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RESEARCH ARTICLE

# Frequency of Diseases Inducing a Systemic Oxidative Stress in 175 Patients with Intracranial Aneurysms

***Thierry Patrice, MD, PhD[1*], Romain Bourcier, MD[2], Hubert Desal, MD, PhD[2], Bertrand Rozec, MD, PhD[1] and Yvonnick Blanloeil, MD[1]***

[1]*Anesthesiology and Intensive Care, Laënnec Hospital, Nantes, France*

[2]*Neuroradiology, Laënnec Hospital, Nantes, France*

***Corresponding author:** *Dr. T Patrice, Laboratoire de Photobiologie, Anaesthesiology and Intensive Care, UF 9380, PHU3, Laënnec Hospital, 44093 Nantes, France, Tel: (33)-2-40-16-56-75; (33)-2-40-16-53-37, Fax: (33)-2-40-16-59-35*

## Abstract

**Background and purpose:** Oxidative stress (OS) could be involved during intracranial aneurysms (ICA) progression but knowledge about comorbidities likely to induce OS is poor. We studied the medical and surgical history of patients with an ICA discovered after a subarachnoidal haemorrhage (SAH) or unruptured (UIA).

**Methods:** 175 patients, 58 with a UIA, had been successively recruited from a single centre. Their medical history, comorbidities and treatments had been gathered from hospital files, general practitioners, relatives and patients. Frequency of each diseases had been compared between UIA and SAH groups and to the French population prevalence (FPP) issued from national organisations.

**Results:** A "significant" medical or surgical history was absent in 14% of patients. Withdrawn smokers were more frequent in the UIA group. Dyslipidaemias, diabetes, were more frequent ($p < 0.05$) in the SAH group than FPP. High blood pressure, other cardiovascular diseases were not higher than FPP. Migraines and psychiatric disorders, hypothyroidism, cancers and benign tumours were significantly elevated. Twelve orphan diseases were diagnosed, most of them involving connective tissue disorders, others being of unknown origin. Twenty five percent of women had a heavy gynaecological history. A surgical history was more frequent in the UIA group. NSAID, aspirin, antidepressants were found prescribed in a higher proportion than the FPP.

**Conclusion:** Central nervous system diseases, orphan diseases and tumours are abnormally more frequent in this cohort as compared to the FPP likely to induce a significant oxidative stress-related systemic impairment. Further studies are required to check whether ICA without noticeable comorbidities could be predominantly familial and represent a particular entity.

## Keywords

Subarachnoidal hemorrhage, Intracranial cranial aneurysm, Co-morbidity, Risk factors, Stroke

## Abbreviations

AMI: Acute Myocardial Infarction; ANSM: Agence nationale de sécurité du médicament et des produits de santé; ASA: American Society of Anesthesiologists; CERIN: Centre de recherche et d'information nutritionnelles; FPP: French Population Prevalence; GA: General Anesthesia; HAS: Haute autorité de santé; IASP: International Association for the Study of Pain; ICA: Intracranial Aneurysm; INESS: Institut national d'excellence en santé et en services sociaux (Québec, Ca.); INPES: Institut national de prévention et d'éducation pour la santé; INVS: Institut national de veille sanitaire; INSERM: Institut national de la santé et de la recherche médicale; LLOA: Lower Limb Obliterating Arteriopathy; ROS: Reactive Oxygen Species and Peroxides; SAH: Subarachnoidal Haemorrhage; SD: Standard Deviation; SOS: Secondary Reactive Oxygen Species and Peroxides; UIA: Unruptured Intracranial Aneurysm

## Introduction

The prevalence of intracranial aneurysms (ICA) is variable and controversial though a quoted estimated of 3% implies that aneurysms concern 2 million persons in France. Despite intense research, causes and thus the natural history of ICAs remain largely unknown. When it is generally considered that an important proportion remains silent, ICAs account for 85% of subarachnoidal hemorrhage (SAH), with an annual incidence of 9/100000. The therapeutic decision for unruptured

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intracranial aneurysms (UIA) represents a challenge as treatment risks have to be balanced against an unknown probability of rupture. Risk factors implicated in ICAs are modifiable for some of them as smoking or hypertension and some not as family history [1], genetic factor [2] or vessel wall architecture [3]. Some co-morbidities have emerged, although considering mainly familial diseases [4] when the specificity of causal factors was discussed for others [5]. Finally environmental factors had also been described to play a role in SAH and we have recently demonstrated the association of partial oxygen pressure with medical history as a risk factor of aneurysm rupture [6]. It has been suggested that oxidative stress might play a role in both ICA genesis and rupture [7]. One can hypothesize that oxidative stress can be normal but acting on abnormally responding tissues, i.e for genetic reasons, or that patients are supporting a heavy oxidative stress likely to promote aneurysm growth from a limited nonspecific vessel wall injury. Oxidative stress, namely, the imbalance between reactive oxygen species (ROS) production and elimination, can include autoxidation of glucose, shifts in redox balances, and reduced or impaired activities of antioxidant defense enzymes or the direct consumption of physiological antioxidants. Any redox reaction is likely to involve a certain level of oxidative stress, leading to a cascade of deleterious events when defenses are overtaken. Risk factors had been identified but only very few studies analyzed the whole medical past of patients with IAC when each disease would influence the inflammatory status of patients, therefore influencing evolution of ICAs through nonspecific oxidative stress pathways. On the other hand, a number of occurrences between ICAs and comorbidities had been described in the literature [8] but the rational link misses often.

The aim of the present paper was to demonstrate that patients with ICAs were not free of previous diseases, and that these were likely to have induced a strong oxidative stress eventually participating to ICA progress if not initiating it. It was not the aim of the paper to identify any disease as a direct cause of ICA but to demonstrate that a nonspecific oxidative stress related hypothesis for ICA is sustainable and not unrealistic. This would support the idea that besides direct genetic or local causes, ICA development could be promoted by oxidative stress occurring randomly with concomitant diseases. Patients without such diseases could represent specific familial or genetic types of ICA. We thus report here the medical histories of 175 patients continuously recruited from a single unit with silent or disrupted ICAs and analyze whether the prevalence of their recorded diseases in the past differed from the general French population corresponding prevalence (FPP).

## Patients and Methods

175 patients have been analyzed (Table 1), consecutively recruited for 2 separated studies, one devoted to the measurement of resistance to oxidative stress in UIAs or SAH, partly published [9], one analyzing weather conditions at time of SAH [6] admitted in the unit from January 1st 2013 to December 31st 2013. Diagnosis of ICAs had been confirmed by Nuclear Magnetic Resonance and/or angio-scanography and data had been completed concerning each patient's medical history, including operating sessions as well as treatments prescribed at time of recruitment. Sources of information were patients themselves, relatives, medical doctors and various hospital files. Although their role cannot be ignored, benign infantile diseases had not been recorded. We cannot exclude that a number of significant diseases and treatments could have been missed but all diseases counted really occurred. Our study thus probably underestimates incidence of co-morbidities. It is also possible that UIA patients being followed up for years were more documented than SAH patients. Clinical histories had been found extremely rich and generated various oxidative stress disorders [10]. Only patients unable to provide any marked souvenir of disease and without any clinical file were scored as 0. Prevalence of

**Table 1:** Characteristics of 175 Patients with an ICA according to their medical (Med) or surgical (Surg) history. UIA: Unruptured intracranial aneurysm (ICA); SAH: Subarachnoidal haemorrhage.

| ICAs | Total | Age | % | Female | Age | % | Male | Age | % |
|---|---|---|---|---|---|---|---|---|---|
| **Total** | 175 | 54.3 | 100.0 | 111 | 55.4 | 63.4 | 64 | 52.4 | 36.6 |
| **SAH** | 117 | 53.6 | 66.9 | 72 | 54.7 | 61.5 | 45 | 51.8 | 38.5 |
| **UIA** | 58 | 55.8 | 33.1 | 39 | 56.8 | 67.2 | 19 | 53.7 | 32.8 |
| **No med history** | 33 | 51.9 | 18.9 | 19 | 54.0 | 17.1 | 14 | 47.0 | 21.9 |
| **SAH** | 24 | 51.5 | 20.5 | 16 | 53.2 | 22.2 | 8 | 49.4 | 17.8 |
| **UIA** | 9 | 51.0 | 15.5 | 3 | 61.0 | 7.7 | 6 | 31.0 | 31.6 |
| **No surg history** | 66 | 49.8 | 37.7 | 38 | 51.0 | 34.2 | 28 | 48.2 | 43.8 |
| **SAH** | 52 | 48.2 | 44.4 | 27 | 48.8 | 37.5 | 25 | 47.6 | 55.6 |
| **UIA** | 14 | 55.6 | 24.1 | 11 | 56.2 | 28.2 | 3 | 53.3 | 15.8 |
| **No med or surg history** | 25 | 50.3 | 14.3 | 12 | 51.6 | 10.8 | 13 | 52.3 | 20.3 |
| **SAH** | 23 | 50.6 | 19.7 | 11 | 50.6 | 15.3 | 12 | 51.2 | 26.7 |
| **UIA** | 2 | 64.0 | 3.4 | 1 | 62.0 | 2.6 | 1 | 66.0 | 5.3 |

each disease and prescriptions at the mean age of 50 years for men or women were obtained for the French population. Concerning prescriptions, institutional data were often missing and references from other western countries had to be found. Sources most often from the web, all mentioned, had thus been originating from French governmental organizations and controlled by at least one another source. Orpha.net[a] had been used to estimate the frequency of rare diseases. We choose French sources despite the trouble that it could bring to the reader as one cannot ascertain that populations are comparable worldwide.

Statistical analysis was based on the comparison of groups of individuals as a function of general population data. Chi2 test was used for the comparison of percentages, Mann-Whitney U test for the comparison of data according to groups of patients, Spearman rank's test for correlations. Due to the number of parameters, statistics were not detailed. "Significant" meant that "p" was less than 0.05. When only close to significance it was noted either in the text or in table captions.

[a]http://www.orpha.net/orphacom/cahiers/docs/FR/Liste_maladies_rares_par_ordre_alphabetique.pdf

## Results

### General

Among the 175 patients who had been diagnosed with an ICA, 67% were after a SAH and 33% diagnosed with a UIA (Table 1). Women accounted for more (63.4% of each cohort) but age of discovery, 54 (extremes 82-17), did not significantly differ according to gender or circumstances of discovery. No "significant" medical or surgical pathology had been noted in 14% of the whole cohort. Surgically relevant diseases were less frequently noted before a SAH (44.4%, $p < 0.001$), and surgery was significantly more frequent for UIA than SAH ($p < 0.001$) or the calculated FPP (35% not operated) for patients aged 45-55 yrs [11]. Occurrence of a significant medical history was comparable in UIA or SAH groups reaching 80-85%. Only 3.4% of patients in the UIA group (2.6% in the female group) had no medical or surgical history.

### Risk factors

The repartition of active, non-smokers and withdrawn was similar to the FPP[b]. Withdrawn smokers

[b]http://inpes.santepubliquefrance.fr/30000/actus2015/013-tabac-donnees-barometre-2014.asp

**Table 2a:** Diseases considered as «classical risk factors» among a cohort of 175 Patients with an Intracranial Aneurysm: Unruptured intracranial aneurysm (UIA); SAH: Subarachnoidal haemorrhage; FPP: French population prevalence; F: Female; M: Male. Data significantly (5% or less) differing from the FPP are squared.

| Characteristics % | | Whole | SAH All | SAH F | SAH M | UIA All | UIA F | UIA M | FPP 50 yrs | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| **Smoking** | **Never** | 48 | 57 | 58 | 55.5 | 22.4 | 30 | 16.6 | 46 | INPES |
| | **Active** | 38 | 34 | 36 | 31 | 40 | 40 | 55 | 35 | INPES |
| | **Withdrawn** | 14 | 6 | 2 | 13 | 26 | 30 | 27 | 19 | INPES |
| **Alcohol & drugs** | | 11 | 12 | 7 | 20 | 8.6 | 10.2 | 5.3 | 10 (daily) | INPES |
| **Dyslipidemia** | | 28 | 36 | 35 | 37 | 12 | 12.8 | 10.5 | 30 | Ferrieres, et al. [12] |
| **Diabetes** | | 26 | 34.2 | 35.5 | 33.3 | 8.6 | 7.7 | 10.5 | 5 | INVS |
| **Hypertension** | | 38 | 44.8 | 43.6 | 47.4 | 44 | 43.6 | 47.4 | 35 < P < 45 | INVS |
| **BMI** | *Mean values* | 24.8 | 24.9 | 24.6 | 24.7 | 24.7 | 25.4 | 24.2 | | |
| **BMI > 24** | | 29 | 26 | 22 | 29 | 37 | 41 | 32 | 18<br>Epilepsy 1 | Eurostat |
| **Migraines** | | | | | | | | | Epilepsy 1 | |
| **CNS &** | | 35 | 33.3 | 32 | 35.5 | 39.6 | 31.6 | 43.6 | Migraines 13 | IASP, INSERM |
| **Psychiatrics** | | | | | | | | | Depression 4<br>24 < P < 6 UCA | Vlak, et al. [4] |
| **Familial strokes** | | 21.1 | 17.1 | 18.1 | 15.6 | 29.3 | 30.8 | 26.3 | 1.2 < P < 4 | Mozaffarian, et al. [24], HAS |
| **Coronaropathy** | | 5 | 34.1 | 1.4 | 6.6 | 7 | 7.7 | 55.3 | 1.9 < P < 3.9<br>Asymp 18 | INVS, Calvet, et al. [20] |

were more in the UIA group ($p < 0.01$) (Table 2a and Table 2b). Alcohol or cannabis consumption[c] was close to the cumulated FPP (less than 10% for daily consumers[d]) except for males of the SAH group (20%). Frequency of dyslipidemias in the SAH group corresponded to the FPP[e] but dyslipidemias [12] or diabetes[f] were more frequent in the SAH group ($p < 0.001$). Frequency of high blood pressure (HBP) was at the upper limit of FPP[g]. Patients with a BMI higher than 24 were more frequent than the FPP[h] but only slightly in the UIA group. Frequency of migraines was not higher than FPP (11% vs. 13% FPP[i]) but occurrence of cumulated neurological or psychiatric diseases (including severe depressions n =

[c]http://www.ipubli.inserm.fr/bitstream/handle/10608/171/?sequence=6

[d]http://inpes.santepubliquefrance.fr/10000/themes/alcool/consommation-alcool-france.asp

[e]http://www.realites-cardiologiques.com/wp-content/uploads/sites/2/2010/11/0214.pdf

[f]http://invs.santepubliquefrance.fr/Dossiers-thematiques/Maladies-chroniques-et-traumatismes/Diabete

[g]http://invs.santepubliquefrance.fr/Dossiers-thematiques/Maladies-chroniques-et-traumatismes/Maladies-cardio-neuro-vasculaires/L-hypertension-arterielle

[h]http://ec.europa.eu/eurostat/documents/2995521/7700908/3-20102016-BP-FR.pdf/6a7f5689-11b2-4862-8b29-d5bf59795b87

[i]https://www.iasp-pain.org/files/Content/ContentFolders/GlobalYearAgainstPain2/VisceralPainFactSheets/1-Epidemiology_French.pdf

**Table 2b**: Other concomittant diseases among a cohort of 175 Patients with an Intracranial Aneurysm: Unruptured intracranial aneurysm (UIA); SAH: Subarachnoidal haemorrhage; FPP: French population prevalence; F: Female; M: Male. Data significantly (5% or less) differing from the FPP are squared.

| Characteristics % | Whole | SAH All | SAH F | SAH M | UIA All | UIA F | UIA M | FPP 50 yrs | Reference |
|---|---|---|---|---|---|---|---|---|---|
| **Coronaropathy** | 5 | 3.41 | 1.4 | 6.6 | 7 | 7.7 | 5.3 | 1.9 < P < 3.9<br>Asymp 18 | INVS, Calvet, et al. [20] |
| **Valvulopathy** | 1.7 | 2.6 | 2.8 | 2.2 | 0 | 0 | 0 | 2 < P < 6 | Nkomo, et al. [13] |
| **Arythmia** | 5.1 | 2.6 | 2.8 | 2.2 | 10.3 | 12.8 | 5.3 | | |
| **AMI** | 2.3 | 1 | 1.4 | 0 | 5.2 | 7.7 | 0 | 3 | INSERM |
| **LLOA** | 4 | 1.7 | 2.7 | 0 | 8.6 | 10.2 | 5.2 | 0.8 < P < 7 | INSERM |
| **Total cardiovasc** | 18.1 | 11.31 | 11.1 | 11 | 31.1 | 38.4 | 15.8 | | |
| **COPD** X | 11.4 | 9.4 | 9 | 9.7 | 15.5 | 20.5 | 5.2 | 4 < P < 8 | INVS |
| **Vascular** | 15 | 13 | 14 | 11 | 19 | 28 | 0 | 11 < P < 24 | Varicose V |
| **Benign tumors** | 16.7 | 14.5 | 18 | 9 | 20.7 | 23 | 16 | 9 | INVS |
| **Cancers** | 13.4 | 10.3 | 10 | 11 | 19 | 23 | 10.5 | P < 5 | INCa |
| **Inflam. & endoc** | 26.3 | 22.2 | 25 | 17.8 | 34.5 | 38.5 | 26 | | |
| **hypothyroidism** | 7.5 | 8 | | | | | | 0.4-2 | Wémeau, et al. [13] |
| **Lithiasis & $Ca^{++}$ disorders** | 13.1 | 13.7 | 10.3 | 15.8 | 12.1 | 15.3 | 11.1 | Urinary 10<br>Biliary 20 | Daudon M, et al. [14]<br>SNFGE |
| **Gynaecology** | 25.1 | 22.2 | 34.7 | - | 31.0 | 46.2 | - | | |

**Table 3:** Prevalence (%) of medications in 175 patients with an intracranial aneurysm. Unruptured intracranial aneurysm (UIA); SAH: Subarachnoidal haemorrhage; FPP: French population prevalence.

| Medications % | Whole | SAH AI | UIA All | FPP 50 yrs |
|---|---|---|---|---|
| **Aspirin** | 15.4 | 14.5 | 17.2 | 12 |
| **Paracetamol & NSAID** | 9.1 | 11.1 | 9 | 5-8 |
| **Other neurotrophic drugs** | 9.7 | 10 | 4 | NR |
| **Antidepressants** | 17 | 21 | 10 | 11 |
| **Total** | 40 | 56 | 21 | NR |
| **Proton pump Inhibitors** | 6 | 7 | 2 | 8-14 |
| **Beta blockers** | 14 | 12 | 8.6 | < 8 |
| **ACEI/ARA II** | 18 | 13.7 | 26 | P < 10 (All), P < 30 (HBP) |
| **Calcium channel inhibitors** | 7 | 6 | 8.5 | P < 30 |
| **Anticoagulants (incl VKA)** | 8.5 | 11 | 2.5 | 0.6, Incidence 4% per year |
| **Thyroid hormones analogues** | 7 | 9 | 3 | 0.5-2 |
| **Contraceptive, incl.** | 18.3 | 19.7 (W 23.6) | 15.5 (W 20.5) | 20-30 |

14, 8% vs. 4% FPP[j]) was higher than FPP (35% vs. a calculated FPP of 25%, $p < 0.01$). Familial histories of ICA or strokes reached 21% in our whole cohort when the FPP is less than 4%. As noted above ICAs were more frequent in women ($p < 0.01$).

## Cardiovascular histories

Coronaropathies, valvulopathies [13], arrhythmias, high blood pressure were not more frequent than the corresponding FPP. Arrhythmias were strangely significantly more frequent in UIA patients. Acute myocardial infarction (AMI) and lower limb obliterating arteriopathy (LLOA) were more frequent in the UIA group than the SAH but not significantly, due to the cohort's size. However the cumulative frequency of cardiovascular diseases was higher for UIA patients than SAH and FPP ($p < 0.01$).Other vascular diseases, among them varicose veins, were at a comparable frequency with FPP. Chronic obstructive pulmonary disease, leading to a low $pO_2$, was elevated (11%) and more in UIA (15%) and women as compared to FPP (4-8%)[k].

## Other diseases (Table 2b)

Benign and malignant tumors were at a higher frequency than FPP[l,m] in the whole cohort ($p < 0.001$) as well as in UIA as compared to SAH group ($p < 0.01$). The cumulative frequency of tumors reached 30% of patients as compared to a FPP of less than 20% (including symptomatic gastrointestinal polyps). Hypothyroidism was found in 7% of patients in both UIA and SAH groups as compared to 0.5 to 2% for the FPP [14] and close to significance ($p < 0.06$) but substitutive hormonal treatment was at a normal frequency (Table 3). Other chronic inflammatory situations including allergies were not more frequent than the FPP. Frequencies of nephrolithiasis [15] or cholelithiasis[n] were not elevated as compared to FPP (10 and 20% respectively). 25% of women (34% in the SAH group) have had a severe gynecologic disease leading either to surgery or to a long term medical treatment.

## Rare diseases or syndromes

12 patients (Table 4) had been diagnosed with a disease present at a frequency lower than 1/2000 in the French population and one at a frequency of 1/1500 (a Klinefelter syndrome) representing 7.5% of the whole cohort. They distributed similarly between UIA 3 out of 58, (5%) and SAH 10 out of 111, (9%). These rates appear highly significant even if we consider as the highest frequency 1/2000 which is the lowest of the

[j]https://www.inserm.fr/thematiques/neurosciences-sciences-cognitives-neurologie-psychiatrie/dossiers-d-information/depression

**Table 4:** Orphan diseases among a cohort of 175 Patients with an Intracranial Aneurysm: Unruptured intracranial aneurysm (UIA); SAH: Subarachnoidal haemorrhage; FPP: French population prevalence; F: Female; M: Male.

| N° | Diagnosis | FPP | Sex | Group |
|---|---|---|---|---|
| 9 | Lupus erythematosus disease | 1/2000 | F | UIA |
| 37 | Ehler danlos syndrome | 1/10000 | F | UIA |
| 41 | Klinefelter syndrome | 1/1500 | M | UIA |
| 68 | Distilben induced uterine hypoplasia | 4/100000 | F | SAH |
| 94 | Recklinghausen's disease | 1/10000 | F | SAH |
| 113 | Narcolepsy | 1/M | F | SAH |
| 131 | Charcot marie tooth disease | 1/10000 | M | SAH |
| 132 | Moya Moya disease | 1/32000 | M | SAH |
| 141 | Alzheimer's disease < 50 yrs | 1/200000 | M | SAH |
| 152 | Mesencephalic angioma | 1/1000 | M | SAH |
| 153 | Hemophilia A | 1/10000 | M | SAH |
| 159 | Rare congenital thrombophilia | 1/50000 | M | SAH |
| 169 | Double orifice right ventricle plus pulmonary atresia | 1/10000 | M | SAH |

[k]http://invs.santepubliquefrance.fr/Dossiers-thematiques/Maladies-chroniques-et-traumatismes/Broncho-pneumopathie-chronique-obstructive-et-insuffisance-respiratoire-chronique/Surveillance-epidemiologique-de-la-broncho-pneumopathie-chronique-obstructive-et-de-l-insuffisance-respiratoire-chronique-en-France

[l]https://www.cerin.org/rapports/epidemiologie-des-cancers-en-france-avec-infographie/

[m]http://www.e-cancer.fr/Professionnels-de-sante/Les-chiffres-du-cancer-en-France/Epidemiologie-des-cancers

[n]http://www.snfge.org/sites/default/files/SNFGE/Formation/Abrege-HGE/abrege-hge-cd_2015_chap13_item274_ue8.pdf

**Table 5:** Number of patients having had at least one general anesthesia (GA) in a cohort of 175 patients with an intracranial aneurysm. Unruptured intracranial aneurism (UIA); SAH: Subarachnoidal haemorrhage; FPP: French population prevalence. Without GA: Wo GA; App: Appendicectomy; Osteo. Art: Osteo Articular; Gyn: Gynecological surgery.

| | Wo G | % | GA | % | Indication for surgery (numbers) |
|---|---|---|---|---|---|
| **SAH** | 56 | 47.9 | 61 | 52.1 | |
| **Female** | 30 | 41.7 | 42 | 58.3 | 13 App., 6 Osteo.Art., 13 Gyn. |
| **Male** | 26 | 57.8 | 19 | 42.2 | 4 App., 4 Osteo.Art |
| **UIA** | 14 | 24.1 | 44 | 75.9 | |
| **Female** | 11 | 28.2 | 28 | 71.8 | 8 App., 10 Osteo. Art., 13 Gy |
| **Male** | 3 | 15.8 | 16 | 84.2 | 4 App., 7 Osteo. Art |

**Table 6:** Examples of events likely to occur and their influence on oxidative stress.

| Disease, syndrome or treatment | Main consequences |
|---|---|
| Inflammation | WBC production of ROS, increased energy needs |
| Clotting | $O_2$ and energy consumption, increased glycolysis and proteolysis, inflammation |
| Atherosclerosis | Increased lipid metabolism, ischemia |
| Diabetes | Increased polyol pathway, proteins glycation |
| Ischemia | Mitochondrial dysfunction, lipid peroxydation, arachidonic acid catabolism, inflammation |
| Cancers | Toxic agents, ischemic areas, increased metabolic needs, inflammatory responses |
| Chemo or radiotherapy | Cytolysis, release of ROS, impairment of food intake |
| Surgery | Tissue inflammation, ischemia, foreign materials<br>Ischemia reperfusion, healing process |
| Anesthetics | Renal or hepatic toxicity, cell repair, variations of pO |

orphan diseases noted.

### Treatments

General anesthesia (Table 5) had been performed in 50% of patients with SAH and in more than 70% of UIA patients ($p < 0.002$). Percentage of appendicitis was similar in women of UIA or SAH groups. Medications (Table 3) are prescribed correlatively to diseases. However some appear over represented as compared to the FPP as prescriptions might be performed out of approved indications. Aspirin and NSAID are over prescribed and if we add them to antidepressant and other neurotrophic drugs as anti-epileptics or anti-emetics, 40% of the cohort received at least one of them routinely. Anticoagulants including oral anticoagulants had been prescribed in 8.5% of the cohort when a rate of 0.6% per month is noted in the general population but are involved in "only" 4% of hemorrhages per year in the French population. Other medications do not appear to be over represented, which does not imply an absence of role.

## Discussion

Short term mortality of SAH ranges from 35 to 50% and with moderate to severe long-term disability in 50% of survivors. Among other causes of ICAs and SAH, oxidative stress had been reported. However this oxidative stress could result from a local situation or could be related to a less specific situation, i.e during a systemic disease, but having a local impact. As ICAs are usually considered as a specific disease, past medical histories are rarely documented. If analysis of classical risk factors had been reported in most other studies, to our knowledge we present here the longest series of patients with ICAs with a tentatively exhaustive analysis of their medical histories. Again this is not the aim of our paper to identify direct causes of ICAs but to demonstrate that patients with ICAs are submitted to a significant oxidative stress likely to exert an unspecific role on ICA development.

Oxidative stress, during which ROS are generated, is a normal consequence of any energy production reaction and the main source is the co-enzymes located in the mitochondria. A ROS is a molecule with an $O_2$ having an unpaired electron on its outer orbit, making this molecule available for many chemical reactions. Normally ROS are neutralized by antioxidants, nearly completely, before they could induce a significant damage to molecules present in their vicinity [16]. In the case of abnormal needs of energy or $pO_2$ changes, normal pathways are overtaken and abnormal ROS concentrations begin to rise, inducing direct damages locally or systemically in the case of long lasting ROS, damages inducing in turn other ROS. Events can thus combine into heavy oxidative stress eventually barely compatible with physiological antioxidative defenses (Table 6). ROS production will thus depend on the energy needs, substrates and $O_2$ availability. At first, ROS produced are of high energy, i.e. hydroxyl or alkoxyl radicals, and short lifetime. Singlet $O_2$ which is an excited state of an electronically normal molecule but extremely reactive having two unpaired electrons available for an oxidation, can be added to ROS. These species will early damage targets at a high rate. These damages represent in a certain sense an elimination, but damaged molecules often become ROS of lower energy but of longer lifetime, i.e. superoxide anion or hydrogen peroxide representing a systemic risk. Finally end-products or ROS of low energy can re-activate, although at a low rate, ROS of high energy, making the whole process much longer than the initial event.

Patients in the history of which we were not able to find any noticeable event appear to be in a surprisingly small number when one refers to the classically reported situation of SAH discovery. However our results were coherent, in fact even low, with those reported in the world [17]. In addition some diseases, migraines, endocrine disorders, cancers and gynecological diseases were over represented as compared to the "normal" French population. One cannot exclude that these diseases, cumulated their effects, i.e. their inflammatory and oxidative related effects, and could participate to the ICA development. Some risk factors are pointed out, the most common being gender as 60% of SAH and UIA are diagnosed in women. Sex differences could be related to the influence of steroids decreased in the post-menopausal period [18]. However another explanation could be simply related to the high rate of severe gyne-

cological diseases, reaching more than 30% in women, likely to induce inflammation and oxidative stress, without any age-related counterpart in men. Other classical risk factors are of similar rates in men and women but if more frequent in men they could exert their long term effects only mildly at the mean age of 50. However withdrawing from smoking appears to be beneficial as patients are more in the UIA group, when they were previously in the active group, making the percentage greater than in the SAH group. Diabetes and dyslipidemias are more frequent in patients with SAH than UIA in which they remain close to FPP or lower. This could be related to an excessive ROS production induced by co enzymes during glucose or lipids metabolism [19]. A greater frequency of high BMI in UIA could be a manifestation of the paradoxical effect of obesity [20] and thus be considered as a variable independent of diabetes and dyslipidemias. Elevated frequencies in UIA patients of cardiovascular [21], chronic obstructive pulmonary disease histories or obesity could either be considered as ultimate "lucky" findings before the SAH onset or on the contrary the witness of patients progressively habituated to these disorders. These disorders generate a high oxidative stress but one can hypothesize that patients being in their 50's, thus still young, can mobilize high levels of antioxidants, women being more resistant than men. This would fit to other findings [22] in which women had a lightly decreased resistance to oxidative stress as compared to men but much less complications during diabetes mellitus.

Neurological symptoms [23] or personal and family history of strokes [24], whatever their origin, [1] are known to be elevated in patients with ICAs underlining the role of vascular dysfunction as well as the potential role of smoking on endothelial cells impairment via oxidative stress [25-27]. This impairment could also correlate with the high rate of tumors either benign or not although it was not noted in a comorbidity analysis from a database [28]. It is known from the studies by Folkman [29,30] that a direct relationship exists between the tumor growth and vasculature growth, abnormal although non-malignant. Even if hemodynamics [31] and geometry [3] are impaired in ICAs the number of endothelial cells must increase when the basal membrane thickness decreases making the vessel wall becoming fragile, mechanisms also present during cancer growth, even additionally increased with abnormal coagulation patterns. Manifestations of calcium (involved in vessel homeostasis and coagulation) disorders were not found elevated in our study.

Other over represented diseases in patients with ICAs could also act alone or as co factors leading to the impairment of basal membranes. Among them hypothyroidism [32] which was more in our whole cohort (7.4%) than in the FPP (0.4-2%) but similar in UIA (4 cases, 6.8%) and in SAH (10%). It correlated well to the rates noted by Newman, et al. [28]. Hypothyroidism affects all metabolic pathways including energy production and thus oxidative stress [33] but also connective tissues growth. An interesting issue was the high number of rare diseases in our cohort, a number that could be underestimated as prevalence of some endocrine diseases might involve rare mechanisms. Some of these associations had already been noted within the literature [8], although scattered, as well as their possible role on structural abnormalities of ICAs vessel wall.

In fact most recorded diseases could either be a cause or a consequence of oxidative stress or connective tissue damages, which is not strange as both are ubiquitous. ICAs would appear in these cases to be part of a more complex syndrome and not simply sporadic. Familial ICAs account for 7 to 20% of aneurysmal SAH and could be a separate entity [34] that could be represented by those of our cohort without any medical or surgical history. However if research looking for family genes is active [35] it leads to an inextricable bush of links, even when only genes involved in the vessel wall are considered [36] even without considering synthesis and synthesis regulation of each of them. Considering genes involved into metabolic pathways, i.e. energy production, could be a better option than studying structural ones as a link between risk factors, genetics and diseases on one hand, and oxidative stress on the other, could then be established. But a simple redox mechanism issued from impairments due to past diseases could explain as well ICA's evolution. This could also explain why atmospheric changes, in appearance mild, following a seasonal and nictemeral rhythm, could lead to a catastrophic cascade of events in patients being in instable metabolic equilibrium at the level of their ICA [6].

This would also explain the role of treatments, particularly surgery that can be considered as a curative treatment of a disease inducing a significant oxidative stress. It induces a short term increased and limited in time oxidative stress but suppresses a long term cause. Prevalence of appendectomies was similar in our cohort in UIA, SAH and in FPP suggesting that there was no bias when reporting surgical events in our study[o]. The number of GAs was elevated in ICA patients as compared to FPP (if ASA score over 2 is considered) but 50% of SAH patients had one when the other half had not. This suggest that GA has no impact on ICA disruption and it correlates well with the protective effect to endothelium described with anesthetics [37]. Among surgical procedures 22% had been for gynecological disorders and it corresponded to only 11% in the SAH group. The significance of an elevated frequency of GA in UIA patients as compared to SAH could thus be that the impact of diseases is abruptly interrupted and

[o]https://www.has-sante.fr/portail/upload/docs/application/pdf/2012-12/rapport_appendicectomie_vd_2012-12-17_16-14-27_74.pdf

thus of shorter duration when surgery was performed, reducing the risk of oxidative stress over a longer period of time and thus the risk of disruption.

Although approved indications barely reflect the number of patients really prescribed with NSAID in the general population, it appears that an over prescription correlates with the over representation of migraines, psychotic disorders or other neurologic diseases. It is not surprising that NSAID are over represented as they are known to impact diseased endothelia nor that platelet aggregation inhibitor [38], and anticoagulants were particularly present in the SAH group. Proton pump inhibitors were not so much prescribed as compared to NSAID and other anti-inflammatory drugs when it should be their main indication. Anticoagulants are largely over prescribed the year preceding the SAH. Incidence of hemorrhages directly anticoagulant-related is estimated to 4% per year[P] but 8.5 in our cohort to which one could add the 14.5% of acetyl salicylic acid prescribed patients. This suggests that SAH under anticoagulants, are the complications of ICAs rather than a direct consequence of anticoagulant treatment.

Finally substitutive hormonal treatments followed the rate of hypothyroidisms and are over represented. Considering the multiple roles of thyroid hormone, it is difficult to identify a precise mechanism although a direct role on the vessel wall structure would not be unrealistic [39].

## Conclusion

If one cannot exclude that some would exert a mechanistic effect on predisposed persons, risk factors must be revisited, eventually on a per country basis since some of those classically described do not appear more frequent in patients with an ICA than in the FPP. In addition some diseases, not yet considered as risk factors, seem to be overrepresented in our cohort as well as in recent retrospective studies [28]. Therefore one cannot exclude that a number of ICAs would be a part of a more systemic and complex syndrome. From this point of view a redox process impairing particularly connective tissues could be a possibility. Oxidative end products issued from the metabolism are known to act on structures or tissues of long lifetime, among them collagen, smooth muscle cells and endothelial cells allowing thus cumulative effects. The more frequently ill you are, the more ill and the more at risk of having an ICA you will be. A better knowledge of comorbidities, helped by large databases, considering diseases not as entities separated from each other but sharing common denominators, could lead to a better understanding of ICAs physiopathology and thus to an appropriate preventive strategy. The development of the so-called "big data" would thus be of critical importance in the epidemiology and nosology of ICAs.

[P]http://ansm.sante.fr/Dossiers/Les-anticoagulants/Les-anticoagulants-en-France-Etudes-et-surveillance/%28offset%29/0


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