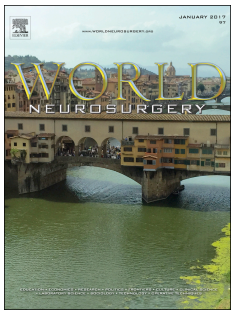

Article:
Narata, A.P., Janot, K., Bibi, R. et al. (2019) Reversible brain edema associated to flow diverter stent procedures: a retrospective single-center study to evaluate frequency, clinical evolution, and possible mechanism. World Neurosurgery, 122. e569-e576. ISSN: 1878-8750

https://doi.org/10.1016/j.wneu.2018.10.103

Accepted Manuscript



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PII: S1878-8750(18)32401-X

DOI: https://doi.org/10.1016/j.wneu.2018.10.103

Reference: WNEU 10547

To appear in: *World Neurosurgery*

Received Date: 30 August 2018

Revised Date: 14 October 2018

Accepted Date: 16 October 2018

Please cite this article as: Narata AP, Janot K, Bibi R, Herbreteau D, Perrault C, Marzo A, Cottier J-P, Reversible Brain Edema Associated to Flow Diverter Stent Procedures: A Retrospective Single Center Study to Evaluate Frequency, Clinical Evolution and Possible Mechanism, *World Neurosurgery* (2018), doi: https://doi.org/10.1016/j.wneu.2018.10.103.

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Previous presentation: ISC 2018, Los Angeles, CA, poster presentation on January 25th 2018.

Disclosure of funding: authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria, educational grants, participation in speaker's bureaus, membership, employment, consultancies, stock ownership or other equity interest, and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationship, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript; authors confirmed that this study did not receive any financial support from public organizations or private companies.

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RUNNING TITLE: Brain Edema After Flow Diverter Stent

KEY WORDS: brain edema, flow diverter stent, intracranial aneurysm

ABSTRACT

BACKGROUND: hemorrhage and ischemia after flow diverter stent (FDS) procedures for intracranial aneurysms are the most common complications and have been extensively described. Temporary brain edema (TBE) is an unknown complication that could be associated to particular FDS procedures.

OBJECTIVE: to estimate frequency, clinical presentation, imaging finding and possible mechanisms associating TBE and FDS.

METHODS: unruptured aneurysms treated with FDS implantation performed in our service from June 2015 to March 2018 were reviewed. Medical antecedents, endovascular procedure, pre and post treatment clinical assessment, aneurysm characteristics and image records were collected. Artery diameters of patients developing TBE were also calculated in order to investigate any correlation between TBE and anatomical descriptors.

RESULTS: total of 179 FDS in 176 patients were reviewed. Six patients (3.4%) presented with symptomatic TBE and all TBE patients had undergone FDS implantation from middle cerebral artery (MCA) to the internal carotid artery (ICA). Pearson Product-Moment Correlation Coefficient (PPCC) found smaller MCA diameter and ratio MCA/ICA in these 6 patients (respectively PPCC= -0.619,$p<0.04$ and PPCC= -0.647,$p<0.03$). Hemorrhagic and ischemic complications were less frequent than TBE (2.3% and 1.1% versus 3.4%).

CONCLUSIONS: TBE was more frequent than ischemic or hemorrhagic complications after FDS in this study. It seems to be associated to a particular FDS positioning in small arteries, inducing flow changes and BBB disruption.

INTRODUCTION

Flow diverter stenting (FDS) is a relatively recent technique that has been used in the treatment of intracranial aneurysms with high aneurysm occlusion rates. Morbidity and mortality related to procedure were respectively 5% and 4% in a meta-analysis study, however ischemic spots could be found in diffusion-weight imaging (DWI) in more than 80% of asymptomatic patients compared to symptomatic ischemic thromboembolic lesions being estimated to 6%[1,2]. Global ischemic complications are estimated from 1.7 to 5.6 % with a lowest rate recently described when aspirin is associated to ticagrelor[3]. Hemorrhagic complications were described in 3 to 4.3% of studies, with high morbidity and mortality rates for massive intra-parenchymal hemorrhage (50% and 45%) with delayed onset[3,4].

Temporary brain edema (TBE) after FDS is an unknown complication with very few cases in the literature. Some brief reports described few patients that presented brain edema after FDS procedure associated to neurological impairment. Brain edema and neurologic symptoms seem to disappear in few days without permanent lesions. Chiu AH et al. described 1 patient where FDS could increase blood flow when covering a large aneurysm neck and create a hyperperfusion syndrome[5]. In a series of 66 aneurysms treated with FDS in 59 patients, 2 patients (3.4%) presented TBE after a treatment of large aneurysms. Magnetic resonance imaging (MRI) did not show ischemia, hemorrhage or hyperperfusion in perfusion MRI (PWI). Symptoms started by neurological impairment few hours after procedure and completely disappeared in some days. MRI follow up of patients presenting TBE became normal after 1 week. The hypothesis to explain this phenomenon was the higher blood flow in the parent vessel redirected by the FDS that could consist in an increased risk of hemorrhagic complication. TBE (3.4%) was comparable to ischemic and hemorrhagic complications rates described in the literature[6].

Considering that TBE might be underestimated, the potential tendency for hemorrhagic transformation and unknown mechanism, this study reviewed our experience with FDS since June 2015 looking for patients who developed TBE. Imaging analysis, clinical presentation and evolution were analyzed in this study in order to observe frequency and discuss possible mechanisms of TBE.

METHODS

Patient Selection and Clinical Data Collection

Patients with unruptured intracranial aneurysms, pre-operative computed tomography (CT) or MRI and treated with FDS in our institution from June 2015 to March 2018 were retrospectively reviewed. Patients with ruptured aneurysms and treated with FDS were excluded to avoid any influence of subarachnoid hemorrhage on TBE estimation. Institutional Review Board approval was obtained without necessity of consent for retrospective and anonymous data collection. Endovascular techniques, imaging data, clinical evaluation at baseline/during hospitalization and at 3 months were collected.

Patients who developed severe headache and/or neurologic impairment associated to brain swelling findings on CT and MRI were identified as patients with TBE and separately analyzed.

Stent Procedure

Patients received double anti-platelet therapy with aspirin 160 mg associated to ticagrelor 90 mg twice per day; heparin was used only during intervention. FDS procedures were conducted under general anesthesia and fluoroscopy with a biplane X-ray system (General Electric Healthcare Innova IGS 650, MA, USA) using contrast agent (Iopamiron 300, Guerbet, France) for standard angiography acquisitions. Co-axial access was composed by 8F long sheath and 5F/6F intermediate catheter. 3 different FDS are present in this study and were deployed following standard techniques. Devices and catheters are listed in Supplemental Table 1.

Image Review and Statistical Analysis

All patients who presented severe headaches and/or neurological impairment were investigated with a CT with dual-energy reconstruction to eliminate hemorrhage immediately after symptoms onset and MRI in the following hours. Patients investigated by MRI protocol including at least DWI, fluid-attenuated inversion recovery imaging (T2FLAIR) and time of flight imaging (3D-TOF) were included. MRI at 3 months follow-up was performed on all patients. PWI and CT perfusion (PCT) were analyzed when available.

For all patients who developed TBE, CT and MRI images were performed in acute phase and at 3 months follow-up. 3 independent neuroradiologists (JPC, KJ, APN) analyzed all imaging records. The same neuroradiologists performed additional analysis for patients

with a FDS between middle cerebral artery (MCA) and internal carotid artery (ICA) by measuring 3 artery diameter: distal ICA, proximal MCA (M1) and proximal anterior cerebral artery (ACA-A1) in a 3D rotational angiography imaging performed using Osirix (http://www.orisix-viewer.com) before the stent procedure, reporting its arithmetic average value and their standard deviation to quantify interobserver variability. Reliability of these measures was assessed with two-way, mixed intraclass correlation coefficients (ICC) showing high reliability (ICC=0.992, 95% CI 0.989 to 0.995). Pearson Product-Moment Correlation Coefficient (PPCC) was used to identify links between clinical outcome and anatomical descriptors.

RESULTS

Patient Population, Complications and Aneurysms Characteristics

A total of 176 patients with unruptured aneurysms in 179 FDS procedures were reviewed (3 patients presented bilateral ICA aneurysms). Ischemic complications were observed in 2 patients (1.1%) and hemorrhagic in 4 patients (2.3%). During 3 months follow-up period, 3 patients (1.7%) died after hemorrhagic complications (1 subdural hematoma and 2 massive sub-arachnoid hemorrhage). Aneurysms were mostly located in the ICA (93.3%) and measuring less than 10 mm (53.6%). Supplemental Table 2 shows a database overview.

TBE Population: General Characteristics, Clinical Evaluation and Image Analysis

Six patients (3.4%) presented with symptomatic temporary brain edema from 176 patients reviewed. All of them developed symptoms in the first 24h after intervention and lasted maximum 72h. FDS was implanted from MCA to ICA in these 6 patients (Figure 1). The same stent positioning was present in 5 other patients who did not develop any symptom. Separate analysis of these 11 patients suggests that no demographic data, aneurysm characteristics, endovascular material/device or medical antecedents could predict TBE (Supplemental Table 3). However, PPCC showed significant correlation between TBE and artery diameter: M1/ICA ratio (PPCC= -0.647, $p<0.03$) and M1 diameter (PPCC= -0.619, $p<0.04$) were smaller in the group of patients who developed brain swelling (Table 1, Figure 2).

CT showed sulcal effacement and subarachnoid contrast enhancement in MCA and ACA territories. No restriction sign on DWI or abnormalities in perfusion tests confirmed that no ischemic lesion is been constituted. Hemorrhagic complications, in particularly subarachnoid hemorrhage, were excluded with dual-energy CT and T2FLAIR. Sulcal effacement (brain edema) and cortical contrast enhancement (BBB disruption) were present in all 6 patients based on CT images. (Figure 1 and 3). 3 months control did not show any reminiscent TBE lesions

DISCUSSION

Brain Edema: Blood Brain Barrier Constitution, Hydrostatic and Osmolar Mechanisms

Capillary endothelial cells, astrocytes, periocytes and epithelial basal membrane constitute blood brain barrier (BBB), and brain edema could be induced by an increase of pressure in the capillary (hydrostatic or osmolar) or toxicity on cell tights junctions[7].

Increased flow and BBB disruption were previously described in hyperperfusion syndrome after carotid artery stenting that normally shows mild changes in PWI[8]. FDS could change compliance of the vessel wall on MCA-ICA segment and intensify pressure waves transmission to distal vessels (capillary compartment) leading to BBB disruption and hyperperfusion syndrome. Decreased arterial elasticity could be considered as a quick removal of Windkessel effect: increased pressure transmitted to distal territories after FDS could be considered correlated to BBB disruption and brain edema[9]. This viewpoint was already considered in the literature where decrease in Windkessel effect could partially explain BBB disruption and IPH after FDS[10].

Considering perfusion tests, PWI is not a quantitative exam and it is necessary to compare to the opposite hemisphere or previous PWI performed before treatment to precisely confirm a status of hyperperfusion[11]. From these 6 patients with brain edema, we performed PWI or PCT in only 3 patients, and no patient presented clear perfusion asymmetry when compared to the opposite side. Considering brain edema in a very early beginning, we observed sulcal effacement and contrast enhancement in all 6 patients using CT images. MRI with gadolinium injection (when performed) could also demonstrated contrast enhancement, but MRI was mostly performed to exclude ischemic lesions.

Looking at studies describing unilateral TBE after endovascular procedures without ischemic lesions, we found similar CT images in contrast neurotoxicity reports after endovascular procedures. Mechanism of brain edema is probably related to increased osmolality, toxicity by the iodine atoms and/or BBB permeability. General clinical presentation is also similar: neurologic impairment onset is immediate or some hours after intervention (headaches and neurologic impairment in 12-24 hours in our study), benign evolution over few days with CT normalization[12]. Quantity of low osmolar contrast should respect 5ml/kg of patient weight and inferior to 300 ml/intervention, and we observed maximum 3mg/kg and 210ml in the study. Neurotoxicity incidence varies from 0.3-1% and we found 3.4% of patients with brain edema[13]. However, presence of contrast enhancement in

this study is very similar to previous published reports of contrast neurotoxicity that could suggest that probably a hemodynamic process caused disruption in the BBB (without hyperperfusion syndrome) and facilitated contrast penetration, as quantity and contrast density were respected[14].

FDS Positioning, Arteries Diameter and Flow Disruption

FDS placed from MCA to ICA was associated with brain edema in 6 patients, 5 patients with same FDS positioning did not develop TBE. Statistic analysis of artery caliber suggests that brain edema was more frequent in patients with smaller MI diameter. Considering stent implantation as a bypass between ICA-MCA, we could consider blood flow changes being more sensitive in small MCA caliber with more distal impact. Flow diverted through significantly reducing caliber vessels amplifies Bernoulli effect (velocity increases while pressure decreases) leading to BBB dysfunction without hyperperfusion and contrast impregnation[15].

We did not identify hemorrhagic or permanent complication in the 6 patients with TBE. Considering that BBB was affected by flow changes, control of arterial blood flow could be concerned in the post-operative period. After our first 2 cases of TBE, we imposed maximum systolic blood pressure control similar to the protocol applied for cervical carotid stent where hyperperfusion syndromes were associated to hemorrhagic complications[6,11,16].

Limitations

This study is a retrospective single center study that has limitations. The fact that we separately analyzed a specific group of 6 patients presenting neurologic impairment and TBE with same FDS positioning in all patients, and then we looked for common elements to another group of 5 patients with same stent positioning but no TBE, might have induced bias in our analysis. The small number of patients affected limits any conclusion about physiopathology and efficient clinical management.

SUMMARY

TBE was more frequent than ischemic or hemorrhagic complications (3.4% versus 1.7% and 2.3% respectively) in this study and similar results to a previous study based on 59 patients[6.] Analyzing separately our 6 patients, TBE seems to be associated to a particular stent positioning that could induce flow changes and BBB disruption, particularly in smaller arteries. Neurologic impairment is transitory and disappears progressively during the first week after procedure. We did not observe any hemorrhagic transformation whereas arterial blood pressure was systematically controlled. In spite of impressive findings in CT, no permanent lesion was found in the 3 months control images. Analyses of further similar cases are necessary to understand the BBB disruption mechanism after FDS and identify unsafe FDS positioning.

CONCLUSION

TBE seems to depend on FDS positioning and artery diameter. In this study, all patients affected by TBE were treated with a FDS placed distally in MCA and proximally in ICA, and also MCA diameter was smaller in patients who developed TBE. Further research will be necessary to confirm these preliminary findings.

SOURCES OF FUNDINGS

Authors did not receive any financial support concerning this study.

DISCLOSURES

None

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FIGURE LEGENDS

Figure 1. Recanalized left ICA aneurysm re-treated with FDS implantation from MCA to ICA (A, B). Patient developed severe headache and right hemiparesis 12h after intervention. CT showed diffuse brain swelling on left hemisphere (C) and no ischemic lesion on DWI (D).

Figure 2. Distribution of M1diameter (A) and M1/ICA ratio (B) for swelling and no swelling datasets. Patients who developed transient brain edema after FDS presented smaller M1 diameter and M1/ICA ratio (<0.8).

Figure 3. CT shows contrast enhancement on left hemisphere that could simulate subarachnoid hemorrhage (A). Dual-energy CT (B) and T2FLAIR (C) exclude presence of blood in the subarachnoid space. PWI did not show significative changes in perfusion (D).

TABLE 1. List of materials and devices and distribution over the patient population

Long sheath	All procedures	Brain swelling (6 patients)
Neuron Max, Penumbra, Alameda, USA	107	4
IVA, Balt, Montmorency, France	62	2
5F/6F intermediate Catheter		
Fargo, Balt, Montmorency, France	45	1
Navien, Covidien, Irvine, CA	89	3
Catalyst, Stryker, Freemont, CA	45	2
FDS		
PED, ev3/Covidien, Irvine, CA	132	3
Surpass, Stryker, Freemont, CA	33	2
P64, Phenox, Bochum, Germany	14	1

FDS=flow diverter stent; PED=Pipeline Embolization Device.

TABLE 2. Demographic data, antecedents and aneurysms characteristics of 176 patients

Sex		
Female	102	58%
Male	74	42%
Age	9-82 years old	51 years old (medium age)
Location		
ICA	167	93.3%
Basilar	3	1.7%
Vertebral (+PICA)	4	2.2%
MCA	2	1.1%
ACA	1	0.6%
PCA	2	1.1%
Size		
≤10 mm	96	53.6%
10-20mm	80	44.7%
≥20mm	3	1.7%
Medical Antecedents		
Diabetes	11	6.2%
Arterial Hypertension	52	29.5%
Smoke	81	46%
Polycistic Kidneys	1	0.5%
Symptomatic complication rates (176 patients)		
Ischemic	2	1.1%
Hemorragic	4	2.3%
Death before 3 months	3	1.7%

ICA=internal carotid artery; PICA=posterior inferior cerebellar artery; MCA=middle cerebral artery; ACA=anterior cerebral artery; PCA=posterior cerebral artery; DAPT=double antiplatelet therapy.

TABLE 3. Anatomical data of patients with FDS MCA-ICA positioning

Patient	Sex	Age	Location	A1 (mm)	M1 (mm)	ICA (mm)	M1/ICA	A1/ICA	Outcome
1	M	36	ICA/L	1.9±0.12	2.5±0.06	3.2±0.10	0.8	0.6	swelling
2	F	74	ICA/L	2.5±0.06	2.7±0.06	3.7±0.06	0.7	0.7	swelling
3	M	69	ICA/L	1.9±0.12	2.5±0.10	3.3±0.10	0.8	0.6	swelling
4	F	62	ICA/L	2.0±0.10	2.7±0.06	4.1±0.23	0.7	0.5	swelling
5	F	47	ICA/R	1.2±0.10	2.5±0.00	2.7±0.06	0.9	0.4	no swelling
6	F	43	Tip ICA/R	2.1±0.12	2.9±0.12	3.6±0.10	0.8	0.6	no swelling
7	F	51	ICA/R	1.9±0.12	2.9±0.15	3.5±0.00	0.8	0.6	no swelling
8	M	51	ICA/L	2.4±0.06	2.7±0.10	3.4±0.10	0.8	0.7	no swelling
9	M	39	ICA/L	1.9±0.12	3.0±0.06	3.4±0.10	0.9	0.6	no swelling
10	M	49	A1/R	2.0±0.06	2.7±0.06	3.0±0.06	0.9	0.6	swelling
11	F	59	ICA/L	2.0±0.06	2.3±0.10	3.1±0.12	0.8	0.7	swelling

FDS=flow diverter stent; MCA=middle cerebral artery; ICA=internal carotid artery; A1=first segment of anterior cerebral artery; M1=first segment of median cerebral artery; M1/ICA=ratio between M1 and ICA; A1/ICA=ratio between A1 and ICA; L=left side; R=right side.

TABLE 4. Demographic data and aneurysm characteristics of patients with FDS MCA-ICA positioning

	Brain oedema	No brain oedema
Total of patients	6	5
Sex		
Female	3	3
Male	3	2
Medium Age (years)	59	47
Location		
ICA	5	4
Basilar	0	0
Vertebral (+PICA)	0	0
MCA	0	0
ACA	1	1
PCA	0	0
Size		
≤10 mm	3	4
10-20mm	2	1
≥20mm	0	0
DAPT		
Aspirin + Clopidogrel	0	1
Aspirin + Ticagrelor	6	4
Medical Antecedents		
Diabetes	0	0
Arterial Hypertension	3	2
Smoke	2	2
Polycistic Kidneys	0	0
Neurologic Symptoms		
HE only	2	0
NI only	0	0
HE+NI	4	0
Symptoms Onset		
≤12h	0	-
12-24h	6	-
≥24h	0	-
Symptoms Duration		
<48h	0	-
48-72h	6	-
Death before 3 months	0	0

FDS=fow diverter stent; MCA=middle cerebral artery; ICA=internal carotid artery; PICA=posterior inferior cerebellar artery; ACA=anterior cerebral artery; PCA=posterior cerebral artery; DAPT=double antiplatelet therapy; HE=headache; NI=neurologic impairment.