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Moyamoya disease manifesting with bilateral involvement of the proximal vertebral arteries: A case report

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Abstract:

Moyamoya disease (MMD) is a cerebrovascular disorder characterized by progressive occlusion of intracranial arteries, often leading to stroke and intracerebral hemorrhage. While MMD classically affects the intracranial vasculature, we present an unusual case of bilateral vertebral steno-occlusion, resulting in vertebrobasilar insufficiency in a 37-year-old man with MMD and treated with angioplasty and stenting of the dominant vertebral artery. Review of the literature demonstrates proximal vertebral artery involvement to be a rare manifestation of moyamoya disease. This report contributes to the understanding of the clinical spectrum of MMD and emphasizes the need for vigilance and awareness of the possibility of extracranial vascular complications in affected individuals.

Keywords:

Extracranial, ischemic stroke, moyamoya disease, stenting, vertebral artery occlusion, vertebrobasilar insufficiency

Introduction

Moyamoya disease (MMD) is recognized as a major cause of stroke in both children and adults.[1] The incidence observed in East Asian countries such as South Korea is estimated at 2.3 per 100,000 individuals. In other parts of the world, such as North America, the incidence of MMD is much lower, reported at 0.09 per 100,000 individuals.[2] MMD may manifest with stroke, hemorrhage, transient ischemic attack, headache, or seizures.[3] Although the hallmark of MMD is the progressive steno-occlusion of the intracranial vasculature, there are reports of extracranial involvement of MMD, particularly in association with cardiac manifestations or with genetic syndromes such as Alagille syndrome.[4,5] Extracranial vertebral occlusive disease, however, is uncommon, and there is limited knowledge about its clinical management.

In this paper, we illustrate an extraordinary case of a patient diagnosed with MMD manifesting with vertebrobasilar insufficiency secondary to bilateral vertebral ostial stenosis and occlusion. Although extracranial MMD has been previously reported to involve the renal and coronary arteries, as well as the intracranial portion of the vertebral arteries, bilateral extracranial vertebral artery involvement is not well described. Here we report a case of bilateral proximal vertebral artery disease, treated with endovascular angioplasty and stenting.[6,7]

Case Report

A 37-year-old man, nonsmoker with the past medical history of hypertension and a family history of MMD, presented to the emergency department with a 2-week history of intermittent episodes of dizziness,

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nausea, and vomiting. The symptoms were constant and worsened with activity, making the patient unable to walk. At admission, the patient was awake and alert, with a Glasgow Coma Scale of 15, but in the neurologic examination, the patient displayed vertical and horizontal nystagmus along with resting tremor, which prompted a code stroke activation. Computed tomography angiography (CTA) demonstrated nonopacification of the left middle cerebral artery (MCA) and diminutive and decreased caliber of the right MCA [Figure 1]. CTA of the neck showed no abnormalities in the soft-tissue, skeletal, or other structures, except occlusion at the origin of the right vertebral artery. Further workup with magnetic resonance imaging (MRI) did not demonstrate any acute infarct on diffusion-weighted imaging, mass lesion, or hemorrhage. The patient was discharged home and given aspirin 81 mg and meclizine.

One week later, he returned to the emergency department due to persistent and worsening dizziness, nausea, and vomiting. The examination revealed left gaze-beating nystagmus and upgaze torsional nystagmus. Given the history and pattern of vascular occlusion observed in the initial CTA, digital subtraction angiography was performed. Angiographic runs demonstrated bilateral occlusion of the M1 and M2 segments of the middle cerebral arteries, with partial reconstitution through small, irregular collateral vessels, and a diminished right A1 segment. There was extensive collateralization of the bilateral MCA territories through leptomeningeal vessels, including from the skull base by various lenticulostriate branches, and the inferior division territory of the left MCA through the posterior circulation [Figures 2 and 3].

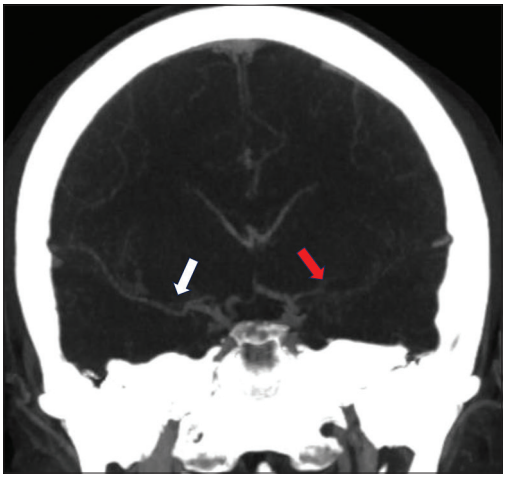

Figure 1: Computerized angiographic images at initial presentation. Although the parenchyma did not display signs of acute ischemic injury, there was evidence of nonopacification of the left middle cerebral artery (MCA) with the distal reconstitution (red arrow). Furthermore, there were small irregularities and diminutive M1 and M2 segments of the right MCA (white arrow), with distal reconstitution from leptomeningeal anastomoses.

Angiography of the right subclavian artery demonstrated occlusion of the origin of the right vertebral artery. The distal cervical and intracranial portions of the right vertebral artery were reconstituted through the distal branches of the right deep cervical artery, ascending cervical artery, and neuromeningeal trunk of the right ascending pharyngeal artery. There was retrograde opacification of the middle cervical segment of the vessel, with antegrade flow into the V3 and the V4 segments as well as posterior inferior cerebellar artery, suggestive of proximal occlusion [Figures 4 and 5]. Furthermore, the left vertebral artery was dominant without significant flow limitation but had approximately 70% (1.8/5.8 mm) stenosis at its origin [Figure 6a]. The case was presented in the multidisciplinary neurovascular conference and consensus was to proceed with angioplasty and stenting of the origin of the left vertebral artery, which was performed without any complications [Figure 6b]. On clinical follow-up 2 weeks postprocedure, the patient was functionally independent (mRS = 0) with significant improvement in his dizziness.

Discussion

In the illustrated case, the patient presented with the typical radiographic manifestation of MMD in the intracranial vasculature, which includes bilateral proximal MCA occlusions (M1 and M2 segments), narrowing of the right A1 segment, as well as extensive collateralization of the bilateral MCA territories. However, the uniqueness of the case lies in the bilateral vertebral ostial involvement causing vertebrobasilar insufficiency, prompting endovascular intervention. No other alternative explanations or risk factors for the extracranial disease, such as trauma, substance use, cervical spine instability, or congenital malformation,

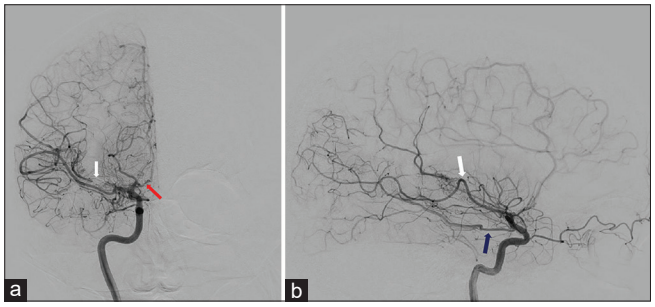

Figure 2: Anteroposterior (a) and lateral (b) right internal carotid angiographic runs at presentation. The caliber of the right internal carotid artery was normal, with adequate filling along the cervical, petrous, cavernous, and supraclinoid segment. The ophthalmic artery was also well visualized, and there was a prominent right posterior communicating artery (blue arrow). The right A1 segment was narrowed (red arrow), and there was evidence of minimal filling of the superior division of the M2 segment (white arrows). The right middle cerebral artery territory received the majority of its supply through numerous leptomeningeal collaterals from the distal right anterior cerebral artery. Moreover, there was prominent collection of fine, irregular collateral vessels with a net-like appearance in the vicinity of the M1 and M2 segments consistent with moyamoya disease.

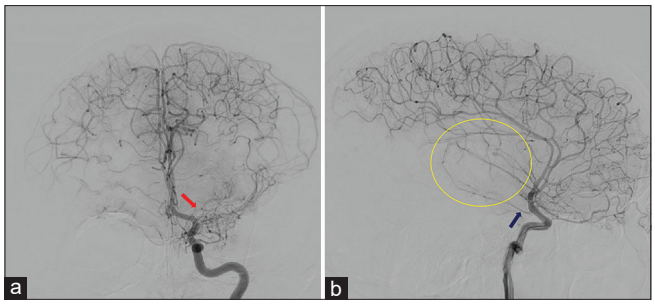

Figure 3: Anteroposterior (a) and lateral (b) left internal carotid angiograms at presentation. The caliber of the internal carotid artery was normal without filling defects along the cervical, petrous, cavernous, and supraclinoid segment. The ophthalmic artery was also well visualized, but the caliber of the posterior communicating artery was much smaller than the right side (blue arrow). There was a lack of filling of the left M1 segment (red arrows), creating an area of oligemia in the distal middle cerebral artery territory (yellow circle). The left middle cerebral artery territory receives a significant supply from leptomeningeal collaterals from the distal anterior cerebral artery. There is also evidence of the development of collateral circulation of the skull base as seen by the numerous lenticulostriate branches.

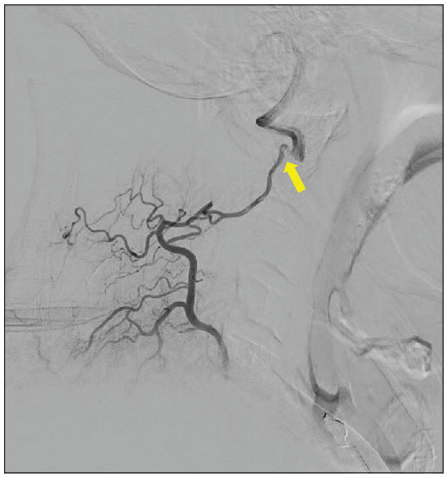

Figure 5: Digital subtraction angiography of the right subclavian artery. The deep cervical artery is prominent and was seen arising from the costocervical trunk. This trunk has a prominent anastomosis with the V3 segment of the right vertebral artery (yellow arrow) at the level of C1 with partial distal opacification of the right V4 segment and right posterior inferior cerebellar artery.

were found in the extensive review of the patient's person and family history. Considering all of these aspects, along with the strong family history of MMD, the most likely explanation for the patient's presentation was extracranial involvement of MMD.

Understanding the pathogenesis of MMD is of utmost importance for formulating hypotheses regarding differential arteriopathy based on vessel location, as well as for elucidating the factors contributing to extracranial steno-occlusion in certain patients. MMD is now defined as a multifactorial disorder, in which genetic factors play a key role in its occurrence and progression.[8-10] Abnormalities in embryonic cerebrovascular development, antithyroid autoantibodies, and along with other inflammatory

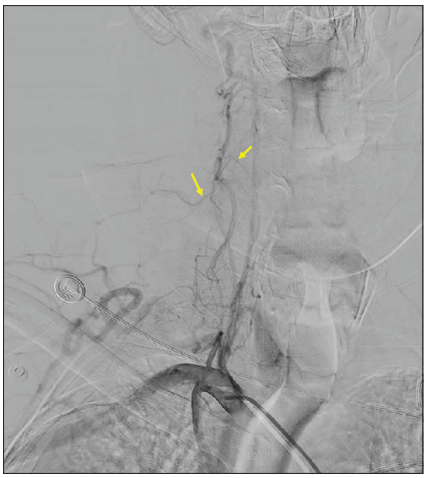

Figure 4: Right vertebral artery occlusion. The right subclavian artery was patent without evidence of dissection. The origins of the thyrocervical and costocervical trunks were patent. The right vertebral artery was evidenced to be occluded at its origin. However, there was evidence of collateral flow received through the right inferior thyroid artery and ascending cervical artery (yellow arrows), which reconstituted the artery distally.

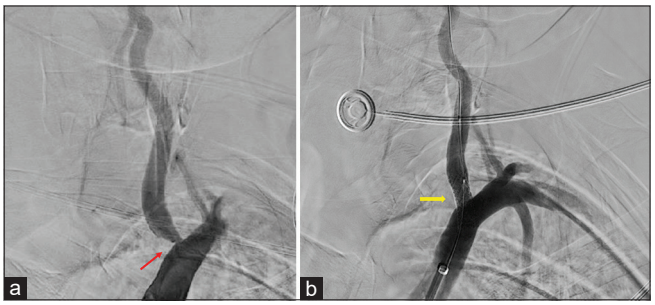

Figure 6: Left vertebral artery proximal stenosis at the initial digital subtraction angiography (a) and after stenting (b). The right subclavian artery is patent without evidence of dissection. On a, there was evidence of an 70% stenosis at the origin of the left vertebral artery when it bifurcates from the left subclavian artery (red arrow). On (b) successful stenting of the stenosis at the origin of the left vertebral artery when it bifurcates from the left subclavian artery (yellow arrow).

and infectious conditions have all been implicated in the pathogenesis of MMD.[11] RNF213 is arguably the gene that has undergone the most extensive evaluation in the pathogenesis of MMD. The significance of Arg4810Lys RNF213 variants has been further validated through the occurrence of subsequent ischemic events in meta-analyses and large-scale Japanese cohorts.[9,12] Other authors have illustrated the role of inflammatory cascades influencing aberrant angiogenesis and vessel remodeling.[13] More recently, analysis of gene expression in the MCA has revealed overexpression of NMUR1, a gene involved in regulating vasomotor tone. The overexpression of NMUR1 was 2.98-fold higher in patients with MMD compared to healthy controls and 7.22-fold higher compared to the superficial temporal artery (STA).[10]

Thus, one hypothesis explaining the preferential compromise of the intracranial vasculature is the elevated

vasomotor tone of the internal carotid artery (ICA) and its terminal branches, leading to progressive arterial stenosis.[14] This hypothesis should also be examined in the posterior circulation as it could explain the extracranial involvement of MMD, more commonly a unilateral phenomenon that has been increasingly reported in recent literature. The bilateral vertebral ostial stenosis and occlusion in our case could have resulted from high vasomotor tone. Bilateral vertebral ostial stenosis attributed to high vasomotor tone has been reported in animal studies; however, to our knowledge, it has not been previously demonstrated in humans.[15]

Another plausible explanation that has set the basis for hypotheses on the patterns of steno-occlusion is histopathologic analysis. Conventionally, MMD arteriopathy involves thickening of the intima, fragmentation of the internal elastic lamina, and the attenuation of the media.[1] Histopathologic analysis of MCA specimens of MMD patients has demonstrated a higher intimal thickness in the MCA compared to healthy controls.[16] However, the comparisons between the MCA and the STA have revealed differences in intimal thickness, fibrin deposition, and elastic lamina composition.[17] Inflammation appears to play a role in the divergent compromise of intracranial and extracranial vasculature. Both macrophages and T-cells appear to be key protagonists in the cascade that leads to intimal hyperplasia.[18]

Higher flow and differences in hemodynamics have also been hypothesized to play a role in the preferential compromise of intracranial vessels in MMD. Kim *et al*. conducted a case–control study comparing MMD patients to normal controls, performing simulations through computational fluid dynamics using reconstructed geometries from magnetic resonance angiographies.[19] Their study revealed notable morphological and hemodynamic distinctions in the intracranial extradural ICA among MMD patients. However, whether these hemodynamic alterations contribute to or result from ICA bifurcation stenosis requires further evaluation. Similarly, Sun *et al*. utilized phase-contrast MRI to quantify flow in the extracranial vessels, revealing higher flow rates in the vertebral arteries compared to healthy counterparts, as a result of the less flow rates in the anterior circulation.[20] Hence, it is hypothesis that the higher flow at the vertebral artery origin, and the turbulence arising as a site of bifurcation, could trigger changes in vasomotor tone, which in turn may lead to increased inflammation, ultimately leading to vessel remodeling and stenosis.

In MMD patients, the vertebral arteries and the anastomosis of the extracranial carotid arteries play a significant role in compensating for the reduced blood supply of the middle cerebral arteries.[21] However, in the illustrated case, the vertebral arteries were significantly affected, reducing collateral supply and resulting in hypoperfusion of the posterior circulation. Thus, vertebral ostial stenting was performed to improve perfusion of the vertebrobasilar system, with good clinical and angiographic results. Stenting of the left vertebral artery was deemed the most suitable treatment for this patient. The right vertebral artery presented extensive steno-occlusion, precluding endovascular intervention. In contrast, focal stenosis on the left side was amenable to angioplasty and stenting. Other treatments available for patients with MMD, including revascularization surgery were considered in this scenario but not feasible due to the proximal extracranial location. This decision was based on the following factors: our patient did not have evidence of occlusion of the ICA, and there was robust intracranial collateral supply in both cerebral hemispheres which was clinically and angiographically evident. Angioplasty and stenting of the left vertebral artery re-established adequate flow within the vertebrobasilar circulation, in addition to providing improved collateral supply into both cerebral hemispheres. However, additional revascularization procedures might be considered in the future if occlusion of the intracranial arteries progresses.

A few publications have reported the involvement of extracranial vessels in MMD. Many of these studies focused on stenosis of the renal artery in association with MMD.[22,23] Other publications have explored the relationship with Alagille syndrome and coronary artery stenosis.[6,7] Vertebral artery steno-occlusion secondary to MMD has been rarely reported in the literature, with only a handful of cases available. Miyamoto *et al*. were the first one who reported bilateral occlusion of the vertebral arteries at the craniovertebral junction (V3).[24] However, other authors have reported occlusion in the V2 segment (C4 to C2), V3 segment (C2 to dura), and V4 segment (intradural) of the vertebral artery in patients with MMD, which were partially intracranial segments.[6,7,25] Conversely, the bilateral vertebral artery disease in this case involved the V1 segment (preforaminal), more precisely, at its origin from the subclavian artery. This case presents the rare instance of the extracranial manifestation of MMD, specifically that with involvement of the vertebral arteries in patients presenting with symptoms of vertebrobasilar insufficiency. We highlight this case to help elucidate possible atypical manifestations of this complex disease and to provide valuable comprehension into the therapeutic considerations for similar cases. This unique presentation serves to remind clinicians that common diseases may have uncommon presentations.

Conclusion

While extracranial involvement in MMD has been reported in association with renal artery stenosis and other syndromes, the occlusion and stenosis of the vertebral artery origin, as observed in this case, is a rare occurrence. This highlights the necessity of considering such atypical presentations and expanding our understanding of MMD's pathophysiology through continued research.

Author contributions

OA: Writing (original draft preparation); FRV, JF, MY: Writing (review & editing); CSO: Supervision, writing (review & editing); JHG: Conceptualization, supervision, writing (original draft preparation).

Ethical policy and institutional review board statement

Not applicable.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated and/or analyzed during the current study.

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Conflicts of interest

There are no conflicts of interest.

References

1. Kuroda S, Houkin K. Moyamoya disease: Current concepts and future perspectives. Lancet Neurol 2008;7:1056-66.
2. Zhang H, Zheng L, Feng L. Epidemiology, diagnosis and treatment of moyamoya disease. Exp Ther Med 2019;17:1977-84.
3. Pettersson SD, Olofsson HK, Ali S, Szarek D, Miękisiak G, Ogilvy CS. Risk factors for ischemic stroke after revascularization surgery in patients with moyamoya disease: An age-stratified comparative meta-analysis. World Neurosurg 2023;173:146-57.e14.
4. Assaf SN, Assaf AN, Assaf MN, Taylor J, Adam JM, Harrell J, *et al.* Extracranial microvascular complications of moyamoya disease leading to left ventricular systolic dysfunction. J Med Cases 2023;14:88-94.
5. Delaney S, O'Connor G, Reardon W, Murphy SJ, Tierney S, Ryan BM, *et al.* Extracranial and intracranial vasculopathy with "moyamoya phenomenon" in association with Alagille syndrome. Front Neurol 2018;9:1194.
6. Deng X, Zhang D, Zhang Y, Wang R, Wang B, Zhao J. Moyamoya disease with occlusion of bilateral vertebral arteries and the basilar artery fed by the collateral vessels of vertebral arteries: A rare case report. J Clin Neurosci 2017;42:116-8.
7. Kinoshita Y, Kohshi K, Yokota A. Moyamoya disease of adult onset brain stem haemorrhage associated with bilateral occlusion of the vertebral arteries – Case report. Acta Neurochir (Wien) 1998;140:181-4.
8. Ihara M, Yamamoto Y, Hattori Y, Liu W, Kobayashi H, Ishiyama H, *et al.* Moyamoya disease: Diagnosis and interventions. Lancet Neurol 2022;21:747-58.
9. Ishigami D, Miyawaki S, Imai H, Shimizu M, Hongo H, Dofuku S, *et al.* RNF213 p.Arg4810Lys heterozygosity in moyamoya disease indicates early onset and bilateral cerebrovascular events. Transl Stroke Res 2022;13:410-9.
10. Pettersson SD, Koga S, Ali S, Enriquez-Marulanda A, Taussky P, Ogilvy CS. Cerebral artery overexpression of the NMUR1 gene is associated with moyamoya disease: A weighted gene co-expression network analysis. Cerebrovasc Dis 2024. [doi: 10.1159/000538035].
11. Kim SJ, Heo KG, Shin HY, Bang OY, Kim GM, Chung CS, *et al.* Association of thyroid autoantibodies with moyamoya-type cerebrovascular disease: A prospective study. Stroke 2010;41:173-6.
12. Torazawa S, Miyawaki S, Imai H, Hongo H, Ishigami D, Shimizu M, *et al.* RNF213 p.Arg4810Lys wild type is associated with *de novo* hemorrhage in asymptomatic hemispheres with moyamoya disease. Transl Stroke Res 2023. [doi: 10.1007/s12975-023-01159-z].
13. Dorschel KB, Wanebo JE. Physiological and pathophysiological mechanisms of the molecular and cellular biology of angiogenesis and inflammation in moyamoya angiopathy and related vascular diseases. Front Neurol 2023;14:661611.
14. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. Arterioscler Thromb Vasc Biol 2005;25:932-43.
15. Cates MJ, Steed PW, Abdala AP, Langton PD, Paton JF. Elevated vertebrobasilar artery resistance in neonatal spontaneously hypertensive rats. J Appl Physiol (1985) 2011;111:149-56.
16. Takagi Y, Hermanto Y, Takahashi JC, Funaki T, Kikuchi T, Mineharu Y, *et al.* Histopathological characteristics of distal middle cerebral artery in adult and pediatric patients with moyamoya disease. Neurol Med Chir (Tokyo) 2016;56:345-9.
17. Sun SJ, Zhang JJ, Li ZW, Xiong ZW, Wu XL, Wang S, *et al.* Histopathological features of middle cerebral artery and superficial temporal artery from patients with moyamoya disease and enlightenments on clinical treatment. J Huazhong Univ Sci Technolog Med Sci 2016;36:871-5.
18. Masuda J, Ogata J, Yutani C. Smooth muscle cell proliferation and localization of macrophages and T cells in the occlusive intracranial major arteries in moyamoya disease. Stroke 1993;24:1960-7.
19. Kim T, Bang JS, Kwon OK, Hwang G, Kim JE, Kang HS, *et al.* Morphology and related hemodynamics of the internal carotid arteries of moyamoya patients. Acta Neurochir (Wien) 2015;157:755-61.
20. Sun W, Ruan Z, Dai X, Li S, Li S, Zhang J, *et al.* Quantifying hemodynamic changes in moyamoya disease based on two-dimensional cine phase-contrast magnetic resonance imaging and computational fluid dynamics. World Neurosurg 2018;120:e1301-9.
21. Tateoka T, Yoshioka H, Wakai T, Hashimoto K, Ogiwara M, Kinouchi H. Analysis of vascular perfusion territory using selective intraarterial injection CT angiography before and after revascularization surgery in patients with moyamoya disease.

J Neurosurg 2023;139:1294-301.
22. Baek JW, Jo KI, Park JJ, Jeon P, Kim KH. Prevalence and clinical implications of renal artery stenosis in pediatric moyamoya disease. Eur J Paediatr Neurol 2016;20:20-4.
23. Liu E, Zhao H, Liu C, Tan X, Luo C, Yang S. Research progress of moyamoya disease combined with renovascular hypertension. Front Surg 2022;9:969090.
24. Miyamoto S, Kikuchi H, Karasawa J, Nagata I, Ikota T. Moyamoya disease associated with bilateral occlusion of the vertebral artery. Surg Neurol 1984;22:21-8.
25. Abramyan A, Fu AY, Patel K, Sun H, Roychowdhury S, Gupta G. Neurovascular considerations in patients with down syndrome and moyamoya syndrome. Childs Nerv Syst 2024;40:1617-21.