The Value of High-Resolution Vessel Wall Magnetic Resonance Imaging in the Diagnosis and Management of Primary Angiitis of the Central Nervous System in Children

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Purpose: High-resolution vessel wall-magnetic resonance imaging (VW-MRI) has been used to detect regional vessel wall pathology, significantly contributing to the diagnosis of primary angiitis of the central nervous system (PACNS) from other arteriopathies. In this study, we aimed to describe three cases of PACNS initially presenting as acute ischemic stroke, diagnosed and followed up with VW-MRI.

Methods: The medical records of three patients diagnosed with PACNS were retrospectively reviewed. We also reviewed the clinical application of VW-MRI in published articles for the pediatric cases since 2016.

Results: The initial presenting symptoms were headache, diplopia, confused mentality, hemiplegia, dysarthria, and dizziness. All patients had acute infarction on brain MRI, with suspicion of vasculopathy on magnetic resonance angiography. VW-MRI revealed narrowing of vessels with concentric wall thickening and diffuse enhancement in the anterior cerebral artery (n=1), middle cerebral artery (n=1), posterior cerebral artery (n=2), lenticulostriate artery (n=1), anterior inferior cerebellar artery (n=1), and vertebral artery (n=1), suggestive of vascular wall pathology. After excluding the possible etiologies of vasculitis, the clinical diagnosis of PACNS was established. Three patients received high-dose steroid and cyclophosphamide therapy. Two patients were treated with long-term azathioprine based upon the findings of persistent vessel enhancement on VW-MRI. All patients were regularly followed up with VW-MRI for more than 1 year. We summarized the clinical and radiological features of the published pediatric cases using VW-MRI to date.

Conclusion: High-resolution VW-MRI plays an important role in diagnosing childhood PACNS, as results correlate with disease activity.

Keywords: Vasculitis, central nervous system; Magnetic resonance imaging; Stroke; Child
Introduction

Primary angiitis of the central nervous system (PACNS) is characterized by inflammation and destruction of vessels, leading to ischemic changes in the vascular territory [1,2]. PACNS is a cause of childhood stroke and can potentially result in life-threatening neurologic deficits if it is not recognized or treated properly. Brain biopsy is a definitive test, and transfemoral cerebral angiography (TFCA) is the gold standard for the diagnosis of PACNS. However, those tests are invasive and not widely available, especially in pediatric patients. Laboratory tests with blood or cerebrospinal fluid (CSF) and standard brain magnetic resonance imaging (MRI) are neither sensitive nor specific, and magnetic resonance angiography (MRA) and computed tomography angiography (CTA) only suggest vascular stenosis or irregularity, but are not confirmative for distinguishing PACNS from other arteriopathies [3].

In recent research, gadolinium enhancement of the vessel wall on high-resolution intracranial vessel wall-magnetic resonance imaging (VW-MRI) has been used to classify the etiologies of ischemic stroke in adults [4-7]. Unlike conventional vascular imaging techniques, such as MRA, CTA, or cerebral angiography, which show the contour of the arterial lumen, VW-MRI directly provides information about the arterial wall, allowing the detection of regional vessel wall pathology. However, only a few cases have been reported in which VW-MRI was used in children [8-11].

The aim of this study is to show the value of VW-MRI in the differential diagnosis and management of PACNS in children. We describe three cases of clinically diagnosed PACNS that initially presented with acute ischemic stroke, in which the clinical diagnosis of PACNS was reached with the aid of VW-MRI.

Materials and Methods

This study included three patients who were clinically diagnosed with PACNS at Samsung Medical Center between December 2018 and May 2020. Data on age at diagnosis, sex, family history, clinical characteristics, neurological examinations, laboratory findings, image findings, medical therapy, and treatment response were collected retrospectively based on patients’ medical records. This study was approved by the Institutional Review Board of the Samsung Seoul Hospital (IRB No. 2020-05-049). Written informed consent by the patients was waived due to a retrospective nature of our study.

Intracranial vessel wall imaging was performed using high-resolution, 3-T MRI equipment (Achieva, Philips Medical System, Best, The Netherlands). The vessel wall imaging protocol included three-dimensional pre- and post-contrast fast T1-weighted images (T1WI) and proton density (PD) images with multiplanar reconstruction. T1WI was performed using a three-dimensional turbo spin echo (TSE) sequence with the following parameters: repetition time (TR)/echo time (TE) = 650 ms/18 ms; TSE factor 32; field of view = 180 × 180 × 35 mm; matrix size = 512 × 512; voxel size = 0.700 × 0.700 × 0.703 mm³; and spectral presaturation with inversion recovery fat suppression. The parameters used for the PD images were TR/TE = 2,000 ms/16 ms, TSE factor 8, field of view = 240 × 180 × 143 mm, voxel size 0.486 × 0.486 mm, reconstruction matrix size = 880, number of signal averages = 2, and slice thickness = 6.6 mm. Vessel walls were visualized using the black-blood technique with pre-regional 80-mm-thick saturation pulses to saturate the incoming arterial flow.

We also reviewed the clinical application of VW-MRI in published articles describing pediatric cases since 2016.

Results

The radiologic findings and clinical course of the three cases are shown in Fig. 1 and Supplementary Fig. 1, respectively [8-11].

1. Case 1
An 8-year-old boy experienced headaches and diplopia, with transient motor weakness 3 weeks prior. He had normal development and no medical history. He visited a local hospital, where brain MRI showed multifocal acute infarction in the left occipital lobe and bilateral cerebellum. His symptoms worsened within 1 day. Repeated brain MRI revealed an increase in the extent of the infarct, and brain MRA findings were suspicious for left posterior cerebral artery (PCA) occlusion. The initial impression was mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) because he had mildly elevated lactic acid levels (3.14 mmol/L) at the local hospital. He was started on clopidogrel and the mitochondrial cocktail: a combination of coenzyme Q1, L-carnitine, lipoic acid and multivitamins (retinol, tocopherol, ascorbic acid, thiamine, riboflavin, nicotinamide, pyridoxine, cyanocobalamin, dexamphenol, biotin, and cholecalciferol). He also received steroid pulse therapy (methylprednisolone; 15 mg/kg/day) because the possibility of vasculitis was not completely ruled out. MELAS genetic testing was negative.

The patient was referred to our hospital for further evaluation and management on the 3rd day of steroid pulse therapy. On admission, he complained of headache, dizziness, and diplopia. In addition, he was diagnosed with right homonymous hemianopsia and cerebellar dysfunction based on a neurological examination. The white blood cell count, hemoglobin, and platelet count were 19,750/μL, 13.7 g/dL, and 321,000/μL, respectively. His lactic
acid level was normal. Inflammatory markers, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), and the results of coagulopathy testing with autoimmune antibodies were unremarkable. Echocardiography, including a cardiac shunt test, was negative and showed no structural abnormalities. Thoracoabdominal CTA, abdominal ultrasonography, and lower extremity Doppler ultrasonography revealed no findings of thromboembolism. We could exclude paraneoplastic thromboembolism because whole-body positron emission tomography showed no evidence of malignancy. After methylprednisolone pulse therapy for 3 days followed by methylprednisolone at 1 mg/kg/day, the patient’s condition deteriorated, with symptoms including partial seizures, headache, right facial palsy, and decreased mentality shortly afterward. Oxcarbazepine and diphenylhydantoin were administered as antiseizure medications. Brain MRI and MRA demonstrated progression of the infarction with aggravated occlusion of the left PCA (Fig. 1Aa and Ba). TFCA was performed because of suspicion of vasculopathy. He showed multifocal segmental stenosis with oc-

Fig. 1. Comparison of brain images in patients with primary angiitis of the central nervous system. Case 1: Brain magnetic resonance imaging (MRI) (Aa) shows a multifocal infarction in the left occipital lobe and thalamus on fluid-attenuated inversion recovery (FLAIR). Magnetic resonance angiography (Ba) reveals left posterior cerebral artery (PCA) occlusion (arrow). High-resolution vessel wall-magnetic resonance imaging (VW-MRI) was performed, and post-contrast T1-weighted images (T1WI) obtained before treatment (Ca) show wall enhancement of the left PCA, which disappeared in follow-up post-contrast T1WI (Da) obtained after treatment. Case 2: T2-weighted image (Ab) demonstrates acute infarction in the left basal ganglia, insula, and frontotemporoparietal lobe. Magnetic resonance angiography (Bb) shows a decreased caliber of the left middle cerebral artery (MCA) (arrow) and anterior cerebral artery (ACA) (arrowhead). Post-contrast T1WI of VW-MRI (Cb) shows enhancement of the left proximal ACA (arrow). Follow-up post-contrast T1WI of VW-MRI (Db) shows disappearance of the vascular wall enhancement. Case 3: Initial brain MRI (Ac) shows an infarction in the right cerebellum on FLAIR. The right anterior inferior cerebellar artery is not seen on magnetic resonance angiography (Bc, arrow). There is focal enhancement at the basilar tip in post-contrast T1WI of VW-MRI (Cc). Follow-up post-contrast T1WI (Dc) shows disappearance of the enhancement.
clusion in the left PCA and superior cerebellar artery (SCA), which was more severe than the findings of previous MRA performed at another hospital. To identify the regional wall pathology, we used high-resolution intracranial VW-MRI, which revealed multiple vessel wall enhancements suggestive of vasculitis (Fig. 1Ca).

Under the clinical diagnosis of PACNS after excluding other causes of vasculitis, we maintained and slowly tapered the steroid dosages to oral prednisolone at 1 mg/kg/day and observed neurologic improvement in the patient. However, he had an additional newly developed infarction with acute headache and vomiting on day 30 and was treated with cyclophosphamide (750 mg/m² body surface area [BSA]) monthly for 4 months as induction therapy, followed by azathioprine (25 mg daily) maintenance therapy. After initiation of cyclophosphamide, he had no recurrent headache, and vessel wall enhancement became less evident at the 2-month follow-up VW-MRI. After 2 years, there was no vessel wall enhancement (Fig. 1Da) despite the remaining luminal narrowing at the left proximal anterior cerebral artery (ACA) and left PCA, and azathioprine was discontinued. He gradually showed clinical improvements in ataxia, dysmetria, and cognitive function sufficient to return to school, and showed only mild clumsiness at the most recent follow-up.

2. Case 2
An 11-year-old girl presented with a sudden onset of confused mentality, right hemiplegia, and dysarthria. She had no history of fever or systemic illness. Brain MRI indicated acute ischemic infarction in the left basal ganglia, but CTA showed normal findings, without any steno-occlusive lesions in the bilateral cerebral arteries. The laboratory test results, including the evaluation of infection, autoimmune diseases, metabolic diseases, and coagulopathy, were normal. Echocardiography was normal, with a negative saline shunt test. During heparinization, brain MRI revealed an interval increase in the extent of the acute infarction involving the left thalamus and cerebellum, and the right anterior inferior cerebellar artery (AICA) was poorly visualized on MRA (Fig. 1Ac and Bc). Laboratory tests of inflammatory markers, varicella-zoster infection, autoimmune antibodies, and coagulopathy were unremarkable. Echocardiography was normal with a negative saline shunt test. On day 2, VW-MRI was performed, which revealed wall enhancement and irregular margins of multiple cerebral arteries (Fig. 1Cc), and suspected thrombus in the right AICA. In addition, he had cough and sputum with a positive result of Mycoplasma pneumoniae antibody titer (1:2,560), and roxithromycin was administered orally. With the suspicion of vasculitis, he received high-dose steroid therapy (15 mg/kg/day for 5 days) and acetylsalicylic acid for thrombotic lesions. Nevertheless, he experienced acute motor weakness on the left side 3 weeks after the first treatment. Motor power decreased to 3/5 in the left arm and leg. He developed a new infarction in the right pons with multiple vessel wall enhancements. PACNS was suggested after clinical exclusion of other etiologies of vasculitis. In addition to the second course of high-dose steroid therapy, monthly cyclophosphamide (750 mg/m² BSA) was initiated. His motor power improved to normal without neurologic sequelae, and vessel wall enhancement resolved on the most recent VW-MRI (Fig. 1Dc). No recurrence was observed after tapering oral prednisolone.

The clinical and radiological features of the pediatric cases using VW-MRI published to date are summarized in Table 1.

3. Case 3
A 6-year-old boy presented with recurrent dizziness, vomiting, and ataxia for more than 1 month. He had no history of trauma. The neurological examination findings were normal upon admission. His brain MRI demonstrated multistage infarction, mainly involving the left thalamus and cerebellum, and the right anterior inferior cerebellar artery (AICA) was poorly visualized on MRA (Fig. 1Ac and Bc). Laboratory tests of inflammatory markers, varicella-zoster infection, autoimmune antibodies, and coagulopathy were unremarkable. Echocardiography was normal with a negative saline shunt test. On day 2, VW-MRI was performed, which revealed wall enhancement and irregular margins of multiple cerebral arteries (Fig. 1Cc), and suspected thrombus in the right AICA. In addition, he had cough and sputum with a positive result of Mycoplasma pneumoniae antibody titer (1:2,560), and roxithromycin was administered orally. With the suspicion of vasculitis, he received high-dose steroid therapy (15 mg/kg/day for 5 days) and acetylsalicylic acid for thrombotic lesions. Nevertheless, he experienced acute motor weakness on the left side 3 weeks after the first treatment. Motor power decreased to 3/5 in the left arm and leg. He developed a new infarction in the right pons with multiple vessel wall enhancements. PACNS was suggested after clinical exclusion of other etiologies of vasculitis. In addition to the second course of high-dose steroid therapy, monthly cyclophosphamide (750 mg/m² BSA) was initiated. His motor power improved to normal without neurologic sequelae, and vessel wall enhancement resolved on the most recent VW-MRI (Fig. 1Dc). No recurrence was observed after tapering oral prednisolone.

Discussion
This study describes the usefulness of VW-MRI in the clinical diagnosis and treatment of PACNS in three children. All patients...
<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Age</th>
<th>Presenting symptoms (n)</th>
<th>MRA findings (n)</th>
<th>Vessel wall enhancement on VW-MRI (n)</th>
<th>Clinical diagnosis (n)</th>
<th>CASCADE classification (n)</th>
<th>Treatment (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ohno et al. (2016) [8]</td>
<td>2</td>
<td>7 mo–5 yr</td>
<td>Fever (2) Malaise (2) Headache (1) Hemiparesis (2) Dysarthria (1)</td>
<td>Stenosis or occlusion (2)</td>
<td>Positive (2) Negative (0)</td>
<td>PACNS (2)</td>
<td>NA</td>
<td>Steroid (2) Immunosuppressants (1)</td>
</tr>
<tr>
<td>Stence et al. (2017) [9]</td>
<td>16</td>
<td>6 mo–19 yr</td>
<td>NA</td>
<td>Normal (1) Stenosis or occlusion (14) Vessel wall irregularity (6) Pseudoaneurysm (1)</td>
<td>Positive (13) Negative (3)</td>
<td>PACNS (4) Antiphospholipid Antibody syndrome (1) Idiopathic cause (2) Moyamoya (1) Dissection (1) VZV vasculitis, vasculopathy (2) Invasive mucormycosis (1) Cardioembolic (1) Radiation-induced vasculopathy (1) Takayasu's arteritis (1) ADA2 deficiency (1)</td>
<td>Unilateral FCA (10) Bilateral cerebral arteriopathy (2) Cardioembolic (1) Aortic/cervical arteriopathy (2) Other/idiopathic (1)</td>
<td>Steroid (4) Immunosuppressants (2)</td>
</tr>
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presented with acute ischemic stroke, suggesting vasculopathy. VW-MRI revealed evidence of vessel wall inflammation. This allowed a rapid etiologic evaluation and shortened the number of complicated steps. Although all three patients partially recovered with steroid pulse therapy, they eventually received cyclophosphamide for recurrent attacks or progression. We conducted follow-up with serial VW-MRI to monitor the treatment response, which was helpful in determining the timing and duration of immunosuppressive therapy.

Childhood PACNS is an inflammatory brain disease, which is defined by newly acquired focal and/or diffuse neurologic deficits and/or psychiatric symptoms in a child 18 years of age or younger, together with angiographic and/or histologic evidence of vasculitis in the absence of an underlying systemic condition known to cause or mimic these findings, as stated in the Calabrese criteria [1]. Children with PACNS present with a variety of symptoms such as headache, seizures, encephalopathy, behavioral or mood changes, and neurologic deficits such as hemiparesis and acute visual, speech, sensory, and balance deficits [12]. They may have fever, fatigue, or nausea as nonspecific symptoms of systemic illness. Laboratory investigations, including a complete blood count, CRP, ESR, von Willebrand factor antigen, CSF analysis, and autoimmune markers should be considered as part of the initial work-up, but none of these are confirmative or diagnostic. The patients described in this study presented with headaches, dizziness, seizures, altered mentality, or motor weakness, according to the territory of the infarction. The patients did not have any distinct abnormal laboratory findings. Although the first patient had mild leukocytosis, it was not diagnostic considering previous steroid therapy before the laboratory test and normal inflammatory markers. We noted mycoplasma infection in the third patient, but it was not clear whether this was a preceding factor of CNS inflammation. However, we made a conclusive clinical diagnosis of PACNS, rather than mycoplasma-induced vasculitis, because the patient’s condition became worse despite the steroid and antibiotic treatment.

MRI and cerebral angiography are important for establishing a diagnosis of PACNS. MRI, including T2/fluid-attenuated inversion recovery sequences and diffusion-weighted images, reveals ischemic parenchymal lesions according to vessel territories [13]. Conventional cerebral angiography shows characteristic findings suggestive of vessel inflammation. For instance, luminal narrowing, stenosis, beading, irregularity, aneurysms, presence of collaterals, vessel attenuation, or reduced flow can be observed [14,15]. In our first case, there were typical findings of vasculitis, such as severe stenosis at the left proximal PCA, occlusion of the left P1-P2 junction, and segmental stenosis along the left SCA. CNS vasculitis secondary to infection, such as varicella-zoster virus or mycoplas-
MRI is a non-invasive modality for assessing arterial wall pathology and complications and the possibility of false-negative results. In pediatric patients, considering the risk of procedure-related complications and the lack of typical angiographic findings, it is invasive and limited, especially as a definitive diagnostic method for PACNS when there is a lack of evidence of infection, such as viral antibodies or clinical symptoms, to differentiate secondary CNS vasculitis of infectious causes from PACNS [16-20].

Recently, high-resolution VW-MRI has been used for intracranial arterial wall imaging, mostly in adults [4-6]. Compared to conventional arterial imaging techniques such as CTA, MRA, or TFCA, which focus on the arterial lumen, VW-MRI visualizes the arterial wall, directly identifying pathologic changes. Because black-blood T1WI before and after intravenous gadolinium contrast can show the vessel wall directly, it is a useful adjunct to conventional imaging for differentiating the causes of intracranial arteriopathy [21]. It also plays an important role in clarifying the etiology of ischemic stroke or transient ischemic attack [22]. Lesions can be detected using VW-MRI through vessel wall structure, thickening, or enhancement. The patterns (concentric, eccentric, or focal and nodular) and distribution (solitary or multifocal) of vessel wall enhancement are also important features. The American Society of Neuroradiology provides consensus recommendations for the clinical application of intracranial VW-MRI in differentiating among causes of intracranial arterial narrowing, such as intracranial atherosclerotic plaque, vasculitis, reversible cerebral vasoconstriction syndrome, and arterial dissection [6]. Although there is a lack of information about the sensitivity and specificity of VW-MRI in each disease, VW-MRI combined with MRA improves diagnostic accuracy compared to MRA alone in the evaluation of suspected vasculopathies [23,24]. Two studies reported reclassifications of stroke etiology using VW-MRI in cases originally classified as “undetermined” based on the luminal imaging findings alone [22,25].

High-resolution VW-MRI is useful in the diagnosis of PACNS, the main pathology of which is inflammation of the arterial wall, by demonstrating vessel wall thickening and contrast enhancement [9,10]. Cerebral angiography is the radiological gold standard for identifying vascular changes [14]. However, fully demonstrating the lesion requires additional orthogonal views, a specialized team, and general anesthesia in young children. From this point of view, VW-MRI has the advantages of sensitivity and noninvasiveness. By showing vessel wall involvement, VW-MRI makes it possible to distinguish the etiology of arteriopathies. Although brain biopsy is the definitive diagnostic method for PACNS when there is a lack of typical angiographic findings, it is invasive and limited, especially in pediatric patients, considering the risk of procedure-related complications and the possibility of false-negative results. VW-MRI is a non-invasive modality for assessing arterial wall pathology and enables the early diagnosis of PACNS. Gadolinium vessel wall enhancement might be correlated with disease activity, reflecting vessel inflammation. To evaluate the progression of disease activity or the effectiveness of treatment, it is necessary to repeat vessel wall imaging during therapy. VW-MRI could be an appropriate modality to evaluate the clinical course, rather than invasive angiography.

The resolution of vessel wall enhancement with the improvement of clinical symptoms could be an indicator that immunosuppressive treatment should be ceased. The use of VW-MRI to diagnose adult PACNS has increased [5,26]; however, it is not commonly used for childhood PACNS, a much rarer condition [8-11].

We reviewed the literature on pediatric cases using VW-MRI to date, as summarized in Table 1. Fifty-three patients were included from four studies between 2016 and 2020. Ohno et al. [8] reported two cases of PACNS diagnosed with VW-MRI. Stence et al. [9] suggested that VW-MRI is beneficial in children with stroke because strong vessel wall enhancement at stroke onset was associated with arteriopathy progression in follow-up imaging. Dlamini et al. [10] reinforced the utility of VW-MRI in pediatric stroke, and also described pre- and post-contrast VW-MRI findings with the patterns of vessel wall enhancement, although specific etiologic associations with patterns were not clearly identified. Perez et al. [11] investigated nine patients with the inflammatory subtype of focal cerebral arteriopathy and reported that measures of vessel wall enhancement in VW-MRI were not correlated with the severity or progression of arteriopathy. Since the number of cases was too small and the information regarding description and classification was highly heterogeneous across these four studies, the ability to conduct a statistical analysis was limited. Therefore, further studies of VW-MRI in pediatric patients are necessary.

We report three cases of childhood PACNS diagnosed based on the findings of vessel wall inflammation using high-resolution VW-MRI after excluding other possible causes of cerebral angiitis. The first patient in our series showed recurrent acute infarction without a definite diagnosis, despite a thorough work-up. VW-MRI revealed narrowing of vessels with concentric wall thickening and diffuse enhancement. These findings played a critical role in the diagnosis of PACNS and in predicting the progression of inflammation. In the second and third cases, VW-MRI gave a direct clue for reaching the diagnosis of PACNS without TFCA. The finding of vessel wall enhancement on VW-MRI furnished important evidence of vasculitis, differentiating the possible etiologies of vasculopathy. The early diagnosis of PACNS prompted the introduction of immunosuppressive treatment. The treatment plan for the third patient was uncertain because of chronic symptoms and nonspecific laboratory findings when he was transferred to our hospital. VW-MRI supported the diagnosis of PACNS with the initiation of...
immunosuppressants, and the patient fully recovered without any neurologic deficits. Because VW-MRI showed vessel wall enhancement, which indicates active inflammation, we also followed up patients with serial VW-MRI to monitor the disease course and to determine the duration of treatment. Better neurologic outcomes seem to be attributed to an earlier diagnosis with VW-MRI. Although our study was a retrospective study with a small sample size at a single center, which limits the generalizability of the results, the practical use of VW-MRI in the diagnosis and management of childhood PACNS is meaningful. A systematic approach towards establishing the exact sensitivity and specificity of VW-MRI in diagnosing childhood PACNS remains a topic for further research.

In summary, high-resolution VW-MRI is a promising and useful modality for the early diagnosis and follow-up of childhood PACNS, as it directly visualizes vessel wall inflammation. We recommend VW-MRI for patients suspected of PACNS when the differential diagnosis of arteriopathies is difficult with cerebral angiography, or when the angiography procedure is restricted. VW-MRI could play an important role in identifying the pathophysiology of childhood arteriopathies and could aid in an early diagnosis.

**Supplementary materials**

Supplementary materials related to this article can be found online at https://doi.org/10.26815/acn.2021.00437.

**Conflicts of interest**

No potential conflict of interest relevant to this article was reported.

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**References**


