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Clinical study

Recovery of consciousness after a brainstem cavernous malformation hemorrhage: A descriptive study of preserved reticular activating system with tractography

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ABSTRACT

The aim of this study is to describe the imaging features, the relevant anatomy, and the fractional anisotropy (FA) values in diffusion tensor tractography (DTT) of the ascending reticular activating system (ARAS) fiber tracts in 2 patients who recovered from initial altered consciousness after presenting with a brainstem cavernous malformation (BSCM) hemorrhage. A DTT was performed in 2 patients with impaired consciousness after a brainstem cavernous malformation hemorrhage. A 1.5 T scanner was used to obtain the axial tensors. Post-processing was performed and the mean FA values were recorded. The FA maps were used to seed the following regions of interest: the ventromedial midbrain, the anterior thalamus bilaterally, and the hypothalamus bilaterally. The first case presented with posterior displacement of the dorsal raphè fiber tracts, with preservation of all the ascending reticular activating fiber tracts and spontaneous recovery of consciousness after 20 days. The second case presented with no destruction but also had posterior displacement of the inferior dorsal raphè fiber tracts, with recovery of consciousness 1 month after resection surgery. Described in this study are affected fibers of the ARAS, as well as the FA value abnormalities in 2 patients, with recovery of a transient disorder of consciousness after a BSCM hemorrhage.

1. Introduction

Consciousness is a widely-discussed term for a complex process that is not yet fully understood and whose structural basis are not completely known. The component of arousal in consciousness originates in the brainstem and is further developed by the ascending reticular activating system (ARAS) [1,2]. This reticular system plays a key role in the control of the neuronal activities of the cortex and in the focus of our vigilance on stimuli of several somatic and sensory afferent pathways that run through the brainstem, forming a diffuse and complex network that connect through the thalamus directly to the basal frontal cortex [1–5]. With the introduction of new imaging technologies such as the diffusion tensor tractography (DTT), the identification and close description of the ARAS is now possible [3]. The use of DTT to study damage in the structural anatomy of the ARAS enhances comprehension of the pathophysiology in disorders of consciousness (DOCs) [6–9].

Abbreviations: ARAS, ascending reticular activating system; CST, corticospinal tract; DTI, diffusion tensor imaging; DTT, diffusion tensor tractography; FA, fractional anisotropy; CT, Computed Tomography; MRI, magnetic resonance imaging; ROI, region of interest; DOC, disorder of consciousness; GCS, Glasgow Coma Scale; mRS, modified Rankin Scale; MFB, Middle Forebrain Bundle.

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Reports on the description of the neuroanatomic connectivity in patients with different mechanisms of injury involving the ARAS correlates with the clinical finding of impaired state of consciousness [3,9–11] and in the neurological outcome [12]. However, little is known regarding the recovery of consciousness after injury of the ARAS [13–16].

The incidence of cavernous malformations (CMs) is low in the general population ranging from 0.4% to 0.8% [17], however, they are the second most important vascular malformation accounting for 10–15% of all vascular malformations [18], of which 9–35% are located in the brainstem [19]. Brainstem cavernous malformations (BSCMs) have an important anatomical interaction with the ARAS and other critical structures, implicating a more severe clinical course if patients present with a hemorrhage. The location of these lesions and their hemorrhage rates are more than twice that associated with other intracranial CMs [20], manifesting with a wide range of clinical signs and symptoms, including the impairment of consciousness [21]. To the authors' knowledge, this is the first report of a description of the ARAS fiber tracts in patients after a BSCM hemorrhage. This study aims to describe the DTT reconstruction of the ARAS fiber tracts in two patients with a DOC after hemorrhagic presentation of BSCM. Both patients in this report recovered their normal consciousness, awareness and wakefulness.

2. Methods

2.1. Patients and definitions

Clinical and neuroimaging data of two patients, 1 Hispanic female and 1 Hispanic male with acute BSCM hemorrhage and DOC admitted at the intensive care unit (ICU) of the Hospital Infantil Universitario de San José, Bogota, Colombia are presented in this report. The two patients recovered their consciousness after 1 month from the hemorrhage and were selected for diffusion tensor imaging (DTI) and DTT analysis of the ARAS. The magnetic resonance imaging (MRI) protocols were performed when patients were hemodynamically stable and when other physiological disturbances were controlled (i.e. no electrolytic or metabolic abnormalities were present which could affect the level of consciousness). The MRI was performed on both patients 17 and 12 days respectively after hospital admission. A multidisciplinary team, including neurologists, intensivists and neurosurgeons we involved in decision-making and critical care. During the hospital stay, the clinical assessment included physiotherapy, occupational therapy, nursing, rehabilitation medicine, and speech and language therapy. Clinical decisions always included the family of the patients, who were often present over prolonged periods, even during the ICU stay. A standard clinical evaluation for the diagnostic assessment process included a detailed clinical history, a review of medication, the standard imaging, a standard electroencephalogram (EEG) when subclinical seizure activity was suspected, and a fully detailed neurological evaluation, including evaluation with the Glasgow Coma Scale (GCS) and the modified Rankin Scale (mRS) in the acute setting. Both patients were carefully evaluated and assessed every day during their hospital stay by the multidisciplinary team of intensivists, neurologists and neurosurgeons.

This work is based on the general principles of human research ethics set forth in the Helsinki Declaration. The purpose of the study is to obtain scientific knowledge for a better diagnosis and a more precise evaluation that may eventually help to predict or improve the neurological outcome of these patients. It adopts the resolution 8430 of 1993 of the Ministry of Health of Colombia, and is based on the definitions of risk contained in the corresponding article of that law, for which it classifies this study as a risk-free research, since it is a retrospective study based on medical records information. Authorization was requested to our Institutional Ethics Board to include the information of the patients in this study, preserving their identity both in the analysis of the information and in the images presented. This is a retrospectively reviewed case series with approval by the Fundación Universitaria de Ciencias de la Salud Review Board. Partial results of this manuscript were previously at the presented at the 54th AANS Annual Scientific Meeting, Los Angeles, California. For an adequate interpretation of the clinical status of the patients, for all the terms mentioned in this manuscript regarding any DOC, the corresponding definitions were adopted from the clinical guidelines of the Royal College of Physicians [22], including the definitions of consciousness, awareness, coma, etc.

2.2. Imaging acquisition

A *General Electric Signa Excite ® HDXT* (1.5 T GE Healthcare, Milwaukee, W I, E.U.) was used to obtain the images. The following sequences were acquired for both patients: 1) axial T1-weighted structural/anatomical; 2) axial T2-weighted; 3) axial Diffusion Weighted Imaging (DWI), and 4) axial DTI. Each structural image in T1 had 140 slices (1 mm thick, without GAP (free space), matrix = 320 × 192, TR = 650 ms, TE = 22 ms, FOV = 22) and acquisition time = 2 min and 35 s, covering the entire brain volume. The structural images in T2 contain 22 cuts (6 mm thickness, GAP 1 mm (free space), matrix = 320 × 256, TR = 6.000 ms, TE = 97.44 ms, FOV = 24) and acquisition time = 1 min and 20 s, covering the entire brain volume. Each DWI image has 30 slices (2 mm thickness, without free space, resolution = 2 mm isotropic, matrix = 128 × 128, TR = 1000, TE = 102.3 ms, flip angle = 90), planar imaging and acquisition time = 6 min, covering the entire brain volume. For the isometric DTI sequence, a spin echo-planar (EPI) sequence with 24 directions were used in an axial plane without angulation. Images were obtained from the base from the skull to the vertex. Each axial tensor sequence has 920 images, matrix = 100 × 100, TR = 14000–17000, TE = minimum, thickness 2.5, spacing = 0.0, NEX = 1, Pixel = 2.5, FOV = 250, b value = 1000, acquisition time = 7 min.

2.3. Processing

A manual tracing of each region of interest (ROI) and the corresponding deterministic fiber tracking were performed with Functool 9.4.04b™ (by © *General Electric Medical Systems*). Correction of EPI distortions (scaling + translation + shearing) was applied. The ARAS fiber tracts were reconstructed by selection of fibers passing though the ROIs. The ARAS pathways are so-called neurotransmitter-specific, including fibers coming from specific nucleus. These nuclei include serotonergic in the raphè of the rostral pons and midbrain, noradrenergic in the rostral pons, dopaminergic in the ventral tegmentum of the caudal midbrain, cholinergic in the caudal midbrain and rostral pons, and glutamatergic in the rostral pons. These fibers project to the hypothalamus (regulation of autonomic function and sleep-awake cycles), the thalamus (integration and modulation of arousal brainstem stimuli), the basal forebrain (cortical activation and autonomic integration), and the cortex [1]. In this study, we traced 3 different ROIs, trying to include all proximal and distal ARAS fiber tracts: the first ROI in the caudal ventromedial mesencephalon, the second in the ventral/anterior thalamus (bilaterally) and the third in the hypothalamus (bilaterally). The hypothalamic ROI was traced in a formatted coronal tensor, in both lateral walls of the third ventricle. Mean, maximal and minimal fractional anisotropy (FA) values were acquired. (Supplementary data, appendix 1 and 2) Each ROI area was also recorded. 6 different tracts were differentiated in

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the reconstructions: an intra-thalamic gating pathway complex, the dorsal raphè (DR) pathway, the medial forebrain bundle (MFB), the ventral tegmental tract and the dorsal tegmental tract. (Fig. 1) The compromise of the fibers was determined with the classification and grading system for fiber tract changes in DTI described by Kovanlikaya et al., modified by Lazar et al. [23,24].

3. Results

3.1. Case 1

A 60-year-old woman presented to the emergency room (ER) with a two-hour sudden loss of consciousness without spontaneous recovery, associated with a right hemiparesis. The patient had no previous history of any neurological deficit. Past medical history included uncontrolled hypertension, treated with losartan oral tablet 50 mg/day. On examination, the following vital signs were recorded: (1) blood pressure of 179/100 mmHg, (2) pulse of 76 beats per minute, (3) respiratory rate of 16 breaths per minute, and (4) oxygen saturation of 97%. Her neurological evaluation presented with an initial GCS of 7 T (eye response 2, verbal response 1 with tube (T), and motor response 4). Pupils were 3 mm reactive to light, with no cranial nerve involvement. A right hemiparesis 3/5 was observed, with a right extensor plantar response. No meningeal signs were noted. She was intubated in the emergency room (ER) and transferred to the intensive care unit (ICU).

A Computed Tomography (CT) scan and a contrast MRI of the brain were performed at days 1 and 17 of her hospital stay respectively. A left pontine hemorrhagic lesion was observed showing a T1 hyper-intense halo with a T2 heterogeneous hypo-intense "berry" appearance suggesting a left pontine cavernous malformation (Fig. 2). Gradient echo sequences showed hypo-intense signal, consistent with blood in different stages. The angiogram showed no vascular abnormality. The surgical decision-making group selected a complete microvascular resection of the BSCM as the best approach for this case, however the patient's family denied surgical treatment. The patient remained in the ICU for 25 days. After day 20 the patient presented spontaneous recovery of consciousness, recovering from coma. A normal interaction with examiners was noted. She was extubated on day 24. The patient presented with phlebitis that recovered after treatment with intravenous administration of oxacillin for 10 days. The rest of her hospital stay was unremarkable. Four months after discharge, the patient's follow-up did not demonstrate any DOC, however she continued to experience persistent right hemiparesis.

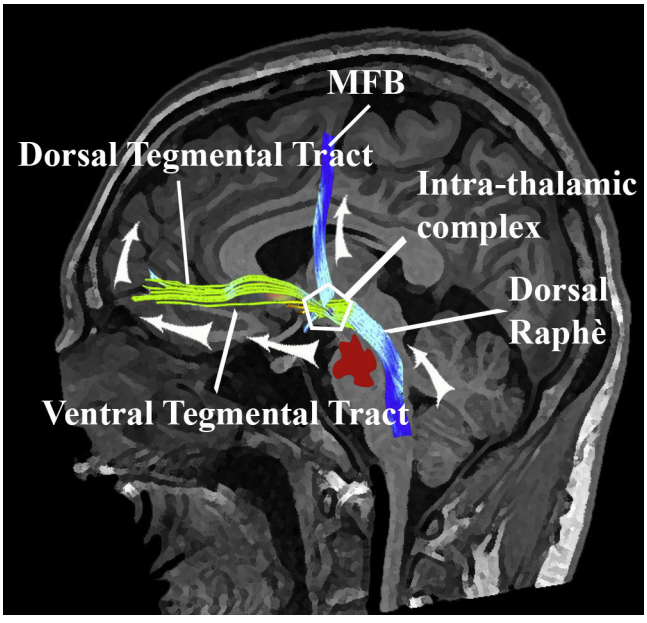

Fig. 1. Schematic illustration of the reconstruction of the ARAS fiber tracts with tractography in a normal subject. The different tracts of the ARAS can be observed resembling a "y". A hemorrhage is represented by a red image. MFB: Middle Forebrain Bundle.

3.2. Case 2

A 34-year-old male presented to the ER with history of a five-day sudden-onset bilateral occipital headache that was moderate in severity. The patient also had multiples episodes of nausea and vomiting. The day prior to presentation, the patient's gait became unstable and he experienced paresthesias in both upper extremities. The patient had no relevant past medical history. On arrival, the following vital signs were recorded: (1) blood pressure of 116/76 mmHg, (2) pulse of 78 beats per minute, (3) respiratory rate of 16 breaths per minute, and (4) oxygen saturation of 97%. The physical exam was unremarkable. Positive findings in the neurological evaluation only demonstrated a right sixth cranial nerve palsy. A CT scan of the head showed a midline pontine hyperdense lesion. Additionally, a contrast MRI of the brain was performed, showing an upper ventral mesencephalic and pontine hemorrhagic lesion with a T1 hyper-intense and T2 hypo-intense heterogeneous lesion, demonstrating a characteristic "popcorn" appearance, with a rim of signal loss, which demonstrated blooming on the susceptibility weighted imaging (SWI) sequence. (Fig. 3). The diagnostic cerebral angiography showed no vascular abnormalities. One week after admission the patient had a sudden loss of consciousness, associated with quadriparesis, right third cranial nerve palsy, and bilateral compromise of the sixth cranial nerve. The patient had a GCS score of 3 T. A repeat CT scan of the head demonstrated an increase in the hemorrhage volume as well as a non-communicant secondary hydrocephalus. Additionally, a repeat MRI with diffusion tensor tractography demonstrated a posterior displacement of the dorsal raphè tracts (see Fig. 4).

The surgical decision-making group selected an emergent endoscopic third ventriculostomy, with a complete microvascular resection of the AVM as the best approach for this case. A right fronto-pterional approach was performed, followed by a right trans-sylvian microvascular approach with a complete resection of the BSCM. The surgery and perioperative period was uneventful. The final pathology results demonstrated findings compatible with a BSCM. The patient remained in coma for 30 days. On day 30 (postoperative day 23) spontaneous recovery of consciousness was noted. Adequate interaction with examiners was observed although the patient continued to have persistent compromise of the sixth cranial nerve bilaterally and quadriparesis 3/5. Forty-five days after the procedure the patient was discharged home with follow up as an outpatient. No neurological deterioration was found and control MRI demonstrated no residual BSCM. Two-year follow-up demonstrated a near complete recovery from his quadriparesis with a residual right sixth cranial nerve palsy.

4. Discussion

The utility of preoperative DTI in the surgical management of BSCM has been described elsewhere [25]. Recently, Jang SH and Sank SY described the injury of the lower ventral and dorsal ARAS in patients with pontine hemorrhage [26]. They described a decrease in the FA values in a probabilistic tracing of the ARAS, as well as a decrease in the tract volume of the lower ventral and dorsal ARAS tracts. Although they performed a comparative analysis with a control group, the anatomic description of the fibers is

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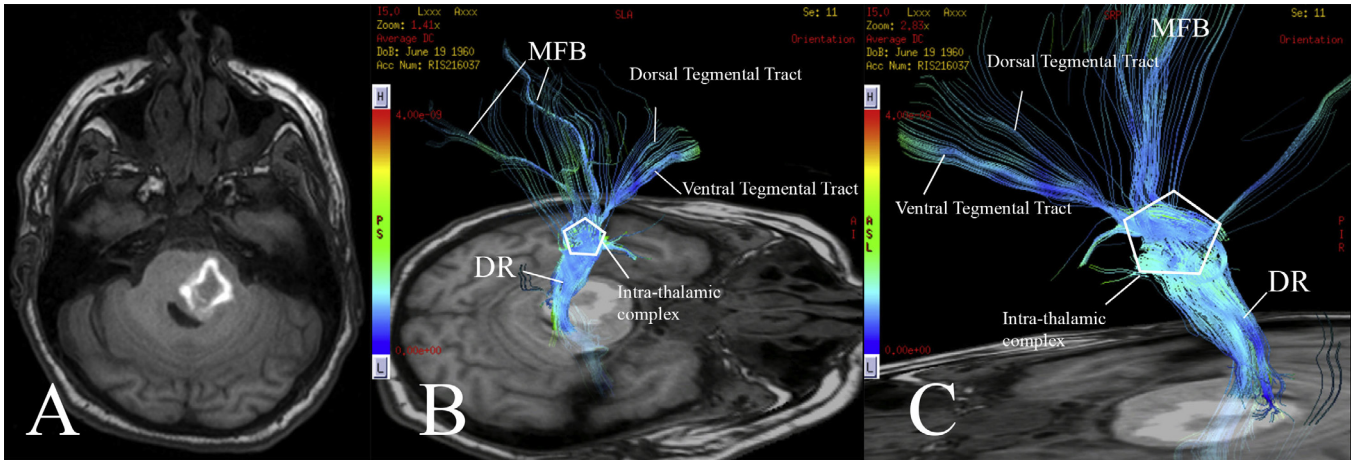

Fig. 2. Fusion of an axial T1 non-enhanced magnetic resonance imaging with tractography tracing of the ascending reticular activating system. (A) An axial non-enhanced T1 showing a left pontine cavernous malformation with hemorrhage. Left (B) and right (C) superior-lateral views of the fusion of the tractography and the T1 demonstrating the hemorrhage displacing posteriorly the dorsal raphè fiber tracts. The ventral and dorsal tegmental tracts remain intact, as well as the Middle Forebrain Bundle tracts bilaterally. *DR = dorsal raphè, MFB = Middle Forebrain Bundle.*

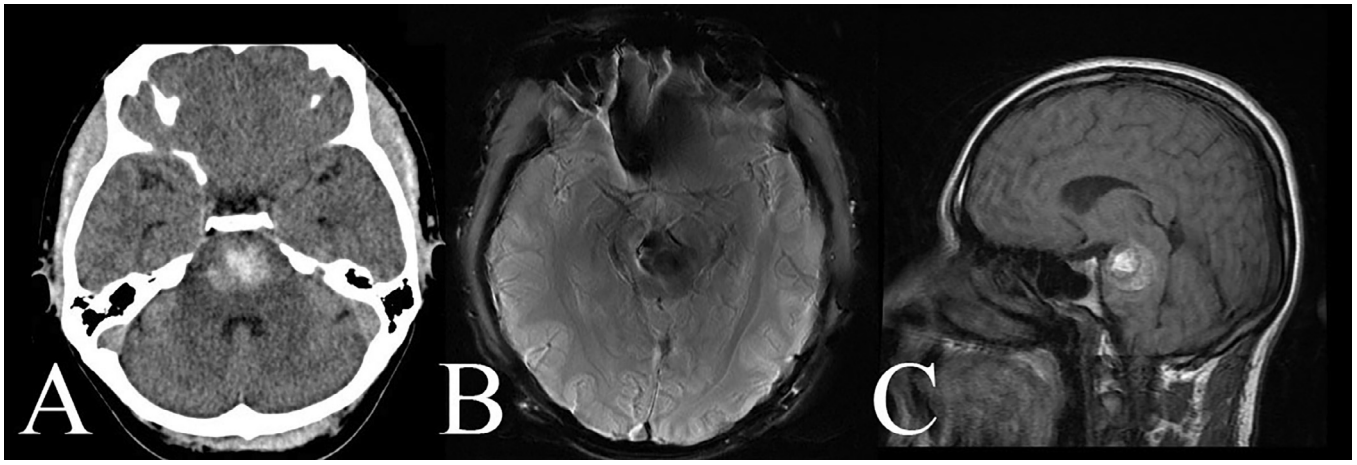

Fig. 3. (A) Axial Computed Tomography scan, (B) axial susceptibility weighted imaging (SWI), (C) and sagittal non-enhanced T1 images showing a heterogeneous hemorrhagic lesion consistent with a pontine and mesencephalic cavernous malformation.

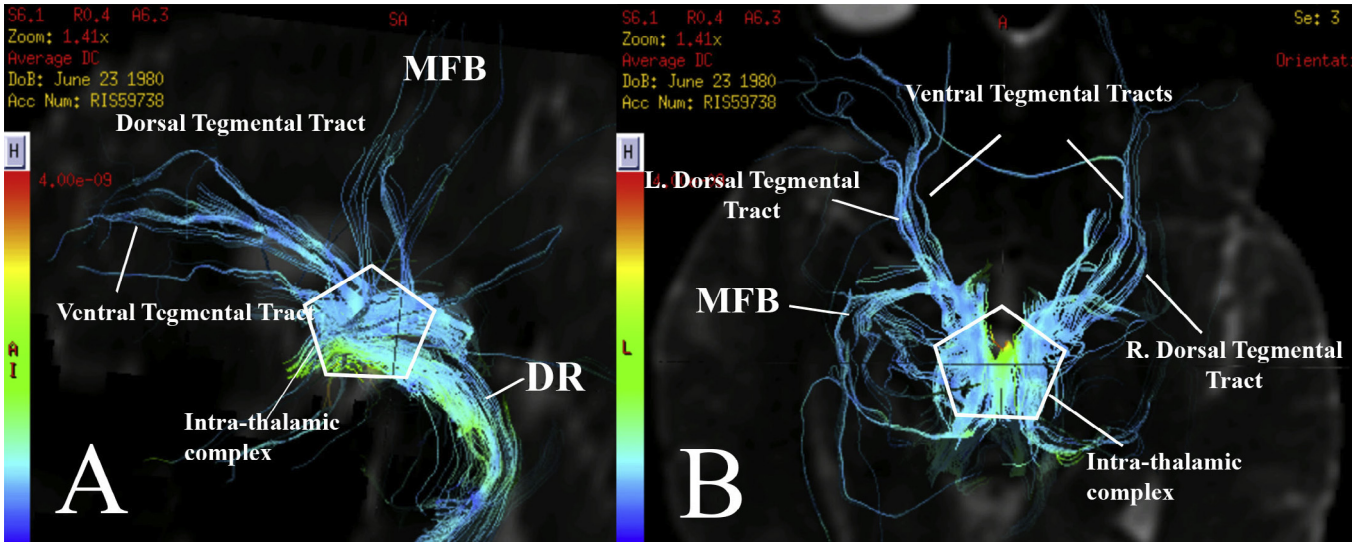

Fig. 4. (A, B) Tractography of the ascending reticular activating system (ARAS). The main tracts of the ARAS are illustrated. A posterior displacement of the dorsal raphè (DR) fibers is observed. Changes in average diffusion coefficient of DR fiber tracts are noted in green. MFB = Middle Forebrain Bundle, DR = Dorsal Raphè, L. Dorsal Tegmental Tract = Left Dorsal Tegmental Tract, R. Dorsal Tegmental Tract = Right Dorsal Tegmental Tract.

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not detailed. Our study did not perform a probabilistic analysis of the fibers; however, we want to enhance the anatomic description of these images. Description of ARAS fibers reconstructed with 1.5 T scanners have been reported elsewhere [3,5,10,15]. However, to the authors' knowledge this is the first study with a 1.5 T magnet, where the compromise of ARAS fibers due to a BSCM are described in detail, denoting the ventral tegmental tract, the dorsal tegmental tract, the intra-thalamic complex, the DR and the MFB tracts. Reconstructing the ARAS in this way makes it more feasible for physicians to do it in a shorter period of time (7 min) in a clinical field, in comparison with other techniques such as high angular resolution diffusion imaging (HARDI) tractography, where one scan can take up to 5 h to be performed [1].

There are recent studies regarding the reconstruction of the ARAS using MRI tractography [1,3,5,6,10,15,27]. The goals of those studies was to elucidate the neuro-anatomic changes after TBI to determine the potential of recovery of consciousness [6], as well as establishing tractography as a tool for predicting outcomes or treating DOC [12,28]. Moreover, the conventional deterministic tractography is a relatively quick study, however costly, and involves the knowledge of the technique for carrying out the study and the appropriate software and trained personnel for the post-processing of the acquisitions.

For now, it is possible to identify the ARAS with deterministic tractography as demonstrated in this study. New models of probabilistic tractography can even visualize other mathematically possible structural connections of the ARAS [3,5,10,15], giving more information than just FA reconstructed fibers. In both cases, however, the limitation of ellipsoid-based imaging, and little sensitivity for low FA values of the ARAS, a pathway that is both functional than structural, makes it difficult to isolate the arousal system in fiber tracking. Low FA values have been observed previously on the midbrain [29] and in the thalamus [30], so this could explain why most of these non-ARAS fiber tracts were not reconstructed in our study. Future segmentation of brainstem nuclei with the proposed atlas of the ARAS [1] will make it easy to reproduce the ROI seeding to compare adequately FA values in isolated ARAS fiber tracts, however this process is delicate and difficult to perform with 1.5 T imaging information. Indeed, this tool remains operator-dependent and observer-dependent. Furthermore, this instrument needs to be powered to use it as an accurate clinical tool. A higher resolution MRI magnet could potentially uncover additional tracts not seen with a lower Tesla machine.

Regarding the mean FA values, the first case presented a decrease mean FA value in the left thalamus and the second case presented decreased FA values in the left hypothalamus. (Supplementary data, appendix 1 and 2) These values were compared to mean FA values of the ARAS tracts in healthy subjects [3]. Both patients had distortion of DR fiber tracts, however the first case demonstrated only deviated fibers (score 2), while the second case had deformed the DR fiber tracts (score 3), with partial defects on the tract [23,24]. The abnormal clinical and radiological findings of the patients are presented on Table 1.

Our study has some limitations; this is a report of two cases, however we could reconstruct the ARAS in both cases showing similar findings on the compromised dorsal raphè tract likely leading to the DOC. Other limitation of this study was that we were unable to perform a sub-millimetric analysis of the fibers; differentiation of lateral and middle fibers of the dorsal tegmental tract and the ventral tegmental tract was not possible in this work. Further studies performed with normal subjects could evaluate the mean diffusivity and the number of fibers in each subject, thus determining the variability of these parameters within an expected normal range.

In respect to the DR fiber tracts, most of the serotonergic innervation of the brain cortex, the basal frontal lobes, the thalamus and the hypothalamic areas comes from the DR nucleus, which contains 5-HT and non-5HT neurons, which contribute to regulation of the sleep-wake cycle through their mediation of the effects of afferent inputs [31]. Azmitia et al. recognized 6 different tracts ascending from the DR nucleus of the rat [32]: the DR forebrain tract, the median raphè forebrain tract, the DR nucleus cortical tract, the DR nucleus periventricular tract, the DR arcuate tract, and the raphè medial tract. For the purposes of this study, all the ascending tracts including those coming from the medial raphè were grouped in a DR tract. Additional sub-segmentation of the DR nuclei and of the corresponding ascending fibers could elucidate additional submillimetric information in further studies. We believe that compromise of the ARAS in this segment could be associated with a better neurological prognosis, compared with deviation or disruption of ARAS fibers in other locations like the dorsal and ventral tegmental tracts. Further studies with HARDI tractography and other q-ball processing of tractography of these fibers are required.

Table 1
Clinical and radiological remarkable findings.

	Case 1	Case 2
Localization of BSCM	Midline pons	Left pons
Disorder of consciousness	Coma	Coma
Compromised tracts	Dorsal Raphè	Dorsal Raphè
ROIs with decreased FA values	Left thalamus	Left hypothalamus

BSCM = Brainstem Cavernous Malformation, ROI = region of interest, FA = fractional anisotropy.

5. Conclusions

MRI tractography is a tool that is available for the reconstruction of the ARAS demonstrating few fibers ascending through the brainstem. We could reconstruct the ventral tegmental tract, the dorsal tegmental tract, the DR, the MFB, and the intra-thalamic complex tracts fibers. Use of tractography in patients with disorders of consciousness could provide additional useful information about prognosis. Affected fibers of the ARAS secondary to the BSCM hemorrhage and the FA value abnormalities in the ARAS in two patients are described. From this report, the two patients that were presented had a compromise in the DR tract. Future automated seeding based on the FA values will reduce the inter-observer/inter-operator differences for this reconstruction.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2018.10.074.

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