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REVIEW

Arteriovenous Malformations: A Diagnostic and Therapeutic Challenge☆

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Abstract Many dermatologists are largely unfamiliar with arteriovenous malformations (AVMs). This is partly due to the low prevalence of these lesions and to the fact that they are generally managed by other specialists, in particular, interventional radiologists and pediatric, maxillofacial, and plastic surgeons. In this article, we review the recommended nomenclature for AVMs and look at their clinical manifestations and diagnosis, as well as the ideal type and time of treatment. AVMs should be managed from a multidisciplinary approach, and the dermatologist's primary goal should be to make a proper diagnosis and thereby avoid unnecessary treatments.

PALABRAS CLAVE
Malformación vascular;
Arteriovenoso;
Anomalías vasculares de alto flujo

Malformaciones arteriovenosas: un reto diagnóstico y terapéutico

Resumen Muchos dermatólogos están muy poco familiarizados con las malformaciones arteriovenosas (MAV). Ello es debido, en parte, a la baja prevalencia de dichas lesiones y al hecho de que generalmente suelen ser tratadas por médicos de otras especialidades, en particular radiólogos intervencionistas de adultos y pediátricos, médicos maxilofaciales y cirujanos plásticos. En este artículo revisamos la nomenclatura recomendada para las MAV y nos centramos en sus manifestaciones clínicas y en su diagnóstico, así como en el tipo ideal y el tiempo de tratamiento. El manejo de las MAV debe hacerse desde una aproximación multidisciplinar, siendo el objetivo principal de los dermatólogos realizar un correcto diagnóstico para evitar, de este modo, tratamientos innecesarios.

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Introduction

Arteriovenous malformations (AVMs) are high-flow vascular anomalies due to a failure of embryogenesis. They involve a direct communication between an artery and a vein with no intervening capillary bed.[1]

Nomenclature

AVMs represent only 10% to 15% of vascular malformations, but we must ask ourselves whether the nomenclature is being used correctly.

Is the Nomenclature Used Correctly?

In the past, terms such as salmon patch, strawberry hemangioma, port wine stain, and angioma were often used indistinctly in the nomenclature of vascular malformations and tumors, with no differentiation of the clinical, histopathological, and therapeutic aspects, despite their distinct etiologies and pathogenesis.

It was only in 1982 that Mulliken and Glowacki[2] developed a classification by uniting the histological structure and appearance of the predominant endothelium with the biological behavior of the vascular anomalies.

That classification was redefined by Mulliken and Young in 1996 and adopted by the International Society for the Study of Vascular Anomalies (ISSVA). In the new classification, vascular malformations were defined by their predominant component, separating the lesions into malformations and tumors. Malformations were subdivided into low and high flow. This system is today considered to be the reference classification.[3]

In the 1988 Hamburg classification, vascular malformations were defined according to the predominant vascular lesion (arterial, venous, arteriovenous shunt, or combined/mixed) and were divided into truncular or extratruncular depending on whether or not major axial vessels were involved.

However, in a recent review of articles cited in PubMed in 2009, Hassanein and Mulliken[4] drew attention to the fact that the term *hemangioma* was used erroneously in 71.3% of cases, demonstrating that nomenclature is still a significant problem and that it can lead to confusion when prescribing treatment (such as propranolol, for example), which may not be indicated. Genetic tests and diagnostic investigations based on the molecular biology of the lesion, flow rate, and response to pharmacological treatments will be taken into account in the classification of AVMs in the near future.

Etiology

The most widely accepted theory of the etiology and pathogenesis of AVMs postulates that these lesions are due to an increase in the number of vessels caused by a defect in vascular development, particularly angiogenesis.[5] The most common site of AVMs is the brain and it is here that they have been most extensively studied. Although we do not know if findings from the study of cerebral AVMs can be extrapolated to extracranial AVMs, a number of angiogenic factors, such as vascular endothelial growth factor and platelet-derived growth factor, do appear to be implicated. It has been suggested that this is the cause of the dynamic vascular disturbance present in AVMs, producing an early alteration of angiogenesis, in contrast to what occurs in venous malformations; this is supported by the increase in the serum level of metalloproteinases detected in cases of AVM. The STAT proteins (signal transducers and activators of transcription) are also involved in the pathophysiology of angiogenesis in AVMs. A group of these proteins, specifically the STAT 3 proteins, is most active in the fetal period and may play a significant role in angiogenesis. Thorough knowledge of this process will help us to develop a more specific and appropriate treatment in each situation in the future.

A great deal of research still remains to be done on the genetic importance of these disorders and their triggering factors.

Do Triggering Factors Exist?

Yes, triggering factors have been identified. The known factors include hormonal changes (adolescence, pregnancy), infections, trauma, and surgical procedures. Infection is the factor most frequently implicated in the acquired acral AVMs.

Despite these identified factors, many AVMs remain in a quiescent phase throughout their life while others progress rapidly; this has also been seen with malignant tumors, in which some tumors disseminate rapidly while others of similar origin and stage remain stable. These 2 situations can be explained by the Knudson concept,[6] in which incomplete penetrance of the affected genes leads to marked variability in clinical expression.

For Buckmilller et al.,[7] however, AVMs behave as true slow-growing tumors, based on the demonstrated presence of cell turnover, which does not exist in venous, capillary, or lymphatic malformations.

Have Advances Been Made in Genetics?

The majority of AVMs are sporadic, with no genetic defects detected. Genetic alterations have been identified in some forms of familial AVM (Table 1),[8] including hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome),[9] attributed to a mutation of *endoglin* (*ENG*),[10] and the activin receptor-like kinase-1 gene (*ALK-1*),[11,12] which affects transforming growth factor beta (TGFβ) signaling. Mutations have also been detected in *ACVRLK1* and *SMADH4*. In capillary malformation-AVM syndrome there is a mutation in the *RASA1* gene[13] on chromosome 5q 13–22, whose dysfunction produces an alteration of the Ras signaling pathway (due to an alteration of protein p120 RasGAP).

There are many forms of syndromic AVM (Table 2), as is the case for patients with mutations of the PTEN gene (Cowden, Proteus, and Bannayan-Riley-Ruvalcaba syndromes), who also develop arteriovenous anomalies.[14–16] Other syndromes associated with AVMs include Cobb syndrome (vertebral and spinal cord AVMs with metameric cutaneous capillary involvement), Parkes-Weber syndrome (generalized hypertrophy of a limb associated with an AVM and a capillary malformation [CM]), Bonnet-Dechaume-White