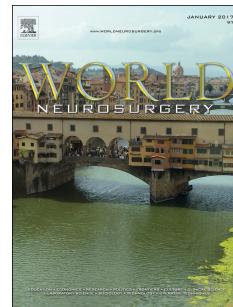


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## A RARE CASE OF POSTINFECTIOUS MOYAMOYA SYNDROME: CASE REPORT AND REVIEW OF THE LITERATURE

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# A RARE CASE OF POSTINFECTIOUS MOYAMOYA SYNDROME: CASE REPORT AND REVIEW OF THE LITERATURE

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## ABSTRACT

### Background

Postinfectious Moyamoya syndrome (MMS) is a rare vasculopathy that can follow a meningitis. Only 9 cases of MMS following a meningitis have been reported in literature. We present a unique case of MMS after a meningitis caused by *A. fumigatus* and *E. coli* and review all cases of MMS post-meningitis in literature.

### Case Description

A 41 years-old man was admitted to our Emergency department for sudden hypoesthesia in left arm and an intense headache not responsive to drugs. The CT scan and the MRI showed acute ischemic lesions in the right centrum semiovale associated to bilateral chronic watershed cerebral ischemic lesions. The cerebral DSA documented a typical Moyamoya pattern. In anamnesis, the patient suffered from meningitis due to *A. fumigatus* and *E. coli* infection after neurosurgery for subependymoma of the fourth ventricle two years before. Lab tests, clinical investigation and imaging ruled out any other cause of vasculopathy and led to the final diagnosis of postinfectious MMS. The patient started a medical therapy with oral acetyl salicylic acid, verapamile and prednisone while surgical approach was excluded in the first instance.

### Conclusions

Physicians should be aware of an uncommon but severe complication of meningitis such as MMS, even several years after the infection. Neuroimaging is essential for the diagnosis and to exclude other causes of neurological symptoms in these patients.

## CASE REPORT

A 41years-old man was admitted to our Emergency department for an intense headache not responsive to drugs. Two-years before, the Patient underwent a neurosurgical operation for a subependymoma of the fourth ventricle; in the early post-operative period, he developed a meningitis related to *Aspergillus fumigatus* and *Escherichia Coli* successfully treated with specific antibiotic and antimycotic drugs.

Physical examination demonstrated only a mild hypoesthesia in left arm. The CT scan showed multiple hypodensities in the white matter of both cerebral hemispheres. The MRI disclose two acute ischemic lesions in the superior temporal gyrus and in the supramarginal gyrus in the right hemisphere, associated to bilateral chronic watershed cerebral ischemic lesions. Bilateral severe stenosis of the distal ICA, the M1 segments of MCA and the A1 segments of ACA were identified at the MR-angiography. Vessel wall MR-study excluded atherosclerotic disease, proving only a mild concentric wall thickening of bilateral distal segments of ICAs (Fig.1).

The DSA showed a typical Moyamoya pattern with occlusion of both the distal ICA, the M1 segments, and the A1 segments with the presence of tangle of tiny vessels (“puff of smoke”) along the course of lenticulo-striatal arteries; leptomeningeal and trans-dural collateral networks was also detected; posterior circulation was spared from the disease (Fig. 2).

Several lab tests were run to identify the cause of this vasculopathy. Blood count, coagulative screening and inflammatory indexes were normal. Cerebrospinal fluid analysis including infective searches were negative. Active infections of the central nervous system, such as EBV, CMV, HSV 1-2, VZV, Measles Virus, Rubella Virus, Mumps Virus, Echovirus, Toxoplasma, *Borrelia Burgdorferi*, JCV, Enterovirus and *Mycobacterium tuberculosis* were ruled out.

Serum autoantibodies (rheumatoid factor, ANA, cANCA, pANCA, anti-ENA, anti-dsDNA, anti-RNP, anti-transglutaminase, anti-gliadin and anti-endomysium) were investigated and an autoimmune origin was excluded.

Finally, the genetic test for R4018K polymorphism of gene RNF213 was performed, but it was negative in the patient.

Therefore, since the absence of inflammatory or infectious signs, the history of meningitis and the clear imaging of Moyamoya pattern, we reached the diagnosis of postinfectious Moyamoya syndrome (MMS) due to previous meningitis caused by *A. Fumigatus* and *E. Coli* (Fig. 3).

According to the few data in literature, surgical approach (direct or indirect re-vascularization) was excluded in first instance and the patient started a medical therapy with oral acetyl salicylic acid, verapamil and prednisone.

Clinical and MRI follow-up was performed at 3, 9 and 18 months. At 3 months, the patient was asymptomatic (modified Rankin Scale 0) despite MR imaging demonstrated new small ischemic lesions in acute phase in the watershed areas of the right hemisphere. 9 and 18 months follow-up showed stability of the clinical course and MRI findings. According to the good clinical course, surgical treatment is still excluded. Patient is currently continuing the medical therapy with acetyl salicylic acid and verapamil.

## DISCUSSION AND LITERATURE REVIEW

Moyamoya vasculopathy is a rare disease characterized by a progressive stenosis or occlusion of the intracranial internal carotid artery (ICA) and/or the proximal portion of the anterior cerebral artery (ACA) and middle cerebral artery (MCA). This steno-occlusive pattern is associated with a compensatory development of a collateral networks from thalamoperforating and lenticulostriate arteries, appearing as a “puff of smoke” on conventional angiography (“moyamoya” in Japanese). Beside these, pial collateral arteries

from the posterior circulation and transdural collateral arteries, most often from external carotid artery's (ECA) branches, can be found. At late stages of the disease, ICAs are totally occluded and anterior parenchymal vascularization relies essentially on these collateral networks.<sup>1</sup>

We distinguish between Moyamoya disease (MMD), which refers to isolated and primary Moyamoya vasculopathy, and Moyamoya syndrome (MMS), when the typical vascular alterations are secondary to other neurological or extra-neurological pathologies.

In US, the annual incidence rate of MMD/MMS is 0.086/100,000 persons, about ten times lower than in East Asian countries; instead the incidence of MMS seems to be higher in Western countries than in East Asian countries.<sup>1</sup>

Clinical presentation is usually characterized by transient or permanent symptoms related to cerebral ischemia (caused by the steno-occlusive vascular lesions), or intracranial hemorrhage (due to the rupture of fragile Moyamoya vessels): hemiparesis, sensory impairment, aphasia/dysarthria or migraine-like headache are the most common ones.

Diagnosis of Moyamoya vasculopathy is based on imaging by the visualization of distal stenosis of one or both internal carotid arteries and/or their branches (ACA and MCA), and the presence of neovascularization represented by Moyamoya vessels and collateral circulation. MRI has a key role in the diagnosis and follow up, but the gold standard is cerebral conventional angiography, which essential both for the diagnosis and grading of the disease.<sup>2</sup>

Once the diagnosis is reached, it is fundamental to rule out all the potential acquired causes of MMS, even if it is often difficult to determine whether the association is causal or incidental. Therefore it is important a rigorous interview of the patient, detailed physical examination, and a set of complementary lab tests in order to identify the main causes of MMS. Among these, previous cranial or neck irradiation is the most frequent associated cause, followed by previous meningitis (especially *Mycobacterium tuberculosis* meningitis), cerebral vasculitis,

autoimmune disease (Syogren's syndrome, lupus anticoagulant), prothrombotic disorders, haematological diseases (sickle cell anaemia, haemolytic anaemia, aplastic anaemia), metabolic diseases (glycogen storage disease type 1, hyperlipoproteinemia type 2A, hyperthyroidism), genetic/chromosomal disorders (neurofibromatosis, Down's syndrome, tuberous sclerosis, retinitis pigmentosa and fibromuscular dysplasia), drugs (phenobarbital and oral contraceptives), neoplasms (craniopharyngioma and Wilm's tumour), and cranial trauma.<sup>3</sup>

The pathogenesis of postinfectious vasculopathy is unknown. Several mechanisms have been proposed: inflammatory infiltration (vasculitis) due to the infective agent with reactive vasospasm and residual organic stenosis; an autoimmune process towards the cerebral blood vessels triggered by the infection (therefore host susceptibility to autoimmune disease may be considered); intravascular thrombosis, even if it has not been a frequent finding.<sup>3,4</sup>

Pathological analysis of the affected vessels is characterized by a concentric and eccentric fibrocellular thickening of the intima, leading to lumen stenosis, while inflammatory or atherosclerotic changes are absent. Electronic microscopy has shown myonecrosis involving the vasa vasorum that may explain the structural abnormalities.<sup>5</sup>

Only 9 cases of MMS following a meningitis have been reported in literature (table 1).

Mycobacterium tuberculosis was isolated in 4 patients,<sup>6-9</sup> Streptococcus pneumoniae in 3 patients,<sup>3,4,10</sup> Treponema pallidum and Haemophilus influenzae type C in one case each.<sup>5,11</sup> We found no reports of similar cases caused by Escherichia Coli or Aspergillus Fumigatus in the literature of the PubMed database.

Time between meningitis and the onset of Moyamoya pattern was extremely variable. In 1 patient Moyamoya pattern developed in 30 days, in 4 patients between 1-12 months, and in 4 patients after one year (as our case); in the latter group, the infectious agent involved was the Mycobacterium tuberculosis. In particular, Kashiwagi et al,<sup>6</sup> Nakayama et al,<sup>7</sup> Kitahara et al,<sup>8</sup> respectively reported 3 cases of MMS following a meningitis by M. tuberculosis occurred in

Japan; all the patients suffered of meningitis during the childhood and MMS became symptomatic more than 20 years later. Two of them presented with ischemic symptoms and one with intraparenchymal hemorrhage. Umesh et al<sup>9</sup> presented the other case of MMS related to M. tuberculosis and even in this case the vascular alterations arose many years later (9 years) than meningitis.

Migraine-like headache was the most frequent symptoms at the onset of MMS (4 patients), followed by hemiparesis (3 patients) and seizures (2 patients).

All cases showed bilateral involvement of the anterior cerebral circulation. Involvement of posterior circulation was present in 7 cases, 3 of which were consequent to Streptococcus pneumoniae meningitis.

3 patients developed a rapidly worsening of the clinical conditions and died in a few months. 2 out of 3 cases the microorganism involved was S. pneumoniae;<sup>4,10</sup> the other was T. pallidum.<sup>11</sup>

Pathological analysis of the vessels was performed in 2 patients: both the authors described the absence of inflammation or atherosclerosis changes in the vessels' wall but a diffuse collagenosis involving the periadventitial tissue, such as a chronic vascular injury.<sup>4,5</sup>

Out of the 9 patients, 4 were medically treated with antiplatelet drugs, anticoagulants and/or corticosteroids, with variable efficacy observed. Concerning the therapy, no guidelines are currently available. Medical treatment with long-term oral antiplatelet therapy is usually started, even if there is no demonstrated data of its efficacy. Surgical treatment, based on direct or indirect revascularization, should be considered on case-by-case basis. Up to now, no curative treatment allows the regression of the occlusive arterial lesions, therefore clinical and imaging follow-up must be always continued, even because of the high risk of angiopathy progression.<sup>1</sup>

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## **DECLARATIONS OF INTEREST**

None.

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## REFERENCES

1. Guey S, Tournier-Lasserve E, Hervé D, et al. Moyamoya disease and syndromes: from genetics to clinical management. *Appl Clin Genet*. 2015 Feb 16;8:49-68.
2. Tarasów E, Kułakowska A, Łukasiewicz A, et al. Moyamoya disease: *Diagnostic imaging Pol J Radiol*. 2011 Jan-Mar; 76(1): 73–79.
3. Pinardi F, Stracciari A, Spinardi L, et al. Postpneumococcal Moyamoya syndrome case report and review of the postinfective cases. *BMJ Case Rep*. 2013; 2013: bcr2012006726.
4. Czartoski T, Hallam D, Lacy J, et al. Postinfectious vasculopathy with evolution to moyamoya syndrome. *J Neurol Neurosurg Psychiatry*. 2005 Feb; 76(2): 256–259.
5. Palacio S, Hart RG, Vollmer DG, et al. Late-developing cerebral arteropathy after pyogenic meningitis. *Arch Neurol*. 2003 Mar;60(3):431-3.
6. Kashiwagi S, Abiko S, Harada K, et al. Ischemic cerebrovascular complication in tuberculous meningitis; a case of Fröhlich syndrome and hemiparesis. *No Shinkei Geka*. 1990 Dec;18(12):1141-5.
7. Nakayama Y, Tanaka A, Nagasaka S, et al. Intracerebral hemorrhage in a patient with moyamoya phenomenon caused by tuberculous arteritis: a case report. *No Shinkei Geka*. 1999 Aug;27(8):751-5.
8. Kitahara M, Kaneko U, Fujiwara S, et al. A case showing angiographically moyamoya vessels combined with intracranial calcification. *No Shinkei Geka*. 1986 Mar;14(3 Suppl):367-72.
9. K Umesh, K Shilpa. A very rare case report of late presentation of Moyamoya syndrome in a child with history of tubercular meningitis. A case report. *The Internet Journal of Neurology*. 2008 Volume 12 Number 1.
10. Dou Z, Chen H, Cheng H, et al. Moyamoya syndrome after bacterial meningitis. *Pediatr Invest*. 2018;2:134-136.

11. Morgello S, Laufer H. Quaternary neurosyphilis in a Haitian man with human immunodeficiency virus infection. *Hum Pathol*. 1989 Aug;20(8):808-11.

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**FIGURE LEGEND**

Fig.1: MRI on admission: Axial FLAIR (A), T2-weighted (B) and DWI (C) images show bilateral chronic watershed cerebral ischemic lesions. Axial and sagittal T2-weighted (D, E) images demonstrate wall thickness of petrous and cavernous segments of the right ICA. Axial pre (F) and post contrast (G) SPIR T1-weighted black blood images prove concentric wall thickness of petrous segments of the right ICA and homogenous enhancement of the vessel wall after contrast. MR-angiography (H, I): coronal and sagittal reconstructions TOF MIP images evidence bilateral severe stenosis of distal ICA (right>left), M1 and A1 segments.

Fig.2: Cerebral DSA: right (A) and left (B) CCA injections show a typical Moyamoya pattern with occlusion of both the distal ICA, M1 and A1 segments, the presence of tangle of tiny vessels (“puff of smoke”) and leptomeningeal and trans-dural collateral circulation from the ECA. Right vertebral artery injection (C) proves normal appearance of posterior circulation and the existence of leptomeningeal collateral vessels from both PCAs. Left ECA injection (D) evidences leptomeningeal and trans-dural collateral circulation, in particular from MMA. Lateral projection of left ICA (E).

Fig.3: MRI before neurosurgery (A, B): coronal and axial post contrast T1-weighted MIP images show normal appearance of cerebral circulation. MRI at MMS onset (C, D): coronal and axial post contrast T1-weighted MIP images prove bilateral severe stenosis of distal ICA, M1 and A1 segments.

REFERENCE	INFECTIVE AGENT	AGE OF MENINGITIS	TIME OF MMS ONSET	SYMPOMTS AT MMS ONSET	CEREBRAL ANGIOGRAPHY
Czartosky et al <sup>4</sup>	<i>S. pneumoniae</i>	20 yo	9 days	left hemiparesis, right 3rd nerve palsy	stenosis of left M1 and left A1; involvement of posterior circulation
Dou et al <sup>10</sup>	<i>S. pneumoniae</i>	2 yo	5 months	seizures, coma	bilateral stenosis of ICA and M1, involvement of posterior circulation
Pinardi et al <sup>3</sup>	<i>S. pneumoniae</i>	55 yo	3 months	headache, left paresthesia	bilateral stenosis of A1, M1 and ICA, involvement of posterior circulation
Palacio et al <sup>5</sup>	H.I. type C	51 yo	2 months	headache	bilateral stenosis of ICA and M1, involvement of posterior circulation
Morgello et al <sup>11</sup>	<i>T. pallidum</i> in HIV	22 yo	10 months	headache, impaired vision	bilateral stenosis of A1, M1 and ICA, involvement of posterior circulation
Umesh et al <sup>9</sup>	TBC	1 yo	9 years	seizures	bilateral stenosis of ICA and M1, involvement of posterior circulation
Kashiwagi et al <sup>6</sup>	TBC	childhood	more than 20 years	left hemiparesis	bilateral stenosis of A1, M1 and ICA
Nakayama et al <sup>7</sup>	TBC	2 yo	40 years	headache	bilateral stenosis of ICA
Kitahara et al <sup>8</sup>	TBC	10 yo	26 years	left paresthesia, left hemiparesis	stenosis of right ICA, left M1; involvement of posterior circulation
Our Case	<i>E.coli</i> , <i>A.fumigatus</i>	39 yo	2 years	headache	bilateral stenosis of A1, M1 and ICA

