenita, moya moya disease, UBA2 gene

Introduction

Biotinidase Deficiency (BD) is an uncommon autosomal recessive disorder resulting from a mutation in the BTD gene, which causes impaired biotin recycling, disrupted energy metabolism, oxidative stress, and damage to the blood-brain barrier. Elevates the risk of neurovascular incidents such as strokes.

The dysfunction of the UBA2 (ubiquitin-like modifier-activating enzyme 2) gene, resulting from deletion, frameshift, missense, or nonsense mutations, is linked to Aplasia Cutis Congenita with Ectrodactyly (ACCES) syndrome. It exhibits autosomal dominant inheritance with significant variability in expressivity, even among family members. The majority of patients display scalp defects, whereas ectrodactyly is comparatively rare. Nevertheless, more variable and less apparent digital and skeletal anomalies frequently exist. Early growth deficiency and neurodevelopmental delays are frequently

observed.[2] Moya Moya Disease (MMD) is an uncommon cerebrovascular disorder marked by the progressive constriction of the internal carotid arteries.[3] This case report details a 6-year-old child exhibiting acute stroke alongside notable dysmorphic features, underscoring a rare correlation between Biotinidase Deficiency and ACCES syndrome, which may contribute to Moya Moya Disease, indicating that neurovascular complications arising from both conditions could result in stroke and Moya Moya disease.

Case Report

A 6-year-old male, born of a fourth-degree consanguineous marriage, exhibited acute weakness in the left upper limb and difficulty ambulating, accompanied by left-sided facial weakness for one day, necessitating further evaluation. The child had no prior history of seizures, trauma, or hospitalization; the antenatal and birth history was unremarkable. He was completely immunized but exhibited mild global developmental delay, low intelligence, and difficulties with speech and language. During the physical examination, notable characteristics were observed, including brachycephaly, a flat occiput, low-set ears, post-axial polydactyly of the right fifth toe, left eye strabismus, several café au lait spots on the body (<0.5 cm), myopia, and a high-arched palate (Figures 1 and 2). No lesions on the scalp were observed. The CNS examination revealed left-sided hemiparesis accompanied by left-sided facial palsy.

Figure 1

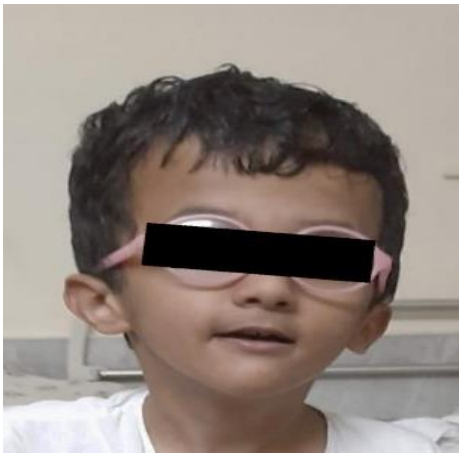
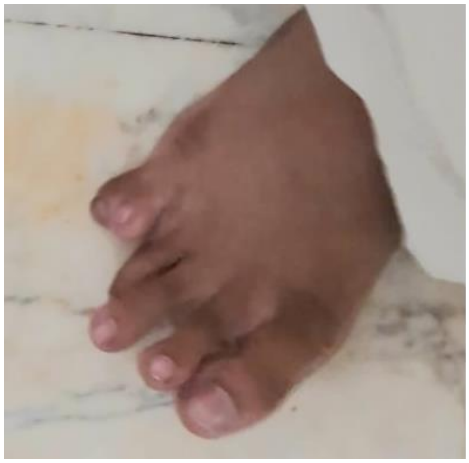


Figure 2



As part of the stroke evaluation, hemogram , hemoglobin electrophoresis was conducted to exclude sickle cell disease and thrombophilia profiles were done which were normal. Additionally, the anti-nuclear antibody test (ANA) via immunofluorescence (IF) was performed, yielding normal results. Serum Creatine Phosphokinase (CPK) was elevated at 1717 U/L (normal range 55-170U/L).The MRI of the brain with angiography demonstrated infarcts in the right middle cerebral artery territory, subependymal nodules, a cerebellar subarachnoid cyst, and grey matter abnormalities, heterotopia and dysgenesis, stenotic occlusion of the supraclinoid internal carotid artery, and bilateral supraclinoid internal carotid artery stenosis (right greater than left) with collateral circulation indicative of Moya Moya disease. Considering the dysmorphic characteristics and slight developmental delay Whole exome sequencing (WES) was conducted, revealing the subsequent findings.

1. Biotinidase deficiency (OMIM# 253260) - BTD Heterozygous missense variant c.908A>G p.His303Arg (Chr3:15644824A>G) in the BTD gene The identified variant has been designated as Pathogenic (P), indicating it has a substantial effect on our patient.
2. Aplasia Cutis Congenita and Ectrodactyly Skeletal Syndrome (OMIM#619959) - UBA2 Variant 1 (c.1765A>C, p.Ile589Leu): The exome data analysis revealed a homozygous missense variant c.1765A>C, p.Ile589Leu (Chr19:34469063A>C) in the UBA2 gene. The identified variant has been categorized as a Variant of Uncertain Significance (VUS).

This variant is unreported in the literature. However, when considered together, it indicates that both anomalies may play a significant role in the neurological and neurovascular pathophysiology leading to stroke and Moya-Moya disease. Biotinidase enzyme activity was performed which was low suggestive of deficiency.

Course and treatment

The patient received treatment with aspirin and physiotherapy. Biotin supplementation commenced, resulting in marked clinical enhancement and swift recuperation. The patient was scheduled for elective revascularization surgery upon the neurosurgeon's recommendation.

Discussion

Biotinidase deficiency may aggravate endothelial dysfunction and oxidative stress, contributing to the pathophysiology of Moya Moya Disease. Approximately 10 variants of ACCES syndrome are documented, exhibiting diverse skeletal and neurodevelopmental manifestations. UBA2 is essential for the post-translational modification of proteins through sumoylation by attaching the SUMO1 (small ubiquitin-like modifier) protein. In contrast to ubiquitination, sumoylation not only directs proteins for degradation but also participates in cell cycle regulation, subcellular trafficking, signal transduction, stress responses, and chromatin structural dynamics.[4] Our study has identified a pathogenic variant in the BTD gene and a variant of uncertain significance in Aplasia cutis congenita syndrome that has not been previously reported. When syndromic features accompany an acute event, a thorough evaluation is necessary to identify any correctable cause.

Conclusion

Children exhibiting developmental delays, dysmorphic characteristics, and neurological symptoms should undergo prompt evaluation through whole exome sequencing, and chromosomal array testing should be conducted if warranted. A potential double mutation may have resulted in a stroke and the

manifestation of Moya Moya disease in our case. Analysis of copy number variants (CNVs) for identified pathogenic genes should be conducted whenever feasible and economically viable. Timely diagnosis and biotin supplementation can avert severe cerebrovascular complications in potentially curable conditions.

References

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