Diffusion tensor imaging in human global cerebral anoxia: correlation with histology in a case with autopsy

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DIFFUSION TENSOR IMAGING IN HUMAN GLOBAL CEREBRAL ANOXIA: CORRELATION WITH HISTOLOGY IN A CASE WITH AUTOPSY.

IMAGERIE DU TENSEUR DE DIFFUSION DANS LE COMA POST-ANOXIQUE : CORRELATION AVEC L'HISTOLOGIE

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We report the case of a 58-year-old man (Figure) in a profound coma after a 30-min-long cardiac arrest who benefited of a brain MRI 6 weeks after the accident (1.5-T MRI scanner, SIEMENS Avanto MR, Erlangen, Germany) with DTI acquisition (30 directions, b = 1000 sec/mm^{2,} TR = 6800 msec, TE = 99 msec, FOV=230×230 mm^2, matrix 128×128, 3.5 mm slice thickness). FA, parallel diffusion ($D_{//}$) and perpendicular diffusion ($D_{\perp}$) maps were computed and compared voxelwise to a probabilistic voxel-based atlas of fractional anisotropy as well as parallel and perpendicular diffusion based on 19 healthy subjects. Z-score maps were computed. The patient died from sepsis. An autopsy was performed. Brain sections were stained with Luxol fast blue cresyl violet to analyse myelin and immunostained for neurofilaments to detect white matter axons. DTI images analysis demonstrated extensively reduction of white matter FA, whereas $D_{//}$ and $D_{\perp}$ were elevated. $D_{//}$ and $D_{\perp}$ modifications reflect axonal and myelin lesions, respectively, whereas FA reflects white matter global disorganization. Histological analysis was in accordance with DTI data demonstrating extensive demyelination and widespread axonal loss. Global cerebral anoxia after cardiac arrest resuscitation is one of the most common causes, with traumatic cerebral injury, of chronic disorders of consciousness (1).

The distribution and severity of brain damage following global ischemia is proportional to the duration and severity of ischemia and is modified by the selective vulnerability of the different cell types and brain regions (2). Neurons are the most vulnerable cells, in particular in the CA1 region of the hippocampus, followed by those in the basal ganglia, cerebral cortex and the Purkinje cells of the cerebellum (2). Moreover, border zones, between two vascular territories, are more vulnerable because of the poor blood supply (2). Among glial cells,

oligodendrocytes are the most vulnerable cells (2). The grey matter lesions observed are not uniform in the different brain regions and can extend from selective neuronal necrosis to tissue necrosis (2, 3). These lesions are associated with white matter leukoencephalopathy, combining demyelination, axonal loss and focal regions of necrosis (2).

MRI is able to assess these lesions, on T2-weighted images demonstrating signal abnormalities in the hippocampus, the cortex – preferentially in the border zones – and in the parietal, occipital and frontal regions, the basal ganglia and the cerebellum (4-7). Moreover, the MRI appearance of the lesions depends on the delay between the cardiopulmonary arrest and the date the MRI was performed, extending in the gray matter from an edematous appearance at the early phase to atrophy sometimes associated with cortical laminar necrosis at the late phase (4, 8). White matter abnormalities can also be detected on T2-weighted MR images, but are usually delayed, observed only after the late subacute period (14–20 days) (4).

Diffusion-weighted imaging (DWI) seems to be more accurate for the detection of lesions and the determination of their extension in the early acute period than other conventional MR sequences (4, 6). DWI could help in determining the prognosis at the early phase after cardiopulmonary resuscitation, as the extension of the lesions and low ADC values within the lesions seem to be related to poor outcome (6-10). Diffusion tensor imaging (DTI) is a recent MRI technique that can characterize the neuronal architecture of the brain white matter in vivo by probing the diffusion of water molecules in tissues. The degree of directionality of water in the tissue is described by the fractional anisotropy (FA). The diffusion process is often modeled in each voxel as a 3×3 symmetric definite positive matrix. The largest eigenvalue of this matrix is related to the main diffusion direction along the fiber bundle,

namely the parallel diffusion ($D_{//}$), and the mean of the two other eigenvalues is related to the diffusion direction perpendicular to the fiber bundle, namely the perpendicular diffusion ($D_{\perp}$). Recent studies have shown that $D_{//}$ and $D_{\perp}$ provide additional information on white matter structures that is more specific to underlying histological processes, as compared to FA. $D_{//}$ seems to reflect diffusivity along the axon in relation to axonal integrity, whereas $D_{\perp}$ seems to reflect diffusivity perpendicular to the axon, in relation to degree of myelination (11, 12). Diffusion tensor imaging could be of particular interest in the evaluation of white matter injuries in patients with global cerebral anoxia after cardiac arrest resuscitation, as demonstrated in a hypoxic-ischemic neonatal rat model that combined FA and trace : increased $D_{\perp}$ with no significant change in $D_{//}$ appears to characterize noncystic white matter injury with reduced myelination, whereas reduction in both $D_{\perp}$ and $D_{//}$ characterize severe damage with loss of structural integrity and necrosis (13).

In conclusion, DTI modifications, particularly $D_{//}$ and $D_{\perp}$, seem to be in accordance with histological data. DTI acquisition and postprocessing are easy to perform and could contribute additional information on biological processes in white matter injuries, as compared to morphological MRI. However, these preliminary data need to be confirmed on a larger cohort of patients.

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LEGEND OF THE FIGURE :

Figure : Axial FLAIR-weighted MR images at the occipital lobe level (a) demonstrating extensive white matter hyperintense signal and atrophy (arrow). Z-score statistical maps at the same level obtained from the comparison of the patient's FA (b), parallel diffusion (c) and perpendicular diffusion (d) maps with the volunteers atlas demonstrating reduction of patients white matter FA, whereas $D_{//}$ and $D_{\perp}$ were elevated (Purple corresponds to a decrease from normal and red to an increase). Coronal histological sections of right occipital lobe white matter stained with Luxol fast blue cresyl violet (x1) (e) (×400) (f), immunostained for neurofilaments (×400) (g), demonstrating myelinic pallor due to demyelinization (arrow head) associated to severe axonal loss demonstrated by little staining for neurofilaments (star).

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No conflict of interest

Figure

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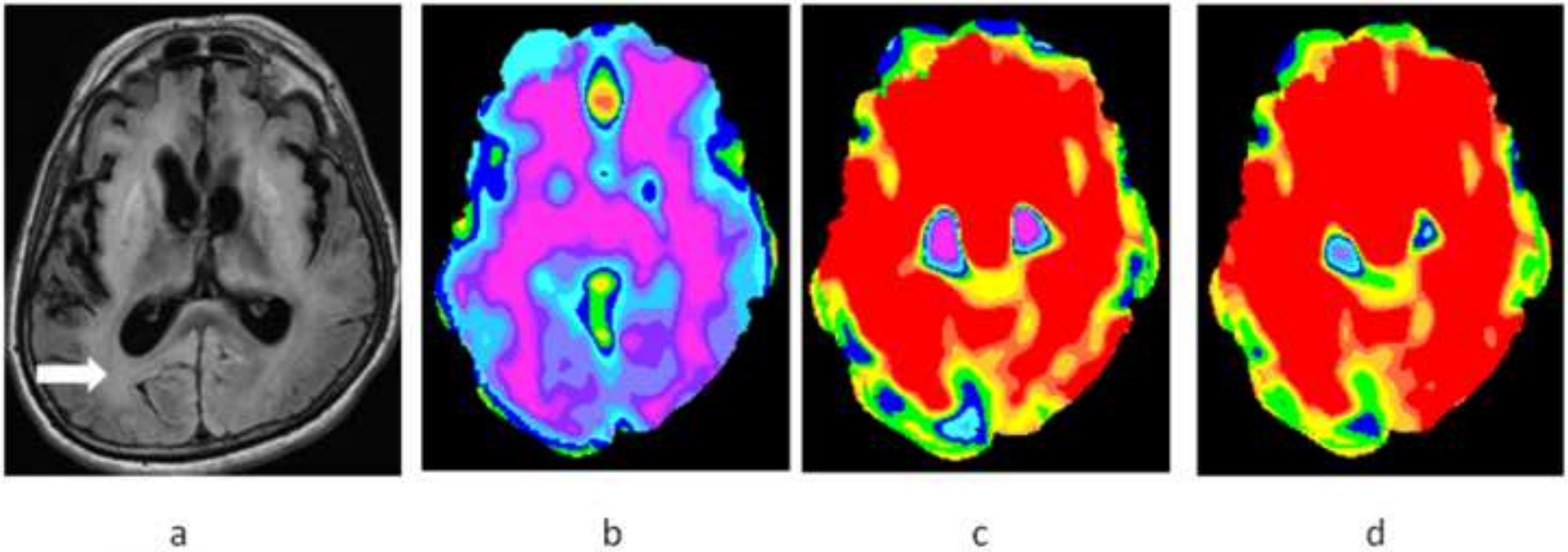

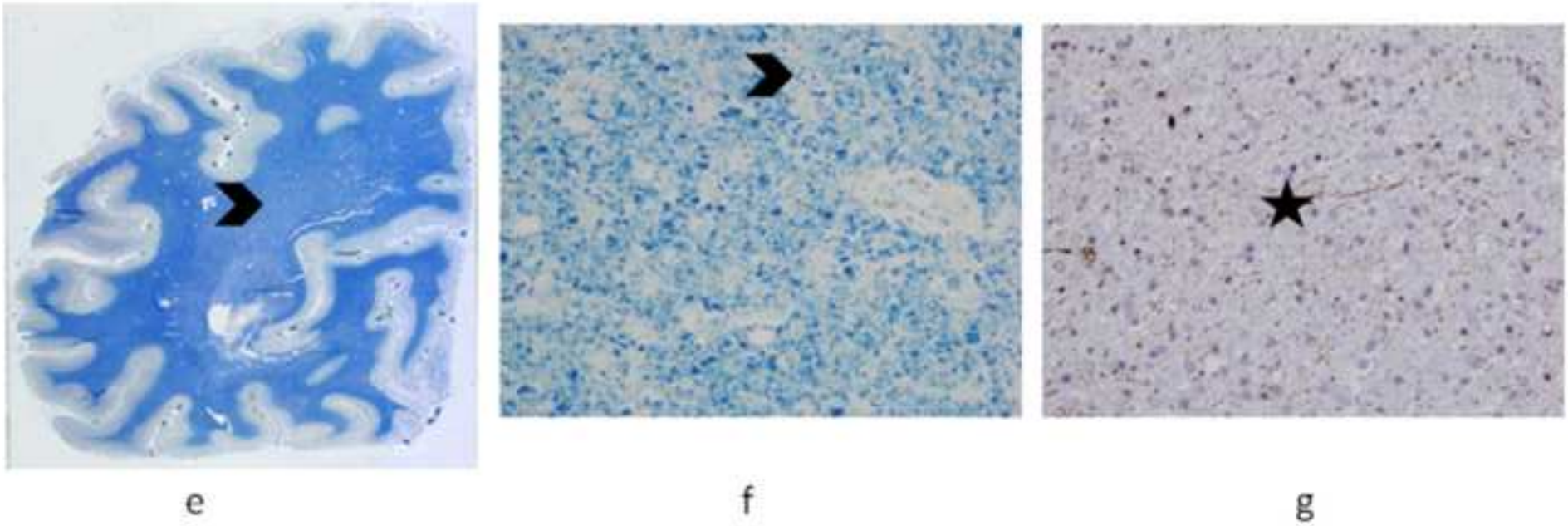

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Strasbourg december the 30, 2009

To the Editorial Staff

Dear Colleagues,

We are pleased to resubmit after revision the enclosed manuscript entitled "DIFFUSION TENSOR IMAGING IN HUMAN GLOBAL CEREBRAL ANOXIA: CORRELATION WITH HISTOLOGY IN A CASE WITH AUTOPSY" by Stéphane Kremer et al.

All modifications suggested by the editorial board have been taken into account :

- Point 0 : we modified the presentation of the manuscript.
- Point 1 : We completed the description of the lesions and their pathophysiology
- Point 2 : We agree with the reviewers comment about grey matter lesions after cardiac arrest resuscitation. But we focused our case report only on white matter abnormalities studied with DTI.
- Point 3 : The DTI examination has been performed 6 weeks after the cardiac arrest. We think that it could be more interesting to perform the MRI examination earlier. Diffusion-weighted imaging seems to be more accurate for the detection of lesions and the determination of their extension in the early acute period than other conventional MR sequences. Moreover Diffusion-weighted imaging could help determine the prognosis at the early phase after cardiopulmonary resuscitation, as the extension of the lesions on diffusion-weighted magnetic resonances images and the low value of ADC in the lesion seem to be related to poor outcome.
  But in this case the delay between DTI examination and autopsy was very short (8 days) and allows a direct comparison of both techniques.

We are looking forward to receive your editorial decision,

Sincerely yours

Stéphane Kremer