Received:
3 September 2015

Revised:
13 January 2016

Accepted:
18 February 2016

<http://dx.doi.org/10.1259/bjr.20150732>

Cite this article as:

Jiang D-Z, Zhong Y, Zhou D-Y, Wu W-Q, Wu G-Y, Quan H. Application of brain multi-*b*-value diffusion-weighted imaging (DWI) in adolescent orphans from AIDS families. *Br J Radiol* 2016; **89**: 20150732.

FULL PAPER

Application of brain multi-*b*-value diffusion-weighted imaging (DWI) in adolescent orphans from AIDS families

¹DA-ZHEN JIANG, ¹YANG ZHONG, ¹DING-YI ZHOU, ¹WEI-QING WU, ²GUANG-YAO WU, PhD and ¹HONG QUAN, PhD

¹Key Laboratory of Artificial Micro- and Nano-structures of Ministry of Education, School of Physics and Technology, Wuhan University, Wuhan, China

²Medical Imaging Department of the Zhongnan Hospital, Wuhan University, Wuhan, China

Address correspondence to: Dr Hong Quan

E-mail: csp6606@sina.com

Da-Zhen Jiang and Yang Zhong contributed equally to this work.

Objective: To evaluate the application value of multi-*b*-value diffusion-weighted imaging (DWI) with mono-exponential model and stretched-exponential model in the diagnosis of HIV-positive patients.

Methods: Multi-*b*-value (0, 50, 150, 200, 400, 600, 800 s mm⁻²) DWI was performed in 23 adolescent orphans from AIDS families, including 15 HIV-positive subjects and 8 HIV-negative healthy subjects. Apparent diffusion coefficient (ADC) values were fitted by mono-exponential model; distribution diffusion coefficient (DDC) values and heterogeneity index (α) values were fitted by stretched-exponential model in bilateral basal ganglia, then non-parametric tests were performed.

Results: The signal intensity attenuation in multi-*b*-value DWI could be well described by both mono-exponential model and stretched-exponential model. In the left basal ganglia, mean α -values in HIV-positive subjects ($\alpha = 0.848 \pm 0.068$) were significantly lower than that in healthy subjects ($\alpha = 0.923 \pm 0.050$, $p = 0.013$). There was no statistical difference of α -values between HIV-positive subjects and healthy control subjects in the right basal

ganglia. Apart from these, there were also no statistical differences of DDC values or ADC values between two groups in bilateral basal ganglia (all $p > 0.05$). In bilateral basal ganglia, DDC values were positively correlated with ADC values in HIV-positive patients (right basal ganglia: $r = 0.832$, $p = 0.000$; left basal ganglia: $r = 0.770$, $p = 0.001$) as well as in healthy cases (right basal ganglia: $r = 0.927$, $p = 0.001$; left basal ganglia: $r = 0.878$, $p = 0.004$). Receiver operating characteristic (ROC) curve analysis yielded area under the ROC curve (A_z) values of 0.817 ($p = 0.014 < 0.05$) in the left basal ganglia. The sensitivity and specificity were 62.5% and 86.7%, respectively.

Conclusion: Through the study of asymptomatic HIV-positive subjects when $b < 1000$ s mm⁻², we can see stretched-exponential model DWI can provide more information than mono-exponential model DWI.

Advances in knowledge: Multi-*b*-value DWI was performed in subjects with HIV. DWI measurements could be neuroimaging biomarkers of cerebral injury in the course of HIV infection.

INTRODUCTION

Since AIDS was first reported in 1981, 36.9 million (34.3 million–41.4 million) people globally are living with HIV (end 2014).¹ It is estimated that about one thousand children are born to HIV-positive mothers every day.² In China, about 0.5 million people are infected with HIV and 15% of HIV-infected people are in the age range of 15–24 years. A majority of AIDS adolescents live in developing countries.¹ AIDS severely harms adolescent health; therefore, adolescents with AIDS have become a focal point in AIDS research.

HIV/AIDS has resulted in a substantial increase in the number of orphans internationally, and United Nations

International Children's Emergency Fund estimates that by 2020, 40 million youth may have lost one or both of their parents because of HIV/AIDS.³ Living in a unique social environment, orphans with AIDS endure double pressure of disease and family and therefore are a vulnerable group. HIV-positive adolescent orphans mentioned in this article were born with HIV. Their incubation period is quite long. Although they were in the incubation period, the immune system of HIV-positive adolescent orphans might be different from the adolescent orphans of the same age.

MRI is an attractive imaging modality in clinic, because of its exquisite soft tissue contrast and lack of ionizing

radiation.⁴ MRI technology and functional MRI technology have broad application in the diagnosis of HIV-infection-related diseases.^{5–13} Advanced MRI techniques include perfusion-weighted imaging (PWI), diffusion tensor imaging, MR spectroscopy (MRS) and diffusion-weighted imaging (DWI). Suzuki et al⁵ reported that MRI can diagnose toxoplasmosis encephalitis in HIV infection. Bladowska et al evaluated early cerebral dysfunction in asymptomatic HIV infection by PWI.^{6,14} Mueller-Mang et al⁷ studied the cervical spinal cord in HIV-positive patients by diffusion tensor imaging. Harezlak et al⁸ evaluated central nervous system injury in HIV infection by proton MRS. Zacharia et al⁹ studied early stage of central nervous system lymphoma in HIV infection by DWI and MRS. Conventional DWI (which is usually performed using b -values of 0 and 1000 s mm^{-2})¹⁵ is widely used in the diagnosis, prognosis and treatment assessment of diseases.^{16–18} Recently, scholars have studied HIV-positive patients with conventional DWI^{9,11,13} and have made certain achievements. However, multi- b -value DWI applied to studying HIV-positive patients is much less concerned. Moreover, asymptomatic HIV infection, a group which is often neglected, is hardly taken into consideration in scientific research.^{6,9,14,19}

In this study, asymptomatic HIV-positive adolescent orphans, who were born with HIV owing to mother-to-child transmission, were scanned using DWI with multi- b -value. The immune system of infants was immature and immune system function was poor. The subjects in this study were born with HIV. Although they are in the asymptomatic stage, their nervous system may have been attacked by HIV. Some scholars^{6,14,19–21} indicated that central nervous system has been involved in the course of HIV infection in the early stage of the disease. We hope to identify the damaged parts of the nervous system and make a prediction of opportunistic infections by analyzing apparent diffusion coefficient (ADC), distribution diffusion coefficient (DDC) and heterogeneity index (α) values.

METHODS AND MATERIALS

Patients

From July 2013 to August 2013, 23 adolescent orphans (13 males and 10 females; mean age 16.4 ± 1.4 years, range 14–18 years) were included. 15 of them (8 males and 7 females; median age 17 years) were born with HIV owing to mother-to-child transmission. The remaining 8 adolescent orphans (5 males and 3 females; median age 17 years) were born without HIV, regarded as healthy control subjects. In this study, the exclusion criteria were as follows:

- (1) history of neurological diseases (e.g. opportunistic intracerebral infections, brain neoplasms)
- (2) history of psychiatric disease (e.g. depression, schizophrenia)
- (3) definite changes in brain structure and the presence of abnormal signal on conventional MRI examination.

All of the subjects and data were from the Zhongnan Hospital of Wuhan University. The study was approved by the School of Physical Science and Technology, Wuhan University and Ethics Committee of the Zhongnan Hospital of Wuhan University. All participants have been informed of the scanning process before this study and submitted their written approval letters to engage in this study.

MRI

All subjects were examined with a 3.0-T MR scanner (Siemens MAGNETOM® Trio 3.0 T; Siemens Healthcare, Erlangen, Germany). Whole brain conventional MRI involves: sagittal turbo spin echo (TSE) sequence T_1 weighted imaging, repetition time (TR) = 700 ms, echo time (TE) = 9.6 ms; axial TSE-fat saturation sequence T_2 weighted imaging, TR = 2000 ms, TE = 76 ms; coronal TSE turbo inversion recovery magnitude sequence T_2 weighted imaging, TR = 3800 ms, TE = 68 ms. The multi- b -value DWI was performed with an echoplanar imaging sequence, and the orientation of DWI is the lateral axis which is identical to the conventional MRI. Scanning parameters are TR = 3400 ms, TE = 85 ms, flip angle = 90° , number of excitations = 4, matrix = 192×192 , scanning slices = 20, slice thickness = 5 mm, the interslice distance = 0 mm, field of view = 219×219 mm and the scan time is 62–65 s (Figure 1).

Statistical methods

Statistical parameter mapping (SPM) software was used to realign all multi- b -value DWIs and complete space smoothing. Oval regions of interest were placed in the ventral area of lenticular nucleus in bilateral basal ganglia on DWIs with MRIcro software. The sizes of regions of interest range from 95 to 100 mm^2 . All DWI signal strength was fitted with Origin 8.0 software (OriginLab). The initial values are needed to fit the data. However, different initial values will have a certain impact on the results of fitting. In order to obtain accurate data, we repeated fitting three times and then got three ADC values, three DDC values and three α -values. Next, we calculated mean ADC values, DDC values and α -values. DWI signal strength was fitted, following Equations (1) and (3). The mono-exponential model is mathematically described as follows:

$$S(b)/S_0 = \exp(-ADC \times b) \quad (1)$$

where $S(b)$ is the signal intensity with diffusion weighting value, S_0 is the signal intensity when $b = 0 \text{ s mm}^{-2}$, b is the b -value, which is calculated for a standard square-shaped gradient pulse pair as follows:

$$b = \gamma^2 \times G^2 \times \delta^2 (\Delta - \delta/3) \quad (2)$$

where, Δ is the interval between the leading edges of the motion probing gradient pulses, δ is the duration of one MPG pulse, G is the strength of the motion probing gradients and γ is the gyromagnetic ratio. Firstly, *in vivo* water movement of tissues is influenced by various factors such as pressure gradient and capillary perfusion and osmotic gradients and bulk tissue movements. Secondly, the motion of water is impeded by microstructures such as cell membranes and macromolecules. Thus, the measurement of diffusion coefficient, in tissues is only an estimation of pure water diffusivity and is termed ADC.⁴ The stretched-exponential model is mathematically described as follows:

$$S(b)/S_0 = \exp[-(DDC \times b)^\alpha], \quad (3)$$

where $S(b)$, S_0 and b are as previously mentioned. DDC is the distribution diffusion coefficient and α is the heterogeneity index.

Figure 1. Images from an HIV-positive 16-year-old female. Diffusion-weighted imaging (DWI) with *b*-value of 0 s mm⁻² (a), 50 s mm⁻² (b), 150 s mm⁻² (c), 200 s mm⁻² (d), 400 s mm⁻² (e), 600 s mm⁻² (f) and 800 s mm⁻² (g) in the basal ganglia. The red ellipse in each DWI is the regions of interest. For colour image see online.

Statistical analyses

Statistical analyses were processed with SPSS® Statistics 19.0 software (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL). Differences between the HIV-positive subjects and healthy control subjects were assessed according to each DWI parameter (ADC, DDC and α) using non-parametric tests. Correlation between ADC value and DDC value was assessed using Pearson's correlation coefficient. If *p*-values < 0.05, it was considered statistically significant. The ROC curve analysis was performed using SPSS v. 19.0. The diagnostic accuracy was calculated by measuring the area under the ROC curve (*Az*).

RESULTS

Fitting results

As *b*-value (within $b < 1000$ s mm⁻²) increases gradually, both mono-exponential model and stretched-exponential model describes well signal strength attenuation in DWI (Figure 2).

Statistical results

Results are displayed in Tables 1–3. In the left basal ganglia, the mean α -value in HIV-positive subjects ($\alpha = 0.848 \pm 0.068$) was significantly lower than that in healthy subjects ($\alpha = 0.923 \pm 0.050$, $p = 0.013$). There was no statistical difference in α -values between HIV-positive subjects and healthy control subjects in the right basal ganglia ($p > 0.05$). The results did not show any significant differences between HIV-positive subjects and healthy control subjects with regard to the DDC values and ADC values (all $p > 0.05$) in bilateral basal ganglia (Tables 1 and 2). In the basal ganglia, ADC and DDC values of the same group showed significant positive correlation (Table 3). The area under the ROC curve (*Az*) was 0.817 ($p = 0.014 < 0.05$) in the left basal ganglia. The α ROC curve cut-off point is 0.913, and the

sensitivity and specificity were 62.5% and 86.7%, respectively (Figure 3).

DISCUSSION

DWI is a kind of non-invasive MRI, which can reflect the physiological structure and pathological state of *in vivo* tissue according to the Brownian motion of water molecules.^{16,17} The *b*-value is an important parameter in DWI. It is a summary

Figure 2. Diffusion-weighted imaging (DWI) signal attenuation data (taken from a voxel in DWI of basal ganglia of an HIV-positive subject and a healthy subject) with varying values of *b*. sb, single strength with varying values of *b*; s0, single strength when *b*-value is 0.

Table 1. Mean heterogeneity index (α), distribution diffusion coefficient (DDC) and apparent diffusion coefficient (ADC) values in regions of interest (mean $\pm$ standard deviation)

Subjects	α	DDC ($\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$)	ADC ($\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$)
Right HIV+ BG	0.906 $\pm$ 0.067	0.730 $\pm$ 0.104	0.782 $\pm$ 0.070
Left HIV+ BG	0.848 $\pm$ 0.068 ^a	0.707 $\pm$ 0.092	0.805 $\pm$ 0.078
Right healthy BG	0.931 $\pm$ 0.036	0.782 $\pm$ 0.094	0.819 $\pm$ 0.088
Left healthy BG	0.923 $\pm$ 0.050	0.756 $\pm$ 0.073	0.793 $\pm$ 0.067

BG, basal ganglia; HIV+, HIV-positive.

^a α -value in HIV-positive subjects is significantly lower than that in healthy subjects ($p < 0.05$).

measure of different pulse sequence parameters and captures the level to which the signal is made sensitive to the diffusion process.²² The mono-exponential model of DWI shows that the diffusion mode of water molecules within a voxel is single. Then the diffusion rate within a voxel can be quantified by means of the ADC value. The stretched-exponential model introduced a new parameter (α), varying between 0 and 1 and defines α as heterogeneity index, which relates to the degree of intravoxel water diffusion heterogeneity.^{23,24} According to Equation (2), α near 1 indicates low intravoxel diffusion heterogeneity, $\alpha < 1$ shows a distribution of different diffusion rates within the voxel and α near 0 suggests a higher degree of multi-exponential signal decay. It is regarded that there is a continuous distribution rate within a voxel, according to the stretched-exponential model. The DDC can be regarded as an ADC approximation which is weighted by the volume fraction of water in each part of the continuous distribution.⁴ As we all know, multiple experimental data points might reduce systematic errors which occur when few data points are used in the calculation.^{25–27} In our study, the ADC, DDC and α -values which were fitted by signal strength of seven b -values might be more accurate than that by traditional two b -values. At present, most studies on stretched-exponential model DWI were almost under the situation that $b > 1000 \text{ s mm}^{-2}$, neglecting the study when $b < 1000 \text{ s mm}^{-2}$.^{15,28,29} The study of stretched-exponential model DWI is a supplement to mono-exponential model DWI when $b < 1000 \text{ s mm}^{-2}$. In this study, asymptomatic HIV-positive adolescent orphans were performed DWI with multi- b -value within $b < 1000 \text{ s mm}^{-2}$.

In this study, the results showed there was statistical difference of α -values between asymptomatic HIV-positive subjects and healthy control subjects in the left basal ganglia. It indicated multi- b -value DWI can reflect HIV preclinical abnormality that conventional imaging system cannot display. In this study only α -values showed statistical difference between two groups, therefore, it is the main feature. The basal ganglia, situated at the

base of the forebrain, have relationship with lots of functions including stabilizing voluntary motor movements, regulating muscle contractility and processing of proprioception afferent impulse.³⁰ Basal ganglia plays very important roles in the normal physiological activity of human; therefore, many scholars have studied on this region.^{8,31,32} Suzuki et al reported a case of patient with AIDS with small yet highly intense signals in the basal ganglia but no imaging features of toxoplasmosis encephalitis when brain gadolinium T_1 weighted imaging was performed. In the subsequent treatment, the course of treatment and the clinical symptoms of the patient could fully prove that abnormal high signal intensity can provide important reference value for the diagnosis of toxoplasmosis encephalitis.⁵ Our study also showed that the basal ganglia of the brain were abnormal before the appearance of clinical symptoms and imaging features of opportunistic intracerebral infections. Of course, more than one disease can cause abnormality in the basal ganglia, and what kind of disease causing this abnormality remains to be investigated.

Our experimental results showed that there was abnormality in unilateral basal ganglia in HIV-infected subjects. In the left basal ganglia, mean α -values in HIV-positive subjects were significantly lower than that in healthy subjects ($p = 0.013$). It indicates that the brain structure of subjects might be abnormal in the left basal ganglia. Bekiesinska et al made a summary of unilateral basal ganglia lesions in children and adults.³³ A scholar showed that there was abnormality in unilateral brain regions of asymptomatic HIV-infected subjects. Bladowska found that the relative blood volume values of HIV-infected persons were significantly lower than those of healthy controls in the right side of the temporal-parietal cortex and the left side of prefrontal cortex.^{6,14} All of the HIV-infected persons had no mental illness, brain opportunistic infections and intracranial tumours, and no definite changes in brain structure and

Table 3. Correlation analysis between distribution diffusion coefficient and apparent diffusion coefficient values in the same group

Subjects	r -value	p -value
Right HIV+ BG	0.832	0.000
Left HIV+ BG	0.770	0.001
Right healthy BG	0.927	0.001
Left healthy BG	0.878	0.004

BG, basal ganglia; HIV+, HIV-positive.

Table 2. Non-parametric tests heterogeneity index (α), distribution diffusion coefficient (DDC) and apparent diffusion coefficient (ADC) values

Subjects	α	DDC	ADC
p -value (right BG)	0.548	0.265	0.169
p -value (left BG)	0.013	0.294	0.506

BG, basal ganglia.

Figure 3. The heterogeneity index receiver operating characteristic (ROC) curve in the left basal ganglia.

abnormal signal exists in conventional MRI examination. They thought that PWI could reflect changes in unilateral brain regions before HIV induces neurocognitive disorders. The situations of asymptomatic HIV-positive subjects in our study were same with those in the study by Bladowska. Our experimental results also showed abnormality in unilateral brain regions in HIV-infected subjects. It showed that water molecule diffusion and the way of signal intensity attenuation were abnormal in the organization of early subclinical stage.

However, many scholars^{34–36} showed that there was abnormality in bilateral basal ganglia in some patients. Corti et al³⁴ found that there was abnormality in bilateral basal ganglia in patients with AIDS with central nervous system cryptococcosis. Hegde et al³⁵ showed bilateral basal ganglia lesions in a 37-year-old HIV-seropositive male with central nervous system toxoplasmosis by MRI. Lee et al³⁶ found that there was abnormality in bilateral basal ganglia in diabetic uremic patient by DWI. However, there are no contradictions between our study and their studies,^{34–36} because our objects and the former research objects were different. There were opportunistic infections or brain tumours or disease infection in their subjects. Our subjects are asymptomatic HIV-positive.

Mono-exponential model DWI has important clinical value in diagnosis of many diseases.^{29,37} There were some good results in the diagnosis of patients with HIV/AIDS. Cloak et al³⁸ showed that there was statistical difference of ADC values between HIV infections and HIV-negative healthy control subjects. This study showed that in

bilateral basal ganglia, DDC values are positively correlated with ADC values in HIV-positive subjects as well as in healthy subjects (all $p < 0.05$). Meanwhile, there is similar conclusion in some studies.^{29,37} It also reflects the close relationship between mono-exponential model DWI and stretched-exponential model DWI.

In addition, the stretched-exponential model DWI has two parameters (DDC and α), which can provide more plentiful information than the mono-exponential model DWI. In some studies, α is an important evaluation index. Kwee et al¹⁵ found that mean α -values in the area of high-grade gliomas were significantly lower than that in the contralateral basal ganglia of tumours. Our study showed that in the left basal ganglia, there was statistical difference of α -values between HIV-positive subjects and healthy control subjects. However, there was no statistical difference of all DDC values and ADC values between HIV-positive subjects and healthy control subjects (all $p > 0.05$). This indicated that α -value could show the difference which the DDC and the ADC values could not reflect. It indicated that stretched-exponential model DWI is a supplement to mono-exponential model DWI in the study of asymptomatic HIV-positive subjects when $b < 1000 \text{ s mm}^{-2}$.

However, there are some deficiencies in this research. Firstly, the object of this study is a special group so that we had some difficulties in collecting samples, leading to the limited sample size. Secondly, the basal ganglia were chosen as the sole research part in this study. We would consider more parts of the brain in the future research.

CONCLUSION

In our study, the signal intensity attenuation in multi- b -value DWI can be well described by both mono-exponential model and stretched-exponential model. Through the study of asymptomatic HIV-positive subjects when $b < 1000 \text{ s mm}^{-2}$, we can see stretched-exponential model DWI can provide more information than mono-exponential model DWI. This research might play a role in making a prediction of opportunistic infections for the asymptomatic HIV-positive subjects.

FUNDING

This work was supported by the National Natural Science Foundation of China (10875092), the Natural Science Foundation of Hubei Province, China (2012FKB04449) and the Elekta (Shanghai) Instruments Ltd Teaching and Research Foundation. We would like to express our heartfelt gratitude to the Medical Imaging Division of the Zhongnan Hospital of Wuhan University.

REFERENCES

- UNAIDS. Together we will end AIDS [EB/OL]. Available from: <http://www.unaids.org/en/>
- Radfar SR, Sedaghat A, Banihashemi AT, Gouya M, Rawson, RA. Behaviors influencing human immunodeficiency virus transmission in the context of positive prevention among people living with HIV/acquired immunodeficiency syndrome in Iran: a qualitative study. *Int J Prev Med* 2014; **5**: 976–83.
- Maughan-Brown B. Stigma rises despite antiretroviral roll-out: a longitudinal analysis in South Africa. *Social Sci Med* 2010; **70**: 368–74. doi: <http://dx.doi.org/10.1016/j.socscimed.2009.09.041>
- Tam HH, Koh DM. *Diffusion-weighted MR imaging [M]//Functional Imaging in Oncology*. Springer Berlin Heidelberg; 2014. pp. 307–24.
- Suzuki K, Masuya M, Matsumoto T, Ito N, Ohishi K, Maeda M, et al. High-intensity signals in the basal ganglia from gadolinium-enhanced T1-weighted MRI as an early change in toxoplasma encephalitis in an AIDS patient. *J Infect Chemother* 2010; **16**: 135–8. doi: <http://dx.doi.org/10.1007/s10156-010-0026-Z>
- Bladowska J, Knysz B, Zimny A, Małyszczak K, Kołtowska A, Szewczyk P, et al. Value of perfusion-weighted MR imaging in the assessment of early cerebral alterations in neurologically asymptomatic HIV-1-positive and HCV-positive patients. *PLoS One* 2014; **9**: e102214. doi: <http://dx.doi.org/10.1371/journal.pone.0102214>
- Mueller-Mang C, Law M, Mang T, Fruehwald-Pallamar J, Weber M, Thurnher MM. Diffusion tensor MR imaging (DTI) metrics in the cervical spinal cord in asymptomatic HIV-positive patients. *Neuroradiology* 2011; **53**: 585–92. doi: <http://dx.doi.org/10.1007/s00234-010-0782-6>
- Harezlak J, Cohen R, Gongvatana A, Taylor M, Buchthal S, Schifitto G, et al; HIV Neuroimaging Consortium. Predictors of CNS injury as measured by proton magnetic resonance spectroscopy in the setting of chronic HIV infection and CART. *J Neurovirology* 2014; **20**: 294–303. doi: <http://dx.doi.org/10.1007/s13365-014-0246-6>
- Zacharia TT, Law M, Naidich TP, Leeds NE. Central nervous system lymphoma characterization by diffusion-weighted imaging and MR spectroscopy. *J Neuroimaging* 2008; **18**: 411–17. doi: <http://dx.doi.org/10.1111/j.1552-6569.2007.00231.x>
- Pellegrino D, Gerhardt J, Porfirio FM, Santos EdB, Dauar RF, Oliveira AC, et al. Ring enhancing intracranial lesion responding to antituberculous treatment in an HIV-infected patient. *Rev Inst Med Trop São Paulo* 2010; **52**: 285–7.
- Soto-Hernández JL, Moreno-Andrade T, Góngora-Rivera F, Ramírez-Crescencio MA. Nocardia abscess during treatment of brain toxoplasmosis in a patient with aids, utility of proton MR spectroscopy and diffusion-weighted imaging in diagnosis. *Clin Neurol Neurosurg* 2006; **108**: 493–8. doi: <http://dx.doi.org/10.1016/j.clineuro.2005.01.010>
- Gongvatana A, Cohen RA, Correia S, Devlin KN, Miles J, Kang H, et al. Clinical contributors to cerebral white matter integrity in HIV-infected individuals. *J Neurovirol* 2011; **17**: 477–86. doi: <http://dx.doi.org/10.1007/s13365-011-0055-0>
- Park BS, Yu IK, Lee BH. Progressive multifocal leukoencephalopathy isolated to posterior fossa in a patient with AIDS: DWI and 1H-MRS features. *J Korean Soc Radiol* 2010; **63**: 403–7. doi: <http://dx.doi.org/10.3348/jksr.2010.63.5.403>
- Bladowska J, Zimny A, Kołtowska A, Szewczyk P, Knysz B, Gąsiorowski J, et al. Evaluation of metabolic changes within the normal appearing gray and white matters in neurologically asymptomatic HIV-1-positive and HCV-positive patients: magnetic resonance spectroscopy and immunologic correlation. *Eur J Radiol* 2013; **82**: 686–92. doi: <http://dx.doi.org/10.1016/j.ejrad.2012.11.029>
- Kwee TC, Galbán CJ, Tsien C, Junck L, Sundgren PC, Ivancevic MK, et al. Intravoxel water diffusion heterogeneity imaging of human high-grade gliomas. *NMR Biomed* 2010; **23**: 179–87. doi: <http://dx.doi.org/10.1002/nbm.1441>
- Partridge SC, McDonald ES. Diffusion weighted magnetic resonance imaging of the breast: protocol optimization, interpretation, and clinical applications. *Magn Reson Imaging Clin N Am* 2013; **21**: 601–24. doi: <http://dx.doi.org/10.1016/j.mric.2013.04.007>
- Boyer AC, Gonçalves LF, Lee W, Shetty A, Holman A, Yeo L, et al. Magnetic resonance diffusion-weighted imaging: reproducibility of regional apparent diffusion coefficients for the normal fetal brain. *Ultrasound Obstet Gynecol* 2013; **41**: 190–7. doi: <http://dx.doi.org/10.1002/uog.11219>
- Mortimer A, O'leary S, Bradley M, Renowden SA. Pitfalls in the discrimination of cerebral abscess from tumour using diffusion-weighted MRI. *Clin Radiol* 2010; **65**: 488–92. doi: <http://dx.doi.org/10.1016/j.crad.2009.12.012>
- Lentz MR, Kim WK, Lee V, Bazner S, Halpern EF, Venna N, et al. Changes in MRS neuronal markers and T cell phenotypes observed during early HIV infection. *Neurology* 2009; **72**: 1465–72. doi: <http://dx.doi.org/10.1212/WNL.0b013e3181a2e90a>
- Valcour V, Sithinamsuwan P, Letendre S, Ances B. Pathogenesis of HIV in the central nervous system. *Curr HIV/AIDS Rep* 2011; **8**: 54–61. doi: <http://dx.doi.org/10.1007/s11904-010-0070-4>
- Heaton RK, Franklin DR, Ellis RJ, McCutchan JA, Letendre SL, LeBlanc S, et al; CHARTER Group; HNRC Group. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *J Neurovirol* 2011; **17**: 3–16. doi: <http://dx.doi.org/10.1007/s13365-010-0006-1>
- Baumann PS, Cammoun L, Conus P, Do KQ, Marquet P, Meskaldji D, et al. High b -value diffusion-weighted imaging: a sensitive method to reveal white matter differences in schizophrenia. *Psychiatry Res* 2012; **201**: 144–51. doi: <http://dx.doi.org/10.1016/j.psychres.2011.08.003>

23. Bennett KM, Schmainda KM, Rowe DB, Lu H, Hyde JS. Characterization of continuously distributed cortical water diffusion rates with a stretched-exponential model. *Magn Reson Med* 2003; **50**: 727–34. doi: <http://dx.doi.org/10.1002/mrm.10581>
24. Bennett KM, Hyde JS, Rand SD, Bennett R, Krouwer HG, Rebro KJ, et al. Intravoxel distribution of DWI decay rates reveals C6 glioma invasion in rat brain. *Magn Reson Medicine* 2004; **52**: 994–1004. doi: <http://dx.doi.org/10.1002/mrm.20286>
25. King AD, Ahuja AT, Yeung DK, Fong DK, Lee YY, Lei KI, et al. Malignant cervical lymphadenopathy: diagnostic accuracy of diffusion-weighted MR imaging. *Radiology* 2007; **245**: 806–13. doi: <http://dx.doi.org/10.1148/radiol.2451061804>
26. Koh DM, Collins DJ, Orton MR. Intravoxel incoherent motion in body diffusion-weighted MRI: reality and challenges. *AJR Am J Roentgenol* 2011; **196**: 1351–61. doi: <http://dx.doi.org/10.2214/AJR.10.5515>
27. Chan JH, Tsui EY, Luk SH, Fung SL, Cheung YK, Chan MS, et al. MR diffusion-weighted imaging of kidney: differentiation between hydronephrosis and pyonephrosis. *Clin Imaging* 2001; **25**: 110–13. doi: [http://dx.doi.org/10.1016/S0899-7071\(01\)00246-7](http://dx.doi.org/10.1016/S0899-7071(01)00246-7)
28. Anderson SW, Barry B, Soto J, Ozonoff A, O'Brien M, Jara H. Characterizing non-gaussian, high *b*-value diffusion in liver fibrosis: Stretched exponential and diffusional kurtosis modeling. *J Magn Reson Imaging* 2014; **39**: 827–34. doi: <http://dx.doi.org/10.1002/jmri.24234>
29. Bennett KM, Hyde JS, Schmainda KM. Water diffusion heterogeneity index in the human brain is insensitive to the orientation of applied magnetic field gradients. *Magn Reson Med* 2006; **56**: 235–9. doi: <http://dx.doi.org/10.1002/mrm.20960>
30. Stocco A, Lebiere C, Anderson JR. Conditional routing of information to the cortex: A model of the basal ganglia's role in cognitive coordination. *Psychol Review* 2010; **117**: 541–74. doi: <http://dx.doi.org/10.1037/a0019077>
31. Şenocak E, Oğuz KK, Özgen B, Kurne A, Özkaya G, Ünal S, et al. Imaging features of CNS involvement in AIDS. *Diagn Interv Radiol* 2010; **16**: 193–200. doi: <http://dx.doi.org/10.4261/1305-3825.DIR.2182-08.1>
32. Plantinga BR, Temel Y, Roebroek A, Uludağ K, Ivanov D, Kuijf ML, et al. Ultra-high field magnetic resonance imaging of the basal ganglia and related structures. *Front Hum Neurosci* 2014; **8**: 876. doi: <http://dx.doi.org/10.3389/fnhum.2014.00876>
33. Bekiesinska-Figatowska M, Mierzevska H, Jurkiewicz E. Basal ganglia lesions in children and adults. *Eur J Radiol* 2013; **82**: 837–49. doi: <http://dx.doi.org/10.1016/j.ejrad.2012.12.006>
34. Corti M, Villafañe MF, Negroni R, Arechavala A, Maiolo E. Magnetic resonance imaging findings in AIDS patients with central nervous system cryptococcosis. *Rev Iberoam Micol* 2008; **25**: 211–14. doi: [http://dx.doi.org/10.1016/S1130-1406\(08\)70051-2](http://dx.doi.org/10.1016/S1130-1406(08)70051-2)
35. Hegde AN, Mohan S, Lath N, Lim CT. Differential diagnosis for bilateral abnormalities of the basal ganglia and thalamus. *Radiographics* 2011; **31**: 5–30. doi: <http://dx.doi.org/10.1148/rg.311105041>
36. Lee EJ, Park JH, Ihn Yk, Kim YJ, Lee SK, Park CS. Acute bilateral basal ganglia lesions in diabetic uraemia: diffusion-weighted MRI. *Neuroradiology* 2007; **49**: 1009–13. doi: <http://dx.doi.org/10.1007/s00234-007-0299-9>
37. Kwee TC, Galbán CJ, Tsien C, Junck L, Sundgren PC, Ivancevic MK, et al. Comparison of apparent diffusion coefficients and distributed diffusion coefficients in high-grade gliomas. *J Magn Reson Imaging* 2010; **31**: 531–7. doi: <http://dx.doi.org/10.1002/jmri.22070>
38. Cloak CC, Chang L, Ernst T. Increased frontal white matter diffusion is associated with glial metabolites and psychomotor slowing in HIV. *J Neuroimmunol* 2004; **157**: 147–52. doi: <http://dx.doi.org/10.1016/j.jneuroim.2004.08.043>