Amer J Hum Genet 24:348–349, 1972

Annotation:

Leber's Optic Atrophy, a Possible Example of Maternal Inheritance

ROBERT P. ERICKSON[1]

Leber's disease (now in its centenary) is markedly familial yet its mode of inheritance is moot. This disease is an acutely occurring optic atrophy which frequently shows some restoration of vision after the acute phase. There may be signs of inflammation of the disc, and prechiasmatic arachnoiditis is frequently found if surgical exploration is undertaken. A theory of transmission of Leber's optic atrophy by cytoplasmic inheritance was proposed some time ago [1, 2] but has not been widely accepted, largely because of disagreement over the percentage of carriers and affected offspring in various pedigrees [3, 4]. Most of the recent genetic hypotheses [5] have been based on the assumptions that (1) males do not transmit the disease, that (2) half of the sons of "carrier" females are affected, and that (3) the gene is transmitted, though infrequently expressed phenotypically, by very significantly more than 50% of the daughters of these female carriers. The argument for maternal inheritance has been reopened by Wallace [6, 7], who has argued effectively for maternal inheritance, possibly of a slow virus, of Leber's optic atrophy. His conclusions resulted from the study of a kindred which showed an unusually high incidence of affected males and of males with associated neurological problems (the later being considered a variant of the disease) [8].

Although Wallace accepts the possibility that the transmission to males can be much more than 50%, I herein use other published data to argue that all offspring of a carrier female inherit the "agent," be it transplacentally or via the ooplasm. Such a conclusion simplifies the above premises to (1) maternal transmission of an "agent" to all offspring with (2) partial sex limitation of susceptibility to the "agent." Maternal inheritance in man has been postulated to be involved in the inheritance of anencephaly and spina bifida [9], while maternal transmission of scrapie in sheep [10] is well documented. Sex-limited expression of a disease is a familiar situation which may well apply here.

Van Senus [11] found evidence of a strong familial correlation of age of onset of the amaurosis. It is probable that the high incidence of affected males (100%) in Wallace's pedigree is not unusual but is a consequence of the complete detection possible with the low age of onset in this kindred (by the age of 10 as compared with an average age of onset of 24.4 years in van Senus's large series). It is also possible that a more virulent form of the "agent" is being maternally transmitted

[1] Department of Pediatrics, University of California Medical Center, San Francisco, California 94122.

in this sibship. Improved diagnostic techniques and greater longevity should provide more accurate data on transmission in other pedigrees.

Tove Seedorff [12–14] has extended the pedigrees of Lundsgard [3] and found that every daughter of a carrier could be demonstrated to be a carrier if she has had at least two sons surviving to age 60. It is hard to provide 120 years of observation on each male, but only about 22% of males (8–10 of 45 at risk) from pedigree A born between 1839 and 1901 and who lived to at least age 60 were not affected [12], while 33% of males who lived to age 70 from pedigree C (12 at risk) were not affected [3, 13]. I cannot break van Senus's [11] cases down in this fashion, but it is very possible that a much higher incidence than the overall 52% of affected males found across 10 generations (excluding offspring born after 1910) would be found for males who have lived to age 60 and who, with their families, have been examined by ophthalmologists.

I conclude that probably all offspring of carrier females receive the agent while there is sex limitation of phenotypic expression. Perhaps transplacental infection is more likely than cytoplasmic inheritance, since spermatozoa have recently been shown to be able to transmit nonnuclear genetic material to the egg [15], albeit in a very artificial situation.

REFERENCES

1. Imai Y, Moriwaki D: A probable case of cytoplasmic inheritance in man: a critique of Leber's disease. *J Genet* 33:163–167, 1936
2. Ronne H: The inheritance of Leber's disease (cytoplasmic inheritance). *Acta Ophthal* (Kobenhavn) 22:203–213, 1944
3. Lundsgard R: Leber's disease. A genealogic, genetic, and clinical study of 101 cases of retrobulbar optic neuritis in 20 Danish families (thesis). *Acta Ophthal* (Kobenhavn) 21, suppl.:3–306, 1944
4. Ronne H: Cytoplasmic inheritance in Leber's disease. *Acta Ophthal* (Kobenhavn) 23:89–93, 1943
5. Waardenburg PJ: Some remarks on the clinical and genetic puzzle of Leber's optic neuritis. *J Genet Hum* 17:479–496, 1969
6. Wallace DC: A new manifestation of Leber's disease and a new explanation for the agency responsible for its unusual pattern of inheritance. *Brain* 93:121–132, 1970
7. Wallace DC: Leber's optic atrophy: a possible example of vertical transmission of a slow virus in man. *Aust Ann Med* 19:1–4, 1970
8. Wilson J: Leber's hereditary optic atrophy—some clinical and aetiological considerations. *Brain* 86:347–362, 1963
9. Nance W: Anencephaly and spina bifida: a possible example of cytoplasmic inheritance in man. *Nature* (London) 224:373–375, 1969
10. Dickinson AG, Young GB, Stamp JT, et al: An analysis of natural scrapie in Suffolk sheep. *Heredity* 20:485–504, 1965
11. van Senus AHC: Leber's disease in the Netherlands. *Docum Ophthal* 17:1–162, 1963
12. Seedorff T: Leber's disease. *Acta Ophthal* (Kobenhavn) 46:4–25, 1968
13. Seedorff T: Leber's disease II. *Acta Ophthal* (Kobenhavn) 46:985–992, 1968
14. Seedorff T: Leber's disease III. *Acta Ophthal* (Kobenhavn) 47:23–29, 1969
15. Brackett BG, Baranska W, Sawicki W, et al: Uptake of heterologous genome by mammalian spermatozoa and its transfer to ova through fertilization. *Proc Nat Acad Sci USA* 68:353–357, 1971