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LETTER TO THE EDITOR

# Moyamoya disease and paranoid schizophrenia: Causality or casualty

*Dear Editor:*

Moyamoya disease is a rare cerebrovascular disease, commonly presented as neurologic deficits. We describe a challenging case of a woman with a medical history of paranoid schizophrenia, who presented with a psychotic episode and was finally diagnosed with moyamoya disease. The greatest risk is a diagnostic delay due to the absence of typical neurological symptoms of moyamoya disease.

A right-handed Argentinian (Korean parents) female in her late 20s, a former smoker (10 pack-year), experienced a first-episode psychosis consisting of paranoid delusion and sensory-perceptual alterations. She underwent a cranial computed tomography (CT) scan, which was normal. At the time, she was diagnosed with paranoid schizophrenia and received treatment with aripiprazole improving positive psychotic symptoms, although complete remission was not achieved. Previously, as a teenager she had already experienced olfactory reference syndrome, religious and theft delusions and restrictive eating patterns, causing significant affective consequences but having a satisfactory overall functioning.

She was free of new psychotic episodes until 7 years later, when she was admitted to our psychiatry unit with a 2-month history of delusional jealousy based on psychotic interpretations of neutral stimuli, accompanied by auditory hallucinations, emotional lability, social isolation, irritability and restrictive diet. The first diagnostic impression was an exacerbation of paranoid schizophrenia. Despite normal neurological examination, a routine brain magnetic resonance imaging (MRI) scan (Fig. 1A–D) and an MR angiography (Fig. 1E–F) were performed in order to exclude neurological pathology. These neuroimaging techniques showed a vascular pattern compatible with bilateral moyamoya disease, as well as, chronic ischemic lesions in frontal and parietal lobes, leukoaraiosis and hippocampal asymmetry suggestive of left hippocampal malrotation. The diagnosis of moyamoya disease was later confirmed by arteriography (Fig. 1G–L), which also classified the moyamoya disease as Suzuki and Takaku's stage III.

The neuropsychological assessment[1] showed significant executive dysfunction. In addition, total, cognitive, motor and non-planning impulsivity (Barratt Impulsiveness Scale (BIS)-11) scored above the cut-off point. However, no cognitive impairment (Screen for Cognitive Impairment in Psychiatry (SCIP)-S), depression (Beck Depression Inventory (BDI)), anxiety (Beck Anxiety Inventory (BAI)) or catatonia (Bush-Francis Catatonia Rating Scale (BFCRS)) was observed.

Further evaluation ruled out entities causing moyamoya syndrome, including atherosclerosis, autoimmune diseases, meningitis, brain tumors, traumatic brain injury or cranial irradiation.

She was given aripiprazole (30 mg/day) with the resultant improvement of symptoms. Acetylsalicylic acid (100 mg/day) was added to the treatment for the prevention of cerebrovascular events. On outpatient follow-up 6 and 12 months post-discharge, the patient's symptoms were well-controlled and she had resumed to her daily activities and work.

Exclusively psychiatric manifestations of moyamoya disease are extremely rare. We present a case of psychotic presentation of moyamoya disease.

We reviewed the moyamoya disease cases with psychiatric manifestations found in the scientific literature, focusing on those with psychotic symptoms. We used PubMed database and the search strategy was: (moyamoya disease) OR (moyamoya syndrome) AND ((psychiatric) OR (psychosis) OR (psychotic) OR (schizophrenia)) AND (case). We limited the results to case reports published in the last 20 years (from January 1, 2002 to January 1, 2022). This search produced 28 articles. We excluded pediatric cases and articles that did not report psychiatric manifestations. We included a previous article due to its clinical relevance. The search was conducted independently by 2 of the authors (SLLP and NRL). We identified fourteen articles, which are summarized in online Supplemental Table 1.

Moyamoya disease is an uncommon cerebrovascular disorder of unknown etiology characterized by stenosis of the terminal internal carotid arteries and fragile compensatory collateral vessels.[2] The highest prevalence is observed in Korea, Japan and China. Its classical clinical presentation accounts for motor, sensory, speech and visual disturbances, as well as, seizures, headache or cognitive impairment

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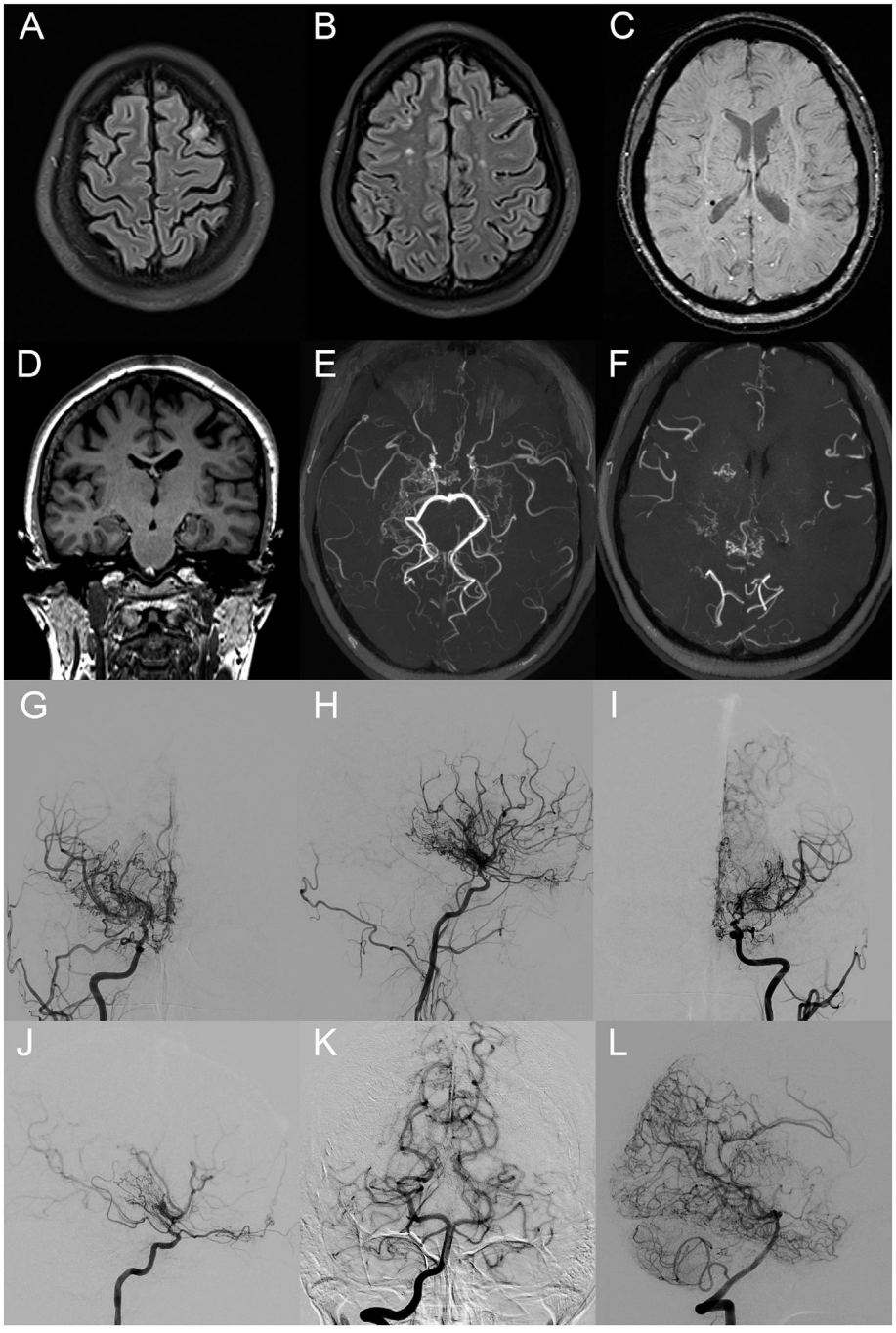


**Fig. 1** Imaging study in the patient presented. A–F. Brain magnetic resonance (MR) study. Axial T2 FLAIR images showed chronic cortical lesions in the left frontal cortex (A), and several subcortical gliotic foci in the white matter of both hemispheres (B). C. Axial SWI image evidenced deep left periventricular microbleed. D. Coronal T1 image showed hippocampal asymmetry suggestive of left hippocampal malrotation. E, F. Axial time of flight (TOF) MR sequence showed severe bilateral stenosis at the terminal internal carotid artery portion, decreased flow signal in M1 segments of both middle cerebral arteries, an increase in the diameter of both posterior cerebral arteries, as well as, abundant collateral vessels in basal ganglia and basal cisterns, which were more predominant in the right hemisphere. Pial collateral vessels were also observed (F). Altogether, these changes resulted in a decreased flow in both hemispheres, especially in the left one (E, F). G–L. Cerebral arteriography study in the patient. Anterior (G, I) and lateral (H, J) projection views showed critical stenosis at the terminal portion of right (G, H) and left (I, J) internal carotid arteries, together with an important network of collateral vessels originating from the lenticulostriate, ophthalmic and anterior choroidal arteries (G–D). Posterior (K) and lateral (L) projection views showed increased bilateral posterior cerebral artery diameter (K) and multiple pial collaterals from the posterior cerebral arteries (L). No extra-intracranial anastomoses were observed. Altogether, these findings confirmed the diagnosis of moyamoya disease, classified as Suzuki and Takaku's stage III.

involving executive function, processing speed, verbal memory and fluency. However, psychiatric manifestations are also found, being depression and anxiety the most commonly observed, although psychosis has also been reported.[3] It is worth noting that moyamoya disease may be unrecognized in clinical practice depending on the symptoms presented and it may be misdiagnosed as a psychiatric disorder, implying a diagnostic delay of even years.[3]

The mechanism underlying these symptoms includes recurrent ischemic and hemorrhagic strokes and transient ischemic attacks, being the cerebral cortex the most affected area.[3] However, cognitive impairment (executive function, expressive language abilities and mental efficiency) in moyamoya disease has also been reported in the absence of visible stroke on MR imaging,[4] suggesting that chronic cerebral hypoxia secondary to hypoperfusion may be enough to produce clinical repercussion without the need of infarct. This has therapeutic implications as hypoperfusion may be reversible by surgical revascularization.[4]

Psychiatric manifestations in moyamoya disease can precede or be concomitant to neurological deficits, and are also considered a sequela of the illness. Psychiatric manifestations may result as a consequence of the neurological disability after stroke events or may be secondary to the moyamoya disease diagnosis implications. However, infarction of specific brain areas and the hypoperfusion observed in moyamoya disease can be also the direct cause of the development of mood disorders.[5,6] Importantly, acute psychiatric symptoms in a moyamoya disease patient should make us suspect a new vascular event.[3]

The treatment for moyamoya disease consists of preventing vascular events with long-term antiaggregant therapy. Surgical revascularization should be considered for symptomatic patients.[3] Previous studies have demonstrated that surgical revascularization also prevents and improves cognitive function in moyamoya disease patients. This improvement is achieved through the resolution of hypoxia in cerebral tissue, as evidenced by PET studies.[7] Interestingly, quantitative hemodynamic techniques including PET, SPECT, dynamic perfusion CT, MR imaging with contrast or Doppler ultrasonography, may help to detect early hypoperfused cerebral areas, in which neuronal death has not occurred yet.[8]

The effectiveness of psychotropic therapies to treat psychiatric manifestations in moyamoya disease remains controversial. In fact, treatment resistance in psychiatric disorders is a red flag to consider other diagnoses, such as moyamoya disease.[3] In the case presented here, the absence of an MRI or MR angiography study during the first-episode psychosis may have delayed the moyamoya disease diagnosis.

Strikingly, we can not discern whether the patient has two different diseases (schizophrenia and moyamoya disease), or whether all the clinical presentation is due to moyamoya disease exclusively. In schizophrenia, hypofunction of the frontal cortex has been previously described,[9] and interestingly, our patient had compromised anterior circulation and frontal cortex lesions, which may contribute to the clinical manifestations. In accordance with this, it has been previously described that moyamoya disease patients with encephalomalacia in frontal lobes have a higher prevalence of paranoid traits when compared with moyamoya disease patients without these changes.[5] Lastly, incomplete hippocampal inversion is more prevalent in patients diagnosed with schizophrenia,[10] and, although a coincidence, our patient had an hippocampal asymmetry.

The strong point of the presented case is relative to the rare association between moyamoya disease and paranoid schizophrenia. Although both pathologies may be related, psychotic manifestation being the first clinical finding of moyamoya disease is also uncommon. The limitations of our study include not being a systematic review, the scarcity of medical information prior to hospitalization, the lack of genetic and familiar study and the lack of longitudinal evolution of the clinical profile.

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## Patient consent

Informed written consent was obtained from the patient involved in this study.

## Ethical considerations

The protocols of the institution on the publication of patient data have been followed and privacy has been respected.

## Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurop.2023.100123.

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