SHORT COMMUNICATION

Effect of Beta-blockers on Extracranial Arteriovenous Malformations

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Extracranial arteriovenous malformations (AVMs) are rare congenital high-flow anomalies caused by abnormal vascular development during embryogenesis. Post-zygotic mutations have been evidenced in several recent cases (1, 2). AVMs most commonly affect the head and neck (47.4%) and the extremities (28.5%). Although present at birth, they are commonly not apparent or asymptomatic until later in life. They may grow because of hormonal changes (puberty, pregnancy), and their natural history can follow 4 stages according to the Schobinger classification: (I) quiescent stage, (II) lesion becomes warmer and larger with a thrill, (III) destruction process, such as ulcers, haemorrhages or bony lytic lesions, (IV) heart failure complication that might be life-threatening, due to intense flow (3, 4). The diagnosis of AVMs is suggested by physical examination and requires, for confirmation, vascular imaging studies, including Doppler ultrasonography, magnetic resonance angiography or arteriography (1, 4).

Current therapeutics for AVMs are limited, and multidisciplinary management remains challenging. When possible, the best curative treatment combines embolization and complete surgical resection. In case of embolization only or partial resection, the rate of growth flares is high (3). Other treatments, such as radiotherapy, thalidomide or mammalian target of rapamycin inhibitors have been tested, without significant positive outcomes (3–7).

Propranolol is a non-selective beta-adrenergic blocker indicated for several conditions, including complicated infantile haemangiomas (8, 9). However, it is not efficient in decreasing other vascular tumours. Properties of propranolol (vasoconstrictor, antiangiogenic and pro-apoptotic effects, along with its inotropic properties leading to a decrease in arterial pressure) could be interesting in AVMs. Only a few data are available in the literature (10, 11). The aim of the current study was to investigate the efficacy and tolerance of systemic beta-blockers in extracranial AVMs.

METHODS

A retrospective monocentric study was conducted at the University Hospital of Tours, France, which is a reference centre for vascular malformations. Inclusion criteria were extracranial AVM confirmed by magnetic resonance imaging (MRI) and treatment with a systemic beta-blocker between January 2012 and May 2020, as well as consent for data collection. Exclusion criteria were: intracerebral AVMs and patients who received beta-blockers for an indication other than the AVM. All data were extracted from patients' medical records (demographic data, data on the AVM and beta-blockers, imaging). Patients were followed-up at consultation or contacted by telephone to collect self-reported outcomes. The primary endpoint was the patient's overall perception of treatment efficacy on a numerical scale from –100 to +100 (–100 being a harmful treatment and +100 being a high efficacy of the treatment). A score >0 was considered a positive effect. The secondary endpoints were: (*i*) changes in pain and changes in volume, self-assessed by the patient from –100 to +100; and (*ii*) changes in radiological volume of the AVM when radiological imaging was performed before and after initiating beta-blockers, with a centralized interpretation (DH). The images were compared in terms of in pre- and per-treatment volume. The final endpoint was tolerance data. Statistical analyses were descriptive (% for qualitative data, means and standard deviation (SD) for quantitative outcomes).

RESULTS

A total of 12 patients were eligible and 7 were included (5 men; 1 patient was not followed in our centre, 2 received beta-blockers for another condition than AVM, and 2 refused to participate). The median age was 55 years (range 20–67 years) and the median age of discovery of AVM was 17 years (range 0–56 years). Characteristics of patients and AVMs are shown in **Table I**. In 4 cases, beta-blockers were the first-line treatment for the AVM. Beta-blockers (propranolol in 5 cases and atenolol in 2 cases) were started because AVM progressed slowly, which did not justify a more invasive treatment, or because other treatments were too risky (Table I). The initial dosage regimen ranged from 7 to 80 mg per day for propranolol and 25 to 50 mg for atenolol, with a median duration of 25 months (range 14–36 months); treatment was still ongoing in 4 patients.

Regarding overall improvement, treatment with beta-blockers was significantly effective, with a mean ± SD overall improvement in self-assessed efficacy of 39.0/100 ± 34.0. The treatment was considered successful in 5 of 7 cases. Mean ± SD self-assessed effects on pain and reduction in volume of the AVM were 6.4/100 ± 10.2 and 21.4/100 ± SD 26.5, respectively. Two patients reported a benefit in self-perception of pulsation of the AVM, which was described as an annoying symptom. Pre- and per-treatment imaging was available for 4 patients and showed, in all cases, no difference in volume after beta-blockers.

Five of 7 patients experienced side-effects: bradycardia, Raynaud's syndrome, tiredness, reduced libido,

Table I. Characteristics of patients, arteriovenous malformations (AVMs) and beta-blocker treatment

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Sex, age, years	Male, 56	Male, 20	Male, 55	Male, 41	Female, 40	Female, 67	Male, 56
Localization of AVM	Face/head	Upper limb	Face/head	Lower limb	Upper limb	Face/head	Face/head
Family history of vascular anomalies	No	No	Haemangioma and AVM	No	Haemangioma	No	No
Age at diagnosis of AVM, years	0	17	0	40	0	56	38
Age at treatment initiation	55	18	54	40	38	65	53
Triggering factor of AVM	Weight gain	No	Surgery	No	No	No	No
Treatments performed before beta-blockers	Embolization, radiotherapy, ligation, surgery	None	Embolization, surgery	None	None	Surgery	None
Schobinger staging	III	I	II	I	I	I	I
Treatment duration (months)	24	3	14	25	33	36	36
Beta-blocker used	Propranolol	Atenolol	Propranolol	Propranolol	Propranolol	Propranolol	Atenolol
Dosage regimen (mg)	80	50	80	60	40	7	25
Treatment initiation criteria	Progression of AVM	Progression of AVM	Bleeding, pain and difficult embolization	Progression and refusal of embolization	No other therapeutic option	Post-embolization	No other therapeutic option
Side-effects of treatment	Decreased libido	None	Tiredness, chilliness extremities, decreased libido	Raynaud's syndrome	None	Cough, tiredness, sadness	Nightmares
Treatment withdrawal	No	No	Yes	No	Yes (anxiety of long-term treatment)	Yes (side-effects)	No

sadness and chilliness (Table I). One patient discontinued beta-blockers because of a cough related to treatment.

DISCUSSION

This study of 7 patients with extracranial AVMs shows that beta-blockers (propranolol and atenolol) were associated with no reduction in volume of the AVM over a median of 14 months, but also with no progression. However, patients perceived an overall improvement, in AVM size and in symptoms. These positive symptomatic effects are probably due to the non-selective constriction of the vascular structures by beta-blockers and consequently decrease the flow within the nidus, thus reducing the symptoms (redness, pain, pulsatility, volume), more than to specific effects on apoptosis of endothelial cells, as observed in infantile haemangiomas (9, 12). However, side-effects, although not severe, are frequent (5 of 7 patients in the current study) and might limit treatment observance.

To our knowledge, this is the first study to report effects of beta-blockers on extracranial AVMs. Two case reports have been published. One reported a 19-year-old woman with AVM on her right lower limb that partially decreased after 5 months of propranolol, then recurred after discontinuation of treatment (10). The other was a 23-year-old woman with a lower lip AVM, which recurred after surgical excision. Propranolol allowed for stopping the progression of the AVM (11).

The main limitations of this study is the small number of patients, but the condition is very rare, the absence of control group and the bias inherent to retrospective studies.

In conclusion, this study supports that beta-blockers are not effective in reducing the volume of extracranial AVMs, but may be of interest in stabilizing the lesions and decreasing symptoms. The best curative option for AVMs is large surgical excision after embolization, but this can rarely be performed. All other options are not efficient, are only slightly efficient, or have a high rate of recurrence (3–7). Therefore, beta-blockers could be integrated in the therapeutic strategy for management of AVM because they have an acceptable safety profile. Perspective studies will focus on therapies targeted to molecular results for AVMs, but data on the effectiveness and safety of these drugs are not yet available (13).

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