

Correspondence

To the Editor:

THE RISK OF INTRACRANIAL ANEURYSMS IN FAMILIES WITH SUBARACHNOID HEMORRHAGE

We read with special interest the paper by Alberts et al.¹ on *The risk of intracranial aneurysms in families with subarachnoid hemorrhage* that recently appeared in the *Journal* since one of our families was used in their analysis.² Alberts et al. address the inherent difficulties of a retrospective, literature-based study such as theirs. We offer the following observations as a case in point. To date we have studied 13 families in whom two or more individuals have had a documented cerebral aneurysm.³ Of these 6 met the, novel, inclusion criteria that Alberts et al. use in their analysis. Of the 31 individuals in whom the presence or absence of an aneurysm was ascertained 9 had a cerebral aneurysm (29%). Once the probands are excluded to avoid ascertainment bias the figure is 3 of 25 (12%). Thus our prospective analysis of these 6 families fails to identify a dominant pattern of inheritance. Further, Alberts et al. suggest that a "strong" family history is suggested when a parent and at least one child has a documented aneurysm. This occurred in 4 of our families where 5 of 19 children (26%) had a cerebral aneurysm. Again when the index cases are removed from analysis the figure is 1 of 15 or 6.7%. Thus we could not support the contention that vertical transmission reflects a strong family history of cerebral aneurysms. Finally, 31 siblings at risk of harbouring an aneurysm were electively angiogrammed. One aneurysm was discovered (3%). The interested reader is referred to a recent paper that we have published on the advisability of elective angiographic screening an surgery of patients at risk of harbouring a familial cerebral aneurysm using a decision analysis model.⁴ Using such an approach we recommended that individuals with a family history of cerebral aneurysm be considered for elective angiography if they are in their third decade: only 2.5% of familial aneurysms destined to rupture do so in the first two decades while over one-fifth of familial aneurysms that will eventually rupture will have done so by age 30 (three-quarters will have ruptured by age 50).⁵ Thus the angiographic screening of patients younger than 20 years will be of little benefit but the benefits of screening will become progressively greater in individuals older than 20 years.

Although we share Alberts et al. enthusiasm for a possible genetic determinant in cerebral aneurysms, especially in families, we feel that they overstate the case, as it is unlikely, based on our data, that a single major gene with dominant inheritance accounts for most – if any – familial aneurysms. Only further prospective epidemiological studies combined with molecular genetic techniques will elucidate this fascinating problem. As we have been using such an approach now for some years we would appreciate it if your readership could make us aware of patients with possible familial cerebral aneurysms to further our studies.

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1. Alberts MJ, Quinones A, Graffagnino C, Friedman A, Roses AD. Risk of intracranial aneurysms in families with subarachnoid hemorrhage. *Can J Neurol Sci* 1995; 22: 121-125.
2. Leblanc R, Lozano A, van der Rest M, Guttmann RD. Absence of collagen deficiency in familial cerebral aneurysms. *J Neurosurg* 1989; 70: 837-840.
3. Leblanc R, Melanson D, Tampieri D, Guttmann RD. Familial cerebral aneurysms: A study of 13 families. *Neurosurgery* (in press).

4. Leblanc R, Worsley K, Melanson D, Tampieri D. Angiographic screening and elective surgery of familial cerebral aneurysms. *Neurosurgery* 1994; 35: 9-19.
5. Lozano A, Leblanc R. Familial intracranial aneurysms. *J Neurosurg* 1987; 66: 522-528.

Reply from the author:

We wish to thank Dr. Leblanc for raising some interesting points related to our recent article dealing with genetic aspects of intracranial aneurysms and subarachnoid hemorrhage.¹ This is an area where Dr. Leblanc and his colleagues have contributed much to medical knowledge and the medical literature.

It is encouraging that in the series cited by Dr. Leblanc, 29% of studied patients were found to have an aneurysm. It is also encouraging that aneurysms were found in 5 out of 19 (26%) children screened. These findings do not approach the 50% incidence expected with a typical autosomal dominant trait. However, in the case of intracranial aneurysms, the trait may show incomplete or aged-dependent penetrance. Therefore, studying patients at one point in time is not sufficient to exclude the development of the phenotype later in life. In addition, other modes of inheritance besides autosomal dominant may be found in some cases.²

We agree with Dr. Leblanc that aneurysmal rupture before the age of 20 is rare. We further agree that rupture before the age of 30 is not rare. In fact, our recent article suggests screening high-risk individuals with MR angiography before the age of 30.¹ This is consistent with the observation of Dr. Leblanc that screening individuals older than 20 will show increasing yields. Other published studies also have advocated a similar approach.³

It is likely that intracranial aneurysms will be found to have both genetic and non-genetic etiologies. However, the plethora of familial cases in the literature strongly support a significant role for genetic etiologies in many instances.^{1,4} It is also possible that more than one gene is responsible for the familial cases of intracranial aneurysms. The presence of genetic heterogeneity is quite common with many other inherited neurologic diseases (Alzheimer's Disease, Charcot-Marie Tooth Disease, Tuberosus Sclerosis, to name but a few). In addition, studying the etiology of genetic cases may provide important clues about the pathogenesis of sporadic cases. We encourage interested physicians to contact us should they wish to participate and contribute to studies to isolate the pathogenic genes that are responsible for this very important disease.

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1. Alberts M, Quinones A, Graffagnino C, Friedman A, Roses A. Risk of intracranial aneurysms in families with subarachnoid hemorrhage. *Can J Neurol Sci* 1995; 22: 121-125.
2. Schievink W, Schaid D, Rogers H, Piepgras D, Michels V. On the inheritance of intracranial aneurysms. *Stroke* 1994; 25: 2028-2037.
3. Juvola J, Porras M, Heiskanen O. Natural history of unruptured intracranial aneurysms: a long-term follow-up study. *J Neurosurg* 1993; 79: 174-182.
4. ter Berg H, Dippel D, Limburg M, Schievink W, van Gijn J. Familial intracranial aneurysms. *Stroke* 1992; 23: 1024-1030.