Cerebaral Hyperperfusion in General Paralysis Patients

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Abstract

Objective

This study aimed to identify the cerebral blood flow (CBF) in patients with general paralysis (GP).

Methods

Three-dimensional pseudo-continuous arterial spin labeling (3D-pCASL) imaging was performed to measure the CBF in twenty patients with GP and twenty healthy subjects(NC). CBF was normalized to reduce variations among subjects. CBF was compared between the groups.

Results

Compared with the healthy subjects, the patients with GP exhibited increased CBF in the frontal lobe, temporal lobe, insular lobe, limbic lobe, and parietal lobe(all $P<0.05$). There was no difference in CBF of the occipital lobe between the GP group and the NC group(all $P>0.05$).

Conclusions Our results suggest that the patients with GP may exhibit regional increased CBF, which may be one of the pathogenesis of general paralysis.

Keywords Neurosyphilis Arterial spin labeling Cerebral blood flow Magnetic resonance imaging

Introduction

Neurosyphilis is a chronic central nervous system infectious disease caused by Treponema pallidum (T. pallidum). General paralysis (GP) is the most serious clinical type of late neurosyphilis, and has a peak incidence of 15-25 years after syphilitic infection. GP usually develops with a sequential presentation of symptoms, including forgetfulness, personality changes, progressive cognitive decline, mood disorders, and behavioral disorders. However, this is different from the other types of dementia, which can be cured by adequate doses of penicillin in the early stage and is considered a“potentially reversible”dementia[1]. GP and Alzheimer's disease (AD) have similar pathophysiology. The atrophy of frontotemporal cortex and hydrocephalus in GP can be found by previous structural magnetic resonance imaging[2]. It has been reported that T. pallidum can cause chronic inflammation of blood vessels, occlusion of arterioles, and microglia activation[3-5]. There is local hoperperfusion in AD patients[6], but whether there is cerebral blood flow (CBF) change in GP has not been reported.

Three-dimensional pseudo-continuous arterial spin labeling (3D-pCASL) has been increasingly adopted as a novel functional technique. This non-invasive magnetic resonance imaging (MRI) modality exploits magnetically labeled arterial blood water as an endogenous tracer for quantifying CBF[7-8]. The perfusion pattern detected by arterial spin labeling (ASL) was greatly consistent with the metabolism or perfusion pattern identified by single photon emission computed tomography (SPECT) and positron emission tomography (PET). SPECT and PET are not always available, therefore, ASL becomes an increasingly promising tool as an alternative to PET and SPECT. Moreover, it is easily repeatable with high reproducibility.

The aim of this study was to clarify the alteration CBF patterns in GP patients. We adopted a 3D-pCASL technique that used fast spinecho acquisition and background suppression to measure the CBF.

Materials and methods

Subjects

In this prospective, observational, and single-center study, twenty GP patients in the neurology department of Beijing Ditan hospital, Capital Medical University, Beijing, China, between January 2018 to December 2019 were enrolled as the case group (GP). Twenty people with normal cognition were recruited from Beijing Ditan hospital as the control group (NC). All GP patients provided written informed consent. The inclusion criteria were as follows: 1) 18-85 years of age; 2) positive TPPA and RPR in the serum and cerebrospinal fluid(CSF); 3) cognitive decline or/and mental behavior disorders; 4) first diagnosed, and not treated with intravenous penicillin; 5) no infarction or scattered old ischemia on brain MRI; 6) willingness to undergo neuropsychological tests. The exclusion criteria were: 1) history of the following diseases: local brain injury, stroke, parkinson's disease, frontotemporal dementia, and Huntington's disease; 2) anxiety, depression, schizophrenia, or mental retardation; 3) alcohol or drug abuse; 4) severely impaired heart, liver, kidney, or lung function; blood disorders; endocrine diseases; 5) history of cancer; 6) ≥1 lacunar infarction or diffuse leukoaraiosis as determined by MRI; 7) dementia caused by other causes, such as trauma, tumor, infection, metabolic disease, normal pressure hydrocephalus, folate, vitamin B deficiency, and hypothyroidism.

Data collection

The following patient data were collected: age, educational background, and neurological symptoms. All subjects were scanned with 3D-pCASL sequence and routine sequence on GE 3.0 T magnetic resonance scanner. The routine sequences include T1-weighted images (T1WI), T2-weighted images (T2WI), fluid-attenuated inversion recovery image (FlAIR), diffusion weighted image (DWI), and susceptibility weighted imaging (SWI). All GP patients were underwent lumbar puncture. All subjects were informed of the purpose of the collection of their information, and this study was approved by the Human and Ethics Committee of Beijing Ditan hospital, Capital Medical University.

Magnetic resonance imaging

All subjects underwent MRI using a GE Discovery MR750W 3.0 T scanner. All subjects were instructed to stay relaxed, close their eyes, and keep their head still during the scan. Rubber earplugs were used to reduce noise to a minimum and foam pads were placed around the heads to reduce movement. Multidirectional (axial, sagittal, coronal) scanning and multiparameter scanning were performed, including conventional MR T1WI, T2WI , FLAIR, DWI and SWI sequences. Multimodal MR included 3D pCASLsequence. The DWI sequence parameters were: TR 4880ms, TE 77.4 ms, b=1000, matrix 256×256, FOV 240 mm×240mm; 3D - pCASL: TR 4852 ms, TE 10.7 ms, matrix 128×128, FOV 240 mm× 240 mm, PLD 1.5s delay.

3D-pCASL CBF calculation

The mean CBF image derived using the ASLtbx software contained some patchy noise, and thus we used a median filter. To evaluate CBF voxelbasically, we normalized the mean CBF images to the standard space[9]. First, each individual 3D-T1 image was coregistered and resliced to its own M0 image. Next, the coregistered 3D-T1 image was normalized to the“avg152T1”image regarded as the anatomically standard image using with the DARTEL (diffeomorphic anatomical registration using exponentiated lie) registration method. Finally, the transformation matrix was applied to the mean region CBF images treated with the median filter. The spatially normalized images were resliced with a final voxel size of approx. 4*4 *8 mm. Each map was then spatially smoothed with a 4-mm full-width at half-maximum Gaussian kernel in order to decrease spatial noise and compensate for the inexactitude of normalization[10].

Statistical analysis

All data were analyzed using the IBM SPSS statistics version 19. Continuous data following Gaussian distribution were displayed as mean±standard deviation(SD), and were analyzed using the independent samples T test. Otherwise, they were presented as a median with interquartile range (IQR) and analysed with Mann-Whitney U test. Meanwhile, $\chi 2$ for categorical variables. A difference

between the groups was considered significant if $P < 0.05$. CBF was analyzed using the independent samples T test. A difference between the groups was considered significant if $P < 0.05$.

Results

General demographics and clinical characteristics

The subjects were all males. No significant differences in age, education, hypertension, diabetes, and stroke were observed between the GP group and normal controls(all $P > 0.05$). GP patients presented different clinical neurological symptoms, including mood disorders (13/20, 65%), cognitive decline(12/20, 60%), behavior disorders(4/20, 20%) and walking and speech disorders(2/20, 10%). In the GP group, the serum RPR was 8-256, and the median serum RPR was 24 (8,56). The CSF RPR was 1-8, and the median was 2 (1, 4). The CSF WBC was 2-77/uL, and the median was 14.5/uL(7, 34). The CSF protein was 20.9 - 108.5 mg / dL, and the mean was 63.41mg/dL. The demographic and clinical characteristics data were shown in Table 1.

The MRI features of GP patients

Of the twenty GP patients, MRI showed normal in six cases, white matter lesions in ten cases, brain atrophy in two cases, white matter lesions and brain atrophy in two cases. The images were shown in Figure 1. The MRI of the NC group were all normal.

Differences in CBF between the GP and NC groups

The 3D pCASL pulse sequence paradigm is plotted in Figure 2. The GP patients exhibited increased CBF in the frontal lobe, temporal lobe, insular lobe, limbic lobe, and parietal lobe (all $P<0.05$). There was no difference in CBF of the occipital lobe

between the GP group and NC group (P=0.412). The data were shown in table 2, figure 3.

Discussion

T. pallidum is often vulnerable to the meninges and can be found in the CSF of 15-40% of early syphilis patients[11]. Neurosyphilis, an infectious neuroinflammatory disorder, could cause diverse neuropsychiatric symptoms mimicking disorders of schizophrenia and dementia. Asymptomatic neurosyphilis is observed in 13.5-20% of patients with untreated or insufficiently treated syphilis, and GP is observed in 5% of asymptomatic neurosyphilis[12]. Bhai et al found that the overall incidence of GP was higher in males than in females[13]. One reason for gender-related differences could be that the current epidemics of syphilis are concentrated among men who have sex with men[14]. The GP patients in our study were all male.

GP patients experienced overall declines in cognitive function, including memory, language, praxis and attention, in agreement with results from previous studies[15]. Recent studies have reported an AD-like pattern in GP patients, such as an overall decline in cognitive functions, brain atrophy, lower CSF Ab42 levels, and lower CSF CysC levels[16]. Some studies have found that there was local hoperperfusion in AD patients[17], but whether there is CBF change in GP has not been reported. To the best of our knowledge, the research on CBF in GP is limited to the change of CBF before and after penicillin treatment[18]. Kitabayashi had reported that quantitative CBF remarkably decreased in GP patients following penicillin treatment, meanwhile, the CSF cell count decreased and the mental status improved rapidly. Syphilis can damage the brain, and the damage is a dynamic process. The increase of CBF indicates the active stage of syphilis, and Treponema pallidum causes inflammatory reaction of cerebral vessels and brain parenchyma; the decrease of CBF indicates the disappearance of encephalitis. However, there is no study on whether there is abnormal CBF in GP patients. In this study,

hyperperfusion were observed in the frontal lobe, temporal lobe, insular lobe, and limbic lobe in the GP group compared with NC group. The exact mechanism of focal increased perfusion in GP is not known but possibility of loss of cerebral vascular autoregulation or compensatory hemodynamic mechanism has been suggested. We suspected that the area with increased CBF indicated that Treponema pallidum had damaged the brain tissue and caused inflammatory reaction.

Studies have shown that the brain inflammation can cause local hyperperfusion. According to one report about twenty patients of various CNS infections including virus, fungus, bacteria, and tuberculosis, about 47% of patients with parenchymal infection showed increased perfusion with ASL, and 77% patients with meningeal infection showed high perfusion with ASL[19]. Previous SPECT and PET studies in cases of herpes and influenza encephalitis showed similar findings [20-22]. Autoimmune encephalitis also has local cerebral hyperperfusion[23-24].

Brain imaging is very important for the differential diagnosis of GP, especially to distinguish GP from functional disease. Cerebral atrophy and subcortical white matter lesions are the most common abnormalities in GP patients[25] , but these are not specific features for GP. In our study, MRI showed normal in six cases, white matter lesions in twelve cases, brain atrophy in four cases, white matter lesions and brain atrophy in two cases. The result was consistent with previous studies[25].

Neurosyphilis is a “great imitator” because it can mimic many types of medical disorders. It is difficult to distinguish between GP and AD disease according to clinical manifestations. This study suggests that we can distinguish these two diseases according to CBF. The CBF value of ASL could detect the changes of CBF earlier than MRI, which provided an important basis for the early diagnosis and treatment of GP. These reports speculated that functional neuroimaging techniques could detect the inflammation-related hyperactivity of the brain.

Limitation

Firstly, our study had a selection bias. The patients in our study all was GP, the late stage of NS. Secondly, this study found increased regional cerebral blood flow in GP patients, but other types of neurosyphilis were not included in the study, and there was no study on the changes of CBF in GP patients before and after penicillin treatment. Patients with GP should be followed up to observe the dynamic changes of clinical and CBF.

To the best of our knowledge, this is the first study using 3D pCASL in the study of GP, and the results suggest a potential compensatory hemodynamic mechanism that protects against pathology in GP. We can distinguish GP from AD by CBF using 3D pCASL.

Abbreviations

ASL Arterial spin labeling

CBF Cerebral blood flow

CNS Central nervous system

CSF Cerebrospinal fluid

3D-pCASL Three-dimensional pseudo-continuous arterial spin labeling

GP General paralysis

MRI Magnetic resonance imaging

T1WI T1-weighted image

T2WI T2-weighted image

Flair Fluid-attenuated inversion recovery image

DWI Diffusion weighted image

SWI susceptibility weighted imaging

SPECT single photon emission computed tomography

PET positron emission tomography

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Availability of data and materials

All relevant data are within the manuscript.

Authors' contributions

WY, WW, and JL conceived and designed the study. JL and SY completed the cranial MRI. WY and JL collected and organized the data and drafted the manuscript. WY and JL performed the statistical analysis. WW completed the final revision of the article. All authors read, reviewed, and approved the final manuscript. YW and JL contributed equally to the work and are co-first authors.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

This study was approved by the ethics committees of Beijing Ditan Hospital (Number 2018-044-01). The participants' relative or legal guardian signed the informed consent to participate in the study.

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