Pathomechanisms Behind Cognitive Disorders Following Ruptured Anterior Communicating Aneurysms: A Diffusion Tensor Imaging Study

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Keywords

Subarachnoid Hemorrhage; MRI; Cognition; Aneurysm

Highlights

- Cognitive disorders are underestimated in the aftermath of an aneurysmal rupture of the anterior communicating complex
- When morphological MR sequences are normal, diffusion tensor imaging might still show signs of microscopic injuries
- Axonal injuries seem to be diffuse, but appear more severe in frontal areas, close to the site of rupture

Declarations

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Consent for publication : All authors of the manuscript gave consent for publication

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ABSTRACT

Introduction

After the rupture of anterior communicating aneurysms, most patients experience debilitating cognitive disorders; and sometimes even without showing morphological anomaly on MRI examinations. Diffusion Tensor Imaging (DTI) may help understanding the pathomechanisms leading to such disorders in this subset of patients.

Methods

After independent assessment, we constituted a population of patients with normal morphological imaging (ACOM group). Then, a case-control study comparing volumetric and voxel-based DTI parameters between the ACOM group and a control population was performed. All patients underwent the full imaging and neuropsychological assessments at 6 months after the aneurysm rupture. Results were considered significant when $p<2.02.10^{-4}$.

Results

Twelve patients were included in the ACOM group: 75% had at least one disabled cognitive domain. Significant differences in DTI parameters of global white matter were noted (average Fractional Anisotropy: 0.915 [±0.05] in ACOM group versus 0.943 (±0.03); $p=1.10^{-5}$) and in frontal white matter tracts (superior fronto-occipital fasciculus and anterior parts of the corona radiata) as well as in the fornix.

Conclusion

Cognitive disorders are under-estimated, and DTI confirmed that, even when conventional MRI examinations were normal, there were still signs of diffuse neuronal injuries that seemed to dominate in frontal areas, close to the site of rupture.

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is the most frequent cause of spontaneous SAH and therefore, its prognosis is extremely unfavorable[1]. In the following months after initial management, two types of patients can be identified: patients who had a severe aneurysm rupture that required heavy care and prolonged hospital stays, therefore more willingly exposed to complications; and who subsequently evolve towards severe disability; and patients for whom the initial presentation and evolution were favorable, and could be discharged free of any objective neurological symptoms. Within this latter group, we commonly noticed during the follow-up, that, although they feature no morphological anomaly on conventional brain Magnetic Resonance Imaging (MRI), they frequently present with neuropsychological and neuropsychiatric disorders that may have disastrous consequences on their quality of life [2–4]. It was particularly noted in series of aneurysm rupture of the anterior communicating complex, possibly related to the immediate vicinity to the frontal lobes, the corpus callosum as well as the frontal part of the circuit of Papez [5,6].

In this domain, Diffusion Tensor Imaging (DTI), could be valuable to explore such disorders that cannot be explained on basic morphological MRI sequences. Accurately detecting the underlying lesions by means of modern imaging technique could be of great use for such patients, as swift management has been proven to promote functional recovery and quality of life [7].

The aim of the study was to compare volumetric and DTI parameters in a population of patients with normal morphological MRIs at 6 months after an aneurysm rupture of the anterior communicating complex, to a healthy control population.

METHODS

The manuscript was prepared according to the STROBE guidelines.

ACOM study

The ACOM study is a monocenter, prospective registry that consecutively included patients with ruptured aneurysms of the anterior communicating complex from 2013 to 2015. Main inclusion criteria were: 1) Age ≥18 years 2) modified Rankin Scale 0-2 and Glasgow Outcome Scale Extended 4-5 at 6 months. Six months after the aSAH, patients included underwent an extensive MRI workup with 3D-T1, Fluid Attenuated Inversion Recovery and DTI sequences as well as full neuropsychological and psychiatric assessments. Key exclusion criteria included contraindication to MRI, surgical clipping and inability to undergo neuropsychological assessment for any reason.

Exploration protocol of the ACOM study

Demographics, clinical and radiological data were prospectively collected. Glasgow Coma scale, World Federation of Neurological Surgeons (WFNS) score were evaluated at admission, GOSE and mRS were both performed at 3 and 6 months

All patients underwent the same standardized imaging protocol 6 months after the aneurysm rupture. All examinations were performed on the same 3 Tesla MRI (SIGNA HDX Advantage, General Electric, USA). Standard protocol of exploration included axial T2 Fluid Attenuated Inversion Recovery (FLAIR), 3D T1 Fast Spoiled Gradient echo (FSPGR), Time of Flight MR angiography, and steady state blood-oxygen-level dependent MR sequences. For DTI, technical parameters were as follows: whole brain axial acquisitions perpendicularly to $\overrightarrow{B0}$ with b=1000 mm^2/s applied in 50 directions; 2.5mm thickness axial slices; matrix: 128x128. Two additional

volumes were acquired at b=0. ASSET parallel imaging was acquired with an acceleration factor of 2. Field of view was 280mm, repetition time: 14000ms and echo time: 85ms.

Various post-processing steps for DTI were performed using Comasoft software (Institut Français de Bioinformatique, France) including motions and eddy currents corrections, segmentation and bone extraction, DTI scalar parameters estimation (Fractional Anisotropy [FA], Mean Diffusivity [MD], axial diffusivity [L1] and radial diffusivity [Lt]), spatial normalization using the FMRIB58_FA (Oxford, UK)[8] template and finally segmentation and averaging of the scalar parameters. Volumetric data were extracted from 3D T1 Fast Spoiled Gradient echo sequences. Freesurfer (Laboratory for Computational Neuroimaging at Harvard, Boston, USA)[9] was used for global analysis of volumetric and DTI scalar parameters, whereas for regional and tract-based analysis of the white matter, the JHU tool (Center for Imaging Science, John Hopkins University, USA)[10] was utilized. Comasoft was also used for generating maps and atlases of DTI scalar parameters.

~~Additional details are available in **Supplementary File.**~~ Furthermore, all patients included were evaluated 6 months after aneurysmal rupture by a neuropsychologist, blinded to any radiological data. Neuropsychological assessment was independently performed by a neurologist (C.A) and a neuropsychologist (A.G) and included the following tests: Mini Mental State Examination, Frontal Assessment Battery, Rey's and 5 words tests, TMT and fluency tests, Wisconsin Card sorting test, Stroop's and Hayling's tests, Theory of Mind test, SEA and Starkstein's test. For neuropsychiatric assessment, anxiety disorders as well as depression were evaluated according to DSM-V classification of mental disorders. Post-traumatic stress disorder (PTSD) was specifically assessed using Horowitz' test.

Present study

The protocol for the presented study was divided in two parts:

1) Constitution of the incident population (ACOM group) after independent reviewing by two neuroradiologists (K.P and F.C). Both investigators reviewed the MRIs of all patients included in the ACOM study and were asked to exclude patients featuring one of the following criteria: 1) Cumulated volume of parenchymal FLAIR hyperintensities > 5 ml 2) Major artifacts on DTI sequences.
2) Case-control (1:2) study comparing T1 volumetric and DTI parameters in the ACOM group in comparison to a control group of healthy volunteers. The control population was composed of 24 healthy adult volunteers who all underwent the exact same imaging protocol.

Figure 1. summarizes the flow of patients included in the study

Statistical analysis

Statistical analysis was performed using EPI Info Software (Version 7.2.3.1, Center for Disease Control and Prevention, Atlanta, USA). Inter-observer correlations kappa coefficients with their 95% confidence intervals were estimated using Cohen's test. Results were considered significant when $p<0.05$.

For comparative analysis, equality of variances was tested using Levene's test. Then, a non-parametric Mann-Whitney U test was performed for comparisons. Adjustment for multi-testing using Bonferroni method was performed and results were considered significant when $p<2.02.10^{-4}$.

Ethical Statement

The protocol of the ACOM study was approved by the local Institutional Review Board (N°040114). All patients included gave written informed consent.

Results

After independent reviewing, inter observer correlation was perfect for patients to exclude from analysis (κ=1). Twelve patients (ACOM group) were finally included (mean age: 53.2 ± 10.4 years) and were compared to 24 healthy volunteers (mean age: 37.0 ±11.1 years). Baseline characteristics of patients ~~and flow of inclusions~~ in the ACOM group are ~~available in **Supplementary File**~~ featured in **Table 1.** There was no difference in global or regional volumes that reached the level of significance.

Of over 240 comparisons of MRI parameters (Volumetric and DTI scalar), **T~~T~~able ~~1~~2.** summarizes the statistically significant ~~differen~~one~~e~~s ~~in DTI parameters~~. On global white matter analysis, differences were found in: global white matter mean Fractional Anisotropy (FA) was significantly lower in the ACOM group (0.915 [±0.05] versus 0.943 [±0.03]; $p=1.10^{-5}$) which was confirmed in hemispherical analysis. On white matter tracts analysis, there were significant differences in the corpus callosum (body of corpus callosum mean FA: 0.900 [±0.06] versus 0.965 [±0.05]; $p=2.10^{-4}$), both anterior parts of the corona radiata (ACR) (right ACR mean FA: 0.873 [±0.10] versus 1.029 [±0.06]; $p=1.10^{-5}$; left ACR mean FA: 0.848 [±0.04] versus 1.000 [±0.07]; $p<1.10^{-5}$), both superior fronto-occipital fasciculus (SFOF) (left SFOF mean FA: 0.847 [±0.11] versus 0.965 [±0.06]; $p= 1.10^{-4}$; right SFOF mean FA: 0.894 [±0.09] versus 0.997 [±0.06]) and finally in the striae terminalis (Fx-ST) of the fornix (right Fx-ST mean FA: 0.914 [±0.08] versus 0.990 [±0.05], $p= 1.10^{-5}$; right Fx-ST mean MD: 1.095 [±0.04] versus 0.984 [±0.05]; $p=2.10^{-4}$; left Fx-ST mean FA: 0.894 [±0.09] versus 0.964 [±0.05], $p= 1.10^{-5}$; left Fx-ST mean MD: 1.095 [±0.07] versus 1.024 [±0.06]; $p= 2.10^{-4}$).

Figure~~s~~ ~~1~~2 and 3. illustrate~~s~~ these findings in ~~two~~ several ACOM patients.

Table 1. Baseline characteristics of the incident population (ACOM group)

Parameter	
Age (years ± S.D)	53.2 ±10.4
WFNS grade (n, %)	
-I	4 (33.3%)
-II	4 (33.3%)
-III	3 (25%)
-IV	1 (8.3%)
-V	0
Fisher Score (n, %)	
-I	2 (16.7%)
-II	1 (8.3%)
-III	2 (16.7%)
-IV	7 (58.3%)
Hydrocephalus at admission (n, %)	2 (16.7%)
Intra-ventricular haemorrhage (n, %)	7 (58.3%)
External ventricular drain (n, %)	7 (58.3%)
Neuropsychological impairement (n, %)	
-None	3 (25%)
-Moderate (1 or 2 domains concerned)	6 (50%)
-Severe (>2 domains)	3 (25%)
Psychiatric disorder (n, %)	
-Depression	6 (50%)
-Post-traumatic stress disorder	3 (25%)

S.D: Standard Deviation; WFNS: World Federation of Neurological Surgeons

Table ~~1~~2. Summary of the main significant differences ($p<2.02.10^{-4}$) in DTI parameters

Parameter	*ACOM group (n=12)*	*Control group (n=24)*	*p-value*
Global analysis			
Global white matter -FA (±S.D.)	0.915 (±0.05)	0.943 (±0.03)	1.10^{-5}
Left hemisphere white matter -FA (±S.D.)	0.915 (±0.05)	0.947 (±0.03)	2.10^{-4}
Right hemisphere white matter -FA (±S.D.)	0.915 (±0.06)	0.939 (±0.03)	2.10^{-4}
Regional analysis			
Corpus callosum • Body -FA (±S.D.) -Lt (±S.D.) • Splenium -FA (±S.D.) -Lt (±S.D.)	 0.900 (±0.06) 1.141 (±0.10) 0.941 (±0.03) 1.166 (±0.11)	 0.965 (±0.05) 1.048 (±0.08) 0.950 (±0.03) 1.083 (±0.07)	 2.10^{-4} 3.10^{-5} 3.10^{-5} 2.10^{-4}
Corona radiata • Anterior part ○ Left -FA (±S.D.) -MD (±S.D.) -Lt (±S.D.) ○ Right -FA (±S.D.) -MD (±S.D.) -Lt (±S.D.) • Posterior part ○ Left -MD (±S.D.) -Lt (±S.D.) ○ Right -MD (±S.D.) -Lt (±S.D.)	 0.848 (±0.04) 1.113 (±0.08) 1.193 (±0.11) 0.873 (±0.10) 1.100 (±0.07) 1.163 (±0.11) 1.095 (±0.05) 1.116 (±0.08) 1.093 (±0.05) 1.106 (±0.07)	 1.000 (±0.07) 1.012 (±0.03) 1.012 (±0.06) 1.029 (±0.06) 1.007 (±0.03) 0.992 (±0.04) 1.008 (±0.03) 1.057 (±0.05) 0.997 (±0.04) 1.990 (±0.05)	 $<1.10^{-5}$ 8.10^{-5} 1.10^{-5} 1.10^{-5} 2.10^{-4} 6.10^{-5} 2.10^{-4} 1.10^{-5} $<1.10^{-5}$ 2.10^{-5}
Posterior thalamic radiations ○ Left -FA (±S.D.) -MD (±S.D.) -Lt (±S.D.) ○ Right -FA (±S.D.) -MD (±S.D.) -Lt (±S.D.)	 0.909 (±0.04) 1.074 (±0.05) 1.124 (±0.09) 0.909 (±0.04) 1.075 (±0.05) 1.145 (±0.09)	 0.940 (±0.04) 1.020 (±0.04) 1.058 (±0.06) 0.937 (±0.05) 1.024 (±0.04) 1.069 (±0.07)	 1.10^{-5} 8.10^{-5} 1.10^{-4} 1.10^{-5} 2.10^{-5} $<1.10^{-5}$
Internal capsule			

• Anterior limb			
○ Left			
-FA (±S.D.)	0.926 (±0.07)	0.996 (±0.03)	5.10^{-5}
○ Right			
-FA (±S.D.)	0.944 (±0.05)	0.996 (±0.03)	6.10^{-5}
Superior fronto-occipital fasciculus			
○ Left			
-FA (±S.D.)	0.847 (±0.11)	0.965 (±0.06)	1.10^{-4}
-MD (±S.D.)	1.161 (±0.13)	1.016 (±0.05)	2.10^{-4}
-Lt (±S.D.)	1.255 (±0.17)	1.030 (±0.07)	4.10^{-5}
○ Right			
-FA (±S.D.)	0.894 (±0.09)	0.997 (±0.06)	1.10^{-4}
-MD (±S.D.)	1.113 (±0.10)	1.002 (±0.04)	1.10^{-5}
-Lt (±S.D.)	1.174 (±0.13)	1.003 (±0.06)	7.10^{-5}
Fornix (*Stria terminalis*)			
○ Left			
-FA (±S.D.)	0.894 (±0.09)	0.964 (±0.05)	1.10^{-5}
-MD (±S.D.)	1.095 (±0.07)	1.024 (±0.06)	2.10^{-4}
-Lt (±S.D.)	1.182 (±0.17)	1.046 (±0.07)	1.10^{-5}
○ Right			
-FA (±S.D.)	0.914 (±0.08)	0.990 (±0.05)	7.10^{-5}
-MD (±S.D.)	1.095 (±0.04)	0.984 (±0.05)	2.10^{-5}
-Lt (±S.D.)	1.160 (±0.08)	1.002 (±0.05)	$<1.10^{-5}$

S.D.: Standard Deviation; FA: Fractional Anisotropy; MD: Mean Diffusivity; Lt: Radial Diffusivity

Discussion

In this study, we were able to show that even in the most favorable population of patients with aneurysm rupture of the anterior communicating complex, who did not sustain major macroscopic brain damages, there were still signs of neuronal injuries on DTI imaging. These microscopic injuries seemed to affect the whole white matter but preferentially the frontal axonal bundles, near the site of rupture.

Cognitive disorders following an intracranial aneurysmal rupture are well-documented and were described to affect between 30 and 55% [7,11] of patients. In the highly selected population featured in this study, 75% of them had at least one disabled cognitive domain, half of them had depression and 25% suffered from post-traumatic stress disorder. These rates are higher than those previously reported in the body of literature, suggesting that the actual prevalence of cognitive impairment is probably underestimated, hence the importance of a comprehensive neuropsychological assessment to properly identify these patients that are sometimes loosely followed because of the apparent normality of their clinical and imaging evaluations.

After comparative analysis with control subjects, we noted no significant differences in brain volumes, confirming the absence of macroscopic sequalae; whereas the entirety of white matter sustained deep alterations of FA. Previously published data that focused on recovered cardiopulmonary arrests [12] and traumatic brain injuries [13] showed that FA could be a powerful marker of clinical outcome, which could also potentially be the case for cognitive disorders after aSAH. In regional analysis, alterations of DTI parameters mostly involved frontal white matter tracts such as the SFOF, the corpus callosum and both ACRs, which is also concordant with recent data from the literature [5,14]. As previously shown in a case-control study including patients with anterior communicating ruptured aneurysms [5], we also found

alterations of MD in parts of the fornix, which is known for its implication in the emotional and memory pathways.

Two main mechanisms have been proposed to explain brain injuries following aSAH [3]: 1) Immediate injuries consecutive to jet damages, whose severity decreases with the distance from the site of rupture 2) Indirect diffuse disorders due to secondary insults (intracranial hypertension, vasospasm, inflammation and ischemia) that possibly induce lesions remotely from the aneurysm site. The results extracted from our analysis suggest that both mechanisms may be involved in the genesis of white matter injuries. As previously shown, additional factors such as pituitary dysfunction [15] may also play a role in cognitive and psychiatric disorders following aSAH.

This work entails several limitations. First and foremost is~~The main limitation of this study is~~ the small volume of patients included, which is a direct consequence of the highly selective inclusion criteria. We were not able to perform exploratory subgroup analyses by lack of statistical power. The heterogeneity of the population is another limit for interpretation, as many confounding factors (SAH grade, delayed cerebral ischemia or length of hospital stay) may have impact on cognitive disturbances. One could argue that by selecting only patient with favorable clinical outcome and normal brain imaging, we could at least manage the extent of heterogeneity. -Also, due to the large number of parameters that were extracted and compared, the multiplicity of statistical tests that needed to be performed decreased the validity of the results, even with Bonferroni correction. Nevertheless, we were still confident in our results considering they were reproduced on several parameters and in matching locations. This is also the first study to prospectively include and follow this subgroup of patients with normal conventional MRIs and the only one to confirm that DTI alterations are actually consecutive to microscopic neuronal lesions and not to parenchymal sequelae. Even though both groups can be considered as young patients, one may note that healthy controls were younger than their

ACOM counterpart. Aging-related white matter integrity has been previously studied using DTI imaging. Most convincing data showed modifications in white matter DTI parameters with normal aging during adulthood, but these mainly occurred later in life, beyond 60 years old [16]. As most of ACOM patients and controls were less than 60, the impact of normal aging in the results should be minimal.

This study does not allow to conclude whether these damages are specifically consecutive anterior communicating aneurysm SAH or only due to aSAH. Future researches will include other aneurysm locations, which may confirm a distance-related impact of aneurysmal rupture.

Conclusion

Cognitive disorders are very common in the aftermath of anterior communicating complex aSAH. When conventional imaging examinations are normal, these troubles might easily be overlooked despite having terrible consequences on the patients' quality of life; hence the value of a systematic neuropsychological assessment, in order to early detect and optimize their management. DTI confirmed that these patients sustained deep white matter damages, and seemed to associate immediate contiguity damage, mainly affecting the frontal tracts; to diffuse neuronal injuries.

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Competing Interest: None

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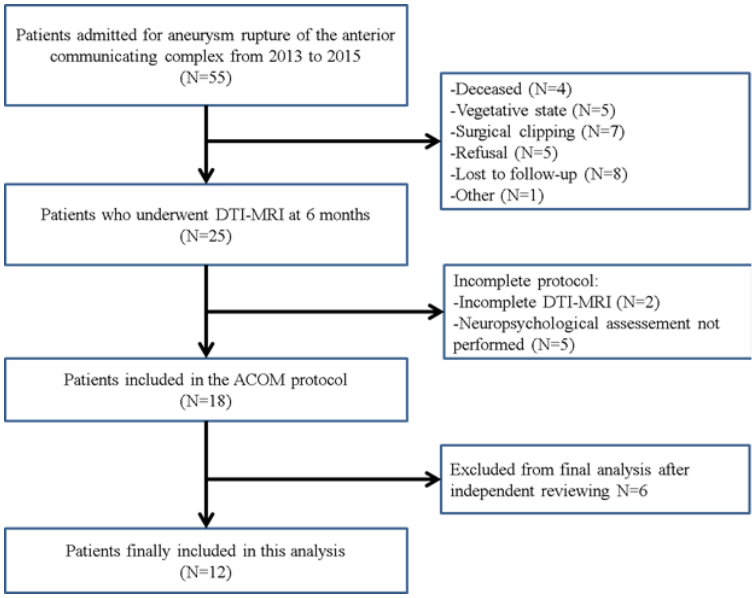
Figure legend

Figure 1. Recruitment Flow Chart



DTI-MRI: Magnetic Resonance Imaging with Diffusion Tensor Imaging sequences

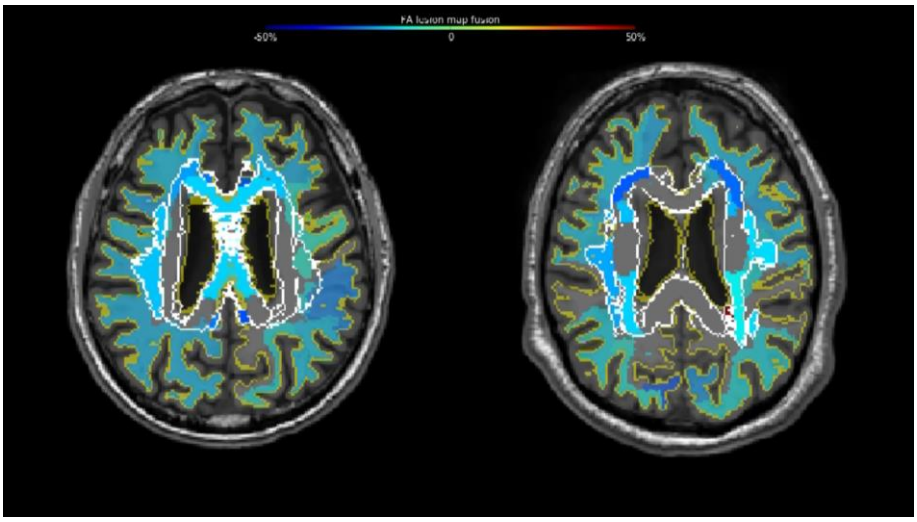
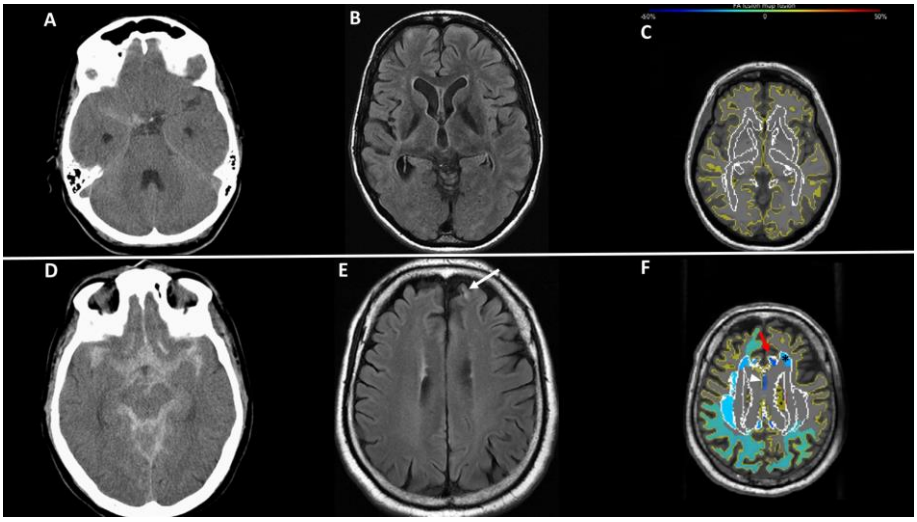


Figure ~~1~~2. Illustrations of white matter changes on DTI in two ACOM patients.

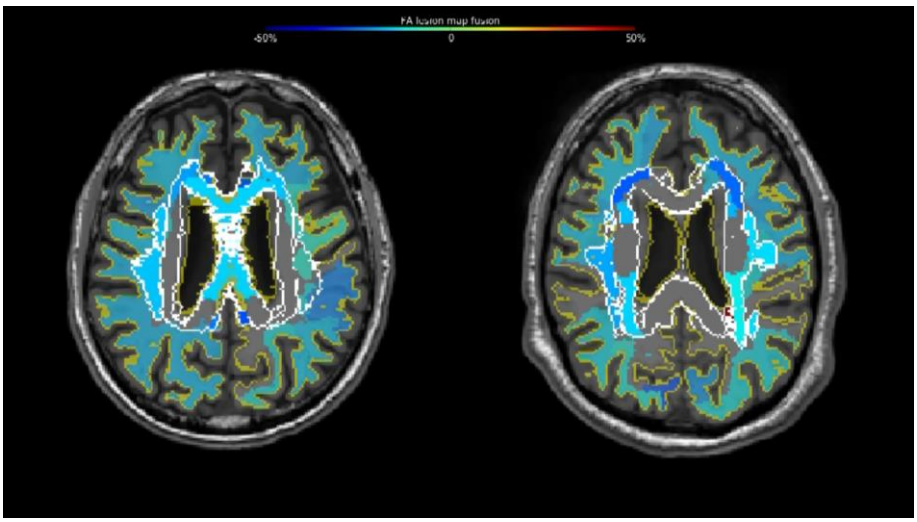


Top row: Fifty-five-year-old patient initially admitted for a World Federation of Neurological Surgeon (WFNS) 1 aneurysmal subarachnoid haemorrhage (aSAH). **A**. Initial Computed Tomography (CT) scan showing a thin SAH in the right sylvian cistern. At 6 months' follow-up, the patient did not present any cognitive impairment or any neurological deficit. **B**. Brain Magnetic Reso~~n~~nance Imaging (MRI) at 6 months (Axial FLuid Attenuated Inversion Recovery

sequence [FLAIR]) showing no significant morphological anomaly. **C**. Fractional anisotropy (FA) atlas of all controls superimposed on the 3D-T1 sequence of the patient. Differences of FA between the patient and the atlas of more than 2 standard deviation are shown according to the colour scale. No differences of FA were seen in the supratentorial white matter.

Bottom row: Fifty-six-year-old patient admitted for aSAH graded WFNS 3. **D**. CT scan featuring thick and diffuse SAH. At 6 months' follow-up, the patient had a severe cognitive impairment on the neuropsychological assessment with 3 disabled cognitive domains (memory, executive and gnostic functions). **E**. Brain MRI at 6 months (Axial FLAIR sequence) showed only a small cortical ischemic sequella of volume < 5mL (White arrow). **F**. FA map showing diffuse areas of FA decrease in the white matter, that seemed to preferentially affect to anterior tracts such as the anterior parts of the corona radiata (black asterisk), the fornix (white arrowhead) and the cingulum (red arrow).

Figure 3. Additional illustrations of Fractional Anisotropy changes on DTI in two ACOM patients severely impaired on neurocognitive evaluation



Fractional anisotropy (FA) atlas of all controls superimposed on the 3D-T1 sequence of each patient. Differences of FA between the patient and the atlas of more than 2 standard deviation are shown according to the colour scale. Left panel: Fractional anisotropy map of a forty-one-year-old patient, 6 months after a World Federation of Neurological Surgeons 1 aneurysmal subarachnoid hemorrhage, showing diffuse alterations in supra tentorial white matter integrity. Right panel: Fifty-nine-year-old ACOM patient, also showing diffuse decreases in white matter FA. This case also illustrates the antero-posterior gradient of FA modifications.