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The Incidence and Prevalence of Thromboangiitis Obliterans in Taiwan: A Nationwide, Population-based Analysis of Data Collected from 2002 to 2011

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OBJECTIVE: To estimate the incidence and prevalence of thromboangiitis obliterans in Taiwan in the period spanning from 2002 to 2011.

METHODS: We identified all incident and prevalent cases with a diagnosis of thromboangiitis obliterans (International Classification of Diseases, Ninth Revision code 443.1) in the period spanning from 2002 to 2011 using Taiwan's National Health Insurance Research Database. We calculated the age- and sex-specific incidence and prevalence rates of thromboangiitis obliterans during the study period.

RESULTS: From 2002 to 2011, 158 patients were diagnosed with thromboangiitis obliterans; of these, 76% were men. Most (63%) of the patients were <50 years old when they were first diagnosed. After reaching 20 years of age, the incidence rate increased with age and peaked among those aged $\geqslant 60$ years. The average incidence rate of thromboangiitis obliterans during the 2002–2011 period was 0.068 per 10^5 years. The incidence of thromboangiitis obliterans decreased with time, from 0.10 per 10^5 years in 2002 to 0.04 per 10^5 years in 2011. The prevalence increased from 0.26×10^{-5} in 2002 to 0.65×10^{-5} in 2011.

CONCLUSION: This is the first epidemiologic study of thromboangiitis obliterans using claims data from a general population in Taiwan. This nationwide, population-based study found that the incidence and prevalence of thromboangiitis obliterans in Taiwan in the 2002–2011 period were lower than those in other countries before 2000. This study also revealed a trend of decreasing incidence with simultaneous increasing prevalence of thromboangiitis obliterans in Taiwan from 2002 to 2011.

KEYWORDS: Thromboangiitis Obliterans; Incidence; Prevalence.

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INTRODUCTION

Thromboangiitis obliterans (TAO) is a nonatherosclerotic, segmental, chronic inflammatory disease. TAO mainly affects the small and medium-sized arteries, veins and nerves of the arms and legs (1). Affected patients usually suffer from ischemic pain, ulcers, or gangrenous patches in the distal limbs (2). If not treated early and adequately, TAO can result in limb amputation (2). There are several diagnostic criteria for TAO. The diagnostic criteria proposed by Shionoya (3,4) in 1983 comprise an onset before the age of 50 years, a smoking history, the presence of infrapopliteal arterial occlusions, either upper limb involvement or phlebitis migrans and the lack of atherosclerotic risk factors other than smoking. In 1993, Mills & Porter (5) proposed another set of diagnostic criteria for TAO, consisting of major and minor criteria. In 1996, Papa et al. (6) suggested a point system for TAO diagnosis. In 2000, Olin JW (1) recommended another set of criteria that included an onset age <45 years with a history of current/recent smoking, the existence of distal limb ischemia proven by noninvasive vascular imaging examinations, the absence of a proximal source of emboli and the presence of coherent arteriographic findings in symptomatic and noninvolved extremities. Von Winiwarter initially defined TAO in 1879 (7), but its etiology and pathogenesis has not been elucidated to date (8). Genetic and environmental factors, particularly tobacco use, have been proposed as risk factors for TAO (9). Although little is known about the exact pathogenesis of TAO and its association with smoking (10), the withdrawal of tobacco use usually halts disease progression and remains the most important treatment to date (10). Anti-angiogenic

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activity is present in the sera of TAO patients (11). However, the efficacy of therapeutic angiogenesis has not been proven in relevant controlled trials.

TAO typically occurs in young male smokers of low socioeconomic status, with a mean age of onset of between 35 and 50 years (4,12,13). Prior epidemiologic studies have shown that TAO is more prevalent in the Middle East and the Far East than in North America and Western Europe, and its prevalence has decreased over time in developed countries (14-16). Most previous epidemiologic studies were conducted using hospital-based data (14,15,17). Although Hida & Ohta (18) reported the number of incident and prevalent cases of TAO in Japan using a nationwide registry database in 2009, they did not calculate the incidence rate and prevalence of the condition. In all patients with peripheral arterial disease, the prevalence of TAO has been reported as 0.5-5.6% in Western Europe, 15-66% in Korean and Japan, and 45-63% in India (19). Few epidemiologic studies have reported the incidence and prevalence of TAO after 2000 (20). Additionally, a paucity of epidemiologic data for TAO has been collected from the general population (21). Furthermore, the incidence and prevalence of TAO in Taiwan have never been studied. We previously conducted a nationwide, population-based epidemiologic study of common variable immunodeficiency using the Taiwanese National Health Insurance Research Database (NHIRD) (20). The aim of the current study was to investigate the prevalence and incidence of TAO during the 2002–2011 period in Taiwan using the NHIRD.

MATERIALS AND METHODS

Study design

The present study utilized a nationwide, retrospective, cohort study design.

Data source

The Taiwan government launched a compulsory, single-payer National Health Insurance (NHI) program on March 1, 1995. The NHI program covered over 98% of Taiwan's population. The National Health Research Institute handled the NHIRD and released encoded NHI-related administrative data, including outpatient, inpatient and enrollment files, for study purposes. Although comprehensive information such as medical services and drug prescriptions were included in the NHIRD, some personal information such as tobacco and alcohol use was not available. This study used multiple NHIRD datasets, including inpatient and ambulatory claims, enrollment and NHI catastrophic illness files from the 1997–2011 period.

The 1997–2011 period inpatient and ambulatory records offer data regarding date of visit/hospitalization, diagnosis, treatment and medical expenditures. Enrollment files delivered enrollment information and demographic data. The Bureau of NHI (BNHI) registered patients with catastrophic or major diseases, including some rheumatic illnesses such as rheumatoid arthritis and TAO. Their enrollment, ambulatory and inpatient claims were distributed as NHI catastrophic illness files. The BNHI issues a catastrophic illness certificate to those who have a catastrophic illness diagnosis, which is validated by at least two specialists after a careful review of a patient's original medical records. Those who are issued a catastrophic illness certificate are excused from copayment.

Study samples

Using the Taiwanese NHIRD, this study identified all TAO patients (ICD9-CM 443.1) who received a catastrophic illness certificate during the 2002–2011 period to calculate the prevalence and mortality rates of TAO. All of the deaths that occurred in patients with TAO, regardless of the cause, were used to calculate the mortality rate (i.e., all-cause mortality). To identify the incident cases, we excluded those who had received a TAO diagnosis before 2002. Age of onset was calculated based on the date of application for a catastrophic illness certificate.

Statistical analysis

We calculated the annual incidence, prevalence and mortality rates of TAO during the 2002–2011 period. We also calculated the age- and gender-specific incidence and prevalence of TAO during this period. All statistical analyses were performed using SAS statistical software, version 9.2 (SAS Institute, Cary, NC).

Ethics

The Ethics Committee for Clinical Research of Taichung Veterans General Hospital approved the study protocol. Because information about personal identification was detached from the dataset before analysis, written informed consent was not attained.

RESULTS

Table 1 and Figure 1 show the age-specific incidence rates of TAO in Taiwan. Between 2002 and 2011, 158 patients were newly diagnosed with TAO; of these, 76% were men. Two men and two women who were under 20 years in age were diagnosed with TAO. The incidence rate increased among individuals over 20 years in age and peaked at age $\geqslant$60 years. Most (63%) of the patients were diagnosed

Table 1 - Age-specific incidence of thromboangiitis obliterans in Taiwan from 2002 to 2011.

	Case number			Person-years			Incidence rate (per 10^5 years)		
Age group	F	M	T	F	M	T	F	M	T
0–9	1	2	3	19050837	20763899	39814736	0.01	0.01	0.01
10–19	1	0	1	16112069	17223717	33335786	0.01	0.00	0.00
20–29	7	20	27	20335969	19005493	39341462	0.03	0.11	0.07
30–39	1	30	31	19137215	19243068	38380283	0.01	0.16	0.08
40–49	8	29	37	17444626	17434089	34878714	0.05	0.17	0.11
50–59	5	17	22	10321223	10007057	20328281	0.05	0.17	0.11
$\geqslant$60	15	22	37	12027557	11781867	23809424	0.12	0.19	0.16

F, Female; M, Male; T, Total.
Thromboangiitis obliterans: ICD-9 code 443.1 with catastrophic illness certificate.

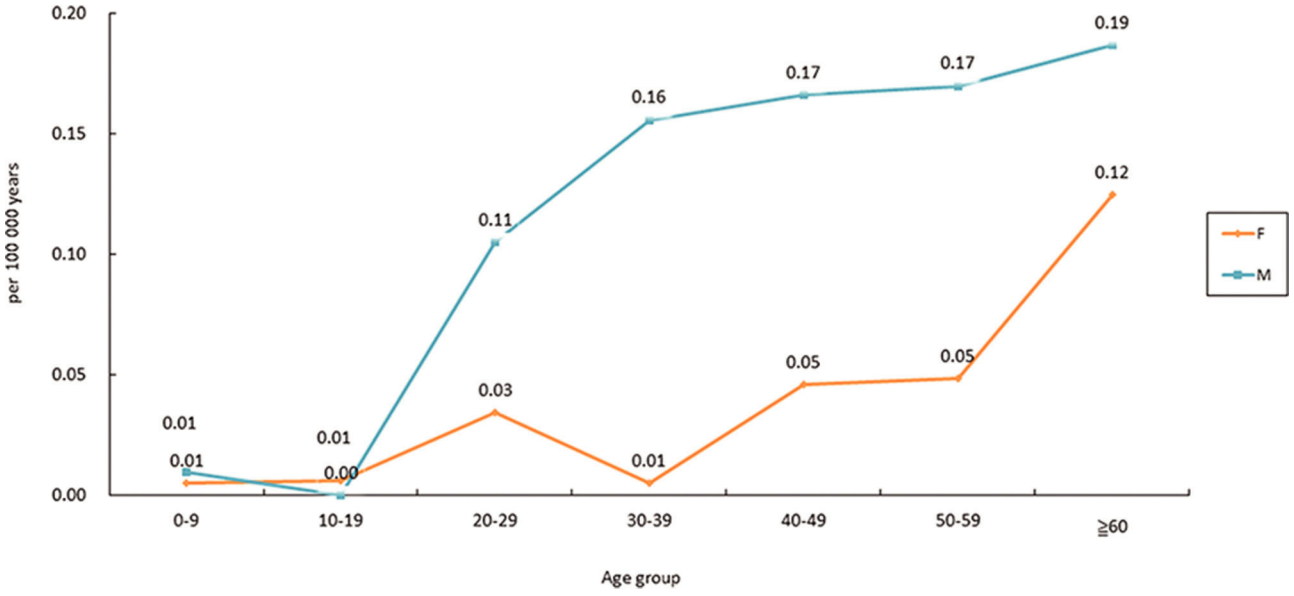

Figure 1 - Age-specific incidence of thromboangiitis obliterans in Taiwan from 2002 to 2011.

Table 2 - Incidence and prevalence of thromboangiitis obliterans in Taiwan from 2002 to 2011.

	Total population (millions)			Incidence case			Prevalence case			Death case			Incidence (per 10^5 years)			Prevalence ($\times 10^{-5}$)		
Year	F	M	T	F	M	T	F	M	T	F	M	T	F	M	T	F	M	T
2002	11.38	11.62	23.01	12	11	23	23	36	59	2	1	3	0.11	0.09	0.10	0.20	0.31	0.26
2003	11.48	11.34	22.81	1	21	22	22	56	78	1	2	3	0.01	0.19	0.10	0.19	0.49	0.34
2004	11.38	11.18	22.56	4	8	12	25	62	87	3	2	5	0.04	0.07	0.05	0.22	0.55	0.39
2005	11.71	11.48	23.18	3	14	17	25	74	99	3	3	6	0.03	0.12	0.07	0.21	0.64	0.43
2006	11.79	11.54	23.33	6	8	14	28	79	107	2	4	6	0.05	0.07	0.06	0.24	0.68	0.46
2007	11.86	11.57	23.44	5	17	22	31	92	123	4	4	8	0.04	0.15	0.09	0.26	0.79	0.52
2008	11.93	11.62	23.55	2	13	15	29	101	130	3	1	4	0.02	0.11	0.06	0.24	0.87	0.55
2009	11.97	11.59	23.56	2	9	11	28	109	137	1	4	5	0.02	0.08	0.05	0.23	0.94	0.58
2010	12.01	11.60	23.61	2	11	13	29	116	145	0	0	0	0.02	0.09	0.06	0.24	1.00	0.61
2011	12.05	11.62	23.67	1	8	9	30	124	154	2	3	5	0.01	0.07	0.04	0.25	1.07	0.65

F, Female; M, Male; T, Total.
Thromboangiitis obliterans: ICD-9 code 443.1 with catastrophic illness certificate.

before reaching 50 years in age, while 23% of the patients were diagnosed after age 60.

As shown in Table 2, the prevalence of TAO increased with time, from 0.26 $\times$ 10^{-5} in 2002 to 0.65 $\times$ 10^{-5} in 2011. On the contrary, there was a trend toward a decreasing incidence of TAO from 2002 to 2011 among both men and women. The incidence rate declined from 0.10 per 10^5 years in 2002 to 0.04 per 10^5 years in 2011. The annual average mortality rate ranged from 0% to 6.5%.

DISCUSSION

To the best of our knowledge, this study is the first population-based epidemiologic study of TAO using claims data from Taiwan. We found a trend of decreasing incidence of TAO, consistent with findings from previous studies that have investigated the epidemiology of TAO in other regions. For example, at Nagoya University Hospital in Japan, 46 new patients with TAO were hospitalized between 1985 and 1989, whereas only 12 new patients were hospitalized between 1990 and 1996 (15). The decreasing incidence rate from 2002 to 2011 in Taiwan may be attributed to improvements in socioeconomic status as well as the decreased smoking rate resulting from the implementation of smoke-free policies (15, 16). From 2002 to 2011 in Taiwan, the gross domestic product (GDP) per capita increased from 13,750 United States dollars (USD) to 20,939 USD, and the total national income (GNI) per capita increased from 14,062 USD to 21,507 USD (22). Additionally, the overall reported smoking rate decreased from 24.2% in 2004 to 16.9% in 2011 (23). Prior studies have also found an association between chronic anaerobic periodontal infection and development of TAO (24,25). We speculate that the decreasing incidence of TAO through the study period is associated with better oral hygiene. However, epidemiologic data regarding the prevalence of periodontal disease in Taiwan are not available to support this hypothesis.

The prevalence of TAO in Taiwan increased from 0.26/100,000 in 2002 to 0.65/100,000 in 2011. The prevalence of TAO in Taiwan was much lower than that estimated for the general population in North America during the 1960s through 1980s (8-13/100,000) (14,26,27). It was also lower

than that in Japan in 1985 (5/100,000) (28). However, no previous studies have reported the prevalence of TAO in the general population during the 2002-2011 period. Variations in diagnostic criteria, study period and race may partly explain the inconsistencies in the prevalence data.

Several studies have shown an increasing prevalence of TAO in women, which is considered to result from increases in smoking practices among women (12,29,30). In our study, the prevalence and incidence of TAO among women in Taiwan remained low throughout the study period. This may be explained by the fact that the smoking rate among women aged over 18 years remained low in Taiwan, being reported as 5.3% in 2002 and 4.3% in 2011 (23). Similarly, a low prevalence of TAO among women has also been found in studies conducted in Japan (28) and Hong Kong (31).

Disease onset before the age of 50 years was included in the commonly used Shionoya classification criteria for TAO (4). In our study, we found that nearly one quarter of the patients were diagnosed with TAO after reaching 60 years of age. One possible explanation for this finding is that the diagnosis of TAO was delayed by over a decade for some of the patients, which may have further caused a delay in discontinuing tobacco use and could be associated with a poorer outcome (32).

It is worth mentioning that we identified 3 patients who developed TAO before reaching 10 years of age in this study. To the best of our knowledge, only a few case reports in the literature have described the development of TAO in children (33-36).

Therefore, we cannot exclude the possibility that these cases were misdiagnosed or miscoded in the NHIRD.

A main strength of this population-based study is its minimized selection bias. However, the study also has some limitations that should be addressed. First, TAO diagnosis was based on claims data; therefore, its accuracy may be of concern. However, the enrollment of those who were issued a TAO catastrophic certificate likely increased the accuracy of diagnosis. Second, because listing in the catastrophic illness registry is not mandatory, some TAO patients who were unwilling to apply for a catastrophic illness certificate may have been neglected in our analysis, leading to underestimation of the incidence and prevalence of TAO. Third, because the NHIRD lacked information regarding cause of death, we were unable to analyze the cause of TAO-associated mortality in Taiwan. Finally, the exact age of disease onset was not accessible from the NHIRD. Some patients may not have visited doctors immediately after symptoms occurred, whereas others may have initially been diagnosed with other diseases. Therefore, we may have overestimated the age of onset in our analysis.

The current study is the first population-based study to describe the epidemiology of TAO in Taiwan using the NHIRD. The incidence and prevalence of TAO in Taiwan during the period spanning from 2002 to 2011 were lower than those in other countries before 2000. This study also revealed a trend of decreasing incidence rate simultaneous with increasing prevalence of TAO from 2002 to 2011.

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AUTHOR CONTRIBUTIONS

Chen HH is the guarantor of the integrity of the entire study and came up with the study concepts, study design and definition of intellectual content, in addition to participating in data analysis, statistical analysis, manuscript preparation, manuscript editing and manuscript review. Chen DY contributed to study concepts and manuscript editing. Lin CH contributed to study concepts, data acquisition, data analysis and statistical analysis. Chen YM contributed to study design, definition of intellectual content and clinical studies. Zheng JF performed literature research, clinical studies and manuscript preparation.

REFERENCES

1. Olin JW. Thromboangiitis obliterans (Buerger's disease). N Engl J Med. 2000;343(12):864-9, http://dx.doi.org/10.1056/NEJM200009213431207.
2. Ates A, Yekeler I, Ceviz M, Erkut B, Pac M, Basoglu A, et al. One of the most frequent vascular diseases in northeastern of Turkey: Thromboangiitis obliterans or Buerger's disease (experience with 344 cases). Int J Cardiol. 2006;111(1):147-53, http://dx.doi.org/10.1016/j.ijcard.2005.12.002.
3. Shionoya S. What is Buerger's disease? World J Surg. 1983;7(4):544-51, http://dx.doi.org/10.1007/BF01655948.
4. Shionoya S. Diagnostic criteria of Buerger's disease. Int J Cardiol. 1998;66(Suppl 1):S243-5; discussion S7, http://dx.doi.org/10.1016/S0167-5273(98)00175-2.
5. Mills JL, Porter JM. Buerger's disease: a review and update. Semin Vasc Surg. 1993;6(1):14-23.
6. Papa MZ, Rabi I, Adar R. A point scoring system for the clinical diagnosis of Buerger's disease. Eur J Vasc Endovasc Surg. 1996;11(3):335-9, http://dx.doi.org/10.1016/S1078-5884(96)80081-5.
7. Ansari A. Thromboangiitis obliterans: current perspectives and future directions. Tex Heart Inst J. 1990;17(2):112-7.
8. Malecki R, Zdrojowy K, Adamiec R. Thromboangiitis obliterans in the 21st century--a new face of disease. Atherosclerosis. 2009;206(2):328-34, http://dx.doi.org/10.1016/j.atherosclerosis.2009.01.042.
9. Berard AM, Bedel A, Le Trequesser R, Freyburger G, Nurden A, Colomer S, et al. Novel risk factors for premature peripheral arterial occlusive disease in non-diabetic patients: a case-control study. PLoS One. 2013;8(3):e37882, http://dx.doi.org/10.1371/journal.pone.0037882.
10. Sr MJ. Buerger's disease in the 21st century: diagnosis, clinical features, and therapy. Semin Vasc Surg. 2003;16(3):179-89, http://dx.doi.org/10.1016/S0895-7967(03)00023-1.
11. Hewing B, Stangl V, Stangl K, Enke-Melzer K, Baumann G, Ludwig A. Circulating angiogenic factors in patients with thromboangiitis obliterans. PLoS One. 2012;7(4):e34717, http://dx.doi.org/10.1371/journal.pone.0034717.
12. Olin JW, Young JR, Graor RA, Ruschhaupt WF, Bartholomew JR. The changing clinical spectrum of thromboangiitis obliterans (Buerger's disease). Circulation. 1990;82(5 Suppl):IV3-8.
13. Sasaki S, Sakuma M, Kunihara T, Yasuda K. Current trends in thromboangiitis obliterans (Buerger's disease) in women. Am J Surg. 1999;177(4):316-20, http://dx.doi.org/10.1016/S0002-9610(99)00046-X.
14. Lie JT. The rise and fall and resurgence of thromboangiitis obliterans (Buerger's disease). Acta Pathol Jpn. 1989;39(3):153-8, http://dx.doi.org/10.1111/j.1440-1827.1989.tb01494.x.
15. Matsushita M, Nishikimi N, Sakurai T, Nimura Y. Decrease in prevalence of Buerger's disease in Japan. Surgery. 1998;124(3):498-502, http://dx.doi.org/10.1016/S0039-6060(98)70095-9.
16. Kobayashi M, Nishikimi N, Komori K. Current pathological and clinical aspects of Buerger's disease in Japan. Ann Vasc Surg. 2006;20(1):148-56, http://dx.doi.org/10.1007/s10016-005-9436-2.
17. Lie JT. Thromboangiitis obliterans (Buerger's disease) revisited. Pathol Annu. 1988;23 Pt 2:257-91.
18. Hida N, Ohta T. Current status of patients with buerger disease in Japan. Ann Vasc Dis. 2013;6(3):617-23, http://dx.doi.org/10.3400/avd.oa.13-00012.
19. Arkkila PE. Thromboangiitis obliterans (Buerger's disease). Orphanet J Rare Dis. 2006;1:14, http://dx.doi.org/10.1186/1750-1172-1-14.
20. Tseng CW, Lai KL, Chen DY, Lin CH, Chen HH. The Incidence and Prevalence of Common Variable Immunodeficiency Disease in Taiwan, A Population-Based Study. PLoS One. 2015;10(10):e0140473, http://dx.doi.org/10.1371/journal.pone.0140473.
21. Malecki R, Kluz J, Przezdziecka-Dolyk J, Adamiec R. The Pathogenesis and Diagnosis of Thromboangiitis obliterans: Is It Still a Mystery? Adv Clin Exp Med. 2015;24(6):1085-97, http://dx.doi.org/10.17219/acem/33322.

22. Directorate General of Budget, Accounting and Statistics, Executive Yuan, Taiwan. http://engdgbasgovtw/mpasp?mp=2.
23. Taiwan tobacco control 2013 annual report. http://health99hpagovtw/educZone/edu_detailaspx?CatId=21764&Type=002&p=2. Assessed July 15, 2015.
24. Iwai T, Inoue Y, Umeda M, Huang Y, Kurihara N, Koike M, et al. Oral bacteria in the occluded arteries of patients with Buerger disease. J Vasc Surg. 2005;42(1):107-15, http://dx.doi.org/10.1016/j.jvs.2005.03.016.
25. Pavlic V V-AV, Zubovic N, Gojkov-Vukelic M. Periodontitis and Buerger's Disease: Recent Advances. Acta Inform Med. 2013;21(4):3, http://dx.doi.org/10.5455/aim.2013.21.250-252.
26. JL J. Thromboangiitis obliterans (Buerger's disease). In: JF Fairbairn JJ, JA Spittell. editor. Peripheral Vascular Diseases. 4th ed. Philadelphia: S.B. Saunders & Co.; 1972. p. 326-49.
27. De Bakey Me CB. Buerger's disease: follow-up study of World War II army cases: Springfield IL: Charles C, Thomas; 1963. p. 21.
28. S S. Buerger's disease (thromboangiitis obliterans). In: RB. R, editor. Philadelphia: WB Saunders; 1994. p. 235-45.
29. Lie JT. Thromboangiitis obliterans (Buerger's disease) in women. Medicine (Baltimore). 1987;66(1):65-72, http://dx.doi.org/10.1097/00005792-198701000-00002.
30. Mills JL, Taylor LM, Jr., Porter JM. Buerger's disease in the modern era.
31. Lau JH, Cheng JSW. Buerger's disease in Hong Kong: a review of 89 cases. Aust N Z J Surg. 1997;67(5):264-9, http://dx.doi.org/10.1111/j.1445-2197.1997.tb01960.x.
32. Piazza G, Creager MA. Thromboangiitis obliterans. Circulation. 2010;121(16):1858-61, http://dx.doi.org/10.1161/CIRCULATIONAHA.110.942383.
33. Geisler E, Viehweger G, Schippan D. [Cerebrovascular processes in children. Contribution to cerebral thromboangiitis obliterans in childhood]. Helv Paediatr Acta. 1965;20(5):476-89.
34. Bologa S, Lustig T. Thromboangiitis obliterans with rickettsial etiology in children. Pediatria (Bucur). 1966;15(1):57-60.
35. Charles-Edouard D, Fernandez de Castro A. Thromboangiitis obliterans in a young girl. Angiologia. 1971;23(3):113-6.
36. Marandian MH, Saboury-Deilami M, Rakchan M, Lessani M, Behvad A, Grouhi M. Thromboangiitis obliterans and distal gangrene in a 5-year-old child. Pediatrie. 1985;40(8):653-7.