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Round table: Giant intracranial aneurysms

Epidemiology, genetic, natural history and clinical presentation of giant cerebral aneurysms

Épidémiologie, génétique, histoire naturelle, physiopathologie et présentation clinique des anévrismes géants

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ABSTRACT

Giant cerebral aneurysms represent 5% of intracranial aneurysms, and become symptomatic between 40 and 70 years with a female predominance. In the paediatric population, the giant aneurysm rate is higher than in the adult population. Classified as saccular, fusiform and serpentine, the natural history of giant cerebral aneurysms is characterized by thrombosis, growth and rupture. The pathogenesis of these giant aneurysms is influenced by a number of risk factors, including genetic variables. Genome-wide association studies have identified some chromosomes highlighting candidate genes. Although these giant aneurysms can occur at the same locations as their smaller counterparts, a predilection for the cavernous location has been observed. Giant aneurysms present with symptoms caused by a mass effect depending on their location or by rupture; ischemic manifestations rarely reveal the aneurysm. If the initial clinical descriptions have been back up by imagery, the clinical context with a pertinent analysis of the risk factors remain the cornerstone for the management decisions of these lesions. Five year cumulative rupture rates for patients with giant aneurysm were 40% for those located on the anterior part of circle of Willis and 50% for those on the posterior part. The poor outcome of untreated patients justifies the therapeutic risks.

Mots clés :
Anévrismes géants intracrâniens
Hémorragie sous-arachnoïdienne
Syndrome pseudotumoral
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RÉSUMÉ

Les anévrismes géants représentent 5 % de l'ensemble des anévrismes intracrâniens et deviennent symptomatiques entre 40 et 70 ans, avec une prépondérance féminine. Dans la population pédiatrique, la fréquence des anévrismes géants est plus élevée que chez l'adulte. L'évolution de ces anévrismes est influencée par un certain nombre de facteurs de risque, en particulier génétiques. L'histoire naturelle de ces anévrismes comprend 3 types de phénomènes : thrombose, accroissement et rupture. Ils sont classés en sacculaire, fusiforme et serpentin. Bien qu'ils se localisent aux mêmes endroits que les anévrismes classiques, les localisations intra-caverneuse et carotidienne proximale prédominent nettement. Les anévrismes géants s'expriment soit en raison de leur effet de masse, soit d'une rupture, les manifestations ischémiques étant beaucoup plus rares. Si les premières descriptions cliniques ont été dépassées par l'imagerie, le contexte clinique avec l'analyse des facteurs de risque restent essentiels pour la prise de décision thérapeutique. Le risque de rupture à 5 ans pour les patients sans antécédents d'hémorragie sous-arachnoïdienne est de 40 % pour les anévrismes de la circulation antérieure, de 50 % pour ceux de la circulation postérieure et de 6 % pour les anévrismes caverneux. Le mauvais pronostic des patients non traités justifie une prise de risque thérapeutique.

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1. Introduction

Giant cerebral aneurysms, defined by a diameter above 25 mm, are often discovered through their mass effect or haemorrhage. If the initial clinical descriptions have been back up by imagery, the clinical context with a pertinent analysis of the risk factors remain the cornerstone for the management decisions for these lesions. The knowledge of the natural history as well as the evolutionary modalities of these aneurysms is critical in making treatment decisions.

In this chapter, epidemiologic, genetic, physiopathology, clinical and natural history of these giant aneurysms will be described, taking in account our multicentre studies and the data reported in the literature.

2. Epidemiology

The prevalence of intracranial aneurysms is estimated to be approximately 2% [1]. The aneurysm is unique (70–75%) or multiple (25–30%) [2]. The risk factors concerning the formation, growth or the rupture of aneurysms include age, sex, smoking, high blood pressure, hypercholesterolemia and atherosclerosis in general [3]. Familial aneurysms may have a larger size at rupture, and are often multiple, which suggests a genetic implication [4].

Giant cerebral aneurysms represent approximately 5% of intracranial aneurysms and become symptomatic in patients between 40 and 70 years of age, but may occur at any age [5,6]. In autopsies series, the rate of giant aneurysms varies between 4.7% [7] and 6.7% [8] of all intracranial aneurysms. In clinical studies, this rate varies from 3% [9] to 13.5% [10].

In most series, there is a female predominance with a ratio ranging from 1:1 to 3:1 [11]; this ratio is inverse for posterior circulation aneurysms and for giant fusiform aneurysms.

In the paediatric population, the occurrence of aneurysms is lower than in adults (0.17 to 4.6%) [12]. However, giant aneurysms occur more frequently in children than in adults [13] (Table 1), 6.9% from 43 intracranial aneurysms in children [14], 14% from 22 [15]. Amacher et al. [1] reported a large proportion of giant aneurysms in a vertebro-basilar location: 15/32 (45.5%). Nevertheless, the high rate of giant aneurysms (23 to 54%) in some paediatric series [13,16–18] can be related to a recruitment bias.

3. Genetics

The pathogenesis of intracranial aneurysms are influenced by a number of risk factors, including genetic variables as proven by higher frequency of aneurysms in some hereditary diseases, including polycystic kidney disease and familial aggregation [20]. Familial aneurysms account for 7 to 20% of patients with cerebral aneurysms [21,22], 5.1% in our population of giant aneurysms [23]. In fact, some diseases are genetically related to cerebral aneurysms, with a majority involving connective tissue and the extracellular matrix [4]. Moreover, the risk of intracranial aneurysm is increased among individuals with first-degree relatives with history of intracranial aneurysm. Genome-wide association studies have identified associations on some chromosomes highlighting candidate genes [24–26]. In addition, genome-wide-linkage studies have revealed a strong linkage with chromosome region 7q11.2 (ELN) (53), 19q13.3 (102 characterised genes), 2p13 (62) or 1p34.3-36-13 [26]. In the particular case of large size aneurysms, the study of Khurana et al. [27] showed that all patients with large ruptured aneurysm were heterozygous for the endothelial nitric oxide synthase (eNOS), suggesting that such genotype may be a factor influencing size at which rupture occurs. Nevertheless in their study with family aneurysms, Huttunen et al. showed the absence of correlation between size and age at the moment of the rupture (risk factor exposition) suggesting that size is mainly the consequence of haemodynamic stress [28].

Table 1
Incidence of giant aneurysms in children.
Incidence des anévrismes géants chez l'enfant.

Authors	Year	N° of cases	N° of giant aneurysms	% Giant aneurysms
Amacher et al. [16]	1981	32	15	45.5
Ostergaard and Voldby [19]	1983	43	2	4.6
Roche et al. [14]	1988	43	3	6.9
Meyer et al. [13]	1989	24	13	54
Proust et al. [15]	2001	22	3	14
Huang et al. [17]	2005	19	7	37
Kakarla et al. [18]	2010	48	16	23
Total/mean		231	59	25.5

4. Physiopathology

Three types of pathological event feature in the natural history of giant aneurysms: spontaneous thrombosis, progressive growth responsible for mass effect and rupture. Giant aneurysms are classified as saccular, fusiform and serpentine.

4.1. Saccular giant aneurysm

The saccular aneurysms with an individualized neck come from the progressive growth of small aneurysms most often on branching sites due to endothelial aggression by the blood flow. Through a repetitive phenomenon of scarring and intravascular clotting, the size of the aneurysm gradually grows [29,30]. Some histopathological studies show in the thrombus, several vascular channels edged with endothelial and muscular cells, suggesting that an increase of the number and size of the channels in this primary thrombus associated with repeated haemorrhage could be the cause of giant aneurysm formation [31].

This gradual growth could also come from repeated haemorrhages inside the wall of the aneurysm [6]. The increased presence of vasa-vasorum at the proximal part of the intracranial arteries would be liable for this angiogenic potential [30].

Frosen et al. [32] demonstrated that the saccular aneurysms are faced with a continuous remodelling which consists of a weakening of the vascular wall very close to proliferation of smooth muscle cells and destruction phase with proteolysis. Giant aneurysms adapt well during a long period of time while subjected to the constraints represented by the wall tension and the other haemodynamic factors without rupture; however, the wall is not strong enough to prevent its distension, and allows the aneurysm to become a giant aneurysm.

4.2. Fusiform giant aneurysm

Fusiform aneurysms originate from the expansion of the entire circumference of the arterial wall. Classically it is accepted that these fusiform aneurysms are the consequence of atherosclerosis or non-atherosclerotic diseases of the conjunctive tissue, such as Ehlers-Danlos syndrome or elastic pseudoxanthoma. However, in a study of 120 patients with fusiform aneurysms, only 6 were atherosclerotic, and 3 harboured a known arteriopathy [33]. However, the incidence of atherosclerosis compared with the infrequency of fusiform aneurysms suggests other possible factors. Fragmentation of internal elastic lamina and neoangiogenesis within the thickened intima are the primary histological features, which suggest that these changes may be one of the earliest processes of aneurysm formation. These changes are subsequently