Perivascular space and neurological disorders

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Abstract: Perivascular space (PVS) is a crevice between two slices of cerebral pia maters, filled with tissue fluid, which be formed by pia mater embolism in the surrounding of cerebral perforating branch (excluding micrangium). Normal PVS (diameter < 2 mm) can be found in almost all healthy adults; however enlarged PVS (diameter > 2 mm) has correlation with neurological disorders probably. The article reviews the formation mechanism, imageology characteristics and the relation with neurological disorders of PVS, which is beneficial to the research of some neurological disorders etiopathogenesis and treatment.

Keywords: perivascular space; mechanism; image; neurological disorders

Perivascular space (PVS) is invaginations of pia mater, containing cerebrospinal fluid (CSF) and accompanying small arteries as they penetrate the surface of the brain (excluding capillary)^[1-2] (Fig. 1). PVS was described in 1849 by Pestalozzi firstly. In 1851, Virchow, the German pathologist, put forward that PVS was a gap under outer membrane of artery in close to capillary. In 1859, the German anatomist, Robin, further confirmed that PVS was located in the outer membrane of cerebral vessel and was close. Therefore, PVS also was called the Virchow-Robin space or V-R cleft^[1]. Many progresses have been made in research about PVS recently, but a lot of disputes about PVS still existed. This paper reviewed the PVS formation mechanism, imageology characteristics and the research progress related to neurological diseases.

1 The PVS formation mechanism

It is still not clear about how PVS be formed. Previously, some scholars thought that PVS might have something to do with inborn heteroplasia, blood vessel degradation abnormality,

infection, vasculitis, and demyelination, *etc.*, that was to say, some diseases resulted in the PVS forming. But these theories could not be verified or negated up to now^[1]. Recent researches tended to stand that PVS was a normal anatomical structure of health body. Just when PVS expansion exceeded certain degree and showed corresponding clinical symptoms, PVS might be considered as the pathology change^[4-5].

Most scholars divided PVS into three classes according to magnetic resonance imaging (MRI): I class: diameter < 2 mm;

Fig. 1 The sketch of the relationship of pia to perivascular space (PVS). An artery is coated by a sheath of cells derived from the pia mater. The sheath has been cut away to show that the PVS. SAS: subarachnoid space. Modified from Zhang ET *et al.*^[3]

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II class: diameter at 2-3 mm; III class: diameter > 3 mm, II and III classes were called big PVS^[4]. Big PVS is usually located in anterior commissure, semi-oval center, brainstem, and capsula extrema^[1,6-13]. PVS above II class was usually considered as the pathologic result.

The etiopathogenesis of big PVS is still not definite. Some scholars put forward that obstruct of the partial tissue liquid in brain may be an important factor of PVS expansion^[14]. But recent research suggested that big PVS might be caused by the obstruct of ventricular drainage^[15-19], especially by obstruct of lymphatic drainage. Some reseachers thought that dilatate PVS belonged to one category of lacunar infarctions^[20], while other researchers considered big PVS might have something to do with age, hypertension, dementia, epilepsy or migraine^[21]. But in addition to age factor, recent researches proved that big PVS had no relationship with above diseases^[22-23].

2 Imageology characteristics and clinical symptoms

2.1 Imageology characteristics Only PVS expansion whose diameter exceeds 0.66 mm can be seen on MRI. Usually, PVS of diameter less than 2 mm is normal anatomical structure and can be seen in healthy subjects of different age groups (Table 1)^[24]. PVS possesses some explicit imageology characteristics on MRI, such as smooth boundary, showing rotundity or line type (depending on different positions and slicing), accompanying with the perforating branch, similar signal with CSF on the T₁WI and T₂WI sequences, no strong contrast and no mass effect. Fluid attenuation inversion recovery (FLAIR) imaging is very important in discriminating between PVS and lacunar infarction: infarction reporting the high signal change, while PVS reporting the low signal changes, same to CSF.

2.2 Clinical symptoms Patients with PVS in above II class usually follow some non-specific symptoms, such as headache (over 50% patients), vertigo, dementia, abnormal visual sense, seizure, syncope, memory and equilibrium obstacle, and attention disorganization. However these symptoms do

not relate to the locations of PVS, and do not follow the development of clinical symptom of patients^[9, 25-27].

3 Big PVS and neurological disorders

3.1 Lacunar infarction It is difficult to discriminate PVS from lacunar infarction on CT before MRI was published. Now the question can be easily solved through MRI FLAIR imaging^[28]. Bokura^[29] also discovered that the size, shape and position of focus are important to discriminate PVS from lacunar infarction according to postmortem. The size is the most important factor: average size of PVS is 1.9 mm × 0.9 mm, and 72% of PVS are less than 2 mm × 1 mm, while the shape of 47% of lacunar infarction is sphenoid type, with mean size 3 mm × 1.6 mm, in which 60% of lacunar infarction are larger than 2 mm × 2 mm. Therefore, the focus whose size is above 3 mm × 2 mm in basal nuclei or brain stem is probable lacunar infarction.

3.2 Primary angiitis of the central nervous system (PACNS) Relations of PACNS and big PVS are still seldom reported. Campi^[30] analyzed brains MRI and pathology from 6 patients with PACNS, in which 4 cases have big PVS, presenting enhancement effect. Campi explained that it resulted from leptomeningitis and increased exudation probably.

3.3 Hydrocephalus Hydrocephalus usually means that circulation of brain tissue fluid is blocked, which produces big PVS. House^[31] reported 12 hydrocephalus cases with big PVS, showing symptoms of cystic dilation, mean diameter larger than 15 mm, and local mass effect. On scarce circumstances, extremely dilated PVS resulted in light hydrocephalus^[32]. The notable question is that big PVS on midbrain would be discriminated from abscess, cystic tumor and parasitic cyst.

3.4 Multiple sclerosis (MS) Studies discovered that big PVS perhaps was a neuroradiology mark of inflammation changes on early stage of MS. Fifty-five percent of patients with MS carried big PVS on white matters of hemisphere and 85% of cases had more than four PVS^[33].

3.5 Myotonic dystrophy (DM) DM is a multisystem disease following several kinds of brain dysfunctions, including leukodystrophy. Costanzo^[34] evaluated the cranial MRI of 41 patients with the adult form of DM and 41 healthy controls. Dilated PVS and white matter lesions (WMLs) were rated

Table 1 Percentage of PVS in healthy subjects of different age groups on MRI

Age (years)	< 20	21-40	41-60	61-80	> 80
PVS (%)	23	33	28	33	18

according to semiquantitative methods. Convexity PVS were more frequent (68% vs 34%) and severer (median scores: 4 vs 0) in DM patients than in controls, while lenticulostriate PVS did not show significant differences in frequency (83% vs 70%) and severity (median scores: 4 vs 3). WMLs were more frequent (66% vs 22%) and severer (median scores: 5 vs 0) in patients. Disease duration was negatively correlated with convexity PVS and positively with lobar (centrum semiovale) WML scores. Therefore author stood that dilated convexity PVS might be one of the initial findings in cranial MRI of DM, preceding the appearance of lobar WMLs.

3.6 Cryptococcal infection in central nervous system (CICNS) Di Costanzo^[35] evaluated 26 cases with CICNS, including 18 males and 8 females, and found ten patients were immunocompromised. The results showed that the most common image of CICNS presented ventricular dilatation in CT and big PVS in MRI. MRI is more sensitive in detecting CICNS like PVS dilatation and leptomenigeal enhancement. Meanwhile meningeal imaging enhancement, hemorrhagic infarction, cryptococcoma and pons abscess also are important symptoms.

3.7 Mental retardation (MR) and neuropsychic disturbance MR is a children disability, characterised by cognitive impairment and concurrent limitations in two or more adaptive skills. MRI has shown abnormalities including big PVS, mega cisterna magna, hypoplasia of the corpus callosum, wide cavum septum pellucidum, white matter alterations, heterotopia and cerebellar hypoplasia^[36]. Artigas^[37] found that big PVS existed in white matter of centrum ovale majus perhaps was a symbol of good prognosis. And Harte^[38] also reported unusual occurrence of progressive megalencephaly and dilated periventricular cystic PVS on MRI in two siblings of a Turkish family. Both affected children presented with psychomotor retardation. Since the patients were of different gender and their parents were consanguineous, this constellation of findings suggested an autosomal recessive trait. Neuropsychic disturbance, such as tension type headache (TTH), also is a common disease on children. Another research studied 58 children, who aged 3-14 years old (mean 10.8 years old), with a clinical diagnosis of migraine (31 children) or TTH (27 children) and underwent cerebral MRI,

taken 30 headache-free patients of the same age (mean 10.2 years old) and 30 adult migraineurs with postpubertal onset of symptoms as controls. The images were reviewed for structural abnormalities in the regions of the small penetrating arteries. Accentuated PVS were found in 61% of the children with migrainous headaches and in 22% of children of those with TTH. Prominent PVS were seen in 27% of the control children and in only 13% of the adults. Small infarcts and gliosis were rare in children with or without headache, but were seen in 30% of adult migraineurs.

4 Summary

Reviewing the researches above, we can conclude that PVS is a special structure existing in normal human body and its formation mechanism and function are still unclear. On the other hand, the PVS above II class usually means the pathologic status and correlates to some nervous system diseases. Further researches in PVS and other relevant factors may provide novel approaches to the mechanism and therapy of a series of neurological disorders.

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血管周围间隙与神经系统疾病

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摘要 血管周围间隙(Perivascular space, PVS)是软脑膜内陷在脑穿支小血管周围(不包括毛细血管)而形成的介于两层软脑膜之间的间隙, 其间充满组织液。正常 PVS 的直径一般小于 2 mm, 存在于几乎所有健康成年人, 而 PVS 的直径增大超过 2 mm, 则与多种神经系统疾病相关。本文就 PVS 的形成机制、影像学特点及其与神经系统疾病的关系作了阐述, 这将对研究一系列神经系统疾病的发病机制和治疗方法有所助益。

关键词: 血管周围间隙; 机制; 影像; 神经系统疾病