

Ischemic stroke in a young adult male as a manifestation of Takayasu's arteritis

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ABSTRACT

Takayasu arteritis is a chronic, inflammatory large vessel arteriopathy that primarily affects the aorta, its main branches, and the pulmonary arteries. Fibrosis and thickening of the arterial wall often occur in later stages, resulting in a cerebrovascular accident. A 20-year old man presented with ischemic stroke of young adults due to Takayasu's arteritis, from which he had been suffering since childhood (age 10). Physical examination showed an abdominal aortic aneurysm, renal artery stenosis, leading to renovascular hypertension, and asymmetrical blood pressure. Aneurysm of abdominal aorta was diagnosed by panaorto-arteriography. Subsequently ischemic stroke of young adults developed, because the arteritis had led to stenosis of the left anterior and middle cerebral arteries, with renovascular hypertension as additional risk factor. On this patient a percutaneous transluminal angioplasty operation of the right renal artery was performed, and it is intended to do an extra-intracranial arterial bypass. Preventive treatment is necessary to stem the extension of the arteritis to other blood vessels.

Keywords: Ischemic stroke, young adults, Takayasu's arteritis, renovascular hypertension

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INTRODUCTION

In Indonesia, stroke is the number three killer after heart disease and cancer. Moreover, according to a survey in the year 2004, stroke is number one killer in governmental hospitals throughout Indonesia. Formerly stroke only affected the elderly, but at present there is a tendency for stroke to endanger people at productive age or even under the age of 45 years. According to the Indonesian Stroke Foundation

(Yayasan Stroke Indonesia, Yastroki), the number of stroke patients in Indonesia has tended to increase in the last decades. The disease tends to affect the younger members of the productive generation. This has the effect of lowering the level of productivity and can lead to disruption of the social-economic situation of the family.⁽¹⁾

The causes of ischemic stroke of young adults in Spain are non-atherosclerotic disorders of the blood vessels, atherosclerosis of the large vessels, cardiac embolism, and hematological

disorders.⁽²⁾ Risk factors for ischemic stroke of young adults in India are metabolic syndromes and smoking.⁽³⁾ In contrast, the most common risk factors causing ischemic stroke of young adults in Taiwan are hyperlipidemia, smoking, hypertension and a family history of stroke. Intracranial stenosis of the carotid and vertebrobasilar systems is more common than extracranial stenosis, while premature atherosclerosis is the most frequent cause of intracranial stenosis.⁽⁴⁾ Stroke in young adults may be a manifestation of narrowing of large and medium-sized arteries, in particular the aorta and its branches. One of the causes of this narrowing is Takayasu's arteritis.⁽⁵⁾

In this case report a discussion is presented of stroke of young adults caused by Takayasu's arteritis, a very uncommon disease.

CASE REPORT

A 20-year old male was admitted to a Hospital, at Karawaci, Tangerang, with the chief complaint of weakness in the right arm and leg since the day before admission. Headache, nausea, vomiting, convulsions or lowering of consciousness were absent. The patient had a past history of renovascular hypertension since 10 years ago. At 10 years of age (December 1997), he underwent preparation of the renal artery and abdominal aorta, fibromuscular excision and prosthetic graft placement on the diagnosis of hypertension and stenosis of the abdominal aorta and right renal artery. The pathologic examination revealed fibrosis of the muscularis of the blood vessels. Five years later, at the age of 15 (December 2002), the patient had a laparotomic resection of the abdominal aortic aneurysm. Abdominal ultrasound at that time detected a suspected aneurysm of the proximal abdominal aorta, while renal and aortic arteriography indicated the presence of a fusiform aneurysm of the distal abdominal aorta, and

severe bilateral renal artery stenosis. Pathology results were consistent with above findings.

On examination the patient was found to be conscious, blood pressure in the right arm was 170/100 mmHg, in the left arm 150/100 mmHg, in the right leg 160/100 mmHg, and in the left leg 150/100 mmHg. The pulse rate was 80 per minute, the breathing rate 20 per minute, and the patient was afebrile. There was no bruit at the location of the carotid artery. Pulsation of the right and left dorsalis pedis arteries was +/+. Chest: heart and lungs were within normal limits. Abdomen: liver and spleen not palpably enlarged, normal intestinal sounds. On neurological examination hemiparesis of the right arm was found, arm muscle strength 3, leg strength 4. Physiological reflexes were +/+, pathological reflexes -/-. There was left hemihypesthesia.

Laboratory results: hemoglobin was 16.8 g per deciliter, white-blood-cell count 8,000 per cubic millimeter, with 0 percents eosinophils, 0 percent basophils, 0 percents stab or band neutrophils, 63 percent segmented neutrophils, 33 percent lymphocytes, and 4 percent monocytes, red-blood-cell count was 5,800 cubic per millimeter, hematocrit was 47 percent, platelet count was 208,000, erythrocyte sedimentation rate was 17 mm per hour. The ureum level was 17 mg per deciliter, the creatinine level was 1.0 mg per deciliter, the uric acid level was 4.8 mg per deciliter, and the blood sugar level was 95 mg per deciliter, SGOT level was 30, SGPT level 27, and total cholesterol level was 210 mg per deciliter. The sodium level was 133 nmol per liter, the potassium level was 4.1 nmol per liter, and the chloride level was 100 nmol per liter. The clotting time, bleeding time, prothrombin time and activated partial thromboplastin time (APTT) were normal. The D-dimer was 0.2 (< 0.3), fibrinogen level was 394 (200-400), and anti DsDNA IgG (EIA) level was 0.28. Cranial computerized tomography (CT) scan on admission was within normal limits (Figure 1).

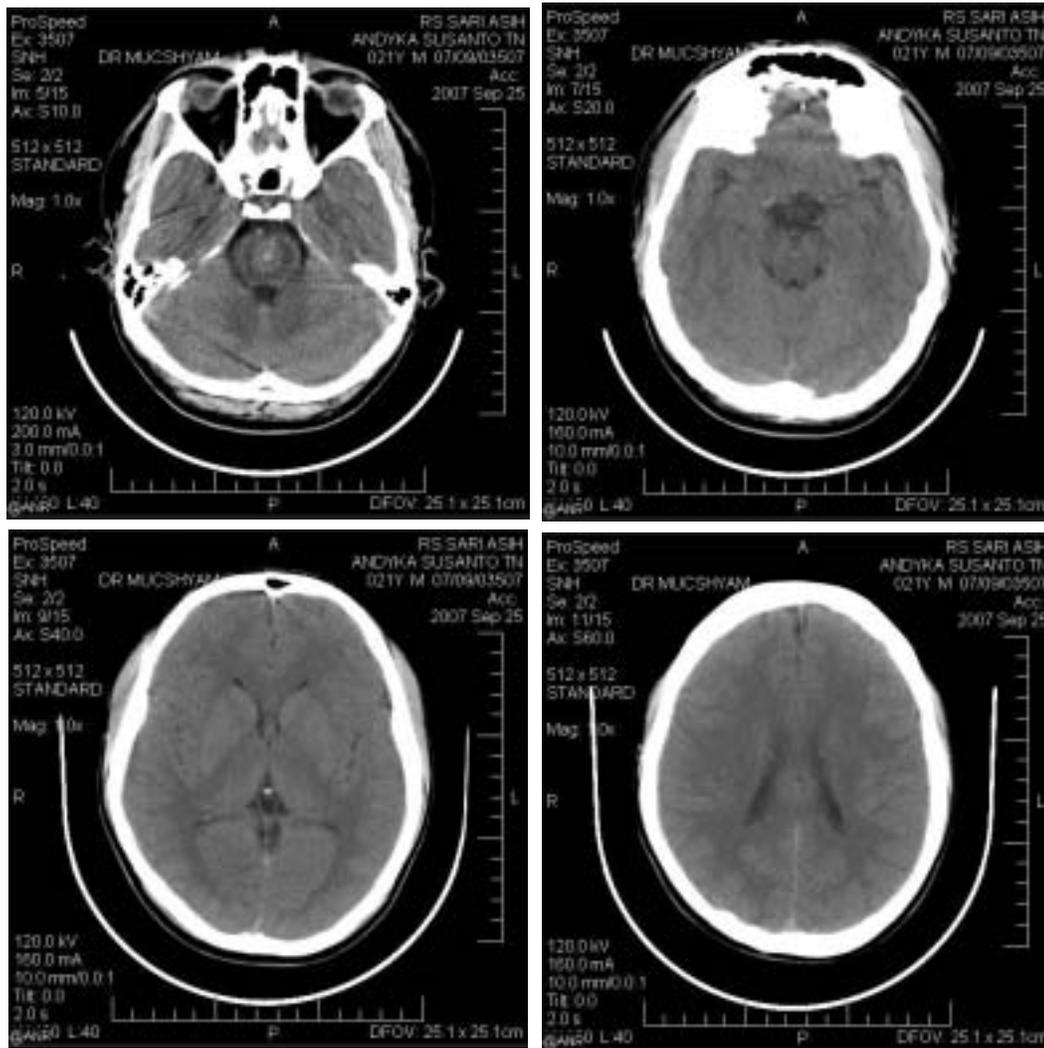


Figure 1. Cranial CT scan performed prior to 2 x 24 hours from onset; still within normal limits

Result of abdominal CT and multi slides (MS) CT angiography showed severe stenosis of approximately 70-90% at the origin of the right renal artery along a length of about 2.5 cm, as a result of extension of a mural thrombus of the abdominal aortic aneurysm. In addition there was mild stenosis of the aorta of about 30 - 50 % at the origin of the left renal artery, along a length of around 0.5 cm (Figure 2). The abdominal aortic aneurysm was located at the level of the L1-L3 disks (Figure 3), starting at the inferior part of the origin of the superior

mesenteric artery, extending past the origin of the renal artery, and ending approximately 4.5 cm above the aortic bifurcation (Figure 4). This aneurysm had a caliber of around 3 cm and a length of approximately 9.5 cm (Figure 5). The proximal portion of the aneurysm (at the level of L1-12, along a length of about 4.5 cm) was ulcerated and accompanied by a very large nodular mural thrombus (measuring around 7,2 by 5 cm), probably post rupture. The left and right suprarenal arteries appeared to be in good condition (Figure 6).

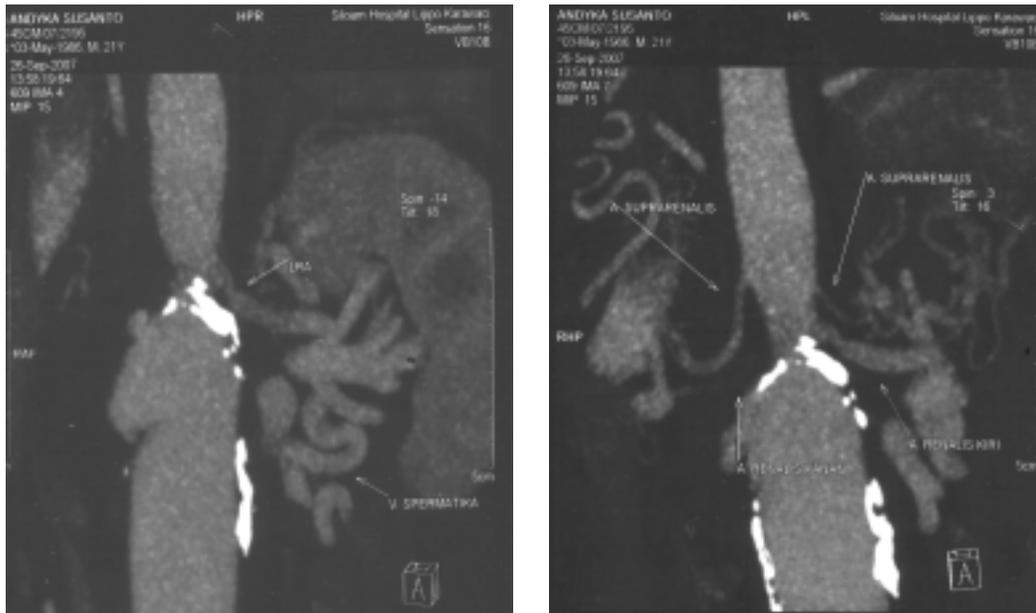


Figure 2. Abdominal CT angiography showing severe stenosis of $\pm 70-90\%$ at origin of right renal artery ± 2.5 cm in length and mild stenosis of $\pm 30-50\%$ at origin of left renal artery ± 0.5 long

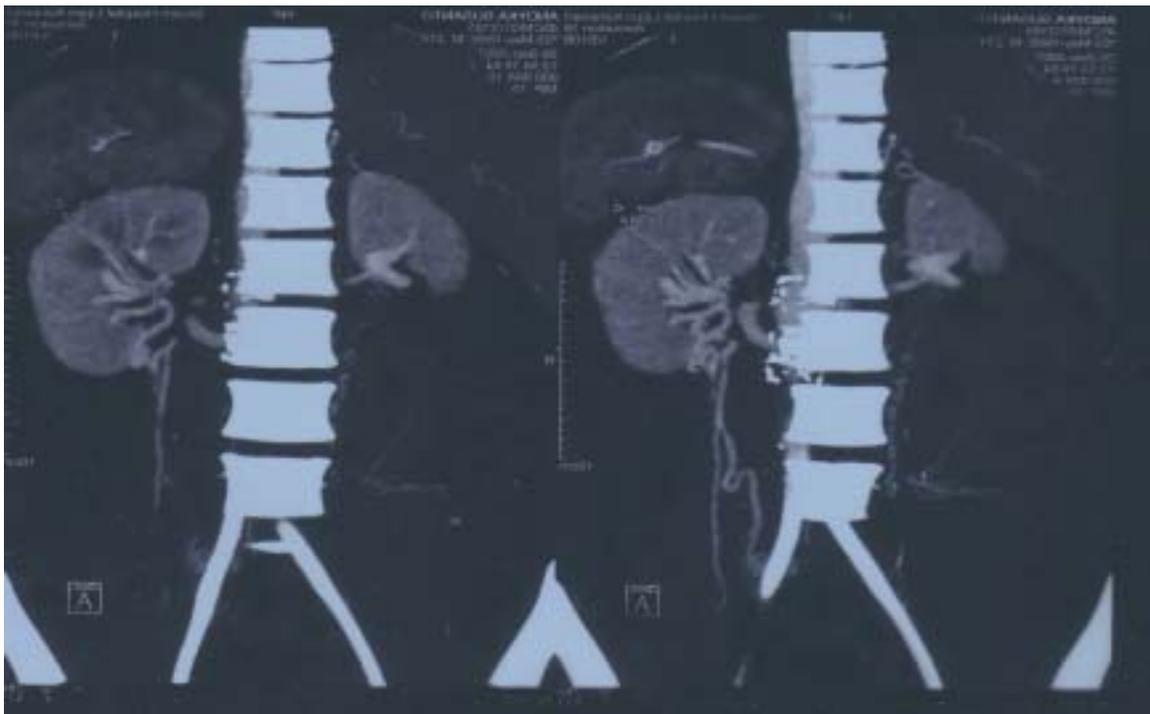


Figure 3. Abdominal CT angiography showing abdominal aortic aneurysm at level of L1 –L3 disks



Figure 4. MSCT angiography shows presence of abdominal aortic aneurysm, starting at origin of superior mesenteric artery, passing origin of renal artery and ending \pm 4.5 cm above aortic bifurcation. Proximal part of aneurysm is ulcerated and accompanied by very large nodular mural thrombus, presumably post rupture

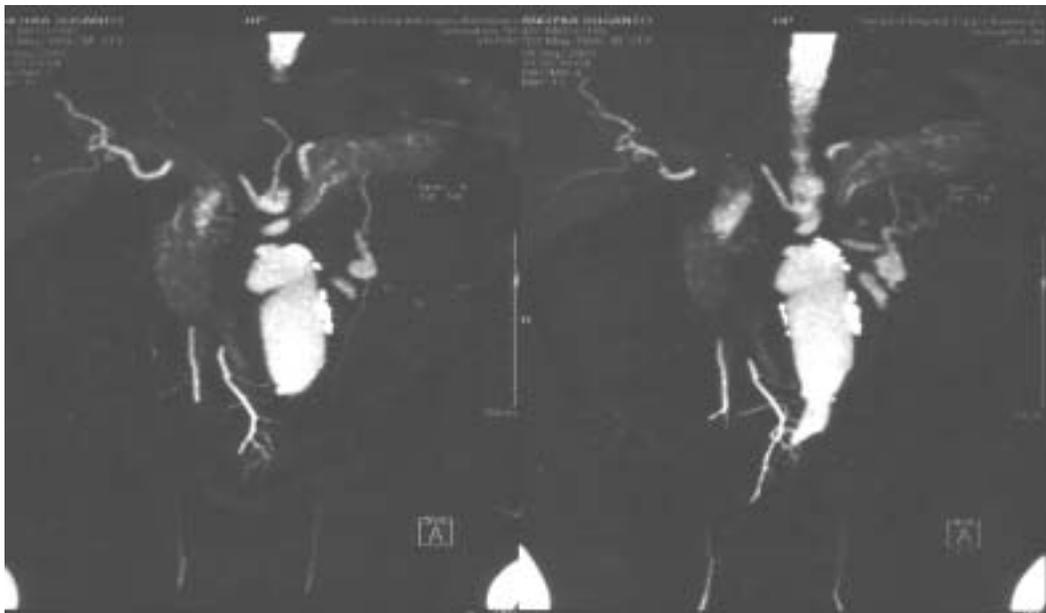


Figure 5. Abdominal CT angiography showing abdominal aortic aneurysm 3 cm in caliber, \pm 9.5 cm long, with calcification of the tunica intima

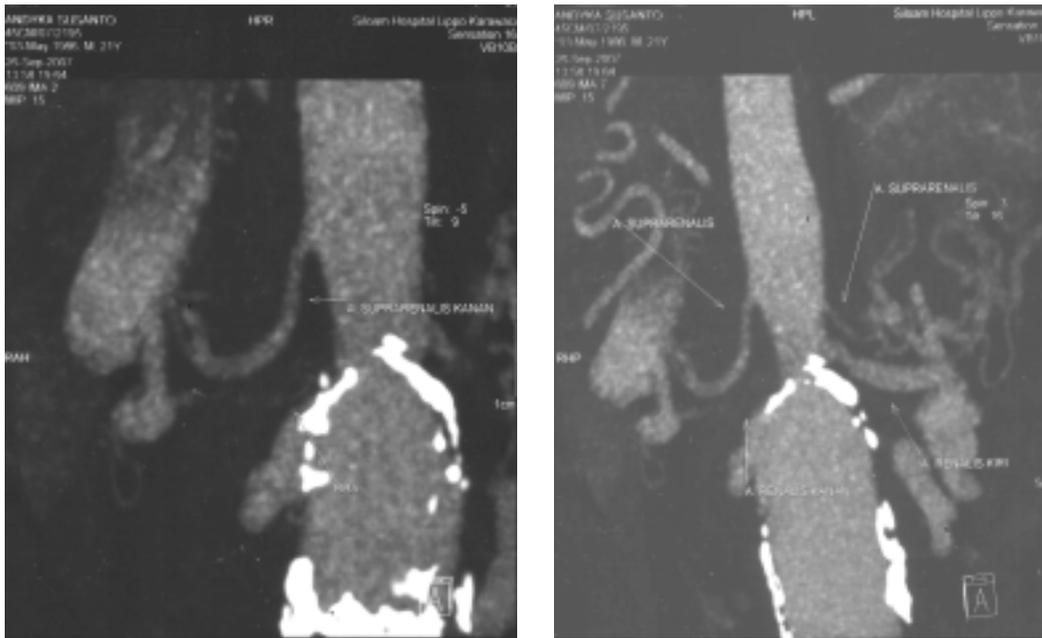


Figure 6. Abdominal CT angiography shows left and right suprarenal arteries to be in good condition

The celiac trunk, common hepatic artery, right and left hepatic arteries, and superior mesenteric artery were of normal form and caliber. No stenosis was seen. The right and left common iliac arteries were within normal limits, while the inferior vena cava was of normal caliber. Intra-abdominal organs were within normal limits.

Results of panaorto-arteriography showed aneurysm of abdominal aorta, beginning from 0.58 cm below the left renal artery, with a maximal diameter of 3.82 cm, and length of 9 cm. Stenosis of left renal artery was 50 % at the origin. (Figure 7 and Figure 8). The right renal artery was small, without any stenosis. The carotid and vertebral arteries were bilaterally normal. The left anterior cerebral artery had a stenosis of 100 % at the origin, collaterals were present (+) distally is but were inadequate. The left middle cerebral artery had a stenosis of 70% (Figure 9). The right and left coronary arteries were normal.



Figure 7. Arteriography showing abdominal aortic aneurysm, starting 0.58 cm below left renal artery, with maximal diameter 3.82 cm, length 9 cm. Left renal artery stenosis of 50 % at origin and small right renal artery

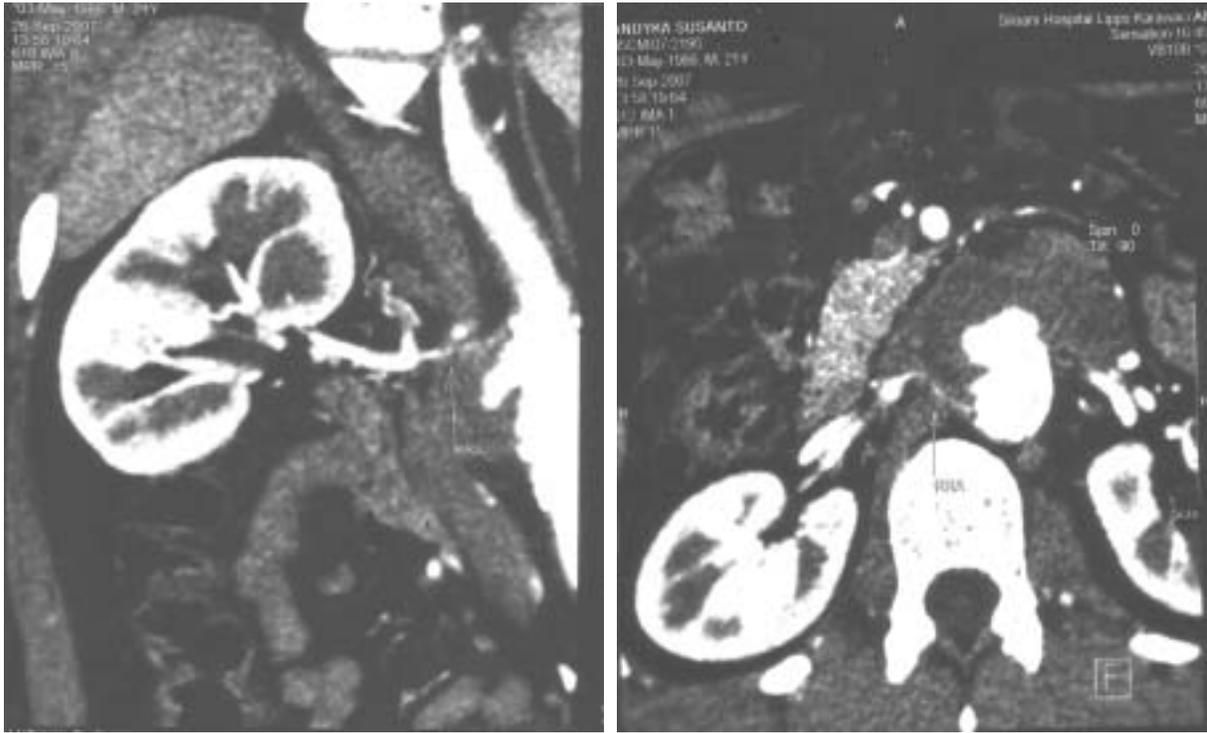


Figure 8. Abdominal CT angiography revealing renal artery stenosis



Figure 9. Intracranial arteriography showing 100% stenosis at origin of anterior cerebral artery with inadequate collaterals distally, and 70% stenosis of left middle cerebral artery

The patient was given the following treatment: antihypertensive therapy: amlodipine 1x5 mg in the morning. Anti-platelet aggregation therapy: thrombo Aspilet 1x1 tablet, clopidogrel 1x1 tablet, petoxyfillin 2x400 mg. Anti hyperlipidemic therapy: simvastatin 1x5 mg in the evening. Neurotropic therapy: citicholin 2x500 mg, piracetam 4x1200 mg. The patient underwent stenting/ Percutaneous Transluminal Angioplasty (PTA) of the right renal artery and an extra-intracranial bypass operation was planned (pending availability of funding).

DISCUSSION

Takayasu's arteritis, also called 'pulseless disease', 'Martorell syndrome', or 'occlusive thromboarthropathy', is an vascular inflammatory disease (granulomatous vasculitis), in particular

of the large to medium-sized arteries, with a predilection for the aortic arch and its main branches, and marked by a progressive inflammatory process of the vessel wall, involving the tunica media and adventitia, and subsequently causing wall thickening, dilatation, aneurysm, stenosis, occlusion and thrombosis. The disease is more common in Asians, and occurs more frequently in females than males, affecting all age groups, most commonly in the second and third decades. The etiology is thought to be an autoimmune process, because there is an association with the human leucocyte antigens (HLA), eg. B51, B52, DRB1 1502 etc. There is also a rise in the concentrations of IL-1, IL-6 and RANTES. Tuberculosis and virus infections are suspected to be a trigger of the vascular inflammation. Clinical manifestations vary from non-specific symptoms to severe sequelae due to involvement of the carotid arteries or other large vessels. There are two stages in Takayasu's arteritis, i.e. the 'pre-pulseless' phase with a non-specific type of inflammation, followed by a chronic phase with vascular insufficiency. The onset is preceded by non-specific systemic symptoms, such as fever, malaise, night sweats, joint pains, anemia, anorexia and loss of weight. After a couple of months or years, symptoms of stenosis and organ ischemia will become apparent, such as diminished pulsation of the artery, vascular bruits, blood pressure difference between the right and left brachial arteries, claudication, renovascular hypertension, retinopathy, aortic regurgitation, coronary vessel disease up to congestive heart failure, neurologic manifestations and pulmonary artery involvement. Clinical symptoms are caused by target organ damage due to involvement of the carotid artery, hypertension due to renal artery stenosis or aortic regurgitation due to aortitis. More than 50% of patients experience neurological symptoms, such as headache, disturbances of vision, convulsions, transient

ischemic attacks (TIA), cerebral infarction, intracerebral hemorrhage and attacks of orthostatic syncope. Approximately 10% of Takayasu's arteritis patients will have ischemic stroke or TIA due to vasculitis or embolism. Cerebrovascular disease is a commonly occurring complication. The thyrocervical trunk, the anterior spinal artery or the circle of Willis may also be involved. Ischemic stroke occurs frequently in the early phase of Takayasu's arteritis (1-2 years after the onset of arteritis), possibly because of inadequate collaterals. Cerebral hemodynamics may possibly also be chronically disrupted, and a mild reduction in blood pressure may lead to cerebral ischemia in the chronic phase of this disease. Hemorrhagic stroke may also occur, including subarachnoid hemorrhage, although less frequently than ischemic stroke. Subarachnoid hemorrhage in Takayasu's arteritis is caused by rupture of an aneurysm. The aneurysm is formed by hemodynamic changes at the circle of Willis, due to agenesis of the internal carotid artery; alternative causative mechanisms of aneurysm formation are immunologic reactions damaging the elastic lamina; necrosis of the vessel wall may also occur, resulting in aneurysmal rupture and hemorrhage. Bruits and diminished pulsation of the artery are the most common symptoms. Most patients experience bilateral stenosis, accompanied by aneurysm in the same segment of the involved vessel. There is a predilection for the aortic arch, but there may also be involvement of the renal artery (28-75%), coronary artery (< 10%), and pulmonary artery (14-100%). The subclavian artery is the vessel most commonly affected (90%), while two-thirds of cases involve the aorta, particularly just above and below the diaphragm. More than half of cases involve the common carotid artery, especially on the left side. The incidence of specific organ involvement varies with ethnicity; in the Japanese the disease mainly affects the

aortic arch and its branches, while in Indian people the abdominal aorta and renal arteries are more commonly involved. Based on the vessels involved, Takayasu's arteritis is classified as type I (aortic arch), type II (aortic arch and descending thoracic aorta), type III (descending thoracic aorta and abdominal aorta), type IV (abdominal aorta), and type V (aortic arch, descending thoracic aorta and abdominal aorta).⁽⁶⁻¹³⁾

Takayasu's arteritis is associated with focal mural inflammation causing sclerosis of the tunica media and intima. On macroscopic examination of the intimal surface, its appearance is irregular, with a network of scar tissue in the form of horizontal lines. When the sclerosis involves the coronary artery, three forms of abnormalities will be apparent, ie. stenosis or occlusion of the coronary ostia or the proximal coronary artery; focal coronary arteritis, which may extend to all epicardial branches; or coronary aneurysm. When the coronary ostia are affected by sclerosis, the result will be luminal narrowing leading to myocardial infarction. The pulmonary circulation may also be affected, usually by systemic artery disease. Histological examination reveals fibrosis of the tunica adventitia, rupture of elastic fibers in the tunica media, proliferation of fibroblasts in the tunica media, luminal narrowing and the presence of multinucleate histiocytes. In Takayasu's arteritis, the artery undergoing partial occlusion will acquire a new large and organized lumen, called the 'vessel-in-vessel' phenomenon, which is not present in systemic arteritis. This phenomenon differs from organized thromboembolism involving blood clots with ingrowth of endothelial cells, hemosiderin, and a myxoid fibrous network with smaller and more numerous vascular tunnels.⁽¹²⁾ The diagnosis of ischemic stroke of young adults in the present case was based on the clinical

symptom of right hemiparesis, even though the results of a head CT scan were within normal limits. The CT scan was made prior to 2 x 24 hours after admission; thus the picture of infarction was absent. The ischemic stroke had its onset in the childhood period, at age 10, starting with an aneurysm of the abdominal aorta and stenosis of the renal artery, the latter resulting in renovascular hypertension. The renovascular hypertension and Takayasu's arteritis were the causes of ischemic stroke in this patient. Renovascular hypertension is secondary hypertension caused by narrowing of blood vessels supplying the kidneys. The most common cause is renal artery stenosis. Renovascular hypertension may lead to complications: hypertensive heart disease, heart attacks, congestive heart failure, vascular damage, renal damage, renal failure, stroke, and blindness. The management of Takayasu's arteritis consists of medical therapy, endovascular therapy/angioplasty with stenting to maintain a patent lumen, or a renal artery bypass (revascularization).⁽¹⁴⁻¹⁶⁾

The differential diagnosis of Takayasu's arteritis is syphilitic aortitis, tuberculous aortitis, lupus and other vascular collagen diseases, 'giant cell arteritis', and Kawasaki disease. There are no diagnostic pathological signs, and the diagnosis is established through a combination of the clinical picture and results of imaging (radiologic). To establish the diagnosis of Takayasu's arteritis, the Ishikawa criteria⁽¹⁷⁾ (Table 1) or the criteria of the American College of Rheumatology may be applied⁽¹⁸⁾ (Table 2). The American College of Rheumatology criteria (1990) consist of: (a) age < 40 years, (b) claudication of extremities, (c) decreased pulsation of the brachial artery, (d) right-left brachial systolic pressure difference > 10 mmHg (e) subclavian or aortic bruit, (f) narrowing or occlusion of the aorta and its proximal branches at angiography.

Table 1. Ishikawa criteria, Takayasu arteritis if meeting 2 major criteria, or 1 major and 2 minor criteria, or 4 minor criteria. Sensitivity is 84%

Category	Ishikawa criteria
Age	< 40 years
Major criteria	Mid-subclavian lesion
Minor criteria	Increased erythrocyte sedimentation rate, high blood pressure, tenderness of carotid artery
Arterial lesions	Lesions of aorta, brachiocephalic artery, common carotid artery, pulmonary artery

Table 2. Criteria of the American College of Rheumatology, Takayasu arteritis if meeting 3 criteria. Sensitivity is 90.5%

Category	American college of rheumatology criteria
Age	< 40 years
Major criteria	Claudication of extremities, decreased brachial pulses
Minor criteria	Brachial blood pressure difference, subclavian or aortic bruit
Arterial lesion	Narrowing of the large arteries

The diagnosis of Takayasu's arteritis is established when any 3 from above 6 criteria are present. The gold standard for examination is angiography. Inflammation and dilatation of blood vessels may be revealed by Doppler ultrasound and magnetic resonance imaging (MRI). ultrasound, CT and magnetic resonance angiography (MRA) may be used for diagnosis of Takayasu's arteritis. MRA can reveal wall thickening and luminal configuration of blood vessels. Helical CT angiography may detect mural thickening of vessel walls, apart from vascular stenosis and occlusion. The erythrocyte sedimentation rate is raised in the acute phase. Although correlation with some HLA types supports an autoimmune etiology, this hypothesis remains unproven.^(11,12,19,20)

The etiological diagnosis of ischemic stroke for this particular patient is considered to be Takayasu's arteritis, based on the clinical picture and imaging test results indicating the presence of abdominal aortic aneurysm, bilateral stenosis of the renal arteries and stenosis of the left anterior and middle cerebral

arteries. The patient fulfills both the criteria of Ishikawa and those of the American College of Rheumatology for the diagnosis of Takayasu's arteritis. The course of Takayasu's arteritis is variable and may lead to spontaneous remission. Treatment mainly consists of steroid administration with a response rate of 50%. Patients unresponsive to steroids may be given cytotoxic drugs, such as cyclophosphamide, azathioprine, mycophenolate mofetil and methotrexate. Treatment is aimed at controlling disease activity and maintaining vascular function, with minimal long-term effects. Surgical treatment and percutaneous intervention therapy, yielding variable results, are recommended in cases not responding to medical therapy or where life-threatening ischemia is present. Approximately 10-15% of patients show monophasic clinical symptoms with fibrosis, stenosis, lowered blood sedimentation rate and absence of inflammatory markers, indicating a subclinical inflammatory phase. In this condition the management of arterial insufficiency by angioplasty, stenting

or surgery is more useful than medical therapy. Indications for surgery are severe renal artery stenosis, claudication of the extremities, stenosis of three or more cerebral vessels or coronary artery involvement. The five-year survival rate is reported to be 83–91%, while the ten-year survival rate is 84%.^(6,11,12)

Laboratory hematological results in this patient did not show an increased blood sedimentation rate as acute phase marker, thus leading to the question of whether a course of steroids is warranted and of the duration of such a course. At present management is aimed at improving the blood circulation with anti-platelet aggregation drugs, control of hypertension and other risk factors, and placement of stenting/PTA in the renal artery to prevent subsequent renal complications. Additionally it is intended to perform an extra-intracranial artery bypass to further improve circulation in the left cerebral hemisphere, thus preventing the occurrence of right hemiplegia and aphasia. The carotid arteries, cardiac and other vessels are still in good condition. It is imperative to implement preventive measures to stem the extension of the arteritic process to other vessels, considering that the patient is still young.

CONCLUSION

A case of Takayasu's arteritis with childhood onset was discussed, which had caused an abdominal aortic aneurysm and renal artery stenosis resulting in the occurrence of renovascular hypertension. Ischemic stroke of young adults occurred with the picture of left anterior and middle cerebral artery stenosis due to Takayasu's arteritis, with renovascular hypertension as additional risk factor. A stenting operation was performed on the right renal artery and an extra-intracranial artery bypass has been planned. Prevention is imperative to stem extension of the arteritic process to other vessels.

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