Prevalence of Cholesteryl Ester Storage Disease

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Cholesteryl ester storage disease (CESD) is an autosomal recessive chronic liver disease caused by lysosomal acid lipase (LAL) deficiency. The gene is located on chromosome 10q23.2-q23.3, and the enzyme is essential for triglycerides and cholesteryl ester hydrolysis in lysosomes. CESD is characterized by hypercholesterolemia, hypertriglyceridemia, HDL deficiency, and abnormal lipid deposition in many organs. In the liver this results in hepatomegaly caused by hepatic steatosis and fibrosis that can lead to micronodular cirrhosis.1 Disease onset takes place during childhood or adolescence. Males and females are affected in about equal numbers. Patients rarely reach the age of 30. Biochemically, the disorder is recognized by largely reduced lysosomal acid lipase activity.2-3 Complete absence of LAL activity causes Wolman Disease, which is normally fatal within the first 6 months of life.1,4 Several groups have identified mutations in the LAL gene underlying CESD and Wolman disease.5-9 Mutations causing Wolman disease produce an enzyme with no residual activity or no enzyme at all, whereas CESD-causing mutations encode for LAL which retains some lipase activity.2 Complete absence of LAL activity causes Wolman Disease, which is normally fatal within the first 6 months of life.1,4 Several groups have identified mutations in the LAL gene underlying CESD and Wolman disease.5-9

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carrier frequency of about 1 in 200 or 5000 per million in the general population.

Assuming Hardy-Weinberg equilibrium, the homozygote carrier frequency can be estimated to 6 per million. Applying these results to the German general population, about 91 E8SJM homozygotes aged 18 years or younger would be expected. Under the assumption that this mutation represents about 50% of all CESD-causing mutations, the prevalence of CESD (homozygotes or compound heterozygotes) among German newborns is estimated at 25 per million, or a total of 366 cases under the age of 18. This estimate is in apparent conflict with the small number of CESD cases reported in the literature.

Even after considering a higher E8SJM prevalence in CESD, for example Lohse et al found E8SJM carriers in 70% of Czech CESD patients, 13 or more cases per million newborns would be expected.

Because most of the reported E8SJM carriers are of European or North American origin, it can be expected that this mutation strongly impacts CESD formation in these countries. Furthermore, a large number of family studies reported so far have never identified a CESD-free E8SJM homozygote. We interpret these findings as evidence for a high penetrance of the mutation and conclude that the here identified disparity between expected and reported cases indicates that CESD should be largely under-diagnosed in Europe and North America.

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.

Disclosures

None.

References


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