Is Anterior Communicating Artery Syndrome Related to Fornix Lesions?

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Abstract. Anterior communicating artery (ACoA) syndrome, which may occur after rupture of ACoA aneurysms, consists of anterograde memory problems, executive dysfunctions, confabulations, and personality changes. Recently, the employment of diffusion tensor tractography (DTT) has related ACoA to microstructural lesions in the cingulum and the fornix, but an accurate characterization of these subjects should be provided. We report the clinical and neuropsychological findings of a patient who developed a severe and persistent amnesia together with significant behavioral changes, as well as her imaging results, where the sole evidence of brain damage was that of the fornix demonstrated by DTT. The four-year neuropsychological follow-up of the subject allows exclusion of other causes. This case demonstrates that microstructural lesions of fornix may lead to persistent amnesia, executive impairments, and behavioral changes and contributes to the knowledge of its role in cognition.

Keywords: Anterior communicating artery syndrome, cingulum, diffusion tensor tractography imaging, fornix

INTRODUCTION

Anterior communicating artery (ACoA), the small vessel connecting the two anterior cerebral arteries, is a common site of aneurysms. Following rupture and surgery on these aneurysms, neurological symptoms may develop consisting of memory impairments, together with executive dysfunctions and personality changes, a pattern that is globally described as “ACoA syndrome” [1]. Despite having been investigated for decades [2, 3], the mechanisms underlying ACoA symptoms are still uncertain. Lesions within the basal forebrain, the small area including the nucleus of Meynert, the diagonal band, the medial septum, and the substantia innominata [4], have been claimed to be responsible for them, albeit with inconclusive results [5, 6]. Recently, however, it has been found that ACoA subjects show damage at the level of the fornices [7], the white matter bundles perfused by the ACoA branches, which contain fibers coming from each hippocampus. The hypothesis comes from the findings of a diffusion tensor tractography (DTT) study which showed, in the absence of any other lesion, microstructural damage in the fornix and the cingulum in a group of patients with ACoA wherein, however, neither the type nor the severity of the cognitive impairments is reported [7].

We describe here a woman who, immediately after rupture and repair of an ACoA aneurysm, developed a severe and persistent amnesia together with significant behavioral changes. She was submitted to an extensive neuropsychological investigation and neuroradiological exams [magnetic resonance imaging...
(MRI), positron emission tomography (PET)), but the sole evidence of brain damage was that of the fornix demonstrated by DTT.

**METHOD**

**Case description**

FB, a healthy 67-year-old, right-handed woman, went to the Neurosurgery Department because of a sudden and splitting headache. CT scan and angiography showed a subarachnoid hemorrhage due to the rupture of a broad based, 3 × 2 mm sized, saccular aneurysm of the ACoA, at the A1-A2 left junction, which was clipped in "early surgery". After the procedure, no neurological impairment was found, but she showed severe memory impairment. She was unable to recall episodes of the immediate past, asked the same questions repeatedly, and often gave confabulated answers.

**Neuropsychological evaluation**

Neuropsychological evaluations were adopted at 6 and 36 months after surgery. Long-term memory was evaluated by the Rey Auditory-Verbal Learning Test [8], the Short Story Test (immediate and delayed recall) [9], and the Rey-Osterrieth Complex Figure Test [10]. Short-term memory was investigated through the Corsi Block Tapping test [9] and the Bi-syllabic Words Repetition test [9]; for Retrograde memory, we employed a structured interview covering past personal events, and the Famous Faces and Events Test [11]. General cognitive abilities were assessed through the Raven’s Coloured Matrices [12] and semantic retrieval through the category fluency tests. Executive functions were measured through the Clock Drawing Test [13], the copy of Rey-Osterrieth Figure [10], the Wisconsin Card Sorting [14], the Trail Making [15], the Verbal fluency semantic [9], the Stroop Test [16], and the Frontal Assessment Battery [17], while mood and behavior were evaluated by the Beck Depression Inventory [18] and the Apathy Scale [19]. The Constructional Praxis Test was used for visuo-constructive abilities [9].

The same tests were used on 9 subjects matched for age and education. All had performances in the normal range.

**Neuroimaging studies**

A conventional brain MRI, that included sagittal T1, axial T2 and FLAIR, and 3D TOF for angiography, and a fluorine-18-fluorodeoxyglucose-PET (FDG-PET) scan were performed after surgery. Brain FDG-PET was acquired for 15 minutes after the patient rested for 15 minutes in a quiet dark room before 250 MBq (18F)-FDG dose ev administration and during the uptake period (20–25 minutes). DTT by Three-tesla MRI was performed at 36 months.

**DTT data acquisition**

FB was scanned using a 3T Philips Achieva scanner equipped with an 8-channel phased-array head coil, using DTT and high-resolution anatomical scan sequences.

The DTT sequence was based on a single-shot spin-echo, echo-planar imaging (EPI) sequence with diffusion sensitizing gradients applied on either side of the 180° refocusing pulse. Diffusion weighted images were acquired with diffusion gradients oriented along 32 non-collinear directions. Specific DTT parameters were: Repetition Time (TR) = 9330 ms, Echo Time (TE) = 102 ms, flip angle = 90°, Field of view (FOV) = 256 × 256 mm², acquisition matrix size = 128 × 128, 50.2 mm thick axial slices (0.7 mm gap), pixel size = 2 × 2 mm², diffusion weighting b = 1000 s/mm². Two repetitions of the complete set were collected and averaged to increase signal-to-noise without introducing motion artefacts. Sensitivity Encoding (SENSE) factor of two was used to reduce scan time and to minimize distortion related to EPI [21]. During each scanning session, along with the DTT acquisition, high-resolution anatomical scans were acquired. The high-resolution anatomical scan (T1- weighted 3-D Magnetization-Prepared Rapid Acquisition Gradient-Echo sequence (MPRAGE)) was used for co-registration with the b = 0 image. Specific T1 scanning parameters: inversion time = 832 ms, TR = 6.7 ms, TE = 3.1 ms, flip angle = 8°, FOV 1/4 256 × 256 mm², matrix size = 256 × 256, slice thickness = 1.2 mm, number of slices = 170, Turbo factor = 240, orientation of slices was sagittal, acquisition time was 10′35″.

Nine age-matched normal volunteers (HCs) (6 males, 68 ± 6 year, age range 61–77), with no neurological impairment in their clinical history nor at the neurological evaluation including Mini-Mental State Examination Test, underwent the same acquisitions protocol within a multi-center research study focusing on memory impairment and they were recruited among patients’ relatives and the hospital team. The local ethical committee’s approval and informed written consent were obtained before the study.
**Fig. 1. Morphological analysis of FB. In a–c, T1 sequence on the three orthogonal planes show the ischemic lesion of the genu of the corpus callosum (white arrow) without significant alterations of the other regions. In d, a coronal FLAIR slice showing no alterations in the site of the ACoA aneurysm following surgery.**

**DTT post-processing**

Images were transferred to an offline workstation for post-processing and were visually checked for quality. Diffusion-weighted datasets were corrected for head motion, and eddy current distortions using a volume-wise coregistration based on FLIRT tool of FMRIB Software Library (FSL) software package (http://www.fmrib.ox.ac.uk/fsl/) [20, 21], and MIPAV (version 2.0, http://mipav.cit.nih.gov). Fiber tracks were generated with Diffusion Toolkit (FACT propagation algorithm, angle threshold 35°, spline-filtered, DWI mask image) and analyzed using Trackvis (http://www.trackvis.org). According to Concha et al. [22], a multi-region-of-interest approach was used to reconstruct tracts of interest which exploits existing anatomical knowledge of tract trajectories. In particular, the fiber tracts for the cingulum and fornix, differentiating the body from the crus components, were extracted. Tracts were selected if they penetrated a selection region located halfway along the tract, and any of the two selected regions drawn at the extremes of the portion we set out to study. For each portion, tract-selection regions were manually drawn on either Fractional Anisotropy (FA) or principal diffusivity color maps.

DTT and subsequent measurements were performed separately for the right and left cingulum and for the body, the right crus and the left crus fornix in each subject. For each tract the total number of fibers (lines), mean FA and apparent diffusion coefficient (ADC), as derived from the tractography, were recorded.

For the statistical analysis, we chose a Bayesian approach that is thought to be prudent, preventing the overestimation of evidence in favor of an effect [23]. We thus used a Bayesian inferential method.
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**Fig. 2. DTT analysis.** Both the left and right Cingulum (respectively lCingulum and rCingulum) in green, and the fornix (respectively the body in red and the crus in yellow) tracts reconstructed in FB and in a representative healthy control (HC).

(SingleBayes.exe) [24] that allows testing if the patient’s values are significantly above (or below) the respective values of a small control sample.

**RESULTS**

**Clinical findings**

FB showed: a) severe impairments of both verbal and visuo-spatial anterograde memory and of temporal ordering of past events; b) mild executive dysfunctions; and c) apathy. Memory disturbances had a severe impact in daily life (Table 1). No sign of callosal disconnection were found.

**Imaging finding**

Conventional imaging showed left supraclinoid aneurysmectomy surgery signs and slight ventricular enlargement with prevalent left ventricular horn. Three-Tesla MRI showed a small gliotic lesion in the corpus callosum (Fig. 1) at the structural imaging, while FDG-PET was unremarkable.

HCs did not show any major morphological alterations apart from few gliotic foci.

**DTT results**

Tracts were successfully identified in all subjects. DTT reconstruction of cingulum and fornix in patient FB demonstrated a reduction of the fornix while cingulum was preserved (Fig. 2). In FB, FA of the fornix was below the range of the values found in HCs, not only at the body level (0.21 versus HCs mean ± standard deviation: 0.30 ± 0.03; p = 0.03), but at the left crus levels as well (0.16 versus HCs mean ± standard deviation: 0.30 ± 0.05; p = 0.03). However, wide variability of lines and ADC values precluded any significant difference between FB and associated HCs. Despite this, the relevant damage in the fornix body was denoted by higher ADC value in FB with respect to most HCs (0.002 versus HCs mean ± standard deviation: 0.001 ± 0.05; p = 0.07)

**DISCUSSION**

The cognitive impairments showed by FB correspond to those described under the term “basal forebrain amnesia”, and are consistent with the pattern described after the rupture of aneurysms of the anterior communicating artery [2, 25, 26]. Indeed,
Table 1

<table>
<thead>
<tr>
<th>Neuropsychological test</th>
<th>6 months</th>
<th>36 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-Mental State Examination (0–30)</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Trail Making Test A (0–inf)</td>
<td>116</td>
<td>120</td>
</tr>
<tr>
<td>Trail Making Test B (0–inf)</td>
<td>358</td>
<td>360</td>
</tr>
<tr>
<td>Trail Making Test A-B (0–inf)</td>
<td>239</td>
<td>240</td>
</tr>
<tr>
<td>Rey Auditory-Verbal Learning Test Immediately (0–75)</td>
<td>20d</td>
<td>22d</td>
</tr>
<tr>
<td>Rey Auditory-Verbal Learning Test Delayed (0–15)</td>
<td>0d</td>
<td>0d</td>
</tr>
<tr>
<td>Rey Complex Figure Test memory (0–36)</td>
<td>0.5d</td>
<td>1d</td>
</tr>
<tr>
<td>Rey Complex Figure Test copy (0–36)</td>
<td>16d</td>
<td>20d</td>
</tr>
<tr>
<td>Frontal Assessment Battery (0–18)</td>
<td>9d</td>
<td>5d</td>
</tr>
<tr>
<td>Verbal fluency semantic (0-inf) per 2 minutes</td>
<td>8.75</td>
<td>10</td>
</tr>
<tr>
<td>Stroop Test (Time)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stroop Test (Errors)</td>
<td>48.5</td>
<td>19</td>
</tr>
<tr>
<td>Wisconsin Card Sorting Test: Category (0–6)</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Wisconsin Card Sorting Test: Perseverative Errors (0-inf)</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Constructional Praxis Test (0–14)</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Beck Depression Inventory (0–63)</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

they consist in severe amnesia of the hippocampal type, mild retrograde amnesia for personal information and temporal tagging, and mild executive dysfunctions (impairments of planning and verbal fluency test, sensitivity to interference), together with apathy. Since these impairments were stable during the long follow-up, it enabled other causes of them to be excluded, as the unmasking of an Alzheimer-like condition due to ESA and subsequent surgery. The conventional MRI did not disclose any lesion in the patient, apart from a small gliotic lesion in the genu of the corpus callosum. The DTT, however, disclosed a relevant FA reduction in the fornix. The finding was compared to that of 9 cognitively healthy matched controls.

Attributing the cognitive impairments of FB to the fornix damage is consistent with a wide literature investigating the role of this structure in memory functions. In actual fact, the fornix, one of the main pathways of the CNS, contains fibers connecting the hippocampus to the mammillary bodies and then to the thalamic nuclei; from here projections go back to the hippocampus, thus closing the loop. Damage to the fornix, thus, can hamper the construction of new declarative memories, and lead to anterograde amnesia, as has been reported in studies on the cognitive consequences of fornix lesions due to other causes [27, 29]. The fornix, furthermore, also contains fibers interconnecting the hippocampus to and from the septal nuclei, the diagonal band, and other mesial frontal areas [30, 31]. Lesions of the fornix can thus impair the connections between the frontal lobe and the hippocampus, an aspect that may explain impairment of the executive dysfunctions. Reduced executive functioning has also been associated with lower fornix integrity in other groups of patients [32–34].

Finally, apathy has also been recently attributed to microstructural damages in the fornix [35]. We are aware that our DTT results showed significant reduction only in FA of the fornix, despite qualitative image differences in FB versus HCs. This aspect may be attributed to the high individual variability of these aspects which, in our view does not significantly impact on the results, though collecting more control subjects and patients would be desirable.

In sum, ACoA syndrome should be considered the result of a disconnection, and fornix integrity should be thoroughly investigated in such cases by imaging techniques including the DTT.

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Authors’ disclosures available online (http://www.j-alz.com/disclosures/view.php?id=2295).

REFERENCES


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