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Vascular intracranial malformations and dementia: An under-estimated cause and clinical correlation. Clinical note☆

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ABSTRACT

Cerebrovascular malformations (CVMs) such as arteriovenous malformations (AVMs) or dural arteriovenous fistulas (DAVFs) represent a possible source of intracranial hemorrhage, but these malformations can also manifest with neurologic disorders secondary to ischemic penumbra from vascular steal. In the latter case, the clinical manifestations are less obvious and characteristic, and may include a varied clinical spectrum ranging from focal deficits to generalized malfunction of the brain parenchyma resulting in dementia. Dementias secondary to CVMs constitute a probably underestimated subpopulation of patients of great interest because they present with devastating but potentially reversible cognitive impairment. We examined the pertinent literature regarding the clinical manifestations of CVMs characterized by cognitive impairment and describe the distinctive clinical features. Our results confirm that cognitive impairment is one of the clinical manifestations of CVMs and is a frequently misrecognized and often late-diagnosed cause of reversible dementia.

Introduction

Rapidly progressive dementia (RPD) is a condition of cognitive decline in an adult that occurs over a period of a few weeks or months. Although prion disorders are the most common causes of RPD [1,8], reversible causes of RPD should always be explored in the differential diagnosis [15,31]. Aside from prion illnesses, atypical presentations of other neurodegenerative disorders, treatable disorders such as autoimmune encephalopathies, infections, and neoplasms are the most common causes of RPD [32]. RPDs have been also linked to vascular malformations such as dural arterial venous fistulas in a number of recent case reports [1]. In the majority of cases, the vascular etiology of dementia is the result of progressive ischemic events. However, some vascular abnormalities of neurosurgical competence may be a cause of RPD in a minority of cases [28,29,31]. The biggest challenge in identifying this cause is that it is frequently dementia disorders that do not fully fit the categorization criteria for vascular forms and are difficult to detect and evaluate on imaging.

With this paper, we wish to highlight the importance of recognizing vascular malformations as one of the causes of RPD, which, if identified and treated promptly, can result in a significant improvement in the patient's cognitive condition.

Vascular malformations involved in cognitive impairment: dural arteriovenous fistulas

Dural arteriovenous fistulas (DAVFs) are lesions that account for 10–15% of intracranial vascular malformations [2] characterized by a

Abbreviations: RPD, Rapidly progressive dementia; DAVFs, Dural arteriovenous fistulas; CSF, cerebrospinal fluid; AVMs, Cerebral arteriovenous malformations; PET, positron emission tomography; DWI, diffusion-weighted imaging; MR-DSA, MR digital subtraction angiography; DSA, Digital subtraction angiography; SPECT, single-photon emission computed tomography.

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shunt between dural arteries and a venous sinus or cortical vein [3]. DAVFs can initiate a rapid decline in neurocognitive function with, at times, Parkinson's-like symptoms. The incidence of dementia as a presenting symptom of high-grade DAVFs has been reported as 1–11% of cases [9,10]. DAVFs can have a wide variety of clinical manifestations depending on their location and angiographic features [4,5]. Cognitive impairment, affecting memory, computation, orientation, visuospatial function, and language, may be present in patients with DAVFs [6,7]. Usually, such impairment is manifested by a state of disorientation over time, inability to walk, amnesia, short-term memory impairment, and difficulty in reading [7,8].

The explanation for this presentation is a large number of DAVFs that led to global cerebral dysfunction through a combination of hypoperfusion of the cerebral cortex due to venous hypertension and venous white matter infarcts [11,12] given the location of the disease.

The exact pathogenesis of dementia development in patients with DAVF remains largely unknown [13,14,15]. Imaging changes and pathologic findings support the hypothesis that the clinical course results from the delivery of excessive volumes of blood flow into a venous system with outflow obstruction. Venous congestion, the result of hypertension with impaired parenchymal venous drainage [12], and ischemia occur from the downstream effect of arterialization of cortical venous drainage from cortical venous hypertension [16], leading to cerebral venous congestion [17]. There are two investigated mechanisms of DAVF-induced dementia: cortical dementia and thalamic dementia due to edema of deep gray and white matter structures [4]. The "two types" of DAVF-induced dementia have been described, each of which has its distinct clinical and neuroimaging characteristics [31]. The mechanism of RPD in patients with the cortical variant is thought to be disturbance of cerebrospinal fluid (CSF) reabsorption due to medullary venous congestion secondary to occlusion or venous hypertension of the normal draining sinus or direct reflux into a medullary vein from the DAVF resulting in arterialization of the medullary veins [4]. Cortical dementia due to DAVF is characterized by rapidly progressive cognitive dysfunction, including impairment of verbal fluency and language comprehension, and memory dysfunction that is often accompanied by focal cortical deficits. In the thalamic form, the clinical features may be explained by hypertension of the deep venous system, leading to bilateral basal ganglia/thalamus dysfunction with posterior fossa venous stasis. DAVF with deep venous drainage manifesting as bilateral thalamic and basal ganglia edema can result in cognitive and memory impairment, parkinsonism, and hypersomnolence [2,3,18] (Fig. 1). Thalamic dementia due to DAVF is characterized by rapidly progressive cognitive dysfunction including disorientation, executive dysfunction, attention deficit, memory impairment, confabulation, and disinhibition [6,11,12,19,20,21]. Once a DAVF is identified as the cause of dementia syndrome, prompt treatment should be initiated, as the rapid neurological decline has been reported within days of the initial diagnosis of DAVF [11,12]. DAVFs represent a potentially treatable and reversible cause of dementia.

Treatment with endovascular or surgical techniques carries a low risk of complications and is associated with a high degree of success, often leading to complete resolution of present symptoms and MRI abnormalities [19]. Indeed, there are numerous cases reported in the literature in which there is clinical, radiological, and cognitive improvement after removal of the venous shunt.

Vascular malformations involved in cognitive impairment: cerebral arteriovenous malformations

Cerebral arteriovenous malformations (AVMs) are congenital vascular lesions in the brain parenchyma, characterized by a tangled mass of arteries and veins devoid of smaller vessels and capillaries [2]. The arteries shunt blood under high pressure directly into the draining low-pressure veins, without the pressure-lowering effect of smaller vessels and capillaries. This results in an increased risk of rupture and hemorrhage as well as hypo-perfusion of the surrounding brain tissue, which ultimately results in a reduction of oxygen and nutrient delivery,

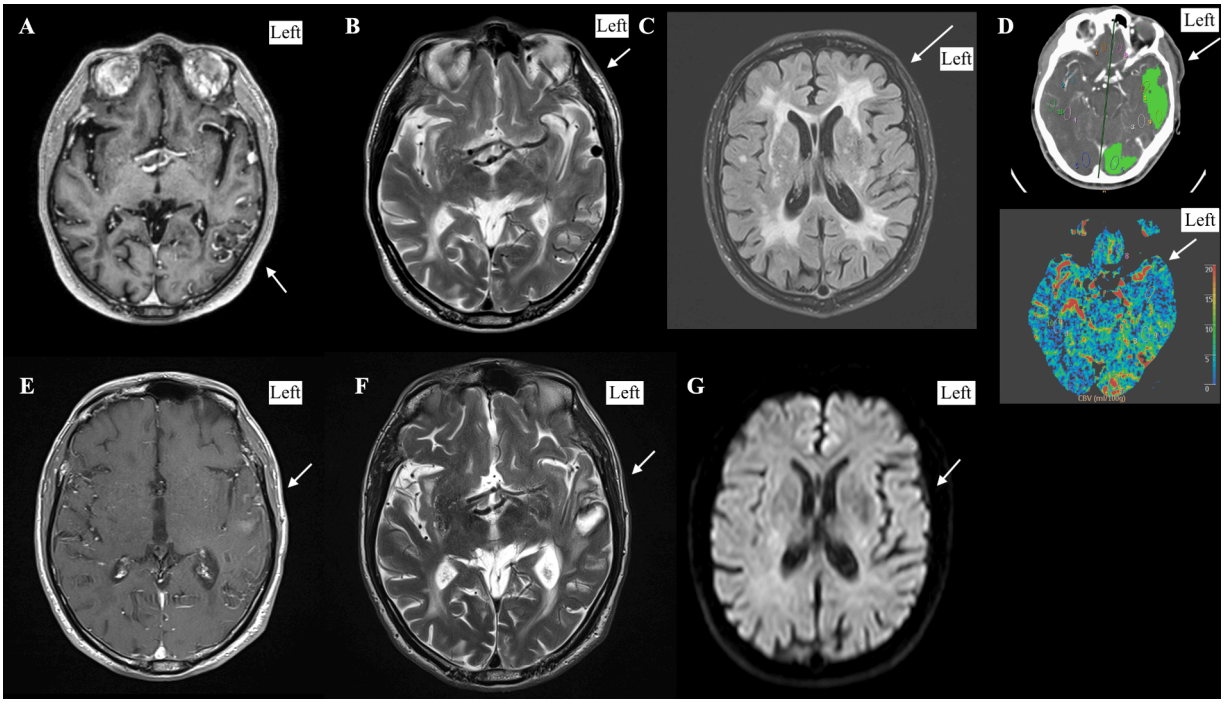

Fig. 1. Images show the case of a 66-year-old patient with onset of rapidly progressive dementia (RPD). During diagnostic investigations to identify the cause of dementia, a left parieto-occipital dural arteriovenous fistula (DAVF) with deep venous outflow is evident. T1-weighted MRI images with mdc (A) and T2-weighted (B) show the presence of vascular abnormalities without signs of bleeding (white arrow). T2-fluid liquid attenuated (FLAIR) and DWI (C) images document areas of cerebrovascular distress likely from blood theft, this finding was then confirmed with CT perfusion imaging (D) (white arrow). Images E-F-G show radiological control at 1 year postoperatively with partial regression of cognitive symptoms.

and impairment of clearance of waste metabolites like carbon dioxide [22,23].

Often, AVMs are asymptomatic and go undetected unless there is a clinical event (hemorrhage or seizure). Unlike other brain lesions, AVMs per se do not often cause cognitive dysfunction (Fig. 2). The reason lies in a brain's functional organization may be abnormal with functional centers dispersed away from the anatomic lesion. This could occur due to AVM formation during early brain development. Rather, hemorrhage, leakage of blood from the AVM, is more often responsible for functional/cognitive changes seen in patients with AVMs. Pathological data have shown that approximately 12% of AVM's become symptomatic and the others are captured either inadvertently or at autopsy [24].

In most cases reported in the literature, there is a longstanding assumption that AVMs cause focal cognitive deficits by a "steal phenomenon''; that is, by directing increased blood flow toward the AVM and away from other regions of the brain [25]. The cerebral steal mechanism is thought to decrease normal perfusion and cause hypoperfusion in adjacent and distant brain areas. Some studies have found normal cognition in AVM patients, while other studies have demonstrated cognitive impairment in this patient population. These mixed findings may be due to the heterogeneity of the patients studied (for example, AVMs of differing sizes and locations, differing degrees of steal). Other studies [26] have reported that between 50 and 80% of AVM patients have impaired general cognitive ability. Clear characterization of the cognitive profile found in AVM patients is yet to be fully determined, [27] although the improvement in dementia after the surgical interruption of the retrograde inflow by the open surgical approach was remarkable [28].

These cases do not prove the pathological processes of vascular 'steal', but the theory has been proposed by many authors. Is argued that an AVM with one of three characteristics is more likely to cause 'steal phenomena' (large size, angiomatous change, and peripheral venous drainage).

Advances in the understanding of the hemodynamics of AVMs, seem to have been undertaken to elucidate cognitive and emotional results of surgery. In neuro-surgical studies subtle but functionally important psychological sequelae as well as psychological improvement may easily be overlooked. Yet, 23% of patients obtained scores below two standard deviations of the appropriate average in two or more tests, which may suggest some negative influence of the AVM on mental functioning. Such low scores were found most frequently in psychomotor speed, learning, and memory tasks, i.e., tasks with a high sensitivity to disturbance of cognitive function irrespective of the cause or locus of cerebral dysfunction [29].

Other researchers [24] disagree with the "steal" hypotheses. They demonstrated that an AVM patient with chronic cerebral hypotension did not have any functional cognitive impairment. In addition, they used positron emission tomography (PET) to study patients with AVMs and demonstrated that while these patients did have hypoperfusion in surrounding tissue, they did not have any parenchymal volume loss, and the metabolism was normal [23,24].

Seems to be, however, a relatively benign neurobehavioural development after excision of a supratentorial AVM, with mostly reversible early postoperative disturbances in brain function [30].

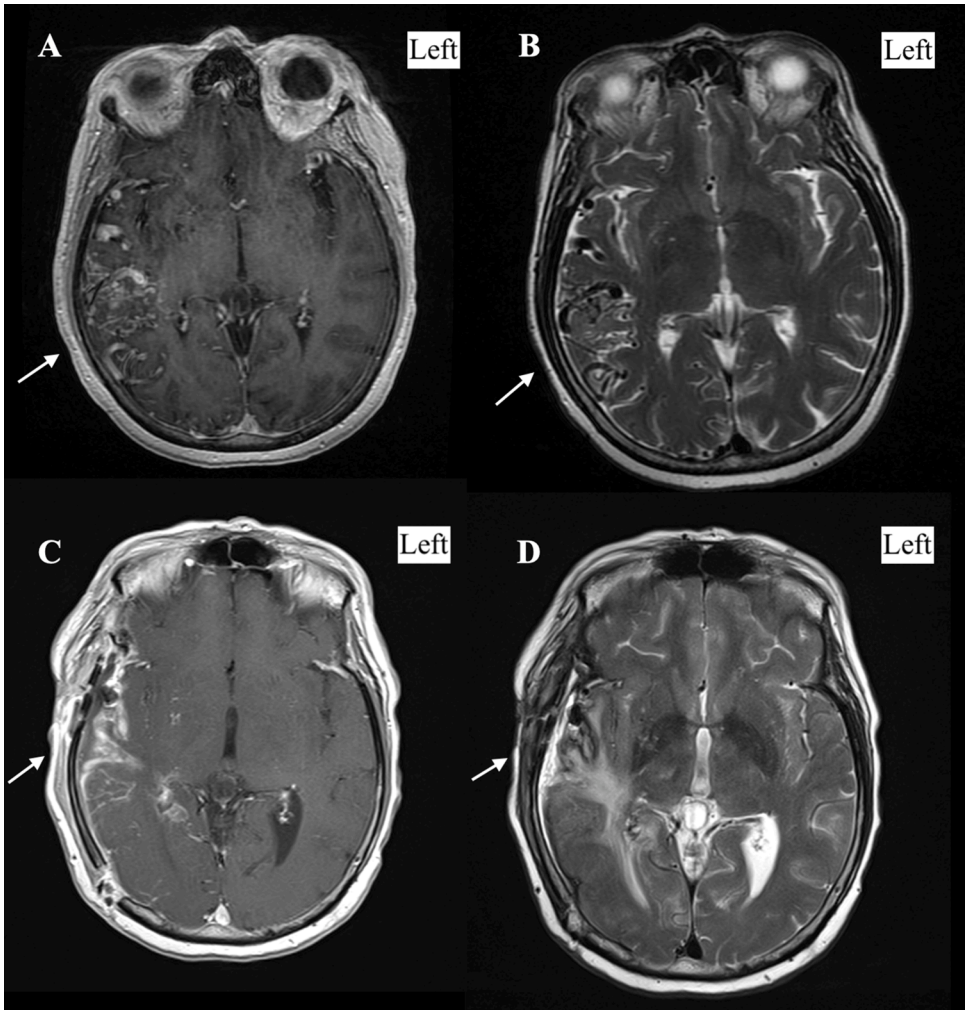

Fig. 2. The figure shows the case of a 59-year-old patient with seizure onset. Since about a year before, it was reported by family members the presence of cognitive impairment with difficulty in recognizing people. MRI images (A-B) document the presence of a surgically treated right temporo-parietal artero-venous malformation (AVM) with deep venous drainage (white arrow). Postoperative MRI follow-up (C-D) performed after six months shows the outcome of the removal of the vascular lesion; the patient had complete regression of symptoms within three months.

Discussion

Despite the relatively small number of cases reported in the literature, cognitive impairment in vascular malformations such as DAVF and AVM are not so rare, and we believe it is often misdiagnosed. In our review, the incidence of dementia-debut in intracranial vascular malformations is variably reported from 6% to 25% of all series [7,8,29].

Since with a first level exam such as an intracranial CT scan, a malformation of this type is often not visible, the dementia specialist often does not even consider the possibility of engaging in second-level examinations such as angio-CT scan (Image 3), brain-MRI (Image 2) with diffusion-weighted imaging (DWI) and still less MR digital subtraction angiography (MR-DSA) or intracranial Digital subtraction angiography (DSA) [5,10]. A more recent introduced single-photon emission computed tomography (SPECT) exam in clinical practice has demonstrated a decreased cerebral blood flow in different areas of the brain [6,8]. In an RPD, the diagnosis of vascular malformation is easy to be ignored and delayed or missed, and prescribing DSA is necessary for probable DAVFs patients [31].

Neurologists and clinicians generally are familiar with the differential diagnoses of slowly progressive neurodegenerative dementias, but the diagnosis of RPD entails a different diagnostic approach. Although there is no clear definition for the time frame of an RPD, the author typically uses the term to refer to conditions that progress from onset of the first symptom to dementia (decline in more than one cognitive domain with functional impairment) in less than 1 to 2 years, although most occur over weeks to months.

Perhaps the prototypical RPDs are prion diseases, such as Jakob-Creutzfeldt disease, and the non-Jakob- Creutzfeldt disease group comprises 25% to 44% of all referrals [1,2].

Taking into account the cases reported in the literature, it is clear that FAVDs more frequently can begin with a PDR, while in the case of AVMs, the onset with cognitive impairment is more often associated with ischemic or hemorrhagic phenomena and only rarely (and notionally sometimes) [22,23] there is an onset of RPD given by a steal phenomenon. Therefore it is appropriate in the latter case to perform a differential diagnosis admitting the coexistence of the two pathological phenomena. In any case, however, second-level imaging examinations and a possible neurosurgical evaluation can greatly help to discover a cause of RPD reversible with surgery, with an optimal functional outcome for the patient. Due to their curable nature, the diagnosis of DAVFs must be suspected when facing an RPD picture, even more so if it is associated with characteristic abnormalities of the hemispheric white matter.

Disclosure of interest

Regarding the topics of the present paper, the authors have nothing to disclose.

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Ethical approval

All procedures performed in studies involving human participants were by the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This article does not contain any studies with animals performed by any authors.

Informed consent

Informed consent was obtained from all individual participants included in the study.

The patient has consented to submitting this review article to the journal.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that all have approved the order of authors listed in the manuscript of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work. There are no impediments to publication, including the timing of publication, concerning intellectual property. In so doing, we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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Declaration of Competing Interest

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