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Review

Hemorrhage risk and clinical features of multiple intracranial arteriovenous malformations

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ABSTRACT

The aim of this report is to examine clinical characteristics, treatment strategies, and annual hemorrhage incidence rate for patients with multiple arteriovenous malformations (MAVM). The PubMed and EMBASE databases and the arteriovenous malformations (AVM) database at The Johns Hopkins Hospital were searched to identify patients with MAVM. Data related to demographics, clinical features, management, and treatment outcomes were analyzed with descriptive statistics. Thirty-eight patients met the inclusion criteria. The annual hemorrhage incidence rate was 6.7%. Surgical intervention remained the most common single-modality treatment from 1949–2011. Between 1990 and 2011, multiple-modality treatment strategies (36% of cases) were employed more frequently. The most common presenting features were neurological deficit (74%) and hemorrhage (63%). In patients undergoing staged treatment of MAVM, hemorrhage of an untreated nidus (n = 5), visualization of a new nidus (n = 9), and disappearance of an untreated nidus (n = 2) were observed. Limitations of this study include small sample size and reporting bias. The annual hemorrhage incidence rate for MAVM patients was approximately two- to three-fold greater than the reported annual hemorrhage rates for solitary AVM. Combining different treatment modalities has become the most common management strategy. The potential instability of remaining nidi with staged or incomplete treatment necessitates close follow-up in these cases.

1. Introduction

Solitary brain arteriovenous malformations (AVM) are uncommon, with prevalence estimates ranging from 1.34–18 per 100,000 [1]. The reported incidence of multiple arteriovenous malformations (MAVM) ranges from 0.3–3.2%, with an average incidence of 1.9% [2–7]. AVM are rare congenital vascular lesions that form in the absence of capillary beds allowing direct communication between arteries and veins within the cerebral parenchyma. The high-flow arteriovenous shunt generates distended tangles of rupture-prone vessels [1,2,8,9]. The annual risk of hemorrhage associated with AVM in the general population ranges between 2–4% per year [1,8,10,11]. Currently there are no reports of the annual hemorrhage risk for patients with MAVM. Our objectives in this study are to report two new MAVM patients, review previous MAVM reports in the literature to investigate clinical characteristics and management trends, and estimate the annual hemorrhage risk in patients with MAVM.

2. Methods

2.1. Study selection

PubMed and EMBASE databases were searched for "multiple", "arteriovenous", and "malformations" through to 19 November 2014. The references of reviewed studies were examined for additional relevant citations. There were no publication date restrictions. Publications in English meeting search criteria were reviewed. We also retrospectively reviewed an Institutional Review Board-approved institutional AVM database for additional patients with MAVM. The medical records of patients meeting inclusion criteria were reviewed.

To meet inclusion criteria, patients had to be at least 21 years old and have at least two distinct AVM nidi separated by brain parenchyma. MAVM patients with hereditary hemorrhagic telangiectasia (HHT) were excluded from this study given fundamental differences from sporadic AVM; the predominant micro AVM (less than 1 cm nidus size) of HHT are associated with a low risk of hemorrhage, and are often treated conservatively with medical management alone [4]. Cases of Wyburn–Mason syndrome were

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included because they are sporadic, their natural history resembles that of AVM not associated with phakomatosis, and the treatment approaches for both types of brain AVM are also similar [12].

2.2. Data extraction

Epidemiological data of patient age, patient sex, presenting symptoms, number of hemorrhagic events, number of AVM nidi, nidus location, laterality, nidus size, arterial feeding vessels, venous drainage characteristics, management, duration of follow-up, and treatment outcome were extracted. Nidus size was categorized as follows: AVM under 3 cm were considered small, 3 to 6 cm medium, and over 6 cm large [13].

Treatment modalities were classified as: surgery, embolization, radiosurgery, conservative management, or a combination. For analysis of treatment strategies, cases were categorized as occurring between 1949–1989 or 1990–2011. Embolization and radiosurgery were first reported as a treatment for cerebral AVM in 1960 and in the 1970s, respectively [14,15]. These periods include at least 19 years in which all treatment modalities were available.

2.3. Annual hemorrhage incidence rate calculations

Annual hemorrhage incidence rate was calculated by dividing the number of patients with at least one hemorrhage during the at-risk period (excluding hemorrhage at presentation) by the aggregate number of person-years of at-risk period [16]. The "at-risk period" was defined as the time from each patient's diagnosis of AVM to either complete obliteration of all nidi or the end of follow-up. If a patient hemorrhaged prior to confirmed diagnosis of an AVM, and the hemorrhage location was consistent with the location of the AVM, then the time of the hemorrhage was considered the time of diagnosis. Clinical and demographic characteristics between patients for whom data were presented to allow for incidence rate calculations (the "included group") and those for whom the reported data were insufficient (the "excluded group"), were compared and statistical analysis performed (Supp. Table 1).

2.4. Nidal instability

Based on the available data within the reports, a subset of patients was analyzed for nidal instability following the initial phase of treatment. Nidal instability was considered present if there was hemorrhage of an untreated nidus, appearance of a new nidus, or disappearance of untreated nidus.

2.5. Statistical analysis

Descriptive statistics were performed with the acquired data. Fisher's exact test was performed for categorical variables and Welch two-sample *t*-test was performed for continuous variables using the R.app GUI 1.53 (6335 Leopard build 64-bit) statistical package. The significance level of *p* values was 0.05.

3. Results

3.1. Literature and institutional database searches

The searches of PubMed and EMBASE together yielded 3007 citations. Of these, 669 were duplicates and 2346 were unique citations. Nineteen citations from these databases met the criteria for inclusion and contained reports of 26 patients [2,5–7,17–31]. Reports of 10 additional patients were found in eight references from the reviewed papers [32–39]. In total, 36 patients from the literature met our inclusion criteria. Our institutional AVM data-

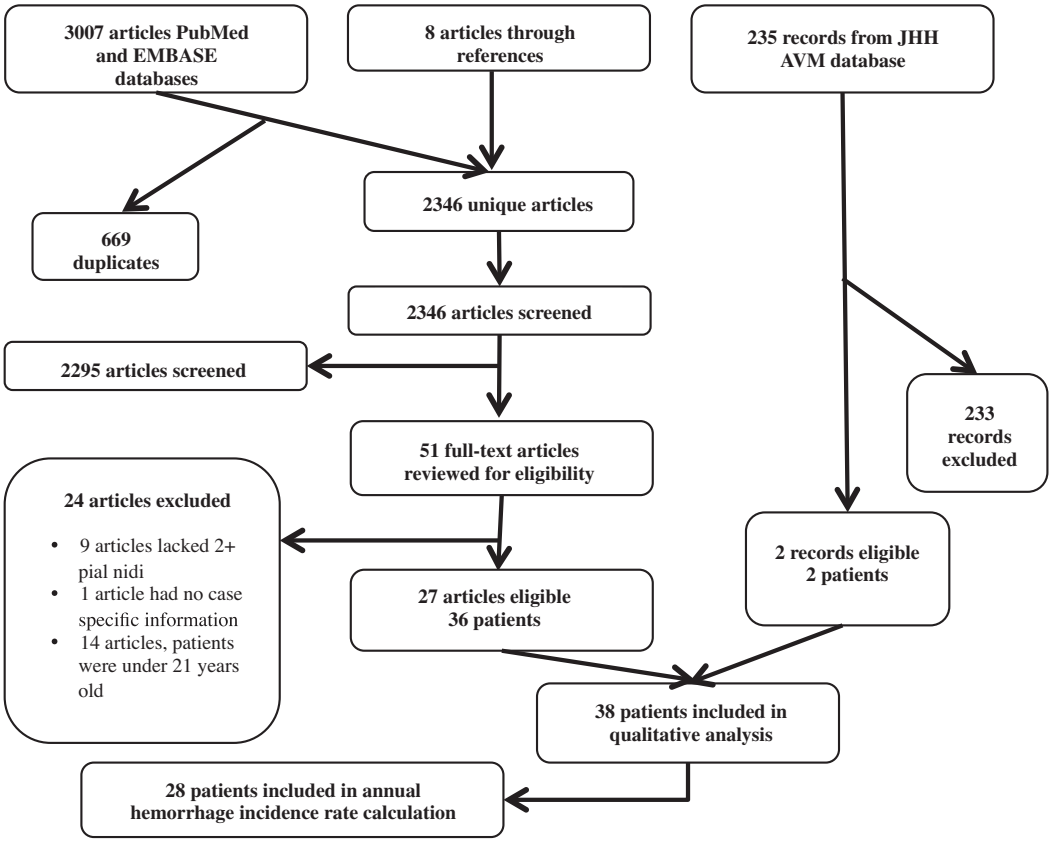

Fig. 1. Flowchart of database search for multiple arteriovenous malformation case reports. AVM = arteriovenous malformation, JHH = Johns Hopkins Hospital.