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CLINICAL MANIFESTATIONS OF LYSOSOMAL ACID LIPASE DEFICIENCY (LAL-D): THE INTERNATIONAL LAL-D REGISTRY

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Background: Lysosomal acid lipase deficiency (LAL-D) is a rare, autosomal recessive disease caused by pathogenic variants in the LIPA gene. Lysosomal accumulation of cholesteryl esters and triglycerides leads to cirrhosis and dyslipidemia across a clinical spectrum, and affect both infants and children/adults.
Aims: An international registry (NCT01633489; Alexion Pharmaceuticals, Inc.; 2013–ongoing) was established to better understand the natural history of lysosomal acid lipase deficiency (LAL-D) and to evaluate long-term treatment outcomes.
Methods: Baseline findings for patients enrolled through July 1, 2019 are presented. Of 190 patients enrolled, 35 were excluded from this analysis (*LIPA* carrier, deceased at enrollment, unconfirmed LAL-D diagnosis); 155 patients with confirmed LAL-D diagnosis were included (12 infants, 143 children/adults). LAL enzyme activity analysis was performed for 145/154 patients (94%) and genetic testing for 128/154 patients (83%).
Results: Of 105 children/adults with reported *LIPA* mutations, 39 were homozygous and 34 were compound heterozygous for the common *LIPA* mutation E8SJM (c.894G>A); 6 infants with reported *LIPA* mutations were homozygotes and 2 were compound heterozygotes. Of the 155 patients, 62% were <18 years, 52% were male, and 85% were white. Median (range) age at clinical onset was 0.2 years (0.0–0.7) among infants and 6.0 years (0.0–41.3) among 133 children/adults with data; median (range) age at diagnosis was 0.2 years (−0.1 to 1.2) among infants and 10.8 years (0.2–53.6) among 135 children/adults with data. Manifestations that raised suspicion of LAL-D were reported in 149/155 patients. Infants (12 with data) presented predominantly with hepatomegaly (75%), splenomegaly (58%), nausea/vomiting (58%), and diarrhea (50%), and 50% had a known family history of LAL-D. Children/adults (n=143) presented predominantly with elevated alanine aminotransferase levels (67%), hepatomegaly (66%), and elevated aspartate

aminotransferase levels (65%). Of 74 children/adults with baseline liver biopsy, 58% had microvesicular steatosis, 16% had micro- and macrovesicular steatosis, and 32% had lobular inflammation. Of the 155 patients, 6% had a medical history of cirrhosis. Analyses exploring the genotype-phenotype relationship will be presented.
Conclusions: Registry data of >150 LAL-D patients demonstrate early symptom onset, variable clinical manifestations, and a significant diagnostic delay in children/adults.

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