A Systematic Review of Diffusion Tensor Image Analysis along the Perivascular Space and its Clinical Applications

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Abstract

The diffusion tensor image analysis along the perivascular space (DTI-ALPS) method is used to assess the glymphatic system function in subjects for non-invasive purpose. Growing research suggests an association between various diseases and glymphatic system dysfunction. This review focusses on the application of the DTI-ALPS method in various diseases. Furthermore, the relationship among ALPS index, cognitive function and glymphatic system activity is systematically summarized.

Keywords

DTI-ALPS; Non-invasive; Glymphatic System Dysfunction; Cognitive Function.

1. Introduction

Recently, Taoka et al.[1] proposed a method “diffusion tensor image analysis along the perivascular” (DTI-ALPS) based on DTI to assess the function activity of the glymphatic system. This method can achieve the purpose of non-invasive in humans because no contrast medium is used[1].

The ALPS index is calculated from the ratio of diffusivity value sets of the projection fibers (z-axis) to the association fibers (y-axis) in the lateral ventricle body[2]. Diffusivity is measured by placing region of interest (ROI) in two directions which are perpendicular to the main fiber (x-axis), and the main fiber diffusivity reflects the water diffusivity along the perivascular spaces (PVS). The ALPS index is calculated by dividing the mean of the x-axis diffusivity of the projection fibers (Dxproj) area and the x-axis diffusivity of the association fibers (Dxassoc) area by the mean of the y-axis diffusivity of the projection fibers (Dyproj) area and the z-axis diffusivity of the association fibers (Dzassoc) area: ALPS index = mean (Dxproj, Dxassoc) / mean (Dyproj, Dzassoc).

The ALPS index is positively correlated with the score of the mini mental state examinations (MMSE), and reduced glymphatic system activity results in a lower ALPS index[1]. Thus, this method can reflect the subjects’ current cognitive state and the activity of the glymphatic system. Subsequently, the DTI-ALPS method is used to measure the glymphatic system in various neurological and psychiatric disorders. Taoka et al.[3] reported the reproducibility of the DTI-ALPS method they established to evaluate glymphatic system function in different image acquisition parameters. Although the factors including imaging plane, head position and echo time (TE) may affect the ALPS index, DTI-ALPS is still an effective method to evaluate glymphatic system function[3].

The glymphatic system, defined by Iliff et al[4], is waste clearance system in the central nervous system, which is an indispensable intracranial environment for nutrient exchange and metabolism[5]. The exchange between cerebrospinal fluid (CSF) and interstitial fluid (ISF) along the PVS achieves homeostasis[6], and promotes the clearance of harmful metabolites or proteins wastes produced by the brain[7, 8]. Recent studies have shown that the glymphatic system dysfunction is associated with

ISSN: 2414-1895 DOI: 10.6919/ICJE.202210_8(10).0015

pathophysiology of many neuropsychiatric diseases, such as Alzheimer's disease (AD)[9], idiopathic normal pressure hydrocephalus (iNPH)[5], Parkinson's disease (PD)[10], type 2 diabetes mellitus (T2DM)[11], stroke[12], and dementia[13]. Therefore, proper assessment of glymphatic system function from a pathophysiological perspective may help radiologists interpret neuroimaging findings[14].

This review focusses on the application of the DTI-ALPS method in various diseases. Furthermore, the relationship among ALPS index, cognitive function and glymphatic system activity is systematically summarized.

2. DTI Technique

The DTI-ALPS method is widely used to explore the glymphatic system[15]. DTI-ALPS avoids intrathecal or intravenous injection of contrast agent tracer when evaluating the glymphatic system[8], so it is non-invasive.

DTI is a common tool for analyzing and evaluating the changes in the neural structure of the brain and capturing microstructural changes of white matter (WM)[16]. Fractional anisotropy (FA) and mean diffusivity (MD) are two important and common metrics to evaluate the fiber integrity[17]. MD reflects the mean water diffusion rate from the voxel level, but it does not reflect the direction of diffusion[18]. FA reflects the degree of anisotropy of water molecules in WM and the value of FA ranges from 0 to 1. The relationship between DTI metric changes and WM microstructure has been investigated by recent study, such as patients with stroke[19], Parkinson' s disease (PD)[20], sleep disorder[21], and Alzheimer's disease[3]. The glymphatic system is based on the exchange of CSF and ISF, and because this exchange process can be observed by DTI technique, DTI can be used to evaluate the glymphatic system.

3. DTI-ALPS in Neurological Disease

3.1 Cerebrovascular Disease

Stroke is the second leading cause of death and the third leading cause of disability combined in the world[22], a growing body of research aim to investigate the changes and causes of glymphatic system dysfunction in stroke by DTI-ALPS method. The ALPS index of cerebral infarction hemisphere is significantly lower than that of contralateral healthy hemisphere, and significantly lower in stroke patients than in normal subjects[12]. In particular, glymphatic system impairment in the ipsilateral side of the lesion confirmed in patients with spontaneous intracerebral haemorrhage (sICH), or haemorrhagic stroke, and the ALPS index can reflect the duration of sICH[23].

Glymphatic system may be damaged in the process and development of cerebral small vessel disease (CSVD)[24]. Zhang et al.[25] established modified ALPS index (mALPS-index), which can represent the clearance function of the glymphatic system in patients with CSVD.

Carotid atherosclerosis (CAS) and cerebral amyloid angiopathy (CAA) are two common pathogenesis of early high-risk cerebrovascular disease, which can lead to vascular cognitive impairment[26]. Enlarged PVS in the basal ganglia (BG) may induce the impairment of the glymphatic system and cognitive in patients with CAS, while resulting in the decrease of the ALPS index[26]. There are three main aspects which are significantly correlated with the ALPS index involving CSVD severity, cognitive impairment and disease recurrence in CAA[27]. Although Lee et al.[28] systematically investigated the glymphatic system of migraine with and without aura, there is no significant difference in the glymphatic system function between the two groups. Interestingly, there is impairment of the glymphatic system in patients with cluster headache[29].

One study reported the associations between glymphatic system function and transient global amnesia (TGA) and recurrent TGA. Compared with healthy controls, the ALPS index has no significant difference in patients with TGA, while it varies significantly in patients with recurrent TGA. In summary, recurrence may have a certain impact on the impaired glymphatic system function of TGA patients[30].

3.2 Central Nervous System Disease

Structural and functional disorders of the central nervous system (CNS) can result in glymphatic system impairment[31]. Multiple sclerosis (MS) and neuromyelitis optical spectrum disorders (NMOSD) are both demyelinating disease of the CNS[32]. Based on DTI-ALPS, growing evidence has indicated that MS[33] and NMOSD[34, 35] patients display lower ALPS index compare with healthy controls, and glymphatic system impairment may result in clinical disability.

Glymphatic system dysfunction in glioma[36] and meningiomas with peritumoral brain edema (PTBE)[37, 38] has been demonstrated. A negative correlation between the ALPS index and PTBE volume is found, and lower ALPS index reflected the insufficient clearance function of the glymphatic system. Cancer pain (CP) with malignant tumors can seriously affect life quality, Wang et al.[39] verified that glymphatic system impairment were closely related to CP, and the ALPS index inversely correlated with the degree of CP. After pain relief intervention, the ALPS index exhibits a slow increase, and the function of the glymphatic system is recovered.

Impaired glymphatic system after iNPH decreases the ALPS index and cognitive function[40-42]. However, the ALPS index is improved in iNPH patients after lumboperitoneal shunt surgery, which indicates the recovery of glymphatic system function[43].

3.3 Neurodegenerative Disease

The brain and spinal cord are mainly made up of neurons, and loss of neurons and/or their myelin sheaths can lead to neurodegenerative diseases, which is irreversible[44]. Neurodegenerative diseases can be divided into acute and chronic neurodegenerative diseases according to their pathological causes. The typical diseases of acute neurodegenerative diseases include AD and PD, while the typical diseases of chronic neurodegenerative diseases include hemorrhagic and ischemic vascular diseases of the nervous system, and epilepsy[45].

Lower ALPS index reflects glymphatic system dysfunction in AD cases[46]. Recent studies[13, 47] applied DTI-ALPS to investigate cognitive function in patients with AD, mild cognitive impairment (MCI), and healthy controls. The ALPS index is significantly correlated with the MMSE. There are significant differences in the ALPS index among the cognitively normal group, the MCI group and AD group, respectively, which suggest that DTI-ALPS could be used to evaluate cognitive function and estimate the risk of dementia in different subjects.

In order to investigate glymphatic system activity and cognitive functions in PD patients, Chen et al.[48] found that lower ALPS index indicated damage of the glymphatic system and also reflected lower cognitive levels. Therefore, the ALPS index can be used as a biomarker of the glymphatic system in patients of PD. Further research demonstrated that the ALPS index was negatively correlated with age and disease severity[49, 50].

It has been hypothesized that there is glymphatic system impairment in patients with epilepsy. Based on this hypothesis, the ALPS index was significantly positively correlated with DTI parameters (FA, MD) and negatively correlated with age in focal epilepsy cases[51, 52], and there was a significantly lower ALPS index in status epilepticus cases[53]. Temporal lobe epilepsy (TLE)[54] and juvenile myoclonic epilepsy (JME)[55] are analyzed, the ALPS index of patients is significantly lower than that of healthy controls, and not associated with age at epilepsy onset.

4. DTI-ALPS in Vascular Risk Factors

It has been proved that the impairment of the glymphatic system is associated with cerebrovascular risk factors, such as aging, hypertension, and diabetes mellitus.

The age dependence of the glymphatic system was evaluated by DTI-ALPS, there was a second-degree distribution between age and the ALPS index which peaked at age 40[56]. Due to aging, the function of the glymphatic system and cognitive was reduced[57]. Furthermore, the potential connection between iron deposition and glymphatic system function in the normal aging brain was detected[58]. It is important to note that the ALPS index of females is significantly higher than that of males[59].

Hypertension may cause suppression of the glymphatic system function, DTI-ALPS analysis showed lower ALPS index in the elderly with hypertension compared to the normal elderly[7]. Type 2 diabetes mellitus (T2DM) is an common risk factor for cognitive decline. Lower ALPS index and water diffusivity along the PVS concerning T2DM were found by Yang et al.[60]. Hence, the ALPS index can be used as a biomarker for glymphatic system dysfunction caused by hypertension or diabetes mellitus.

5. DTI-ALPS in Other Disease

The growing body of evidence indicated significant associations between glymphatic system function with sleep diseases, including sleep impairment[61, 62], obstructive sleep apnea (OSA)[63-65], and idiopathic rapid eye movement sleep behavior disorder (iRBD)[21, 66]. These research studies demonstrated lower ALPS index reflected glymphatic system dysfunction in patients. These showed positive associations between the ALPS index and cognitive status, cerebral gray matter volumes, and suggested sleep diseases contributed to increased risks for AD and PD[63, 66].

A recent study found decreased ALPS index in patients with end-stage renal disease (ESRD), which was demonstrated as a disease with impaired glymphatic system[67]. The ALPS index increased significantly in HIV having combination antiretroviral therapy (cART) has also been reported[68].

6. Conclusion and Outlook

In conclusion, this review summarizes recent studies of the DTI-ALPS method, showing that the DTI-ALPS method may provide neuroimaging evidence for glymphatic system activity in subjects. The ALPS index can be used as a biomarker to estimate the glymphatic system function and assess the cognitive status, disease severity and prognosis recovery of subjects.

However, the glymphatic system function in patients has not been studied longitudinally using the DTI-ALPS method, and there are certain subjective factors when calculating the ALPS index. In addition, the sample size is small, the influence of stress and mood disorders on the glymphatic system are ignored. Therefore, it is necessary to further develop DTI-ALPS method to systematically evaluate the glymphatic system function and promote it to be applied in a wide range of clinical applications in the future.

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