Morphological Effects of Glutaminase Deficiency

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Abstract

We have studied fibroblasts of 3 cases of glutaminase deficiency and identified a novel inherited metabolic disorder (Kuilenberg et al., 2026). Patients presented with a broad spectrum ranging from early-onset global developmental delay to lethal early neonatal encephalopathy. We have studied three infants from two unrelated families who presented clinically with neonatal onset refractory burst-suppression epileptic encephalopathy and respiratory failure, progressing to either a persistent vegetative state or early death. One of the 3 patients is still alive. Metabolic and genetic investigations, together with brain magnetic resonance imaging, demonstrated 2 different homozygous, unreported missense variants in glutaminase. These variants result in elevated glutamine concentrations in the cerebrospinal fluid and cystic lesions. Analysis of the fibroblasts of these patients using Transmission Electron Microscopy, demonstrated ultrastructural effects on the morphology of the nucleus, swelling of the lysosomes, mitochondria and the ER, altered Golgi stacks and accumulation of glycogen. All together, these morphological alterations across the cellular architecture, indicate a broad cellular stress phenotype secondary to Glutaminase deficiency that disturbs various homeostatic processes. Our analysis of this rare disease will shed light on more common disorders, such as Hepatic encephalopathy and urea cycle defects.

References

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