Preliminary Study of Nine HIV-Associated Central Nervous System Complications from Imaging Analysis

Xichao Xia¹, Xiangli Ma¹, Mengwei Wei¹, Mingxia Zhang¹, Juan Cui², Bingqin Shi², Hongwen Li², Hongjun Li³, Liu Rongzhi²*, Sui Liu¹, Xinyi Wang¹, Xiaoping Chen¹, Qian Zhao¹, Fan Yang¹ and Xiaoyan Du¹

¹Medicine College of Pingdingshan University, Pingdingshan, 467000, Henan Province, China
²Basic Medicine College of Nanyang Medical University, Nanyang, 473041, Henan Province, China
³Department of Medicine, Beijing You an Hospital, Capital Medical University, Beijing 100069, China

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Abstract
The central nervous system (CNS) is preferentially vulnerable to HIV infection with respect of chronic exposure to HIV in the brain as well as combination infection of HIV and opportunistic pathogens that can lead to cognitive impairment. In order to shed light of characterizations of HIV-associated CNS complications, 9 HIV-associated CNS complications were analyzed by computed tomography (CT) and magnetic resonance imaging (MRI). In the 9 cases, characterizations of HIV-associated encephalitis, HIV-associated encephalitis of toxoplasma infection, cytomegalovirus infection, cryptococcosis infection and herpes simplex infection, HIV-associated white matter complication, HIV-associated cerebral infarction, HIV-associated cerebral encephalitis of syphilis infection, and HIV-associated cerebral glioma were detected by imaging. These HIV-associated CNS complications not only respectively showed few common features of non-HIV-associated CNS complications, but exhibited specific traits. HIV-associated CNS complications showed typical clinical and radiological presentations are sufficient to establish the diagnosis.

Introduction
Several advances result in a great improvement of the care and prognosis of HIV-positive (HIV+) individuals in the past 20 years [1]. The first major advancement is an understanding of the direct relationship between HIV replication and subsequent immunological and clinical progression [2]. In addition, application of combination antiretroviral therapy (CART) can provide effective systemic suppression of HIV replication [3].

The third major change in the care of HIV+ patients is the ability to monitor the efficacy of CART through the reliable and widespread measurement of CD4+ helper T cells, plasma HIV RNA levels and antiretroviral resistance profiles, all of which are now fully integrated into routine clinical care in the developed world and used to optimize treatment for individual patients. Noteworthy, various of HIV-associated complications are also gradually emerging in the past. Efficient diagnose of HIV-associated complications gains great concern and play important role in promoting treatment of AIDS patients [4]. The central nervous system (CNS) is preferentially vulnerable to HIV infection as chronic exposure to HIV in the brain can lead to cognitive impairment (NCI) [5].

Unfortunately, in this condition, several factors also are involved into the influence on landscape of HIV-associated CNS infections including fungus, bacterium,
virus and parasite that form HIV-related opportunistic infections of the CNS [6]. Since the introduction of the antiretroviral therapy (ART) drug and development of the CART, there has been an expected decrease in the incidence of HIV-associated CNS complications [6]. However, as to almost every AIDS patient, the development of HIV-associated CNS complications remains an important issue for them, as it affects not only survival and quality of life, but also everyday functioning [7]. Nevertheless, despite our increasing knowledge and understanding of HIV-associated CNS complications, there is still no definitive marker or specific treatment. Several infections of the nervous system, such as toxoplasmosis, are much more common in patients with HIV than in other immunosuppressed states, although the mechanisms underlying this observation are not fully understood [7,8].

However, the clinical and radiographic presentation of HIV and opportunistic CNS infections in the setting of HIV infection function as an important player to understand characterizations of patients. Therefore, elucidation of characterizations of HIV-associated CNS complications plays an important role in diagnose and treatment. In order to further shed light of clinical characterizations of HIV-associated CNS complications, in the current study, 9 cases of HIV-cerebral complications were analyzed by imaging.

Materials and Methods

Patient selection

The study was approved by Ethical Review Committee of Nanyang Medical University. Available participants were approached and informed of the study objectives, procedure and confidentiality issues by study coordinator. Patients who decided to participate in this study and provided written informed consent were asked to complete a survey to assess presence of HIV/AIDS-related symptoms.

Methods

Quantity of CD4+T cell was measured using flow cytometry instrument (BD, USA) according to kit instructions. Histological analysis was performed by HE staining.

Diagnosis of pathogens was fulfilled by microbe culture. Imaging analysis was conducted by computed tomography (CT) and magnetic resonance imaging (MRI), respectively.

Results

HIV-associated encephalitis

Case 1, a female, 48 years, was definitely diagnosed as AIDS by (centers for disease control and prevention, CDC) and showed diarrhea, vomiting and occasional outbreak of epilepsy. Quantity of CD4+T cell was 95/μl. Multiple spot lesions with a blur margin showed a long T1 and long T2 signal that were fund in white matter of bilateral frontal lobes and cortex of parietal lobe. In addition, these signals were mainly occurred in that of bilateral frontal lobes. A strong of T2WI signal was observed by MRI (Figures 1a and 1b). Cerebral blood flow showed an asymmetric distribution in the right and left brains by perfusion imaging (PWI) (Figure 1c).

Figure 1: HIV-associated encephalitis. a is the result of sagittal view of T1 MRI. b is the result of axial view of T2 MRI. c and d are the results of PWI. e is the result of DTI. Lesion is marked as black arrow.

Strips of decreased signal region in white matter of bilateral frontal lobes and parietal lobe and decreased
fractional anisotropy (FA) value were fund by diffusion tensor imaging (DTI) (Figure 1c).

Sparse fiber bundles were detected in left frontal lobe and parietal lobe (Figure 1e). An obvious decrease of n-acetylaspartate and creatine level was detected in white matter of left frontal lobe and parietal lobe. Patient was diagnosed as HIV-associated encephalitis.

In addition, heterogeneous signal and signal of cerebrospinal fluid were fund in this lesion (Figures 2a and 2b). After injection of gadobenate dimeglumine, a small of enhanced signals were detected in lesion of left frontal lobe and occipital lobe by diffusion weighted imaging (DWI) (Figure 2c). Results of perfusion scan showed a lower signal of cerebral blood fluid compared with that of opposite part was fund in left frontal lobe and occipital lobe (Figure 2d).

A decreased signal of white matter and significant decreased FA value were fund in the left frontal lobe, temporal lobe, junction of frontal lobe and temporal lobe, junction of parietal lobe and occipital lobe by DTI (Figure 2e). Scenario of transverse fiber bundle with a spare distribution was detected in left frontal lobe, temporal lobe, occipital lobe in with respe (Figure 2f).

A lower value of NAA and Cr was fund in lesions and ratio of between NAA and Cr was 1.23. The simple movement test of right hand showed an obvious decrease of activated area by movement was occurred in precentral gyrus and ascending parietal convolution of left brain. Numbers of Toxoplasma gondii were fund under the microscope by cerebrospinal fluid culture in the laboratory. Patient was diagnosed as AIDS-associated encephalitis of toxoplasma infection.

**HIV-associated meningitis of cytomegalovirus infection**

Case 3, a male, 15 years, was definitely diagnosed as AIDS by CDC and showed headache, fever, movement disorder of left lower limb. Quantity of CD4+T cell was 60/μl. Patch of T2WI signal was fund in the basal ganglia of right brain. Tentorium cerebelli showed a blur margin. A strong enhanced signal was fund in region of basal ganglia in contrasted with that of opposite part by perfusion scan (Figure 3c). Symmetric white matter signal of bilateral basal ganglia and fiber bundle of right and left brains were fund by DTI (Figures 3d and 3e). Increased NAA peak was fund by MRS. Infection of cytomegalovirus showed a positive result by blood and body fluid examination in the laboratory. Patient was diagnosed as HIV-associated cerebral meningitis of cytomegalovirus infection.

**HIV-associated cerebral meningitis cryptococcosis infection**
Case 4, a male, 33 years, was definitely diagnosed as AID by CDC and showed headache, fever, confusion, dysfunction of speaking and positive symptom of neural reflex. Quantity of CD4+T cell was 11/μl. Visible multiple focal masses with big patch shape and equal length of T2 T1 signal were found in basal regions of bilateral brains, corona radiates, cortex of frontal and lobe and parietal lobe, white matter of subcutaneous, genu and pad of corpus callosum and right thalamus. Short T1 and short T2 signal was observed in the different lesions (Figures 4a and 4b).

Limited high signal lesions and a part of the ring lesions were fund in right frontal lobes, temporal lobe, left cerebellum, bilateral basal ganglia, genu and pad of corpus callosum. A significant enhancement of signals was fund in lateral ventricles of bilateral brains, sulcus of left temporal lobe and tentorium cerebelli by CT enhancement scanning (Figure 4c).

A higher signal of CBF was detected in lesions of right brain by perfusion scan (Figure 4d). DTI showed a lower FA value occurred in most lesions above mentioned, especially in right frontal lobe and basal ganglia. Sparse fiber bundle were fund in right temporal lobe (Figures 4e and 4f). Values of NAA/Cr and Cho/Cr were respectively 0.76 and 0.69 that showed a decrease trend. Cryptococcal infection was identified by culture of blood and body fluid in the laboratory. Patient was preliminary diagnosed as HIV-associated cerebral meningitis of cryptococcosis infection.

**Figure 3:** HIV-associated meningitis of cytomegalovirus infection. a is the result of axial view of MRI. b is the result of sagittal view of MRI. c and d are the results of PWI. e is the result of DTI. Lesion is marked as black arrow.

**Figure 4:** HIV-associated cerebral meningitis of cryptococcosis infection. a and b are results of axial view of MRI. c is the result of axial view of DWI. d and e are the results of PWI. f is the result of DTI. Lesion is marked as black arrow.

**HIV-associated cerebral meningitis of herpes simplex infection**

Case 5, a female, 8 years, was definitely diagnosed as AID by CDC and showed weakness of right limb. Quantity of CD4+T cell count was 21/μl. Lesions with...
shapes of patch and spot showed a long T1 and long T2 signal that was fund in white matter right and left brains, thalamus, basal ganglia and brain stem. Enhanced signals were observed in around lesions, but not in lesions (Figures 5a and 5b). A lower signal of CBF was observed in lesions by the perfusion scan (Figure 5c). A lower of FA value of lesion was fund contrasted with that of opposite part by DTI. In addition, scenario of sparse fiber bundles was fund in the left side (Figure 5d-5f). Results of MRS showed value of NAA was significantly decreased. Widened cerebral sulcus and schizencephaly, inflation of ventricles of brain were detected. Herpes simplex virus was fund by culture of blood and body fluid in the laboratory. Patient was diagnosed as HIV-associated cerebral encephalitis of herpes simplex virus infection.

**Figure 5:** HIV-associated cerebral meningitis of herpes simplex infection. a is the result of sagittal view of MRI. b is the result of axial view of MRI. c and d are the results of PWI. e and f are results of DTI. Lesion is marked as black arrow.

**HIV-associated white matter complication**

Case 4, a male, 63 years, was definitely diagnosed as AID by CDC and showed intermittent fever, cough, headache. Quantity of CD4+T cell was 70/μl. Long T2 signal of multiple spots with blur margin and bilateral symmetry was fund in bilateral centrumovales. Large patches of long T1 and long T2 signal with fuzzy margin were fund in right cerebellum and brain stem. An enhanced signal of T2WI was observed in lesion by treatment of compression of water and greasy as well as DWI (Figures 6a and 6b). After vein injection of GD bopta, no obvious enhancement of signal was observed in bilateral centrum semiovale lesion, but a slight enhanced signal in junction of right cerebellar lesions and meninges (Figures 6c and 6d). Symmetric signals of CBF were detected in left and right hemispheres by perfusion scan (Figure 6e). A lower FA value was observed in bilateral frontal lobe, parietal lobe, temporal lobe by DTI. Sparse fiber bundle were occurred in bilateral frontal lobes (Figure 6f). Value of NAA/Cr was significantly reduced. Patient was diagnosed as HIV-associated white matter complication.
**HIV-associated cerebral infarction**

Case 7, a male, 34 years, was definitely diagnosed as AIDS by CDC and showed fever. Quantity of CD4+T cell was 14/μl. Small spots of long T1 and long T2 signal were found in right pons. Enhanced signals of spots with clear boundary were observed by DWI (Figure 7a-7d). A decreased signal of white matter and lower FA value were detected in both sides of bilateral temporal lobes by DTI (Figure 7e). Few and scattered fiber bundles were found in bilateral temporal lobes (Figures 7f and 7g). With a simple exercise test of right hand, activated areas of movement were located in precentral gyrus and ascending parietal gyri of left brain, posterior parietal cortex. Activated area of cerebellum were significantly increased and showed a more widened scope with respect of that of normal population (Figure 7h). Patient was diagnosed as HIV-associated cerebral infarction.

**HIV-associated cerebral encephalitis of syphilis infection**
Case 8, a male, 35 years, was definitely diagnosed as AIDS by CDC and showed cognitive disorder and movement dysfunction. Quantity of CD4+T cell count was 74/μl. Multiple patchy lesions with a fuzzy boundary showed long T1 and long T2 signals that were fund in right temporal lobe, frontal lobe, parietal lobe. Right lateral ventricle was pressed and became narrow. A strong of T2WI signal was fund by treatment of compression of water and greasy, and DWI (Figures 8a and 8b). After vein injection of gadobenate dimeglumine, an obvious enhanced signal was fund in gyrus of right temporal lobe, sagittal sinus and tentorium of cerebellum (Figures 8c and 8d). A lower FA value was observed in right temporal lobe compared with that of opposite part by DTI (Figure 8e). Syphilis virus was detected by culture of blood and body fluid in the laboratory. Patient was diagnosed as HIV-associated encephalitis of syphilis infection.

HIV-associated cerebral glioma

Case 9, a male, 42 years, was definitely diagnosed as AIDS by CDC and showed headache and muscle weakness of left limbs. Quantity of CD4+T cell was 134/μl. Mixture of irregular signals was fund in junction of gray matter and white matter of right parietal lobe, and subcortical. A slight shorter T1 signal and equal T2 signal were observed in lesions in which multiple long T1 signals and long T2 signals, and an obvious occupying effect were fund. In addition, sheet long T1 and long T2 signal of edema was occurred around of lesion. An enhanced signal of T2WI was detected by treatment of compression of water and greasy and DWI (Figure 9a and 9b). A lower signal of liquefactive necrosis showed was fund by DWI (Figure 9c). After vein injection of gadobenate dimeglumine, enhanced signals with garland shape was observed in heterogeneous surrounding of lesion, an obvious enhanced signal in texture of lesion, no enhanced signal in area of liquefactive necrosis (Figure 9d). Results of DTI showed that the FA value of right parietal lobe was significantly decreased in contrasted with that of opposite part. In addition, decreased fiber bundles were fund in right lesion of white matter. A part of bridging fiber bundles was interrupted (Figures 9e and 9f). Values of NAA/Cr and Cho/Cr were respectively 0.7
and 0.67 that showed a decrease trend. Patient was diagnosed as HIV-associated cerebral glioma.

**Figure 9:** HIV-associated cerebral glioma. a and b are results of axial view of CT. c and d are results of axial view of DWI. e is the result of PWI. f is the result of DTI. Lesion is marked as black arrow.

### Discussion

Encephalitis of AIDS patients, one common type of cerebral complications, is mainly caused by HIV infection. In the normal condition, HIV infection can directly cause damage to the nervous system that result in cognitive and behavioral disorders. Clinical manifestations of patients are dementia, mental retardation, lower cognitive ability, ataxia, dysfunction movement and behavior [9]. Generally, diffused and/or focal cerebral white matter abnormalities, widened cerebral sulcus, enlarged cerebral ventricles, reduced total brain volume, sheet long T1 and long T2 signal are fund by MRI [10]. In addition, different degree of brain atrophy, individual lobar atrophy and ventricular inflation, local enlargement of sulcus, crack, pond and ventricle are detected in CT [11].

In AIDS patients, toxoplasma encephalitis caused by T. gondii infection is one most common complication of opportunistic infections. Lesions located in the junction of gray matter and white matter derived from basal ganglia, thalamus and cerebral hemisphere showed a high incidence [12]. Nervous system is also affected by toxoplasma infection characterized by mental symptoms including of headache, dizziness, confusion, memory loss, coma. Meanwhile, movement disorders of weakness, numbness of limb, pain, convulsions, paralysis, incontinence, ataxia are observed [13]. Equal density shadow of nodes combined with low density shadow of edema around nodes, large patchy equal density shadow with ring shape in low density region are observed stratum of brain by CT. Nodes, ring shapes of enhanced signal of lesions, obvious different signals of edema, occupying effect are detected by enhanced scanning [14]. MRI shows T1WI of lesions with low signal intensity, T2WI with an intermediate one, edema around lesions with a high one. After vein injection of contrast agent, high signal intensity is observed in lesion, no change of signal in edema [15]. In addition, cerebral spinal fluid of clinical laboratory examination is helpful to diagnose HIV-associated encephalitis of toxoplasma infection.

In the patients, CMV invade first results in an injury on retina, then optic nerve, posterior limb of the internal capsule and occipital lobe of brain, that cause blurred vision of eyes. A symmetrical low density of shadow occurred in occipital lobe of brain, white matter of frontal lobe, thalamus and posterior limb of internal capsule were fund by CT, but brain atrophy was not observed [16]. CMV infection occurred in the late stage of HIV infection can result in drowsiness, mental insane, confusion of consciousness, aphasia, blurred vision, epileptic seizure, and inhibitory effect on function of central nervous system at last stage. Sheet lesions with long T1 and long T2 signal around ventricles and small sheet diffused lesion with long T1 and long T2 signal in white matter are detected by MRI [17,18]. Ependyma shows an enhanced signal, but the texture of brain dose not exhibit enhanced signal. Compared with that of CMV-infected patients, patients of HIV-associated cerebral meningitis of cytomegalovirus infection don’t show special characterizations of imaging. Culture of CMV and DNA analysis of cerebral spinal fluid are helpful to diagnose HIV-associated cerebral meningitis of cytomegalovirus infection.

Cryptococcosis, an opportunistic pathogen, its infection can cause a damage on meninges and basal ganglia of central nervous system. Swelling of soft tissue, muddy of piamater, aggregation of meninges is observed by visible [19]. Imaging of cryptococcal meningitis showed consolidation of meninges, changes of brain parenchyma, hydrocephalus and cerebral atrophy [20]. In advanced stage, fibroblast proliferation and fibrosis
of meningeal collagen are finally fund that can lead to an event of arachnoid and piamater thickening, even to mutual adhesion of them. In the last stage, it can cause a blockage of apertura medialis ventriculi quarti, apertura lateralis ventriculi quarti, ring pool of midbrain that in turn formed hydrocephalus [21]. Polysaccharide antigen examinations of staphylococcus aureus capsular in serum and cerebrospinal fluid are contributed to diagnose the cryptococcosis infection of the nervous system.

After herpes simplex virus infection, complications of skin and mucous membrane are widely fund in AIDS patients, but encephalitis is rarely observed. In destroy of immune function, HSV is reactivated and spread into brain [22]. Neuropsychic symptoms of headache, fever and epilepsy are observed in clinical. In addition, weakness, lethargy, ataxia, aphasia and other symptoms are also observed [23]. Asymmetrical distribution of lesions are detected by imaging, mainly occurred in middle region of temporal lobe, hippocampus, orbital surface of frontal lobe, parietal lobe and cingulate lesions and also in hypothalamus, medulla oblongata and pons. Asymmetrical necrosis of temporal lobes of left brain and right brain, and bleeding are also fund [24].

Manifestations of HIV-associated cerebral white matter complication are characterized by memory disorders, hemianopia, hemiplegia, language disorder. Disorders of memory, language and personality disorder are mainly feature of symptoms of early stage, fever and headache are seldom fund in the course [25]. Formed fusion zone of demyelination formed by multiple lesions is fund in white matter. Cerebral hemisphere is more vulnerable compared with that of cerebellum, especially in the junction of subcortical gray matter and white matter [26]. A wide range of multiple lesions of demyelination has an asymmetric distribution in white matter of brain, but lesions of spinal cord in cerebellum and brain stem are relatively rare. Lesions of white matter with round or oval shape show a multiple, asymmetry that is mainly occurred in low density shadow. After injection of contrast media, no enhanced signal and mass are captured, but few mild enhanced signal and occupying effect are fund in the gray matter. MRI results show that no T1WI signal is observed or lower signal lesions. In addition, T2WI signal of white matter show a high signal shadow, clear boundary, without space occupying effect and specific feathers. In addition, T1WI signal of white matter generally show multiple and asymmetric lesions, without occupying effect [27]. Increased Cr value and decreased NAA value are detected by MRS spectrum.

After HIV infection, vascular intimain of jury, opportunistic infection and drug abuse can cause local artery stenosis and/or complete occlusion that result in HIV-associated cerebral infarction characterized by cerebral ischemia, hypoxia, necrosis and nerve dysfunction [28]. Long-term hypoperfusion in turn cause atrophy of gray matter, cognitive impairment and dementia. Imaging results show the site and shape of lesions are associated with distribution of small and medium-sized arteries. Lesions showed a low-density shadow with plaque, small or lager sheet, no occupying effect. No obvious signal is fund by in enhancement scanning. Before cerebral infarction, with a treatment of arteriography, irregular artery development and wall with smooth and wide range are observed by MRI [29]. After cerebral infarction, homogeneous of heterogeneous low-density signal of infarction are observed by CT. Outward extended bottom margin of infarction with triangular and fan-shape, and boundary from unclear to clear is detected. Infarction often showed multiple sizes of lesions that are extend into cortical and subcortical [30]. Typical low T1WI signal and high T2WI are detected by MRI. Results of MRI enhancement show sheet signal of lesion and enhanced signal of cortex of gyrus. In addition, signal of cerebromalacia is similar with that of cerebral spinal fluid.

In the patients of HIV-associated complication of syphilis of infection, incidence of neurosyphilis has reached to 23.5%. Compared with that of non-HIV-infected patients, patients of HIV infection show a higher incidence and faster progression [31]. Generally, meninges vascular neurosyphilis and encephalitis of herpes simplex virus share a few of imaging manifestations in the clinical that cause a difficult for diagnose. Notably, neurosyphilis is slower onset in respect with that of encephalitis of herpes simplex virus, and mild atrophy of temporal lobe and inflation of temporal horn, but encephalitis of herpes simplex virus often show an occupying effect. An asymmetrical stenosis of large vessels and aneurysm-like expansion of small blood vessels are detected by cerebral angiography [31,32]. Segmental stenosis and vascular occlusion usually are occurring in the upper and horizontal segments of carotid artery supraclinoid, middle artery of brain and initial segment of anterior artery of brain [33].

In the patients of HIV-associated brain glioma, chronic headache and progressive deterioration of complication are often observed. A low-density shadow or mixed density shadow is fund by CT. Meanwhile, edema and an occupying effect of space around tumor are detected. Irregular ring enhanced signal with nodules is fund by
enhancement scanning [34]. Glioblastoma is generally occurred in old peoples those show necrosis and haemorrhage. Signals of imaging are obvious heterogeneous. Mixture of signals derived from numbers of long T1 and long T2 signal and a little of other signals are detected by MRI. Irregular ring shape of strengthen signal is detected by enhancement scanning. It is important work to distinguish the difference between glioblastoma and lymphoma. Noteworthy, in respect with that of lymphoma, a closely arrangement, little of water content, a slightly equal length signal of T1T2 of tumor cells are fund by MRI. In addition, after treatment of enhancement, a heterogeneous signal with strong enhancement is detected with respect of emergence of obvious edema, but no ring intensified signal is observed [35,36].

In conclusion, HIV infection and combination of HIV and opportunistic infections can result in complex clinical manifestations and different characterizations of imaging. Diagnose of HIV-associated CNS complications is a challenge for clinicians in respect of diversity of pathogen, multiple sites of lesions characterized by different features. Typical clinical and radiological presentations are often sufficient to establish the diagnosis.

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Conflict of Interest

None declared.

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