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Diffusion kurtosis imaging as a neuroimaging biomarker in patients with carbon monoxide intoxication

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ABSTRACT

Attempting suicide by burning charcoal can lead to carbon monoxide (CO) intoxication and cognitive deficits. Changes in white matter (WM) quantified by diffusion tensor imaging (DTI)-derived parameters have been validated to reflect cognitive test scores. As diffusion kurtosis imaging (DKI) measures biological microstructures using non-Gaussian diffusivity, we assessed the added-information of DKI with neuropsychological test scores as the major outcome measure.

A total of 45 patients were enrolled and compared with 30 age-matched controls. The patients were stratified into acute or chronic phase according to the intervals of intoxication and assessments. WM status was assessed using tract-based spatial statistics for DKI and DTI topographies, and the sensitivity/specificity of either model was tested using area under the curve (AUC) analysis. To evaluate their clinical significance, values of DKI- and DTI-derived parameters were extracted from seven regions of interest (ROI) and correlated with neuropsychiatric scores.

The kurtosis parameters were lower in the patients than in the controls but none of the parameters provided differentiations between the acute or chronic phase. Kurtosis fractional anisotropy (KFA) had a higher AUC than fractional anisotropy while the other 3 DTI parameters had higher AUC than the corresponding DKI ones. In clinical correlations, KFA value of right posterior WM correlated with visual memory ($r = 0.326$, $p = 0.029$), and KFA values of bilateral posterior WM correlated with the digit forward score (right: $r = 0.302$, $p = 0.043$; left: $r = 0.314$, $p = 0.036$).

Although DTI was more sensitive in reflecting disease status, KFA may be more sensitive and specific than fractional anisotropy in cognitive test score predictions.

1. Introduction

Charcoal burning is one of the most common methods of committing suicide in Taiwan (Kuo and Conwell, 2008) and the systemic sequelae are related to carbon monoxide (CO) intoxication. The cognitive deficits have been associated with white matter (WM) demyelinating and axonal injuries (Kim and Chang, 2003; Chang and Chang, 2010) while the diffusion tensor imaging (DTI) (Pierpaoli and Basser, 1996) is the most commonly used magnetic resonance imaging (MRI) method to evaluate the intracranial changes. DTI parameters such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) or radial diffusivity (RD) confer different pathological meanings (Chang and Chang, 2010) that also correlate significantly with memory, judgment, executive or verbal generation test scores (Chang and Lee, 2009; Chang and Chang, 2010, 2011; Chang and Hsiao, 2015).

Although the DTI-derived parameters have been proved to provide specifics of tissue disruption, theory of DTI is mainly based on Gaussian diffusivity. The assumption may not be completely valid in biological tissues showing non-Gaussian diffusion (Jensen, 2017). Analysis of diffusion kurtosis in the brain (Lazar and Jensen, 2008) may be more ideal in which Q-space imaging (Cohen and Assaf, 2002), diffusion spectrum imaging (DSI) (Wedeen and Hagmann, 2005) or diffusion

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kurtosis imaging (DKI) (Jensen and Helpern, 2010; Steven and Zhuo, 2013) have been subsequently developed. The direct comparison of DTI, DKI and DSI suggested that DKI have less angular error than that by DTI and qualitatively comparable to that of DSI (Glenn and Kuo, 2016). In terms of balancing the longer scanning time of DSI and systemic error of DTI, DKI may be potentially more suitable for the evaluation of WM changes in CO intoxication.

The DKI-derived parameters include mean kurtosis (MK), axial kurtosis (AK), radial kurtosis (RK) and kurtosis fractional anisotropy (KFA). MK is the average of the diffusion kurtosis along all diffusion directions, AK is the axial direction of the diffusion ellipsoid, RK is measured along the radial direction of the diffusion ellipsoid, and KFA is derived from the kurtosis tensor (Glenn and Helpern, 2015). Evidence from the translational research supported that increased kurtosis indicates increased cellular microstructural density, such as with cytotoxic edema or the growth of tumor cells (Hui and Fieremans, 2012). In contrast, decreased kurtosis in degenerative diseases (Struyfs and Van Hecke, 2015) often suggests myelin destruction or cell loss. Clinical validations have been confirmed. In demyelination or Alzheimer disease (Falangola and Guilfoyle, 2014), decreased MK were found. In acute infarction (Hui and Fieremans, 2012; Umesh Rudrapatna and Wieloch, 2014) or in brain tumors (Van Cauter and Veraart, 2012; Jiang and Jiang, 2015), increased MK were found. There is a paucity of information regarding the microstructural properties measured by DKI in acute and chronic encephalopathy after CO intoxication. Based on the literature of CO intoxication, demyelination and axonal changes have been well documented in pathology studies (Plum and Posner, 1962). We hypothesized that kurtosis parameters may be lower in the patient group.

To confirm the hypothesis, we performed a tract-based spatial statistical (TBSS) analysis in patients after CO intoxication and compared the topographical changes of DTI and DKI. The patients were further stratified into acute or chronic phase (Huang and Chang, 2013) for further understanding the temporal changes of DKI parameters in a cross sectional manner. For clinical significance, the DKI/DTI parameters changes in the corpus callosum or deep WM were measured in a region of interest (ROI)-based manner and correlated with neurobehavioral scores.

2. Material and methods

2.1. Subject enrollment

The neurology clinic at Kaohsiung Chang Gung Memorial Hospital recruited CO-intoxicated patients from February 2013 to July 2016. A total of 45 patients diagnosed with CO intoxication were included into this study. Diagnosis of CO intoxication was based on a history of charcoal burning or elevated carboxyhemoglobin level (> 10%) at the emergency room (Chang and Chang, 2011). The patients were further divided into acute (n = 19) and chronic phase (n = 26) depending on the intervals between intoxication and time of study enrollment (Chen and Chang, 2013; Chen and Huang, 2013). Patients with intervals less than 3 months were classified into the acute phase group.

In addition, 30 age-matched healthy subjects from the normative database were adapted as controls for neuropsychological testing and brain imaging comparison study. None of the control subjects had a history of neurologic or psychiatric disorders, and all had normal MR imaging and basic blood test results (liver and renal function tests, electrolytes, and complete blood cell counts). All patients and controls received cognitive tests and brain MRI. The ethics committee of Chang Gung Memorial Hospital approved the study protocol.

2.2. Cognitive testing

The general cognitive ability was evaluated by Mini-Mental State Examination (MMSE). Verbal episodic memory was evaluated by Chinese Version Verbal Learning Test (CVVLT) and the total scores of the 4 learning trials and 10 min recalls were used for the statistical analysis (Chang and Kramer, 2010). Visual memory was detected by the recollection of modified Rey-Osterrieth complex figure after a 10-min delay. We assessed semantic verbal fluency as recording the number of animals generated in one minute. Executive function assessments included digit forward span, digit backward span, time and correct lines in trail making test, Stroop Interference test and design fluency test. All of the tests were administered to both the patients and the controls for statistical comparison of non-standardized tests.

2.3. MR imaging protocols

MR imaging was performed using the 3.0 T scanner (Excite, GE Medical System, Milwaukee, WI) equipped with echo- planar capability. DTI was performed using a single- shot echo-planar sequence with gradients applied in 61 non-collinear directions. Forty contiguous slices of 4 mm thickness were obtained without any gap. For DKI, b values of 0, 1000 and 3000 s/mm^2 were used. Axial images were acquired using the following parameters: TR/TE = 12875/83.5; FOV, 192 mm; matrix size, 128 × 128. The total image acquisition time was 40 min.

2.4. Image preprocessing and TBSS

Diffusion Kurtosis Estimator (http://academicdepartments.musc.edu/cbi/dki) was used to process the DKI and DTI parameters (Tabesh and Jensen, 2011). In this study, the DTI parameters include FA, MD, AD, radial RD and the corresponding kurtosis parameters were KFA, MK, AK and RK.

The FA data from all of the subjects were aligned into a common space using a non-linear image registration toolkit (Rueckert and Sonoda, 1999). FA was calculated from realigned diffusion tensor and then projected onto a mean FA skeleton, with the resulting data used for voxel-wise comparison across subjects. The FA data were compared using permutation-based non-parametric inference on cluster size (Nichols and Holmes, 2002) and the Randomise 2.0 software. A restrictive statistical threshold was used (Threshold-Free Cluster Enhancement threshold, $p < 0.05$, corrected for multiple comparisons). Abnormal WM tracts by FA map were identified based on the atlas prepared at Johns Hopkins University (Wakana and Jiang, 2004).

After using the FA images to achieve non-linear registration and stages of skeleton formation, the projection vectors from each individual participant were estimated onto the mean FA skeleton. The non-linear warps and skeleton projections were then separately applied to the DTI or DKI eigenvalue images. The resulting statistical maps were threshold at $p < 0.05$ corrected at cluster level for multiple comparisons.

2.5. Regional correlation analysis

To understand the clinical significance, the DKI- or DTI-parameter values from 7 ROIs were extracted. The ROIs included genu (1,268), body (1, -12, 25) and splenium of corpus callosum (1, -38, 12), bilateral frontal corona radiata (right [29, 42, -1]; left [-29, 42, -1]) and bilateral posterior WM (right [33, -57, 12]; left [-33, -57, 12]) (Fig. 1A-E). Each ROI is represented by a diameter of 5 mm radius of sphere centered in the Montreal Neurological Institute coordinates and the mean value of the ROI sphere was extracted. The rationale for the setting of coordinate diameters enabled to represent the general conditions of WM areas without overlapping with the gray matter structure.

2.6. Statistical analysis

The data represented mean and standard deviation. Chi-Square test was used to compare the categorical variables and student's *t* test for