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Endovascular strategy for unruptured cerebral aneurysms

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ABSTRACT

The treatment of unruptured intracranial aneurysms (UIAs) remains complex and not clearly defined. While for ruptured intracranial aneurysms the management and the treatment option (surgery or endovascular treatment) are well defined by several trials, for asymptomatic UIAs the best management is still currently uncertain. The rationale to treat an UIA is to prevent the rupture and its consequent SAH and all complications derived from hemorrhage or reduce/eliminate neurological palsy. Although this statement is correct, the indication to treat an UIA should be based on a correct balance between the natural history of UIA and treatment risk. Patient's clinical history, aneurysm characteristics, and strategy management influence the natural history of UIAs and treatment outcomes. In the last 10 years and more, two important large multicenter studies were performed in order to analysis of all these factors and to evaluate the best treatment option for UIAs. The aim of this paper is to try to synthesize the possible indications to the endovascular treatment (EVT), when and how to treat an UIA.

1. Introduction

The treatment of unruptured intracranial aneurysms (UIAs) remains complex and not clearly defined. While for ruptured intracranial aneurysms the management and the treatment option (surgery or endovascular treatment) are well defined by several trials [1,2]; for asymptomatic UIAs the best management is still currently uncertain.

The prevalence of UIAs is estimated at 2–4% of the adult population with an incidence of subarachnoid hemorrhage (SAH) due to their rupture at 10/100,000/year [3]. High morbidity and mortality (45–75%) rate due to SAH are very well known and described, despite the current technique of treatment and reanimation assistance [4].

Despite the fact generally intracranial aneurisms are asymptomatics up to their rupture, they can have an unspecific symptom as frequent headache resistant to medical treatment or they can be disclosed by nerve palsy or compression effect to nervous structures.

Thanks to the great development of mini-invasive imaging techniques in the last 20 years with CTA or MRA, the incidence of "incidental finding" of asymptomatic UIAs are frequent and increasing, making hard, complex and controversial the decision about the indication to the treatment.

The rationale to treat an UIA is to prevent the rupture and its consequent SAH and all complications derived from hemorrhage and to reduce or eliminate nerve palsy, if present. Although this statement is correct, the indication to treat a UIA should be based on a correct balance between the natural history of UIA and treatment risk (surgery or endovascular).

The natural history of UIAs and treatment outcomes are influenced by:

- *Patient's clinical history*, such as previous aneurysmal SAH, age, and coexisting medical conditions (collagenopathy and other genetic condition), alcohol-abuse, smoking;
- *Aneurysm characteristics*, such as size, location, and morphology;
- *Strategy management*, such as the experience of the surgical or endovascular team and the treating hospital.

In the last 10 years and more, two important large multicenter studies were performed in order to analysis of all these factors and to evaluate the best treatment option for UIAs [5,6].

Although the criticisms and controversies derived from these studies, they represent the basis for the management of UIAs and they can be used to search the best indication treatment.

The aim of this paper is to try to synthesize the indication to endovascular treatment (EVT), when and how to treat an UIA.

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2. Indications to treatment: when to treat an UIA?

When to treat an UIA? This is the real problem! Many factors can influence the choice and the type of treatment of UIAs according to ISUIA 1 and 2 studies:

(1) *Patient clinical history*, such as age, and coexisting medical conditions, alcohol-abuse, smoking, previous aneurysmal SAH;
(2) *Aneurysm characteristics*, such as size, location, morphology and its symptom;
(3) *The hemodynamic environment*;
(4) *Factors in management*, such as the experience of the surgical or endovascular team and the treating hospital.

All these factors can be analyzed and combined each other to make the choice between to treat and not to treat.

(1) "Patient clinical history" is one of the elements to research. Sex, age and patient-environment influence the choice.

By ISUIA 1 and 2 [5,6], aneurysms were more frequent in female-group (55–60%) than male-group, and by ISAT study more SAH occurred in female-group [2]. The age is an important factor that can influence the natural history of UIAs and its outcome. Patient with an age over than 60 is associated with a statistically significant increased risk of rupture. About the outcome, as illustrated by ISUIA 2, a morbidity and mortality rate of 6.5% for patients <45 years old, 14.4% for patients 45–65 years old, and 32% for patients >64 years old were registered [6]. In any case, even if the aneurysm is discovered in early-age, the choice of treatment could be considered during the follow up time according to the 5-year cumulative rupture risk rate by ISUIA 2 in order to prevent rupture [6]. Smoking, hypertension and alcohol-abuse represent a risk factor to develop aneurysm and to increase the incidence of rupture, even if those factors are not statistically significant in other experience [7].

The presence of inherited diseases (adult polycystic kidney diseases, Ehlers–Danlos Syndrome, NF1, Bourneville disease, FM dysplasia, Marfan diseases) is associated with a higher risk of developing an aneurysm: 7–40% of ADPCKD-patients have a UA [5]. The familial history of SAH represents a risk factor and it means that there may be a genetic involvement. These familial predispositions are recognized as a non-modifiable risk factor for the formation and rupture of intracranial aneurysms. The Familial Intracranial Aneurysm (FIA), a multicenter international study, assess the genetic and other risk factors for formation and rupture of UIA comparing the FIA study cohort with the ISUIA-data with regard to patient demographic data, aneurysm location and multiplicity. To improve comparability, all patients in the ISUIA who had a family history of IAs or subarachnoid hemorrhage were excluded by the study, as well as all patients in both cohorts who had a ruptured IA prior to study entry: of 983 patients enrolled in the FIA study with definite or probable IAs, 511 met the inclusion criteria for this analysis. Of the 4059 patients in the ISUIA study, 983 had a previous IA rupture and 657 of the remainder had a positive family history, leaving 2419 individuals in the analysis. Multiple aneurysms were more common in the FIA patients (35.6% vs. 27.9%, $p < 0.001$). The FIA patients had a higher proportion of IAs located in the middle cerebral artery (28.6% vs. 24.9%), whereas ISUIA patients had a higher proportion of posterior communicating artery IAs (13.7% vs. 8.2%, $p = 0.016$). Heritable structural vulnerability may account for differences in IA multiplicity and location. Several investigations into the underlying genetic mechanisms of IA formation are ongoing [8].

(2) "*Aneurysm characteristics*": size, type, location, morphology and "symptoms" influence the indication to the treatment.

The aneurysm sizes, associated to the location (anterior or posterior circulation), represent the best predictor of rupture and the best indication criteria. By ISUIA 1 data [5], the rate of rupture of aneurysms of patients without prior SAH affected by UIA <10 mm was less than 0.05%/year, while in the prior SAH patients-group, the rate was approximately 11 times as high (0.5%/year). The rupture rate of aneurysms that were 10 mm or more in diameter was less than 1%/year in both groups, but in group 1, the rate was 6% the first year for giant aneurysms ($\gg$25 mm in diameter). Rupture occurs more frequent for aneurysms located at posterior circulation (posterior communicating artery, vertebro-basilar/posterior cerebral, and basilar tip). Among the patients without prior SAH with posterior communicating, vertebro-basilar/posterior cerebral, and basilar tip UIAs >25 mm in diameter, the risk of rupture was 45% at 7.5 years; 10–24-mm UIAs and, 10-mm UIAs in the same locations carried rupture risks of 15% and 2% over 7.5 years, respectively. In all other locations, the rupture risks at 7.5 years for >25-mm, 10–24-mm, and 10-mm UIAs were 8%, 3%, and 0%, respectively [5–7,9].

In the USUIA 2 the 5-year cumulative rupture rates for patients who did not have a history of subarachnoid hemorrhage with aneurysms located in internal carotid artery, anterior communicating or anterior cerebral artery, or middle cerebral artery were 0%, 2.6%, 14.5%, and 40% for aneurysms less than 7 mm, 7–12 mm, 13–24 mm, and 25 mm or greater, respectively, compared with rates of 2.5%, 14.5%, 18.4%, and 50%, respectively, for the same size categories involving posterior circulation and posterior communicating artery aneurysms [6].

For the very small aneurysms ($\leq$3 mm) the management and treatment indication remain unclear. For this size, the risk of rupture in the natural history is very low (according to ISUIA 2 the rupture rate for this size is approximately 0%/year) compared to the endovascular complications rate (thromboembolic events and intraoperative rupture). In the ATENA subgroup study, Pierot et al. reported a similar endovascular risk treatment in patients with very small or with large aneurysm. Because the risk of spontaneous rupture is lower in very small aneurysm their management will include follow up MRI and active treatment in case of morphological modification [10].

Considering the statement that cerebral aneurism formation is based on wall-vessel alteration (aneurismal wall has a lower level of elastin and collagen; ruptured aneurysm has an increased expression of elastase compared to unruptured aneurysm; extracellular matrix alteration with less and brief fibers combined to environment risk factors), the presence of symptoms such as mass effect, nerve palsy (according to its location) in a patient with a known or unknown UIAs, an abnormal headache resistant to medical therapy supposes an aneurysm grown-activity prior its rupture [11]. In this case symptoms onset justifies the indication treatment as soon as possible.

(3) *The hemodynamic environment* in unruptured aneurysm could influence the natural history. Hemodynamic factors are thought to play an important role in the initiation, growth, and rupture of cerebral aneurysms. They act on the vessel wall and they can be distinguished in:

- Hydrostatic pressure: arterial blood pressure.
- Dynamic pressure: circulating blood impinges on the vessel wall.
- Shear stress: frictional shear force on the endothelium parallel to the vessel wall. The Maximum Shear Stress (MSS) represents the interaction between different layers of blood within the aneurysm and it has an important role in platelets activation with thrombus formation; the Wall Shear Stress (WSS) represents the moving blood strength