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Sudden-death of infant with lysosomal acid lipase deficiency successfully completing sebelipase alfa clinical trial

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Infantile Lysosomal Acid Lipase Deficiency (LAL-D) is a rare, progressive genetic disorder with a median survival <5 months. A global phase 2/3 clinical trial was initiated in infants <6months to assess sebelipase alfa (LAL-CL03), a recombinant human LAL enzyme. The sole USA subject enrolled was identified at 5.5 months of life with calcified adrenal glands and presented with severe cachexia, vomiting, abdominal distension, hepatosplenomegaly, ascites, liver failure with steatosis and anemia and thrombocytopenia. He met none of the Denver Developmental milestones. LAL-D was diagnosed by enzyme assay, and genotype ultimately confirmed. He was treated with weekly enzyme replacement therapy (ERT) infusions; two at 0.35 mg/kg, escalated to 1.0 mg/kg, at which point he began showing significant clinical and biochemical improvements. His dose was increased to 3.0 mg/kg with no untoward infusion reactions and sustained biochemical and clinical improvement. He successfully completed the trial at his birthday, and by then had achieved near age-appropriate development. Following his discharge from the study, the participant continued to receive weekly outpatient infusions without complications. At 15 months, 7 days after his last ERT, the subject was found in the early morning dead in bed. A complete autopsy revealed him at the 3rd percentile for weight, length, and head circumference with no congenital anomalies. There was a mural thrombus in the right atrium, mild left ventricular hypertrophy, severe pulmonary congestion, massive mesenteric lymphadenopathy, severe hepatomegaly with bridging fibrosis and early cirrhosis, calcified adrenals, splenomegaly, and normal brain. Microscopic analyses showed pulmonary edema with intra-alveolar macrophages, multinucleate giant cells with cholesterol clefts; normal cardiovascular system; infiltration of all gut regions and layers by xanthomatous cells with lipid vacuoles, liver with prominent fibrosis of portal triads and bridging. The autopsy diagnosis of exclusion was that the large mural thrombus suggested a conduction abnormality and sudden cardiac death.

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