

CONNECT-ADSL: A WORLDWIDE PATIENT-CENTERED EXPERIENCE AS A KEY FOR EXPANDING MEDICAL KNOWLEDGE IN ADENYLOSUCCINATE LYASE DEFICIENCY (ADSL)

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Summary

- To describe the clinical features and genotype of a cohort of children with ADSL deficiency
- Collecting data allowed us to increase the knowledge of the disease
- Genotype characterization allowed to expand the spectrum of ADSL mutation

Background: Adenylosuccinate lyase deficiency (ADSL) is an ultrarare neurometabolic recessive disorder of purine metabolism caused by biallelic mutations in the *ADSL* gene (MIM *608222) that lead to a wide range of clinical manifestations whose pathogenic mechanisms are not yet fully understood (Mouchegh K, et al., 2007, Jurecka A, et al., 2008). The aim of the study is to describe the clinical features and genotype of a cohort of affected children subscribed to a worldwide parents' patients association.

Materials and Methods: Data were collected through "Our Journey with ADSL deficiency Association" using a web survey directly filled in by parents.

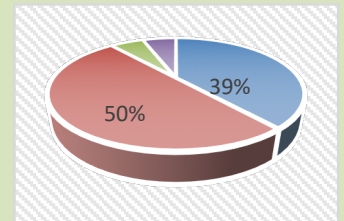
Results: Eighteen patients (12 males, 6 females, age 6 months – 17 years, median age 10.92 years \pm 7.28 SD), from 13 families and different geographical areas were enrolled over a period of 12 months. The age at onset ranged from birth to the first three years (median age 0.63 years \pm 0.84 SD) but we observed a wide range of variability in the age at diagnosis (two months till 17 years, median age 6.42 years \pm 6.12 SD). The first sign was psychomotor delay in 8/18 patients, epilepsy in 3/18, psychomotor delay and epilepsy in 3/18, others (apneas, hypotonia, nystagmus) in 3/18.

Diagnosis was made by Whole Exome Sequencing (WES) in about 40% of patients.

Seven patients were affected by type I of ADSL deficiency, nine by type II and one by fatal neonatal form. Ten genetic variants of uncertain significance (VUS) were identified (6), six classified as novel variants with different structural impacts on the ADSL protein.

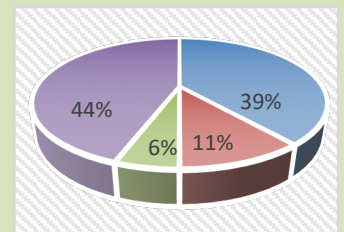
Conclusions: Collecting data from a virtual cohort of patients seemed to have a real impact on the knowledge of the disease. Genotype characterization allowed physicians to expand the spectrum of ADSL and to better define, adding clinical and/or biochemical data, the biological effects of novel variants.

Different phenotypic classes of patients



- Neonatal fatal form
- Type I form
- Type II form
- No symptoms

Different method for diagnosis



- WES
- WES + biochemical test
- Segregation analysis
- Biochemical test

References:

1. Mouchegh K, Zikanova M, Hoffmann GF et al. Lethal fetal and early neonatal presentation of adenylosuccinate lyase deficiency: observation of 6 patients in 4 families. *J Pediatr* 2007;150(1):57–61, e52
2. Jurecka A, Zikanova M, Tylki-Szymanska A et al. Clinical, biochemical and molecular findings in seven Polish patients with adenylosuccinate lyase deficiency. *Mol Genet Metab* 2008b;94(4):435–442