Brain Disorders & Therapy
ISSN: 2168-975X

Al-Jehani and Alabbas, Brain Disord Ther 2017, 6:1
DOI: 10.4172/2168-975X.1000228

Review Article OMICS International

Epilepsy and Intracranial Vascular Malformations: A Possible Missing Link!

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Abstract

The development of brain arteriovenous malformations (AVMs) remains enigmatic. Their usual presentation with hemorrhage could be a devastating event. Their second mode of presentation; Seizure poses a mechanistic, diagnostic and therapeutic challenge. For the most part, vascular development and flow abnormalities are implicated in the development of seizures in the context of brain AVMs. Proposed is a hypothesis in which common cortical and vascular development pathways lead to perturbation of the vascular phenotype resulting in arteriovenous shunting while simultaneously leading to focal form of cortical dysplasia conducive of seizure.

Keywords: Intracranial vascular malformation; Epilepsy; Seizure disorders; Cortical development; Cortical dysplasia

Background

Cerebral cavernous malformations (CCMs) and arteriovenous malformations (AVMs) represent the major part of the spectrum of intracranial vascular malformations (IVM) [1]. They represent a common source of hemorrhage in young adults, which are the most common cause of intracerebral hemorrhage (ICH) in young adults that often heralded by an epileptic seizure at presentation to medical attention [2,3]. IVM can cause seizures without any intracerebral hemorrhage, representing the second devastating manifestation of IVMs occurring in 15% of all AVM patients [4]. In addition, many of these AVMs and CCM lead to what is known as "non-hemorrhagic focal neurological deficits" for which many possible pathophysiologic mechanisms have been proposed, including inflammatory process and cerebral autoregulatory failure around IVMs [5,6]. This could be as severe and devastating as migraine headaches and Todd's paresis and at time could be indistinguishable from a seizure event [7].

IVM development is poorly understood, and a number of them are discovered in the course of the workup of another neurologic condition or complaint or seldom during the screening of families of a known affected patient with IVM. The prevalence of these lesions is reported around 1:625 for CCM and 1:2000 for AVM although this could vary considerably depending on geographical location [8,9]. Taken broadly, this represents a large pool of potential patients with lesions epilepsy that could potentially suffer from refractory seizures.

Due to the poorly understood disease process and the limited number of IVM patients compared to other disease conditions, there is a significant debate as to the trigger for treatment of an incidental AVM, i.e. one that has not yet bled [10]. This debate becomes more troublesome when seizures are provoked or are of concern in the individual patient presentation. In a patient presenting with seizures in the context of an AVM, no clear guideline exist as to when one should consider the obliterative strategies of such malformations or follow a non-operative attitude and resting with anti-epileptic medications for control of seizures. Furthermore, with recent improvement in imaging modalities, even minute amounts of hemorrhages around the IVM can be detected and used to justify obliterative therapy regardless of the seizure status. This dichotomy in approaching IVMs presenting with seizures gets deepened when one considers that some of these IVMs don't have overt seizures and are only associated with subclinical non-convulsive seizures. These factors would complicate the choice of "event" whether clinical or electrographic; would be considered a trigger for obliterative treatment.

In order to delve into solving this dilemma, one has to first understand the epileptogensis in IVMs. For seizures in IVMs, several mechanisms have been proposed including neuron loss, glial proliferation, derangement of neurotransmitters, and free radical formation [11]. All these explanations are considering these pathological findings as result of the presence of the IVM. For this particular reason, one of the strategies to address IVMs is surgical resection, as this is presumed to reduce the seizure tendency by eliminating or at least controlling secondary epileptogensis [12]. On the other hand, this concept is challenged by an opposing view that there is no benefit from surgical resection as the resection itself might create an "epileptogenic scars". Such a question would be difficult or even impossible to answer in a non-controllable and un-randomizable clinical condition and surgical intervention.

But, What if we are looking at the wrong target?

Hypothesis and Supporting Evidence

Several studies on AVM development implicate genetic derangements of factors like the tumor necrosis factors, tumor growth factors, inter-leukeins, vascular endothelial growth factors and many others in the formation, or should we say, malformation leading to the existence of AVM's [13]. Recent evidence implicates genes of the Notch signaling pathway in the development of AVM's [14]. As these genes are involved in arterial differentiation and venous regression, their abnormalities lead to the formation of the nidus with direct arterio-venous shunting. Of interest, the mutations of these factors

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Received May 04, 2016; **Accepted** February 07, 2017; **Published** February 13, 2017

Citation: Al-Jehani H, Alabbas F (2017) Epilepsy and Intracranial Vascular Malformations: A Possible Missing Link! Brain Disord Ther 6: 228. doi: 10.4172/2168-975X.1000228

are also known to perturb cortical development. Phenotypically, most AVMs are classically described as that of a triangular malformation stemming for the ventricular surface with a draining vein either toward the superficial or deep venous outflow. This is, for the most part, reminiscent of the column of theory of cortical development [15]. The latter suggests that each and every segment of the ventricular zone is responsible for populating a column of cortex with neural and glial elements. One can intuitively assume that the same patterning is possible in the vascular elements.

Implications and Discussion

If the assumption that both neural and vascular developmental processes are guided, in part; by sets of common and shared genetic pathways, it is fair to think that the derangement of one genetic pathway could lead to the development of the AVM and focal cortical malformation contained within that particular deranged "cortico-vascular" column. Accordingly, the development of seizure could be attributed clinico-pathologically to an underlying cortical dysplasia or malformation rather than a vascular mal-development or blood flow abnormality in the area of the AVM [16,17].

This hypothesis would be easily being stable if we analyze the brain tissue around the AVM. Unfortunately, IVM surgery is one of the most refined in micro-neurosurgery, in which the brain around the IVM is respected. It must be minimally manipulated, leaving the underlying and surrounding brain out of reach to our scientific inquiry. This would be even more prudent if this particular part of the brain is "eloquent". Having access to this tissue around the IVMs will enable the study of this assumed mal-adaptive mechanism and what the developing brain utilizes while facing a hostile lesion like an AVM. As it stands, autopsies of patients harboring AVMs might provide some answers. An answer that would probably refine our understanding of cortical-vascular genetic interaction in relation to epileptogentic AVM's. Another way to obtain answers is through functional brain imaging in the form of diffusion tensor imaging to visualize the tracts in the brain as well as functional MRI. These were always labeled difficult in the vicinity of an AVM due to its strenuous blood flow pattern [18,19]. What if these studies are affected not by merely the blood flow but rather the cortical map-development assumed here. A change in our understanding of these mechanisms would require different imaging strategies like perfusion MRI and special MRI sequences to detect blood products within and around the IVMs to elucidate the burden of each component and correlate that with such clinical events as hemorrhage and seizures. If studied objectively and reproducible results are obtained, this will enable physicians to employ alternate or even novel treatment plans for epilepsy in AVMs. Such strategy would mean a specific regimen is designated to each individual patient based on a genetic recipe of his or her own making.

Conclusion

This individualized treatment approach could result in better seizure control without resorting to the blinded or reflexive surgical excision of the AVM hoping to reduce seizure tendency. More importantly, this will help avoid all together the risk of secondary epileptogensis due to persistent AVM presence or the formation of unnecessary surgical scarring.

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