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Received, January 30, 2020.
Accepted, February 3, 2020.

Prediction of Unruptured Intracranial Aneurysm Evolution: The UCAN Project

BACKGROUND: Management of small (<7 mm) unruptured intracranial aneurysms (UIA) remains controversial. Retrospective studies have suggested that post gadolinium arterial wall enhancement (AWE) of UIA on magnetic resonance imaging (MRI) may reflect aneurysm wall instability, and hence may highlight a higher risk of UIA growth. This trial aims at exploring wall imaging findings of UIAs with consecutive follow-up to substantiate these assumptions.

OBJECTIVE: To develop diagnostic and predictive tools for the risk of IA evolution. Our aim is to demonstrate in clinical practice the predictive value of AWE for UIA growth. The growth will be determined by any modification of the UIA measurement. UIA growth and the UIA wall enhancement will be assessed in consensus by 2 expert neuroradiologists.

METHODS: The French prospective UCAN project is a noninterventional international wide and multicentric cohort. UIA of bifurcation between 3 and 7 mm for whom a clinical and imaging follow-up without occlusion treatment was scheduled by local multidisciplinary staff will be included. Extensive clinical, biological, and imaging data will be recorded during a 3-yr follow-up.

EXPECTED OUTCOMES: Discovering to improve the efficiency of UIA follow-up by identifying additional clinical, imaging, biological, and anatomic risk factors of UIA growth.

DISCUSSION: A prospective nationwide recruitment allows for the inclusion of a large cohort of patients with UIA. It will combine clinical phenotyping and specific imaging with AWE screening. It will enable to exploit metadata and to explore some pathophysiological pathways by crossing clinical, genetic, biological, and imaging information.

KEY WORDS: Aneurysm, Trial, MRI, Growth, Intracranial aneurysm, Wall enhancement, CAWE

Neurosurgery 0:1–7, 2020 DOI:10.1093/neuros/nyaa093 www.neurosurgery-online.com

GENERAL INFORMATION

Study Dates

Recruitment phase: August 2019 to august 2021, this study is ongoing

Follow-up phase: August 2020 to April 2024

Funding Agencies

This study was supported by a grant from the French Ministry of Health (U-CAN, 2019, PHRC-19-0394)

ABBREVIATIONS: AWE, arterial wall enhancement; **CAWE,** circumferential arterial wall enhancement; **CI,** confidence interval; **EQ-5D,** EuroQol-5D; **MRI,** magnetic resonance imaging; **QOL,** quality of life; **UIA,** unruptured intracranial aneurysm

Supplemental digital content is available for this article at www.neurosurgery-online.com.

Registry

(Clinical Trial) NCT02712892

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The overall prevalence of unruptured intracranial aneurysm (UIA) is estimated to be between 2% and 4% in the general population.[1,2] IA rupture is a devastating event with a mortality rate as high as 40%.[3] Therefore, prediction and thus prevention of IA rupture is an interesting way of research to reduce the impact of this serious complication. Currently, the management or the follow-up for asymptomatic UIA is still based on the benefit-risk balance without clear guidelines.[4-6]

According to the natural history model for IA proposed by Yonekura et al,[7] IA may remain stable for a long time after formation, may form and grow before rupture, or may rupture immediately after aneurysm formation. Consequently, the growth of IA could be used as an imaging marker and may predict the risk of rupture. A systematic review from Gondar et al[8] with the follow-up of 3855 patients identified an estimation of a yearly growth probability of 3.85% (95% CI 3.4% to 4.3%).[8] Hence, follow-up imaging of untreated UIAs is recommended, several studies having suggested that growing UIAs have an increased risk of rupture.[9-12] According to Inoue et al[13] and Villablanca et al,[12] UIA growth increases the risk of rupture by a factor 10 and the annual rupture rate for a growing UIA ranges between 2.4% and 18% per patient-year. Furthermore, in a meta-analysis with 4990 IAs, the annual risk of rupture was associated with over a 30-fold higher when UIAs were growing than stable.[14] However, guidelines from the American Heart Association and European Stroke Organization lack recommendations on which patients' follow-up imaging should be considered for and at what time interval it should be performed.[9,15]

In this context, the identification of a specific individual-based marker for higher risk of IA growth can help to the therapeutic choice. A performant imaging marker for UIA instability would permit physicians to choose between conservative management and requiring invasive treatment to prevent rupture.

Preliminary studies have demonstrated that aneurysmal wall enhancement (AWE), using high-resolution vessel wall magnetic resonance imaging (MRI), is linked to IA instability (ie, ruptured, symptomatic, or growing over time). Indeed, some studies that included ruptured IAs and UIAs studied by a 3.0-T MRI with vessel wall sequences suggest that circumferential aneurysmal wall enhancement (CAWE) was more frequently present in unstable rather than in stable IAs.[16-19] In a study focused on a large monocentric cohort of more than 300 UIAs, it was demonstrated that strong CAWE was a more specific marker to discriminate stable from unstable UIAs (specificity 84.4%).[20]

STUDY GOALS AND OBJECTIVES

In order to bring to light specific biomarkers of instability, a prospective multicentric study warrants the demonstration in clinical practice of the predictive value of AWE for UIA growth. Such an investigation will allow to set up a secure, efficient, and personalized follow-up for each IA. Having an individual-based imaging marker for UIA instability would permit physicians to characterize and discriminate IA as appropriate for conservative management or as requiring invasive treatment to prevent rupture.

STUDY DESIGN

The French prospective UCAN project is a noninterventional international wide and multicentric prospective cohort.

Objectives and Endpoints

Primary Objective

Our aim is to evaluate in clinical practice the predictive value of UIA wall enhancement for UIA growth. It will allow setting up a secure, efficient, and personalized follow-up.

Primary Endpoint

In order to evaluate the informative value of AWE for UIA growth, we will consider as primary endpoint the growth of the UIA after the complete follow-up at 3 yr. This event could occur at any time during the follow-up if an UIA becomes symptomatic but will be systematically assessed at 1 and 3 yr by MRI. UIA growth will be assessed blindly and independently by 2 expert neuroradiologists, routinely involved in UIA management and disagreement will be solved by consensus with involvement of a third expert. UIA wall enhancement status will be defined independently by 2 different expert neuroradiologists, with >5 yr experience in intracranial vessel wall imaging. Disagreement will be solved by consensus with involvement of a third expert.

Secondary Objectives

- Determination of clinical, genetics, or biological factors related to the growth of UIA.
- Determination of clinical, genetics, or biological factors related to rupture of UIA.
- Evaluation of the quality of life (QOL) of untreated patients with UIA during the follow-up.
- Detection of other AWE variation patterns related to growth during the follow-up in order to improve the follow-up of UIA patients.

Secondary Endpoints

- Clinical, genetic (blood serum level of circulating ANGPTL6), and biological (plasma factors as circulating ANGPTL6 levels, metalloproteinase) features recorded.
- Incidence of growth, stratified by clinical, genetics, or biological features.
- Incidence of IA rupture, stratified by clinical, genetics, or biological features.
- Completion of standardized EuroQol-5D (EQ-5D) questionnaire to measure QOL patients (50)

- Construction and evaluation of an automatized tool of AWE patterns, as compared to the visual analysis of experts, in the form of a decision-making tool.

Definition of UIA and AWE

A typical UIA is a saccular arterial dilatation localized at an intracranial bifurcation. The phenotyping of UIA is performed in each center by experienced interventional neuroradiologists, neurologists, and neurosurgeons to exclude other IA types (ie, fusiform-shaped, dissection) and to include only typical UIA.

The definition of AWE is broad, encompasses both thin and thick, partial or circumferential enhancements, and does not capture focal eccentric enhancement. In a recent study focused on patients with UIA, a thick (>1 mm) circumferential pattern of wall enhancement demonstrated the highest specificity for differentiating between stable and unstable UIA.[20]

In this study, the presence of AWE will be graded with the classification proposed by Edjlali et al.[20]

Inclusion and Exclusion Criteria

The recruited population is composed of subjects carrying unruptured asymptomatic typical IA of bifurcation for whom a clinical, a biological, and an imaging follow-up, without occlusion treatment, was scheduled by local multidisciplinary staff.

Inclusion Criteria

- Subject carrying unruptured, asymptomatic, and untreated typical IA of bifurcation, measured on conventional imaging (MRI, computed tomographic angiography, or digital subtraction angiography) between 3 and 7 mm of larger diameter.
- Ability to be followed up during 3 yr decided in consensus multidisciplinary gathering.
- Age > 18 yr old.
- UIA discovery less than 24 mo ago.

Noninclusion Criteria

- A failure to obtain informed consent.
- Contraindications for undergoing an MRI scan include heart pacemaker, a metallic foreign body (metal sliver) in their eye, or aneurysm clip in their brain (severe claustrophobia)
- Contraindications for a gadolinium contrast medium injection (estimated glomerular filtration rate below 30 mL/min/1.73 m^2, previous or pre-existing nephrogenic systemic fibrosis, previous anaphylactic/anaphylactoid reaction to gadolinium containing contrast agent, acutely deteriorating renal function, pregnancy and breast-feeding)
- A fusiform-shaped, mycotic, or IA in relation with an arteriovenous malformation dissecting IA
- A family history of Ehlers-Danlos syndrome, polycystic kidney disease, fibromuscular dysplasia, Marfan's syndrome, or moyamoya disease.
- Intracavernous UIA because the sinus cavernous that is fulfilled with venous blood precluded a reliable assessment of AWE.
- Partially or completely thrombosed UIA because of the inherent enhancement of the parietal layer in that case.

METHODOLOGY

This study presents the following characteristics: international, multicentric, and prospective cohort.

Data Recorded

Clinical Data

Data related to environmental risk factors are collected for each included patient like smoking history, parameters such as high blood pressure, diabetes mellitus, hypercholesterolemia, alcohol consumption, and body mass index. In order to better interpret the apparition of the contrast enhancement of the UIA, a very precise interview will be carried out to unravel recent infections, dental care, or any other acute as well as chronical or recent event that can lead to inflammatory reactions. In case of multianeurysm in one patient, if one aneurysm is treated during the study, follow-up of other untreated aneurysms will be maintained. If all aneurysms of one patient are treated during the study, research follow-up will be suspended. Information about treatment will be collected. Moreover, the standardized EQ-5D questionnaire will be administrated in order to measure the impact of follow-up on patient's QOL.

Biological Data

The biocollection will consist of blood sampling: 10 mL for DNA analysis during the inclusion (V0), and 10 mL of plasma at each visit (V0, V1 at 1 yr and V2 at 3 yr).

Imaging Data

Sequences will be made coherent for each center and each MRI, to optimize the evaluation of AWE. Imaging the vessel wall implicates a 3T MRI with specific 3D T1 fast spin echo sequence, realized before and after gadolinium injection. Hence, the spatial resolution is crucial for the analysis of such a small vessel part, and every participating center will have to obtain a 3D T1 fast spin echo sequence with a spatial resolution of at least 0.9 × 0.9 × 1 mm. Such sequence usually lasts 5 min. The optimal protocol will follow these parameters: field of view, 23 × 23 × 16 cm^3; repetition time/echo time, 600/11.5 ms; spatial resolution: 0.45 × 0.45 × 0.5 mm; matrix, 288 × 288 × 160 interpolated to 512 × 512 × 320.

DISCUSSION

With the UCAN project and using a combination of innovative aspects in terms of approach, interdisciplinary collaboration, and technologies, we aim to improve the prediction of IA growth by

identifying advanced but routinely accessible imaging parameters as well as clinical, anatomic, and biological risk factors for IA growth. This project establishes new directions for optimal and personalized management of UIAs to decrease the impact of futile follow-up and the risk of unrecognized, evolving UIA. Overall, we could also expect to improve the impact of follow-up on the patient's QOL.

TRIAL STATUS

This is an ongoing study.

SAFETY CONSIDERATIONS

No adverse event or reaction can be associated with this study as it consists on a noninterventional study with no impact on care. The onset of an adverse reaction associated with patient care in the course of this protocol shall be reported in the suitable vigilance system (pharmacovigilance, biovigilance, hemovigilance, medical device vigilance, etc).

FOLLOW-UP

Three visits are planned.

Visit 0: MRI with contrast injection, Blood sampling for serum, plasma, and genetics
Visit 1: 1 yr after inclusion, MRI with contrast injection, blood sampling for serum and plasma
Visit 2: 3 yr after inclusion, MRI with contrast injection, blood sampling for serum and plasma

DATA MANAGEMENT AND STATISTICAL ANALYSIS

This is a prospective, multicenter cohort study with 1000 patients.

A review of the data will be conducted at the end of the study, before the statistical analysis. During this review, the following will be present: principal investigator, project manager, clinical research associate (CRA) monitoring, data manager, a statistician, and anyone concerned with the protocol. The aim will be to review the progress of the study on the possible problems and classify possible deviations in minor or major.

Demographic, clinical, MRI, genetics, or biological data will be recorded per patient. For categorical and binary variables, counts and percentages will be calculated. For continuous variables, means, standard deviations, the minimum and maximum, medians, and interquartile range will be calculated. For binary variables such as gender, counts, percentages, and 95% CIs will be calculated, and *P*-values may be presented for hypothesis generating purposes. Pearson's chi-squared test or Fisher's exact test will be performed when appropriate. The Mann-Whitney U and t-tests will be performed to test for statistical differences in continuous parameters (based on distribution and count). For patients lost to follow-up, the status of the last follow-up examination will be recorded. Analyses will be performed using the R statistics software (R Foundation for Statistical Computing, Vienna, Austria) through the Rstudio interface (RStudio, Inc., Boston, Massachusetts).

No interim analysis is planned.

Principal Analysis on Primary Endpoint

Our aim is to demonstrate in clinical practice the predictive value of UIA wall enhancement for UIA growth. The growth will be determined by any modification of the UIA measurement at the end of the follow-up and categorized as present/absent. UIA wall enhancement will be assessed in consensus by 2 expert neuroradiologists and categorized as present/absent.

To demonstrate the predictive value of AWE for UIA growth, we will measure the ability of AWE to discriminate between stable and unstable UIA through a diagnostic accuracy study. We will compute sensitivity, specificity, accuracy, and negative and positive predictive values for presence/absence of AWE to identify unstable status. Related 95% CI for each measure will be calculated using the binomial Clopper-Pearson method.[21] The association between AWE and UIA growth will be tested through a Pearson's chi-squared test or Cochran-Mantel-Haenszel test, if stratification is necessary. Monte Carlo simulation method will be used for estimating *P*-values.

Intra and inter-reader agreement for presence/absence for AWE and, separately, for growing status will be assessed calculating intra/interclass correlation by Cohen Ķ.

Analysis of Secondary Endpoints

Determination of clinical, genetics, or biological factors related to the growth of UIA.

Conditional univariate logistic regression models will be applied to explore the putative association between UIA growth and patient clinical, genetic, and biological features. A multiple logistic regression model will be thus applied to identify patient characteristics and assess their combined effect on UIA growth. Age and sex will be considered as confounder variables.

Determination of clinical, genetics, or biological factors related to rupture of UIA.

The same methods will be used also to identify patients characteristics related to rupture of UIA.

Evaluation of the QOL of untreated patients with UIA during the follow-up.

Responses to the EQ-5D questionnaire will be analyzed in order to determine the evolution of patient's QOL during the follow-up. Differences will be measured between 2 different intervals of follow-up. Detection of other AWE variation patterns related to growth during the follow-up. Based on the large sample size, the prospective and standardized follow-up, and the number of accurate variables registered in UCAN, we will integrate the whole of the recorded anatomic and clinical data in order to enrich the predicting strategy in the form of a risk score. The large

number of variables will be used in order to identify combinations of markers that can help with predicting growth (and ultimately rupture). If such (most likely nonlinear) combinations of variables exist, they can be a great help in managing UIA prevention. Given the large number of variables and the variability in distribution of their shapes (normal, multimodal, categorical, etc), we will adopt decision methods such as multidimensional reduction methods or regression trees. As a result, we hope to identify a subset of variables—possibly assembled into a score—which can determine AWE patterns and thus predict the UIA growth.

Statistical Justification of the Number of Inclusions

We know from precedent studies[20] that 17% of individuals with AWE manifest an unstable UIA. Among individuals without AWE, the proportion of unstable UIA is 5%. A sample size of almost 300 patients is needed to show a significant difference of the proportion of unstable UIA between AWE and not AWE patients ($\beta = 90\%$ and $\alpha = 5\%$). From the same study, we know that any UIA wall enhancement was seen in 42% and UIA instability was encountered in 10% of UIA patients. To have enough unstable UIA to make multivariate analysis, we can expect more than 50 evolutions among UIA. With 1000 patients, we can expect between 50 and 75 evolutions and 420 to 450 apparitions of any enhancement.

Moreover, the current data from the literature give estimations of the specificity of AWE to discriminate between unstable and stable UIA between 60% and 85%.[20] In our selected population, we expect this proportion, ie, the proportion of negative AWE among not growing UIA, to be at least the same after 3-yr follow-up. With an alpha risk set to 0.05 and an expected specificity of 60%, a population size of 1000 patients will give us a total width of CI of 6% [95% CI 56.9%-63.1%], using binomial (Clopper-Pearson) "exact" calculation (see **Table**, **Supplemental Digital Content** for a summary of 95% CI according to different scenarios, supplementary data).

The expected level of statistical significance is 5%.

The image analysis is ensured by

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QUALITY ASSURANCE

A monitoring shall be carried out by the Research Division Promotion Department. A CRA will remotely conduct quality control on the data reported in the case report forms. The monitoring plan is defined in close cooperation between the study team and the responsible institution according to the objectives of the study, based on an internal Research Division procedure.

The onsite monitoring visits shall be organized after making arrangements with the investigator. The CRA should be able to consult on each site:

- the enrolled patients' data compilation records,
- the patients' medical and nursing files,
- the investigator file.

Within the scope of this study, an inspection or audit may be conducted. The sponsor and/or participating centers should be able to provide inspectors or auditors with access to the data.

EXPECTED OUTCOMES OF THE STUDY

We expect to improve the UIA follow-up and management by identifying additional clinical, anatomic, biological, and imaging factors of UIA growth. This project is designed to establish new individual biomarkers including imaging biomarkers for optimal early recognition of UIAs prone to evolve, in order to improve UIA management, and will use a combination of innovative aspects in terms of approach, interdisciplinary collaboration, and technology. It will provide novel tools for identification of high-risk individuals and for improving efficiency of UIA follow-up. The gain in knowledge on additional risk factors will also pave the way for novel, noninvasive treatment strategies and timing of treatment in future clinical practice.

DURATION OF THE PROJECT

The period of the study will be 5 yr. We have scheduled a recruitment period of 2 yr (August 2019 to August 2021) and a follow-up period of 3 yr.

PROJECT MANAGEMENT

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ETHICS

Patient Information

The investigator undertakes to inform the patient of the protocol in clear and accurate terms (information form appended). The investigator shall provide the patient with a copy of the information form. This document shall specify to the patient that he/she has the option of refusing to take part in the study and can withdraw at any time.

Ethical Review Board

The sponsor commits to submit the study project to the prior authorization of an ethical review board. The information sent concern on one hand the modalities and the nature of the research, and, on the other hand, the guarantees planned for the persons taking part in the study.

Source Data and Document Access Rights

Each patient's medical data shall only be provided to the affiliated body of the study director or any person duly authorized thereby, in confidential conditions. If applicable, the affiliated body of the director may request direct access to the medical file for the purposes of verification of the procedures and/or data in respect of the clinical trial, without breaching confidentiality and within the limits authorized by the legislation and regulations.

Computerized data and submission to the French data protection authority (CNIL)

The data gathered during the study shall be held on computerized file, as per the 2004 amendment of the French data protection act of January 6, 1978, the law n° 2018-493 of June 20, 2018 on the Protection of Personal Data and Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016 on the protection of individuals with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation). The protocol falls within the scope of the MR004 methodology applied by.

Disclosures

This study was supported by a grant from the French Ministry of Health (U-CAN, 2019, PHRC-19-0394). The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Acknowledgments

We are also grateful to the UCAN collaborators, consisting of Bourcier R, Daumas-Duport B, Lenoble C, Alexandre PL, Detraz L, Pellerin A,

Lintia-Gaultier A, Auffray-Calvier E, Aguilar J, Desal H (University Hospital of Nantes); Pasco A, L'Allinec V, Tanguy J-Y, Labriffe M, Girot JB (University Hospital of Angers); Anxionnat R, Tonnelet R, Derelle AL, Barbier C, Bracard S, Gory B (University Hospital of Nancy); Ferré JC, Raoult H, Eugène F, Gauvrit JY, Paya C (University Hospital of Rennes); Gentric JC, Ognard J, Douraied B (University Hospital of Brest); Chivot C (University Hospital of Amiens); Papagiannaki C, Gerardin E (University Hospital of Rouen); Januel AC, Bonneville F, Cognard C, Michelozzi C, Darcourt J (University Hospital of Toulouse); Levrier O, Aguettaz P (Hospital of Clairval, Marseille); Naggara O, Trystram D, Rodriguez-Regent C, Ben Hassen W, Boulouis G, Meder JF (Saint Anne Hospital—Paris); Rouchaud A, Mounayer C, Saleme S (University Hospital of Limoges); Houdart E, Labeyrie MA (University Hospital of Lariboisière AP-HP); Pierot L, Soize S (University hospital of Reims); ariel F, Barreau X, Berge J, Marnat G (University hospital of Bordeaux); Caroff G, Spelle L, Ozanne A (University hospital of Kremlin Bicêtre, AP-HP); Shotar E, Clarencon F (University Hospital of Pitié Salpétriere, AP-HP); Herbreteau D, Janot K, Cottier JP (University hospital of Tours); Desilles JP, Blanc R, Piotin M (Fondation Roschild – Paris)

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Supplemental Digital Content. Table. Accuracy of the estimator of the specificity of AWE in our population, based on the hypothesis of 1000 included patients (binomial Clopper-Pearson approximation for 95% CI estimation).