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Research report

Altered gray and white matter microstructure in Cushing's disease: A diffusional kurtosis imaging study

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ABSTRACT

Exposure to chronic hypercortisolism has multiple adverse effects on brain biology in humans. Cushing's disease (CD) represents a unique and natural human model for examining the effects of hypercortisolism on the brain. This cross-sectional study used Diffusional Kurtosis Imaging (DKI) to investigate the microstructure alterations in both white matter (WM) and gray matter (GM) of CD patients and to determine the relationship of these changes with clinical characteristics. DKI images were obtained from 15 active CD patients. DKI parametric maps were estimated through voxel-based analyses (VBA) and compared with 15 healthy controls matched for age, sex and education. In addition, correlations were analyzed between the altered DKI parameters and clinical characteristics. Compared with healthy controls, CD patients mainly exhibited significantly altered diffuse parameters in the GM and WM of the left medial temporal lobe (MTL). The mean values of increased radial diffusivity (RD) of CD patients in GM of the left hippocampus/parahippocampal gyrus correlated positively with the clinical severity of CD. Additionally, we also found altered kurtosis parameters in the cerebellum and frontal lobe. DKI imaging of CD patients could represent complementary information in both white matter and gray matter. The impairment of the left MTL might explain some part of the memory and cognition impairments in CD patients.

1. Introduction

Exposure to chronic hypercortisolism has multiple adverse effects on brain biology in humans (Aszalos, 2007), and a variety of memory problems and cognitive impairments can be induced by hypercortisolism (Sonino and Fava, 2001). The precise pathogenesis of hypercortisolism-induced brain alterations is still under exploration, and it is complicated by the fact that clinical diagnosis is limited to pathological examinations (Andela et al., 2015).

Cushing's syndrome (CS) is a rare clinical syndrome characterized by excessive endogenous exposure to cortisol. The majority (70%) of CS patients have adrenocorticotropic hormone (ACTH)-producing pituitary tumors (Cushing's disease (CD)) (Newell-Price et al., 2006). The average incidence of newly diagnosed CD cases was 2.4 cases per million per year (De Martin et al., 2006). Patients with CS/CD manifest all the characteristic features of excessive cortisol exposure, including memory problems and cognitive impairment (Newell-Price et al., 2006).

CD/CS represents a unique and natural human model for examining the effects of prolonged exposure to increased levels of endogenous cortisol on the brain (van der Werff et al., 2015). In 1992, Starkman et al. found a relationship among hippocampal volume reduction, memory dysfunction and elevated cortisol levels in CS patients (Starkman et al., 1992). Previous MRI studies have described alterations in brain structures, cerebral metabolites and brain function in CS/CD patients (Andela et al., 2015). These abnormalities are believed to be associated with clinical characteristics (Santos et al., 2014). Some of these abnormalities are partially reversible after resolution of the hypercortisolism (Bourdeau et al., 2002; Khiat et al., 2000). Approximately five structural MRI studies examining brain characteristics have evaluated the gray matter (GM) volumes with Voxel-based morphometry (VBM) (Andela et al., 2013). Recently, two diffusion tensor-

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imaging (DTI) studies had demonstrated widespread reductions in integrity of white matter (WM) tracts throughout the brain (Pires et al., 2015; van der Werff et al., 2014). Previous structural studies mainly evaluated the hippocampus, and the first MRI studies in CS/CD patients did not have access to modern and more sophisticated analytical tools (Andela et al., 2015). Moreover, all the previous structural studies evaluated the gray matter or white matter separately.

The hippocampus is easily affected by long-term exposure to glucocorticoids because this area is rich in mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) (de Kloet et al., 2005). However, the detrimental effects of hypercortisolism on the human brain are mainly mediated by the GRs through gene transcription (Forget et al., 2002), and unlike the MRs, GRs are widely distributed throughout the brain (Alonso, 2000). Thus, the effects of hypercortisolism on the brain may be global, and an explorative whole-brain structural analysis, including both the gray matter and white matter, is needed.

Diffusional Kurtosis Imaging (DKI), which aims to describe the non-Gaussian aspect of water diffusion, is an extension of DTI in that it not only maintains the ability to estimate the standard diffusion tensor metrics but also provides non-Gaussian diffusion, termed diffusional kurtosis (Hui et al., 2008). As an extension of DTI, with improved accuracy and sensitivity in detecting the microstructural changes, not only could diffusion parameters of DKI provide additional information regarding tissue substructure of white matter, especially in regions containing tract crossings, but the kurtosis parameters could also provide information on the microstructural complexity of gray matter (Jensen et al., 2005). Additionally, the increase of the diffusion parameters in DKI also correlates with gray matter reduction in Alzheimer's disease (Struyfs et al., 2015; Wang et al., 2017; Yuan et al., 2016). DKI has been used in many studies, including studies on both normal and pathological conditions, such as cerebral infarction, aging, Alzheimer's disease and Parkinson disease (PD) (Guo et al., 2016). However, to our knowledge, no assessment has been performed to investigate the microstructural properties of patients with hypercortisolism using DKI.

The purpose of this explorative whole brain study is to evaluate the microstructural changes in CD patients. Our hypothesis was that DKI might provide complementary information in both white matter and gray matter, especially in the structures around the hippocampus. We also analyzed the correlations between different aspects of brain microstructural changes and clinical characteristics.

2. Results

2.1. Demographic and clinical data

Table 1 shows the demographics, clinical severity, hormone levels and disease duration of the CD patients and healthy controls (HC). Because of the matched study design, no differences in age or sex between patients with CD and controls were present. Additionally, there was no difference in education time between CD patients and control subjects. None of the subjects in the healthy control group reported any comorbidities or was taking exogenous glucocorticoid medication.

2.2. Group differences in WM and GM

Compared with the HC group, the CD group showed widespread alterations in WM, including increased mean diffusion (MD) in the splenium of the corpus callosum (CC), the bilateral frontal lobe, and the left temporal lobe. Axial diffusivity (AD) increased mainly in the bilateral frontal lobe, and radial diffusivity (RD) increased mainly in the left temporal lobe. Fractional anisotropy (FA) decreased mainly in the splenium of the corpus callosum and the left temporal lobe (Fig. 1A). The results are listed in Table 2.

In the gray matter, compared with the HC group, the CD group showed increased MD, RD and AD in the left hippocampus/-parahippocampal gyrus and the left temporal lobe, increased radial kurtosis (RK) in the right cerebellar hemisphere, decreased axial kurtosis (AK) in the left frontal lobe and decreased mean kurtosis (MK) in left cerebellar hemisphere (Fig. 1B). The results are listed in Table 3.

Notably, the alterations in GM and WM overlapped in the left medial temporal lobe, including increased MD and RD in the WM of the left temporal lobe, and increased MD and RD in the GM of the left hippocampus/parahippocampal gyrus and the left temporal lobe (Fig. 2).

Table 1
Demographic and clinical characteristics of study patients and control subjects.

Characteristics	CD (n = 15)	HC (n = 15)	P values
Age (years)	39.0 ± 10.21	36.87 ± 9.29	0.51
Gender (male/female)	3/12	3/12	1
Education time (years)	13.47 ± 1.99	14.00 ± 2.27	0.5
Illness duration (months)	50.77 ± 13.11	/	
Urinary Free Cortisol (μg/24 h)	786.91 ± 612.72	/	
Plasma Cortisol(8AM) (μg/dL)	28.23 ± 10.94	/	
Plasma ACTH (pg/mL)	107.89 ± 69.58	/	
CSI	6 ± 2	/	
QoL	49 ± 8	/	

Abbreviations: Values are expressed as mean ± SD. CD = CD patient group; HC = healthy control group. The P value for age level between two groups was obtained by two sample *t*-test; The P value for gender distribution in the two groups was obtained by chi-square test.

2.3. Correlation analysis

In the correlation analyses of CD patients, the mean values of increased RD of the GM in the left hippocampus/parahippocampal gyrus correlated positively with the Cushing's syndrome severity index (CSI) scores ($r = 0.55$, $p = 0.034$) (Fig. 3). No other correlations were found for any DKI values in the WM with any of the hormone levels, clinical severity or QoL. Furthermore, there was no correlation between the disease duration and altered DKI values in the ROI of the GM. After excluding the outsider case at the extreme (aCD8), the mean values of the increased RD of the GM in the left hippocampus/parahippocampal gyrus correlated positively with the CSI scores, and a positive correlation was found between the mean values of the increased MD and the CSI scores. The details of the correlation analyses are presented in the additional file-3.

3. Discussion

To our knowledge, this is the first study demonstrating the microstructural properties in both white matter and gray matter of patients with hypercortisolism using DKI. In the present study, preliminary results showed an increased water molecule diffusivity in both the GM and WM of the left medial temporal lobe. Furthermore, the increased diffusion parameter values of the GM in left hippocampus/parahippocampal gyrus correlated positively with the clinical severity of the CD. This is the major finding of our study.

The mechanism through which memory and cognition are impaired in patients with hypercortisolism is still unclear. The medial temporal lobe (MTL) is a key region in the formation and consolidation of conscious or declarative memory and includes the hippocampus and parahippocampal gyrus (Schultz et al.,