We report a case of progressive multifocal intracranial distal arterial branch occlusive disease in a young adult who smoked heavily and used oral contraceptives. The distribution of the angiographic lesions and the associated telangiectasias and rete mirabile resemble Moya-Moya disease except for clearly absent proximal carotid arterial disease. This type of distal multifocal cerebral arterial occlusive pattern appears to be a very rare manifestation of cigarette and oral contraceptive use. The patient has remained without symptoms for >3 years off oral contraceptives and cigarettes and on antiplatelet agents. (Stroke 1987;18:519-523)
intact. Neuropsychological testing revealed a mild constructional dyspraxia and severely deficient short and long-term visual retention. She had numerous difficulties with cognitive tasks, especially with delayed recall of verbal and visual stimuli. Her cranial nerve examination was remarkable for a subtle right homonymous hemianopia, upper motor neuron weakness of the right face, and poor initiation of saccades. Motor exam revealed subtle increased tone and dysdiadochokinesis in the right upper extremity. Her reflexes and power were normal. Sensory exam showed mild decreased graphesthesia on the right hand.

Serum chemistries, complete blood count and differential, platelet count and morphology, coagulation studies, urinalysis, serum protein electrophoresis, triglycerides, cholesterol, lipoprotein electrophoresis, fibrinogen, VDRL, ANA, complement factors, rheumatoid factor, blood culture, serum viscosity, and sedimentation rates were normal. Chest x-ray and ECG were normal. Skin tests for tuberculosis were unreactive without anergy to controls. CSF analysis revealed a protein of 45 mg/dl, glucose 60 mg/dl (serum 89 mg/dl), 0 cells, IgG of 5.3 mg% (nl = 0-4.7 mg%), albumin 51.1 g/dl (nl = 5-33 g/dl), no oligoclonal banding, and a myelin basic protein of 2.6 ng/ml (0-5.1 ng/ml). CSF cultures and VDRL were negative. Two-dimensional and M-mode echocardiography and visual and brainstem evoked responses were normal. A phenobarbital level was 15 /g/ml. Head computed tomography scan revealed a small contrast-enhancing lucency in the left temporo-occipital junction immediately posterior and inferior to the atrium of the left lateral ventricle. There was a suggestion of small lucencies in the posterior portion of the left thalamus and posterior limb of the left internal capsule.

Four-vessel cerebral angiography revealed multiple occlusions of the secondary frontoparietal branches of the left middle cerebral artery (MCA) (Figure 1). Several frontal secondary and tertiary branches of the left MCA and anterior cerebral artery were occluded. Lush transthalamic and transpial collateralizations (telangiectasias and rete mirabile) were seen. Multiple tertiary branches of the right MCA and anterior cerebral artery also showed similar occlusions with transpial collateralization. Larger arteries at the base of the brain, the arch, and the neck were spared. Leptomeningeal biopsy was considered; however, the patient declined. Platelet function during admission revealed increased aggregation of platelets spontaneously using the optical density technique with adenosine diphosphate as the stimulus (Bom's method).

The patient was placed on aspirin, 325 mg/day, and dipyridamole, 25 mg t.i.d., and maintained on phenobarbital, 60 mg q.h.s. She stopped smoking. She has remained without symptoms, including seizures, for >3 years and has gradually improved in all areas of her neurologic deficits. Repeat platelet aggregation studies on therapy showed hypoaggregability of her spontaneous and induced aggregation parameters.

Discussion

To our knowledge, this is the first reported case of an atypical Moya-Moya pattern of multifocal, solely intracranial, distal branch arterial occlusive disease with telangiectasias associated with cigarette and OC use. In the vast majority of Moya-Moya cases, the supraclinoid internal carotid artery and major branches of the MCA show prominent occlusion evidence of hyperaggregable platelets, specific etiology, or pathologic processes. Atypical Moya-Moya disease has been seen previously in ischemic disease and arteriosclerotic disease.

Some authors believe this angiographic pattern results from slow arterial occlusions of the circle of Willis with subsequent proliferation of collateral arteries. Hilal and coworkers demonstrated telangiectasia of vessels in the basal ganglia functioning as transcerebral collaterals to the leptomeningeal branches of the MCA. They felt that this hypervascularity was favored by the young ages of the patients and the gradual nature of the arterial stenosis. Our patient's pattern of secondary and tertiary branch occlusion of the left MCA with total sparing of the carotid, circle of Willis, and proximal MCA vessels is highly atypical and quite uncharacteristic of the classic descriptions of Moya-Moya disease. The collateralization and rete mirabile "puff of smoke" pattern distally are very characteristic of Moya-Moya, although telangiectasia is not diagnostic. Our case, then, suggests that occlusive carotid arterial disease proximal to the circle of Willis is not necessary for the appearance of rete mirabile.

Okawara and Calkins described 2 young women with ischemic stroke associated with OC use and angiography resembling classic Moya-Moya disease including proximal large vessel disease. One had abnormal platelet studies, hyperfibrinogenemia, and hypertriglyceridemia attributed to the OC. No note was made of smoking history.

Migraine accompaniments or equivalent as the only explanation for our patient's strokes is probably untenable. There was no case history or family history of migraine. She had associated seizures, and this angiographic pattern has not been reported with migrainous infarction. There was no laboratory or angiographic evidence for vasculitis. Further, she had a relatively benign clinical course, absence of confusion and prominent headache, and an asymptomatic follow-up period of >3 years without specific antivasculitis therapy. The mildly elevated CSF IgG may be seen as a response to a heterogeneous group of CNS insults, including cerebral ischemia. There was also no systemic, auscultative, ECG, or echocardiographic evidence of a cardiac embolic source. Accelerated atherosclerotic cerebrovascular disease was not supported by laboratory or angiographic data.

Kalendovsky and coworkers described 4 young patients with cerebrovascular occlusions and increased
FIGURE 1. Lateral (A) and frontal (B) views of left common carotid arteriogram show multiple tangles of tiny collateral vessels (bold arrows) resulting from branch occlusions. Anterior cerebral artery is occluded and reconstituted at point marked by crossed arrow. A generalized paucity of peripheral branch filling is most noticeable in the anterior parietal territory (star in A). Internal carotid artery and proximal main trunks of the anterior cerebral and middle cerebral arteries are not involved (arrowheads in B). Proximally stenosed left posterior cerebral artery (open arrows in A) is reconstituted by the anterior choroidal artery and was the only involved portion near the circle of Willis, all other disease being more peripheral.
platelet aggregability. Three patients had a history of OC use; 3 also had associated vascular headaches for some years prior to their first occlusive event. Angiograms were described as showing proximal internal carotid or MCA occlusions or luxury perfusion without abnormal blood vessels. Al-Mefty and coworkers reported 22 cases of transient ischemic attacks with increased platelet aggregation and adheresiveness, excluding those with other complicating pathology (including OC use). In 2 cases, aged 12 and 18 years, angiography revealed multiple occlusions of small branches of the MCA.

Preliminary data suggest that even 2 cigarettes smoked in succession can increase platelet stickiness, though these authors were measuring adheresiveness, not aggregability. Subsequent results have been conflicting concerning smoking and increased platelet aggregation. Small studies of immediate effects suggest an increased platelet activation with smoking, while data from other investigators increase, including the most recent and extensive prospective study to date. Our patient had a 2-3 pack-a-day cigarette history for several years prior to her initial presentation. Smoking is an independent risk factor for stroke, although it is unclear that this is necessarily responsible for the increased platelet aggregability in our patient.

Increased platelet aggregation. Our patient was off OC for approximately 2 weeks when the initial platelet hyperaggregability was found. The exact length of time that OC influence platelet activity after discontinuation has not been established. The etiology of our patient's platelet hyperaggregability is probably related to some combination of cigarette smoking, OC use, and ischemia, or less likely, a primary platelet disorder. How OC and cigarettes multiply each other's risk for thromboembolic disease, including stroke, has not been established.

Specific coagulation abnormalities apart from platelet hyperaggregability have been described in association with OC use. These include elevated Factor VIII, fibrinogen, and plasminogen as well as reduced antithrombin III and fibrinolytic activator activity. Cerebral angiographic abnormalities associated with OC use and stroke include predominantly proximal large vessel stenosis, "heaping," or occlusion in both the anterior and posterior circulations. Moya-Moya pattern may also be seen. Pathologically, intimal hyperplasia of the carotid artery and MCA with or without thrombosis has been described. Anti-estrogen antibodies have been detected in women taking OC. These antibodies may be found from the third week of OC use and for months, if not years, after OC are discontinued. The development of these antibodies occurs in 90% of patients on OC with thromboembolism. These antibodies may provide further insight into the pathophysiological mechanisms of OC-related stroke.

Treatment with aspirin and dipyridamole in conjunction with the discontinuation of cigarette smoking and OC use to date has been successful for > 3 years, consistent with the presumed etiology. Our patient discontinued her antiplatelet therapy and has been asymptomatic for 6 months and is still off OC and cigarettes, making a primary platelet disorder somewhat less likely. Subsequent platelet function testing off therapy, OC, and cigarettes was not performed. If the platelet hyperaggregability was involved in causing rather than resulting from the cerebral ischemia, OC use, and cigarette smoking, then an acquired platelet abnormality may be one factor in multifocal distal cerebral arterial branch occlusions.

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References


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