Case Report

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Cangrelor use in a pediatric patient with aneurysmal subarachnoid hemorrhage

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Abstract

We herein report the case of a pediatric patient suffering from subarachnoid hemorrhage (SAH) due to a ruptured internal carotid artery (ICA) saccular aneurysm. Considering the unfavorable anatomy and irregular shape of the aneurysm, a flow diverter (FD) stent was positioned in addition to coils in an acute setting. Cangrelor (Kengreal, Chiesi, USA) IV bolus followed by maintenance IV infusion was administered in addition to ASA at the time of intervention. Transitioning from cangrelor to thienopyridine (clopidogrel) was done the day after the procedure without any ischemic or hemorrhagic complications. The patient was discharged symptom-free 24 days later. We discuss technical considerations focusing specifically on antiplatelet therapy management.

Keywords

Aneurysmal subarachnoid hemorrhage, pediatric population, endovascular treatment, Cangrelor, flow diverter

Introduction

The incidence of intracranial aneurysms (IAs) in the pediatric population is low, accounting for 1.6–7 % of all IAs across all age groups[1,2] though rupture rate in pediatric IAs is surprisingly high compared to adults.[3,4]

Endovascular management of ruptured IAs in pediatric patients has shown efficacy with several techniques[5,6] including FDs.[7–9]

Nevertheless, FD placement in an acute setting in the pediatric population poses the problem of antiplatelet therapy handling.

We describe a unique case of a 9-year-old boy with aneurysmal subarachnoid hemorrhage treated with FD and cangrelor.

Case presentation

A 9-year-old boy was admitted to the emergency department of our Institution for a sudden headache and vomiting refractory to medical treatment. CT scan revealed diffuse subarachnoid hemorrhage (SAH) in basal cisterns and right sylvian cistern with moderate ventricular dilatation (Fisher grade 1, Figure 1(A) and (B)). CT angiography (CTA) demonstrated the presence of an internal carotid artery (ICA) saccular aneurysm (Figure 1(C) and (D)). A subsequent angiography confirmed an irregularly shaped polylobulated aneurysm located within the intradural segment of the right ICA (Figure 2(A) and (B)).

The aneurysm was classified as saccular primarily due to its location. However, given the patient's age and the morphology, a dissecting origin of the aneurysm could also be considered. Nonetheless, the type of aneurysm would not have impacted the choice of treatment.

After multidisciplinary consultation, endovascular approach was chosen to occlude the aneurysm. Considering the risk of hydrocephalus and the possible need of antiplatelet therapy related to the endovascular embolization technique, an external ventricular drainage (EVD) was positioned right before the procedure.

Endovascular procedure

Bilateral femoral artery access was performed with 5F introducer sheaths. A 5F guiding catheter was positioned at the origin of both ICAs.

A balloon occlusion test revealed good collaterals through the anterior communicating artery (AcoA) (Figure 3(A) and (B)). Nevertheless, a large anterior choroidal artery (AchA) was noticed to arise in close proximity to the neck of the aneurysm (Figure 3(C) and (D)). Therefore, parent vessel occlusion was excluded and a reconstructive technique was

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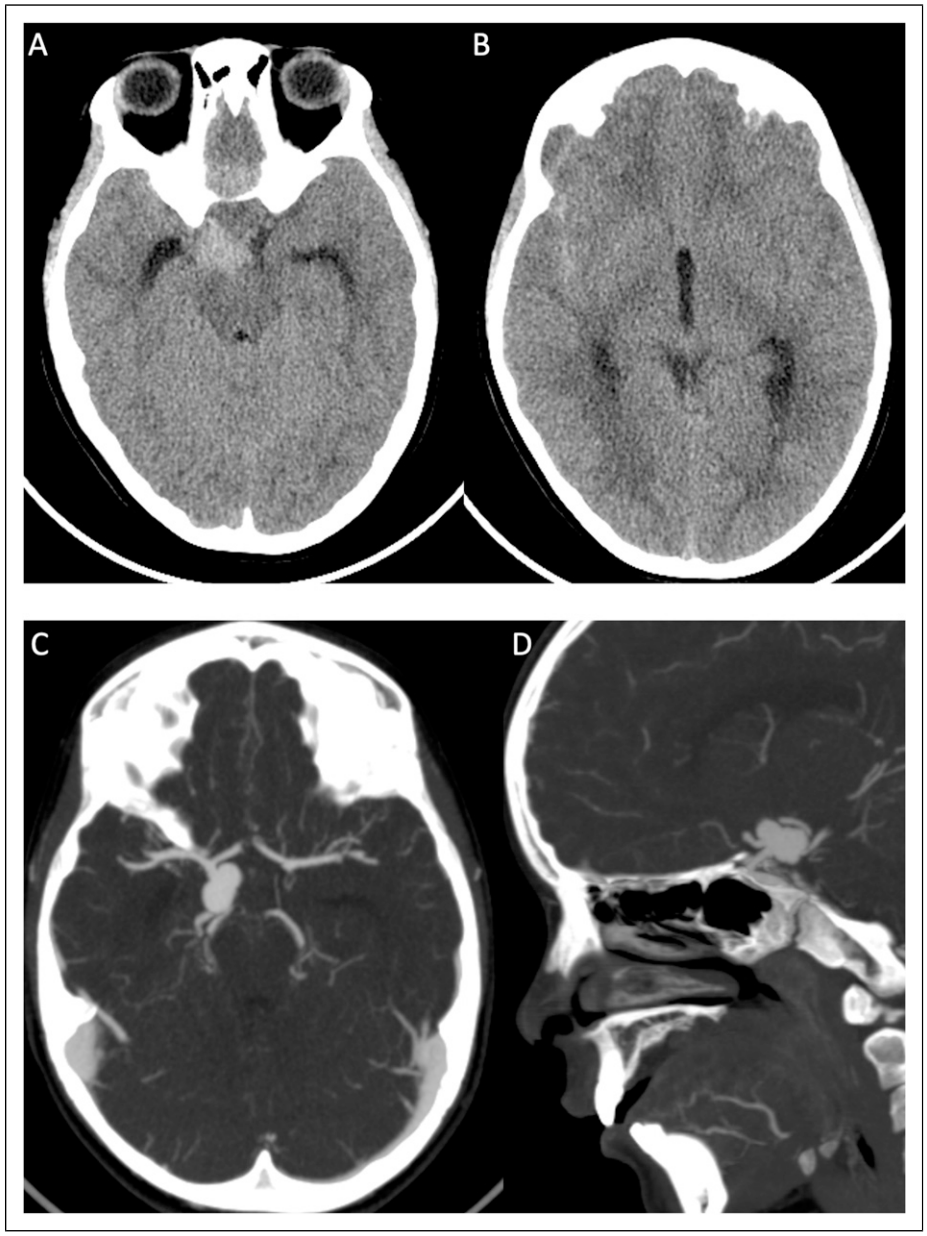

Figure 1. CT scan showing basal cisterns and right sylvian fissure subarachnoid hemorrhage. CT angiography showing the presence of ICA aneurysm located within the posterior communicating segment.

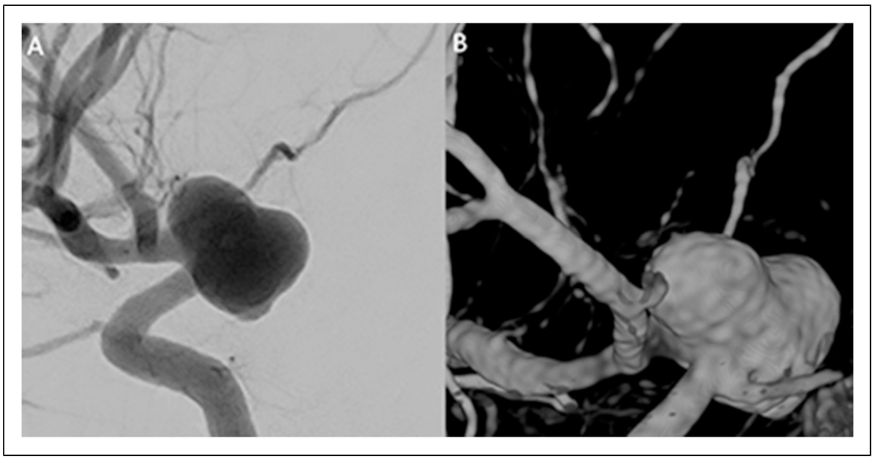

Figure 2. Digital subtraction angiography (A) and 3D reconstructions (B) better demonstrating the aneurysm morphology and connections to parent vessel.

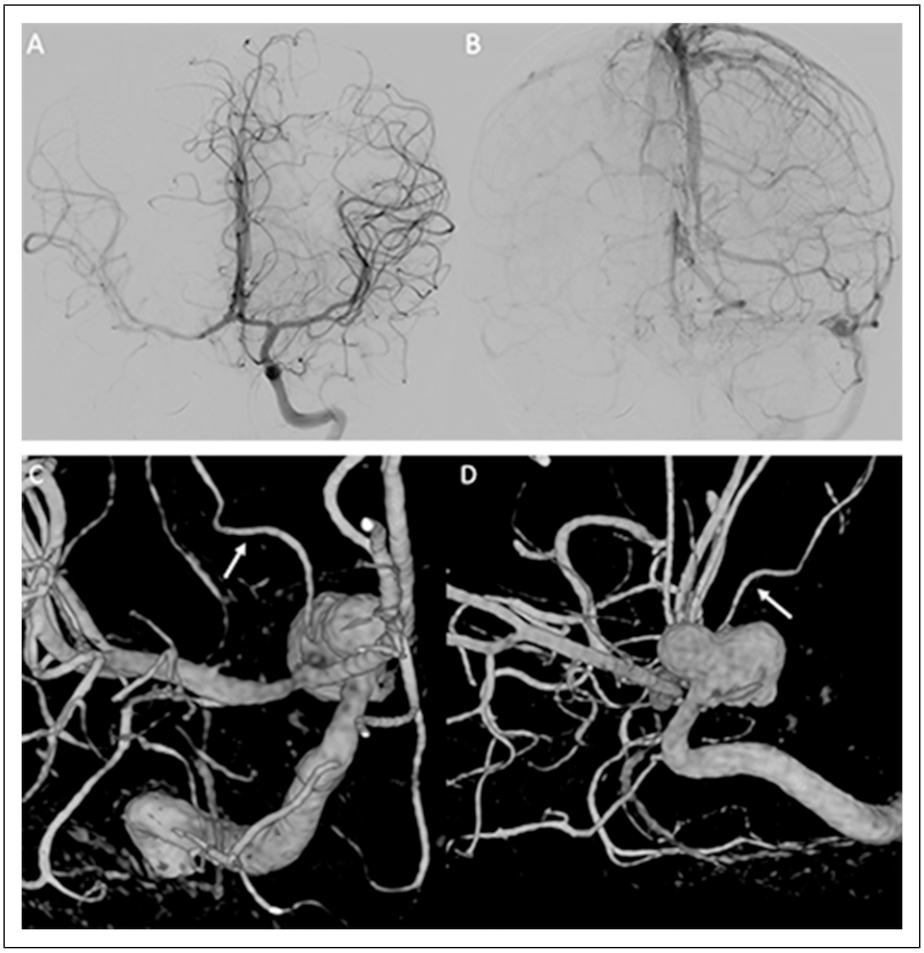

Figure 3. Digital subtraction angiography in antero-posterior view in arterial (A) and venous (B) phase demonstrating good collaterals through AcoA. 3D reconstructions (C, D) showing the origin of AchA (arrow) close to the aneurysm neck.

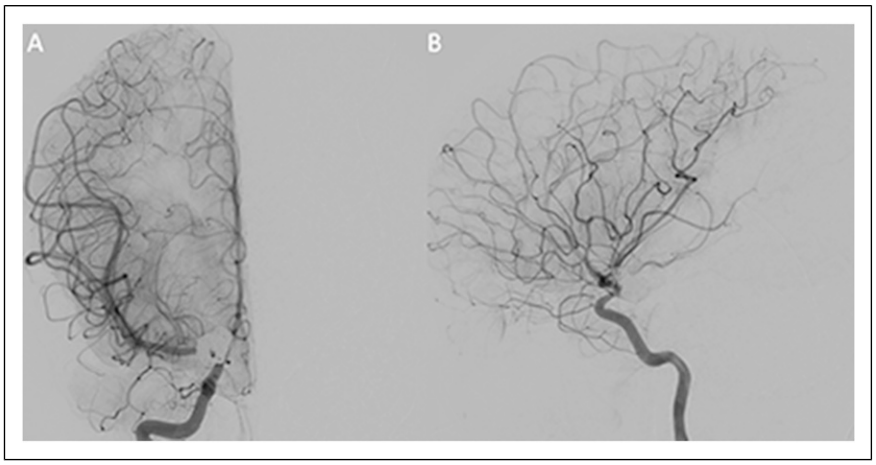

Figure 4. Digital subtraction angiography in antero-posterior (A) and latero-lateral (B) view showing aneurysm occlusion and patency of intracranial vessels.

chosen, with flow diverter stent (FD—Derivo embolization device, Acandis GmbH & Co. KG, Pforzheim, Germany) deployed from middle cerebral artery (MCA) to the cavernous portion of ICA in addition to coils (Figure 4(A) and (B)).

The procedure was performed under systemic heparinization (i.e., 50UI/kg + heparin in flushing lines 5000 UI/l). Activated clotting time (ACT) was maintained between 220s and 260s for the entire duration of the procedure. Just before stent deployment, 5 mg/kg acetylsalicylic acid (ASA) was intravenously (IV) administered as bolus and IV infusion of cangrelor was started as bolus dose (30 ug/kg) followed by maintenance infusion (2 ug/kg/h) for 12 h.

A 12-h control CT scan excluded signs of hemorrhagic complications, and a CTA confirmed persistent patency of ICA. Loading dose of 300 mg of clopidogrel was then

administered via a nasogastric tube (i.e., approximately half of the loading dose indicated in adults[10]), in addition to 2 mg/kg of ASA. Double antiplatelet therapy (DAPT) with 2 mg/kg/die of ASA and 1 mg/kg/die of clopidogrel was therefore started. On 15th post-operative day, the patient was symptom-free. CT scan did not show rebleeding or ischemic complications. On 24th post-operative day, the patient was discharged free of any neurological deficit (modified Rankin scale 0).

Discussion

Cangrelor is an IV P2Y12-receptor antagonist that reversibly and directly antagonizes the platelet receptor.[11] It does not require metabolic activation with an immediate onset warranted when given as a bolus and infusion. The plasma half-life is 3–6 min, and platelet activity returns to normal within 60 min after discontinuation of the infusion, ensuring a rapid offset.[12]

Cangrelor showed efficacy and safety first in interventional cardiology[13] and then also in Neurointervention[14] as an alternative to other antiplatelet agents. Its pharmacokinetics allows prompt use in emergency and at the same time the possibility of a rapid reversal of antiplatelet effect in case of complications or if surgery is required.

On the other hand, the use of cangrelor in pediatrics has been documented in the literature with only case studies regarding interventional cardiology.[15,16]

FDs for ruptured intracranial aneurysms have showed acceptable safety and efficacy rates in selected cases in adult population[17,18] and in childhood.[7–9] The major drawback of FD in an acute setting is the stent's thrombogenic potential, requiring antiplatelet medications, and finally increasing both hemorrhagic (from aneurysm itself, from brain hematoma or EVD insertion) and thrombotic risk.[17] The rapid onset and offset of antiplatelet effect make cangrelor the ideal drug for such circumstance,[14] although there is no literature concerning management of cangrelor for pediatric population in Neurointervention.

With regards do antiplatelet dosage, in the acute phase we used the same weight-based regimen approved from our Institution for cangrelor in adults and widely used in Neurointervention.[19] Concerning transitioning from cangrelor to clopidogrel, cangrelor high receptor occupancy prevents the binding of clopidogrel's active metabolite to the P2Y12 receptor, leading to a lack of platelet inhibitory effect. Nevertheless, if clopidogrel is administered at the end of the cangrelor infusion, this interaction may be avoided, allowing sufficient time for Cangrelor to wash out from the system and subsequent binding of clopidogrel's active metabolite to the P2Y12 receptor.[20] Clopidogrel onset of action ranges between 2- and 8-h depending primary on bolus dose,[12] while normalization of platelet function after cangrelor administration occurs within 60 min after discontinuation.[21] Nevertheless, clopidogrel administration at the termination of cangrelor infusion leads to an anticipated degree of platelet inhibition.[22] Indeed, company's IFUs advise 600 mg loading dose of clopidogrel just after discontinuation of cangrelor.[10] We decided to use half of loading dose advised in adults by company's IFUs (i.e., 600 mg). The latter could have led to the discontinuation of platelet inhibition between the offset of cangrelor activity and the onset of clopidogrel, but clopidogrel full loading dose is not usually given in childhood.[23]

The maintenance antiplatelet regimen was based on our management protocol of antiplatelet therapy in children in agreement with current literature (i.e., 2 mg/kg/die for ASA and 1 mg/kg/die for clopidogrel[11,23]).

To our knowledge, this is the first case in which cangrelor was used in Neurointervention in an acute setting in childhood.

Although this is a single case-report, we found that acute antiplatelet regimen with cangrelor in the pediatric population could be feasible with a tailored weight-based approach and no substantial modifications from adults' protocol.

Conclusion

Childhood aneurysmal SAH, even if rare, is a critical condition requiring prompt and effective treatment. In selected cases with unfavorable anatomy, FDs may be helpful as in adults.[7–9] Further investigations on safety and efficacy of cangrelor in the pediatric population may improve the handling of this drug, which may become a valuable tool to deal with such complicated and severe condition.

Author contributions

RR designed data collection tools, drafted, and revised the paper. Remaining authors approved final draft.

Declaration of conflicting interests

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Ethical statement

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

The Institutional Review Board approved the study and waived informed consent based on the retrospective nature of the study.

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Appendix

Abbreviations

ICA	Internal carotid artery
SAH	Subarachnoid hemorrhage
FD	Flow diverter stent
IA	Intracranial aneurysm
CTA	CT angiography
EVD:	External ventricular drainage
AcoA	Anterior communicating artery
AchA	Anterior choroidal artery
MCA	Middle cerebral artery
ACT	Activating clotting time
ASA	Acetylsalicylic acid
DAPT	Double antiplatelet therapy
IV	Intravenous.