Interdisciplinary Neurosurgery 22 (2020) 100851

Contents lists available at ScienceDirect

Interdisciplinary Neurosurgery

journal homepage: www.elsevier.com/locate/inat

Antithrombotic therapy of Cerebral cavernous malformations

ARTICLE INFO

Keywords:
Antithrombotic therapy
Cerebral cavernous malformations
Slow-flow vascular anomaly
Intracerebral venous anomaly
Treatment of peripheral venous anomalies

ABSTRACT

Cavernous malformations are recognized as the most common vascular anomalies in the brain, that often lead to hemorrhage with neurological symptoms. Usually the treatment is surgical removal or stereotactic radiotherapy. We present a case of a slow-flow vascular anomaly located in the cavernous sinus with recurrent partial thrombotic areas. Inspired by treatment of peripheral venous anomalies antithrombotic therapy was initiated instead of surgery or stereotactic radiotherapy. This led to complete spontaneous resolution of the lesion and normalization of symptoms within nine months. The patient never showed any symptoms over a period of eight years while continuing antithrombotic therapy. Based on this case this therapy may be a reasonable approach to treat intracerebral venous anomalies.

1. Introduction

The International Society for the Study of Vascular Anomalies (ISSVA) has published a classification of vascular anomalies (Table 1). Cerebral cavernous malformations are recognized as the most common vascular anomalies in the brain [1]. Venous malformations (VM) are responsible for about 50% of vascular anomalies in the periphery and only 5–15% in the central nervous system [2]. Due to their slow flow and low pressure they tend to develop recurrent thrombosis [3]. This raises the risk for venous congestion, voluminous increase and hemorrhage. The clinical presentation often varies dependent on the location, the extent of thrombosis and presence of hemorrhage. The patients are treated conservatively, surgically or with stereotactic radiotherapy [1]. We present a venous anomaly with spontaneous resolution of symptoms after conservative treatment.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

2. Case report

A 39-year-old woman presented with diplopia which occurred five days before she came to the hospital. Ophthalmological examination found a paresis of the left abducens nerve.

Cerebral magnetic resonance imaging (MRI) showed a small suspicious lesion of 1.5 mm in diameter in the left cavernous sinus (Fig. 1a).

Four months after the first diagnostic investigation the paresis of the left abducens nerve was dissolved but recurred two months later with the same intensity as before.

The subsequent MRI (05/2012) showed a progress in size to 11 mm in diameter (Fig. 1a). In catheter angiography the cavernoma exhibited a partial early arterial stain with a delayed venous circulation (Fig. 1b). The intermittent symptoms of the patient and the image results were compatible with a cavernoma of the cavernous sinus with intermittent thrombosis of particular lesion caverns. To prevent from recurrent thrombosis antithrombotic therapy was initiated in analogy to treatment of peripheral venous malformations. Clopidogrel 75 mg per day was administered because of a reported allergy to Aspirin.

Nine months after the start of antithrombotic therapy the paresis of the left abducens nerve had disappeared and the patient had no focal deficits. Multiple performed follow-up MRI within three years showed a continuous decrease in size until complete recovery was reached (Fig. 1a). The patient never showed any symptoms within eight years while continuing drug therapy with Clopidogrel every second day.

3. Discussion

In our case, the vascular anomaly met all clinical and imaging diagnostic criteria to qualify as low flow VM. Patients with low flow vascular malformations of the head and neck also have a higher incidence of developmental venous anomalies [2]. The slow blood flow typical in VMs is associated to the deposition of red cells and platelet aggregation with subsequent occlusion, hypertension, and rupture of the venous structures [1]. This mechanism can explain dynamic evolution of VMs. Hemodynamic stress potentially influences the development of neoangiogenesis and endothelial proliferation of VMs [5]. These determinants may induce again hemodynamic stress what may lead in a cyclic manner to the expression of both proliferative and neoangiogenetic factors [6]. Immunohistochemical studies showed the

Table 1
ISSVA classification for vascular anomalies, list of associated genes in VMs [4].

Venous malformations	Associated gene
Common VM	TEK (TIE2)/PIK3CA
Familial VM cutaneo-mucosal (VMCM)	TEK (TIE2)
Blue rubber bleb nevus (Bean) syndrome VM	TEK (TIE2)
Glomuvenous malformation (GVM)	Glomulin
Cerebral cavernous malformation (CCM)	CCM1 (KRIT1), CCM2 (Malcavernin), CCM3 (PDCD10)
Familial intraosseous vascular malformation (VMOS)	ELMO2
Verrucous venous malformation (formerly verrucous hemangioma)	MAP3K3

https://doi.org/10.1016/j.inat.2020.100851
Received 14 July 2020; Accepted 26 July 2020
Available online 04 August 2020

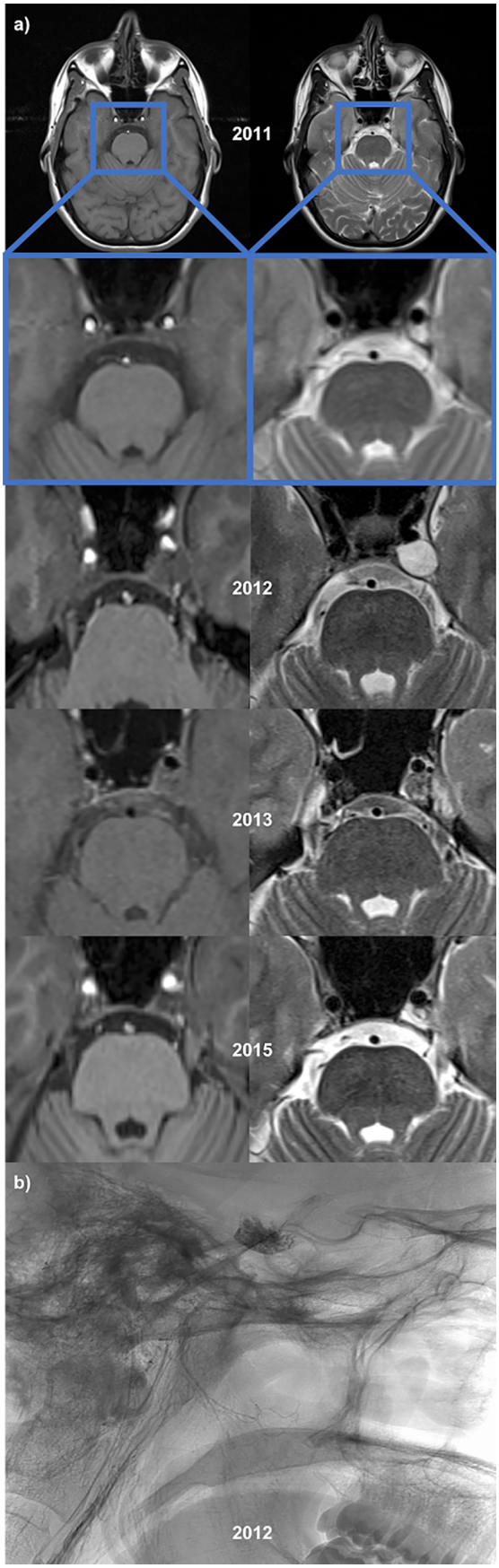

Fig. 1. a) T1 (left) and T2 (right) MRI transversal sequences of the cavernous sinus chronologically ordered. Note the maximal volume of the lesion in 2012 and before initiation of antithrombotic therapy. b) Late arterial enhancement in the posterior caudal part of the cavernous sinus after contrasting the left external carotid artery in the lateral view.

production of the vascular endothelial growth factor and its receptors, as well as other growth factors FGF2, TGFB1, several structural and matrix proteins, suggesting angiogenetic activity and potential of de novo generation in these malformations [5]. The genetic mutations in familial cases linked to three genetic loci (CCM1, CCM2, and CCM3) also influence formation of VMs and predispose to thrombosis [1]. VM in our case could be classified as a peripheral venous malformation with location in the cavernous sinus and blood supply via extracranial vessels (Fig. 1b). Inspired by treatment of peripheral low flow venous anomalies, conservative treatment with anti-aggregation therapy was considered. Our hypothesis was confirmed by the positive outcome with complete resolution of symptoms. Considering this successful concept antithrombotic therapy could be a reasonable treatment for intracerebral venous anomalies of this kind.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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