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Recurrent Stroke as a Presenting Feature of Takayasu Arteritis in an Adolescent: A Case Report and Literature Review

Vasiliki Sgouropoulou[1], Efthymia Vargiami[1], Maria Kyriazi[1], Sofia Kafterani[1], Stella Stabouli[1], Georgios Tsigaras[1], Athanasia Anastasiou[2], Maria Trachana[1], Dimitrios Zafeiriou[1]

[1] 1st Department of Paediatrics, Hippokration General Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece;
[2] Department of Radiology, Hippokration General Hospital, Thessaloniki, Greece

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Abstract: Takayasu arteritis is a large vessel vasculitis, characterized by granulomatous inflammation of arterial vessels, that typically affects the aorta, its main branches and pulmonary arteries. Disease diagnosis is a challenge and requires awareness of the condition, as clinical signs can be not specific. We report a case of an adolescent with recurrent stroke diagnosed with Takayasu arteritis. A diagnosis of Takayasu arteritis was established due to angiographic findings in the magnetic resonance angiography in conjunction with systolic blood pressure discrepancy, arterial hypertension and increased acute phase reactants. Takayasu arteritis is a rare cause of ischemic stroke in children. However, stroke may be the first manifestation of the disease. Clinical experience and multidisciplinary approach, including aggressive treatment, is essential for the favourable outcome of the disease and the reduction of the associated morbidity and mortality.

Mailing Address: Vasiliki Sgouropoulou, MD., MSc., PhD., Konstantinoupoleos 49, 54642, Thessaloniki, Greece; Phones: +302 310 892 498, +306 972 232 877; e-mail: vsgouro@hotmail.com

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Introduction

Takayasu arteritis (TAK) is a rare chronic inflammatory disease that typically affects the aorta, its main branches and pulmonary arteries. TAK is categorized as a large vessel vasculitis according to the 2012 International Chapel Hill Consensus Conferences (CHCC) definition (Jennette et al., 2013). Vessel inflammation shows adventitial thickening, leucocytic infiltration of the tunica media and intimal hyperplasia leading to extensive vessel stenosis, which is a major risk factor for stroke. Disease diagnosis is a challenge and requires awareness of the condition and a high index of suspicion, as in the acute early phase symptoms are usually non-specific and specific biomarkers are absent. Clinical features vary depending on the affected vessels. The EULAR/PRINTO/PReS classification criteria for TAK in children are being applied as diagnostic criteria with high sensitivity and specificity, 100% and 99.9% respectively (Ozen et al., 2010). Early detection and aggressive management of the disease are essential for optimizing outcome and reducing the associated morbidity and mortality. We present a case report of an adolescent with recurrent stroke diagnosed with Takayasu arteritis and a review of the literature.

Case report

A 16-year-old male presented to the emergency department with left arm weakness and facial nerve palsy on the left side 15 hours after the onset of the symptoms. His medical history revealed post-Salmonella reactive arthritis at the age of 12 and a smoking habit over the last two years. Additionally, a previous hospitalization 10 days ago was mentioned due to left hemiparesis, left facial palsy and an episode of transient loss of consciousness, followed by confusion, slurred speech and loss of urine. Magnetic resonance imaging (MRI) of the brain had been performed that revealed a recent right ischaemic infarct in the basal ganglia and magnetic resonance angiography (MRA) disclosed narrowing of the A1 segment of anterior cerebral artery, while the findings of the magnetic resonance venography (MRV) of the brain were normal. The patient was evaluated by the team of pediatric neurologists and a thorough diagnostic investigation was performed. Serology tests, including hepatitis B and C virus, human immunodeficiency virus, Toxoplasma, rubella, *Borrelia burgdorferi*, Epstein-Barr virus, measles, Parvovirus B19, Herpes simplex virus and *Mycoplasma pneumoniae* were negative. The patient had been tested for thrombotic risk factors, including anticardiolipin antibodies (IgG, IgM), anti-beta2-glykoprotein I antibodies (IgG, IgM), factor V Leiden, factor II, protein C and S, antithrombin III, hyperhomocysteinemia and lupus anticoagulant and the findings had been normal. Echocardiography had been performed and normal findings had been disclosed. The patient was started on aspirin (100 mg/daily) and as the clinical condition was improved, he was discharged with a follow-up appointment.

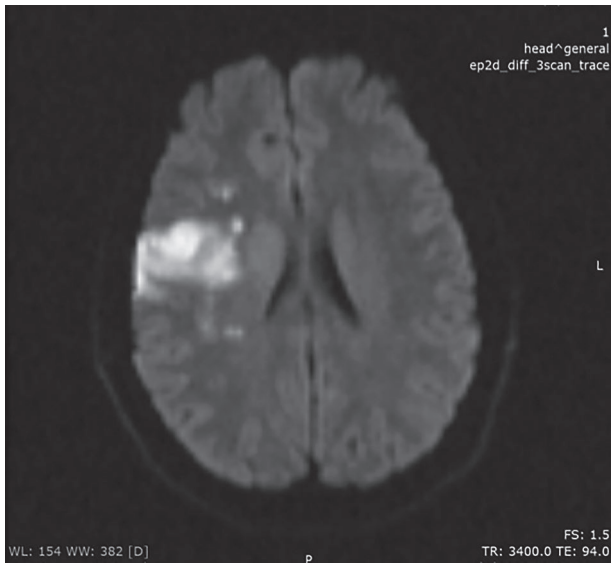

Figure 1 – Brain magnetic resonance imaging showing right middle cerebral artery infarct.

Upon hospital admission, neurological examination revealed left facial nerve palsy, decreased strength and sensation in the left upper extremity and weak reflex response on the left side. Brain MRI revealed right middle cerebral artery infarct (Figure 1) and MRA disclosed narrowing of the right middle cerebral artery, right anterior cerebral artery and right posterior communicating artery. MRA of the neck also unveiled narrowing and thrombosis of the right internal carotid artery (Figure 2). The patient was additionally started on anticoagulant therapy with low

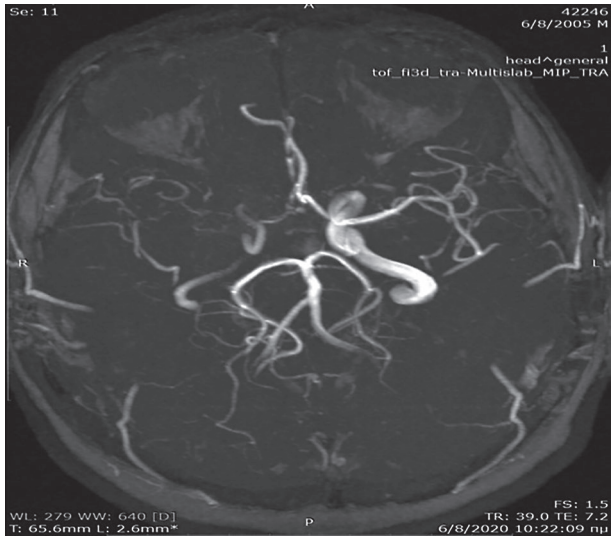

Figure 2 – Magnetic resonance angiography of cerebral arteries showing absence of flow in the right internal carotid.

molecular weight heparin (LMWH). The laboratory results were normal. On day 3 the patient developed high grade fever, without further deterioration of his neurologic condition. The laboratory results revealed neutrophilic leukocytosis (white blood cell count 19.5 K/UI [Neu 91.6%]) and elevated acute phase reactants, C-reactive protein 108.6 mg/l (N: <6.0) and erythrocyte sedimentation rate (ESR) 13 mm/h (N: 1–10). Blood and urine culture and nasal swab for SARS-CoV-2 by RT-PCR were negative. Chest X-ray, ultrasound scan of the abdomen and computed tomography angiography (CTA) of the thoracic and the abdominal aorta were unremarkable. Upon clinical examination, the patient showed systolic blood pressure discrepancy. Blood pressure of the right lower extremity was 144/66 mm Hg and of the left lower extremity 95/56 mm Hg. There were no decreased or absence of peripheral artery pulses. Based on clinical examination, laboratory tests and imaging findings the patient was diagnosed with Takayasu arteritis. Assessment of disease activity was achieved using the Paediatric Vasculitis Activity Score (PVAS), which was calculated at 20/63. The patient was treated with intravenous methylprednisolone pulse (1 g/day for 3 consecutive days), followed by oral prednisolone (60 mg/day). Cyclophosphamide was also administered at a dose of 500 mg/m^2. There was an amelioration of the patient's clinical symptoms, including improved mobility of left upper limb and complete recovery of facial palsy. Laboratory results were normalized and after

Table 1 – PSOM-SNE measurements in month 0, 3, 6 and 18

Month	Pediatric Stroke Outcome Measure Subscales and Outcomes					Total score
	left sensorimotor domain	right sensorimotor domain	language production	language comprehension	cognition-behaviour	
0	2.0	0.5	1.0	1	0.5	5.0/10
3	1.0	0.0	0.5	0	0.0	1.5/10
6	0.5	0.0	0.0	0	0.5	1.0/10
18	0.0	0.0	0.0	0	0.0	0.0/10

PSOM-SNE – Pediatric Stroke Outcome Measure Short Neuro Exam

Table 2 – Hand Grip Strength measurements in month 0, 3, 6 and 18

Month	
0	Application failure
3	29 kg (high risk)
6	33.5 (some risk)
18	42

a 10-day hospitalization the patient was discharged, receiving a physiotherapy and speech-language therapy referral. Over the following 3 months, the patient was administered 5 cyclophosphamide infusions, as per protocol, and oral prednisolone was tapered to 20 mg per day. His neurological condition presented further improvement and laboratory results remained normal. The reliable and objective disease-specific measure of neurological recovery after childhood stroke, the Pediatric Stroke Outcome Measure Short Neuro Exam (PSOM-SNE) and the Hand Grip Strength (HGS) were applied and confirmed the gradual clinical improvement of the patient from month 0 to month 18 (Table 1). A significant degree of deviation in PSOM-SNE is recorded in detail in the sectors: hemiparesis, hemifacial weakness, other motor deficit, difficulty with drinking, dysarthria, language deficit and comprehension, cognitive or behavioural deficit. In the HGS test the impossibility of its implementation was presented in the initial assessment with first application in month 3 and clinical improvement in all the tests until month 18 (Table 2). A follow-up MRA of brain and neck was performed 6 months later, showing additionally a narrowing of the A2 segment of right anterior cerebral artery and the MRI of the abdominal aorta revealed stenosis of the inferior mesenteric artery, leading to further imaging of the lower extremities which also revealed stenosis in the right posterior tibial artery. At that point, the patient was infected with SARS-CoV-2, presenting a short course of the disease and a complete and rapid clinical recovery. The dose of oral prednisolone was increased to 40 mg/day and the biological agent Tocilizumab was added in his treatment at the dose of 162 mg/week subcutaneously. Furthermore, the patient's serum creatinine increased (Cr: 1.25 mg/dl) and his GFR (glomerular filtration rate) was reduced below normal ranges, while the 24-hour urine protein test result was normal. An abdominal ultrasound and a CTA of renal arteries was performed, revealing no abnormalities, followed by a renal biopsy confirming the above result. To this day, 18 months from the disease onset, patient's neurological condition and neuroimaging remains stable, manifestations have majorly subsided and laboratory results are normal (Cr: 0.95 mg/dl). Methotrexate was added in his treatment, as he presented arthritis in his right elbow. He is closely monitored by the paediatric neurologist, rheumatologist, nephrologist and rehabilitation team.

Discussion

Takayasu arteritis is a large vessel vasculitis, characterized by granulomatous inflammation of arterial vessels. Several previous studies reported a prevalence of Takayasu arteritis that ranges from 4.7 to 33 cases per million in European population (Onen and Akkoc, 2017). The prevalence of stroke in Takayasu is estimated to be around 5–20%, based on small studies (Duarte et al., 2016; Kim and Barra, 2018). Diagnosis of Takayasu arteritis remains a challenge for the clinical

doctor, as it usually presents with non-specific symptoms at the early stages such as fever, headaches, weight loss and rash. As inflammation progresses, organ specific symptoms emerge, due to stenosis, occlusion and ischaemia. Takayasu patients have a variable clinical presentation with the most common clinical symptom in children being hypertension secondary to renal artery stenosis (Mathew et al., 2016). Although neurological manifestations are not common as the initial presentation of Takayasu arteritis in children, stroke should be a red flag and further investigation should be carried out (Zhou et al., 2011). Stroke occurrence at any point along the progression of Takayasu arteritis could result in neurological sequelae, including neurological impairment, recurrence of stroke and epilepsy (Couture et al., 2018). Fan et al. (2019) reported that patients who present with stroke, heart failure or coronary artery involvement at early stages of the disease, usually lead to worse progression of the disease and require close monitoring. Induction therapy of Takayasu arteritis requires high dose of glucocorticoids combined with non-biologic disease modifying agents, based on the EULAR treatment guidelines for Takayasu arteritis in adults. In cases of major relapse, such as the one presented in this report, biological agents such as Tocilizumab should be considered (Hellmich et al., 2020). In our case, a 16-year-old patient, with a history of reactive arthritis and a recent cerebral infarct, presented with a recurrent ischaemic stroke. Strong clinical suspicion led to prompt diagnosis of Takayasu arteritis and aggressive treatment with high doses of methylprednisolone and cyclophosphamide was administered. The initial good clinical response was followed by COVID-19 infection. Follow-up imaging revealed new-onset angiographic abnormalities, while the patient presented increased serum creatinine, with normal renal biopsy findings. Treatment with Tocilizumab was initiated and methotrexate was added and the clinical condition of the patient, 18 months later, remains stable. In our case, acute ischemic stroke was the first clinical presentation of Takayasu arteritis. We highlight the significance of early diagnosis of systemic vasculitis in children that defines the disease course and prognosis of the disease. Takayasu arteritis is a rare and potentially life-threatening condition in children and requires high suspicion from the clinical doctor. All paediatric patient with suspected systemic vasculitis should be directed to a referral center, as the diagnosis and treatment is challenging and requires multidisciplinary monitoring.

Conclusion

Takayasu arteritis should be included in the differential diagnosis of stroke in all young patients. Even though ischaemic stoke is rare as the first presentation of Takayasu arteritis, clinical suspicion can lead to early diagnosis and to prompt treatment, in order to minimize the disease progression and improve the prognosis.

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