An Unusual Case of Stroke as the Initial Manifestation of Early Takayasu Arteritis with Normal Erythrocyte Sedimentation Rate (ESR): Diagnosis and Treatment

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Patient: Female, 37-year-old
Final Diagnosis: Ischaemic stroke secondary to Takayasu arteritis
Symptoms: Altered mental status • limbs claudication
Medication: —
Clinical Procedure: —
Specialty: Neurology

Objective: Rare coexistence of disease or pathology

Background: Takayasu arteritis is a rare systemic inflammatory vasculitis of granulomatous nature. The etiology of Takayasu arteritis is still unknown and it affects the aorta and its main branches. Takayasu arteritis is more common in Asians and women of childbearing age. However, ischemic stroke as the initial manifestation of Takayasu arteritis is uncommon. We report a young, stroke patient in early Takayasu Arteritis with normal ESR who improved with immunosuppressants.

Case Report: A previously healthy young patient was admitted to hospital due to lethargy, limbs claudication, and altered mental status. The patient was also febrile, hypertensive, and her physical examination revealed carotid artery tenderness and a loud carotid bruit suggestive of carotid stenosis or an active inflammatory process. Her erythrocyte sedimentation rate was normal. Magnetic resonance imaging of the brain showed acute ischemic stroke and a computed tomography angiogram showed typical angiographic features, so the diagnosis of Takayasu arteritis with acute ischemic stroke was made. The patient’s condition improved with corticosteroid therapy without residual neurological deficits.

Conclusions: In conclusion, stroke may rarely be the first symptom of Takayasu arteritis, and the ESR value may be normal even in early, active disease. A normal ESR value should not lead to false reassurance. A thorough clinical examination and angiographic features remain the criterion standard for the diagnosis of Takayasu arteritis. The mainstay of treatment for Takayasu arteritis consists of glucocorticoids and immunosuppressants. Further studies are needed to demonstrate the therapeutic benefit of antithrombotic and vascular intervention in this clinical entity.

Keywords: Giant Cell Arteritis • Ischemic Stroke • Takayasu Arteritis • Vasculitis • Vasculitis, Central Nervous System

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Background

The stroke incidence rate in Singapore has increased from 192 to 257.6 per 100,000 population from 2007 to 2019. Of all stroke cases in 2019, only 7.8% of patients were under 50 years of age [1]. Takayasu arteritis is rare, mainly affects women, and usually occurs in the 2nd or 3rd decade. The incidence of Takayasu arteritis varies from 2.6 per million in Western countries to 40 per million in Asia [2]. It can affect multiple blood vessels, such as the renal artery, aorta, common carotid artery, brachiocephalic trunk, and subclavian arteries [3]. The incidence of stroke in this clinical entity is approximately 10% to 20% [4-6], but stroke as the initial manifestation of Takayasu arteritis in young patients is rare [4,7-10]. In young patients without significant cardiovascular risk factors, other systemic and vascular diseases, including Takayasu arteritis, must be considered.

Case Report

A 37-year-old woman with no significant past medical history presented to the Emergency Department with acute loss of consciousness for 5 min and altered mental status. After going to the market in the morning of admission and returning home, she had a witnessed collapse to the ground and an ambulance was called.

She reported having generalized lethargy and limbs discomfort. She had also been intermittently confused for 3 days before admission. Otherwise, she reported no other systemic symptoms. She was not taking any long-term medication. The patient also denied use of hormonal therapy, oral contraceptives, steroids, and traditional Chinese medicine. There was no known family history of autoimmune, cardiac, or cerebrovascular diseases.

On examination, the patient appeared to be lethargic and required multiple prompting for history-taking and physical examination. Although she was hypertensive at presentation and had a blood pressure of 150/80 mmHg, there was no differential blood pressure on both arms. The pulses were strong and equal, there was no radio-radial or radio-femoral delay. She also had a low-grade fever with a temperature of 37.8°C and a loud bruit in the left carotid artery on the second day of admission. Otherwise, she was hemodynamically stable and there were no peripheral stigmata of infective endocarditis. Her neurological examination revealed mild dysarthria and mild weakness of the right upper and lower limbs with a Medical Research Council grade of 4. There was no aphasia, visual field defects, or visual and sensory neglect. There were also no sensory deficits or ataxia. Her initial National Institutes of Health Stroke Scale (NIHSS) score was 6.

To investigate the altered mental status, contrast-enhanced magnetic resonance imaging of the brain was performed, which showed acute infarcts over the left caudate head nucleus, left lentiform nucleus, and left insular ribbon (orange arrows).
A computed tomography angiogram (CTA) was then performed to further assess the intracranial and extracranial blood vessels. CTA showed obstruction of the intracranial and extracranial left ICA with a filling defect after bifurcation, suggestive of thrombus (Figure 2). There was also a circumferential soft tissue cuff involving the innominate artery, bilateral CCA, and proximal left ICA (Figure 3). On CTA, filling defects were also noted over the M1 segment of the left middle cerebral artery (MCA) and the superior M2 branch, suggestive of a thrombus (Figure 4).

Further investigations were performed to determine the etiology of the stroke. Results of serum thrombophilia testing, including protein-C and protein-S levels, anti-thrombin III, fasting homocysteine level, and factor V Leiden gene test, were normal. In addition, given the angiographic findings, screening for systemic autoimmune disease was performed to rule out other large vessel vasculitis. Her double-stranded DNA antibodies, lupus anticoagulant, and beta-2glycoprotein antibodies were negative.

In view of her fever, the possibility of septic embolism was considered. However, microbiological analyses such as blood and urine cultures, urinalysis, acid-fast bacilli in sputum, and tuberculosis polymerase chain reaction were negative. The HIV and syphilis tests were negative. Erythrocyte sedimentation rate (ESR) and C-reactive protein were normal. Transthoracic echocardiogram and 72-h Holter monitoring performed to rule out cardioembolic causes of stroke were normal. There were no arrhythmias, atrial fibrillation, vegetations, masses, or intracardiac thrombus.

Based on the Ishikawa’s modified diagnostic criteria, our patient met the obligatory criterion of age less than 40 years at onset and fulfilled 4 of the 9 minor criteria, namely neck pain suggestive of carotid artery tenderness, hypertension on admission, and CTA findings showing involvement of the common carotid artery and brachiocephalic trunk. In addition, she also met the American College of Rheumatologists (ACR) diagnostic criteria based on age of onset of 40 years or younger, claudication of the extremities, and angiographic features. Therefore, based on the clinical and angiographic findings, the diagnosis of Takayasu arteritis was made.

The patient was then referred to the rheumatologist and treatment for Takayasu arteritis was initiated. Intravenous hydrocortisone 100 mg every 8 h for 3 days followed by switch to oral prednisolone 1 mg/kg per day for 6 months. Warfarin was also administered as there was a thrombus in the left ICA, which put her at high risk of recurrent ischemic episodes. Her mental and neurological status improved 3 days after starting steroid treatment. CT aortogram of the rest of the vessels was not performed due to cost. Subsequently, the patient was transferred back to her home country for further follow-up and treatment. A telephone consultation and review 1 year after the patient’s discharge revealed that she was stable and had no residual neurological deficits with oral steroids and immunosuppressant.

**Discussion**

According to the Ishikawa modified diagnostic criteria, the presence of 2 major criteria or 1 major and 2 or more minor criteria or at least 4 of the 9 minor criteria has a sensitivity of 84% and a specificity of 95% for the diagnosis of Takayasu arteritis [11]. In addition, the ACR diagnostic criteria

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**Figure 3.** Axial plane of CT angiogram illustrating circumferential soft tissue cuffs of right common carotid artery (CCA) (green arrows) and right innominate artery (blue arrows).

**Figure 4.** Axial plane CT angiogram showing occlusion of the left MCA-M1 occlusion (blue arrow) and the superior branch of MCA-M2 division. (yellow arrow).
for Takayasu arteritis yield a specificity of 97.8% and a sensitivity of 90.5% when 3 or more criteria are present [12]. Our patient met both the modified Ishikawa and ACR diagnostic criteria for Takayasu arteritis.

Although her ESR and CRP levels were normal, she was treated as having active disease in view of the systemic features, including fever and carotid bruit, suggestive of vascular stenotic lesions or inflammation with typical angiographic features [13]. It is also worth noting that although ESR is the most commonly used clinical monitoring tool, reliance on ESR to assess active Takayasu arteritis can lead to delayed treatment, as it has a sensitivity of only 72% and a specificity of 56% [14]. The manifestations of Takayasu arteritis can range from asymptomatic disease to severe neurological deficits. In the early stages of the disease, patients can present with non-specific symptoms such as weight loss, night sweats, or low-grade fever, which may be followed by carotid or neck pain. In the later stages of Takayasu arteritis, symptoms suggestive of end-organ ischemia can occur, such as stroke, seizures, and limb claudication [15]. A recent population-based study by Sung Soo Ahn et al found that most strokes occurred within the first 6 months after the diagnosis of Takayasu arteritis [16], which supports the observation that ischemic stroke as the initial presentation of Takayasu arteritis is uncommon, especially in young patients. Compared with previous studies and observations in which patients had an elevated ESR [7-10], our case illustrates the rare presence of a normal ESR in a patient with active Takayasu arteritis and thus the importance of early recognition of this clinical entity through careful history-taking and physical examination.

The benefit of glucocorticoids and immunosuppressants in patients with Takayasu arteritis is supported by the report by Russo et al suggesting the development of vascular occlusion due to inflammation-related vascular damage, leading to a high risk of cerebral ischemic events [17]. However, to date, robust clinical trials providing a conclusive consensus for the treatment of Takayasu arteritis are lacking. Recent systemic reviews of available therapies are small studies, so they may not be accurately represent the optimal treatment plans for this clinical entity, although glucocorticoid and immunosuppressive therapies have been shown to provide good clinical benefit and are the mainstay of therapy according to cases reported in the past [15] Sung Soo Ahn et al found no statistically significant benefit of immunosuppressant use in reducing the risk of stroke in patients with Takayasu arteritis, but the study was limited by the small number of patients, and further research is needed to determine the benefit of immunosuppressants in preventing stroke in patients with Takayasu arteritis [16].

Regarding the use of antithrombotics in Takayasu arteritis with stroke, de Graeff et al suggested that antiplatelet agents are helpful in patients with ischemia [18]. In addition, a retrospective study by de Souza et al showed a possible protective effect of antiplatelet agents in reducing ischemic events [19]. However, given the retrospective nature and small sample size of the study, it is difficult to draw firm conclusions about the benefit of antithrombotic therapy in Takayasu arteritis. Sung Soo Ahn et al showed that there was no statistically significant association between the use of antiplatelet and the incidence of stroke [16]. These results echoed the EULAR guidelines, which do not recommend the routine use of antiplatelet agents in patients with Takayasu arteritis [15]. In our patient, the decision to use anticoagulation was based on the potential risk of recurrent ischemic stroke in view of the ICA thrombus. However, routine use of anticoagulation has not been recommended by previous studies. A study by de Souza et al showed no reduction in ischemic risk with anticoagulation. This is consistent with the observation of Saadoun et al, who did not recommend routine use of anticoagulation [20]. A meta-analysis by Jeong et al suggests a possible benefit of anticoagulation in preventing severe ischemic events in patients with large vessel vasculitis, but this result should be interpreted with caution due to the small sample size and the fact that only 1 patient with Takayasu arteritis was included in the study [21]. It is also worth noting that although our patient improved and did not have a recurrence of an ischemic event after anticoagulation, corticosteroid therapy was also started at the same time. Therefore, it is difficult to prove a clear therapeutic relationship between anticoagulation and the reduction of the risk of an ischemic event. Therefore, larger prospective studies will be needed in the future to determine the protective effect of anticoagulation in patients with Takayasu arteritis.

A recent case reported by Dai et al suggests a possible benefit of endovascular and bridging therapy (mechanical thrombectomy and angioplasty) in patients with acute ischemic stroke due to Takayasu arteritis [9]. In the patient reported by Dai et al, there were clear indications for endovascular therapy, such as severe neurological deficits with dense hemiplegia, aphasia, and an NIHSS score of 16. Furthermore, mechanical thrombectomy and angioplasty were performed early, within 6 h of symptom onset. In addition, a study by Mason et al, which looked at the main indication for surgical intervention in patients with Takayasu arteritis, recommended that vascular intervention be considered if patients had clinical features such as uncontrolled hypertension due to renal artery stenosis, coarctation of aorta, aortic regurgitation, ischemic heart disease, mesenteric ischemia, and severe claudication of the extremities [22]. However, our patient had mild symptoms, with an NIHSS score of 6 without cardiovascular disease and was admitted to the hospital 3 days after the onset of symptoms. Therefore, she may not have been a suitable candidate for bridging therapy or surgery. There are previous publications reporting arterial injury associated with inflammation.
and cellular proliferation after endovascular therapy, leading to restenosis and complications [23,24]; therefore, careful consideration of procedural risks and benefits must be made before bridging therapy.

Conclusions

In conclusion, acute stroke as the initial diagnosis of Takayasu arteritis has rarely been reported. The ESR level may be normal even in early and active Takayasu arteritis, and its normality should not lead to false reassurance. Therefore, in young stroke patients who are otherwise healthy and have no significant cardiovascular risk factors, a wide range of differential diagnoses must be considered, including inflammatory vasculitis such as Takayasu arteritis, which is rare but may respond well to corticosteroid therapy and immunosuppressants. Further studies are needed to demonstrate the therapeutic benefit of antiplatelet agents or anticoagulants and vascular intervention in this clinical entity.

Declaration of Figures’ Authenticity

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