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Original research article

How to avoid false positive hyperdense middle cerebral artery sign detection in ischemic stroke

Robert Chrzan^{*}, Agnieszka Gleń, Andrzej Urbanik

Radiology Department, Jagiellonian University Medical College, Kopernika 19, 31-501 Kraków, Poland

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ABSTRACT

Objectives: The aim of the study was to find how to differentiate hyperdense middle cerebral artery sign (HMCAS) in stroke patients from asymmetric hyperdensity not related to stroke, by comparison of the CT density values typical for HMCAS to the values in normal or atherosclerotic middle cerebral artery (MCA).

Methods: The group analyzed consisted of 100 patients with ischemic stroke, presenting HMCAS on the admission CT. Density measurements in HU were performed in the hyperdense segment of the involved MCA, contralateral MCA, brain cortex adjacent to the hyperdense MCA. The control group consisted of 100 patients with no symptoms of cerebral stroke. Density measurements in HU were performed: in the M1 segment of right and left MCA, brain cortex adjacent to the more dense from right or left MCA.

Results: In the stroke group the median values obtained were: in the hyperdense MCA 59 HU, contralateral MCA 41 HU, brain cortex 36 HU. In the control group the median values obtained were: in the more dense MCA 43 HU, contralateral MCA 40 HU, brain cortex 34 HU. The range of HMCAS/contralateral MCA density ratios in stroke only slightly overlapped the range of more dense MCA/contralateral MCA density ratios in non-stroke patients.

Conclusion: The ratio of hyperdense MCA CT density/contralateral density is a good tool to differentiate HMCAS from asymmetric hyperdensity not related to stroke. The threshold ≥ 1.16 provided 100% sensitivity and 97% specificity, whereas ≥ 1.22 provided 94% sensitivity and 100% specificity.

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1. Introduction

Non-contrast computed tomography (CT) brain examination is still the most commonly used imaging modality in patients with clinical symptoms of acute ischemic brain stroke [1–3]. The procedure is chosen as it is widely available, fast and inexpensive. It is performed to rule out intracranial pathologies mimicking stroke such as tumor, to exclude intracranial

hemorrhage not allowing thrombolysis and also to assess early symptoms of stroke.

In the hyperacute phase during the first 3 h after onset, typical brain tissue abnormalities possible to observe in CT are: loss of gray-white matter differentiation, especially loss of distinction among the nuclei of the basal ganglia (lenticular obscuration), blending of the densities of the cortex and underlying white matter in the insula (insular ribbon sign) and over the convexities (cortical ribbon sign), as well as cortical

^{*} Corresponding author.

E-mail address: rchrzan@mp.pl (R. Chrzan).

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hypodensity and parenchymal swelling causing gyral effacement.

In some patients, it is also possible to see in CT a hyperdense segment of the artery, representing direct imaging of an intravascular thrombus. Sometimes it may be the earliest and only visible CT sign of ischemic stroke. This can be localized in any vessel, but it is most often observed in the middle cerebral artery (MCA) as hyperdense middle cerebral artery sign (HMCAS) (Fig. 1).

Such increased attenuation may be found in a long segment of MCA, especially the proximal portion or, usually distally, may be limited to a very short segment, as an MCA dot sign.

In histopathological studies the composition of the thrombus is defined as typical for early phase (RBC – Red Blood Cell Count dominant and RBC proportion equal to fibrin) and late phase (fibrin dominant and organized fibrin). Hyperdense artery sign on CT is usually seen in early phase thrombus composition [4,5].

HMCAS recognition is crucial for radiologists, because it may help to save the patient in the proper time window for thrombolysis (4.5 h from stroke onset to rTPA treatment [1]).

HMCAS may be a valuable predictor of the final severity of stroke. In patients with cerebral ischemic stroke involving MCA region and no early signs of brain tissue ischemia on admission CT, HMCAS is associated with significantly lower Alberta Stroke Program Early CT Score (ASPECTS) in the follow up CT. Long hyperdense MCA segment is generally associated with a large area of brain tissue damage; however, short hyperdense MCA segment does not exclude large area of brain tissue damage [6].

In patients with HMCAS shown by baseline CT, treated with intravenous thrombolysis, the size of hyperdense MCA segment correlates with the effects of treatment and the final outcome. Shobha [7] found that short-length HMCAS (<10 mm) disappeared in 85.7% of cases, medium-length HMCAS (10–20 mm) – in 37.5% and long-length HMCAS (>20 mm) did not disappear in any of the cases.

The persistence of HMCAS on the follow-up CT after intravenous thrombolysis is an early predictor of poor functional outcome [8,9].

Furthermore, the location of the thrombus in the proximal or distal part of the vessel is important for the prognosis of the patient. Man [10] found that proximal HMCAS predicts an unfavorable outcome of intraarterial thrombectomy for acute stroke. Similarly, Li [11] showed that poor neurological recovery post intravenous thrombolysis was confined to proximal HMCAS cases, contrary to distal HMCAS cases.

Zou [12] concluded that HMCAS is also associated with increased risk of hemorrhagic transformation after intravenous thrombolysis for patients with acute ischemic stroke.

HMCAS is seen in about one third to one half of cases of angiographically (DSA – digital subtraction angiography) proven thromboses [13,14], so the sensitivity is rather low.

The specificity of the sign is much higher, however, in some cases, false positive results of HMCAS are reported, because of advanced atherosclerotic disease, especially with asymmetric calcifications.

Commonly, it is easy to confirm a calcified plaque as a reason for a hyperdense vessel segment, because of high CT density values typical for calcifications.

However, in some, usually older patients, a generally increased density of the arterial wall is observed, but not reaching the threshold of calcifications. Such a hyperdense vessel on the background of adjacent brain tissue may be misinterpreted as HMCAS, particularly in asymmetric head position during scanning (Fig. 2).

Apart from atherosclerosis, there are only very rare reports of false positive HMCAS seen in herpes simplex virus (HSV) encephalitis [15].

The aim of the study was to find how to differentiate HMCAS in stroke patients from asymmetric hyperdensity unrelated to stroke, by comparison of the CT density values typical for HMCAS to the values in normal or atherosclerotic MCA.



Fig. 1 – Hyperdense middle cerebral artery sign (HMCAS) in a stroke patient.



Fig. 2 – Generally increased density of the arterial wall because of atherosclerosis in a non-stroke patient.

2. Material and methods

The group retrospectively analyzed consisted of 100 patients – 48 females and 52 males, aged 39–97 years (mean 74 years, SD 11.2 years), with cerebral ischemic stroke involving MCA region, diagnosed and treated in the University Hospital in Cracow in the years 2011–2016, presenting hyperdense middle cerebral artery sign (HMCAS) on the admission CT examination and with infarcts confirmed on the follow-up CT.

In all the patients analyzed we observed a change in the density or size of the hyperdense segment on the follow-up CT. Thus, our study design assumed that HMCAS observed was due to the acute occlusion of this hyperdense segment of the artery.

In 51 (51%) patients stroke involved the left MCA region, whereas in 49 (49%) patients – the right MCA region.

In all the patients from the analyzed group CT density measurements in HU were performed:

- in the hyperdense segment of the involved MCA,
- in the symmetrical segment of the contralateral MCA,
- in the brain cortex adjacent to the hyperdense MCA segment.

Subsequently the following ratios were calculated:

- hyperdense segment density/contralateral segment density,
- hyperdense segment density/brain cortex density,
- contralateral segment density/brain cortex density.

The control group consisted of 100 patients – 55 females and 45 males, aged 50–94 years (mean 74 years, SD 12.3 years), diagnosed in the University Hospital in Cracow in the year

2015, with no clinical or radiological symptoms of cerebral stroke.

In all the patients from the control group CT density measurements in HU were performed:

- in the M1 segment of the right MCA,
- in the M1 segment of the left MCA,
- in the brain cortex adjacent to the more dense from right or left M1 MCA segments measured as above.

Then the following ratios were calculated:

- the more dense from right or left M1 segment density/contralateral M1 segment density,
- the more dense from right or left M1 segment density/brain cortex density,
- contralateral M1 segment density/brain cortex density.

All the CT brain examinations were performed using no intravenous contrast media, 2.5 mm or 3 mm slices, 120–130 kV, 102–342 mAs.

All the density measurements were performed twice and averaged to reduce the measurement errors. In every case ROI (region of interest) was adjusted to cover only the measured artery or brain cortex.

The statistical tests used during comparisons were: Wilcoxon's test (a non-parametrical alternative to Student's t-test for dependent samples), Welch's t-test (an alternative to Student's t-test for independent samples, if variances equality is not confirmed using Levene's test), Mann–Whitney's test (an alternative to Student's t-test for independent samples if the distribution of a feature is not normal).

The Shapiro–Wilk's test was used to assess agreement between the distribution of a feature and theoretical normal distribution.

The statistical calculation was made by R software version 3.3.1 (www.r-project.org).

3. Results

In the group of patients with stroke and HMCAS the CT density measurements were as follows:

- in the hyperdense segment of the involved MCA median 59 HU (41–78 HU, SD 6.9 HU),
- in the symmetrical segment of the contralateral MCA median 41 HU (30–59 HU, SD 5.5 HU),
- in the brain cortex adjacent to the hyperdense MCA segment median 36 HU (27–48 HU, SD 4.2 HU).

The following ratios were obtained:

- hyperdense segment density/contralateral segment density median 1.43 (1.16–2.03, SD 0.2),
- hyperdense segment density/brain cortex density median 1.65 (1.06–2.70, SD 0.3),
- contralateral segment density/brain cortex density median 1.15 (0.73–1.93, SD 0.2).

In the control group of patients with no stroke the CT density measurements were as follows:

- in the M1 segment of the right MCA median 42 HU (30–54 HU, SD 4.5 HU),
- in the M1 segment of the left MCA median 41 HU (31–49 HU, SD 3.9 HU),
- in the more dense from right or left M1 MCA segments measured as above median 43 HU (31–54 HU, SD 4.3 HU),

- in the contralateral M1 MCA segment median 40 HU (30–49 HU, SD 3.9 HU),
- in the brain cortex adjacent to the more dense from right or left M1 MCA segments median 34 HU (24–44 HU, SD 3.4 HU).

The following ratios were obtained:

- the more dense from right or left M1 segment density/contralateral M1 segment density median 1.05 (1.00–1.21, SD 0.0),
- the more dense from right or left M1 segment density/brain cortex density median 1.24 (0.88–1.74, SD 0.2),
- contralateral M1 segment density/brain cortex density median 1.17 (0.85–1.55, SD 0.1).

The measurements of the absolute values of CT densities revealed that the HMCAS density in stroke was of course significantly higher than both contralateral MCA density in stroke (Fig. 3) ($p < 0.001$ in Wilcoxon's test) and the more dense MCA density in non-stroke patients (Fig. 4) ($p < 0.001$ in Welch's test).

However the range of HMCAS density values largely overlapped the ranges of the other foregoing values.

The vessel CT density/adjacent brain cortex density ratio defines the relative 'brightness' of vessel on the background of darker brain tissue.

The HMCAS/brain cortex density ratio in stroke was also significantly higher than both the contralateral MCA/brain cortex density ratio in stroke (Fig. 5) ($p < 0.001$ in Wilcoxon's test) and more dense MCA/brain cortex density in non-stroke patients (Fig. 6) ($p < 0.001$ in Mann–Whitney's test).

However, again the range of HMCAS/brain cortex density ratios largely overlapped the ranges of the other foregoing ratios.

Finally, the hyperdense vessel density/contralateral vessel density ratio defines the relative 'brightness' of vessel compared to the contralateral vessel.

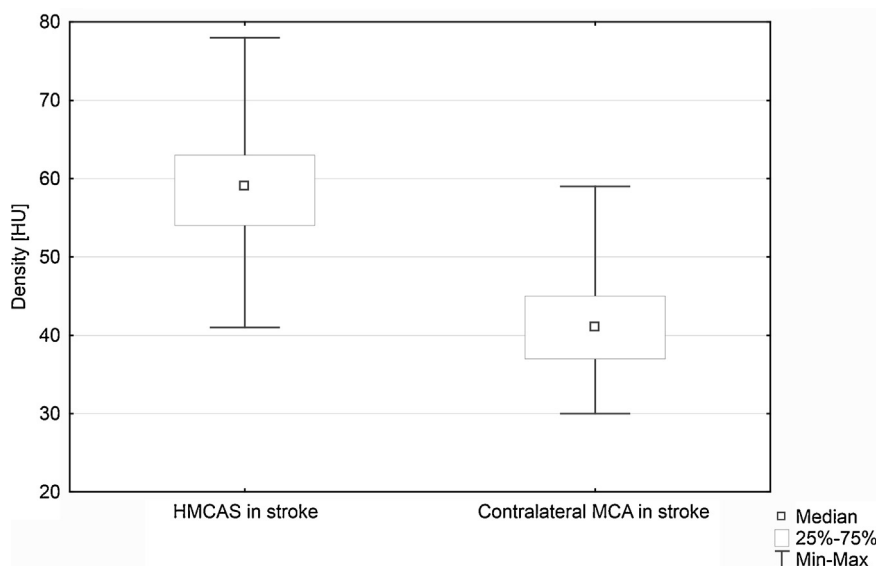


Fig. 3 – Box and whiskers diagram: HMCAS density vs. contralateral MCA density in stroke patients.

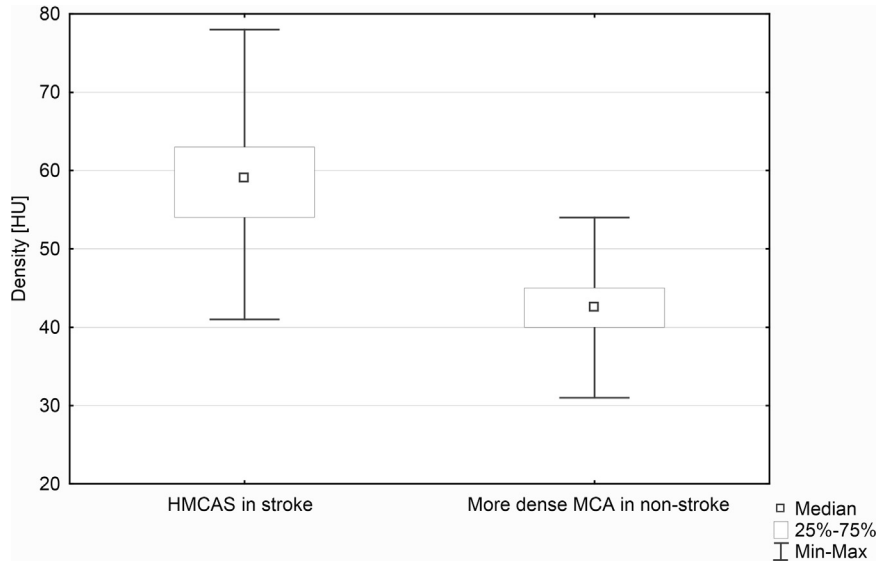


Fig. 4 – Box and whiskers diagram: HMCAS density in stroke vs. more dense MCA density in non-stroke patients.

The HMCAS/contralateral MCA density ratio in stroke was significantly higher than more dense MCA/contralateral MCA density ratio in non-stroke patients (Fig. 7) ($p < 0.001$ in Mann-Whitney's test).

The range of HMCAS/contralateral MCA density ratios in stroke only slightly overlapped the range of more dense MCA/contralateral MCA density ratios in non-stroke patients.

Using the threshold ≥ 1.16 for the hyperdense vessel segment/contralateral vessel segment density ratio it was possible to differentiate HMCAS in stroke patients from asymmetric hyperdensity not related to stroke in non-stroke patients with 100% sensitivity and 97% specificity.

Using the threshold ≥ 1.22 for the hyperdense vessel segment/contralateral vessel segment density ratio it was possible to differentiate HMCAS in stroke patients from asymmetric hyperdensity not related to stroke in non-stroke patients with 94% sensitivity and 100% specificity.

4. Discussion

Accurate diagnosis of HMCAS in acute stroke patients is very important, because the sign is typically associated with a

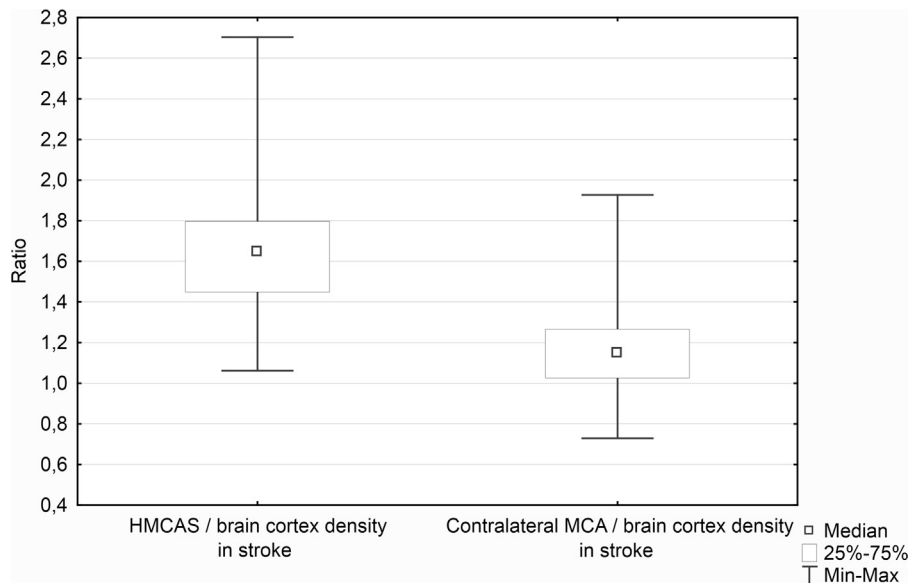


Fig. 5 – Box and whiskers diagram: HMCAS to brain cortex density vs. contralateral MCA to brain cortex density in stroke patients.

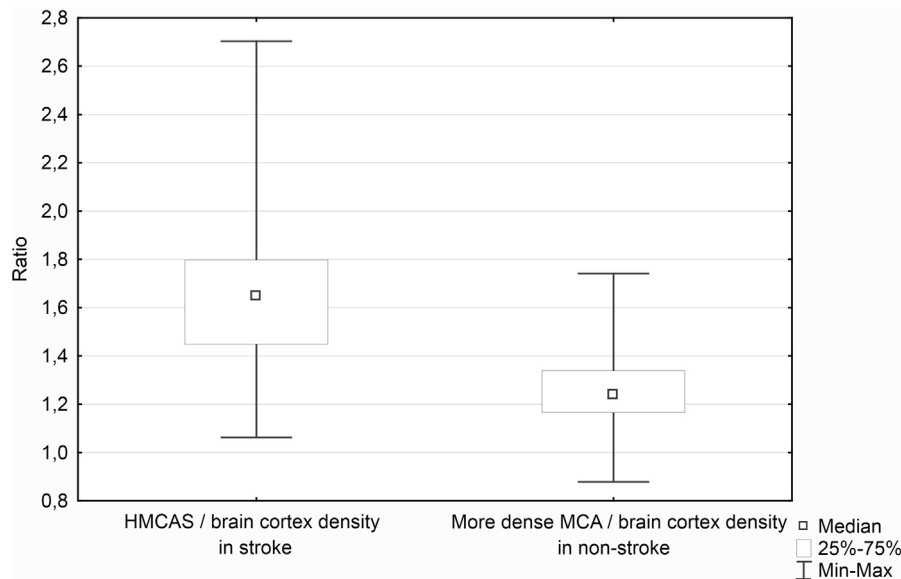


Fig. 6 – Box and whiskers diagram: HMCAS to brain cortex density in stroke vs. more dense MCA to brain cortex density in non-stroke patients.

poorer clinical outcome, larger volume strokes, more severe neurological deficits and worse effects of thrombolytic treatment [13,16–19].

In most of the papers concerning HMCAS, it is defined only qualitatively, for example as “MCA denser than its contralateral counterpart” [20,21], “more dense than adjacent or equivalent contralateral arteries but noncalcified” [22] or “density of the MCA higher than that of the surrounding brain, with disappearance on bone window and unilaterality” [23,8] or simply as “classification done by a local radiologist according to general practice” [19].

Liebeskind [4] reported the mean attenuation of HMCAS as 61 HU (± 8) for the group of only 10 HMCAS cases analyzed in his research. His value is close to our result 59 HU.

Simons [5] before histopathological study of thrombus extracted by endovascular retrieval, measured the mean attenuation of hyperdense artery as 43.1 HU (± 8.7) for the group of 29 cases, however it included not only MCA, but also ICA (internal cervical artery) and basilar artery.

Koo [15] found the mean attenuation of HMCAS as 54 HU (46.7–61.2 HU), versus 41.9 HU (37.3–61.1 HU) in unaffected vessels and 41.3 HU (39.7–43.0) in non-stroke controls. Because

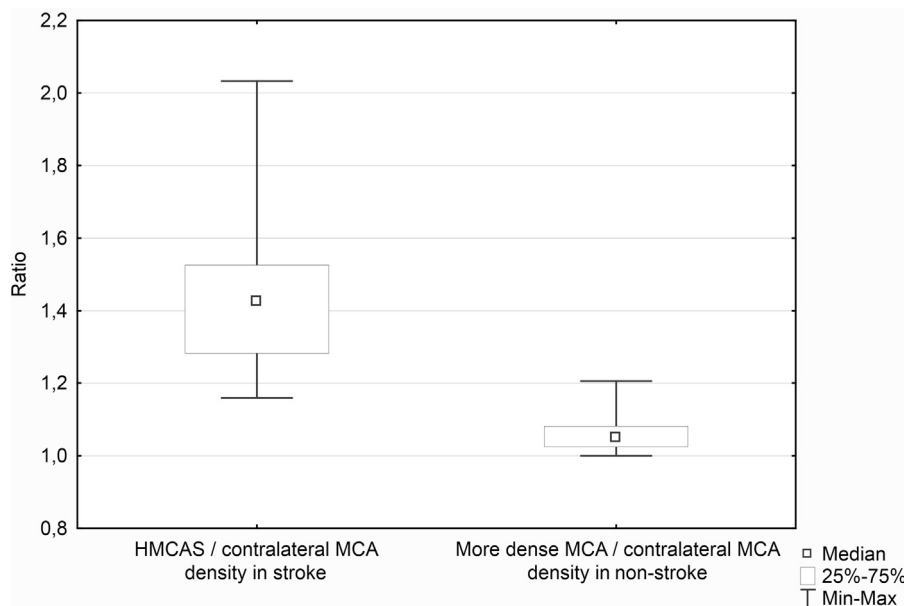


Fig. 7 – Box and whiskers diagram: HMCAS to contralateral MCA density in stroke patients vs. more dense MCA to contralateral MCA density in non-stroke patients.

of the overlapping of HMCAS and unaffected vessels densities, he suggested to use not only the criterion of absolute density >43 HU, but additionally the ratio of hyperdense MCA density/contralateral vessel density >1.2 to get a 100% specificity. However his work included only 18 cases of stroke patients.

The ratio threshold 1.2 is very close to our result, and the mean density values of 54 HU for HMCAS and 41.9 HU for unaffected vessels are close to our values – respectively 59 HU and 43 HU.

Haridy [24] in a subgroup of 106 patients with stroke and HMCAS present, found the mean attenuation of HMCAS as 59 HU and the median ratio of hyperdense MCA density/contralateral MCA density as 1.44 (1.09–2.00), whereas in a subgroup of 48 patients with stroke but HMCAS absent he found the mean attenuation of affected MCA as 42.9 HU and the median ratio of affected MCA density/contralateral MCA density as 1.02 (0.84–1.47).

In his subgroup with stroke and HMCAS present, the mean attenuation of HMCAS as 59 HU is the same as in our study and the median ratio of hyperdense MCA density/contralateral MCA density as 1.44 is practically the same as in our study – 1.43.

However in his subgroup with stroke and HMCAS absent, the upper limit of range (0.84–1.47) for the ratio of affected MCA density/contralateral MCA density is rather difficult to explain – why the artery almost 1.5 times denser than the contralateral one was not classified as HMCAS according to Haridy's own qualitative definition: “HMCA defined as an MCA denser than its contralateral counterpart”?

Detection and assessment of HMCAS on routine non-contrast CT examinations may be limited by large slice thickness of up to 5 mm, compared to the MCA diameter of only 2–3 mm. It results in partial volume effects blurring the intraluminal hyperdensity and lowering HMCAS detection sensitivity. Therefore, some authors suggest using thin slices of about 1 mm for the assessment of non-contrast CT examinations performed using multidetector CT scanners in stroke patients, which may considerably increase the sensitivity [22,25,26].

In our study we used slice thickness of 2.5–3 mm, comparable to the MCA diameter.

In cases of borderline values obtained of the hyperdense MCA segment CT density/contralateral segment density ratio, to increase the accuracy, it is suggested to perform additional reconstruction of axial slices from raw CT data, using as thin slices as possible. In many CT scanners it may be performed, because a standard brain protocol typically uses thicker slices to reduce noise for brain tissue.

In some portion of patients with acute partial anterior circulation stroke (PACS according to Oxfordshire Community Stroke Project (OCSF) classification), hyperdensity of MCA is the effect of atherosclerosis, but the more distant acutely occluded portion of the artery is either non-hyperdense or simply undetectable in CT. In our study, in all the patients with cerebral ischemic stroke and HMCAS on the admission CT, we observed a change in the density or size of the hyperdense segment on the follow-up CT. Thus, our study design assumed that HMCAS observed was due to the acute occlusion of this hyperdense segment of the artery. Of course, in clinical practice, using only admission CT, it is not possible to assess the dynamics of change. Thus everybody should be aware of

the case of false positive HMCAS in a patient with more distant non-hyperdense occluded portion of the artery. However, in such a case, our study results may help to confirm hyperdensity as the effect of atherosclerosis.

CTA (computed tomography angiography) performed just after non-contrast CT during the same session, provides direct imaging of real location and size of the thrombus. Thus, using CTA as the verification technique for patients with cerebral ischemic stroke and HMCAS on non-contrast CT, would be an excellent method to measure the sensitivity and specificity of HMCAS. Unfortunately in our group of 100 patients presenting HMCAS on the admission CT, in 65 cases no CTA was performed during the same session, so we used follow-up CT with infarcts confirmed, as the verification technique. However, the aim of our study was not to assess the real sensitivity and specificity of HMCAS, but only to find how to differentiate HMCAS in stroke patients from asymmetric hyperdensity not related to stroke.

5. Conclusions

The ratio of hyperdense MCA segment CT density/contralateral segment density may be a good tool to differentiate HMCAS in stroke patients from asymmetric hyperdensity unrelated to stroke. In our study the threshold of this ratio ≥ 1.16 provided 100% sensitivity and 97% specificity, whereas ≥ 1.22 94% sensitivity and 100% specificity.

Conflict of interest

None declared.

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