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Case report

Delayed reperfusion therapy for ischemic stroke tandem occlusion with subsequent secondary prophylaxis of cerebral ischemic events: A case report and literature review ☆

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ABSTRACT

Mechanical thrombectomy is currently the gold standard treatment of large vessel occlusions, especially in anterior circulation acute ischemic stroke. At the same time, the problem of tandem occlusions seems especially important since most of the major clinical mechanical thrombectomy studies did not specifically evaluate patients with concomitant extracranial occlusions or critical stenoses.

To date, there is no universally accepted optimal treatment strategy for such tandem lesions in acute ischemic stroke: it remains unclear which lesion – intracranial or extracranial – should be treated first. The selected reperfusion method should be based on the patients' individual characteristics, data from non-invasive radiologic studies, and the stroke team experience.

We present a case of successful reperfusion therapy of acute tandem occlusion of the right internal carotid artery, followed by contralateral carotid artery stenting in a patient with stenosing extracranial atherosclerosis.

☆ Competing interests: This report has not been published and is not under consideration for publication elsewhere. We have no conflicts of interest to disclose.

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Introduction

Mechanical thrombectomy (MT) is currently the standard treatment for large cerebral and precerebral vessel occlusions, especially with acute ischemic stroke (AIS) in the anterior cerebral circulation [1–4]. Meanwhile, the tandem occlusion (TO) issue seems crucial because most fundamental clinical studies in the mid and late 2010s (MR CLEAN, ESCAPE, SWIFT PRIME, REVASCAT, EXTEND-IA, DAWN, DEFUSE-3, and HERMES meta-analysis) did not purposively assess patients with concomitant extracranial occlusion or critical stenosis [5–10]. To date, there has been no generally accepted optimal treatment strategy for AIS with a tandem lesion.

The term TO is commonly understood as occlusion or critical stenosis of the extracranial, internal carotid (ICA) or vertebral arteries (VA) and concomitant intracranial occlusion of a major vessel [11–13]. TO incidence in the general population of patients with AIS due to large vessel occlusion (LVO) is approximately 10-15%. Extracranial lesion etiology is mostly atherosclerotic - 78% of total TO number vs 22% constituting ICA dissections [11,14].

TOs especially due to LVOs of intracranial ICA sections and MCA M1 segment poorly respond to intravenous tissue-type plasminogen activators (ivTPA) and are known as predictors of unfavorable outcome with conservative treatment [11,12,15,16]. Given low ivTPAs efficacy in TOs, mechanical recanalization of target LVO represents an important area of TO reperfusion therapy.

It remains unclear which lesion (intracranial or extracranial) should be treated first. Intracranial approach proponents speak of benefits of rapid recanalization of cerebral occlusion without loss of time to extracranial lesion. Meanwhile, extracranial approach supporters stress primary elimination of thromboembolism cause and provision of better passability of supporting and distal access catheters [12,13,17].

Also, optimal treatment tactics for extracranial occlusion and/or critical stenosis has not been determined. Should one perform recanalization and ad hoc stenting or be content with primary angioplasty alone? If only percutaneous transluminal angioplasty (PTA) is to be performed, at what period should carotid artery stenting (CAS) be performed and is it necessary at all? CAS approach proponents call for benefits of complete extracranial stenosis treatment in 1 intervention, whereas primary PTA supporters mention unsafe prescription of dual antiplatelet therapy (DAPT) in acute AIS with increasing risk of peri- and postoperative hemorrhagic complications. It has resulted in several endovascular treatment tactics [11–13,18,19]:

- Isolated intracranial MT;
- MT with subsequent ICA angioplasty and/or CAS;
- PTA and/or CAS stenting with subsequent intracranial MT.

When deciding to perform PTA and/or CAS in 1 intervention with MT, the extent of anticoagulant therapy performed and the need for prescribing DAPT are not completely clear. The TITAN Collaboration, in a recent review of TO treatment options and methods, has divided therapeutic intervention options on extracranial stenoses as follows [11]:

- CAS after MT with full-scale DAPT;
- CAS after MT without DAPT;
- Primary PTA without CAS;
- Leaving extracranial stenosis as it is.

Papanagiotou *et al.*, in a major 2018 TO treatment meta-analysis, compared different extracranial intervention options in patients with anterior circulation AIS [20]. Successful reperfusion rate when combining intracranial MT and extracranial intervention was higher than isolated treatment

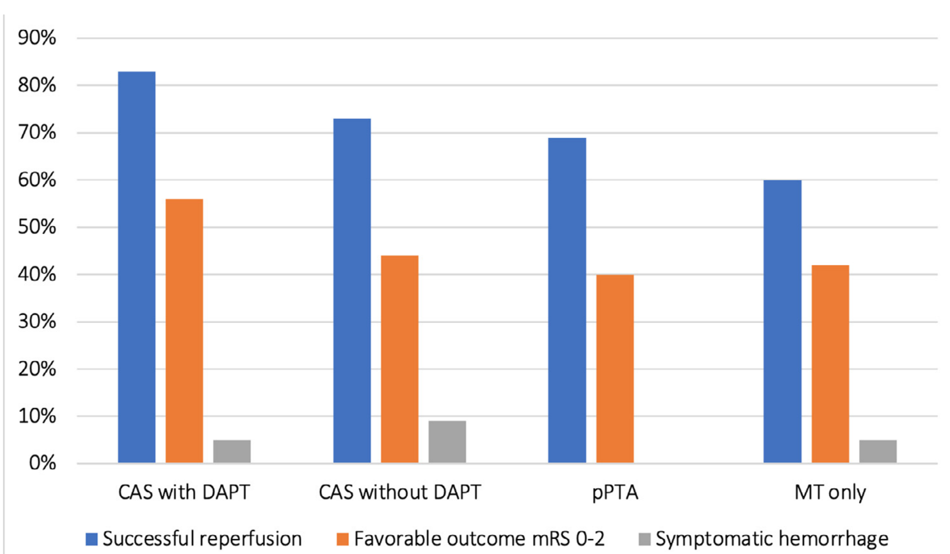

Fig. 1 – Outcomes rate in TO treatment groups according to meta-analysis by Papanagiotou *et al.* [16]. TO, tandem occlusion; CAS, carotid artery stenting; DAPT, dual antiplatelet therapy; pPTA, primary percutaneous transluminal angioplasty; MT, mechanical thrombectomy; mRS, modified Rankin Scale.

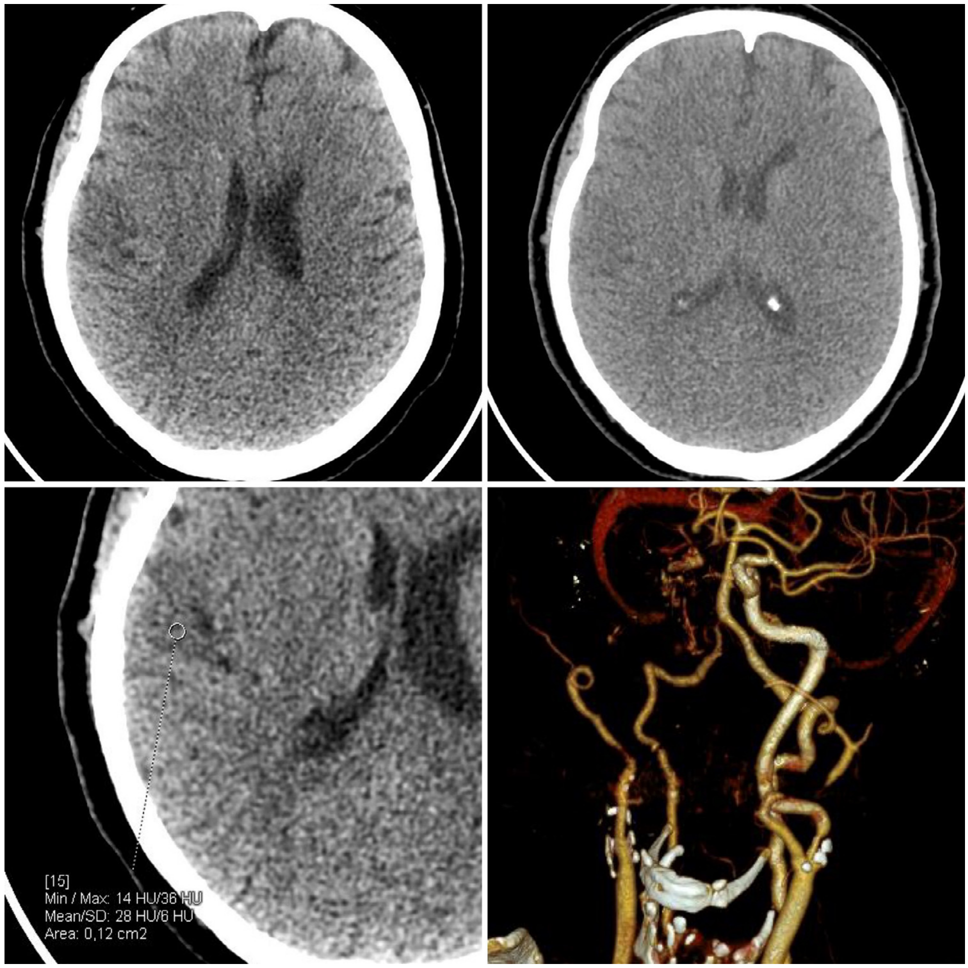

Fig. 2 – Native CT and CT angiography findings on admission. *Top left, top right, bottom left*: native CT data - 2.2 x 2.8 cm hypodense zone (26 Hounsfield units, HU), impaired differentiation of gray and white matter of the precentral and postcentral gyri; *bottom right*: CT angiography data - right ICA occlusion in the C1 segment, weak filling of the right ICA terminus with a contrast agent. CT, computed tomography; HU, Hounsfield units; ICA, internal carotid artery.

of intracranial occlusion alone: 79.4% vs 60.2% (OR = 2.04, 95% CI = 1.18-3.51; *P* = .011), without association with ivTPA. Successful reperfusion rate in the CAS group with DAPT was 83.1% vs 60.2% in the isolated MT group (OR = 2.66, 95% CI = 1.38-5.50; *P* = .003) and 74% in the CAS group without DAPT prescription, although there was no statistical difference in outcomes compared to the latter group. Favorable outcome rate (mRS $\leq$ 2) was not statistically different in all the groups. Mortality rate in the stenting group with DAPT was significantly lower than isolated MT (9.5% vs 17.1%; OR = 2.04, CI = 1.18-3.51; *P* = .011) without significant difference in symptomatic hemorrhagic complications. The authors concluded that the patient group with single step TO treatment with stenting against the background of DAPT prescribed featured higher successful reperfusion rate vs other methods (Fig. 1).

It is worth noting that, analyzing epidemiology of the meta-analysis above, we have found that average time from symptom onset to MT was 279.8 ± 213.1 minutes (4.5 hours on average). Thus, despite the unconditional value of the analysis, the described approaches and treatment strategies for intra- and extracranial AIS lesions cannot be projected to the patient population receiving reperfusion during a delayed time window. These are usually patients with already partially formed ischemic core and prescribing a full DAPT dose when choosing single-step stenting with full intraoperative anticoagulation and. DAPT may have disastrous consequences. The combination of MT and isolated pPTA with CT follow-up after 12-24 hours may be a possible treatment option for extracranial lesion in case of late admission with TO and patient meeting DAWN study criteria. Then, in the absence of hemorrhagic complications of reperfusion, delayed stenting, or endarterectomy (CEA) of the culprit extracranial lesion can be performed.

Endovascular techniques in patients with TO-caused AIS are of particular importance, especially with contraindications to ivTPAs and/or unknown timing of symptom onset with a large penumbral area. Selecting revascularization method and reperfusion strategy should be based on individual patient characteristics, noninvasive diagnostic data, and the operating team's experience.

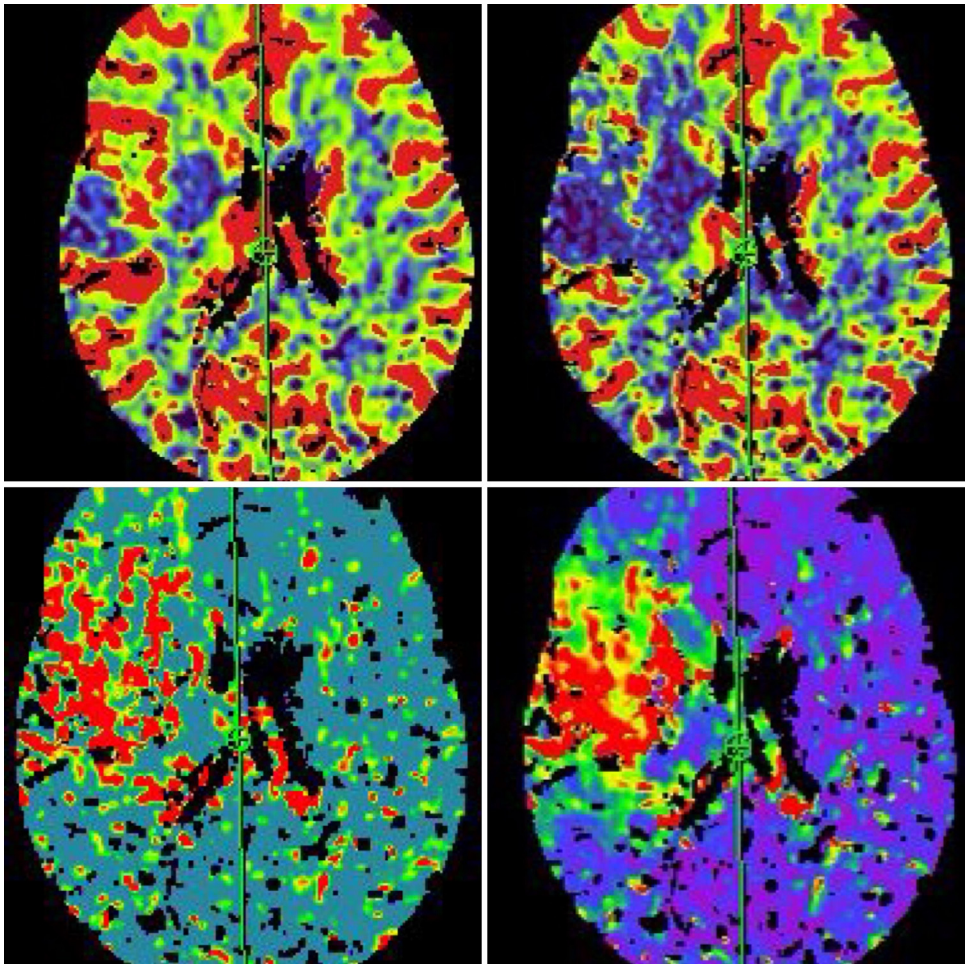

Fig. 3 – CT perfusion images. ***Top left*****: relatively normal CBV with small infarction core;** ***top right*****: decreased CBF;** ***bottom left*****: decreased MTT;** ***bottom right*****: increased TTD. CT, computed tomography; CBV, cerebral blood volume; CBF, cerebral blood flow; MTT, mean transit time; TTD, time to drain.**

Case report

A 67 years-old female, was delivered by ambulance to the ER of Saint-Petersburg City Hospital №40 at around 3 PM in serious condition, diagnosed with acute cerebrovascular accident. The patient's present relatives had last seen her in full health over 16 hours before, prior to going to bed. Her husband had returned at lunchtime to find her confused beside the bed, with her left arm and leg immobile, with correct but slow speech and with considerably asymmetrical face. Neurologic state on ER examination: clear consciousness, mild dysarthria, left facial asymmetry, left-sided hemiparesis grade 1, left hemihypesthesia – NIHSS (National Health Institute Stroke Scale) score of 16.

Within 15 minutes after admission, a CT brain scan was performed: signs of 2.2 × 2.8 cm hypodense zone, impaired differentiation of gray and white matter, smoothing of the right sulcus in the insular lobe, precentral and postcentral gyri, signs of a hyperdense area in the M1-M2 segment of the right middle cerebral artery (MCA) over 2.2 cm long, ASPECT score of 8.

CT angiography verified atherosclerosis of extracranial arteries with stenosis of the left ICA in the C1 segment over 80%, right ICA occlusion with weak terminus opacification and occlusion of the M1 segment of the right MCA (Fig. 2).

Given symptoms onset time (16+ hours), pronounced neurological impairment (16 points), and a small infarcted area, CT cerebral perfusion was performed: core volume at 26.9 cm^3, penumbra volume at 40.6 cm^3 (60.13% ratio). Color mapping demonstrated preserved cerebral blood volume, decreased cerebral blood flow, mean transit time, and increased time to drainage, indicating a significant area of potentially salvageable brain tissue with a small infarction zone (Fig. 3). Coagulogram, biochemical and clinical blood tests revealed no deviations from the norm. The patient was prepared for endovascular reperfusion and transported to the cathlab.

According to CT angiography, the aortic arch corresponded to ACCF Type 2. Therefore, without expecting difficulties with catheterization of the left common carotid artery (CCA), right common femoral artery (CFA) access was chosen. Considering known vascular anatomy of large extra- and intracranial vessels according to CT angiography, cerebral angiography (CAG) stage was skipped to reduce time to reperfusion.

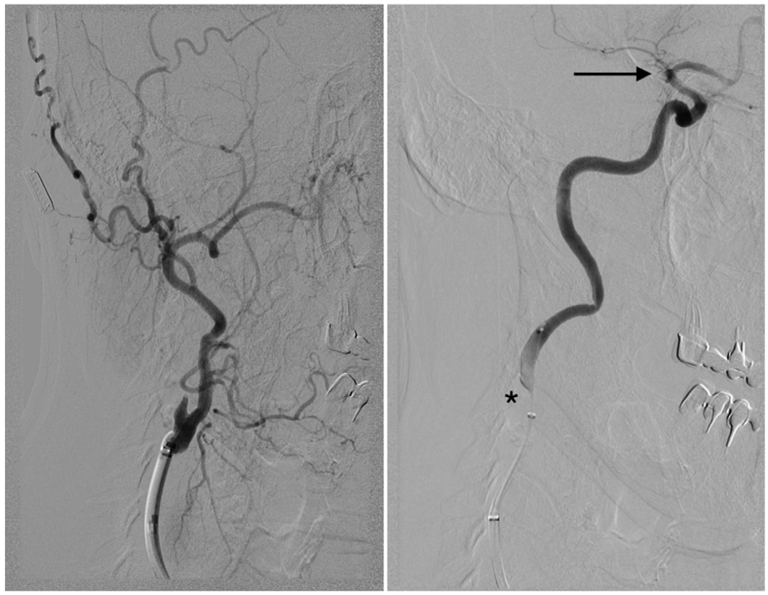

Fig. 4 – Right ICA and MCA TO. ***Left*: ICA occlusion; *right*: right MCA M1 segment occlusion (indicated by the arrow), the asterisk indicates previously occluded C1 segment. ICA, internal carotid artery; MCA, middle cerebral artery; TO, tandem occlusion.**

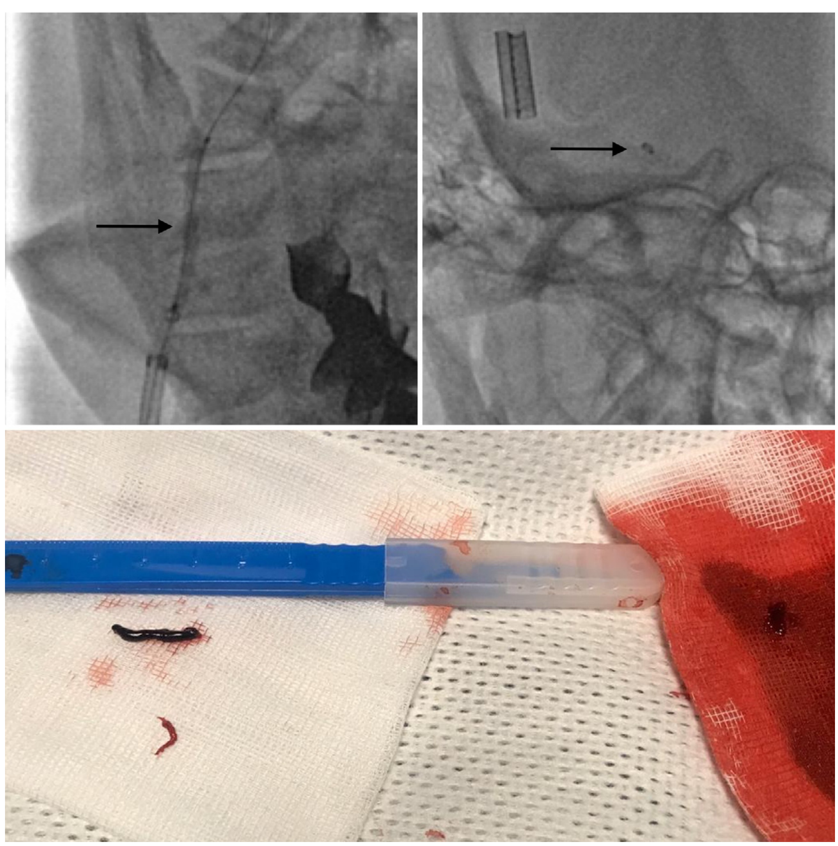

Fig. 5 – PTA and MT. ***Top left*: ICA PTA (the balloon indicated by the arrow); *top right*: an aspiration catheter in the right MCA M1 segment (indicated by the arrow); *bottom*: thromboemboli obtained. PTA, percutaneous transluminal angioplasty; MT, mechanical thrombectomy; ICA, internal carotid artery; MCA, middle cerebral artery.**

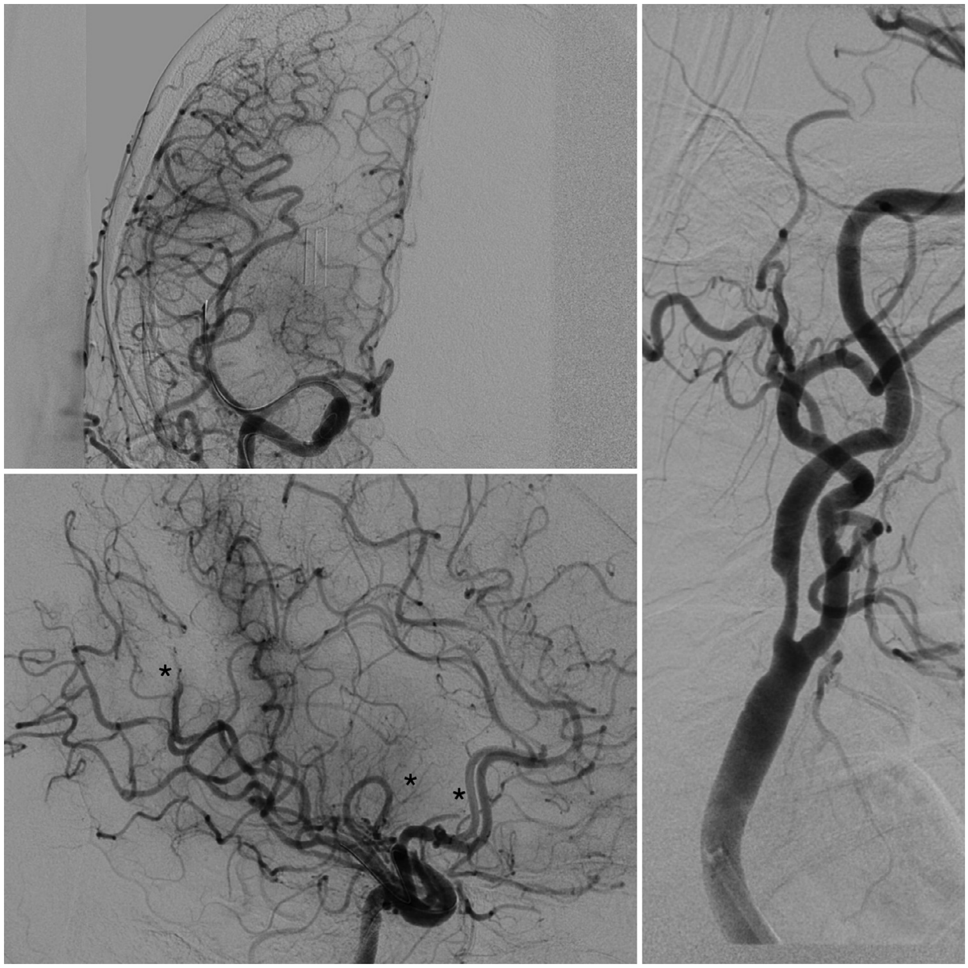

Fig. 6 – Restored blood flow in right ICA and MCA. *Top left*: frontal projection; *bottom left*: lateral projection, lack of contrasting along the anterior parietal, prefrontal, and precentral arteries (asterisks); *right*: the result of balloon angioplasty and «dottering» of the right ICA stenosis, residual stenosis remains up to 80%. ICA, internal carotid artery; MCA, middle cerebral artery.

A Neuron Max 088 (Penumbra, USA) guide catheter was inserted directly without sheath through the right CFA into the descending aorta. A diagnostic JR4 5F 125cm catheter (Cordis, USA) was inserted into the guide catheter, right CCA catheterization was performed, and Neuron Max was raised to the right ICA ostium using telescopic technique. Saline drip (normal 0.9% NaCl saline without heparinization) and cerebral telescopic systems were assembled: a Traxcess 0.014 guidewire (Microvention, Terumo, Tokyo, Japan), a Rebar-27 microcatheter (Medtronic, USA), and a Sofia Plus 6F aspiration catheter (Microvention, Terumo, Japan). The guidewire was passed through the occlusion into the distal ICA without technical difficulties, the microcatheter was passed beyond the occlusion zone, the ICA was contrasted, M1 occlusion of the right MCA was confirmed (Fig. 4).

Attempts of aspiration from the ICA with Sofia Plus were unsuccessful due to critical ICA stenosis; the Rebar was removed from the guidewire using the Nanto technique [21]. A Sprinter Legend 2.0 × 30 mm balloon catheter (Medtronic, USA) was inserted along the guidewire through the Sofia catheter, and ICA C1 segment PTA was performed to pass the tool to the intracranial occlusion site (Fig. 5). The Sofia was re-delivered to the C7 segment, and the Neuron Max was delivered through the stenosis to the C2 segment without technical difficulties. On repeated aspiration, the Sofia was passed into M1, followed with 90-sec aspiration and thromboemboli retrieval (Fig. 5).

Control angiogram showed restored blood flow along the right MCA, a floating thrombus in the C1 segment at the guide catheter's distal tip, evacuated by direct aspiration through the Neuron Max. Control angiography: restoration of antegrade blood flow of MCA M1, diminished flow along the anterior parietal, prefrontal, and precentral arteries. Considering AIS in the non-dominant hemisphere and the ischemic zone formed in the territory partially vascularized by the mentioned occluded arteries, the anterior parietal, prefrontal, and precentral arteries were not recanalized (Fig. 6).

The question of what happened to the ICA C1 segment after PTA and dottering with the Sofia Plus and Neuron catheters and whether it was necessary to urgently stent C1 remained open. Angiographic control revealed absence of flow-limiting dissections and residual C1 stenosis up to 80%. It was

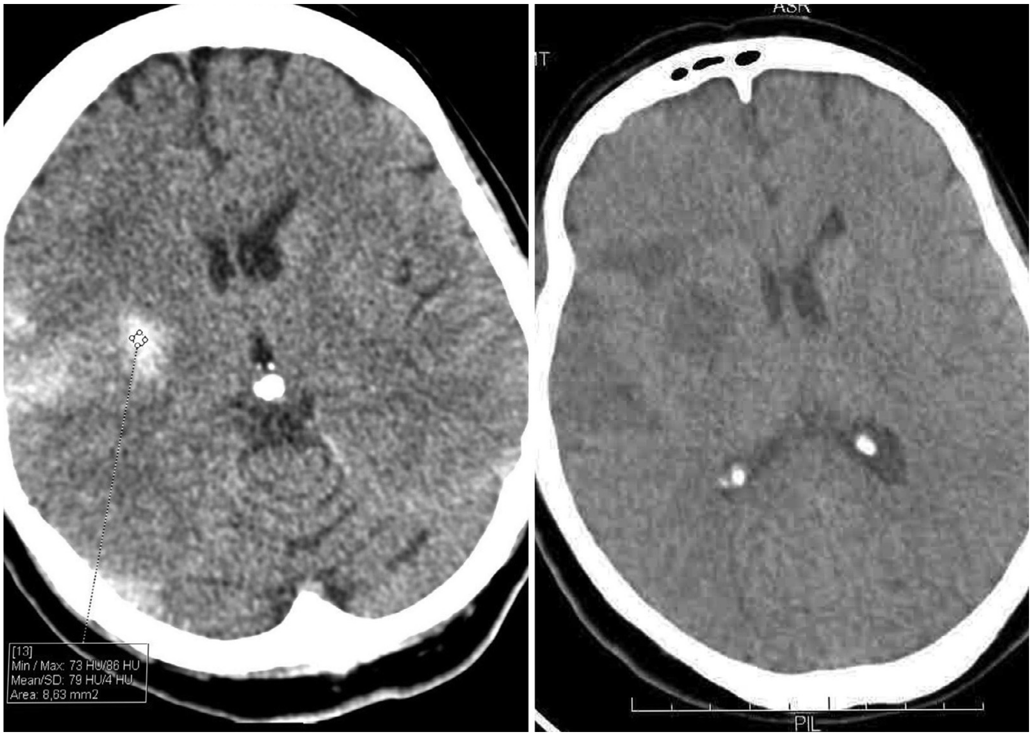

Fig. 7 – CT control 24 (left) and 48 (right) hours after PTA and MT. *After 24 h*: CM ischemic core density, less likely blood (average density at 79 HU); *after 48 hours*: increased density areas had completely disappeared. CT, computed tomography; PTA, percutaneous transluminal angioplasty; MT, mechanical thrombectomy; CM, contrast medium; HU, Hounsfield units.

decided to refuse ICA stenting in favor of pPTA performed (Fig. 6). The Neuron guide catheter was removed from the right CCA, and selective catheter CAG was performed: left ICA stenosis in the C1 segment >80%; the left ICA, extra- and intracranial segments of the left vertebral artery without signs of stenosing and aneurysmal deformity; the right vertebral artery hypoplastic to V4 level.

The right CFA was closed with an AngioSeal 6F (Terumo, Tokyo, Japan), and a peripheral Arteriofix 22G catheter (B. Braun, Germany) was inserted into the right radial artery for invasive hemodynamic control and maintenance of normotension in the early postoperative period. The patient was transferred to the ICU for follow-up.

Twenty-four hours after the MT, the NIHSS score was 6 - facial asymmetry, dysarthria, and weakness in the left extremities remained up to grade 3. A control brain CT scan was performed: the ischemic core was filled with a contrast medium (CM), less likely with blood (average density at 79 HU is more likely to correspond to CM). Before deciding on DAPT loading and possible ICA stenting, we repeated CT after another 24 hours for hemorrhage differential diagnosis: increased density areas had completely disappeared (Fig. 7).

On the 4th day after thrombectomy (NIHSS score 4), a DAPT loading dose (aspirin 300mg + clopidogrel 600mg) was given, a Neuron Max 088 guide catheter was introduced through the left CFA directly into the CCA using telescopic technique along the JR4 125cm. Angiograms showed complete blood flow restoration in the anterior parietal, prefrontal, and precentral arteries, residual stenosis of the right ICA C1 segment ~70% (Fig. 8).

Distal embolic protection 3.5-5.5 mm FilterWire EZ (Boston Scientific, USA) was guided distally to the stenosis and opened in the C2 segment; a 7-10 × 40 mm Protege Tapered stent (Medtronic, USA) was implanted from the ICA to the CCA (Fig. 9), post-dilatation was performed with a 5.0 × 20 mm RX Viatrac 14 Plus balloon catheter (Abbot, USA). Control angiography of the right ICA revealed no embolism signs, and the left CFA was closed with an AngioSeal 6F (Terumo, Tokyo, Japan). One day after stenting (day 5 after thrombectomy), NIHSS score was 2 (limb strength was fully restored, mild dysarthria and facial asymmetry persisted). Considering significant contralateral ICA C1 stenosis, CAS was electively recommended for secondary AIS prevention. On the 9th day after MT, the patient was discharged on optimal medical therapy.

After a month and a half, left ICA stenting was performed: a Destination 6F catheter (Terumo, Tokyo, Japan) was telescopically introduced into the left CCA through the right femoral access, distal protection with FilterWire EZ 3.5-5.5 (Boston Scientific, USA) was used, the 7-10 × 40 mm Protege Tapered stent (Medtronic, USA) was implanted followed by post-dilatation with a 5.0 × 20mm RX Viatrac 14 Plus balloon catheter (Abbot, USA) (Fig. 10). Control angiography of the left ICA revealed no embolism signs; the right CFA was closed with the AngioSeal 6F (Fig. 11).

One day after the second CAS, an ICA ultrasound (US) was performed (Fig. 12). On discharge from the hospital after the second CAS, neurologic impairment was insignifi-

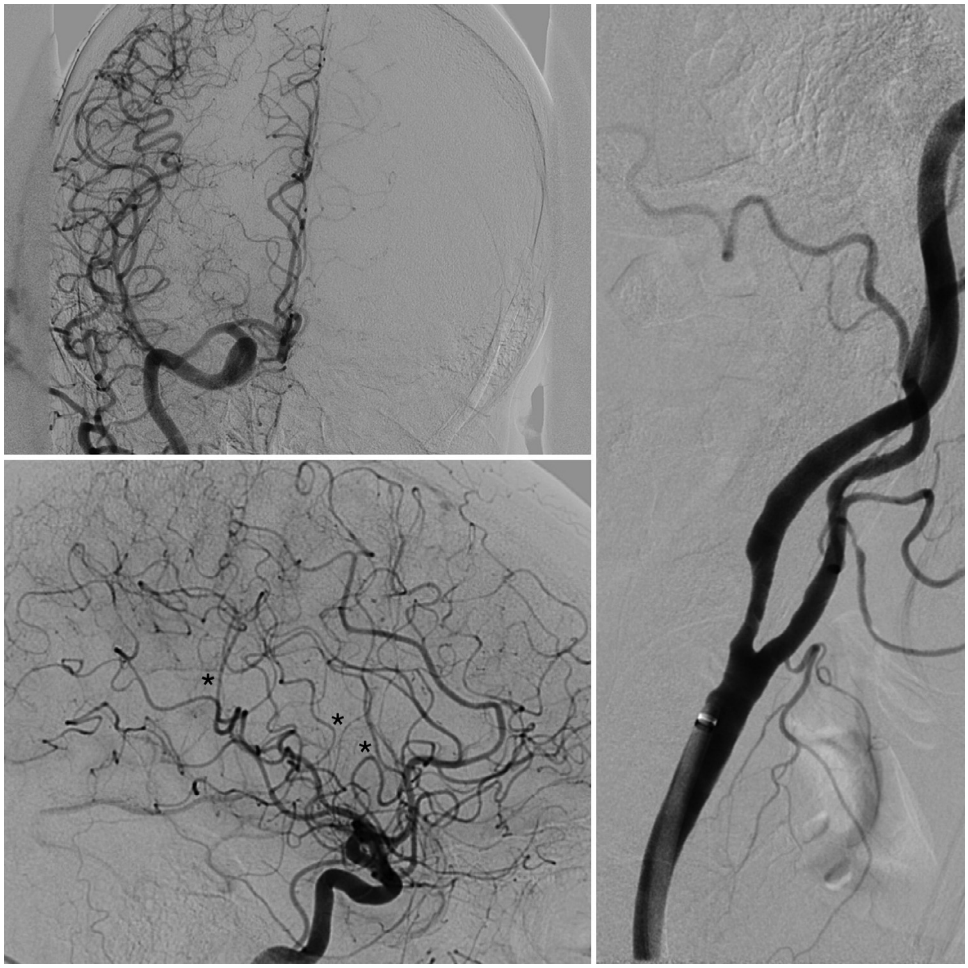

Fig. 8 – Control angiography before right ICA stenting. *Top left*: frontal projection; *bottom left*: lateral projection, blood flow restoration in the anterior parietal, prefrontal, and precentral arteries (asterisks); *right*: the result of PTA and «dottering» of the right ICA stenosis, significant residual stenosis remains. ICA, internal carotid artery; PTA, percutaneous transluminal angioplasty.

cant, AIS consequences persisted as slight facial asymmetry (Fig. 13). At check-up examinations 90 days, 3 and 12 months after the stroke date the score by the modified Rankin scale (mRs) was 1 to 0, the Rivermead mobility index was 14 to 15 points. As for summer of 2021 the patient has completely returned to her daily activities, the photo was taken with her consent.

Discussion

Current AHA/ASA and ESO Guidelines for treatment of AIS patients (2018) have no clear position regarding MT strategy in patients with AIS conditioned by TO. Also, the Guidelines present cautious approach to MT in total occlusion of the ICA C1 segment. They emphasize ineffectiveness of isolated ivTPA therapy and complexity of staged invasive approach with a high risk of embolism of a new territory and hemorrhagic complications [1–3].

Thus, approach to this patient group remains individual. In our case report, we have shown successful TO reperfusion with pPTA of the right ICA C1 followed by aspiration thrombectomy from the M1 and C1 segments in the patient with significant time of AIS symptom onset and a large, preserved area of ischemic penumbra.

In this clinical case, MT indication was the patient's compliance with DAWN study criteria: NIHSS score of 16, age >18 years, ASPECT score of 8, the ischemic core with a volume of <51 cm^3 according to CT perfusion data [1,22]. The patient had no absolute MT contraindications, with the coagulation (INR, APTT), biochemical (blood glucose) and clinical blood tests within normal limits. The decision to perform emergency MT was made by our team, based on a combination of diagnostic and clinical criteria as to modern guidelines. Conservative AIS therapy in the described case would be incomparably less effective, given increased risk of neurological symptom progression with decreasing penumbra area over time. Effectiveness of pPTA with MT and delayed right ICA CAS as a method of extracranial occlusion recanalization can

Fig. 9 – Delayed right ICA stenting. *Top left*: stent deployment from the ICA to the CCA; *bottom left*: PTA in the implanted stent; *right*: stenting result visualizing the ICA/CCA implanted stent. ICA, internal carotid artery; CCA, common carotid artery; PTA, percutaneous transluminal angioplasty.

be judged by absence of hemorrhagic complications from potential DAPT ad hoc prescription. Selection of the method of secondary AIS prevention in the left ICA vascular region was also left with our team consisting of a neurologist, endovascular and vascular surgeons. Relevant guidelines for treatment of stenosing carotid atherosclerosis indicate preferable choice of CEA alongside medical therapy for asymptomatic stenoses of 60%-99% [23]. Given the patient follow-up period after right ICA stenting >1 month, no restenosis or thrombosis signs according to the US scan, the patient's good DAPT adherence, our in-patient hospital's experience in CAS (60-70 CAS/per year), we decided to perform stenting. As of writing this article, the patient follow-up period has been >12 months.

In TO-induced anterior circulation AIS with symptom onset of 6-24 hours and a large area of ischemic penumbra, based on CT or MR perfusion findings, MT and pPTA with delayed CAS may be the method of choice, and CAS of contralateral stenosis may be safely selected for secondary AIS prevention. Further studies are required to assess applicability and reproducibility of the described approach in routine clinical practice.

Patient consent

The patient has read the article "Delayed reperfusion therapy for ischemic stroke tandem occlusion with subsequent secondary prophylaxis of cerebral ischemic events: A case report and literature review" in full (including text, figures, and supplementary material) and agree to its publication. The patient is fully aware of the implications of publication and accept any associated risk. In particular, she understands that, despite anonymization, it is possible that she may be identified based on the details or images contained in the article. While the authors and the publisher will make efforts to minimize this risk, confidentiality cannot be guaranteed.

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Fig. 10 – Left ICA stenting. ***Top left*****: telescopic insertion of the guide catheter in the CCA (the catheter's distal end is indicated by an asterisk);** ***bottom left*****: residual stenosis in the implanted stent;** ***right*****: stent post-dilatation result, the implanted stent in the ICA/CCA is visualized, residual stenosis up to 20% (the arrow indicating exposed anti-embolic protection). ICA, internal carotid artery; CCA, common carotid artery. ICA, internal carotid artery; CCA, common carotid artery.**

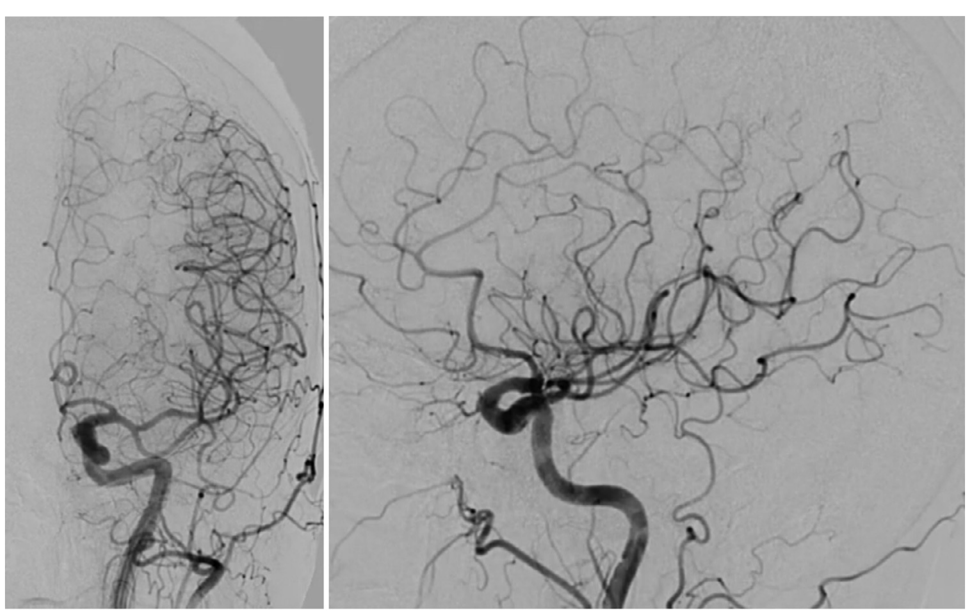

Fig. 11 – Control angiography after left ICA stenting. ***Left*****: frontal view, no embolism signs;** ***left*****: lateral view, no embolism signs. ICA, internal carotid artery.**

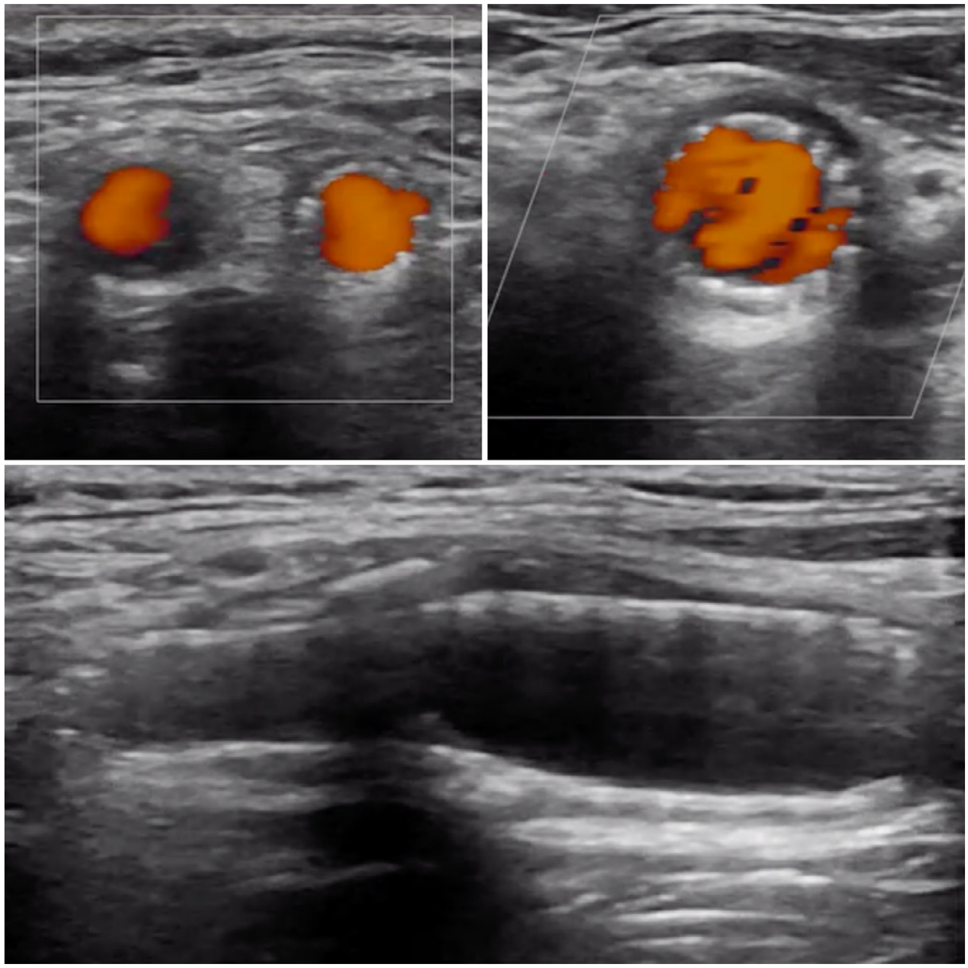

Fig. 12 – Control US examination of the left carotid arteries. *Top left*: ICA stent cross-section, color Doppler imaging showing magistral blood flow in the stent; *top right*: CCA stent cross-section, color Doppler imaging showing magistral blood flow in the stent; *bottom*: ICA/CCA stent longitudinal section, the stent implanted from the ICA into the CCA visualized. US, ultrasound; ICA, internal carotid artery; CCA, common carotid artery.

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The patient understands that she will receive no financial benefit or compensation from publication of the article.

Fig. 13 – The patient after left ICA stenting. The photo was taken 52 days after the MT, AIS consequences persist as slight facial asymmetry, no neurologic impairment. ICA, internal carotid artery; MT, mechanical thrombectomy; AIS, acute ischemic stroke.

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