Prenatal Diagnosis and Genetic Counseling for Niemann-Pick C Disease

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Niemann-Pick C disease is a genetic disease with an autosomal recessive mode of inheritance. If we can identify the mutations in the index case, then the genotype of a relative person in terms of carrying the defective allels may be reliably determined. However, it is not currently possible to ascertain the status of a person from the general population, due to the complexity of NPC1 gene sequencing and its polymorphic nature.

Prenatal diagnosis is also possible under the conditions described below.

M.T. Vanier and colleagues made an observation: in three families, the possibility was suggested that symptomatic heterozygotes was the what the therapists confronted, but finally it was ruled out in two of them (the third family could not be investigated totally). Two disease-causing NPC1 mutations had been identified in

each index case. In both families, the father of the proband developed progressive symptoms compatible with an adult onset neurologic form of Niemann-Pick disease type C. Subsequently, complete gene sequencing revealed one allele carrying the mutation transmitted to the affected child, and another (not transmitted) disease-causing mutation on the other allele. These individuals were thus NP-C1 homozygotes with an adult onset form.

These exceptional histories show quite well only some of the problems eventually posed by the clinical heterogeneity of NP-C and its complexities, and the possible underestimation of adult-onset form of the disease.

Prenatal diagnosis of NP-C should be offered to all of the couples who are at risk. The highest chances of a positive yield and sufficient sample for analysis are achieved using chorionic villus sampling (CVS) at 10-12 weeks, but one should be aware that they are also possible on amniotic cells.

Molecular genetic analysis is today and by far the preferred strategy, for several reasons. Unlike the cellular biology testing using filipin staining, it does not require cultured cells and a lengthy elaborate work up.

The results can be obtained much earlier in pregnancy, and the tests can basically be set up in any good molecular biology laboratory. However, it requires that mutations have been identified on both alleles in the index case, or at least that suitable intragenic markers have been identified in the nuclear family.

Today, few laboratories offer a prenatal test using the cellular biology strategy, which should be considered as a last resort due to its many drawbacks. Results will not be reached until 5-7 weeks after the sampling; the tests are technically difficult; besides, they are fully reliable only when the proband has shown severe abnormalities. The above limitations exclude at least 15-20% of the families.

Keywords: Prenatal diagnosis; Genetic counseling; NPC

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