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High-resolution MRI vessel wall imaging in varicella zoster virus vasculopathy

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Abstract

Contrast-enhanced vessel wall imaging high-resolution MRI (HRMR) has revealed vessel wall thickening and enhancement in multiple intracranial vasculopathies, including varicella zoster virus (VZV) vasculopathy. We retrospectively reviewed a database of patients with virologically-verified VZV vasculopathy, who underwent initial and follow-up HRMR between April 2011 and May 2014. Six patients were identified. Baseline demographic and clinical characteristics were collected, including stroke risk factors, history of VZV-related disorders, neurological presentation, course and antiviral treatment. Initial HRMR in patients with VZV vasculopathy demonstrated various patterns of stenosis, vessel wall thickening and enhancement, predominantly in terminal internal carotid artery segments and the M1 segment of the middle cerebral arteries. Follow-up HRMR showed improvement of stenosis, with reduced vessel wall thickening and enhancement at multiple times after treatment. HRMR has the potential to assist in diagnosis and treatment of VZV vasculopathy.

Keywords

Angiography; MRI; High-resolution; Varicella zoster virus; Vasculopathy; Treatment

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Conflict of interest statement

All authors report no conflicts of interest.

1. Introduction

Varicella zoster virus (VZV) vasculopathy produces transient ischemic attacks and stroke [1]. In the largest series of VZV vasculopathy, neurovascular imaging (conventional angiography or magnetic resonance angiography) demonstrated intracranial vessel involvement in up to 70% of the cases [2]. Angiography frequently reveals stenosis in the distal internal carotid or middle cerebral arteries, and pathologic and virological analysis reveals inflammation and viral antigen mostly in the arterial adventitia and media [3]. VZV vasculopathy is typically treated with intravenous acyclovir sometimes followed by oral antivirals, although optimal treatment and duration remains to be determined. While treatment reduces further stroke [4], the course of resolution of vessel inflammation and stenosis is unknown. Recent studies using contrast-enhanced vessel wall imaging high-resolution MRI (HRMR) showed that vessel wall thickening and enhancement correlate with vessel wall inflammation in central nervous system vasculitis [5], including VZV vasculopathy [6,7], however, data on follow up imaging after treatment has not been previously published. Knowledge of the extent and evolution of vessel wall enhancement, which likely reflects inflammation, may help to guide treatment. Here, we report the first study of HRMR carried out at multiple time intervals, including initial and follow-up exams in 6 patients with VZV vasculopathy.

2. Materials and methods

Using a retrospective imaging database of patients who underwent HRMR between April 2011 and May 2014, we identified patients who had a diagnosis of VZV intracranial vasculopathy. The patients were included only if they had initial and subsequent follow up HRMR as part of the evaluation. Baseline stroke risk factors, history of VZV-related disorders, neurological presentation, course and antiviral treatment. The diagnosis of VZV vasculopathy was verified by the presence of anti-VZV IgG antibody in CSF, with reduced serum/CSF ratios of anti-VZV IgG antibody indicative of intrathecal synthesis of anti-VZV IgG antibody [8], in patients with intracranial vessel involvement shown by vascular imaging.

Imaging was performed on 3T whole-body scanners (Skyra; Siemens, Erlangen, Germany). The first sequence was a standard multislab 3D TOF-MRA sequence centered in the circle of Willis for lumenographic identification of any stenosis. High-resolution imaging ensued using four T1-weighted spin-echo sequences in the coronal, axial and sagittal planes. The first scan was without contrast, and the following 3 were with contrast (Gadobutrol, Gadovist; Bayer Schering Pharma, Berlin, Germany): (1) a non-contrast T1 coronal 2-mm section with no gap (TR/TE = 11/544 ms), matrix = 256 × 256, and FOV=130×130 mm; (2) a post-gadolinium T1 coronal 2-mm section with no gap and fat suppression and a saturation band (TR/TE = 11/544 ms), matrix = 256×256, and FOV = 130× 130 mm; (3) a post-gadolinium T1 axial 2-mm section with no gap and fat suppression and a saturation band (TR/TE=11/750 ms), matrix=256×256, and FOV= 130×130 mm; and (4) a post-gadolinium sagittal 2-mm section with a 0.4-mm gap and no fat suppression and a saturation band (TR/TE=10/600 ms), matrix= 256×256, and FOV=130× 130 mm.

Intracranial vascular imaging data on the initial and subsequent HRMR and MRA were reviewed by two experienced neuroradiologists (F.K.H., S.J.), who were blinded to clinical outcomes, treatment modalities and duration. Clinical outcome was classified as stable if there were no recurrence of strokes or new neurologic symptoms after treatment, or as worsening if stroke recurred or symptoms progressed despite therapy. Imaging outcome on HRMR was classified as stable, improved or worsened, based on changes in vascular stenoses and pattern of enhancement.

3. Results

Clinical characteristics, imaging and treatment are summarized in Table 1. Six patients with a diagnosis of VZV vasculopathy underwent initial and follow up HRMR between April 2011 and May 2014. Clinical presentation, treatment and its duration, as well as interval timing of imaging was very heterogeneous. Four patients presented with recurrent ischemic events, one with a single stroke event, and one with progressive cognitive decline. Of the patients with recurrent ischemic events, 3 of them also had non-specific symptoms that were not initially attributed to the ischemic events, including headache, dizziness, fatigue and memory changes. Three patients had hypertension, 2 had hyperlipidemia, 1 had diabetes mellitus, and 3 were smokers. One patient had herpes zoster ophthalmicus 2 months before ischemic presentation, and 3 had varicella during childhood. One patient had a liver transplant and was taking tacrolimus 5 months before cerebrovascular symptoms. No other patients were immunosuppressed at baseline. After the onset of symptoms, the diagnosis of VZV vasculopathy was delayed by 1 month to 2 years, and was subsequently made based on CSF studies in association with intracranial vascular involvement. Five patients had a cerebral angiogram, one demonstrating a focal stenosis with post-stenotic dilatation, and the other four with diffuse irregularities and stenoses. All patients had brain ischemic changes on presentation, 2 with acute hemispheric infarcts, 3 with acute hemispheric and subcortical infarcts and bilateral subcortical white matter changes, and 1 with bilateral diffuse subcortical white matter changes.

All patients underwent HRMR on initial visit with a timing that varied from 1 month to 2 years from the onset of initial symptoms. Five of 6 patients (patients 1, 2, 4–6) had vascular stenoses and vessel wall enhancement on HRMR. In patient 3, motion-degradation precluded adequate assessment of thickening and enhancement, although stenosis was evident in the A1–A2 junction of the ACA bilaterally. Two patients had 1 follow-up HRMR, 3 patients had 2 follow-up HRMRs and 1 patient had 4 follow-up HRMRs.

All patients were treated with intravenous acyclovir followed by oral valacyclovir, with variable durations at the discretion of the treating neurologist and infectious disease specialist. Steroids were also given to some patients at the discretion of the treating physicians, as shown in Table 1. In patient 1, who was treated with intravenous acyclovir for 8 weeks followed by oral valacyclovir for 12 months, and in patient 2, who was treated with intravenous acyclovir for 3.5 weeks followed by oral valacyclovir for 3 months, follow-up HRMR showed complete resolution of both stenoses and enhancement at 21 months (Fig. 1) and 3 months (Fig. 2), respectively. Patient 3, who was treated for 5 weeks with intravenous acyclovir followed by oral valacyclovir for 4 months, had a motion-degraded HRMR, but

MRA revealed ACA stenosis at presentation, which improved 6 months later. Patient 4, who was treated with intravenous acyclovir for 6 weeks, had improvement of enhancement with stable stenosis at 4 months (Fig. 3). None of these 4 patients had stroke recurrences. Patient 5, who was treated with intravenous acyclovir for 4 weeks followed by oral valacyclovir for 4 weeks, had resolution of enhancement without change in stenosis at 4 months (Fig. 4); however, the cognitive decline evident at presentation gradually progressed. Patient 6 had persistent enhancement with progression of stenoses at 5 months (Fig. 5); despite antiviral treatment, cerebral ischemia recurred and he died 8 months after onset of disease.

4. Discussion

We present 6 cases of VZV vasculopathy, all of whom were treated with antiviral agents and had follow-up HRMR. Disease was not confirmed virologically until weeks to months after recurrent ischemia or progressive neurologic symptoms. Lack of antiviral therapy before etiologic diagnosis likely led to progressive intracranial vasculopathy. In this series, all patients underwent additional modalities of vascular imaging, including MRA and/or cerebral angiography, which demonstrated focal and diffuse areas of stenosis. Contrast uptake in the vessel wall at the site of stenosis observed on initial HRMR likely reflected continued virus infection and vessel wall inflammation [5,9]. In our patients, a predominant pattern of vessel wall enhancement was observed involving the terminal ICAs, proximal M1 segment of the MCAs, and occasionally the proximal A1 segment of the ACA and P1 segment of the PCA, with a pattern of proximal and large intracranial vessel involvement. Although VZV vasculopathy can affect large and small intracranial vessels [2], small distal vessels are not well imaged with HRMR. This is certainly a limitation for this imaging technique since it does not provide accurate information on distal intracranial vessels that may be infected with VZV.

The degree of vessel involvement as monitored by HRMR differed among the patients, and evolution of disease varied even during therapy, with resolution of both vessel wall enhancement and stenosis as early as 3 months and as late as 21 months after initial imaging. Resolution of vessel wall enhancement without change in the underlying stenosis, as well as persistent stenosis and enhancement with clinical worsening, were also observed. Such variability might result from different duration of antiviral therapy, or might reflect different stages of arterial involvement by virus, especially since diagnosis was made at intervals ranging from 1 month to 2 years after the onset of symptoms and the timing of initial and follow-up imaging from onset of symptoms was not uniform. Only one patient was on immunosuppressive therapy (tacrolimus) at baseline, and steroids were used in only 3 patients during the treatment. It is possible that the variability in imaging and clinical response may have been influenced by the individual immune response of each patient, however, this cannot be determined in this small group of patients; thus, correlation between clinico-radiologic evolution and immunosuppressive treatment cannot be evaluated in this small cohort.

Optimal antiviral treatment of VZV vasculopathy remains unknown. While administration of intravenous acyclovir for a minimum of 14 days and, in some patients, oral valacyclovir for up to 2 months has been recommended [10]. Treatment duration decisions are based on

the disappearance of clinical symptoms, which does not necessarily indicate eradication of virus infection in the affected arteries. Imaging follow up may suggest ongoing vessel wall involvement despite symptom resolution. Thus, HRMR is a powerful tool to help guide duration of therapy and may also be helpful in the presence of persistent vessel wall enhancement indicating continued inflammation.

This study has several limitations. It has the inherent limitations of a retrospective observational study, with a very small sample size. There was significant variability in the clinical presentation, the interval from disease onset to diagnosis, timing of initial and follow up imaging, as well as variable treatment modalities and duration. HRMR is a technique that is time consuming, not widely available, and that requires cooperative patients; additionally, it provides information centered in the proximal circle of Willis with poor visualization of small distal vessels. While our patients had VZV vasculopathy, they were not exempt from atherosclerotic risk factors, which can also lead to intracranial vessel involvement and it has been reported that contrast enhancement can be seen with atherosclerosis disease [5]. A relationship between VZV and atherosclerotic risk factors has not been established, and an interaction between these conditions cannot be ruled out. The results of our study are hypothesis generating and should be interpreted cautiously. A larger prospective controlled trial is required to confirm our findings, and further investigate the evolution of VZV vasculopathy and response to therapy.

5. Conclusions

In 4 of 6 patients treated with antiviral agents for VZV vasculopathy, clinical stability or improvement correlated with improvement in arterial stenosis, vessel wall enhancement or both. High-resolution contrast-enhanced vessel wall MR imaging can assist in diagnosis and guide management of VZV vasculopathy.

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Abbreviations

HRMR	high-resolution MRI
VZV	varicella zoster virus

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HIGHLIGHTS

- High resolution MRI in VZV vasculopathy showed stenosis, thickening and enhancement
- Follow-up HRMR showed improvement at multiple times after treatment
- HRMR has the potential to assist in diagnosis and treatment of VZV vasculopathy

Fig. 1.

Contrast-enhanced high-resolution MRI (HRMR) over time in Patient 1. Axial HRMR at presentation demonstrates stenosis and vessel wall enhancement of the terminal segment of the right ICA and proximal right MCA (*a*), minimal improvement of stenosis and enhancement 3 months later (*b*), with resolution of stenosis and vessel wall enhancement at 21 months (*c*).

Fig. 2. Contrast-enhanced high-resolution MRI (HRMR) over time in Patient 2. At presentation, coronal (*a*) and axial (*b*) HRMR reveal vessel wall thickening and enhancement of both terminal ICA segments; 3 months later, coronal (*c*) and axial (*d*) HRMR demonstrate resolution of thickening and enhancement.

Fig. 3.

Contrast-enhanced high-resolution MRI (HRMR) over time in Patient 4. At presentation, coronal (*a*), axial (*b*) and oblique magnified views (*c*) demonstrate stenosis, with post-stenotic dilatation of the M1 segment of the left MCA and vessel wall enhancement of the terminal segment of the left ICA and proximal left MCA; 4 months later, coronal (*d*), axial (*e*) and oblique magnified views (*f*) reveal stable stenosis with moderate improvement of the vessel wall enhancement.

Fig. 4.

Contrast-enhanced high-resolution MRI (HRMR) over time in Patient 5. At presentation, coronal views demonstrate vessel wall enhancement of the terminal segment of both ICAs and in the lentiform nucleus and head of the caudate nucleus (*a*), while axial views show enhancement of the M1 segment of the left MCA (*b*); 4 months later, coronal views reveal resolution of enhancement of the terminal segment of both ICAs with reduced enhancement of the lentiform nucleus and head of the caudate nucleus (*c*), and axial views demonstrate resolution of enhancement of the M1 segment of the left MCA (*d*).

Fig. 5. Contrast-enhanced high-resolution MRI (HRMR) over time in Patient 6. At presentation, coronal (*a*) and axial (*b*) views demonstrate stenosis, thickening and vessel wall enhancement of the terminal segments of both ICAs; 5 months later, coronal (*c*) and axial (*d*) views reveal persistent stenosis, thickening and vessel wall enhancement.

Clinical, demographic and imaging characteristics of patients with varicella zoster virus vasculopathy

Table 1

Patient	Presentation	Initial Brain MRI	Initial HRMR	Antiviral Therapy & Clinical Course	HRMR Imaging Outcome After Treatment
1	41 year old female with recurrent episodic focal weakness, sensory deficit, dysarthria and quadrantanopia	Right parietooccipital and right subcortical borderzone infarcts	Stenosis, vessel wall thickening and contrast enhancement: Right terminal ICA and M1 segment of the right MCA (Fig 1a). Vessel wall thickening and contrast enhancement: P1 segment of the right PCA.	Acyclovir: 8 weeks; Oral Valacyclovir: 12 months. Steroids: Methylprednisolone 1 g intravenously daily for 3 days Course: Stable – no stroke recurrence	3-month follow-up: minimal improvement of stenosis and enhancement (Fig 1b); 12-month follow-up: moderate improvement of enhancement and stenosis; 21-month follow-up: resolution of stenoses and enhancement (Fig 1c)
2	53 year old female with recurrent ischemic events: episodic focal weakness, sensory deficit and dysarthria	Right parietooccipital, right subcortical borderzone and left internal capsule infarcts; bilateral subcortical white matter changes	Stenosis: Right M1. Vessel wall thickening and contrast enhancement: bilateral terminal ICAs and bilateral M1 segments of the MCA (Fig 2a, –b).	Acyclovir: 3.5 weeks; Oral Valacyclovir: 3 months Steroids: Prednisone started at 60mg orally daily and tapered over 45 days Course: Stable – no stroke recurrence	3-month follow-up: resolution of stenoses and enhancement (Fig 2c, –d)
3	56 year old man with liver transplant 5 months prior (on tacrolimus), with recurrent ischemic events & rapid cognitive decline	Left posterior parietal and left subcortical infarct borderzone; bilateral subcortical white matter changes	Motion-degraded study; Stenosis: A1–A2 junction of bilateral ACAs No vessel wall thickening or contrast enhancement.	Acyclovir: 5 weeks; Oral Valacyclovir: 4 months Steroids: None Course: Stable – no stroke recurrence	6-month follow-up: motion-degraded study; improved ACA flow; no vessel wall thickening or enhancement
4	45 year old man with single stroke event: focal weakness and dysarthria	Left hemispheric subcortical borderzone infarct	Stenosis, vessel wall thickening and contrast enhancement: M1 segment of the left MCA with post-stenotic dilatation. Vessel wall thickening and contrast enhancement: left terminal ICA, and A1 segment of the left ACA (Fig 3a, –b, –c)	Acyclovir: 6 weeks; Oral Valacyclovir: none Steroids: None Course: Stable – no stroke recurrence	4-month follow-up: stable stenosis with moderate improvement of the enhancement (Fig 3d, –e, –f)
5	66 year old woman with progressive cognitive decline, gait disturbance, urinary incontinence	Bilateral subcortical white matter changes	Stenosis, vessel wall thickening and contrast enhancement: M1 segment of the left MCA and bilateral PCAs. Vessel wall thickening and contrast enhancement: bilateral terminal ICAs and M1 segments of bilateral MCAs (Fig 4a, –b).	Acyclovir: 4 weeks; Oral Valacyclovir: 1 month Steroids: None Course: Gradual progression of cognitive decline	4-month follow-up: stable stenosis with resolution of enhancement (Fig 4c, –d)
6	44 year old man with recurrent ischemic events: focal weakness, dysarthria, with subsequent cognitive decline	Bilateral subcortical infarcts, and bilateral subcortical white matter changes	Stenosis, vessel wall thickening and contrast enhancement: bilateral terminal ICAs and bilateral M1 segments of the MCA (Fig 5a, –b) with beading. Stenosis: basilar artery and bilateral PCAs.	Acyclovir: 5 weeks Ganciclovir: 6.5 weeks Oral Valacyclovir: 3 months Steroids: Methylprednisolone 1 gram intravenously daily for 3 days, followed by Prednisone 60 mg orally daily and tapered over 1 month Course: Multiple recurrent ischemic strokes; expired 8 months after presentation	5-month follow-up: persistent stenoses and enhancement (Fig 5c, –d)

Abbreviations: ICA: internal carotid artery; ACA: anterior cerebral artery; MCA: middle cerebral artery; PCA: posterior cerebral artery; HRMR: high resolution magnetic resonance imaging.