Pearls & Oy-ster: Primary Cerebral Buerger Disease: A Rare Differential Diagnosis of Stroke in Young Adults

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Pearls

- Buerger’s Disease (Thromboangiitis obliterans, TAO) typically occurs in young males aged below 40 to 45 years who have a history of heavy tobacco use.
- The involvement of small and medium-sized vessels with normal proximal arteries and corkscrew-like collaterals in proximity to occluded arteries are angiographic features of TAO.
- Cessation of tobacco use is mandatory to stop disease progression and recurrent strokes.

Oy-sters

- Other causes of distal emboli and occlusions must be excluded for diagnosis of TAO.
- The corkscrew-like collaterals may be missed or misinterpreted on computed tomography or magnetic resonance angiography.
- A primary cerebrovascular manifestation without peripheral vascular ischemic complications is rare but possible.
Case report

A 41-year-old man presented with acute left upper motor neuron facial palsy and dysarthria. He had a past medical history of recurrent ischemic strokes at the age of 26 and 35 years with residual minor right hemiparesis and coordination deficits. Previous strokes were classified as embolic stroke of undetermined source and secondary prevention with acetylsalicylic acid was initiated. The patient had no vascular risk factors except being a heavy smoker (>20 cigarettes/day) for 25 years. Besides occasional marijuana smoking he did not have any illicit drug abuse. He also had no family history of stroke, autoimmune conditions or cancer.

Diffusion weighted and Fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging revealed acute infarction in the right (Figure 1 A) and chronic infarction in the left middle cerebral artery territory (Figure 1 B). We performed a comprehensive etiological work-up including serological screening for coagulopathies and Fabry’s disease, drug screening, Duplex-ultrasound of extracranial and intracranial arteries, cardiac work-up including Holter electrocardiogram for 72 hours and transthoracic and transesophageal echocardiography which were all unremarkable and particularly ruled out patent foramen ovale as potential cardioembolic stroke mechanism.

As Time-of-flight (TOF) angiography showed no occlusion of proximal arteries but prominent small vessels in the right anterior cerebral artery territory (Figure 1 C) suggesting arterio-venous malformation (AVM), we decided to perform a digital subtraction angiography (DSA) which ruled out AVM but revealed multiple stenoses and occlusions of distal cerebral arteries surrounded by corkscrew-like collateral vessels (Figure 1 D-F). In retrospect, these corkscrew-like collaterals originating from
the right anterior cerebral artery (Figure 1D) could already be seen on the TOF images (Figure 1C).

With the suspicion of cerebral vasculitis we performed antibody screening for systemic vasculitis including antineutrophil cytoplasmic-(ANCA), anti-nuclear-(ANA), extractable nuclear antigens-(ENA-A), cardiolipin- and anti-double stranded DNA antibodies (Anti-dsDNA) with negative results. Cerebrospinal fluid analysis was completely unremarkable (cell-count 3 Mpt/l [reference <5], protein-level 388 mg/l [150-450 mg/l], glucose 3.56 mmol/l [2.8-4.4 mmol/l], lactate 1.66 mmol/l [1.3-2.4 mmol/l]) including antigen-tests for Lyme’s disease, neurosyphilis and herpes simplex virus and varicella zoster virus polymerase chain reaction. We further discussed leptomeningeal biopsy which was declined by the patient.

Based on the absence of other stroke etiologies, DSA results, age and smoking status we suspected Buerger’s Disease (Thromboangiitis obliterans, TAO) as stroke etiology. Consistently, Doppler ultrasound of lower extremities showed hitherto clinically asymptomatic occlusions of crural arteries bilaterally which were confirmed by DSA. The patient did not report any Raynaud’s phenomenon, extremity pain or ischemia. Antibody testing showed G-protein receptor auto-antibodies directed against α1-receptor and endothelin A-receptor. Levels of erythrocyte sedimentation rate (ESR 4 mm/1h [reference <15 mm/1h]) and C-reactive protein (CRP 0.7 mg/l [<5.0 mg/l]) were within normal limits.

With the diagnosis of TAO we strongly recommended cessation of tobacco and cannabis abuse. The patient received oral varenicline medication and was referred to our smoking cessation outpatient clinic and stroke follow-up program. At discharge, the patient had recovered from facial palsy and dysarthria. The patient reduced (<5 cigarettes/day) but did not quit smoking after three months of follow-up. During this
time course, he had no further cerebral or peripheral vascular ischemic complications.

Discussion

Buerger’s Disease, first described in 1879 and allocated to its current denotation in 1908, is a non-atherosclerotic segmental inflammatory disease affecting small to medium-sized arteries and veins, most commonly of the lower and upper extremities. \(^1,2\) Involvement of other vascular territories has also been reported.\(^3\) Cerebrovascular involvement in Buerger’s disease is infrequent but clinical, angiographic and pathological demonstration has been reported.\(^4,5,6\) Historical neuropathological data proposed two types of cerebral TAO: Type 1 associated with large artery changes and type 2 associated with medium and small artery changes.\(^6\)

TAO typically occurs in young males aged below 40 to 45 years who have a history of chronic and substantial smoking.\(^7\) The involvement of small and medium-sized vessels with normal proximal arteries and corkscrew-like collaterals in the proximity to occluded arteries are angiographic features of TAO.\(^3\) These features and exclusion of other causes for distal embolization or occlusion are the major diagnostic criteria of TAO.\(^3,7\) Histology is the gold standard to establish a definitive diagnosis but is seldom used in clinical practice due to the risk associated with biopsy.\(^8\) Additionally, a biopsy is rarely needed for diagnosis unless the patient presents with unusual characteristics.\(^3\)

The pathogenesis of TAO remains unclear. There is strong evidence that smoking is crucial for onset and progression of the disease.\(^3,8\) An underlying immune-mediated mechanism is discussed. In detail, immunocompetent cells, elevated pro- and anti-
inflammatory cytokines and various kinds of auto-antibodies including anti-endothelial antibodies, antibodies directed against vessel wall structures such as elastin and collagen, anticardiolipin antibodies, and antineutrophil cytoplasmic antibodies have been identified in patients with TAO.3,8,9

Although widely used, there is no proven evidence for the use of steroids or platelet function inhibitors such as acetylsalicylic acid in TAO.9,10 Recently, agonistic auto-antibodies directed against G-protein coupled receptors associated with prolonged vasoconstriction were found in 9 out of 11 patients with TAO and preliminary studies of immunoadsorption treatment showed promising therapeutic results in advanced disease.8,9 In line with these data, α1-receptor and endothelin A-receptor auto-antibodies were identified in our patient and we discussed an immunoadsorption therapy. However, immunoabsorption was deferred as the patient struggled with smoking abstinence, which should be a precondition for this costly off-label therapy. Randomized controlled trials assessing the effectiveness of immunoabsorption and pharmacological agents are needed.10

The risk of vascular events and limb amputation is significantly higher in patients who continue smoking whereas the only proven treatment strategy to prevent progression of the disease is its complete discontinuation.3,9 We found no studies investigating long-term outcome of TAO with cerebrovascular involvement. In a previous case report of cerebral TAO, the patient stopped smoking and was free of symptoms during 1 year of follow-up.4

In conclusion, this case report should raise awareness for TAO as a rare etiology of stroke in young adults. TAO should be considered in young stroke patients with a significant history of smoking. A primary cerebrovascular manifestation without peripheral vascular ischemic complications is rare but possible. Cessation of tobacco
use is mandatory to stop disease progression and recurrent strokes. At current, there is no evidence-based causative therapy.
References


Figure legend

Figure 1. Imaging findings of cerebrovascular Buerger’s Disease.

Diffusion weighted imaging of the brain (A). Arrows indicate acute infarction in the right middle cerebral artery territory (rostral insular and operculum). FLAIR imaging of the brain (B). Arrows indicate chronic infarction in the left middle cerebral artery territory (frontal region). TOF angiography (C) of the cerebral arteries. The label indicates prominent vessels originating from the right anterior cerebral artery. Maximum intensity projection images of three-dimensional rotational angiography (D). The magnification indicates corkscrew-like collateral vessels in the proximity to an occluded branch of the right anterior cerebral artery. Cerebral angiograms of the anterior and left middle cerebral arteries (E) and the posterior cerebral arteries (D). Arrowheads and magnification indicate corkscrew-like collateral vessels next to occluded vessels.
## Appendix 1: Authors

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