Towards a suggestive facial dysmorphism in adenylosuccinate lyase deficiency?

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Adenylosuccinate lyase deficiency (MIM 103050, ADSL) is a rare autosomal recessive disorder 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\(^8\) have often been described.

ADSL is a homotetramer involved in two distinct steps of purine synthesis, namely (1) the conversion of succinylaminomidazole carboxamide ribotide (SAICAR) into aminomimidazole 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 (succinylaminimidazole carboxamide riboside). The modified Bratton-Marshall test is the most convenient urinary screening test,\(^9\)\(^10\) but conclusive diagnosis requires the identification of S-Ado and SAICAR in urine and cerebrospinal fluid by high performance liquid chromatography (HPLC). The gene for adenylosuccinate lyase has been mapped to chromosome 22q13.1-q13.2,\(^11\) and around 20 different missense mutations and one deletion have been identified so far.\(^11\)\(^-\)\(^13\) Most patients are compound heterozygotes.\(^13\)

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, and thin upper lip. All of these features, characteristic of metabolic disorders, have been described in mitochondrial disorders (respiratory chain\(^14\) and pyruvate dehydrogenase\(^15\) deficiencies), peroxysomal disorders,\(^16\) and fetal alcohol syndrome,\(^17\) 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.

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\(^18\) (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\(^14\) and pyruvate dehydrogenase\(^15\) deficiencies), peroxysomal disorders,\(^16\) and fetal alcohol syndrome,\(^17\) 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.
REFERENCES


Figure 1 Pathways of purine metabolism.

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.


