DELAYED DIAGNOSIS OF AVM PRESENTING WITH STROKE AND SEIZURES IN A YOUNG NIGERIAN: A CASE REPORT.

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ABSTRACT
Background: **Brain arteriovenous malformations (BAVM) are a cause of intracerebral haemorrhage (ICH) and seizures especially in young patients. ICH due to BAVMs seem to have relatively better neurologic outcomes compared to other causes of spontaneous ICH as patients often recover fully. In this report we highlight a case of delayed diagnosis of BAVM in a young man who presented with seizures and stroke.**

Case summary: **A 36-year-old man was referred on account of focal, secondarily generalized tonic clonic convulsions. He had suffered a right ICH 3 years before the index presentation. His general physical and neurologic examination were normal. Electroencephalography revealed right sided focal epileptiform discharges and brain MRI revealed a right parieto-occipital AVM. The seizures were controlled with carbamazepine and he was referred for neurosurgical evaluation.**

Conclusion: **BAVMs are an important cause of intracerebral haemorrhage and attendant neurologic morbidity especially in young individuals. Neuroimaging plays a central role in BAVM diagnosis and MRI is of great value where facilities and expertise for conventional angiography do not exist. In some instances, delayed presentation of BAVM cases may be due to relatively better neurologic outcomes in BAVM-related ICH.**

INTRODUCTION

Arteriovenous Malformations (AVMs) are vascular anomalies that consist of tangles of arterioles in direct connection with venules, without intervening capillaries. Although they can occur in any part of the body, including the central nervous system, brain AVMs (BAVMs) are of concern because of their potential for devastating neurologic sequelae. BAVMs may occur in isolation or as part of vascular disorders such as Osler-Weber-Rendu syndrome, Sturge-Weber syndrome, or moyamoya disease.[1,2]

BAVMs occur relatively rarely and are responsible for about 2% of all strokes.[1,3] The prevalence of BAVMs has been estimated at 15-18 per 100, 000 adults.[4] In a systematic review – based on data from 4 multi-centre studies conducted in New York, Northern California, Scotland, and Sweden – Abecassis *et al.* reported a BAVM incidence of 1.12–1.42 per 100, 000 person-years.[5] There is no robust data regarding epidemiology of BAVM in Nigeria. Over a 5-year period culminating in 1967 at the University College Hospital (UCH), Ibadan, only 19 cases of intracranial vascular malformations were reported. Three of the 19 cases

were isolated BAVMs, while 2 patients had BAVMs as part of Sturge-Weber syndrome.[6] Adeyinka *et al.* in 2005 reported a case of BAVM diagnosed by brain computerized tomography (CT) scan and conventional angiography.[7] Furthermore, in a retrospective review of 62 three-dimensional CT angiography procedures performed at Ibadan over a near 2-year period, five intracranial AVMs were detected.[8] More recently, Adekanmi *et al* found that between 2011 and 2018, approximately 20% of patients with CT-angiography-confirmed intracranial vascular lesions at UCH, Ibadan had BAVMs.[9]

BAVMs usually come to clinical attention because of intracerebral haemorrhage (ICH), seizures, headache, or other focal neurologic deficits. Focal neurologic deficits may occur in the absence of ICH, and may be due to mass effect by large BAVMs, or ischaemia of adjacent areas resulting from vascular steal phenomenon.[1]

In this report, we present the case of a young Nigerian man who presented with seizures, in whom a diagnosis

of BAVM was confirmed, and salient anatomic details delineated with brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA).

CASE SUMMARY

A 36-year-old man was referred to the neurology clinic with a 2-year history of recurrent convulsions. Seizures were described as initially focal with versive features which then progressed to bilateral tonic clonic seizures. Seizures became more frequent in the month preceding his presentation. All episodes of seizures occurred during sleep. The seizures were associated with tongue-biting, sphincteric incontinence, postictal sleep and occasional headaches. However, there was no preceding aura. There was no history of visual impairment or childhood history of head trauma or seizures. He was neither hypertensive nor diabetic and had no known family history of epilepsy. He neither smoked cigarettes, used illicit drugs, nor drank alcohol.

He had been admitted 3 years prior to the index presentation because of a stroke with right hemispheric intracerebral hemorrhage confirmed on computed tomography (CT) scan. The CT images from that admission were however not available for review. Following the stroke, he recovered with no residual neurological deficit.

On examination, he was not pale and there were no telangiectasias. He was conscious and alert, cognition was not impaired, and visual field examination was normal. Cranial nerve, motor, and sensory examination, including higher cortical sensation were normal.

Routine electroencephalography (EEG) was performed using a 16-channel EB Neuro S.p.A. Neurotravel LIGHT machine (Florence, Italy) with electrodes placed according to the 10-20 international system, and hyperventilation performed as activation maneuver. The EEG showed a normal background with focal epileptiform discharges preponderant in the right temporo-parieto-occipital region (Figure 1).
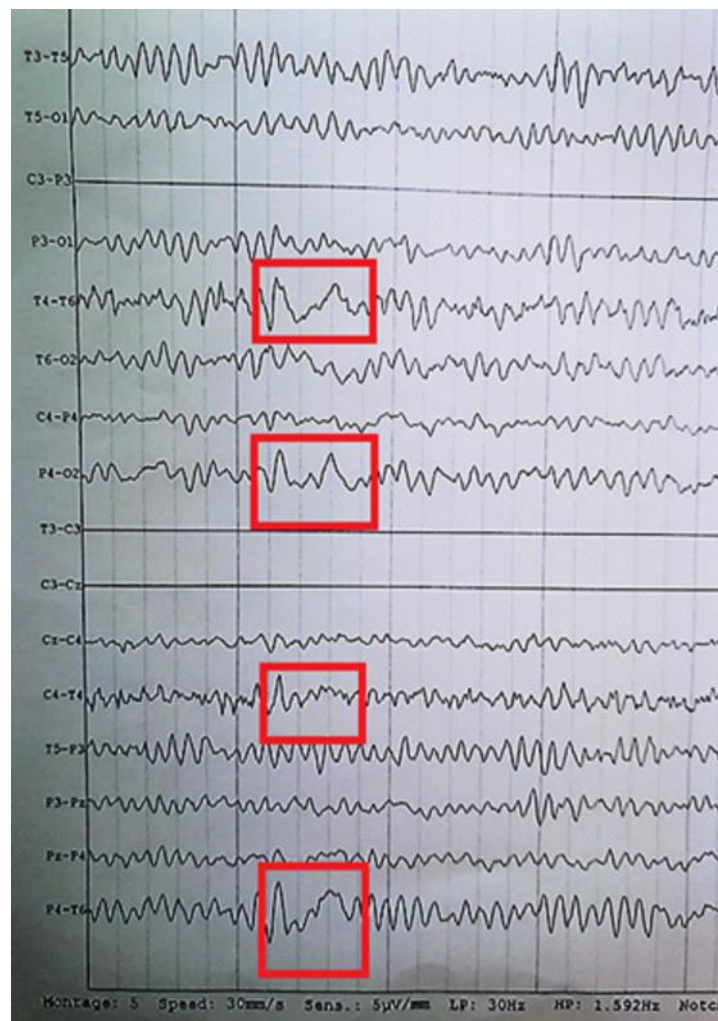
Figure 1: Electroencephalogram showing epileptiform sharp and slow waves predominantly in the right temporal and parieto-occipital derivations (red boxes).
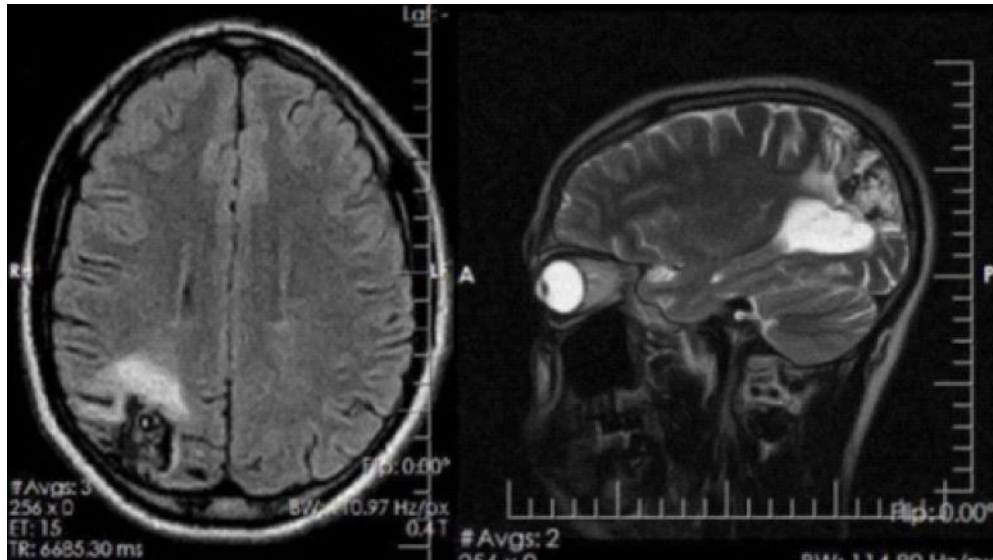
Figure 2: Axial FLAIR, and sagittal T2-weighted images showing multiple, serpiginous signal-void areas, giving the so-called *"bag of worm"* appearance in the right parieto-occipital region. Surrounding hyperintensities represent gliotic changes. Dilatation of the posterior horn of the right lateral ventricle is seen in the sagittal image.

Brain MRI performed with a 0.3T machine revealed an irregular mixed intensity area on all the sequences, in the right parieto-occipital region, measuring 4.7cm x 3.1cm x 2.5cm (LS x AP x TS), It showed multiple, serpiginous signal-void areas, giving the so-called "*bag of worm*" appearance (Figure 2). It showed heterogeneous (serpiginous) enhancement on post-gadolinium T1 - weighted images. Time-of-Flight (TOF) MRA images showed the major feeding artery to have arisen from an opercular branch of the right middle cerebral artery, while the main draining parietal veins emptied into the superior sagittal sinus via the right superficial cerebral vein (Figure 3). There was a surrounding area of FLAIR hyperintensity suggestive of gliotic changes. The adjacent posterior horn of the ipsilateral lateral ventricle was moderately dilated, indicating focal volume loss. The remaining cerebral hemispheres appeared normal.

Within 4 weeks of commencing treatment, his seizures were well controlled with oral carbamazepine (400mg twice daily) and he is being followed up at the neurosurgery clinic.

Figure 3: Time of flight MRA showing feeding artery (an opercular branch of the right middle cerebral artery) and the draining parietal veins which empty into the superior sagittal sinus via the right superficial cerebral vein.

DISCUSSION

Our patient presented with adult-onset seizures and history of intracerebral haemorrhage (ICH), with a diagnosis of BAVM confirmed by brain MRI and time-of-flight (TOF) Magnetic Resonance Angiography (MRA)

BAVMs are the most frequent type of intracranial vascular malformation.[10] They consist of abnormal connections between feeding arteries and draining veins through a complex conglomeration of vascular channels called a nidus, without an intervening capillary bed.[11] The presence of the nidus distinguishes AVMs from AV fistulae in which arteries connect directly with veins.[12] BAVMs may occur anywhere in the brain, but the majority are in the supratentorial compartment.[10] BAVMs may also be superficially located (i.e. in the gyri or sulci of the brain) or located deep within the brain parenchyma.

BAVMs have traditionally been considered congenital lesions resulting from abnormal angiogenesis during early fetal development but remain symptomatically silent till later life.[13] This concept has however been challenged by the rarity of prenatal BAVM diagnosis, and the documentation of de novo formation of BAVMs in adults.[14–16] Kim *et al*[17] proposed a "response-to-injury" theory which involves an inciting event (trauma, infection, inflammation, irradiation, or mechanical stimulation), and a background microscopic vascular anomaly, or genetic predisposition. Candidate gene studies have identified single nucleotide polymorphisms (SNPs) that are associated with increased BAVM risk in humans.[18] However, a recently published genome-wide association study (GWAS) of sporadic BAVM in Caucasians did not reveal any statistically significant association between common SNPs and BAVM occurrence.[19]

As in this case, most patients with BAVM present between ages 20 and 40 years.[1,20,21] The most common presentation is intracerebral haemorrhage. Meta-analyses of BAVM natural history studies reveal that approximately half of patients with BAVM will suffer an intracranial haemorrhage which may be intraparenchymal, subarachnoid, or intraventricular.[5,22] Though relatively rare in the general population, BAVMs are a leading cause of ICH in younger individuals. In a retrospective study of young people (age <40 years) with ICH, ruptured BAVMs were the leading aetiology, accounting for 33% of cases (three times the proportion caused by hypertension in the same study).[23] Seizures occur in almost 30% of patients with BAVM and are the second most frequent presenting symptom. The seizures may be focal, generalized, or as in this case, focal evolving to generalized tonic-clonic convulsions.[24]

Diagnosis of BAVM requires neuroimaging, and digital subtraction angiography (DSA) is regarded as the reference standard of diagnosis.[21,25,26] DSA offers excellent anatomical definition of the AVM nidus, feeding arteries, draining veins and other important architectural elements such as coexisting aneurysms and venous dilatations or stenosis which confer higher risk of AVM rupture.[22] Knowledge of these architectural details are also crucial in planning treatment. DSA also affords evaluation of dynamic properties such early venous drainage, a hallmark of BAVMs.[26] However, DSA is expensive, invasive, exposes patients to ionizing radiation, and may be complicated by serious morbidity especially if expertise is lacking, or the procedure is not routinely performed.

Compared to DSA, cross-sectional imaging techniques like CT scans and magnetic resonance (MR) imaging are more readily available in resource-constrained settings. They are non-invasive and allow precise anatomic localization of the AVM,[26] knowledge of which is paramount since BAVMs located deep within the brain are associated with higher risk of cerebral haemorrhage.[27] Non-contrast-enhanced brain CT is sensitive for acute intracerebral haemorrhage; however, the acute bleed may obscure the presence of an AVM, necessitating CT angiography (CTA). MR imaging can detect AVMs, typically as tangles of signal voids best seen on T2-weighted images.[25,26] It also provides better visualization of adjacent brain structures,[21] another important detail to note in planning treatment. Specialized MR sequences which are sensitive to blood products (e.g. gradient-recalled echo, or susceptibility-weighted sequences) can detect prior haemorrhage. MR angiography (MRA) is a non-invasive albeit less sensitive alternative to DSA.

The utility of CTA, MRI, and MRA in BAVM diagnosis was studied by Gross et al[28] who retrospectively reviewed 125 cases of BAVM, all of which were DSA-confirmed. CTA, T2-weighted MRI and MRA had sensitivities of 90%, 89%, and 74% respectively in detecting BAVMs. CTA was however superior to MRI and MRA in detecting feeding artery aneurysms (sensitivity of 90%, 35%, and 31% respectively, $P_{CTA \, vs \, MRA}$ <0.001), and even more so for intranidal aneurysms (sensitivity of 83%, 0%, and 0% respectively, $P_{CTA \, vs \, MRA}$ 0.005).[28] While DSA offers unparalleled architectural detail relevant to prognostication and treatment planning, the facilities and expertise for safe DSA are often lacking in resource-limited settings. In such areas, CT and MR imaging may be the only diagnostic tools available, and for which local expertise

exists. Therefore, treatment plans are invariably based on these imaging modalities. In our case, brain MRI and TOF MRA provided the exact location of the aneurysm, delineated the nidus, feeding artery as well as the draining veins.

Treatment options for BAVM include surgical resection, embolization, and radiosurgery. The choice of treatment modality is often based on certain BAVM characteristics which determine treatment outcome. The Spetzler-Martin system[29] is a popular BAVM grading system that incorporates three of these characteristics (AVM size, location adjacent to eloquent areas of the brain, and presence of deep drainage). The areas considered eloquent by the authors are the sensorimotor, language, and visual cortices; the thalamus and hypothalamus; the internal capsule and brainstem; the cerebellar peduncles and deep cerebellar nuclei. Points are assigned (size <3cm, 3-6cm, >6cm: 1, 2, and 3 points respectively; relation to an eloquent area, deep drainage: 1 point each), and the Spetzler-Martin grade (ranging from I to V) is the total number of points.[29]

A simplification of this system has been proposed, with grades I and II lesions combined into class A; grade III lesions designated class B; and grades IV and V lesions combined into class C.[30] Class A lesions are typically managed by surgical excision; class B lesions may be managed by excision, embolization, radiosurgery, or a combination of modalities depending on individual cases. Because of poor treatment outcomes, Class C lesions may be managed conservatively or via a staged radiosurgery approach, or palliative endovascular approaches when haemorrhage occurs.[26,31] The index case was referred for definitive neurosurgical intervention.

What is particularly intriguing about our patient is the delay of three years between his initial presentation with a stroke and the second presentation with an adult–onset seizure disorder without any active intervention. Although the possibility of subclinical seizures in the intervening period cannot be entirely excluded, there were no features (e.g. subtle alterations in consciousness or subtle motor phenomena) to suggest their occurrence. This delay may reflect the complete restoration of neurologic function following the initial ICH. It is not unusual for patients like ours who suffer ICH from BAVM to recover fully. Indeed, ICH following BAVM rupture seems to have more favourable outcomes than ICH from other aetiologies. Van Beijnum and colleagues[32] compared outcomes in BAVM-related ICH versus spontaneous ICH (not due to BAVM, trauma, tumour or other structural causes) using data from two Scottish prospective population-based cohort studies. Case fatality at 1 month was 50% for spontaneous ICH versus 11% for BAVM. Compared with BAVM-related ICH, spontaneous ICH was associated with higher odds of death or dependence at 1 year (odds ratio, OR 7.5; 95% confidence interval, CI 3–19). In another study with a larger sample size, BAVM-related ICH was associated with lower odds of death (OR 0.5, 95% CI 0.4 – 0.7), higher odds of home discharge (OR 2.0, 95% CI 1.4 – 3.0), and higher odds of ambulatory independence at discharge (OR 4.4, 95% CI 1.4 – 13.1) compared to other ICH aetiologies.[33] In both studies, favourable outcomes in BAVM patients remained significant after adjusting for other factors – such as ICH volume and location, Glasgow Coma Score, associated intraventricular haemorrhage – known to predict outcome after ICH.

As highlighted in the studies above, relative to other causes, patients who suffer ICH from BAVM have higher odds of survival and functional independence even after accounting for traditional predictors of ICH morbidity and mortality. Having sustained full neurologic recovery after his ICH, our patient perhaps felt no need for additional potentially costly investigations – the cost of which would have been borne out of pocket – to ascertain the aetiology of ICH. Like in our case, age below 55 years, absence of hypertension, and lobar location of haemorrhage increase the likelihood of a vascular or other structural aetiology of ICH.[34,35] Performance of additional neuroimaging modalities to ascertain ICH aetiology is recommended if these factors are present.[36] Had this been done after the initial ICH presentation in our case, the BAVM may have been diagnosed earlier and neurosurgical intervention offered before the onset of seizures.

The delay in presentation may also reflect misconceptions about neurologic disease pervasive in African countries. For instance, almost 14% of respondents in a Nigerian survey believed stroke was the result of evil spirits/witchcraft, while another 13% preferred spiritual healing to orthodox medical care.[37] Similarly, poor knowledge and misconceptions exist about the aetiology of epilepsy in sub-Saharan Africa.[38] Amongst other factors, such misconceptions have been found to contribute to poor health seeking behaviour in Nigerian patients with epilepsy, leading to a significant epilepsy treatment gap.[39]

In conclusion, BAVMs are an important cause of neurologic morbidity, and potentially devastating intracerebral haemorrhage especially in young individuals. Neuroimaging plays a central role in BAVM diagnosis; DSA is considered the gold standard imaging modality. However, facilities and expertise for

DSA are not always available, especially in resource-constrained settings. In such instances, CT and MRI are useful modalities to aid diagnosis and plan treatment. MRI affords precise anatomic location of the AVM nidus and its relationship with adjacent brain tissue. MRA can also detect feeding arteries and draining veins, though is not as sensitive in detecting AVM associated aneurysms. Delayed presentation in some cases of BAVM may be a pointer to relatively better neurologic outcomes in BAVM-related ICH and misconceptions about the aetiology of stroke and epilepsy, especially in African settings.

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