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ORIGINAL ARTICLE

Intracranial aneurysms and their clinical and genetic behaviour☆

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KEYWORDS
Intracranial aneurysms;
Endothelial nitric oxide synthase;
Polymorphisms;
Variable number tandem repeat;
Clinical features

Abstract
Background: Intracranial aneurysms are abnormal dilations of the cerebral arteries of unknown origin. However, some genes have been linked to their formation, as in the case of *NOS3* gene which encodes the endothelial nitric oxide synthase responsible for producing nitric oxide. Several polymorphisms in this gene, in association with a variable number tandem repeat located in intron 4 from *eNOS4* gene, can influence the formation of aneurysms. Therefore, the purpose of this study is to determine the genotype frequencies of *eNOS3* and *eNOS4* genes, and their relationship with intracranial aneurysms.
Material and methods: A prospective case–control study was performed on 79 cases with ruptured intracranial aneurysm and 93 healthy controls. DNA was obtained from all subjects for the study of the *eNOS3* and *eNOS4* genes by molecular techniques.
Results: The GG genotype of *eNOS3* gene showed the largest number of patients ($n = 29$) with a large aneurysm. While the intracranial aneurysms of medium size were found in a higher percentage (50%) in patients with genotype GT. In terms of patient outcomes, it was observed that those with genotype GG had the highest percentage (43.13%) recovery, compared to genotype GT (27.27%).

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Conclusions: The present study shows that there is a tendency of an association between genotypes of *eNOS3* gene with the mean size of the aneurysm, as well as clinical sequelae of the disease in patients with intracranial aneurysms.

PALABRAS CLAVE
Aneurismas intracraneales;
Sintetasa de óxido nítrico endotelial;
Polimorfismos;
Número variable de repeticiones en tándem;
Características clínicas

Aneurismas intracraneales y su comportamiento clínico-genético

Resumen
Antecedentes: Los aneurismas intracraneales son dilataciones anormales de las arterias cerebrales. La etiología es desconocida, sin embargo algunos genes se han relacionado con su formación; como el caso del gen *NOS3* que codifica a la sintetasa de óxido nítrico endotelial encargada de producir óxido nítrico. Varios polimorfismos en este gen en asociación con un número variable de repeticiones en tándem localizado en el intrón 4 del gen *eNOS4* pueden incidir en la formación de aneurismas. Por eso, la finalidad de nuestro estudio es conocer las frecuencias genotípicas de los genes *eNOS3* y *eNOS4* y su relación con aneurismas intracraneales.
Material y métodos: Se realizó un estudio prospectivo de casos y controles. Se estudiaron 79 casos con aneurisma intracraneal roto y 93 controles sanos; de todos se obtuvo DNA para el estudio de los genes *eNOS3* y *eNOS4*.
Resultados: El genotipo GG del gen *eNOS3* mostró el mayor número de pacientes (n = 29) con aneurisma intracraneal grande. Mientras que los de tamaño mediano se encontraron en mayor porcentaje (50%) en pacientes con genotipo GT. En cuanto a la evolución de los pacientes, se observó que aquellos con genotipo GG presentaron el mayor porcentaje (43.13%) de recuperación, en comparación con los de genotipo GT (27.27%).
Conclusiones: Nuestro estudio demuestra que en los casos con aneurismas intracraneales existe una tendencia de asociación entre los genotipos del gen *eNOS3* con el promedio del tamaño del aneurisma, así como con las secuelas clínicas de la enfermedad.

Background

Intracranial aneurysms form part of the group of cerebrovascular disorders, and are defined as abnormal dilations of the cerebral arteries, generally located in the bifurcation of the arteries which form the Circle of Willis. The incidence in the general population is 2–8%.[1–3]

Depending on how they present, intracranial aneurysms can be classified as unruptured, which in most cases are incidental findings on cerebral angiography for a different diagnostic purpose, or at autopsy[1–3]; and ruptured, which usually cause a subarachnoid haemorrhage with manifestations which include: intense headache, nausea, vomiting, focal neurological deficit, and loss of consciousness, amongst others.[4] The mortality rate for ruptured intracranial aneurysms is high (50%), while 25% will suffer permanent disability, paralysis, loss of speech, vision and motor coordination.[1]

To date, the aetiology of intracranial aneurysms is unknown. However, various environmental factors are associated, such as smoking, systemic arterial hypertension and alcoholism.[3,4] Similarly, genetic factors are associated with a predisposition; although there is no defined Mendelian inheritance pattern for this disease, epidemiological studies demonstrate higher autosomal transmission; the first degree relatives of a person with an intracranial aneurysm have a 3–6 times greater risk than that of the general population.[3,4] Genetic studies also show potential sites of susceptible genes, or loci, for the formation of intracranial aneurysms; however, in many populations these results have been contradictory, as in the case of the gene which codes the nitric oxide synthase enzyme (NOS), which is responsible for producing nitric oxide.[3,5–9]

Endothelial nitric oxide synthase (eNOS) is one of the 3 isoforms of NOS, found in the body constitutively[10]; the significance of the production of nitric oxide synthase by eNOS is that it is the most powerful endogenous vasodilator known.[10,11] eNOS is coded by the *NOS3* gene and is expressed principally in the endothelial cells. Various polymorphisms in the gene have been described in association with a variable number tandem repeat (VNTR), located in intron 4 in the *eNOS4* gene, which might affect the expression of the enzyme, and alter the circulating levels of nitric oxide. As an example, it is known that eNOS participates in both haemodynamic and structural functions, and its absence or reduction might cause the vascular wall to weaken or rupture, conditioning susceptibility to the formation of coronary and cerebral aneurysms.[7,10,12–16]