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A Haunting Tremor: A Rare Presentation of an Unruptured Arteriovenous Malformation and Review of Related Literature

Adrian Paul De Leon[1], Criscely L. Go[2]

[1] Department of Neurology, Jose R. Reyes Memorial Medical Center, Manila, Philippines
[2] Department of Behavioral Medicine, Jose R. Reyes Memorial Medical Center, Manila, Philippines

Abstract
Tremor is a common phenomenology characterized by an involuntary rhythmic and oscillatory movement. These are formed from any disruption in the dentate-olivary and the basal ganglia-cerebello-thalamic circuits due to neurodegenerative disease, stroke, head injuries, toxins, drugs, systemic illness, or metabolic disorders, and rarely, arteriovenous malformations (AVMs). Brain AVMs, as compared to AVMs in other anatomic locations, are less commonly studied. The pathophysiology, symptomatic correlation, and etiology of these brain AVMs are less reported, hence, current literature reviewed presented patients with a wide spectrum of signs and symptoms which were linked with AVMs of differing risk based on their diagnostic grading. This case report narrates the experience of a 29-year-old female physician presenting with fine high frequency hand tremors later found out to have a parietal AVM. We will discuss AVMs and their consequent course of diagnosis, treatment, and management.

Keywords: Arteriovenous Malformation, Tremors, Brain Arteriovenous Malformation

1. Introduction

Tremor is a common phenomenology seen in clinical practice. It is described as an involuntary movement that is both rhythmic and oscillatory(Louis, 2019). Several etiopathogeneses can cause tremors such as neurodegenerative disease, stroke, head injuries, toxins, drugs, systemic illness, or metabolic disorders(Kamble & Pal, 2018). However, in movement disorders practice seeing tremors, arteriovenous malformations (AVMs) rarely are the cause(Jurinović et al., 2017).

AVMs are tangles of dysplastic blood vessels which form abnormal fistulas between arteries and veins(Rutledge et al., 2021). These are dangerous structures as direct flow of arterial blood into the veins can lead to disruption of the venous walls and cause fatal hemorrhage. Intracranial AVMs are most diagnosed during the work-up for an acute intracerebral hemorrhage but can be also found incidentally during the evaluation of conditions including chronic headaches and seizures. Moreover, AVMs can also damage parts of the hindbrain, which can result in dizziness, giddiness, vomiting, a loss of the ability to coordinate complex movements such as walking, or uncontrollable muscle tremors(*Arteriovenous Malformations (AVMs)*, n.d.).

We report the case of a female patient with an unruptured AVM presenting who presented with fine hand tremors.

2. Patient Information

Our patient is a 29-year-old female, right-handed, single, Filipino, Roman Catholic, physician from Pampanga who was admitted at the Jose R. Reyes Memorial Medical Center on October 7, 2022 presenting with tremulousness of the right upper extremity of 3 years duration. The tremulousness was observed while reaching for objects, during sustained posture, general activity, and were absent at rest. These would occur intermittently at no particular time of the day. There were no associated cranial nerve deficits, motor and sensory weakness, seizures, nor cognitive impairment. She was able to perform activities of daily living until the time of consultation when she noticed progressive impairment when she would hold instruments like needles. Propranolol provided no relief of symptoms.

On examination, there was a postural and intention tremor on the right upper extremity. There was no cognitive impairment, cranial nerve deficits, motor weakness, sensory loss, nor dysarthria. Her reflexes were likewise normal. The rest of the physical examination was normal. The tremors would intermittently occur.

3. Workup

Routine blood examinations were unremarkable and thyroid function tests were within normal limits. Routine electroencephalography showed no focal changes or epileptiform discharges. Cranial MRI with contrast showed an arteriovenous malformation at the left frontoparietal periventricular region extending into the left lateral ventricle measuring 4.1 x2.8x3.2 cm (AP x W x CC) (Figure 1). Further evaluation of the lesion on cerebral 6-vessel angiography showed a pial type arteriovenous malformation on the left parietotemporal and basal ganglia region supplied by the left internal carotid artery, left middle cerebral artery, left anterior cerebral artery, and left posterior cerebral arteries. Venous drainage was done through the left Vein of Labbe, left Vein of Trolard, and left internal cerebral vein. (Spetzler Martin Grade 5) (Figure 2). The patient subsequently underwent gamma knife surgery with noted improvement of tremor with regain of functions such as writing and holding instruments.

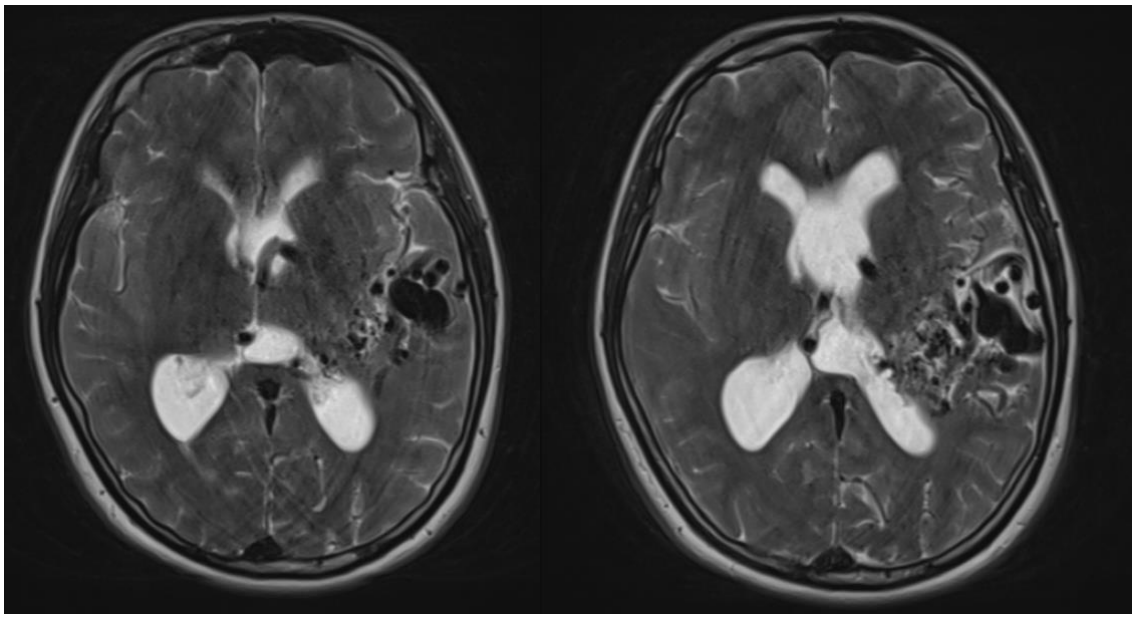

Figure 1: Magnetic resonance imaging brain scan axial T2W.

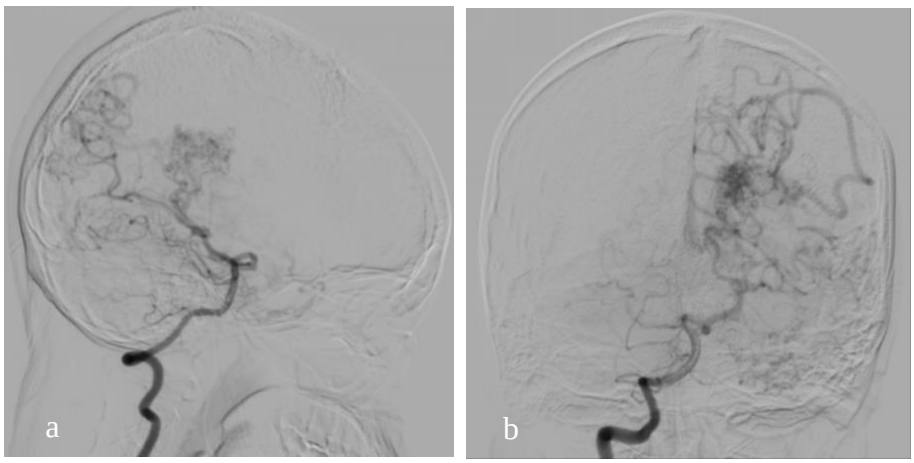

Figure 2: Digital subtraction 4-vessel angiography brain on (a) sagittal and (b) coronal views.

4. Discussion

The presentation of this case was rare in that the only reported symptom was an isolated tremor in the right arm. A quick PubMed literature search for case reports relevant to AVMs in tremors was done (Table 1). In addition, compared to the reviewed literature the attributed AVM in our case is found in the cortical areas superficial to the basal ganglia without other cortical signs.

Table 1: Recent Literature on Cases of Tremors and AVMs.

Author/s	Case Presentation	AVM Location	Intervention	Outcomes
Lobo Antunes et al., 1974	Tremor and dystonia right arm	Left basal ganglia, thalamus, upper mesencephalon	*Undisclosed*	Recurrent re-ruptures
	Tremor left arm Left hemiparesis *Pediatric case*	Right basal ganglia, thalamus, upper mesencephalon	Selective embolization	Unchanged
Krauss et al., 1999	Tremor right arm Seizures Aphasia Abulia Gait disturbance	Left high-frontal cortex and white matter	Clipping of nidal aneurysms	Ruptured twice and subsequently expired
	Tremor left arm Seizures Left hemiparesis Left hemihyphesthesia	Right high-frontal cortex and white matter	Staged partial embolization Surgical resection	Resolution of tremors and seizures Improvement of hemiparesis 2 years post-operatively
Ogungbo et al., 2001	Tremor left arm	Right medial frontal cortex	Embolization Surgical excision	Complete resolution
Demartini et al., 2020	Headache Tremors *Pediatric case*	Cerebellar culmen	Embolization	Developed mutism, dysmetria, dysdiadochokinesia, tremor of head and limbs after 6th month of follow-up

Considering the literature reviewed, tremors are reported secondary to AVMs. However, most case reports show inconsistent improvement after treatment. A remarkable case report is present in the last retrieved report wherein the patient developed cerebellar mutism (CM) and tremors of the head and limbs after the treatment of the AVM(Demartini et al., 2020). The report explains that tremors may not only be a presenting symptom but also a complication of treatment and that CM is a possible complication of posterior fossa AVM.

As such, physicians should be adequately informed about these complications, along with further understanding of the pathogenic mechanisms and underlying anatomical circuit of CM to prevent similar mishaps like this procedure from happening. This is the first case report made locally.

Tremors may be due to various etiopathogeneses such as neurodegenerative disease, stroke, head injuries, toxins, drugs, systemic illness, or metabolic disorders however, its exact pathophysiology is still incompletely understood. The current hypothesis is that the generation of tremors is associated with the dysfunction of two main circuits namely, the dentate-olivary and the basal ganglia-cerebello-thalamic circuits. In the latter, the Globus pallidus internus (GPi) sends inhibitory GABAergic projections to the Ventral intermediate nucleus of the thalamus (Vim) which subsequently project to the motor cortex. as such, increased activity of the Gpi inhibits cortical motor activity. Alternatively, the Dentate nuclei in the cerebellum sends excitatory glutaminergic projections to the posterior part of the Ventrolateral nucleus of the thalamus (VLP) and subsequently the motor cortex. As such, the cerebellum facilitates cortical motor activity(Kamble & Pal, 2018).

The dentate-olivary circuit involves the dentate nucleus, red nucleus, and inferior olivary nucleus (ION) which forms the Guillain-Mollaret triangle. The dentate nucleus sends inhibitory GABAergic projections to the ION which then send excitatory projections to the Purkinje cells of the cerebellum. In addition, the ION also receives projections from the red nucleus. The ION serves an important role in the genesis of tremors in that its neurons demonstrate regular oscillatory depolarizations. These oscillations serve as pacemakers in the temporal coordination and timely processing of motor activity and cerebellar motor learning. Any disruption in these two circuits produce tremor(Kamble & Pal, 2018).

Not much is known about brain AVMs, especially their etiology, according to a recent review article. This article mentioned how brain AVMs can possibly be multifactorial, with influences from genetic mutation and angiogenic simulation(Demartini et al., 2020). There are also mixed beliefs in the development of brain AVMs, including those that believe that they are developed either in utero, from an angiopathic reaction, or following an ischemic or hemorrhagic event(Abecassis et al., 2014).

Systematic literature review studies gave a clearer picture of the epidemiology of AVMs. In one study, the incidence of AVMs is evaluated at 1.12 to 1.42 cases per 100,000 person years, and 38-68% of new cases have first-ever experienced hemorrhage(Abecassis et al., 2014). This study also found that the annual rates of hemorrhage for patients with untreated AVMs range from 2.10% to 2.42%. Another meta-analysis pooling the results of nine studies with a total of 3,923 patients and 18,423 patient-years of follow-up determined other important epidemiologic indicators for AVMs. These include the overall annual hemorrhage rate of 3.0% (95% CI 2.7%-3.4%), with the rate for unruptured AVMs at 2.2% (95% CI 1.7%-2.7%) and ruptured AVMs at 4.5% (95% CI 3.7%-5.5%)(Gross & Du, 2013). The mortality rate is 10-15% of patients who have a hemorrhage, and morbidity varies from approximately 30-50%. There is no sex predilection. Despite the considered congenital origin of AVMs, the clinical presentation most commonly occurs in young adults. The case in this report has conformed to most of these epidemiologic features.

There are differing schools of thought regarding the pathophysiology of AVMs. Initially, they were thought to represent congenital lesions which are a result of disordered embryogenesis, but other studies support the postnatal development of these structures. Pathways which could lead to the postnatal development of AVMs include altered flow dynamics, structural vascular abnormalities, and other underlying molecular mechanisms(Moftakhar et al., 2009). 15% of cases tend to be clinically asymptomatic until such time the presenting symptom occurs, which are: (1) intracranial hemorrhage (in 41-79% of patients); (2) seizures (in 15-40% of patients) which increase in risk as the AVMs tend to have a more cortical location, are large, multiple, and superficial-draining; (3) progressive neurological deficits (in 6-12% of patients); and (4) headaches, to which there are no specific headache features associated with AVMs. Apart from hemorrhage, AVMs become symptomatic by several mechanisms. First is mass effect whereby the size of the AVM is sufficient to exert pressure on the surrounding brain. Second, large volumes of blood shunted by the AVM may lead to a “steal phenomenon.” This leads to transient or permanent ischemia of surrounding areas causing focal dysfunction(Jurinović et al., 2017). The patient in this case presented

with tremors, which is quite different from the common pathophysiologic presentations mentioned and we deemed it necessary to shed light to the rarity of this case locally.

In the diagnosis of AVMs, the Spetzler Martin grading scale is often used. This scale estimates the risk of open neurosurgery for a patient with AVM by evaluating AVM size, pattern of venous drainage, and eloquence of brain location(Frisoli et al., 2021). Small, superficial, and a non-eloquent brain AVM location would usually present as Grade 1 AVMs while larger, deeper, and eloquent brain AVM locations would be given higher grades.

Treatment modalities for these cases involve invasive management, which is recommended for younger patients in the presence of one or more of the high-risk features of an AVM rupture, while medical management is recommended for older individuals with no high-risk features. The Spetzler-Martin grade of the AVM is important to consider as high AVM grades are usually associated with an increased risk of surgical morbidity and mortality risk. Though the case in this report was successfully treated, the observed grade of the case's AVM is enough to warrant high attention from the physician treating the condition as the highest Spetzler-Martin grade was given to the AVM seen.

There is still a paucity of current evidence pertaining to the specific mechanisms as to the development of brain AVMs and how the patient's symptoms correlate with the grading of their AVM, which would have helped greatly in devising an effective treatment and management plan. This case only reported with tremors, yet the Spetzler-Martin grade of the AVM seen in the patient is Grade 5. This indicates the highest surgical morbidity and mortality risk. In conditions like these, it is always important for the physician to exercise a high degree of suspicion to be able to diagnose this condition more efficiently and consequently manage and treat the susceptible patient.

Patient Anonymity, Consent, and Confidentiality

Written informed consent was obtained from the patient for the development and possible publication of this case report, as well as any image from the diagnostic procedures done to the patient which can be seen in this report. All personal information regarding the patient were kept strictly confidential, and any information that could lead to the identification of the patient were removed in accordance with the Data Privacy Act of 2012 and the ethical guidelines in the National Ethical Guidelines for Health and Health-Related Research 2022. The patient fully understood the content of the written informed consent, and is aware that the principal investigator, as well as the hospital's Research Ethics Committee (REC), would have access to their medical records for the purpose of verification prior to presentation of this case.

Declaration of Conflict of Interest

The author declares that there is no conflict of interest.

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