Journal of the Neurological Sciences 385 (2018) 115–118

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

Tamoxifen treatment and occurrence of dural arteriovenous fistulas: An observational study on a series of patients presenting tamoxifen history and diagnosis of DAVf

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ARTICLE INFO

Keywords:
Dural arterio-venous fistula
Tamoxifen
Endovascular therapy
Cerebral angiography

ABSTRACT

Background: Tamoxifen is an estrogen-receptor modulator frequently used in the treatment of non-metastatic breast cancer. Side effects of this treatment are well evaluated but unproven side effects are suspected by case reports. Only one case report evokes a possible association between tamoxifen and dural arteriovenous fistula (dAVF). Authors report in this study their experience on dAVF in women exposed to tamoxifen.

Methods: From 2005 to 2015, 294 patients with a dural arteriovenous fistula were referred to our department. Among these cases, 10 women who harbored 12 dAVFs were under a treatment of tamoxifen at the time of the diagnosis of the dAVF or had a treatment of tamoxifen in the past. There is no exclusion criterion for this observational study.

Results: Ten women were included in this series (mean age: 64). Seven women were under treatment when the first symptom occurred and the three others had already finished their treatment. The mean delay between the initiation of tamoxifen and the occurrence of symptom was 32 months. The most frequent clinical symptom was a tinnitus (8 patients, 80%) followed by headache (3 cases, 30%), chemosis (2 cases, 20%), oculomotor palsy (2 patients, 20%), and ocular hypertension (1 case, 10%). One patient presented a cerebellar hemorrhage and arrived in a comatose state. The fistulous point was located in the transverse sinus (TS) in 9 cases (75%) and in the cavernous sinus in 3 cases (25%).

Conclusions: Our observational study suggests that the occurrence of cranial dAVF could be influenced by tamoxifen. It will be very difficult to establish a causal link between them but a larger comparative study could help.

1. Introduction

Tamoxifen is an estrogen-receptor modulator frequently used these three last decades in the treatment of non-metastatic breast cancer [1]. Although case-control [2] and meta-analysis studies [1] demonstrated its advantage in term of cancer recurrence, this treatment is known for a multitude of side effects, the most frequent cerebrovascular one is the cerebral venous thrombosis (CVT) [1,3]. Contrariwise to the association between CVT and tamoxifen outlet, the occurrence of dural arteriovenous fistulas (dAVF) under or after a tamoxifen therapy is only reported in one recent case report [4]. In our experience, as joint team of neurosurgeons and interventional neuroradiologits, some interesting cases of dAVF in patients under tamoxifen therapy have catched our attention. Therefore, since we had believed in the existence of a possible correlation between the estrogenic treatment and the occurrence of dAVFs, we retrospectively collected our data in order to evaluate the evidence of that.

2. Materials and methods

2.1. Patients selection

We maintained an ongoing prospective database where demographic, clinical and angiographic information regarding patients

Abbreviations: CVT, cerebral venous thrombosis; dAVF, dural arterio-venous fistula; DSA, digital subtraction angiography; mRS, modified Rankin score; TS, transverse sinus

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https://doi.org/10.1016/j.jns.2017.12.026
Received 20 June 2017; Received in revised form 6 December 2017; Accepted 20 December 2017
Available online 23 December 2017
0022-510X/

harboring a cranial dural arteriovenous fistula. From 2005 to 2015, 294 patients with a dural arteriovenous fistula were referred to our department. Medical past history also as significant medication was prospectively recorded. Among these 294 cases (146 male and 148 female), 10 women who harbored 12 dAVFs (one patient developed 3 consecutive dAVFs) were under a treatment of tamoxifen at the time of the diagnosis of the dAVF or had a treatment of tamoxifen in the past.

2.2. Pre-therapeutic clinical examination

At the time of the diagnosis of the dAVFA, each patient underwent a neurological clinical examination and a scrupulous medical history was collected, especially with data about duration and doses of tamoxifen treatment and any other previous or undergoing pharmacological treatment. Then, we particularly looked for the presence of an etiology, the duration of the symptoms, the type of clinical sign and the evaluation of a modified Rankin Score (mRS). The date of initiation of the estrogenic treatment, its dosage and the date of occurrence of the first symptoms were meticulously recorded.

2.3. Angiographic analysis of dAVFs

A six-vessel pre-therapeutic DSA under local anesthesia with 3D reconstruction was conducted for all patients. The number of arterial supplies and their nomenclature, the location of the fistulous point and each vein that was involved by the venous drainage of the fistula were noted. We used the classification of Lariboisiere [5] for dAVFs located without the cavernous sinus and the classification of Barrow [6] for the carotido-cavernous fistulas. The presence of a venous thrombosis, stenosis or ectasia was also recorded during this first examination.

2.4. Treatment of the dAVF

In our institution, each case of dAVF is discussed in a multidisciplinary meeting to decide whether curative treatment of the fistula is indicated. For carotido-cavernous fistulas, the treatment is indicated whether there is a risk of visual impairment without treatment. For "benign" dAVFs (grade I of Lariboisière), the treatment is provided to patients presenting a disabling tinnitus. Curative treatment is more generously proposed for fistulas presenting a cortical venous reflux for their potential risk of bleeding. Endovascular treatment is the first line therapy in our institution and is performed under general anesthesia. Type and quantity of embolic agent used were recorded, as well as the immediate anatomical result and the occurrence of any complication.

2.5. Clinical evolution

The follow-up started at the time of the embolization session (or diagnostic DSA for untreated patients) and finished with the last visit or angiography. Angiographic follow-up was performed 6 months after the treatment to confirm the occlusion of the arteriovenous shunt. A neurological exam with evaluation of the mRS was systematically performed for each visit.

3. Results

3.1. Clinical presentation

Between 2005 and 2015, 10 women presented the diagnosis of cranial dural arteriovenous fistula after or during a treatment by tamoxifen. Patients baseline data and their clinical presentation details are described in Table 1. The mean age was 64 year-old. Each patient received a daily dose of 20 mg of tamoxifen during her treatment. Seven women were under treatment when the first symptom attributable to the dAVF occurred and the three others had already finished their treatment. The mean delay between the initiation of tamoxifen therapy and the occurrence of first symptoms was 32 months and the mean delay between the initiation of tamoxifen therapy and the diagnosis of the dAVF was 45.7 months. The most frequent clinical symptom was a tinnitus (8 patients, 80%). Other neurological symptoms/signs encountered were headache (3 cases, 30%), a chemosis in 2 cases (20%), an oculomotor palsy in 2 patients (20%), and ocular hypertension in 1 case (10%). One patient presented a cerebellar hemorrhage secondary a massive cortical venous reflux and arrived at the hospital in a comatose state. The mean interval of time between the advent of the first symptoms first showed and the diagnosis of the CCF was 10.9 months. Every patient presented a pre-therapeutic modified Rankin scale (mRS) of 1 (7 patients, 70%) or 2 (2 patients, 20%). The patient who presented a cerebellar hemorrhage had a Glasgow coma scale score of 7 at admission (mRS 5).

Table 1
Demographic and clinical data.

Variable	Patients (n = 10)
Age: median (range)	64 (57–73)
Delay between dAVF diagnosis and tamoxifen initiation	45.7 months
Delay between first symptom and tamoxifen initiation	32 months
Clinical signs	
Pulsatile tinnitus	8 (80%)
Chemosis	2 (20%)
Hemorrhage	1 (10%)
Headache	3 (30%)
Ocular hypertension	1 (10%)
Oculomotor palsy	2 (20%)
mRS before treatment	
1	7 (70%)
2	2 (20%)
5	1 (10%)

4. Angioarchitecture

Informations concerning angiographic details of the 12 fistulas are summarized in Table 2. The fistulous point was located in the transverse sinus (TS) in 9 cases (75%) and in the cavernous sinus in 3 cases (25%). The mean number of arterial supplies of the fistula was 3.5 (range: 1–7). The arterial supplies were from branches of both sides in 5

Table 2
Details concerning angiographic characteristics of dAVFs.

Variable	dAVF (n = 12)
Number of arterial feeders (mean (range))	3.5 (1–7)
Location of the fistulous point	
Transverse sinus	9 (75%)
Cavernous sinus	3 (25%)
Arterial supply	
Bilateral supply	5 (41.7%)
Branch of the meningo-hypophseal trunk	4 (33.3%)
Branch of the middle meningeal artery	11 (91.7%)
Artery of the foramen rotundum	1 (9.2%)
Branch of the infero-lateral trunk	2 (16.7%)
Carotid branch of the ascending pharyngeal artery	4 (33.3%)
Branch of the occipital artery	8 (66.7%)
Branch of the posterior meningeal artery	4 (33.3%)
Branch of the posterior auricular artery	2 (16.7%)
Branch of the vertebral artery	1 (9.2%)
Venous drainage pattern	
Venous reflux	5 (41.7%)
Associated sinus thrombosis	6 (50%)
Associated venous stenosis	1 (9.2%)
Venous ectasia	1 (9.2%)
Classification of Lariboisière	
1	7 (58.3%)
2a	1 (9.2%)
2b	2 (16.7%)
2a + b	2 (16.7%)