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Review article

Acute treatment of stroke due to spontaneous calcified cerebral emboli causing large vessel occlusion

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ABSTRACT

Introduction: Calcified cerebral emboli (CCE) are rarely responsible for large vessel occlusion (LVO) in acute anterior stroke, and therefore therapeutic experience is scarce. We sought to expand current knowledge upon therapeutic options with three new cases and a review of current literature.
Methods: Systematic search of patients with acute anterior stroke due to LVO in one comprehensive stroke center throughout a 4 year period. Literature search for reported cases of CCE.
Results: In total, 21 cases (19 found in literature and 3 from our institution) are reported with a median age of 72 years (interquartile range [IQR] 63–80). Eleven patients were treated acutely, 4 of them with endovascular thrombectomy (EVT). Middle cerebral artery (MCA) M1 was the most affected segment and large artery atherosclerosis (LAA) and cardioembolism (CE) was causative in 41% of cases. EVT was significantly superior to intravenous recombinant tissue plasminogen activator (rtPA) at $p = .048$ (Fisher's exact test, chi square 6.7).
Conclusions: Given the small sample reported in literature and no reported randomised studies, definitive recommendations could not be reached. However, considering thrombus composition, thrombolysis is most probably not sufficient and priority should be given to EVT.

1. Introduction

Embolic stroke due to LVO is a significant cause of patient mortality and morbidity, present in up to 27% stroke patients [1]. One of the possible donor sites is a large vessel downstream of the middle cerebral artery, mostly the bifurcation of the common carotid artery, although the brachiocephalic trunk, aortic atherosclerotic plaque and calcified aortic valves could also provide embolic material. Cerebral emboli have several histopathological compositions [2]. Calcified cerebral embolism (CCE), which although rare, is known to result in greater severity of cerebral infarctions in comparison to other types of embolisms, such as fibrous emboli, which is probably due to different embolus composition [1,3]. These calcified emboli may arise from cardiac valves (47%) or calcified atheroma of the aortic arch or carotid arteries (38%) [4]. The cerebrovascular recurrence is significant, with 40% of patients experiencing recurrent stroke [4]. The first case of CCE was identified in 1981 on a computed tomography (CT) scan of the brain [3]. Out of every 100 patients who get a CT done for stroke evaluation, at least 3 have CCE [4].

Acute stroke interventions, after exclusion of ineligible patients, comprise of administration of intravenous thrombolytic therapy with recombinant tissure plasminogen activator (rtPA) and/or endovascular thrombectomy (EVT). However, there is little data available regarding the use, safety and therapeutic efficacy of thrombolysis and EVT in patients with CCE. Recanalisation treatment has produced mixed outcomes in patients with CCE [4]. In order to raise clinical awareness and expand knowledge about this rare clinical syndrome, we report 3 cases of stroke caused by calcified cerebral emboli treated with thrombolysis and review the existing literature.

2. Materials and methods

The study was approved by the institutional review board. Presented cases were found in a retrospective search for acute

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MCA ischemic stroke in the institutional radiological database in the timeframe from 2012 to 2016. The methodology has been published before [5]. We sought to identify all anterior strokes with signs of MCA-occlusion confirmed by CT – angiography. The patients were included, if the onset of symptoms to CT imaging was within 6 h. Additionally, we searched for patients with signs of occlusive thrombus with average intra-vessel Hounsfield units (HU) density over 90. These patients were deemed to have a calcified embolus as the cause of symptoms. The clinical and radiological data is presented here, along with a review of the literature.

The literature review was performed via comprehensive search on PubMed, and we reviewed articles from 1981 to 2017. We used the following terms and keywords: "calcified", "emboli", "ischemic stroke", "thrombolysis", "thrombolysis therapy", "intravenous thrombolytic therapy", "tPA", "rtPA", "stroke", with different Boolean operators. All English abstracts and full texts of the relevant articles were studied. We also manually searched the reference lists of the retrieved articles to identify additional articles.

3. Results

In our institution of the 179 acute MCA occlusions 3 by calcified emboli could be identified, giving a prevalence of 1.7%. All patients were women, above 75 years old and presented within 100 min after symptom onset. All had acute CT angiography performed (Fig. 1). All of emboli were located in the right MCA. Patients 1 and 2 had M1 occlusion and Patient 3 had occlusion of a proximal M2 segment. Patient 1 had multiple calcified emboli (four of them) in the territory of the right MCA, in the other two patients only a singular CCE was found. All patients were treated with recombinant tissue plasminogen activator (rtPA 0.9 mg/kg over 60 min) within the first 2 h of symptom onset. In Patient 2 EVT was attempted, but intravascular access was not possible due to extensive femoral artery calcifications. There were no signs of change in embolus position after treatment on the control CT in Patients 1 and 2, while no embolic material could be seen in the hemorrhagic area in Patient 3. The length of the embolus was 20.7 mm in Patient 1, 9.3 mm in Patient 2 and 6.5 mm in Patient 3. Mean embolus density was 143, 111 and 90 HU for Patients 1, 2 and 3 respectively.

We identified the potential source with CT angiography in all patients. In Patients 1 and 3 there were extensive calcifications in the carotid bifurcation on the symptomatic side, while Patient 2 had a calcified proximal aortic arch. There was no recorded atrial fibrillation in either patient.

The Outcome in our patients was poor, two died and Patient 1 was bedridden with severe impairment and residual mRS of 5.

We found an additional 19 cases in the literature with syndrome of acute ischemic stroke due to calcified emboli (Table 1).

Together with our 3 cases the median age was 72 years (interquartile range [IQR] 63-80), 45% were women, 41% had large artery atherosclerotic infarct (LAA) and cardioembolic (CE) stroke etiology, 9% had undetermined or unknown etiology as classified by Trial of Org 10172 in Acute Stroke Treatment (TOAST). The affected territories were exclusively MCA M1 in 45%, and exclusively MCA M2 in 32%, the remaining group had CCE in either a combination of MCA M1 and ACA, MCA M1 and PCA, exclusively MCA M3 and exclusively PCA P1. Definitive migration of the thrombus after rtPA was documented in 2 patients.

Fifty percent of the patients received no acute treatment for stroke. Of the patients that were treated 64% were given intravenous rtPA, and others received EVT. No combination of both treatment options were reported. In the treatment group, consisting of 11 patients, outcome was reported in 10 patients. Half of them had a good outcome and the other half hat a bad outcome, meaning high dependency or death due to stroke. EVT was the superior treatment compared to rtPA at $p = .048$ (Fischer's exact test, Pearson chi-square 6.7) although the numbers were small.

4. Discussion

Calcified cerebral emboli are most easily detected on native CT. Diagnosis of acute LVO stroke due to CCE could be made after carefully observing following characteristics: a) intravascular hyperattenuation >90 HU, usually in the range of 140–160 HU; b) the hyperattenuation is located in the clinically relevant region; c) detection of occlusion of the corresponding artery on CT. However, about a quarter of patients are misdiagnosed on initial imaging [4], moreover even CT-angiography could be falsely negative, making diagnosis somewhat challenging [6]. It was shown that CCE involve the middle cerebral artery in 83% of the cases. Previously it was thought that the majority of CCEs were non-spontaneous and were complications resulting from invasive cardiac surgical procedures [7]. However, one of the studies showed that 86% of CCEs occurred spontaneously, whereas only 12% resulted from cardiac procedures such as catheterization and manipulation [4,8]. Additional imaging in the form of CT angiography of the aortic arch and neck vessels should be obtained in order to search for the source of emboli and to plan further prophylaxtic measures.

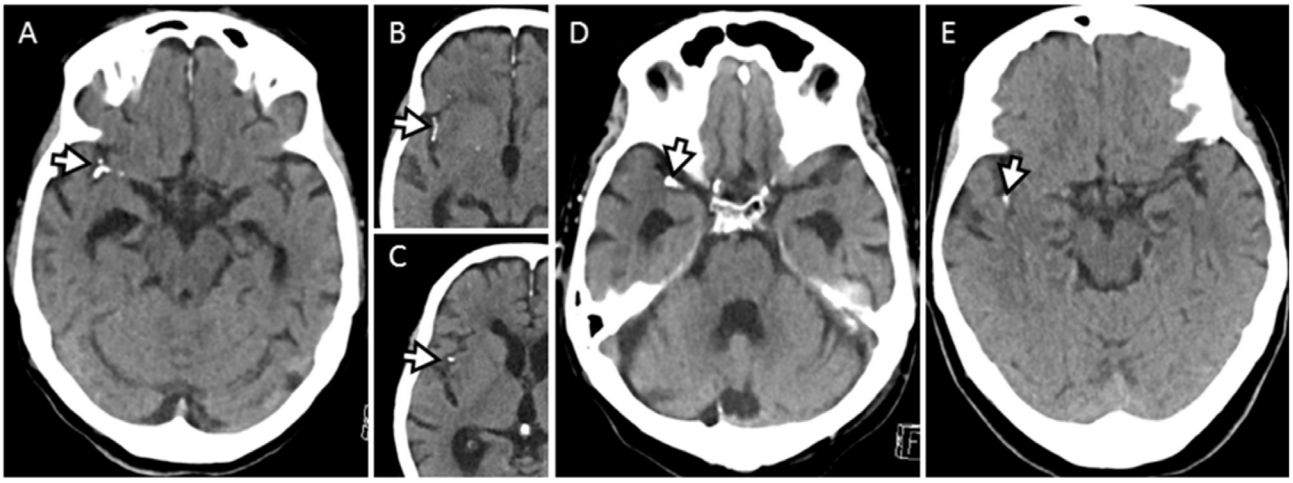

Fig. 1. Calcified emboli in acute ischemic stroke on native brain CT. Closed black arrows showing calcified intravascular material in the middle cerebral arteries on the right side in all patients. Panel A-C: Patient 1, D: Patient 2, E: Patient 3.

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