Case report

Cognitive impairment due to widespread enlarged perivascular spaces✩✩

Yoshitaka Yamaguchi, MDPhD*, Manabu Wada, MDPhD, Luna Kimihira, MDPhD, Hikaru Nagasawa, MDPhD

Department of Neurology, Yamagata Prefectural Central Hospital, 1800 Aoyagi, Yamagata 990-2292, Japan

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ABSTRACT

Perivascular spaces, also known as Virchow-Robin spaces, are usually considered as a normal, asymptomatic finding. However, this finding can occasionally demonstrate an atypical appearance and can be symptomatic. We report herein a rare case of cognitive impairment associated with extremely enlarged perivascular spaces. A 68-year-old Japanese woman visited our hospital with a 1-year history of progressive memory impairment. In addition to temporal disorientation and short-term memory impairment, neuropsychological testing showed frontal lobe-related symptoms such as slowed thinking processes, reduced verbal fluency, attention deficit, and reduced working memory. Magnetic resonance imaging of the brain showed widespread enlarged perivascular spaces almost symmetrically in the subcortical white matter of bilateral hemispheres, prominently in bilateral insulas, and frontal opercula. On 99mTc-ethyl cysteinate dimer single photon emission computed tomography, hypoperfusion was apparent in bilateral insulas and frontal opercula where enlarged periventricular spaces were prominent, whereas cerebral perfusion was preserved in areas where enlargement of perivascular spaces was mild or absent. Because symptoms were consistent with the distribution of the enlarged perivascular spaces and hypoperfusion in the brain, cognitive impairment due to enlarged perivascular spaces was diagnosed. Clinicians should note enlarged perivascular spaces as a potential cause of neurological deficits including cognitive impairment.

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* Corresponding author.
E-mail address: yyamaguchi830@gmail.com (Y. Yamaguchi).
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Introduction

Perivascular spaces (PVS), also known as Virchow-Robin spaces, are fluid-filled perivascular structures that are found around the walls of arteries, veins, and venules in the brain parenchyma [1]. On magnetic resonance imaging (MRI) of the brain, PVS are usually considered normal findings. Slightly enlarged PVS, generally <2 mm in diameter [2], are highly prevalent among healthy elderly population [3]. Enlarged PVS can occur throughout the brain wherever vessels are present.

PVS occasionally demonstrate an atypical appearance reaching a larger size, sometimes exerting mass effects (sometimes called tumefactive PVS) or with a more widespread distribution [4]. Although PVS are usually asymptomatic, extremely enlarged PVS can be symptomatic. For instance, giant PVS in the mesencephalothalamic region can rarely cause hydrocephalus necessitating surgical treatment for neurological improvement [5]. The pathogenesis of extremely enlarged PVS is poorly understood and little has been known about the clinical presentation of extremely enlarged PVS [4]. Cognitive impairment associated with marked enlargement of PVS has been rarely reported [6–10]. In addition, cognitive impairment associated with symmetrical, widespread appearance of enlarged PVS has not been reported. We present herein a very rare case of cognitive impairment associated with widespread appearance of enlarged PVS symmetrically in bilateral hemispheres.

Case report

A 68-year-old Japanese woman visited our hospital with a 1-year history of progressive memory impairment. Her family history was unremarkable. She had a medical history of optic neuritis in the left eye due to an unknown cause 8 years earlier at another hospital. At that time, subcortical white matter abnormalities had been identified in both hemispheres on fluid-attenuated inversion recovery (FLAIR) MRI of the brain (Fig. 1, arrows). Because no symptoms related to those lesions were apparent, including cognitive impairment, the lesions were considered asymptomatic.

On examination, the patient was irritable, impulsive, and showed disinhibited behaviors (eg, she left the consulting room during her medical examination). In addition to temporal disorientation and impairment of short-term memory, neuropsychological tests showed frontal lobe-related symptoms such as slowed thinking processes, reduced verbal fluency, attention deficit, and reduced working memory. Mini-Mental State Examination score was 12/30. In addition, Frontal Assessment Battery score was 5/18. The patient was unable to complete the Trail Making Test A and the Wisconsin Card Sorting Test, which are known to reflect frontal lobe functions [11,12]. Given the symptoms and the results of neuropsychological examinations, dysfunction of frontal lobes was suggested. Results for complete blood count and serum biochemical analyses, including thyroid function, were normal. Serum levels of vitamin B1, B12, and folic acid were normal. Tests for human immunodeficiency virus, syphilis, antinuclear antibody, anti-DNA antibody, anti-SS-A/SS-B antibodies, and anti-aquaporin 4 antibody were also negative. Brain MRI revealed scattered polycystic-like, spotty or linear abnormalities appearing hyperintense on T2-weighted imaging, with an almost symmetrical distribution in the subcortical white matter of bilateral hemispheres except for the posterior lobes (Fig. 2). Lesions were most prominent in bilateral insulas and frontal opercula (Fig. 2, arrows). The lesions showed hypointensity on T1-weighted imaging (Supplemental file. 1) and FLAIR (Supplemental file 2). Because signal intensities were comparable to those of cerebrospinal fluid (CSF) and surrounding brain parenchyma showed normal signal intensities, the lesions were considered to represent enlarged PVS. Except for mild brain atrophy in bilateral frontal and parietal lobes, no abnormalities suggested mass effects, neurodegenerative disorders, or vascular or inflammatory encephalitis. Compared with the results of brain MRI 8 years earlier, the severity of PVS enlargement was more progressed, although the severity of brain atrophy was about the same. On 99mTc-ethyl cysteinate dimer single photon emission computed tomography (SPECT), hypoperfusion was seen in bilateral insulas, and frontal opercula where enlarged PVS were prominent, whereas cerebral perfusion was preserved in areas where enlarged PVS were mild or absent (Fig. 3). Symptoms and results of neuropsychological examination mainly suggested dysfunction of the frontal lobes, consistent with the distribution of enlarged PVS in her brain. The patient was therefore diagnosed with cognitive impairment due to widespread enlarged PVS.

Discussion

We have presented a rare case of cognitive impairment due to widespread enlarged PVS in bilateral hemispheres. When she had presented with enlarged PVS on MRI 8 years earlier, she had shown no signs of dementia, and the lesions were considered asymptomatic. Eight years later, the enlarged PVS had progressed to become symptomatic, causing cognitive impairment. How PVS become enlarged and the downstream consequences of dilatation remain unclear. However, the asymptomatic, and widespread appearance of enlarged PVS 8 years earlier may have represented a preclinical stage of dementia. Although slight brain atrophy in bilateral frontal and parietal lobes had been noted, the severity of brain atrophy remained almost unchanged during the intervening period.

Unlike more common forms of dementia such as Alzheimer’s disease, symptoms, and results of neuropsychological examinations in the present case showed frontal lobe dysfunction. Conventional MRI techniques also failed to identify enlargement of the parahippocampal fissure, which indirectly reflected atrophy of the medial temporal lobe. Furthermore, hypoperfusion on SPECT was detected only in bilateral insulas and frontal opercula with severely enlarged PVS. The pattern of hypoperfusion on SPECT differed markedly from that of neurodegenerative diseases, including frontotemporal dementia. These neuropsychological and radiological findings indicated that the diagnosis in our patient differed from representative neurodegenerative dementias,
Fig. 1 – Fluid-attenuated inversion recovery of the brain 8 years earlier reveals subcortical white matter abnormalities in both hemispheres (allows).

Fig. 2 – Brain magnetic resonance imaging reveals scattered polycystic-like abnormalities appearing hyperintense on T2-weighted imaging in bilateral subcortical white matter, especially in the insula, and frontal lobes bilaterally (arrows). Mild brain atrophy is evident in bilateral frontal and parietal lobes.
such as Alzheimer’s disease or frontotemporal dementia. Although the presence of enlarged PVS reportedly correlated with vascular dementia and poor cognitive performance, radiological findings of small vessel disease such as lacunar infarct or microbleeds were unremarkable in our patient.

To the best of our knowledge, only 5 cases of cognitive impairment associated with enlarged PVS have been reported [6–10]. The characteristics of these cases are shown in Table 1. Reported cases have involved middle-aged or elderly individuals (age range, 63–77 years). Although all cases showed widespread enlarged PVS in the territory of the perforating medullary arteries, categorized as type II PVS [4], the distribution of lesions varied from case to case. In contrast with our case showing a bilateral, relatively symmetrical distribution, all previously reported cases showed laterality in the distribution of PVS. Two cases showed a hemispheric distribution [8,10]. Symptoms related to enlarged PVS differed according to the distribution of lesions and focal neurological signs sometimes occurred in addition to cognitive impairment [6–10]. In 3 cases for which CSF studies were performed, the findings were normal, suggesting that inflammatory or infectious diseases were not involved [6,7,10]. As with our case, 2 cases showed hypoperfusion in the area of enlarged PVS and preservation of perfusion in areas lacking enlarged PVS [8,9]. Furthermore, those 2 cases presented with focal neurological symptoms related to hypoperfusion on SPECT. In 1 case showing memory disturbance and parkinsonism with a left-side dominance, hypometabolism on fluoro-D-glucose positron emission tomography (FDG-PET) was observed predominantly in those cortical areas showing enlarged PVS [10]. Evaluating cerebral perfusion using SPECT or cerebral metabolism on FDG-PET may thus be useful not only for the differentiation from other dementing disorders, but also for the assessment of neurological symptoms related to enlarged PVS.

The mechanisms underlying dilatation of PVS and the actual function of PVS have yet to be adequately clarified. Etiologies related to the enlargement of PVS include aging, hypertension, stroke, cerebral small vessel diseases including lacunar stroke and white matter hyperintensities, systemic inflammation, and multiple sclerosis [13]. Recent studies have shown that PVS are involved in the drainage of interstitial fluid, soluble waste proteins, and metabolic products, including Aβ protein, from the brain in cooperation with brain arteries and glial cells facilitated by aquaporin 4 water channels [14,15]. These systems are collectively referred to as the glymphatic system [14,15]. Interestingly, a recent animal experimental study showed that spontaneously hypertensive rats, as a model of cerebral small vessel disease, presented with concomitantly enlarged PVS and decreased glymphatic transport [16]. Furthermore, a previous study demonstrated that MRI-visible PVS in the centrum semiovale were associated with clinically diagnosed Alzheimer’s disease and brain amyloid burden as evaluated using 11C-Pittsburgh Compound-B PET [17]. These findings suggest the possibility that enlarged PVS may represent a neuroimaging marker reflecting dysfunction of the glymphatic system. The widespread enlarged PVS in bilateral hemispheres in our case might lead to dysfunction of the glymphatic system and decreased clearance of interstitial fluid, resulting in hypoperfusion in the areas of enlarged PVS and subsequent cognitive impairment.
| Ref | Age | Gender | Distribution of enlarged PVS on MRI | Symptoms | SPECT/ FDG-PET |
|-----|-----|--------|-----------------------------------|----------|--------------|
| 6   | 63  | Woman | Bilateral posterior, parietal and frontal lobes (left dominance) | Memory deficits, Reduced spontaneity, marked slowing of thinking process, attentional deficit, memory loss, slight dysarthria, amnestic gait disturbance, etc | N.E. |
| 7   | 67  | Man   | Bilateral frontoparietal, left temporal, and left occipital lobes (left dominance) | Memory deficits, visuospatial dysfunction Parkinsonism with a left-side dominance, etc | N.E. |
| 8   | 77  | Woman | Right temporal, frontal, parietal, and occipital lobes | Memory deficits, left hemianopsia, left mild pyramidal sign, etc | (SPECT) Hypoperfusion in the area of enlarged PVS |
| 9   | 64  | Man   | Bilateral temporal, frontal, and parietal lobes (left dominance) | Memory deficits Parkinsonism | (SPECT) Hypoperfusion in the area of enlarged PVS |
| 10  | 64  | Woman | Right temporal, frontal, and parietal lobes | Memory deficits, impaired attention, fluent aphasia, agraphia, acalculia, etc | (FDG-PET) Hypometabolism in the area of enlarged PVS |
| Present case | 68  | Woman | Bilateral insula, frontal, and parietal lobes | Memory deficits, reduced verbal fluency, reduced working memory, dyscalculia, etc | (SPECT) Hypoperfusion in the area of enlarged PVS |

FDG-PET, 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography; MRI, magnetic resonance imaging; N.E., not examined; PVS, perivascular spaces; Ref, reference; SPECT, single photon emission computed tomography.

In conclusion, we have reported a very rare case of cognitive impairment with widespread, symmetrical enlargement of PVS in bilateral hemispheres. Clinicians should be aware of enlarged PVS as a potential cause of neurological deficits including cognitive impairment. Future studies need to target the mechanisms underlying enlargement of PVS and potential therapeutic targets for enlarged PVS based on preservation of normal glymphatic system function.

**Supplementary materials**

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.radcr.2021.06.043.

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