Epidemiologia degli aneurismi cerebrali

Valeria Tugnoli
U.O. di Neurologia
D.A.I. Neuroscienze-Riabilitazione – AOU di Ferrara

v.tugnoli@ospfe.it

Aneurisma Cerebrale: diagnosi e trattamento

Ferrara, 15 dicembre 2018
Definition

• A cerebral aneurysm is a **focal abnormal dilation of the wall of an artery** in the brain, that are **prone to rupture**.
• Most commonly located at **branching points** of the major arteries at the base of the brain, which course through the subarachnoid space.
For adult without specific risk factors for unruptured aneurysms (UA) the prevalence is 3.2% (Juvela, 2011), autopsy series → 0.2-7.9% → 3 to 12 million Americans; 1.6 million in Germany

- Incidence of intracranial aneurysm = 1 per 10,000 persons/year in the USA
- 20–30% of patients harboring more than one aneurysm
- There has been increased detection of UA due to the frequent use of CT and MRI
- The prevalence is higher in women (3 : 1 ratio), increase with increasing age
- It can occur at any age but are more common in adults than children (2%)
- Annual risk of rupture around 1% (ISUIA, 1998; Wermer et al, 2007).
- It account for about 80–85% of nontraumatic subarachnoid hemorrhages (SAH)
Chinese population

- the female predominance is weaker in the younger age group
- a tendency for males to have a slightly larger aneurysm size than females
- ruptured aneurysms are mostly in the size range of 2–5 mm
- the prevalence of multiple aneurysms was only 2.7% in this cohort
- high proportion of ruptured aneurysms from the PcoA and AcoA
- higher incidence of AcoA aneurysm rupture on the left side and PcoA aneurysm rupture on the right side
• **50% to 80%** of all aneurysms **do not rupture** during the person’s lifetime

• **65% to 85%** of UA are small, <5 to 7 mm in diameter

• **Risk factors for UA**: smoking (risk persists after smoking cessation), hypertension, alcohol, injury or trauma to blood vessels, blood infections, autosomic dominant polycystic kidney disease (5% to 40% and 10% to 30% multiple aneurysms), Marfan’s syndrome, Ehlers-Danlos syndrome type IV, fibromuscular dysplasia, moyamoya disease, sickle cell disease, arteriovenous malformations of the brain, glicogenosys, Fabry,....

• Previous episode of SAH

• **7% to 20%** of pts with aneurysmal SAH have a **1st or 2nd-degree relative** with intracranial aneurysm → screening with AGF-MRI for people with 2 immediate relatives with IA and for all patients with autosomal dominant polycystic kidney disease

• 61 studies including 32,887 IA cases and 83,683 ctrls
• 19 single nucleotide polymorphisms associated with IA
  – chromosome 9 within the CDKN2B antisense inhibitor gene, cyclin-dependent kinase inhibitor 2B antisense inhibitor gene
  – chromosome 8 near the SOX17 transcription regulator gene
  – chromosome 4 near the endothelin receptor A gene. Near the EDNRA gene
  – 10q24.32 (CNNM2), 12q22, 13q13.1 (KL/STARD13), 18q11.2 (RBBP8), and 20p12.1

• Multiple pathophysiologic pathways, mainly involved in vascular endothelial maintenance and extracellular matrix integrity, are likely to contribute to IA development and rupture
Plans are ongoing to sequence the 96 candidate genes in a series of ≈400 additional familial IA.
FMD is a rare (4% population) noninflammatory arterial disease, (97.5% women)

- Arterial beading, stenosis, aneurysm, dissection, or tortuosity
- Dissection (25.7%)
- Aneurysm (21.7%),
  - extracranial carotid, 31%
  - renal 34%
  - intra-cranial arteries 21.5%
  - Aorta 10%
• The prevalence of UCAs was significantly higher in the AIS group (7.7\%) than in the health check-up (3.7\%).
• The mean aneurysm diameter was larger in the AIS group than in the health check-up group (3.75 mm vs. 3.02 mm, P=0.009).
• UCAs were primarily located in the internal carotid artery in both groups, and aneurysms in the middle cerebral artery were particularly common in the AIS group.
• **Hypertension was an independent risk factor of UCA in AIS**
Frequency percentage of type of aneurysm in the studied patients

- Saccular: 65.8%
- Fusiform: 12.9%
- Dismorphic: 14.2%
- Infectious: 1.3%
- Unknown: 5.8%
Classified by pathogenesis

- **Saccular, berry, or congenital aneurysms** = 90% located at the major branch points of large arteries (anterior circulation in 85-95% of cases)
- **Dolichoectatic, fusiform, or arteriosclerotic aneurysms** are elongated outpouchings of proximal arteries = 7%
- **Giant saccular** aneurysms = greater than 25 mm (3-5% of all)
- **Microaneurysms** of small perforating vessels may result from hypertension
- **Multiple saccular** aneurysms are noted in 20-30% of pts with cerebral aneurysms
- **Mirror aneurysms** (occurring at the same locations bilaterally) are found in about 9%
- **Infectious or mycotic aneurysms** are situated peripherally = 0.5%
- **Other distal**: neoplastic aneurysms, rare sequelae of embolized tumor fragments, and traumatic aneurysms
- **Traumatic injury** also may result in dissecting aneurysms in proximal vessels
• Anterior circulation in 85-95% of cases
• Posterior circulation are less frequent (10–20%) with a higher risk of rupture
• Dolichoectatic aneurysms affect predominantly the vertebrobasilar system.
Anterior communicating artery

- The most common site of aneurysmal SAH (34%)
- It accounts for about 21.9%
- Usually, ACoA aneurysms are silent until they rupture.
- Suprachiasmatic pressure may cause altitudinal visual field deficits, abulia or akinetic mutism, amnestic syndromes, or hypothalamic dysfunction.
- Neurological deficits in aneurysmal rupture may reflect intraventricular hemorrhage (79%), intraparenchymal hemorrhage (63%), acute hydrocephalus (25%), or frontal lobe strokes (20%).
Anterior cerebral artery

- Aneurysms of this vessel, excluding ACoA, account for about 5% of all cerebral aneurysms
- Most are asymptomatic until they rupture
- Frontal lobe syndromes, anosmia, or motor deficits
Middle cerebral artery

- It accounts for about 20% of aneurysms, typically at first or second division in the sylvian fissure
- Aphasia, hemiparesis, hemisensory loss, anosognosia, or visual field defects or seizure
Posterior communicating artery

• Aneurysms present at the junction of the termination of the ICA and PCoA account for 23% of cerebral aneurysms; they are directed laterally, posteriorly, and inferiorly.

• III CN, Pupillary dilatation, ophthalmoplegia, ptosis, and hemiparesis may result.
Internal carotid artery

- It accounts for about **4%** of all cerebral aneurysms.
- Supraclinoid aneurysms may cause **III paresis** or variable **visual defects** and **optic atrophy** due to compression of the optic nerve.
- Chiasmal compression may produce **bilateral temporal hemianopsia**, Hypopituitarism or anosmia may with giant aneurysms.
- **Cavernous-carotid** aneurysms ophthalmoplegia and trigeminal sensory loss.
- Rupture produces a carotid-cavernous fistula, SAH, or epistaxis.
Basilar artery

• Basilar tip aneurysms the most common in the posterior circulation, accounting for 5% of all aneurysms.
• Clinical associated with SAH, although bitemporal hemianopsia or an oculomotor palsy may occur.
• Dolichoectatic aneurysms may cause bulbar dysfunction, respiratory difficulties, or neurogenic pulmonary edema.
Vertebral artery or posterior inferior cerebellar artery

- Typically result in ataxia, bulbar dysfunction, or spinal involvement.
Clinical presentation

• Unruptured intracranial aneurysms may be **incidental findings**

• **Compressions**
  – middle cerebral artery aneurysms causing hemiparesis, visual field defect, or seizure
  – anterior communicating artery usually silent. Suprachiasmatic pressure may cause altitudinal visual field deficits, abulia or akinetic mutism, amnestic syndromes, or hypothalamic dysfunction.
  – posterior communicating artery or basilar artery aneurysms causing third cranial nerve palsy,
  – cavernous sinus aneurysms causing a cavernous sinus syndrome
  – basilar distribution aneurysms causing compression of the brainstem

• **Transient ischemic attack** or **cerebral infarction** due to distal embolisation

• **SAH**
• **Muscular defects of the tunica media** and minimal support of adjacent brain parenchyma augment the pathologic potential of **chronic hemodynamic stress on the arterial wall**.

• **Focal turbulence** and **discontinuity of the normal architecture at vessel bifurcations** may account for the propensity of saccular aneurysm formation at these locations

• Distal aneurysms may be smaller, the risk of rupture may be dissimilar due to the relatively thinner wall thickness


Steiger 1987
• **Several mechanosensors** → ion channels, integrins, cell adhesion molecules, G-protein-coupled receptors, have been identified at the apical and basal surfaces of the endothelium → to **identify variations in wall shear stress and adapt lumen diameter**

• Activation of **inflammatory mediators**, such as the master regulator of inflammation, nuclear factor-kappaB (NF-κB)

• **Mechanical stressors** can **denude the endothelium**, triggering the expression of chemoattractants, pro-inflammatory cytokines
It has been hypothesized that IA begins with a **hemodynamically induced endothelial dysfunction** followed by the development of an **inflammatory reaction** and **Vascular smooth muscle cells phenotypic modulation** in the arterial wall that ultimately leads to proteolysis and **extracellular matrix degradation** via **matrix metalloproteinases (MMPs)** and **apoptosis** playing major roles, with concomitant vessel wall inflammation.
• Light microscopic images of murine and human intracranial aneurysm and control artery with elastic Van Gieson staining ➔ destruction of elastic lamina in both murine and human aneurysms (dark blue to black)

Plasma Soluble Human Elastin Fragments as an Intra-Aneurysmal Localized Biomarker for Ruptured Intracranial Aneurysm

Daichi Nakagawa, MD, PhD; Mario Zanaty, MD; Joseph Hudson, BA; Nahom Teferi, MD; Daizo Ishii, MD; Lauren Allan, DO; Pascal Jabbour, MD; Santiago Ortega-Gutierrez, MD, MS; Edgar A. Samaniego, MD; David M. Hasan, MD

Elastin Fragment Level in Human Cerebral Aneurysms 

Nakagawa et al

Clinical Perspective

What Is New?

• A significantly higher concentration of soluble elastin fragment was observed in the lumen of ruptured intracranial aneurysms when compared with nonruptured ones.

What Are the Clinical Implications?

• The results of our study suggest a pathophysiological scenario where a gradual increase in elastin degradation renders the aneurysm unstable, thus precipitating rupture.

![Graph showing comparison between rupture and non-rupture elastin fragments with statistical significance (P<0.001)].
Infiltration of inflammatory (CD45 (red) positive) cells and macrophages (F4/80 (red) positive cells) into the murine and human aneurysm, absence in ctrl.

Destruction of intimal endothelial (MECA32 (red) positive) cells and thickening of the smooth muscle (αSMA (red) positive) cell layer in aneurysm wall.
• There is a **cycle of wall degeneration and weakening** in response to changing hemodynamic loading and biomechanic stress.

• This progressive **wall degradation** drives the **geometrical evolution** of the aneurysm **until it stabilizes or ruptures**.

• **Risk factors** such as location, genetics, smoking, co-morbidities, and hypertension seem to affect different components of this cycle.
Aneurysm growth

- Risk of aneurysm growth over a 4-year period (Burns JD et al Stroke 2009;40:406–411)
- UA < 8 mm → 6.9%
- UA 8–12 mm → 25%
- UA greater than 12 mm → 83%
- middle cerebral artery location
- presence of more than one aneurysm

2-year period Risk factors for growth in:

1) All aneurysms
   Initial aneurysm size, dome/neck ratio
2) Small aneurysms
dome/neck ratio, multilobarity, smoking

*Bor ASE. Stroke. 2015;46:42*
A) Left distal AC artery aneurysm

B) Less than 3 wks from previous saccular aneurysm at the callosomarginal and pericallosal bifurcation
The cumulative incidence of de novo sIAs was 0.23% per patient-year.

Significant: Smoking history and younger age at the first sIA diagnosis.

Pts <40 years at the first sIA should be scheduled for long-term AGF follow-up.
International Study of Unruptured Intracranial Aneurysms (ISUIA)

• Prospective cohort study that followed 1,692 patients with UA, 2mm or larger 1,077 without prior history of SAH → 5 yrs cumulative risk of rupture
• Annual aneurysmal rupture risk of 0.7-1%
• Two important factors in predicting risk of rupture
  1. Size → larger aneurysms (7mm or larger.) = greatest risk;
  2. Location → location on the anterior or posterior communicating artery and presence of a daughter sac
• Irregular multilobular, non-spherical shapes (oval, oblong and multilobulated) were found to be associated with rupture
• Patient factors: younger than 50 yrs, hypertension, multiple aneurysms
• Aneurysms presenting with subarachnoid hemorrhage tend to bleed again at a rate of 9% within the first 72 hours after the initial episode
• Aspirin: the rate was higher among those not taking aspirin (40%) than among those taking aspirin (28%)
Size

Ferrara, 15 dicembre 2018

Yuichi Murayama et al 2015
Site

C-pcom = internal carotid - posterior communicating artery
VABA = vertebral - basilar artery

Ferrara, 15 dicembre 2018
Yuichi Murayama et al 2015
There are many contradictory results in the literature.

**Low WSS** and high oscillatory shear index trigger an inflammatory cell-mediated pathway that could be associated with the growth and rupture of large, atherosclerotic aneurysms,

**High WSS** combined with a positive WSS gradient triggers a mural cell-mediated pathway that could be associated with the growth and rupture of small or secondary bleb aneurysm
There is a progression of PHASES score between stable UIA, growing observed UIA, immediately treated UIA, and SAH groups. PHASES score of $\leq 3$ is associated with a low but not negligible likelihood of aneurysm rupture, and specificity of the classifier is low.

Bijlenga P. Et al, Stroke. 2017;48:2105
Risk of rupture of unruptured intracranial aneurysms

- The estimated incidence of aneurysmal SAH varies widely depending on geographic location, ranging from 3.9-19.4 per 100,000 individuals, with the highest reported rates in Finland and Japan, approximately 6-10/100,000 person-years in USA

---

<table>
<thead>
<tr>
<th>Size</th>
<th>ACA/MCA/ICA (%)</th>
<th>Posterior communicating + posterior circulation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 7 mm no previous SAH</td>
<td>0 (confidence interval?)</td>
<td>2.5 (confidence interval?)</td>
</tr>
<tr>
<td>&lt; 7 mm with previous SAH</td>
<td>1.5 (confidence interval?)</td>
<td>3.4 (confidence interval?)</td>
</tr>
<tr>
<td>7-12 mm</td>
<td>2.6 (confidence interval?)</td>
<td>14.5 (confidence interval?)</td>
</tr>
<tr>
<td>13-24 mm</td>
<td>14.5 (confidence interval?)</td>
<td>18.4 (confidence interval?)</td>
</tr>
<tr>
<td>&gt; 24 mm</td>
<td>40 (confidence interval?)</td>
<td>50 (confidence interval?)</td>
</tr>
</tbody>
</table>

Wermer et al Stroke 2007; Juvela et al 2013
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Sample size</th>
<th>New moon</th>
<th>Waxing crescent</th>
<th>First quarter</th>
<th>Waxing gibbous</th>
<th>Full moon</th>
<th>Waning gibbous</th>
<th>Last quarter</th>
<th>Waning crescent</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>Lithuania</td>
<td>186</td>
<td>23</td>
<td>20</td>
<td>29</td>
<td>31</td>
<td>25</td>
<td>25</td>
<td>23</td>
<td>10</td>
<td>0.092</td>
</tr>
<tr>
<td>Ali et al., 2008</td>
<td>Lebanon</td>
<td>111</td>
<td>28*</td>
<td>7</td>
<td>16</td>
<td>11</td>
<td>18</td>
<td>7</td>
<td>15</td>
<td>9</td>
<td>0.001</td>
</tr>
<tr>
<td>Lahner et al., 2008</td>
<td>Austria</td>
<td>717</td>
<td>78</td>
<td>89</td>
<td>94</td>
<td>92</td>
<td>85</td>
<td>88</td>
<td>101</td>
<td>8</td>
<td>0.84</td>
</tr>
<tr>
<td>Kamp et al., 2013</td>
<td>Germany</td>
<td>655</td>
<td>87</td>
<td>87</td>
<td>83</td>
<td>76</td>
<td>79</td>
<td>87</td>
<td>78</td>
<td>78</td>
<td>0.971</td>
</tr>
<tr>
<td>Total, number</td>
<td></td>
<td>1669</td>
<td>216</td>
<td>203</td>
<td>222</td>
<td>210</td>
<td>212</td>
<td>204</td>
<td>204</td>
<td>198</td>
<td>0.955</td>
</tr>
</tbody>
</table>
The risk of intravenous thrombolysis-induced intracranial hemorrhage in Taiwanese patients with unruptured intracranial aneurysm

Wei Ting Chiu¹²,³, Chien Tai Hong¹²,³, Nai Fang Chi¹²,³, Chaur Jong Hu¹²,³, Han Hwa Hu¹²,³, Lung Chan¹²,³

- Administering r-tPA to patients with a pre-existing aneurysm does not increase the bleeding risk
- Asians are known to have a relatively higher bleeding risk, and little evidence is available regarding the risk of using r-tPA on Asian patients with intracranial aneurysms
Size of Ruptured Intracranial Aneurysm — Is Epidemiology Really Changing?

- Novel epidemiologic trend in Finnish population suggesting a decrease in size of ruptured intracranial aneurysms over the past two decades (2660 patients from January 1989 to December 2008).
- Anterior circulation ruptured intracranial aneurysms accounted for 91% (MCA 33%, ACoA 32%, PCoA 14%, pericallosal A 5%).
- The trend of increase in treatment rates of UA is disproportionate to the rate of increase in population size (especially in developed countries). Larger UA are more likely to be symptomatic and more frequently treated.
- The changes of treatment trends could be an important factor determining average size of ruptured intracranial aneurysms presenting to hospitals.

Korja M et al Stroke 2018
RECOMMENDATION FOR SCREENING

<table>
<thead>
<tr>
<th>Recommendations for screening</th>
<th>Strongly consider screening</th>
<th>Possibly consider screening</th>
<th>Do not recommend screening</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with 2 or more family members with history of UIA or SAH <strong>(8% risk)</strong></td>
<td>Patients with ADPKD without family history of aneurysm</td>
<td>General population</td>
</tr>
<tr>
<td></td>
<td>ADPKD with family history of UIA or SAH</td>
<td>Patients with one family member with UIA or SAH <strong>(4% risk)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients with coarctation of the aorta</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• Pts with UA have 50% excess long-term mortality compared with general population

• Men with treated UA have a survival proportion comparable with matched general population.

• Women have 28% excess mortality after surgical treatment and 23% excess mortality after endovascular treatment

• The reason for this is unclear, cardiovascular risk increases with age more sharply in women than in men