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Benefit of Mechanical Thrombectomy in Acute Ischemic Stroke Related to Calcified Cerebral Embolus

Running title: Insights from the MASC Study and Individual Patient-Based Meta-Analysis

Abstract

Summary

Purpose

Mechanical thrombectomies (MT) in patients with large vessel occlusion (LVO) related to calcified cerebral embolus (CCE) have been reported, through small case series, being associated with low reperfusion rate and worse outcome, compared to regular MT.

The purpose of the MASC (*Mechanical Thrombectomy in Acute Ischemic Stroke Related to Calcified Cerebral Embolus*) study was to evaluate the incidence of CCEs treated by MT and the effectiveness of MT in this indication.

Methods

The MASC study is a retrospective multicentric (n=37) national study gathering the cases of adult patients who underwent MT for acute ischemic stroke with LVO related to a CCE in France from January 2015 to November 2019.

Reperfusion rate (mTICI \geq 2B), complication rate and 90-day mRS were systematically collected.

We then conducted a systematic review by searching for articles in PubMed, Cochrane Library, Embase and Google Scholar from January 2015 to March 2020. A meta-analysis was performed to estimate clinical outcome at 90 days, reperfusion rate and complications.

Results

We gathered data from 35 patients. Reperfusion was obtained in 57% of the cases. Good clinical outcome was observed in 28% of the patients.

The meta-analysis retrieved 135 patients. Reperfusion and good clinical outcome were obtained in 50% and 29% of the cases, respectively.

Conclusion

The MASC study found worse angiographic and clinical outcomes compared to regular thrombectomies. Individual patient-based meta-analysis including the MASC findings shows a 50% reperfusion rate and a 29% of good clinical outcome.

Key words:

Calcified cerebral embolus, mechanical thrombectomy, reperfusion, clinical outcome

Introduction

Mechanical thrombectomy (MT), associated with the best medical treatment (BMT) (i.e.: intravenous thrombolysis if within the time-window), has recently gained acceptance for the treatment of acute ischemic stroke (AIS) with large vessel occlusion (LVO) (1-4).

Despite a high reperfusion rate with the new generation devices (stent retrievers and aspiration catheters) (4, 5), MT may fail as frequently as in 15% to 20% of the cases (1-4). Numerous anatomical factors like the middle cerebral artery (MCA) angulation (6) and the composition of the clot (especially fibrous clots) may influence the reperfusion rate (7).

Calcified cerebral emboli (CCEs) are defined as intracranial emboli of calcic nature. Their prevalence is probably underestimated (8); they have been reported in 2.6% of the patients who underwent unenhanced brain CT scan for the suspicion of AIS. Most of time, CCEs occur spontaneously (8), but they can also be observed after percutaneous cardiac interventions, like transcatheter aortic valve implantation (TAVI) (9) or surgical carotid endarterectomy (10). Their mechanical properties significantly differ from regular clots, which probably accounts for a large part of a lower reperfusion rate in MT (11).

Small case series and case reports tend to show that reperfusion rate is very low in MT for CCE, leading in most cases to poor clinical outcome (12, 13). Two consistent case series were recently been published, the first by Maurer et al (2020) showing a higher reperfusion rate compared to previous reports, but a low rate of good clinical outcome (14). Different results emerged from the study of Bruggeman et al (2021), the largest cohort of CCE yet published (55 patients), indeed CCE were not significantly associated with worse clinical outcome (29%) but with lower reperfusion rate (44%) (15).

The purpose of our work was to report, through a nationwide study, the incidence of CCEs treated by MT, the reperfusion rate of MT in patients with such CCEs and their 90-day mRS. Additionally, we aimed to perform an individual patient-based meta-analysis, including our data, to evaluate reperfusion rate and clinical outcome, and to analyze the independent factors influencing reperfusion and poor clinical outcome at 3 months.

Material and Methods

Design of the study

Multicentric retrospective observational nationwide study and individual patient-based meta-analysis (including the data of the present study).

Patient selection

Inclusion criteria were: adult patients (≥ 18 years) who underwent MT for AIS related to a proximal (i.e.: intracranial internal carotid artery [ICA], M1 or M2 segment of the MCA, according to Fischer's classification (16), or basilar artery occlusion [BAO]) LVO, proven on digital subtraction angiography (DSA), related to a CCE in France from January 2015 to November 2019 (for a total of 37 comprehensive stroke centers). The patients were all identified from each center's mechanical thrombectomy database by contacting the head of the department of all the 37 interventional neuroradiology centers in France. CCE had to be depicted on pre-MT unenhanced CT scan, or on post-MT CT scan in case of reperfusion failure or on pathological examination of the material retrieved from MT (**Fig. 1**). The following criteria were used to define a CCE on CT (one missing criterion resulting in the non-inclusion of the patient): intraluminal hyperdensity of ovoid or round shape on multiplanar reconstructions (axial, coronal and sagittal) of the pre-MT unenhanced CT-scan (or post-MT in case of MT failure), and with a density superior to 70 HU.

Non-inclusion criteria were as follows: pregnancy, patients with a distal occlusion (distal to M2) related to a CCE, patients with no evidence of calcic embolus responsible for the LVO (as defined above).

Patients' demographics and CCE characteristics

Patients' demographics (i.e.: age, sex, pre-MT mRS score, past history of blood hypertension, smoking, diabetes mellitus and initial National Institute of Health Stroke Score [NIHSS] at admission) were systematically assessed through a standardized questionnaire (**Supplemental material**) sent to

the 37 French comprehensive stroke centers. The following CCE's characteristics were collected: length, diameter, density (in Hounsfield units [HU]). The location of the CCE was assessed, as well as the presence of concomitant other CCEs in the brain vasculature. Brain CT scans showing the presence of a CCE were systematically reviewed by two interventional neuroradiologists before inclusion: one senior (experience > 10 years) and one junior neuroradiologist. Patients with missing imaging or without CCE on CT were not included.

MT strategies (associated intravenous [IV] thrombolysis, devices used, number of passes, acute cervical/intracranial stenting, use of balloon guiding catheter [BGC]) were systematically assessed, as well as the procedure duration (time interval from puncture to reperfusion or MT discontinuation). We separated the MT strategy in two groups: contact aspiration only and stent-retriever (SR) ± contact aspiration (simultaneously or sequentially).

Reperfusion/complication

Reperfusion was evaluated on DSA in postero-anterior and lateral projections. Satisfactory reperfusion was defined as a mTICI (modified thrombolysis in cerebral infarction) (17) \geq 2B.

Pathological analysis was performed at the discretion of the center for retrieved CCEs. Briefly, emboli were embedded in paraffin; after cross section and hematoxylin/eosin ± Alizarin red staining, histopathologic analysis was performed.

Procedure-related complications were divided into major and minor complications. Major complications comprised vessel perforation, symptomatic embolus in a new territory, cervical artery dissection requiring aggressive management, symptomatic intracranial hemorrhage according to the ECASS II criteria (18) (responsible for a clinical worsening \geq 4 points on the NIHSS) and puncture site complication requiring a surgical repair or blood transfusion. Minor complications were: asymptomatic procedure-related intracranial hemorrhage, migration of the CCE in the same territory, minor puncture site complication (that did not require surgical repair or blood transfusion).

Clinical follow-up

NIHSS within the 48h after the MT was evaluated, as well as the NIHSS at discharge. Modified Rankin scale (mRS) was graded at 3 months by the neurological team in charge of the patient. A mRS ≤ 2 was considered as a good clinical outcome.

Systematic review of the literature and meta-analysis

A systematic review of the literature and meta-analysis on MT in patient with AIS related to LVO due to CCE was performed according to the PRISMA guidelines (19) (see **Supplemental Materials [Supplemental Methods]**).

Statistical analysis

Continuous variables were reported as means \pm standard deviations (SD); categorical variables as median (interquartile ranges [IQR]). The normality of the distribution was checked using the Shapiro-Wilk test. We evaluated the influence of age, sex, diabetes mellitus, blood hypertension, smoking, post-operative condition, occlusion site, MT technique (stent retriever \pm aspiration or aspiration alone) and the use of a BGC on first: reperfusion rate, and then clinical outcome. This evaluation was performed using an univariate analysis with a Chi² test, a Fisher's exact test, a Student t test or a Mann-Whitney test, as appropriate. Finally, a multivariate analysis using a logistic regression was performed. The same analysis was performed on the database including all the patients extracted from the meta-analysis. All tests were performed using the Rstudio software (Version 1.2.5033); p values less than 0.05 were considered statistically significant.

Results

Study population

*Patients' demographic data are summarized in the **Table 1**.*

We gathered a total of 35 filed questionnaires from the 37 centers performing MT in France. One of the patients has already been reported in a recent case series (14). Mean patient age was 76 ± 15 years (range: 27-95 y). Two third of the patients were women (23/35; 66%); 66% of the patients (23/35) had blood hypertension. Seven out of the 35 patients (20%) had undergone a cardiovascular intervention (including TAVI, coronarography, endarterectomy, pace-maker placement or iliac arteries stenting) prior to the AIS related to a CCE. Most of the CCE were detected on CT before MT. Interestingly, 2 cases were suspected initially on MRI, then confirmed on CT-scan before MT (**Supplemental Table II**).

Median baseline mRS was 0 (IQR: 0-1; range: 0-4) and the median initial NIHSS at admission was 15 (IQR: 9-18; range: 3-24).

Table 1. Patients' demographics of the MASC study

| Characteristics | |
|-------------------------------------|--------------------|
| Sex (M/F) | 12/23 |
| Age (average \pm SD [range]) | 76 ± 15 (27-95) |
| Smoking; n, (%) | 9 (26) |
| Blood Hypertension; n, (%) | 23 (66) |
| Diabetes; n, (%) | 8 (23) |
| Prior Surgical Intervention; n, (%) | 7 (20) |
| Baseline mRS (median [IQR; range]) | 0 [0-1]; (0-4) |
| Initial NIHSS (median [IQR; range]) | 15 [9-18]; (3-24) |

M indicates male, **F**: female, **SD**: standard deviations, **mRS**: modified Rankin scale, **NIHSS**: National Institutes of Health Stroke Scale, **IQR**: interquartile range, **y**: years.

Pretreatment imaging/CCE characteristics

CT findings are available in the Supplemental Material (Supplemental Table I).

MT procedures

Data regarding the MT strategies are displayed in Table 2.

IV thrombolysis was performed in 11/35 patients (31%). BGC was used in 16/35 patients (46%). Most of the patients were treated by stent-retriever (SR) ± contact aspiration (83%) (**Supplemental Fig. II**); the average number of passages was 3.3±2.9 (range: 1-13). The mean procedure duration (puncture to reperfusion or procedure discontinuation) was 82±56 min (range: 32-247).

Table 2. Procedures details and clinical outcomes of the MASC study

| Data | |
|---|------------------|
| IV Thrombolysis; n, (%) | 11 (31) |
| Use of BGC; n, (%) | 16 (46) |
| Stent retriever +/- aspiration*; n, (%) | 29 (83) |
| Contact aspiration alone; n, (%) | 6 (17) |
| Procedure duration; m (range) | 82 min (32-247) |
| Number of passes; m (range) | 3.3 (1-13) |
| mTICI 2B-3; n, (%) | 20 (57) |
| Symptomatic intracranial hemorrhage; n, (%) | 4 (11) |
| NIHSS at discharge (median [IQR; range]) | 8 [2-15]; (0-23) |
| Last follow-up mRS (median [IQR; range]) | 4 [1-6]; (0-6) |
| 90-day mRS 0-2; n, (%) | 8 (28) |

IV indicates intravenous, **BGC**: balloon guiding catheter, **mRS**: modified Rankin scale, **NIHSS**: National Institutes of Health Stroke Scale, **mTICI**: modified Thrombolysis in Cerebral Infarction, **IQR**: interquartile range.

* stent retriever + aspiration used either in combination or sequentially

Reperfusion and clinical outcomes

Reperfusion (mTICI \geq 2B) was obtained in 57% of the cases (20/35 patients) (**Supplemental Fig II**).

Among the 20 retrieved CCEs, 2 (10%) underwent pathological analysis, which confirmed the calcic component of the embolus. Median NIHSS at discharge was 8 (range: 0-23). Six patients were lost to the follow-up at 3 months. A 3-month good clinical outcome was observed in 28% of the patients (8/29).

We recorded 8/35 (22.9%) procedure-related complications; 4 major complications (50%), all consisting in symptomatic intracranial hemorrhages (**Fig. 2**), and 4 minor complications, all being asymptomatic intracranial hemorrhages. Interestingly, in 3/8 (37.5%) complications (two majors and one minor), patients had received IV thrombolysis before the MT procedure.

The univariate analysis showed that only age had an influence on reperfusion ($p = 0.047$) and number of thrombectomy device passes had an influence on poor clinical outcome ($p < 0.05$). However, the multivariate analysis showed that only the number of passes was associated with a poor clinical outcome. None of the other tested factors had any independent influence on either the reperfusion rate or the clinical outcome.

Systematic review of the literature and meta-analysis

Our systematic review the literature retrieved four case series (12, 13) assessing the safety and effectiveness of MT in CCE (**Table 3**). In the first series by Dobrocky et al (13), the reperfusion rate was 12.5% and the rate of 3-month good clinical outcome was 12.5%, as well. Interestingly, in this series, all the MT procedures were performed using only a stent retriever. IV thrombolysis was performed in 25% of the cases in this series. The second case series, published by Koh et al (12), reported a lower reperfusion rate (0%), but better clinical outcomes (40%). It is noteworthy that all MTs were performed using the thrombo-aspiration technique in this case series. In Maurer et al's series (14), reperfusion was observed in 57.5% of the cases (23/40), and good clinical outcome in 26.5% of the cases. Eight patients of this series (14) have already been reported in the above-

mentioned small case series by Dobrocky et al (13). In the last and largest case series published in 2021 by Bruggeman et al (15), reperfusion was obtained for 43% of the patients with CCE (24/55), functional independence (mRS :0-2) was observed in 29% of the cases (15/55).

Overall, we gathered data from 135 patients in our systematic review; mean patients' age was 75 ± 14 years (range: 21-100), 54% of the patients were women. Most of the patients had blood hypertension (66%), 31% were smokers and 25% had diabetes mellitus (**Supplemental Table III**). Median NIHSS at admission was 15 ± 9 (range: 1-38), intravenous thrombolysis and BGC were used in 61% and 38 % of the cases, respectively. Reperfusion rate was 50% and a good 3-month clinical outcome was observed in 29% of the patients; twelve patients were lost to the follow-up at 3 months. (**Supplemental Table IV**).

The overall complication rate was 19% (26/135), with 13 major complications (10% of the overall population), all of them consisting in symptomatic intracranial hemorrhages. The 13 minor complications (10% of the overall population) consisted in non-symptomatic intracranial hemorrhages and stent-retriever per procedural inopportune detachment.

None of the tested variables, including age, use of BGC or IV thrombolysis were significantly associated with good clinical outcome, successful reperfusion or complication rate in the univariate or multivariate analyses.

Table 3. Systematic review of the literature on MT in CCE

| Authors | Year | Journal | Nb of cases | Initial NIHSS score (mean [range]) | Procedure time (mean [range]) | CCE diameter (mean [range]) | mTICI 2b-3 (n [%]) | NIHSS at discharge (mean [range]) | mRS 0-2 at 3 months (n [%]) |
|---------------------------|------|---|-------------|------------------------------------|-------------------------------|-----------------------------|--------------------|-----------------------------------|-----------------------------|
| Koh et al (12) | 2017 | Journal of Stroke and Cerebrovascular disease | 5 | 9.6 (4-15) | 30 min (25-35) | 4.3mm (3-7) | 0 (0) | 4 (2-15) | 2/5 (40) |
| Dobrocky et al (13) | 2018 | JNIS | 8 | 13.5 (4-24) | 126 min (66-192) | 3.4mm (2-4) | 1(12.5) | N/a | 1/8 (13) |
| Maurer et al (14) | 2020 | AJNR | 40 * | 15.2 (1-38) | 93min (23-250) | N/a | 23 (58) | 10.6 (0-42) | 9/34 (27) |
| Bruggeman et al (14) | 2021 | JNS | 55 | 16 (11-29) | N/a | N/a | 24 (43) | N/a | 15/55 (29) |
| Kwak et al (20) | 2018 | Interventional Neuroradiology | 1 | 13 | N/a | 3.7mm | 1 | 4 | 1 |
| Ramirez Moreno et al (21) | 2017 | Neurologia | 1 | 18 | N/a | N/a | 1 | N/a | 1 |
| Present study | | | 35 § | 14 (3-24) | 81 min (32-247) | 2.7mm (1.4-3.8) | 20 (57) | 10 (0-23) | 8/29 (28) |

MT indicates mechanical thrombectomy, **CCE**: calcified cerebral embolus, **mRS**: modified Rankin scale, **NIHSS**: National Institutes of Health Stroke Scale, **Nb**: number, **N/a**: not available, **mTICI**: modified Thrombolysis in Cerebral Infarction.

* 8 cases in this series have already been reported in the article by Dobrocky et al in 2018 (13).

§ 1 case has already been reported in the case series by Maurer et al in 2020 (14).

Discussion

The MASC study is a national database gathering data from French patients suffering from AIS with LVO related to CCE and receiving MT. We sought to obtain the exhaustivity for the study period and were able to collect data from 35 patients in all the 37 French interventional neuroradiology centers. The reperfusion rate in this study was 57%; the rate of good clinical outcome (mRS \leq 2) was 28%. These results of MT for CCE in terms of reperfusion rate and clinical outcome are thus inferior compared to the ones described in the first large studies reporting the results of MT in regular thrombi (1-4).

Incidence of patients treated by MT for a CCE in our study was 0.13% per year (35 patients among the 27,394 patients treated by MT in France during the inclusion period). This incidence is lower than the one reported Walker et al (8): 2.6%. This can be explained by the fact that Walker et al (8) reported the overall incidence of CCEs in patients who underwent a CT scan for the exploration of an AIS. In our study, only patients who additionally received MT were included. Interestingly, in our study, as reported in the literature (8), most of the CCE occurred spontaneously and not in a postoperative context. However, certain specific interventions, like TAVI procedures or carotid endarterectomy, may increase the risk of CCE, due to the heavily calcification burden of these lesions, which may migrate in the cerebral vasculature during or in the aftermath of the procedure.

For the selection of CCEs, we used a cut-off of 70 HU as in the series of Walker et al (8), given the fact that non-calcic thrombi usually have a lower density, ranging from 50-70 HU. Our average CCE density was 428 HU, and the lowest HU observed in our series was 89 HU (**Supplemental Table I**).

The identification of a CCE in LVO may be difficult on pretreatment imaging. Indeed, on MRI, the distinction between a CCE and a regular clot on T2* is usually not possible; appearing as an artefactual hypointense signal. Interestingly, new sequences such as susceptibility-weighted images may help distinguishing calcic material from hemorrhagic lesion (22). In many countries, especially in Europe (including France), MRI is the first line imaging modality for AIS (23), which could lead to misdiagnosed CCEs on pre-MT imaging. Consequently, in centers in which MRI is the first imaging modality for AIS, a cone beam computed tomography (CBCT) acquisition may be systematically

performed before the MT procedure, in the angiogram, to depict a potential CCE. On unenhanced CT scan or CBCT, CCEs typically appear with a round or oval shape and a hyperdensity (428 HU in average in our study). They are usually located on the course of the M1 or proximal M2 segments of the MCA and thus have a diameter close to the one of these vessels (in our study, 2.8 mm in average [range: 1.4-3.8]). It should be mentioned that CCE may be difficult to distinguish from a calcified component of an intracranial atheromatous stenosis. However, such calcified stenoses are rare distally to the ICA terminus; and usually, the calcified component of these stenoses is eccentric and not inside the vessel's lumen (8).

In the MASC study, the reperfusion rate was higher than in the first case series focused on this topic (57% vs. 0 to 44% [12, 13,15]), but similar to one of the most recent data on MT in CCE (58% in Maurer et al's series [14]). Results from the meta-analysis showed a reperfusion rate of 50%. This higher reperfusion rate observed in the Maurer et al's series and in the present case series (MASC data) may be explained by the recent progresses in MT techniques, like the use of combined techniques (SR + contact aspiration), which is one of the most widespread procedure in many centers, including France (24). However, this reperfusion rate (56%) remains lower than the one observed in meta-analyses for regular MT (25) (*Supplemental Results*).

None of the tested factor were predictive of successful reperfusion or functional independence in our meta-analysis.

Pathological analysis was available in only 2 out of the 20 retrieved CCEs (10%). Heavily calcified component associated with fibrous portions were observed on these pathological specimens. This finding supports the fact that CCEs probably originate from calcified heart valves or calcified atheromatous carotid plaques (11).

Good clinical outcome (mRS \leq 2) was observed in 28% of the cases in the MASC study and in 29% of the cases in our meta-analysis. This good clinical outcome rate is lower than the ones reported for regular MT (25). This lower good clinical outcome rate may be explained by the lower reperfusion rate in MT for CCE; it is indeed well established that reperfusion is predictive of good clinical outcome in patients who underwent MT (26).

Limitations of the study

Our study suffers some limitations. First, even if we sought to obtain the exhaustivity on the study period by sending the questionnaire to all the centers performing MT in France (n = 37), its retrospective nature may bring some biases, especially an underestimation of the incidence of MT for CCE. Second, MRI is the first line imaging modality for AIS in France and this can also contribute to the underestimation of the CCE detection. Additionally, pathological analysis was rarely performed (n=2 [10% of the cases] in our study) to confirm the calcic nature of the presumed CCE because pathological analysis of clot material from MT is not a routine practice in most centers. Missing data was the main limitation of the meta-analysis on individual data, since not all the corresponding authors answered to our solicitations. The retrospective nature of the studies from which the individual patient data were extracted may also be a source of bias, so as the apparent “small-study effect” with the cases reports having better results than the larger studies.

Conclusion

The MASC study found similar reperfusion and good clinical outcome rates compared to most recent published data on this topic, but lower reperfusion rate and worse clinical outcome than regular MT not involving CCE. Individual patient-based meta-analysis including the MASC findings shows a 50% reperfusion rate and a 29% of good clinical outcome. Further studies are warranted to determine the best strategy to recanalize intracranial vessels in these challenging cases.

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Figure Captions

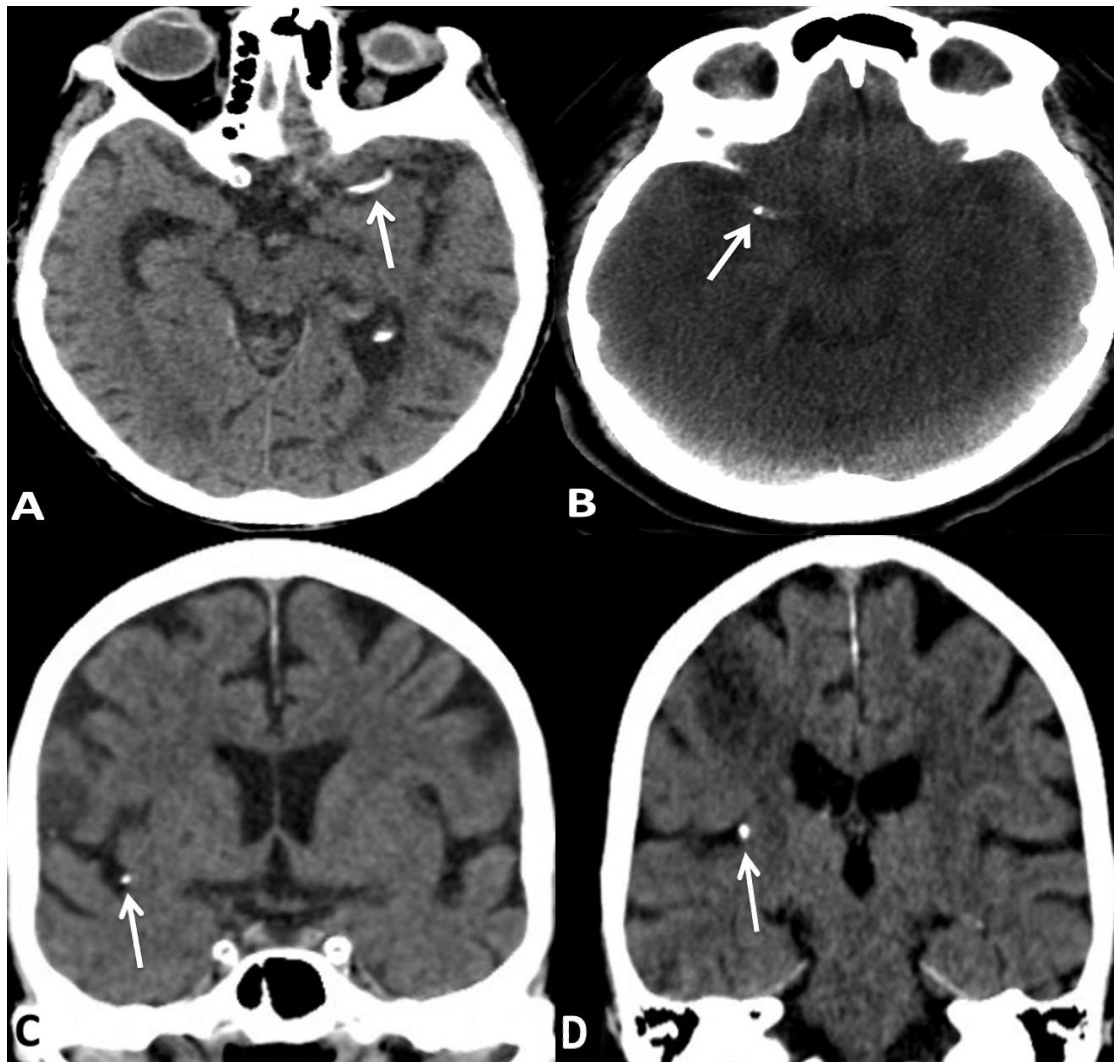


Figure 1.

Examples of imaging features for calcified cerebral embolus (CCE) on non-contrast enhanced CT (NCECT) scan or cone beam CT (CBCT). **A.** NCECT scan, axial slice, showing a CCE located on the course of the left middle cerebral artery (MCA) M1 segment (white arrow). **B.** Non-contrast enhanced cone beam CT (CBCT) performed in the angiosuite, axial slice, showing a CCE on the course of the right MCA M1 segment of (white arrow). **C** and **D.** NCECT scan, coronal reconstruction, showing CCEs located on the course of the right MCA M2 segment in two different patients (white arrows).

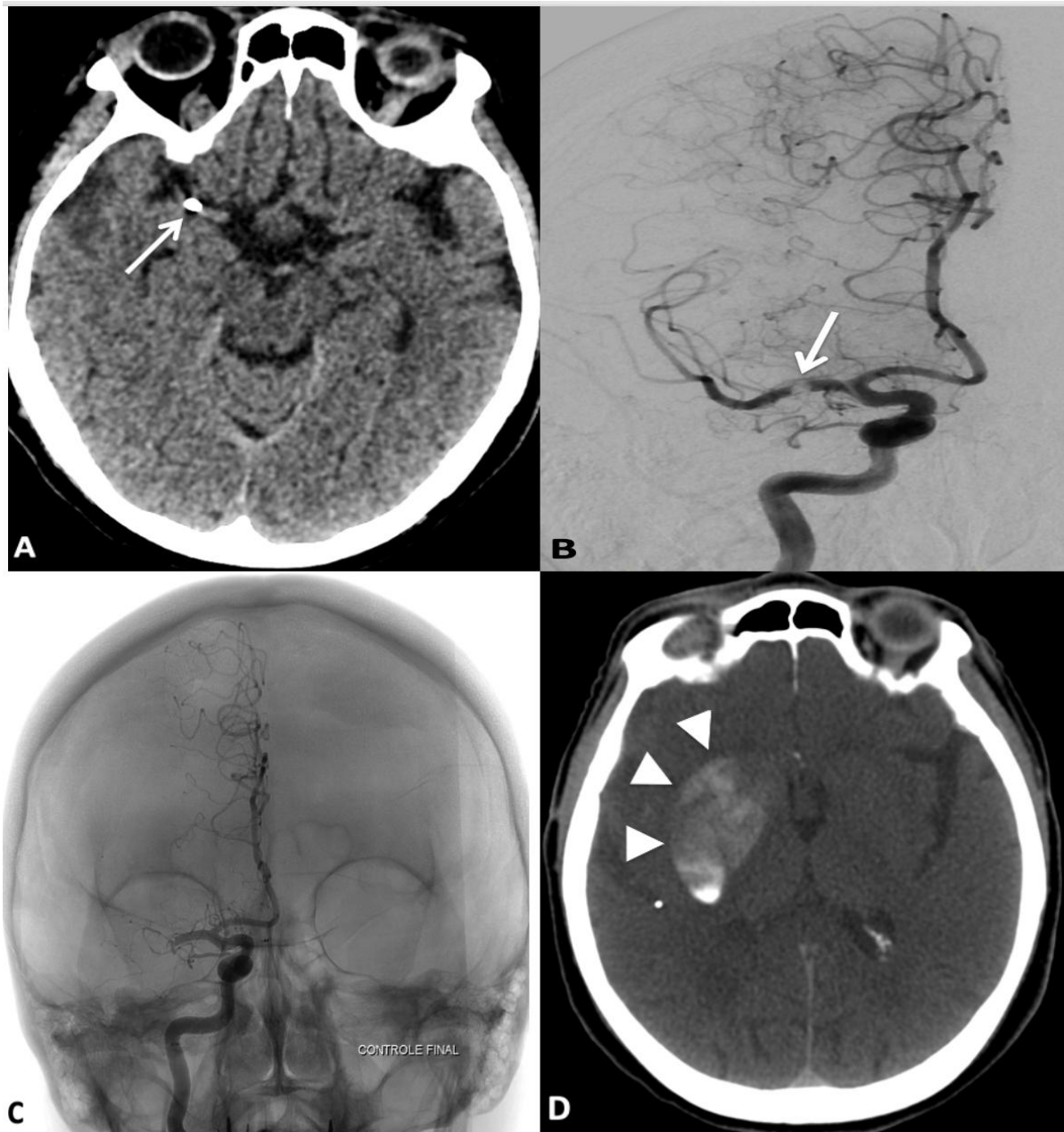


Figure 2.

Eighty-eight-year-old patient (Patient # 23) presenting with an acute onset of left hemiplegia after a left carotid endarterectomy procedure. **A.** NCECT scan, axial slice, showing a 4.4 x 3.7 mm CCE located on the course of the right MCA M1 segment (white arrow). **B.** Right ICA DSA performed at the beginning of the MT procedure (postero-anterior [PA] projection), showing an non-occlusive intra-arterial defect in the right MCA M1 segment due to related to the CCE (white arrow). **C.** Final unsubtracted right ICA DSA in PA projection performed at the end of the procedure, showing persistent occlusion (mTICI = 0) despite 11 passes of different MT techniques. **D.** Post-procedure NCECT scan, axial slice, showing a deep hematoma (white arrow heads).

