



Smith-Lemli-Opitz syndrome

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Surveillance for Smith-Lemli-Opitz syndrome (SLO) began on January 1, 2000. In the first nine months, 27 reports were received of which 10 have been confirmed. The CPSP has been successful in identifying both newly diagnosed patients as well as patients with previous clinical diagnosis of SLO who received biochemical testing. As a result of this successful surveillance initiative, the McMaster University Molecular Diagnosis Laboratory has expanded its diagnostic service to include molecular testing. Molecular testing allows confirmation of diagnosis in deceased patients and reliable carrier testing in families with known mutations. To date, the diagnosis has been confirmed in three deceased patients on whom no biochemical testing was performed, and 14 new patients have been genotyped.

SLO is caused by a generalized cholesterol deficiency resultant from an inherited biochemical defect that causes decreased production of cholesterol from its immediate precursor, 7-dehydrocholesterol (7DHC). SLO ranges from mildly abnormal facial features, with mental retardation and significant behavioural abnormalities, to severe birth defects causing stillbirths and miscarriages. SLO is diagnosed by demonstrating elevated 7DHC in plasma or in amniotic fluid. Sixty-seven different SLO mutations have been identified since the gene for SLO, called DHCR7, was found in 1998.

While it is estimated that SLO occurs in approximately 1 in 60,000 to 1 in 20,000 births in North America, there is evidence that it may be more common. During a 12-month period in 1999-2000, five unrelated cases of severe SLO were diagnosed in Ontario, which may indicate that the incidence of SLO in Ontario is approximately 1 in 26,500. Recent reports and our unpublished observations show that the carrier rate for SLO is 1 in 30 in populations of Western and Northern European ancestry.

Regardless of the extent of their underlying physical defects, surviving patients with SLO universally exhibit, albeit to a varying degree, developmental delay and intellectual impairment. Patients with SLO have a characteristic behavioural phenotype with sensory hypersensitivity, including tactile defensiveness (oral, hands and feet), and an unusual hyper-responsiveness to certain auditory and visual stimuli. Many patients, even with mild clinical disease, manifest significant aggressiveness and self-injury. A severe sleep disturbance with markedly reduced sleep duration, fragmented sleep, and difficulty falling asleep, as well as autistic behaviours are observed frequently.

RESOURCES



Treatment with cholesterol results in a decrease in the frequency of infections, accelerated somatic growth, an improvement in sleep patterns, and a statistically significant decrease in autistic behaviours. Although cholesterol supplementation does not appear to alter the developmental outcome, treatment with cholesterol decreases irritability, hyperactivity, and self-injury and renders patients with SLO more alert, sociable, and affectionate. No side effects of cholesterol therapy have been reported to date. The usual starting dose of exogenous cholesterol is 40 to 50 mg/kg/day, increasing as needed for somatic growth requirements; occasional patients require cholesterol doses of up to 300 mg/kg/day. There is limited evidence that inhibitors of HMG-CoA reductase may augment residual DHCR7 activity of some mutants leading to increase in the plasma cholesterol levels.

Since 1998, SLO mutations have been determined in more than 200 SLO patients. Six common mutations account for more than 2/3 SLO alleles. Some mutations occur more frequently in Western Europeans, others in Slavic, Italian, and French Canadian populations. Correlation of the physical findings and mutations shows that the most severely affected patients have mutations that result in no, or in severely reduced, enzyme activity. Patients with classical SLO have mutation associated with residual enzyme activity, while patients with mildest phenotypes have private or uncommon mutations. A hypothetical heterozygote advantage for Northern Europeans has been suggested based on the increased synthesis of vitamin D from increased levels of 7DHC observed in carriers.

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Questions

SLO is an autosomal recessive condition. All of the following apply to a couple who has had a child with SLO, except:

1. the risk of having an affected child is 25% with each pregnancy.
2. the risk of having a child who is a carrier is 50% with each pregnancy.
3. the risk of having a child with a major birth defect is 3%.
4. in some cases prenatal diagnosis is available as early as 10-12 weeks of gestation.
5. prenatal treatment is available and successfully avoids the birth defects associated with SLO.

A child with SLO may present with any of the following, except:

1. minimal 2-3 toe syndactyly and autistic behaviours in childhood.
2. renal agenesis, oligohydramnios, atrioventricular canal, polydactyly prenatally.
3. holoprosencephaly and intrauterine growth retardation (IUGR) at birth.
4. no obvious birth defects.
5. excessive weight gain.

All of the following are diagnostic of SLO, except:

1. very low plasma cholesterol.
2. low or normal plasma cholesterol and elevated plasma 7DHC.
3. elevated 7CDHC/total sterol ratio in amniotic fluid.
4. reduced activity of 7DHC reductase in cultured skin fibroblasts.
5. presence of two mutations in the *DHCR7* gene.

Answers: 5 - 5 - 1

RESOURCES