Clinical Case Report

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Acute stent thrombosis after stent-assisted coiling in an intracranial aneurysm patient carrying two reduced-function CYP2C19 alleles

A case report

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Abstract

Rationale: Stent thrombosis (ST) remains a thorny issue in spite of dual antiplatelet treatment with aspirin plus clopidogrel after stent-assisted coiling (SAC). We report a first case of acute ST after SAC in an intracranial aneurysm (IA) patient who carries two reduced-function CYP2C19 alleles.

Patient concerns: A 43-year-old Chinese male carrying two reduced-function CYP2C19 alleles was treated with a loading dose of clopidogrel 300 mg and aspirin 300 mg before SAC. Unfortunately, life-threatening ST appeared 0.5 h later after SAC.

Interventions: A total of 100000U of urokinase was used to dissolve ST. Meanwhile, tirofiban and nodroparin was also administrated to prevent recurrent thrombotic events.

Outcomes: A repeated angiography demonstrated a successful reperfusion after thrombolytic treatment.

Lessons: The present case demonstrates that CYP2C19 allele carriers may lead to a suppressed antiplatelet effect of clopidogrel and a high risk of ST in the meantime. Therefore, CYP2C19 genetic testing seems to be able to identify patients-at-risk and optimal antiplatelet treatment should be considered in these fragile populations.

Abbreviations: ADP = adenosine diphosphate, ARC = Academic Research Consortium, cytochrome P450 2C19 = CYP2C19, HPR = high on-treatment platelet reactivity, IA = intracranial aneurysm, PCI = percutaneous coronary intervention, RACA = right anterior communicating artery, SAC = stent-assisted coiling, ST = stent thrombosis, TEG = thrombelastogram.

Keywords: acute stent thrombosis, clopidogrel, CYP2C19 gene polymorphism, high on-treatment platelet reactivity, intracranial aneurysm

1. Introduction

Stent-assisted coiling (SAC) has been widely applied for the treatment of intracranial aneurysm (IA).[1] To date, dual antiplatelet treatment, comprising aspirin plus clopidogrel, is advocated in patients with high thrombotic risk.[2] Whereas, patients are potentially at risk of further thromboembolic events after SAC in spite of positive antiplatelet treatment, and stent thrombosis (ST) is one of the most serious complications in IA patients post SAC.[2]

Clopidogrel, an irreversible inhibitor of the platelet adenosine diphosphate (ADP) P2Y12 receptor, is the standard antiplatelet agent following SAC in order to reduce recurrent thrombotic events.[2] However, about 4% to 30% of the patients treated with clopidogrel display no or a low antiplatelet response, which increased the risk of recurrent ischemic events.[3] One source of the variability may be the metabolism of clopidogrel. It is an inactive pro-drug that requires hepatic metabolism by cytochrome P450 2C19 (CYP2C19) into its active metabolites before interacting with the P2Y12 receptor.[4,5] Subjects who carry reduced-function CYP2C19 alleles (*2 or *3) demonstrate reduced active metabolites of clopidogrel and unsatisfactory antiplatelet effect.[5] Previous studies, including case report, have revealed that mutation of CYP2C19 gene was associated with an increased risk of ST in patients after percutaneous coronary intervention (PCI).[6–8] Currently, no article reported ST in IA patients due to a suppressed antiplatelet activity and we described the first report of acute ST after SAC in a carrier of two CYP2C19 reduced-function polymorphisms.

2. Case report

Approval for the study by the local institutional review board was not required because it was a case report, and the patient provided a written informed consent. A 43-year-old Chinese man

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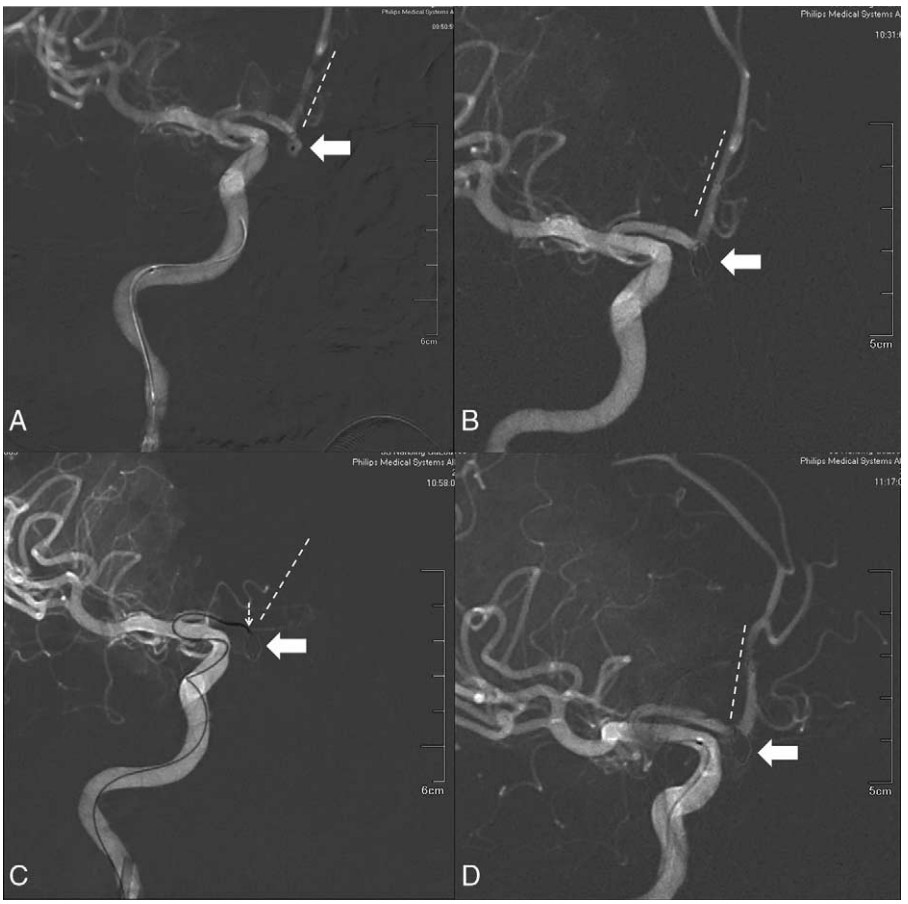

Figure 1. Panel A shows initial intracranial aneurysms in right anterior communicating artery (RACA) (arrows with solid line). Panel B shows a good result after implanting a 4.0 mm × 20 mm bare metal braided stent (dotted line). Panel C shows acute stent thrombosis 0.5 hours later post stenting (arrows with dotted line). Panel D shows successful reperfusion following urokinase treatment (dotted line). RACA = right anterior communicating artery (RACA).

with a history of smoking and dyslipidemia was admitted to our hospital after experiencing the sudden onset of severe headache. Brian computed tomography revealed aneurysm subarachnoid hemorrhage with Fisher grade II and Hunt–Hess grade II. Then, a loading dose of clopidogrel 300 mg and aspirin 300 mg was given before operation. Angiography showed the occlusion of right anterior communicating artery (RACA) in the presence of IA (Fig. 1A). On the basis of angiographic results, we treated the RACA by deploying a 4.0 mm × 20 mm bare metal braided stent. Post-stent angiogram confirmed good stent apposition and flow, and no signs of perforation or thrombus formation (Fig. 1B). The patient's headache improved after SAC, and he was continued on a regimen of aspirin 100 mg and clopidogrel 75 mg once daily.

Unfortunately, 0.5 hours later after operation, the patient developed progressive neurological changes with lethargy, left upper extremity paraplegia, and facial drop (blood pressure 158/95 mm Hg, heart rate 80 beats per minute). Emergent angiography showed thrombotic occlusion of the RACA (Fig. 1C). At this juncture, intra-arterial injection of urokinase (100,000 U totally) was managed using micro-catheter. After thrombolytic therapy, tirofiban at dosage of 2.5 mg/h was continuously administrated via intravenous injection. Meanwhile, nodroparin with dosage of 4100 U twice daily was used through subcutaneous injection. The neurological changes of the patient improved after intensive treatment, and the repeated angiography demonstrated a successful reperfusion in RACA (Fig. 1D). Platelet function testing was performed by employing thrombelastogram (TEG), which showed a low clopidogrel platelet inhibition rate (PIR) of 14.4%. Of note, the patient carries two reduced-function alleles ($^{*}2/^{*}2$) of CYP2C19 and was considered as poor metabolizer of clopidogrel. He was discharged day 7 post-SAC on treatment with intensive antiplatelet therapy (aspirin 100 mg once daily and clopidogrel 150 mg once daily). At seven months follow up, the patient has been doing well without any evidence of recurrent ischemic event, and the repeat TEG result revealed a relatively satisfying clopidogrel PIR of 62%.

3. Discussion

We present an interesting case in which insufficient antiplatelet effect of clopidogrel may contribute to acute ST during the early phase after SAC. To be our best knowledge, this is the first report of acute ST in an IA patient who carries two reduced-function CYP2C19 alleles. According to the Academic Research Consortium (ARC) definition, ST was classified as definite, probable, or possible as well as acute (0 to 24 h), subacute (1 to 30 days), late (31 to 360 days), and very late(>360 days) based on timing after the initial stent implantation.[9] The present case was considered as definite acute ST on the basis of ARC definition.

In terms of acute ST, considerable risk has focused on inter-individual difference in response to ADP-antagonist therapy.[10]

Previous studies, mainly from coronary heart disease patients, have confirmed a relationship between high on-treatment platelet reactivity (HPR) in platelet function testing and subsequent ST.[10,11] A big registry study has showed a 9-fold risk of early ST in HPR patients.[11] In this case, the patient's ADP-induced platelet inhibition rate being 14.4% meant a suppressed antiplatelet activity of clopidogrel and was regarded as a HPR patient, which contribute to the subsequent acute ST. Actually, the antiplatelet effect of clopidogrel is slow onset and requires about 4 hours to achieve a steady platelet inhibition even taking a loading dose of 600 mg.[12] It is noteworthy that the presence of reduced-function CYP2C19 allele was main reason for HPR and acute ST. CYP2C19*2 (rs4244285) was a common single-nucleotide polymorphism of CYP2C19, leading to a protein product with no enzyme activity.[13] The frequency of CYP2C19*2 is <15% in Caucasians and Africans, but affects up to 35% in Asians.[13] Thus, the number of poor clopidogrel metabolizers (CYP2C19*2/*2 or *2/*3) may be higher than previously postulated especially in Asians. Currently, cardiovascular guidelines recommend against routine CYP2C19 genetic testing for clopidogrel-treated patients after PCI, primarily because the results of both pharmacogenetic testing and platelet function testing failed to show significant improvement in outcomes.[14,15] However, no relative data have been addressed in IA patients. Meanwhile, in certain high ischemic risk patients, as presented in this case of an Asian patient undergoing SAC as well as experiencing acute ST, it might be reasonable to conduct risk assessment using genetic and platelet reactivity testing before SAC. Two optimal strategies can be considered in such fragile patients carrying reduced-function CYP2C19 alleles: increasing the dose of clopidogrel, which can improve HPR but has not been demonstrated to reduce major adverse cardiovascular events,[16] or choosing alternative P2Y12 receptor inhibitors, such as ticagrelor and prasugrel that play a more rapid and effective antiplatelet effect than clopidogrel. Although these P2Y12 inhibitors are less impacted by gene polymorphism of CYP2C19, guideline recommends refraining from ticagrelor or prasugrel use in IA patients because of the limited data in this population.[1] Thus, in this patient, a high clopidogrel dose of 150 mg once daily was administrated with no recurrent thromboembolic events during seven months follow up. Based on the clinical setting of this case and present evidence, screening for the risk of early ST (CYP2C19 polymorphisms and HPR) should be considered before initiating SAC treatment and clopidogrel double dose may represent a preferable alternative to clopidogrel standard dose in IA patients who are at high risk of acute ST. In addition, further design of randomized controlled trials on evaluation of novel P2Y12 receptor inhibitors in IA patients is necessary.

4. Conclusion

IA patients carrying reduced-function CYP2C19 alleles may decrease the response to clopidogrel and increase the risk of early ST after SAC. Thus, CYP2C19 genetic testing seems to be able to identify patients-at-risk and optimal antiplatelet treatment should be considered in these fragile populations.

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