Review

Research progress of enlarged perivascular space and sleep disturbance

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Abstract:

The perivascular space is one of the imaging features of cerebral small vessel disease.With the development of imaging technology, the detection rate of enlarged perivascular space in patients with sleep disorders is getting higher and higher, which has gradually attracted people's attention.This review mainly discusses the pathological mechanism of the perivascular space, sleep physiology, and the relationship between the enlarged perivascular space and sleep disorders, in order to provide a theoretical basis for early identification of patients with sleep disorders.

Keywords:

perivascular sp[1]ace; sleep disorders; sleep fragments; obstructive sleep apnea syndrome

1. Perivascular space

Normal function of the perivascular space is very important for the maintenance of brain health.The perivascular space is a series of various channels in the brain surrounding small arteries, capillaries and venules. Its main function is to recirculate through cerebrospinal fluid, exchange with interstitial fluid, and remove metabolic waste (β amyloid, tau protein and α-synuclein, etc.) from the brain at the same time[1]. This function may be Increase during sleep[2]. Comprehensive information from human studies and rodent models shows that the enlarged perivascular space on MRI is a sign of perivascular space dysfunction (normal cerebral fluid and waste removal obstacles and microvascular dysfunction).And the number of perivascular spaces gradually increases with age. No matter how many, they are usually found in specific brain anatomical areas, such as the basal ganglia, hippocampus, midbrain, pons, etc. If there are a large number of them in one area Perivascular space, the perivascular space can be seen in all other typical areas, and there are differences in the number of different areas. Considering that this difference may be related to vascular risk factors[2].

2. Sleep physiology

Human sleep is divided into rapid eye movement sleep and non-rapid eye

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movement sleep.Non-rapid eye movement sleep is subdivided into 4 stages, including sleep spindle and slow wave activity in delta band. Slow wave activity is the main rhythm of deep sleep and may play an important role in regulating sleep rhythm[3].Sleep has the key function of clearing the metabolites and neurotoxic wastes accumulated in the waking central nervous system in the brain, which is essential for maintaining the health of the central nervous system.Studies have shown[4] that when the cerebrospinal fluid tracer flows into the brain of mice, the amount of fluid in the awake mice is reduced by 95%, while in deep sleep, the volume of interstitial fluid in the brain has been expanded by 60% to remove waste faster passes through the astrocyte water channel -4 (AQP4). AQP4 gene mediates the outflow of cerebrospinal fluid from the perivascular space during non-rapid eye movement sleep. Aqp4 polymorphism is associated with individual differences in sleep quality, and regulates the relationship between sleep and brain amyloid deposits[5].At present, polysomnography can be used clinically to monitor and determine the type of sleep disorder.

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3. Enlarged perivascular space(EPVS) and sleep disturbance

Sleep disorders include insomnia, sleep rhythm disorders, sleep-related breathing disorders, parasomnias, and sleep-related movement disorders.

Sleep fragmentation is a state of recurring short-term awakenings during night sleep. It is not difficult to find the high frequency of sleep fragmentation in the elderly in clinical practice. A data shows that the prevalence of insomnia is 30%-48%. The above data are only for sleep patients with non-respiratory symptoms.Most studies have found that there is a close relationship between perivascular space dysfunction and sleep disorders.The Ontario Neurodegenerative Disease Research Program[5] studied the sleep quality of 152 patients with cerebrovascular diseases, using 3T-MRI to measure the volume of PVS, and using the Pittsburgh Sleep Quality Index (PSQI) to assess the quality of sleep, and it was found that the larger the volume of PVS ,the longer the individual needs to sleep, the longer the perivascular space dysfunction may cause behavioral compensatory responses.A study of 561 community-dwelling elderly people recording 24-hour rest-activity rhythmicity[6] found that sleep disorders are closely related to the pathological changes of cerebral small vessel disease and are independent of vascular risk factors. Interrupted 24-hour rest -Activity rhythm can increase the pathological burden of cerebral small vessel disease.A single-center cross-sectional case-control study found that[7], sleep fragmentation in patients with CSVD is more serious, and the degree of sleep fragmentation in patients with CSVD is positively correlated with the severity of white matter lesions and perivascular space expansion. Peripheral space dysfunction leads to a decrease in the clearance of metabolites in the brain, which is similar to the findings of Aribisala et al.[8] that sleep interruption is related to the expansion of the basal ganglia perivascular space.

The most common respiratory-related breathing disorder is obstructive sleep

apnea(OSA) syndrome, which has a lower incidence than non-respiratory-related sleep patients. There is increasing evidence that the enlarged perivascular space is closely related to OSA.A cross-sectional study of 107 OSA patients underwent polysomnography[1] found that EPVS in patients with obstructive sleep apnea may be secondary to sleep disorders, intermittent hypoxemia, and blood flow related to respiratory events The increase in the number of EPVS in OSA patients may be a potential risk factor for cerebrovascular events.A Meta-analysis of the imaging characteristics of OSA patients and cerebral small vessel disease[9] found that moderate and severe OSA has nothing to do with PVS, but the analysis could not explore the causal relationship between OSA and CSVD, and there are few studies on obstructive sleep apnea and PVS, and the research efforts are also insufficient.Huang et al.[10]studied 72 severe OSA patients and 53 non-OSA volunteers found that the severity of OSA was positively correlated with the increase in the basal ganglia and semi-oval pericardiovascular space.A study of Atahualpa residents aged ≥60 years to measure the Pittsburgh Sleep Quality Index[11] found that the relationship between sleep quality and enlarged perivascular space in 338 subjects was significant.And sleep inefficiency was associated with PVS,the increase in the peripheral space is independently related, suggesting that sleep may affect the structural changes of the space around the blood vessels.The results of Song et al.[12]are similar to this.In addition, a rat animal model with a tendency to spontaneously hypertensive stroke was established by chronically implanting a tracheal balloon to block the airway during the sleep cycle to establish a model of OSA. The experimental conclusion is that OSA accelerates the onset of vascular disease of the rat brain[13].

Evidence on the relationship between periodic limb movements during sleep and imaging features of cerebral small vessel disease is limited and inconsistent.In a study involving Atahualpa residents aged ≥60 years[14], polysomnography and MRI were used to find that there was no independent correlation between periodic limb movement related indexes during sleep and enlarged perivascular spaces in elderly residents living in stroke-free communities.In a cross-sectional study, Kang et al. believed that the increase in periodic limb movement-related index during sleep was related to the increase in the total imaging burden of cerebral small vessel disease. At the same time, they believed that periodic limb movement during sleep was a sign of cerebral small vessel disease.A case-control study of 44 restless legs syndrome patients also concluded that the duration of restless legs syndrome may be an independent predictor of the burden of cerebrovascular disease, and may also be a risk factor for asymptomatic cerebral infarction[15].

At present, there are relatively few studies on the relationship between EPVS and sleep disorders, and the specific pathophysiological mechanism has not yet been fully clarified. Further exploration is needed in the future to provide more perspectives for early identification and intervention.

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References

[1]Ferri R, Cosentino FI, Moussouttas M, Lanuzza B, Aricò D, Bagai K, Wang L, McLaughlin B, Walters AS. Silent Cerebral Small Vessel Disease in Restless Legs Syndrome.Sleep. 2016 Jul 1;39(7):1371-7. doi: 10.5665/sleep.5966. PMID: 27091527; PMCID: PMC4909619.

[2]Wardlaw JM, Benveniste H, Nedergaard M, Zlokovic BV, Mestre H, Lee H, Doubal FN, Brown R, Ramirez J, MacIntosh BJ, Tannenbaum A, Ballerini L, Rungta RL, Boido D, Sweeney M, Montagne A, Charpak S, Joutel A, Smith KJ, Black SE; colleagues from the Fondation Leducq Transatlantic Network of Excellence on the Role of the Perivascular Space in Cerebral Small Vessel Disease. Perivascular spaces in the brain: anatomy, physiology and pathology.Nat Rev Neurol.2020 Mar;16(3):137-153.doi:10.1038/s41582-020-0312-z.Epub 2020 Feb 24.PMID: 32094487.

[3]Semyachkina-Glushkovskaya Oxana., Postnov Dmitry., Penzel Thomas., Kurths Jürgen.(2020). Sleep as a Novel Biomarker and a Promising Therapeutic Target for Cerebral Small Vessel Disease: A Review Focusing on Alzheimer's Disease and the Blood-Brain Barrier. Int J Mol Sci, 21(17), undefined. doi:10.3390/ijms21176293.

[4]Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, O'Donnell J, Christensen DJ, Nicholson C, Iliff JJ, Takano T, Deane R, Nedergaard M. Sleep drives metabolite clearance from the adult brain.Science.2013 Oct 18;342(6156):373-7.doi: 10.1126/science.1241224. PMID: 24136970; PMCID: PMC3880190.

[5]Ramirez J, Holmes MF, Berezuk C, Kwan D, Tan B, Beaton D, Scott CJM, Ozzoude M, Gao F, Yu D, Swardfager W, Lawrence-Dewar J, Dowlatshahi D, Saposnik G, Boulos MI, Murray BJ, Symons S, Bartha R, Black SE, Swartz RH; ONDRI Investigators, Lim A.MRI-visible perivascular space volumes, sleep duration and daytime dysfunction in adults with cerebrovascular disease. Sleep Med. 2021 Jul;83:83-88.doi: 10.1016/j.sleep.2021.03.043. Epub 2021 Apr 19. PMID: 33991894.

[6]Sommer R, Yu L, Schneider JA, Bennett DA, Buchman AS, Lim ASP. Disrupted Rest-Activity Rhythms and Cerebral Small Vessel Disease Pathology in Older Adults. Stroke. 2021 Jul;52(7):2427-2431.doi:10.1161/STROKEAHA.120.030870.Epub 2021 Apr 27. PMID: 33902300.

[7]Wang J, Chen X, Liao J, Zhou L, Han H, Tao J, Lu Z. Non breathing-related sleep fragmentation and imaging markers in patients with atherosclerotic cerebral small vessel disease (CSVD): a cross-sectional case-control study. BMC Neurol. 2020 Mar 17;20(1):98.doi:10.1186/s12883-020-01647-x.PMID:32183737;PMCID:PMC7076927.

[8]Del Brutto OH. Sleep-related symptoms and brain morphological changes in older adults. Sleep Med. 2020 Jan;65:150-151.doi: 10.1016/j.sleep.2019.07.021.Epub 2019 Aug 5. PMID: 31735625.

[9]Huang Y, Yang C, Yuan R, Liu M, Hao Z. Association of obstructive sleep

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apnea and cerebral small vessel disease: a systematic review and meta-analysis. Sleep. 2020 Apr 15;43(4):zsz264. doi: 10.1093/sleep/zsz264. PMID: 31696917.

[10]Huang S, Wang D, Zhou H, Chen Z, Wang H, Li Y, Yin S. Neuroimaging consequences of cerebral small vessel disease in patients with obstructive sleep apnea-hypopnea syndrome.Brain Behav. 2019 Aug;9(8):e01364.doi: 10.1002/brb3.1364. Epub 2019 Jul 23. PMID: 31334920; PMCID: PMC6710192.

[11]Del Brutto OH, Mera RM, Del Brutto VJ, Castillo PR. Enlarged basal ganglia perivascular spaces and sleep parameters. A population-based study. Clin Neurol Neurosurg. 2019 Jul;182:53-57. doi: 10.1016/j.clineuro.2019.05.002. Epub 2019 May 6. PMID: 31078956.

[12]Song TJ, Park JH, Choi KH, Chang Y, Moon J, Kim JH, Choi Y, Kim YJ, Lee HW. Moderate-to-severe obstructive sleep apnea is associated with cerebral small vessel disease. Sleep Med. 2017 Feb;30:36-42.doi:10.1016/j.sleep.2016.03.006. Epub 2016 May 4. PMID: 28215260.

[13]Lloyd EE, Durgan DJ, Martini SR, Bryan RM. Pathological effects of obstructive apneas during the sleep cycle in an animal model of cerebral small vessel disease. Hypertension.2015 Oct;66(4):913-7. doi: 10.1161/HYPERTENSIONAHA.115.05764. Epub 2015 Aug 10. PMID: 26259594; PMCID: PMC4567494.

[14]Del Brutto OH, Mera RM, Del Brutto VJ, Castillo PR. Lack of Association between Periodic Limb Movements during Sleep and Neuroimaging Signatures of Cerebral Small Vessel Disease in Stroke-Free Community-Dwelling Older Adults. The Atahualpa Project. J Stroke Cerebrovasc Dis. 2020 Feb;29(2):104497. doi: 10.1016/j.jstrokecerebrovasdis.2019.104497. Epub 2019 Dec 4. PMID: 31810723.

[15] Ferri R, Cosentino FI, Moussouttas M, Lanuzza B, Aricò D, Bagai K, Wang L, McLaughlin B, Walters AS. Silent Cerebral Small Vessel Disease in Restless Legs Syndrome.Sleep.2016 Jul 1;39(7):1371-7. doi: 10.5665/sleep.5966. PMID: 27091527; PMCID: PMC4909619.

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