Argininosuccinic aciduria

Argininosuccinate lyase (ASL) is integral to the urea cycle, which enables nitrogen waste and biosynthesis of arginine, a precursor of nitric oxide. Inherited argininosuccinate lyase deficiency causes argininosuccinic aciduria, the second most common urea cycle defect and an inherited model of systemic nitric oxide deficiency. Patients present with developmental delay, epilepsy and movement disorder. Here we aim to characterise epilepsy, a common and neurodebilitating comorbidity in argininosuccinic aciduria.

Methods: We conducted a retrospective study in seven tertiary metabolic centres in the UK, Italy and Canada from 2020 to 2022 to assess the phenotype of epilepsy in ASA and correlate it with clinical, biochemical, radiological and electroencephalographic data.

Results: Thirty-seven patients aged 1 to 31 years old were included. Twenty-two (60%) patients presented with epilepsy. Median age at epilepsy-onset was 24 months. Generalized tonic clonic and focal seizures were most common in early-onset patients whilst atypical absences were predominant in late-onset patients. Seventeen patients (77%) required antiseizure medications and 6 (27%) had pharmacoresistant epilepsy. Epileptic patients presented with a severe neurodebilitating disease with higher rates of speech delay (p=0.04) and autism spectrum disorders (p=0.01) and more frequent arginine supplementation (p=0.01) compared to non-epileptic patients. Neonatal seizures were not associated with a higher risk of developing epilepsy. Biomarkers of ureagenesis did not differ between epileptic and non-epileptic patients. Epilepsy-onset in early infancy (p=0.05) and electroencephalographic background asymmetry (p=0.0007) were significant predictors of partially controlled or refractory epilepsy.

Significance: Epilepsy in argininosuccinic aciduria is frequent, polymorphic, and associated with more frequent neurodevelopmental comorbidities. We identified prognostic factors for pharmacoresistance in epilepsy. This study does not support defective ureagenesis as prominent in the pathophysiology of epilepsy but suggests a role of central dopamine deficiency. A role of arginine in epileptogenesis was not supported and warrants further studies to assess the potential arginine neurotoxicity in ASA [1)].

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