LETTER TO JMG

Towards a suggestive facial dysmorphism in adenylosuccinate lyase deficiency?

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Adenylosuccinate lyase deficiency (MIM 103050, ADSL) is a rare autosomal recessive disease causing severe mental retardation and/or autistic features.[1 2] Seizures are often observed (80%),[3] varying in age of onset (from newborn to late childhood) and nature (tonic-clonic, "suppression burst" pattern, West syndrome, etc), and are very often resistant to all medication. Around 50% of the children show autistic-like behaviour.[4] Microcephaly is rare (1/13 of reported cases). Non-specific anomalies of the brain, such as hypoplasia of the vermis, cerebral atrophy,[5] lack of myelination,[6] white matter anomalies,[7] and lissencephaly[4] have often been described.

ADSL is a homotetramer involved in two distinct steps of purine synthesis, namely (1) the conversion of succinylaminoimidazole carboxamide ribotide (SAICAR) into aminoimidazole carboxamide ribotide (AICAR), and (2) the conversion of adenylosuccinate (S-AMP) into adenosine monophosphate (AMP) in the inosine monophosphate transformation pathway (fig 1). The diagnosis of ADSL deficiency is based on the detection of dephosphorylated SAICAR and S-AMP products, that is, S-Ado (succinyladenosine) and SAICAr (succinylaminoimidazole carboxamide riboside). The modified Bratton-Marshall test is the most convenient urinary screening test,[8 9] but conclusive diagnosis requires the identification of S-Ado and SAICAr in urine or cerebrospinal fluid by high performance liquid chromatography (HPLC). The gene for adenylosuccinate lyase has been mapped to chromosome 22q13.1-q13.2[10] and around 20 different missense mutations and one deletion have been identified so far.[11–14] Most patients are compound heterozygotes.[15]

Here, we report on a novel case of adenylosuccinate lyase deficiency, sharing a number of clinical features with previously reported cases, and emphasise the facial dysmorphic features hitherto unreported in this condition.

CASE REPORT

The proband, a girl, was the first child of unrelated parents, born after an uneventful term pregnancy. Her birth weight was 3800 g, length was 49 cm, and head circumference was 35 cm. Hypotonia was noted at 6 months of age. She presented with seizures at 20 months, which were not controlled by valproate and clonazepam but by lamotrigine only. She was first referred to our genetic clinic at 27 months of age for mental retardation and facial dysmorphism. She could not sit unaided, she was hypotonic, and she had no speech. Dysmorphic features included small head circumference (−2 SD), brachycephaly, flat occiput, prominent metopic suture, intermittent divergent strabismus, small nose with anteverted nostrils, long and smooth philtrum, a thin upper lip, and low set ears (fig 2). Her weight was 11.2 kg (M) and length 88 cm (−1 SD). All standard laboratory investigations were normal and brain MRI showed non-specific asymmetrical ventricles with hypodensity of the white matter. The EEG showed bifrontal seizures. Blood chromosome analyses were normal. The association of severe developmental delay with seizures was suggestive of a metabolic disorder. The modified Bratton-Marshall urinary test was positive, suggesting ADLS deficiency. This diagnosis was confirmed by measurement of urine and cerebrospinal fluid (CSF) SAICAr and S-Ado by HPLC. Urinary SAICAr and S-Ado concentrations were 4.18 and 3.86 µmol/mg creatinine, respectively, and CSF SAICAr and S-Ado concentrations were 376 and 367 µmol/l, respectively. The SAICAr/S-Ado ratio was 0.92 in urine and 0.97 in CSF. Finally, molecular analyses of the *ASDL* gene showed compound heterozygosity for *ADSL* mutations (M1L and R374W). The mother was found to be heterozygous for the M1L and the father for the R374W mutations.

DISCUSSION

Dysmorphic features have not previously been mentioned in ADSL deficiency. We have had the opportunity to analyse pictures of another case of an ADSL deficient child previously reported by Nassogne *et al*[16] (fig 3). This girl had similar dysmorphic features to our patient, namely brachycephaly, prominent metopic sutures, small nose with anteverted nostrils, long, smooth philtrum, and thin upper lip. All of these features, characteristic of metabolic disorders, have been described in mitochondrial disorders (respiratory chain[17] and pyruvate dehydrogenase[18] deficiencies), peroxysomal disorders,[19], and fetal alcohol syndrome,[20] and could be the result of either toxicity of the abnormal metabolite accumulation or the direct effect of the primary enzyme deficiency. The simplicity of the urinary screening test should allow consideration of this diagnosis when dealing with the association of developmental delay, dysmorphic features, and seizures.

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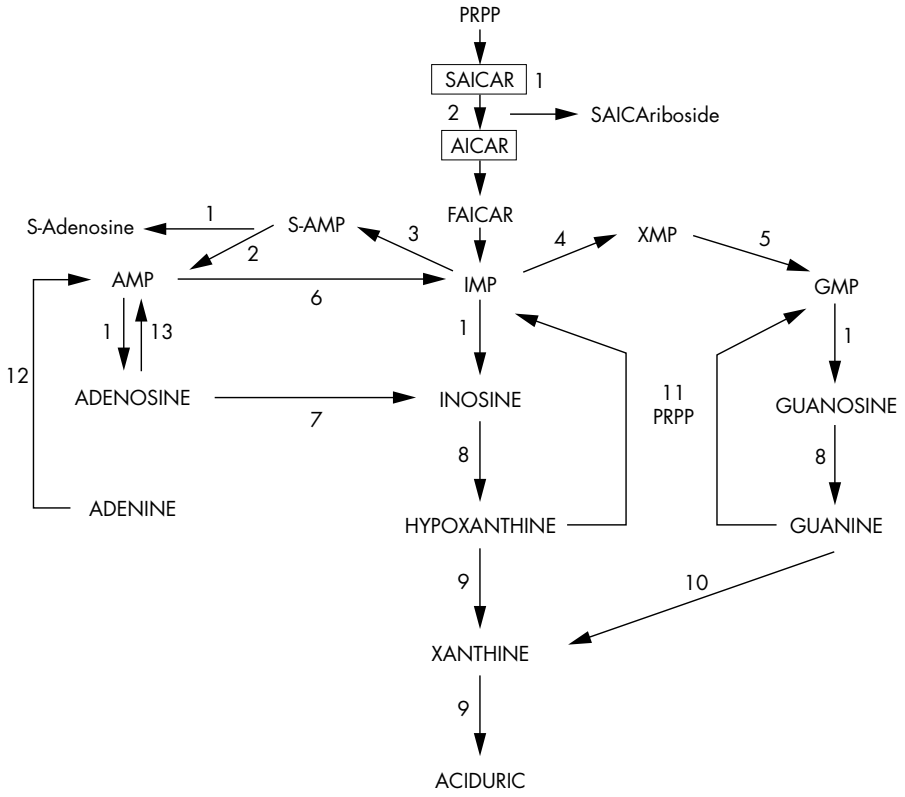
Abbreviations: ADSL, adenylosuccinate lyase deficiency; SAICAR, succinylaminoimidazole carboxamide ribotide; AICAR, aminoimidazole carboxamide ribotide; S-AMP, adenylosuccinate; AMP, adenosine monophosphate; S-Ado, succinyladenosine; SAICAr, succinylaminoimidazole carboxamide riboside; HPLC, high performance liquid chromatography



AICAR: amnioimidazole carboxamide ribotide
SAICAR: succinyl-amnioimidazole carboxamide ribotide
S-Ado: succinyladenosine
AMP: adenosine monophosphate
S-AMP: adenylosuccinate (succinyl AMP)
GMP: guanosine monophosphate
IMP: inosine monophosphate
XMP: xanthosine monophosphate
PRPP: phosphoribosyl pyrophosphate
ENZYMES: 1 = cytosolic 5'-nucleotidase
2 = **adenylosuccinate lyase**
3 = adenylosuccinate synthetase
4 = IMP deshydrogenase
5 = GMP synthetase
6 = AMP deaminase
7 = adenosine deaminase
8 = purine nucleoside phosphorylase
9 = xanthine deshydrogenase
10 = guanine deaminase
11 = hypoxanthine-guanine phosphoribosyl transferase
12 = adenine phosphoribosyl transferase
13 = adenosine kinase

Figure 1 Pathways of purine metabolism.

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Figure 2 Facial dysmorphism in our case. Note the brachycephaly, prominent metopic sutures, small nose with anteverted nostrils, the long and smooth philtrum, and poorly modelled and low set ears.

Figure 3 Facial dysmorphism in the case reported by Nassogne *et al*.[16] Note the small nose with anteverted nostrils, the long philtrum, and the thin upper lip.

Key points

- Adenylosuccinate lyase deficiency (MIM 103050, ADSL) is a rare autosomal recessive disease causing mental retardation, seizures, and autistic features. The diagnosis is based on the detection of the dephosphorylated SAICAR and S-AMP products and the modified Bratton-Marshall test is a simple urinary screening test.
- Here, we report on a new case of adenylosuccinate lyase deficiency presenting with mental retardation, seizures, and facial dysmorphism and having brachycephaly, prominent metopic suture, a small nose with anteverted nostrils, long and smooth philtrum, thin upper lip, and low set ears.
- The analysis of another previously reported child with ADSL shows the same dysmorphic features, which could be the result of toxicity of the abnormal metabolite accumulation.
- We conclude therefore that the diagnosis of ADSL should be considered when dealing with the association of developmental delay, dysmorphic features, and seizures.

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