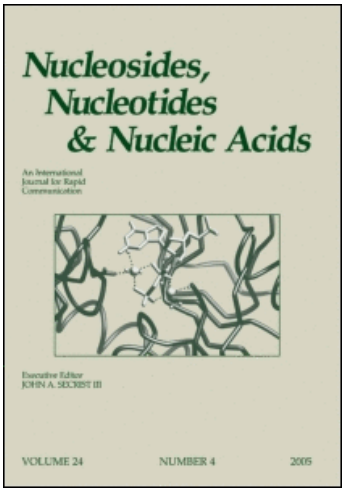

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Adenylosuccinate Lyase Deficiency—First British Case

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ABSTRACT

A deficiency of adenylosuccinate lyase (ASDL) is characterised by the accumulation of SAICAriboside (SAICAr) and succinyladenosine (S-Ado) in body fluids. The severity of the clinical presentation correlates with a low S-Ado/SAICAr ratio in body fluids. We report the first British case of ADSL deficiency. The patient presented at 14 days with a progressive neonatal encephalopathy and seizures. There was marked axial and peripheral hypotonia. Brain MRI showed widespread white matter changes. She died at 4 weeks of age. Concentrations of SAICAr and SAdo were markedly elevated in urine, plasma and CSF and the SAdo/SAICAr ratio was low, consistent with the severe phenotype. The patient was compound heterozygous for 2 novel ADSL mutations; c.9 G>C (A3P) and c.572 C>T (R190X).

Key Words: Adenylosuccinate lyase; Deficiency; ADSL; SAICAriboside; Succinyladenosine.

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INTRODUCTION

Adenylosuccinate lyase (ASDL) catalyses two steps in purine synthesis—the 8th step in the de novo pathway: conversion of SAICAR (succinylaminoimidazole-carboxamide ribotide) to AICAR (aminoimidazole-carboxamide ribotide), and conversion of S-AMP (adenylosuccinate) to AMP (adenylate) in the purine nucleotide cycle. SAICAriboside (SAICAr) and succinyladenosine (S-Ado) accumulate when this enzyme is deficient.[1] Clinical presentations in ADSL deficiency vary from mild psychomotor retardation to epilepsy with convulsions starting within the newborn period. The lower the ratio of S-Ado/SAICAr in body fluids the more severe the clinical presentation.

CLINICAL SYNOPSIS

The female patient presented at 14 days with a progressive neonatal encephalopathy and seizures (multifocal myoclonus and generalised tonic clonic events). There was marked axial and peripheral hypotonia. The brain MRI showed widespread white matter changes. Treatment with oral ribose (10 mmol/kg/day) was ineffective. She died at 4 weeks of age.

METHODS

Urine and plasma were analysed by RPLC with inline diode array detection. The nucleosides and bases were separated using a Hichrom ODS-1 analytical column, with a gradient running from 100% Buffer A (40 mm ammonium acetate, pH 5.0) to 20% buffer B (Methanol:Acetonitrile:Tetrahydofuran; 80:10:10) over 33 minutes. Fibroblast cultures were grown, and the molecular analysis undertaken.[2]

RESULTS

Table 1 shows the high concentrations of SAICAr and SAdo that were detected in the urine, plasma and CSF. The molecular analysis of mRNA showed the presence of a mutation c.9 G>C (A3P) in the homozygous state, but analysis of genomic DNA showed the presence of the mutation in the heterozygous state. Further analysis of

Table 1. Purine metabolites in body fluids.

Metabolites (μmol/l)	Urine	Plasma	CSF
Creatinine	1700	–	–
Uric acid	2060	357	22
SAICAr	1325	34	921
SAdo	925	27	477
SAdo/SAICAr	0.70	0.79	0.52

genomic DNA revealed a second mutation, c.572 C>T, in exon 5 which creates a stop codon in position 190 of the protein (R190X).

DISCUSSION

The low ratios of SAdo/ SAICAr detected in urine, plasma and CSF, are consistent with the severe clinical picture.[2] Analysis of mRNA showed the A3P mutation in the homozygous state. However, analysis of genomic DNA showed the patient was heterozygous for the mutation. A second mutation, c.572 C>T, results in instability of the mRNA synthesized from this allele, and it is rapidly degraded. Both mutations have not been reported previously. This is the first case of ADSL to be reported in the UK. In a previous study by us, 10,000 UK urines were screened for SAICAr and S-Ado and no cases detected.[3] Thus, ADSL deficiency is very rare in Britain.

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