New Trends in Management of Epilepsy in Patients with Cerebral Venous Malformations: Our Experience

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Abstract

Background: Venous vascular malformations, also known as venous angiomas or, more exactly, developmental venous anomalies (DVAs), represent congenital, anatomically variant pathways in the normal venous drainage of the brain area. In general neurological practice, DVAs are not considered epileptogenic, therefore, in conducting neuroimaging as a rule, not taken into account. A positive correlation, however, between the location of DVAs and the electroencephalographic seizure focus is debated.

Materials and Methods: The present study provides a complete analysis of clinical and MRI characteristics of symptomatic epilepsies associated with cerebral venous malformations in children and adults. Patients were selected after a retrospective search through the database of the University Clinic into which, since 2016, patients were prospectively entered. To date (February 2016), there is a total of 5,856 patients with epilepsy of which there are 105 patients with congenital malformations of the brain, and 32 of them were found to have principal diagnosis of DVA.

Results: Cavernous angiomas prevailed among venous anomalies (53.1%); DVAs were registered in 46.9% of cases. The associated analysis of DVA localization and the epileptic seizure types showed a direct relationship in 60.0% cases.

Conclusion: DVAs as a cause of seizures are important to consider when examining patients with epileptic seizures. (Int J Biomed. 2016;6(3):207-212.)

Key Words: brain ● developmental venous anomalies ● cavernous malformation ● epilepsy ● management

Abbreviations

CM, cavernous malformation; CT, computed tomography; CVM, cerebral venous malformations; DVAs, developmental venous anomalies; GRE, gradient echo; ILAE, International League Against Epilepsy; MRI, magnetic resonance imaging; SGTCS, secondary generalized tonic-clonic seizures; SWI, susceptibility weighted imaging; VEM, video EEG monitoring.

Introduction

Cerebral venous malformations (CVMs), also known as venous angiomas or, more exactly, developmental venous anomalies (DVAs), represent congenital, anatomically variant pathways in the normal venous drainage of the brain area. They consist of converging dilated medullary veins that drain centripetally and radially into a transcerebral collector that opens either into the superficial subcortical or deep pial veins.[1] DVAs have no proliferative potential, no direct arteriovenous shunts, and normal brain parenchyma between the dilated veins.[2] Once thought to be rare, they are now considered to be the most common vascular malformations in the central nervous system (CNS).[3,4] Although for many years DVAs were commonly called venous angiomas, the
newer term DVA has been recommended as more appropriate because the involved vessels are not abnormally formed, but apparently merely dilated. The majority of DVAs are found occasionally and never cause symptoms, although there are isolated reports of patients with syndromes attributed to DVAs. For example, DVAs have been reported to cause epilepsy, progressive neurologic deficits, and hemorrhage.\textsuperscript{[5,6]} Chronic, often undetected, microhemorrhages of these lesions result in iron deposition in adjacent brain tissue in the form of hemosiderin, and the iron in this perilesional hemosiderin is thought to play a major role in their epileptogenicity.\textsuperscript{[7,8]} Frequently, convulsions have been associated with venous malformations.\textsuperscript{[9]} A positive correlation, however, between the location of DVAs and the electroencephalographic seizure focus is unusual.

Contrast-enhanced CT, which is no doubt responsible for the recent increase in the number of reported cases of DVAs, is yielding to the far superior imaging ability of magnetic resonance as it becomes routinely available. MRI is thus becoming the primary study medium of choice and the means by which diagnosis of DVAs is verified.\textsuperscript{[10]} Although the standard contrast-enhanced MRI is excellent in depicting DVAs, adjacent hemosiderin from associated cavernomas may not be assessed without the use of gradient-echo or echo-planar imaging, especially with fast spin-echo techniques. On a contrast-enhanced MRI, the cluster of veins in developmental venous anomalies has a spoke-wheel appearance; the veins are small at the periphery and gradually enlarge as they approach a central draining vein.\textsuperscript{[11]} GRE or T2* sequences are able to delineate these lesions better than T1 or T2 weighted images. In patients with familial or multiple cavernous angiomas, GRE T2* sequences are very important in identifying the number of lesions missed by conventional spin-echo sequences. SWI may have sensitivity equal to that of GRE in detecting these capillary telangiectasias in the brain. SWI is also highly sensitive in detecting calcification as compared to T1 and T2 images.\textsuperscript{[12]}

Epilepsy associated with cavernous angioma of the brain is widely recognized. However, in general neurological practice, DVAs are not considered epileptogenic: therefore, in conducting neuroimaging, as a rule they are not taken into account.

**Materials and Methods**

We analyzed clinical and MRI characteristics of symptomatic epilepsies associated with CVMs in children and adults. Patients were selected after a retrospective search through the database (October 2008 – February 2016) of the Neurological Center of Epileptology, Neurogenetics and Brain Research of the University Clinic into which, since 2016, patients were prospectively entered. To date (February 2016), there is a total of 5,856 patients with epilepsy of which there are 105 patients with congenital malformation of the brain, and 32 of them were found to have principal diagnosis of DVAs. We analyzed epidemiological variables such as age, gender, associated risk factors, clinical presentation, radiological data, treatment options, and follow-up. It was performed as a part of complex research No 210-16 «Epidemiological, genetic and neurophysiological aspects of nervous system disorders (central, peripheral, autonomic) and preventive medicine» (state registration No 0120.0807480).\textsuperscript{[13,14]} The present study was approved by the Ethics Committee of Krasnoyarsk State Medical University. Written informed consent was obtained from each patient.

From 2008 to 2016, we included 32 patients with CVMs and symptomatic epilepsy in our study. All patients underwent preliminary anamnestic and clinical selection using stratified randomization. All of the participants were residents of the Siberian Federal District, and had certain diagnosis of symptomatic epilepsy.

Symptomatic epilepsy diagnosis in all patients enrolled in this study was verified using VEM along with carrying out stress tests. All patients underwent brain MRI (T.5 Tesla or higher), including GRE T2* and SWI sequences. Detailed analysis of case history for each patient included debut age, the type of epileptic seizures at debut, and the dynamics of the disease progression.

All statistical analyses were carried out using licensed software package SPSS, version 20.0 (USA). Categorical variables are presented using frequencies and percentages. The data for variation indices with nonparametric distribution are presented with medians and quartiles (Me [P25; P75]).

**Results**

Symptomatic epilepsies associated with CVMs were registered in 17 (53.1%) male patients and in 15 (46.9%) female patients. The age of patients at the time of the survey varied between 4 and 71 years with median of 27.5 (17.5:41.5) years; there were 8 (25.0%) children and 24 (75.0%) adults. The epilepsy onset age varied between 0.4 and 67 years with a median of 9.5 (5:26.5) years. Peak onset of the epileptic seizures varied between 0 and 10 years (17 [53.1%]). The period from epilepsy onset to the brain MRI and DVA identification varied between 0 and 52 years with median of 5.5 (1:11) years.

Distribution of epilepsy seizure types was as follows: simple focal (partial) seizures in 18.8% of cases, complex focal (partial) seizures in 3.1% of cases, combined simple and complex focal seizures in 18.8%, SGTCS in 3.1%, combined simple focal seizures and SGTCS in 15.6%, both complex focal seizures and SGTCS in 21.3%, and simple and complex focal seizures with SGTCS in 25% of cases.

Analysis of pedigrees identified 13 (40.6%) patients with family members or close relatives presenting with congenital malformations and 5 (15.6%) with epileptic seizures.

According to VEM-results, the location of the epileptic discharges was principally presented by frontal lobe seizures (13 [40.6%]) and temporal lobe seizures (13 [40.6%]).

The associated analysis of all CVM localization (by MRI) and location of the epileptic activity (by VEM) showed a direct relationship in 12 (37.5%) cases, a partial relationship with one DVA in 6 (18.8%) cases, and no associations in 14 (43.8%) cases. The associated analysis of DVA localization and the epileptic seizure types showed a direct relationship in 9 (60.0%) (Fig.1) cases and no association in 6 (40.0%) patients. In the latter group of patients, focal cortical dysplasia could serve as an area of beginning epileptic seizures.
Venous anomalies were detected in hereditary diseases such as Von Hippel–Lindau disease in 13 (40.6%) patients, Sturge–Weber syndrome (encephalotrigeminal angiomatosis) in 2 (6.2%) cases, Gorlin-Goltz syndrome in 3.1% cases, and tuberous sclerosis complex in 3.1% cases. Cerebral venous anomalies were isolated in 17 (53%) cases (Fig. 2). Surgical treatment was recommended for focal epilepsy. Cavernous angiomas prevailed among venous anomalies (53.1%); DVAs were registered in 46.9% of cases.

Monotherapy was administered in 78.1% cases; prevailing medications were carbamazepine group drugs (13 [52.0%]). A drug-resistant epilepsy was observed only in 3 (9.4%) cases of CVMs, including two cases of CM and one case of DVAs.

**Fig. 1a.** EEG of a 7-year-old girl: regional epileptiform activity in the right frontal lobe.

**Fig. 1b.** EEG of a 7-year-old girl: regional epileptiform activity in the right frontal lobe with secondary bilateral synchrony.

**Fig. 2.** Brain MRI of a 7-year-old girl with symptomatic focal epilepsy associated with the isolated DVA.

(A). T1 sagittal image: venous angioma of the right frontal lobe involving massive superficial vein.
(B). T2 FLAIR image: atrophy of the right frontal lobe.
(C). SWI: venous angioma of the right frontal lobe.
Discussion

DVAs are extreme variations of normal transmedullary veins that are necessary for the drainage of the white and gray matter.\textsuperscript{[15]} Currently, due to progress in brain investigation, they can be diagnosed with a higher frequency.\textsuperscript{[16-20]}

DVAs are the most commonly encountered vascular malformation in the CNS, accounting for up to 60% of them. Their prevalence is about 2.5% to 9%\textsuperscript{[21]} and they are usually solitary. DVA is a variation of normal venous drainage. It is considered to be formed during Padget’s fourth to seventh stage of development.\textsuperscript{[22]}

A typical venous angioma is composed of a large parent vein that receives an array of radially-oriented tributary veins in a spoke-wheel configuration which looks like «the caput medusa».\textsuperscript{[23]}

It is generally accepted that DVAs are formed during intrauterine life,\textsuperscript{[24,25]} but no consensus exists regarding the mechanism leading to their formation. Their etiology and mechanism of development are unknown, but it is currently accepted that they act like a compensatory system of cerebral parenchyma venous drainage due to early failure, abnormal development, or an intrauterine occlusion of normal capillaries or small transcerebral veins and thrombosis of normal parenchymal veins.\textsuperscript{[22]} These drainage pathways may have developed as a method for maintaining the hemodynamic equilibrium of the transcortical venous drainage.

During embryogenesis, occlusion or maldevelopment occur during the formation of the medullary veins or their tributaries, and as a result, compensation DVA is formed. Thus, the main suggested etiology for DVA formation is an embryologic event that results in either arrested formation or thrombosis of the developing venous drainage of the specific region.\textsuperscript{[26-28]} That is followed by a secondary compensatory mechanism in which embryologic medullary venules persist and cluster locally in a large draining vein.\textsuperscript{[27,29-31]} These might occasionally develop as a result of dominant inheritance of a gene mutation in the short arm of chromosome 9.\textsuperscript{[32]}

DVAs can either drain into deep subependymal veins and the galenic system or drain into superficial cortical veins. The superficial pattern is present in about 70%, while the deep drainage pattern is present in 20% of the population.\textsuperscript{[22,29,33]} The remaining 10% have a combination of the superficial and deep drainage.\textsuperscript{[22,29,33]} DVAs are mostly supratentorial and are found most frequently in the frontal lobe (36% to 56%) followed by the parietal (12% to 24%), occipital (4%) and the temporal lobes (2% to 19%); in the cerebellum (14% to 29%); in the basal ganglia (6%); in the thalamus and ventricles (11%), and in the brainstem (less than 5%).\textsuperscript{[22,29,33]} DVAs may also be present adjacent to brain tumors, infarctions, demyelinating areas, and moyamoya malformations; also associated congenital anomalies of the cerebral arterial system, such as the primitive trigeminal artery, fetal origin of the posterior cerebral arterial system, as well as fetal venous anomalies, such as retention of the primitive facial, occipital, and marginal tentorial sinuses.\textsuperscript{[34]}

The initial diagnosis is typically made in the third decade.\textsuperscript{[35,36]} There is an equal prevalence in men and women. Cerebral venous angioma is usually asymptomatic and may be found occasionally at autopsy or by angiography.\textsuperscript{[21,37]}

DVAs may present with headache, seizure, dizziness, and ataxia.\textsuperscript{[35,38-40]} Prospective studies on venous angiomas have demonstrated a very low rate of both symptomatic hemorrhage (0.34% per year) and neurologic symptoms; bleeding, when it rarely occurs, has been hypothetically blamed on putative neighboring cavernous malformations.\textsuperscript{[41]} Blood flow through venous angiomas is low, and they are thought to drain normally from the brain.

Symptoms can be produced either by venous congestion related to flow obstruction or mechanical compression (hydrocephalus or nerve compression). The clinical sequelae of DVA are likely related to the regional changes that occur near it.\textsuperscript{[42]} They reported histopathologic evidence of vascular remodeling related to altered hemodynamics in the region of DVA, including microvascular wall hyalinization and calcification, which are consistent with chronic regional blood flow alternation and venous hypertension.\textsuperscript{[43]}

Very few cases have been reported in which DVAs were located in the same area as the EEG focus of the seizure.\textsuperscript{[39]} The incidence of seizures associated with symptomatic DVAs ranges from 8% to 29%.\textsuperscript{[33,44,45]} In most of the cases, DVAs were located in a different region with respect to the focus of the seizure.\textsuperscript{[9,45]} or there was another lesion found that could be the cause of epilepsy.\textsuperscript{[38]} DVAs have been reported to be associated usually with generalized seizures,\textsuperscript{[44,46]} but some patients have experienced partial seizures,\textsuperscript{[44,47]} complex partial seizures\textsuperscript{[46]} or even Jacksonian march of motor seizures.\textsuperscript{[11]}

Although cases of existence of DVAs and seizures have been reported, the correlation between them has not been firmly determined.\textsuperscript{[15,22,38,41,45]} The study of Striano et al.\textsuperscript{[15]} revealed that DVAs are rarely found in epileptic patients, as distinct from other vascular malformations, cavernomas in particular. Topographic and/or etiological relationships between DVA and epilepsy are still undefined. Similarly, seizures have been localized to areas not associated with DVA in several studies\textsuperscript{[9,35]} or to associated cortical dysplasias.\textsuperscript{[15]}

DVAs may be associated with abnormal neuronal migration and possible susceptibility to epileptogenesis.\textsuperscript{[19]} However, recent literature suggests that DVAs may be the cause of focal epilepsies in cases where no epileptogenic lesions can be detected.\textsuperscript{[48]} Several mechanisms are postulated based on the following: (1) subclinical hemorrhage, more likely when a DVA is associated with a cavernous malformation\textsuperscript{[9]} and (2) increased inflow or restricted outflow, resulting in intermittent cortical hyperemia and dysfunction creating an epileptic focus.\textsuperscript{[22]}

Patients with DVAs associated with epilepsy require a precise analysis of the seizure pattern and EEG findings, because another epileptogenic lesion may be present which is surgically curable.\textsuperscript{[45]}

MRI is the diagnostic method of choice, showing a starburst pattern of white matter veins converging on a large draining vein in the case of a venous malformation.\textsuperscript{[49]} When cerebral DVAs present symptoms such as cerebral hemorrhage, epilepsy, headache, cranial nerve paresis, and/or cerebral ataxia, surgical intervention has been carried out.\textsuperscript{[37,50-53]} Clinicians should be aware that, though generally benign, DVAs and their associated lesions may represent a complex entity.
with potential for clinical complication requiring, in certain cases, additional imaging investigations and specific medical management.[54,55]

**Conclusion**

A cavernous angioma was found more frequently in our patients with SE. However, DVAs were diagnosed in 46.9% of patients. Association localization of DVAs with localization-related epileptic seizures was observed in 60.0% of cases.

Thus, DVAs as a cause of seizures are important to consider when examining patients with epileptic seizures. The inclusion of SWI in the protocol of neuroradiological studies has allowed us to improve the quality of diagnostic care for patients with symptomatic focal epilepsy in our clinic, and it was useful in the selection of surgical treatment for drug-resistant forms of epilepsy.

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**Competing interests**

The authors declare that they have no competing interests.

**References**

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