Letter by Filippidis et al Regarding Article, “Evaluating Strategies for the Treatment of Cerebral Cavernous Malformations”

To the Editor:

In the October issue of Stroke, we read with great interest the recent article by Li and Whitehead1 documenting the role of RhoA hyperactivation in the pathophysiology of cerebral cavernous malformations (CCMs) and suggesting a potential role for statins to treat these lesions. The authors tried to unveil novel strategies in the field of a noninvasive drug treatment approach for CCMs; however, this article focuses only on statins. Other candidate drugs, like the β-adrenergic receptor blocker, propranolol, demonstrate promising results concerning CCMs and infantile capillary hemangiomas.2–3 In our current communication, we postulate that oral propranolol administration could provide a novel, alternative approach for the treatment of adults and children with familial cavernous malformation cases of the central nervous system.

Recently, Moschovi et al1 published a report describing the administration of 2 mg/kg propranolol per day divided in 2 to 3 doses per mouth for treating a giant CCM in a 7-month-old infant. The lesion demonstrated a significant shrinkage after 10 days of propranolol administration.3

Promising data arise also from the management of cutaneous or nasal capillary infantile hemangiomas with propranolol using the same dosage scheme.2 Leute-Labreze et al2 observed the inhibition of growth of capillary infantile hemangiomas, approaching the total remission target by administering 2 to 3 mg propranolol per day by mouth divided into 2 to 3 doses after appropriate cardiology consultation without any side effects or any associated morbidity and mortality. The underlying pathophysiological mechanism explaining the action of propranolol in capillary malformations includes: (1) the induction of vasoconstriction; (2) the decrease in the expression of the vascular endothelial growth factor and basic fibroblast growth factor angiogenic factors; (3) the triggering of an apoptotic process in the capillary endothelial cells; (4) the inhibition of tubulogenesis in the brain endothelial cells; and (5) the suppression of proliferation, migration, and differentiation of endothelial cells.5

Capillary hemangiomas of the skin share a common genetic background with the familial CCMs.6 Sirvente et al6 observed that 9% of the patients with familial CCMs had also a cutaneous vascular malformation in a series of 417 patients. Interestingly, 86.7% of the patients bearing cutaneous vascular malformations (capillary malformations, hyperkeratotic cutaneous capillary malformations, and venous malformations) in this study group had the KRIT1/CCM1 mutation6 All patients but 1 (92% total) with capillary malformations had a KRIT1/CCM1 mutation.6 The KRIT1/CCM1 mutation is a common mutation in familial CCMs too,1 indicating a strong genetic link between CCMs and cutaneous capillary malformations.

Potentially the common genetic background shared between CCMs and cutaneous capillary malformations could indicate a similar response of CCMs to propranolol. Propranolol is a low-cost medication with a long history of widespread clinical use. It is approved by the European Medicines Agency in Europe and the Food and Drug Administration in the United States and has a remarkably safe clinical profile for systemic administration if the appropriate general precautions concerning the administration of β-adrenergic blockers are followed.2 All these properties indicate that propranolol could potentially be an ideal candidate for treating familial cavernous malformations of the central nervous system. Pilot studies or clinical trials are needed to assess a potential, significant treatment advantage comparing it with other treatment modalities.

Disclosures

None.

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