Osmangazi Tıp Dergisi
Osmangazi Journal of Medicine 2023;

Olgu Sunumu / Case Report

Diagnostic Inexperience of Takayasu Arteritis in Pediatric Neurology: A Case Report and Mini-Review of the Literature

Pediatrik Nörolojide Takayasu Arteritinin Tanısal Deneyimsizliği: Olgu Sunumu ve Literatürün Gözden Geçirilmesi

[1]Turgay Cokyaman, [2]Yücel Sınmaz, [3]Nilüfer Aylanc, [4]Ayşe Burcu Akıncı, [5]Betül Sözeri

[1]Department of Pediatrics, Division of Pediatric Neurology, Çanakkale Onsekiz Mart University, Faculty of Medicine, Çanakkale, Turkey

[2]Department of Pediatrics, Çanakkale Onsekiz Mart University, Faculty of Medicine, Çanakkale, Turkey

[3]Department of Radiology, Çanakkale Onsekiz Mart University, Faculty of Medicine, Çanakkale, Turkey

[4]Department of Pediatrics, Division of Pediatric Hematology and Oncology, Acıbadem University, Faculty of Medicine, Istanbul, Turkey

[5]Department of Pediatrics, Division of Pediatric Rheumatology, University of Health Sciences Istanbul Ümraniye Training and Research Hospital, Istanbul, Turkey

Correspondence:
Turgay ÇOKYAMAN
Department of Pediatrics, Division of Pediatric Neurology, Çanakkale Onsekiz Mart University, Faculty of Medicine, Çanakkale, Turkey
e-mail. drturgay@comu.edu.tr

Abstract

Takayasu arteritis (TA) is a chronic inflammatory vasculitis involving the aorta and its main branches. It usually starts with systemic inflammatory signs after ten years of age. Neurological symptoms seen depend on aneurysmatic, stenotic and thromboembolic events in the affected vessels. It is rarely seen in childhood and presentation with epileptic seizure is extremely rare in infantile age. In this case report, a 22-month-old child who was admitted with epileptic seizure and had a large infarction in the area matching the right middle cerebral artery (MCA) watershed. Symptoms and imaging findings due to infarction developed hours after epileptic seizure. First, low molecular weight heparin treatment was started. Following the development of multiple aneurysmatic-stenotic lesions in the left brachial artery and profunda branch, diagnosed as TA. It was added to oral steroid and azathioprine. Resistant seizures were controlled with levetiracetam and valproic acid in the poststroke period. Multidisciplinary follow-up is ongoing with anticoagulant, antiepileptic and immunosuppressive treatments. TA rarely occurs in the infantile period with acute neurological symptoms such as epileptic seizure and stroke. It is important to make diagnosis early in order to reduce the neurological comorbidities that may occur in the long term.
Keywords: Takayasu arteritis; Seizure; Stroke; Children

Özet

Takayasu arteriti (TA), aort ve ana dallarını tutan kronik inflamatuar bir vaskülittir. Genellikle on yaşından sonra sistemik inflamatuar bulgularla başlar. Etkilenen damarlarda görülen nörolojik semptomlar anevrizmatik, stenotik ve tromboembolik olaylara bağlıdır. Nadiren çocukluk çağında görülür ve infantil yaşta epileptik nöbet ile prezentasyon oldukça nadirdir. Bu olgu sunumunda, epileptik nöbet ile başvuran ve sağ orta serebral arterin (MCA) beslediği alanda geniş bir enfarktüs gelişen 22 aylık bir çocuk sunulmuştur. Enfarktüse bağlı semptomlar ve görüntüleme bulguları epileptik nöbetten saatler sonra gelişti. Önce düşük molekül ağırlıklı heparin tedavisi başlandı. Sol brakiyal arter ve derin dalda çok sayıda anevrizmatik-stenotik lezyon gelişmesi üzerine TA tanısı konuldu. Oral steroid ve azatioprine eklendi. İnme sonrası dönemde levetirasetam ve valproik asit ile dirençli nöbetler kontrol altına alındı. Antikoagülan, antiepileptik ve immünsüpresif tedaviler ile multidisipliner takibi devam etmektedir. TA, infantil dönemde epileptik nöbet ve inme gibi akut semptomlarla nadiren ortaya çıkar. Uzun vadede ortaya çıkabilecek komorbiditeleri azaltmak için erken tanı koymak önemlidir.
Anahtar Kelimeler: Takayasu arteritis, Seizure, Stroke, Children

Received 03.10.2022 Accepted 15.12.2022 Online published 26.12.2022

Cokyaman T, Sinmaz Y, Aylanc N, Burcu Akinci A, Sozeri B. Diagnostic Inexperience of Takayasu Arteritis in Pediatric Neurology: A Case Report and Mini-Review of the Literature Osmangazi Journal of Medicine, 2023;45(1): 135-141 Doi: 10.20515/otd.1176704

1. Introduction

Takayasu arteritis (TA) is a chronic, inflammatory and granulomatous vasculitis that may involve the aorta, aortic arc, abdominal aorta, renal and iliac arteries. Most pediatric cases are diagnosed in the adolescent period and it is more common in the female sex. It is more frequent in Asian countries, especially Japan, compared to the west [1]. In Turkey, the incidence is 12.8 per million adults; however, the incidence in children is not clearly known. The pathogenesis of the disease is not fully known, though fibrosis develops in arterial walls as a result of immune-mediated inflammatory mechanisms. As a result of this situation, there is stenosis in the large arteries and it may cause stroke in 10-20% of patients [2]. To date, presentation with epileptic seizures in early childhood is limited to a few case reports. Our report presents a case attending with focal seizure and confusion in the early childhood period who received TA diagnosis during long-term follow-up.

2. Case report

With no previous health problem, a 22-month-old male patient, born at term by elective cesarean weighing 3300 g, attended with right focal seizure and confusion developing after trivial trauma. With no feature in his history, the child's family history included controlled epilepsy in the father. With no cardiac, hematologic and rheumatologic disease history, the patient had no history of medication use. Height was 85 cm (10-25 p), body weight 10.5 kg (3-10 p), head circumference 49.5 cm (25-50 p), body temperature 36.8 ℃, and heart rate 90 beats/min (according to age 80-110 beats/min). Arterial pressure was 90/45 mmHg (75 p) and no pressure differences were identified between the four extremities. Neurological examination found confusion, right light reflex was weak compared to the left and there was central facial paralysis. Deep tendon reflexes were increased on the left, normal on the right with plantar reflex on the left extensor. Muscle power was 3/5 on the left and normal on the right, with sensory and sphincter examinations normal. Other system examinations did not any pathology. Laboratory tests reported leukocyte count 15.000 (103/uL), hemoglobin 11 g/dL, hematocrit 32%, platelet count 392.000 (x103/uL), C-reactive protein 0.32 mg/dL (0-0.8 mg/dL), erythrocyte sedimentation rate 19 mm/hr. Serum electrolytes, renal and liver function tests, coagulation tests, muscle enzymes and viral serology (Herpes simplex virus type 1-2, Ebstein-Barr virus, Cytomegalovirus, Hepatitis virus A and B) tests did not pathology. Electrocardiography had normal sinus rhythm and echocardiography did not identify pathology. On first attendance, the patient's brain computerized tomography (CT) was assessed as normal; however, magnetic resonance (MR) imaging identified broad infarctus compatible with the right middle cerebral artery (MCA) watershed. MR angiography observed very fine calibration at the right internal carotid artery (ICA) cervical level and after the petrous area, the right MCA and anterior cerebral artery (ACA) were not observed (Figure-1:a-i). Hematologic, cardiologic and infectious research were negative, and the patient had normal tandem mass spectrometry and lactate levels. During follow-up with enoxaparin prophylaxis, the patient developed multiple aneurysms in the right brachial artery and profunda branch and oral steroids and azathioprine were added to treatment on recommendation of pediatric rheumatology. Short-duration focal seizures and worsening electroencephalography (EEG) findings were controlled by oral levetiracetam and sodium valproate treatment. Follow-up continues with multidisciplinary approach by the pediatric neurology, hematology, rheumatology, and physiotherapy and rehabilitation units.

Table-1. Simple approach to pediatric stroke and Takayasu arteritis differential diagnosis.

	Hematological evaluation	Hematology consultation, complete blood count, PT-APTT, D-dimer, fibrinogen, ESR, CRP
		Protein C, S, Antithrombin deficiency
		Factor V Leiden
		Prothrombin *G20210A*
		MTHFR *C677T*
		Lipoprotein (a) elevations
		Sickle cell anemia
Initial evaluation	Cardiological evaluation	Cardiology consultation, ECG, ECHO, murmurs, four limb blood pressure measurements and blood pressure discrepancy Congenital heart disease Endocarditis Rheumatic fever Cardiomyopathy
		Arrhythmia
	Infectious causes	Specific anamnesis, characteristic examination and laboratory findings and consultation with infectious diseases specialist Tuberculosis
		Brucellosis
		Varicella
		Syphilis
Inflammatory vasculitis	Kawasaki disease, Polyarteritis nodosa	Specific anamnesis, characteristic examination and laboratory findings Mostly medium and small vessels are involved
	Giant cell arteritis	Frequent in adults, infrequent in a children
	Moyamoya disease	Characteristic brain MR sign, puff of smoke
Autoimmune diseases	Systemic lupus erythematosus, Sarcoidosis	In teenage, butterfly rash, depression, psychosis, photosensitivity, renal disorder, more nonspecific white matter lesions Lung, lymph nodes, skin and eyes involvement, uveitis and arthritis, very often small vessel vasculitis
Non-inflammatory vasculopathies	Fibromuscular dysplasia	Renovascular disease and hypertension, headache, pulsatile tinnitus, subarachnoid hemorrhage, claudication of the legs or arms, Frequent renal artery involvement, stenosis, occlusion, dissection or aneurysm
	Ehlers-Danlos type IV, Marfan syndrome	Marfanoid phenotype, joint hypermobility, ectopia lentis, stretchy and fragile skin
	Neurofibromatosis type I	Lisch nodules, skin fold freckling, cafe au lait spots, neurofibromas, narrowed or ectatic vessels, vascular stenosis, aneurysm, or moyamoya-like disease
Post-chemotherapy or radiotherapy	Malignancy and treatment history	

PT:prothrombin time, APTT:activated partial thromboplastin time, ESR:erythrocyte sedimentation rate, CRP:c-reactive protein, MTHFR:methylenetetrahydrofolate reductase, ECG:electrocardiography, ECHO:echocardiography, MR:magnetic resonance imaging. [References 3, 14, 15 and 16 were made use for Table-1.]

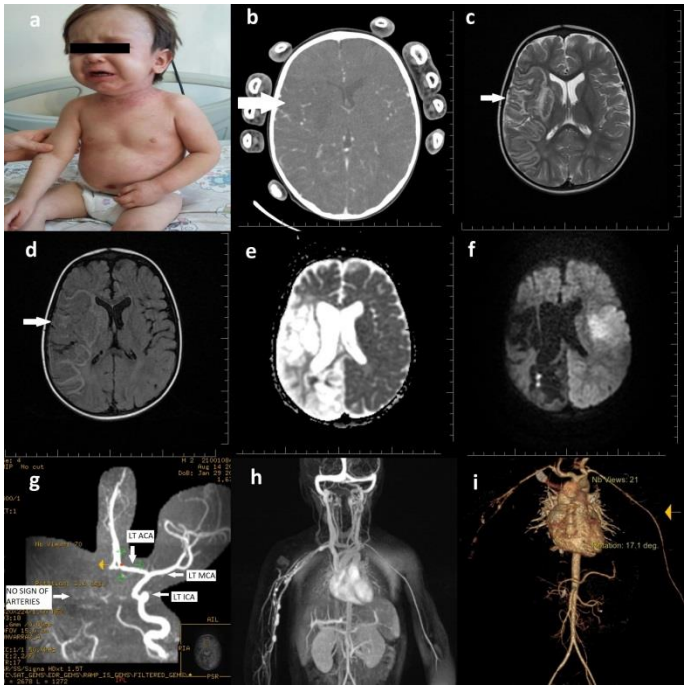

Figure-1. a) patient image (parental permission was obtained), b) initial T1 brain MR; hypointense large subacute infarct area in the right cerebral hemisphere corresponding to the watershed area of the middle cerebral artery, c) axial T2 and d) T2 flair image; subacute hyperintense appearance of the same infarct area, e) three months later, brain ADC image; hyperintense appearance including right hemisphere frontotemporoparietal and occipital lobes, lentiform and caudate nuclei in chronic stage, f) four months later, brain DWI image; large hypointense infarct area in the right hemisphere (chronic stage) but hyperintense new infarct area on the left MCA watershed area, g) brain MR angiography; right ICA and MCA could not be visualized but ACA was visualized thin calibration. Left ACA, MCA, contours and signal intensities were normal, h) one year later, right subclavian MR angiography; multiple aneurysmatic dilatations in the right brachial artery trace, i) upper extremity and abdomen 3D CT angiography; the entire aorta is in normal calibration, and the right common carotid is thinner than the left. Multiple aneurysms are observed in the right brachial artery and its profunda branch.

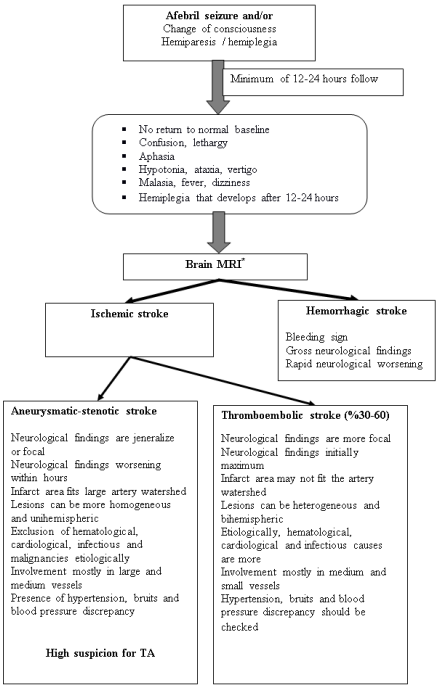

Figure-2. Brief diagnostic scheme for the Takayasu arteritis in pediatric neurology [References 13, 15, 17, 18, 19, and 20 were made use for this diagram in Figure-2.]

3. Discussion

In the pediatric period, very few cases are reported to attend with epileptic seizure in TA. In our case, the initial symptom was afebrile seizure with lengthened postictal confusion and left hemiplegia developing hours later. In the normal progression of disease in TA, attendance with systemic findings like lethargy, weight loss, fever, myalgia and arthralgia in the first phase is at the fore [3]. In the second phase (pulseless phase), arterial stenosis findings become more pronounced with findings like hypertension, claudication and neurological manifestations like headache, dizziness, visual disturbances, transient ischemic attack and stroke observed [4,5]. Our case was attended to with neurological symptoms compatible with the second phase of the disease. In this context, when we examine the literature studies by Sahin et al. (2018), Misra et al. (2015) and Aeschlimann et al. (2017) found mean age of presentation was 12.9, 14 and 12.4 years, respectively [6-8]. Again in these studies, it is notable that the female sex was dominant (nearly 75% of cases). Attendance symptoms were hypertension, bruits and blood pressure (BP) discrepancy. Sahin et al. reported 1/16 cases while Misra et al. reported 2/29 cases presented with epileptic seizure. In the literature, a case report by Weiss et al. (2008) reported that TA presented with epileptic seizure [9]. It has been reported that stenosis of the right vertebral artery and right brachiocephalic arteries was detected in MR and CT angiography in a 14-year-old Hispanic girl who presented with right-sided weakness, right facial droop and confusion. While left frontal ischemia was detected in the initial CT and MR of this case, BP discrepancy between the right and left extremities was reported in the physical examination, but not epileptic seizure [10]. In addition, it was reported that diffuse stenosis of the entire aorta and stenosis of the left subclavian artery 1/3 origin were detected in the CT aortagram of a 10-year-old girl who presented with headache, multiple recurrent seizures and altered consciousness. Interestingly, the diagnosis of PRES was made based on brain imaging findings in this case whose hypertension was detected in the right arm, but whose pulse was not palpable in the left arm [11].

As a result, the presentation of TA with epileptic seizure is a very rarely observed admission symptom and it is not included in the the European League Against Rheumatism / the Paediatric Rheumatology International Trials Organisation / the Paediatric Rheumatology European Society diagnostic criteria [12].

In arterial ischemic strokes, obstruction is generally secondary to thromboembolism and infarctus develops in accordance with by the watershed areas of the affected arteries. Infarctus in thromboembolic events are generally bihemispheric and display heterogeneous patterns, while relatively homogeneous and broad-area infarctus may indicate stenosis in large arteries. Additionally, strokes in small children may occur with findings like convulsions, lethargy, fever and headache which may be very frequently interpreted in favor of central nervous system (CNS) infection. A study by Deda and Teber (2010) revealed the etiologic risk factors for stroke cases monitored in the pediatric neurology clinic in detail [13]. In this study, the majority of stroke cases were revealed to be due to hematologic causes (Factor VIII elevation, Factor V Leiden mutation, Factor IX elevation, protein C and S deficiency, homocysteinemia and prothrombin 20210 A and MTHFR gene mutation). They reported causes of stroke with lower incidence were acquired or congenital heart diseases, CNS infections, malignancies and congenital metabolic diseases.

When we look at the pediatric neurology perspective, it is not a mistaken approach to leave vasculitis like TA toward the end of the list of differential diagnoses for an infant attending with epileptic seizure. In fact, in our case, stroke findings settled 24 hours after epileptic seizure. Considering the difficulty of sedation for brain MR or MR angiography of an infant with continuing postictal confusion or lethargy, priority for hematologic and cardiologic pathologies with identification of

infarctus and exclusion of CNS infections, it is unavoidable that a final diagnosis like TA is delayed. According to our graphical illustration prepared with a review of the literature in order to identify TA, which has severe neurologic sequelae potential, as the cause of stroke in the shortest period, TA should be suspected with identification of the lack of postictal return to normal baseline, the persistence of changes in consciousness such as lethargy-confusion, development of gross motor losses like hemiplegia, and identification of broad and unihemispheric infarctus compatible with large artery watershed area on brain imaging. If results cannot be obtained from hematologic, cardiac and infectious assessments, the diagnosis of TA can be reached from our diagnostic scheme (Figure-2). Knowing anamnesis and specific clinical and laboratory findings for inflammatory and autoimmune diseases included in differential diagnosis will shorten the time to reach the final diagnosis (Table-1).

In conclusion, clues warning of TA may include the continuation of postictal changes in consciousness for a long period after epileptic seizure, the occurrence of gross neurological findings during monitoring and identification of broad infarctus area compatible with large arteries (ICA, MCA or ACA) watershed on brain imaging.

REFERENCES

1. Kohrman MH, Huttenlocher PR. Takayasu arteritis: a treatable cause of stroke in infancy. *Pediatr Neurol.* 1986;2:154-158.
2. Seyahi E. Takayasu arteritis: an update. *Curr Opin Rheumatol.* 2017;29:51-56.
3. Felling RJ, Sun LR, Maxwell EC, Goldenberg N, Bernard T. Pediatric arterial ischemic stroke: Epidemiology, risk factors, and management. *Blood Cells Mol Dis*. 2017;67:23-33.
4. Aydin F, Acar B, Uncu N, et al. Takayasu Arteritis: A Case Presenting With Neurological Symptoms and Proteinuria. *Arch Rheumatol.* 2020;35:287-291.
5. Ghoshal S, Bronen RA, McCarthy PL, Pels SG, Beslow LA. Acute Stroke in a Girl With an Absent Radial Pulse. *Pediatr Neurol*. 2016;62:77-78. doi:10.1016/j.pediatrneurol.2016.06.002.
6. Sahin S, Hopurcuoglu D, Bektas S, et al. Childhood-onset Takayasu arteritis: A 15-year experience from a tertiary referral center. *Int J Rheum Dis.* 2019;22:132-139.
7. Misra DP, Aggarwal A, Lawrence A, Agarwal V, Misra R. Pediatric-onset Takayasu's arteritis: clinical features and short-term outcome. *Rheumatol Int.* 2015;35):1701-1706.
8. Aeschlimann FA, Eng SWM, Sheikh S, et al. Childhood Takayasu arteritis: disease course and response to therapy. *Arthritis Res Ther.* 2017;19:255.
9. Weiss PF, Corao DA, Pollock AN, Finkel TH, Smith SE. Takayasu arteritis presenting as cerebral aneurysms in an 18 month old: a case report. *Pediatr Rheumatol Online J.* 2008;6:4.
10. Davari P, Sutton P, Jones KS. Stroke as the initial presentation of Takayasu's arteritis: A case report. *Radiol Case Rep*. 2020;15:556-559.
11. Karande S, Jagtap S, Joshi A. Posterior reversible encephalopathy syndrome revealing Takayasu's arteritis. *Indian J Pediatr*. 2009;76:218-220.
12. Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. *Ann Rheum Dis.* 2010;69:798-806.
13. Deda G, Teber S. Çocukluk çağı inmeleri / Stroke in childhood. *Dicle Tip Dergisi.* 2010;37:314-20.
14. Söbü E, Özdemir N, Uysal S, Buyru N, Celkan T. Pediatric Stroke: A Single-Center Experience. *J Pediatr Hematol Oncol*. 2019;41:519-524.
15. Di Santo M, Stelmaszewski EV, Villa A. Takayasu arteritis in paediatrics. *Cardiol Young.* 2018;28:354-361.
16. Mathew AJ, Goel R, Kumar S, Danda D. Childhood-onset Takayasu arteritis: an update. *Int J Rheum Dis.* 2016;19:116-126.
17. Al-Shami R, Khair AM, Elseid M, et al. Neuro-imaging evaluation after the first afebrile seizure in children: A retrospective observational study. *Seizure.* 2016;43:26-31.
18. Amagasa S, Uematsu S, Tsuji S, Nagai A, Abe Y, Kubota M. Identification of children with first afebrile seizure for whom neuroimaging is unnecessary. *Seizure.* 2021;93:140-144.
19. Sönmez HE, Demir F, Özdel S, et al. Neuroimaging of Children With Takayasu Arteritis. *J Child Neurol.* 2021;36:642-647.

20. Duarte MM, Geraldes R, Sousa R, Alarcão J, Costa J. Stroke and Transient Ischemic Attack in Takayasu's Arteritis: A Systematic Review and Meta-analysis. *J Stroke Cerebrovasc Dis.* 2016;25:781-791.

Ethics

Informed Consent: The authors declared that informed consent form was signed by the patient.

Copyright Transfer Form: Copyright Transfer Form was signed by the authors.

Peer-review: Internally peer-reviewed.

Surgical and Medical Practies; TC, YS, NA, ABA, BS, Design; TC, Data Collection or Processing; TC, YS, Analysis and Interpretation; TC, BS, Literature Search; TC, YS, NA, ABA, Writing; TC, Editing; TC, NA, ABA, BS

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.