

## A Rare Disease With A Common Liver Phenotype: Cholesteryl Ester Storage Disease (Lysosomal Acid Lipase (LAL) Deficiency)

We are working on a new treatment for Cholesteryl Ester Storage Disease (CESD), a disease that is often misdiagnosed or not diagnosed. CESD is the late onset phenotype for Lysosomal Acid Lipase (LAL) Deficiency, a Lysosomal Storage Disorder, which also has an early onset phenotype known as Wolman Disease that primarily affects infants. CESD can present in childhood but often goes unrecognized until adulthood when the underlying pathology is advanced. Many of the signs and symptoms are common to patients with other liver conditions.

CESD is an autosomal recessive genetic condition and is characterized by hepatomegaly, persistently abnormal LFTs and type II hyperlipidemia. Splenomegaly and evidence of mild hypersplenism may affect some patients. Untreated, CESD may lead to fibrosis, cirrhosis, liver failure and death.

*'We therefore suggest that CESD should more often be considered as a differential diagnosis in liver diseases of unknown (nonalcoholic steatohepatitis or NASH) or known (alcoholic steatohepatitis) origin and in dyslipidemic patients with combined hyperlipidemia and low HDL-cholesterol (Familial Combined Hyperlipidemia). Awareness of the disease combined with efficient diagnostic tools should facilitate the correct diagnosis and therapy of CESD.'*

—Muntoni

### **Disease Risk In Families**

- 25 per million incidence<sup>1</sup>
- Autosomal recessive disorder, LAL deficiency is carried on chromosome 10
- Parents with an affected son or daughter have a 1 in 4 chance of having another affected child

### **Diagnosing CESD**

Patients with Cholesteryl Ester Storage Disease typically have elevated cholesterol and triglyceride levels (type II hyperlipidemia) and may present at an early age with the following liver abnormalities:

- Unexplained hepatomegaly
- Elevated transaminases
- Unexplained fatty liver
- Progressive and/or unexplained chronic liver disease

Type II hyperlipidemia in association with unexplained fatty liver or elevated transaminases in more than one sibling in a family would warrant consideration of a diagnosis of CESD.

Patients with CESD are typically investigated for infectious, metabolic and autoimmune liver disease. Imaging may suggest hepatic steatosis and liver biopsies when performed show accumulation of fat in hepatocytes and Kupffer cells. Periportal fibrosis and cirrhosis is not uncommon. Descriptive terms including sea blue Histiocytosis may be applied to the liver abnormalities.

### **Useful Diagnostic Clues**

- Very low HDL (<10<sup>th</sup> percentile or <35 mg/dL for men and women)
- Excessive hepatomegaly and/or transaminase increase for a given BMI
- Unusual coexisting lymphadenopathy
- Onset of liver abnormalities in childhood
- Clinical suspicion of visceral Niemann Pick not confirmed by enzyme analysis
- Enlarged lymph nodes
- An enlarged spleen that is disproportionate in size to the degree of liver involvement/disease

<sup>1</sup> Muntoni, et al; "Prevalence of Cholesteryl Ester Storage Disease", Arteriosclerosis, Thrombosis, and Vascular Biology, July 19,2010

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## ***Other Manifestations***

- Short stature
- Premature cardiac disease
- Premature stroke
- Malabsorption

## ***Challenges in Diagnosis***

Cholesteryl ester storage disease is rare and can be difficult to diagnose. Recent studies using genetic analysis<sup>2</sup> suggest that heterozygote carriers of a common disease causing mutation for CESD are more common than previously thought with a carrier frequency for this mutation of about 1 in 200 or 5000 per million. Based on these carrier frequencies and the mutation spectrum of published CESD cases this translates to an estimate of approximately 25 cases of CESD per million births.

Delayed diagnosis may be the result of disease under-recognition and/or symptoms being mistaken for those of other disorders, such as:

- Non Alcoholic Fatty Liver Disease (NAFLD)
- Non Alcoholic Steatohepatitis (NASH)
- Alcoholic Liver Disease
- Cryptogenic Cirrhosis

Clinical diagnosis is based upon presentation of signs, symptoms and laboratory abnormalities (lipids, liver transaminases) and may be confirmed by enzyme assay (blood test) detecting low or absent levels of lysosomal acid lipase or in relatives of affected patients by mutation linkage analysis (blood test).

## ***Enzyme and Genetic Testing for LAL Deficiency***

The following web sites provide information regarding labs that provide diagnostic support for LAL Deficiency:

<http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab?db=GeneTests> (search using, “cholesterol ester storage disorder” in disease field)

<http://www.orpha.net/consor/www/cgi-bin/ClinicalLabs.php?lng=EN> (search using, “cholesterol ester storage disorder”)

## **Treating CESD**

No approved treatment is available for LAL deficiency /CESD disease. Clinical trial sites are currently recruiting patients.

**For more information on LAL deficiency or Synageva’s clinical trials, call Synageva Medical Information at (781) 357-9900, email [physicianinfo@synageva.com](mailto:physicianinfo@synageva.com) or visit [www.synageva.com](http://www.synageva.com).**

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<sup>2</sup> ibid