EDITORIAL

Leber's hereditary optic neuropathy

Leber's hereditary optic neuropathy (LHON) has been a puzzle and a fascination to ophthalmologists for many years. Its hereditary nature has been in no doubt since the original description by Leber,¹ although the pattern of inheritance, which does not follow mendelian principles, has until recently been impossible to explain. Our understanding of the disease increased when it became apparent that LHON was transmitted through the mother mainly to her sons, the sons themselves never passing the disease to their offspring. Another advance occurred when it was shown that most daughters and sons of carrier females had a characteristic fundus abnormality, peripapillary microangiopathy.² This satisfied the criteria for a maternally inherited disease.³

One possible explanation for maternal inheritance is the occurrence of a mutant gene on the mitochondrial chromosome. Mitochondria contain several copies of a small circular DNA molecule, which in humans consists of 16,569 base pairs. Mitochondrial DNA differs from DNA in the cell nucleus in being transmitted exclusively by mothers. The most important function of mitochondrial DNA is to help code for a number of enzyme complexes involved in the process of oxidative phosphorylation.

A specific alteration at position 11778 in mitochondrial DNA, resulting in a single aminoacid substitution, has been described in 9 out of 11 families with LHON.⁴ This mutation converts arginine to histidine in the gene for part of Complex I of the respiratory chain. In another study, this mutation was found in only 4 out of 8 families, and was associated with a poor prognosis for visual recovery; 4 of 5 affected males without the 11778 mutation regained useful vision.⁵ All but one of the subjects had a variable mixture of mutant and normal mitochondrial DNA, the relative proportions appearing to be correlated with the risk of developing or transmitting LHON.

The substitution of histidine for arginine in a gene coding for a subunit of Complex I is relatively conservative and may result in only a partial reduction in the mitochondrial production of energy. This would result in an energy deficit similar to that caused by potassium cyanide, a known inhibitor of Complex I activity, and it is possible that this energy deficit could be exacerbated by cyanide.

The strong male bias in LHON cannot be explained by a single mitochondrial gene defect alone. The suggestion of an interaction between a mitochondrial gene defect and an X-linked gene coding for an optic nerve isozyme⁶ has not, however, been supported by multipoint linkage analysis.⁷ In this issue, Franks and Sanders⁸ have alerted us to the difficulties of diagnosing LHON in females when there is no apparent family history of the disorder. This in itself is an important clinical observation. It may also go some way towards explaining the apparent male preponderance in Leber's optic neuropathy.

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References

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