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Sensitivity of visual and quantitative detection of middle cerebral artery occlusion on non-contrast-enhanced computed tomography

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Abstract
Introduction This study aims to investigate diagnostic sensitivity and reliability for the detection of middle cerebral artery occlusion (MCAO) on non-contrast-enhanced computed tomography (NECT) by visual assessment (VA), Hounsfield unit (HU) measurement, calculation of the Hounsfield unit/hematocrit (HU/Hct) ratio, and combination of visual assessment and attenuation measurement (VA+HU).
Methods NECT of 18 patients with angiographically proven MCAO and 18 patients without MCAO were reviewed by two blinded observers. Visual assessment of presence or absence of a hyperdense sign was followed by HU measurement of both middle cerebral arteries (MCA). Sensitivity, specificity, positive predictive value, and negative predictive value were calculated for VA, HU measurement, HU/Hct ratio, and VA+HU measurement. Receiver operating characteristic curve analysis (ROC) was performed to determine the optimal cut-off values for MCAO using attenuation measurements or HU/Hct ratio.
Results Diagnostic sensitivity/specificity was 63 %/91 % for VA, 56 %/88 % for attenuation measurement, 68 %/81 % for HU/Hct ratio, and 75 %/78 % for VA+HU. ROC curve analysis revealed cut-off values of >42.5 HU for attenuation measurements and >1.12 HU/Hct for HU/Hct ratio.
Conclusion Combination of visual assessment with additional attenuation measurement with a cut-off value of 42.5 HU is recommended for most sensitive and reliable detection of MCAO on NECT.

Keywords NECT · Hyperdense artery sign · Middle cerebral artery occlusion · Accuracy

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Introduction

The hyperdense middle cerebral artery sign (HMCAS) was first described in 1983 by Gács et al. demonstrating that on non-contrast-enhanced computed tomography (NECT) scans increased attenuation of middle cerebral artery is suggestive of middle cerebral artery occlusion (MCAO) [1]. As MCAO is associated with severe brain ischemia, poor clinical outcome, and higher mortality, its detection is of prognostic significance and has a significant clinical impact [2–4]. Moreover, the HMCAS provides an earlier recognition of an imminent ischemic infarction at a time when treatment is most likely to be effective and to have an effect on clinical outcome. Recently, the HMCAS has assumed greater therapeutic importance as it might be used to predict clot composition [5], which in turn may impact response to pharmacologic thrombolysis and the likelihood of successful mechanical recanalization [6].

Since NECT is often the first imaging modality for patients with suspected stroke, it is of great importance to determine the most sensitive routine of defining HMCAS for the detection of MCAO. Therefore, we aimed to investigate the influence of attenuation measurement on the diagnosis of MCAO in a setting that is used and recommended in clinical routine in non-enhanced CT imaging in most institutions. We hypothesized that a certain Hounsfield-Unit cut-off improves both sensitivity and interobserver reliability for the detection of MCAO.

Methods

Study population

Four hundred eleven suspected stroke patients presenting to our department between July 2009 and September 2012 underwent NECT as well as CT angiography (CTA). Among these patients we retrospectively identified 18 consecutive patients (11 female and 7 male; mean age 65 ± 15 years) who underwent NECT with MCAO proven by CTA. CTA was performed directly after NECT. Of these 18 patients, 11 underwent additional digital subtraction angiography (DSA), which confirmed MCAO. The median time delay between CTA and DSA is <3 h. Another 18 patients (11 female and 7 male; mean age 67 ± 15 years) matched on gender and age (±1 year) without MCA occlusion on CTA served as control group. Patients with poor image quality or evidence of symptomatic intracranial hemorrhage were excluded.

The study has been approved by the local ethics committee (Ethik-Kommission Ärztekammer Hamburg) and the requirement for informed consent was waived. All examinations were conducted according to the Declaration of Helsinki.

Computed tomography

All CT studies were performed at the same scanner using 256-slice multidetector computer tomography (Brilliance iCT; Philips, Best, The Netherlands). The patients were placed in supine position with their arms beside the body. Scan parameters of NECT were as follows: collimation at sequential acquisition 16×0.625, tube voltage 120 kVp, and tube current 333/310 mAs (infratentorial/supratentorial). Reconstructed slice thickness was 2.5 mm infratentorial and 5 mm supratentorial.

CTA was performed using the following parameters: rotation time 0.4 s, collimation 64×0.625, tube voltage 120 kVp, tube current 300 mAs/slice, and administration of 45 ml of nonionic contrast material with an iodine concentration of 400 mg/ml (Imeron 400; Bracco Altana Pharma, Milan, Italy) injected at a rate of 4 ml/s through an 18-gauge peripheral intravenous catheter which was placed in an antecubital vein. Scanning range was planned in a caudocranial direction. Bolus-tracking software was used to acquire images at peak contrast arrival.

Cerebral angiography

DSA was performed using an Allura Xper FD20/20 angiographic unit (Philips Medical Systems, Best, The Netherlands) with detector matrix of 2,000×2,000 pixels. The MCA circulation was imaged by intra-arterial hand injection of 6 ml of contrast agent with an iodine concentration of 150 mg/ml (Imeron 150; Bracco Altana Pharma, Milan, Italy). All conventional angiographies were performed by an experienced interventional neuroradiologist.

Image analysis

All NECTs were evaluated separately and independently by two observers with more than 4 years of experience in neuroradiology. Both readers were employed at the same institution, worked closely together, and were trained in advance. They were asked to make a final judgment regarding the presence or absence of HMCAS in the M1 segment on NECT. Afterwards, they performed Hounsfield unit (HU) measurements from the M1 segments of the MCAs as reported elsewhere [7]. The readers had not participated in the treatment of any of the patients included in the study. They were unaware of other CTA, MRA, or DSA examinations and were blinded to all patient information other than the images to be read. Each reader was blind to the other observer's assessments. To evaluate intraobserver reliability, a second assessment was made by one reader with a time interval of 4 weeks in an attempt to diminish recall bias.

In order to confirm or exclude MCAO, both observers performed a consensus reading by reviewing DSA and CTA data sets (Fig. 1).

Statistical Analysis

Statistical analysis was performed with commercially available software tools (MedCalc for Windows, Mariakerke, Belgium and Excel, Microsoft Corporation, Redmond, WA, USA). Cohen kappa coefficient was calculated to evaluate intra- and interobserver reliability regarding the presence or absence of HMCAS on NECT. A kappa value of up to 0.19 indicated positive but poor agreement, 0.21–0.40 fair agreement, 0.41–0.6 moderate agreement, 0.61–0.8 good agreement, and greater than 0.8 very good agreement [8].

Furthermore, intra-class correlation coefficient (ICC) [9] and Bland–Altman analysis (BAA) [10] were applied to investigate inter- as well as intraobserver correlation and agreement for HU measurements.

The following ICC interpretation scale was used: poor to fair (below 0.4), moderate (0.41–0.60), excellent (0.61–0.80), and almost perfect (0.81–1) [11].

With DSA or, if not performed, CTA serving as the standard of reference, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the detection of MCAO were calculated for visual assessment, HU measurements, HU/hematocrit (Hct) ratio, and combination of visual assessment and HU measurements.

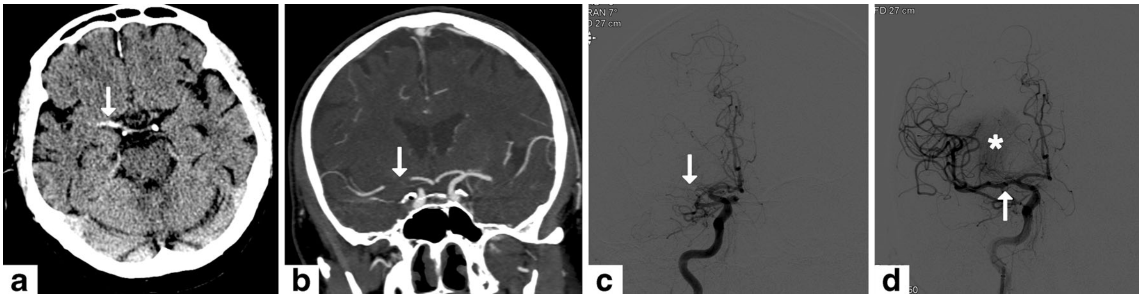

Fig. 1 NECT (**a**), CTA (**b**), and DSA (**c, d**) of a 77-year-old male patient. Transverse NECT demonstrates hyperdense M1 segment of the right middle cerebral artery (*arrow* in **a**). Occlusion was confirmed by CTA (*arrow* in **b**) and DSA (*arrow* in **c**). In this patient, mechanical thrombectomy led to complete M1 reperfusion (*arrow* in **d**) with luxury perfusion of the infarcted basal ganglia (*asterisk*)

Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off values to discriminate patients with MCAO from those without by HU measurements and HU/Hct ratio. The cut-off value derived from ROC curves at the point of highest accuracy was used to calculate the mean sensitivity, specificity, PPV, and NPV for the detection of MCAO by attenuation measurements and HU/Hct ratio on NECT.

Results

Intra- and interobserver reliability

Intra- and interobserver reliability of visual detection of MCAO was moderate (κ=0.56 ± 0.12; κ=0.51 ± 0.11). Quantitative assessment by HU measurement showed excellent to almost perfect intra- and interobserver correlation (ICC = 0.79 and 0.84). BAA revealed limits of agreement ranging between 0.5±11.3 HU (intraobserver) as well as −2.1±10.5 HU (interobserver) (Fig. 2). Intermodality agreement between CTA and DSA for MCAO was 100 %.

Sensitivity, specificity, PPV, and NPV

Sensitivity, specificity, PPV, and NPV of visual assessment, HU measurements, HU/Hct ratio, and combination of visual assessment and HU measurements for the detection of MCAO are listed in Table 1.

ROC curve analysis and cut-off values to identify MCAO by HU measurements and HU/Hct ratio

Highest accuracy for detecting MCAO was achieved for cut-off values of >42.5 HU by HU measurements and a HU/Hct ratio >1.12 (Fig. 3). ROC curve analysis revealed fair accuracy with an area under the curve (AUC) of 0.767 (0.654–0.857) for HU measurements and an AUC of 0.728 (0.613–0.82) for HU/Hct ratio.

Discussion

With regard to the visual assessment of the HMCAS on NECT, our findings correspond to those of prior studies reporting a high specificity ranging from 85 to 100 % and a low sensitivity (27–50 %) [4, 12–15].

Since MCAO is life threatening if not treated in time, false-negative results would have dramatic consequences. Therefore, in screening for stroke, a high sensitivity of a diagnostic test is more important than a high specificity. We achieved the highest sensitivity by visual assessment and additional quantitative density measurements applying a cut-off point of 42.5 HU. As a strength of our study, all patients were scanned on

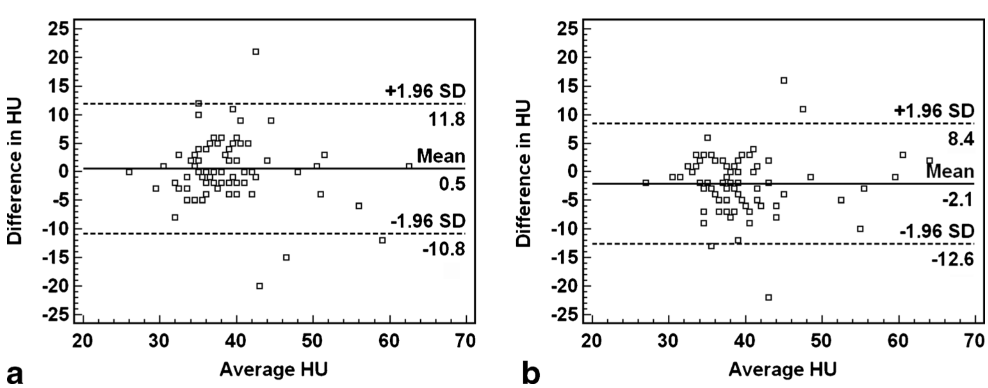

Fig. 2 Bland–Altman plots of intra- (**a**) and interobserver agreement (**b**) for Hounsfield unit measurements performed in the middle cerebral artery

Table 1 Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) with 95 % confidence intervals (CI) of visual assessment, Hounsfield (HU) measurements, hematocrit corrected HU measurements, and combination of visual assessment and HU measurements for the detection of middle cerebral artery occlusion

	Sensitivity	Specificity	PPV	NPV
Visual	63 %	91 %	67 %	90 %
	(36 to 84 %)	(83 to 97 %)	(42 to 85 %)	(80 to 95 %)
>42.5 HU	56 %	88 %	56 %	88 %
	(23 to 80 %)	(76 to 95 %)	(33 to 77 %)	(77 to 94 %)
>1.12 HU/Hct	68 %	78 %	50 %	90 %
	(41 to 89 %)	(69 to 90 %)	(31 to 69 %)	(79 to 96 %)
Visual and >42.5 HU	75 %	81 %	52 %	92 %
	(47 to 92 %)	(68 to 90 %)	(33 to 71 %)	(82 to 97 %)

the exact same CT scanner to avoid differences in the HU values. Given the dependence of HU values on kilovolt peak and filtration, the cut-off value might be different for varying CT scanners and scan parameters [16]. Nonetheless, our results are ~~is~~ in good accordance to previous studies. Koo et al. recommend an absolute density of >43 HU to identify hyperdense MCA associated with acute ischemic stroke [7]. However, they do not report the scan parameters and only 5 of 18 patients underwent additional vascular imaging in their study population. A recent study, investigating the value of attenuation measurements as predictors of basilar artery occlusion, identified a similar cut-off value of 40–42 HU to be optimal using the same tube voltage of 120 kVp [17]. Moreover, they found a significant improvement of the diagnostic accuracy for less-experienced observers. This might be another interesting aspect and a future study would ideally recruit readers of different experience.

In another study, absolute HU values, HU/Hct ratio, and venoarterial HU value differences were found to be a useful adjunct in the identification of intracranial venous thrombosis on NECT [18]. Although x-ray attenuation is highly correlated with Hct levels [19], we did not achieve a higher accuracy by using a normalized ratio of HU/Hct compared with HU measurement alone. Likewise, a previous study, evaluating the use of CT density measurement and HU/Hct ratio in diagnosing acute cerebral venous sinus thrombosis, found only a minor difference between the accuracy of the HU/Hct ratio and the accuracy of the HU measurement alone [20].

As another strength of our study, all patients had a NECT followed by angiography (CTA and/or DSA) performed within 6 h after symptom onset. Several trials demonstrated the excellent correlation between CTA and DSA for the detection and exclusion of large vessel intracranial occlusion [21–23]. A study evaluating the accuracy of CTA and MRA in detecting

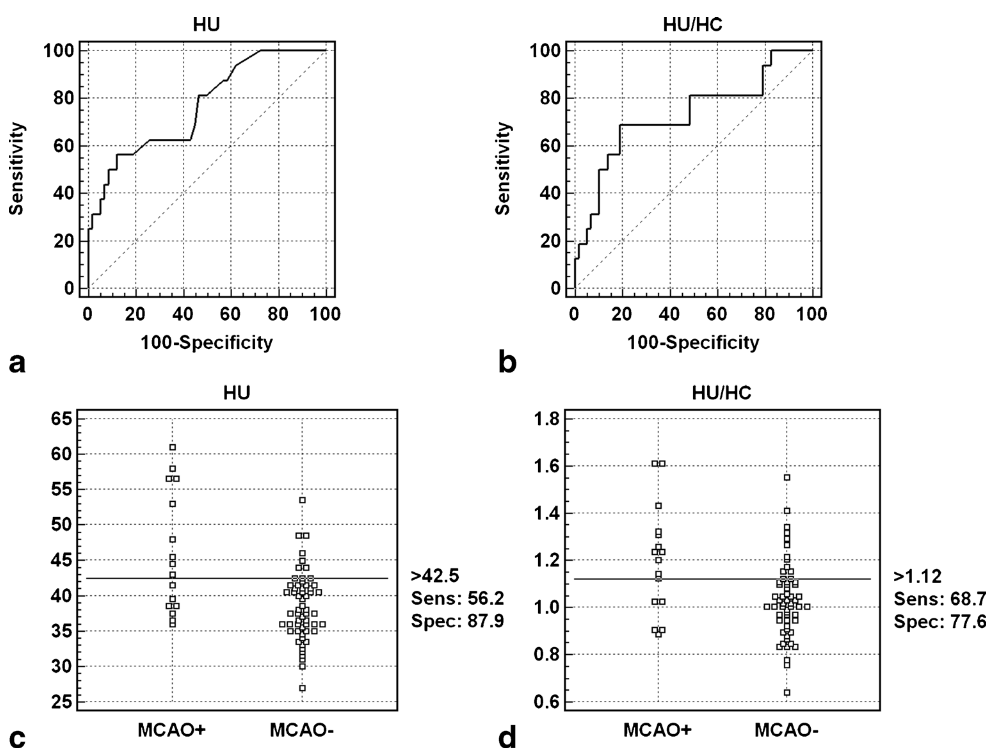

Fig. 3 Receiver-operating characteristic (ROC) curve (**a**, **b**) and dot-plot analysis (**c**, **d**). ROC analysis derived from calculated differences in Hounsfield unit (HU) measurements and hematocrit (Hct) corrected HU measurements of occluded (MCAO+) and non-occluded (MCAO−) middle cerebral artery

MCAO using DSA as reference standard revealed a sensitivity and PPV of 100 % for CTA, significantly better compared to MRA with 87 % and 59 %, respectively [24].

Reviewing the literature concerning the accuracy of the HMCAS for the detection of MCAO, we discovered that most studies lack an adequate reference standard [7, 25–27, 2, 28–30]. An imperfect reference standard might classify results of the index test as being correct when they are actually incorrect. Thus, one recent study affirms that M1 occlusion was determined by time-of-flight MRA (ToF-MRA), which eventually did not distinguish vessel occlusion from slow flow [14]. This might have led to an overestimation of sensitivity and NPV of the HMCAS.

Few studies consequently applied angiography (CTA, MRA, or DSA) to confirm MCAO [12, 13, 31–33, 15]. Missing immediate angiographic verification, it is impossible to distinguish if a normal follow-up CT scan proves the HMCAS on the initial CT scan to be false positive or if the HMCAS was true positive and disappeared under therapy.

Moreover, several studies might suffer from partial verification bias since the reference test was not applied consistently to confirm negative results of the initial CT scan. Most studies also did not include a normal control group, which is essential to make statements concerning specificity and NPV.

To avoid substantial variation in density measurements, we performed the measurements as described by Koo et al. using oval regions of interest (ROIs) instead of three adjacent ROIs of one pixel size as done by Schuknecht et al. [7, 25]. Thus, we achieved an excellent to almost perfect intra- and interobserver correlation.

Prior studies either did not assess or report reliability, or their statistical analysis creates doubt. Thus, Koo et al. estimated intra- and interobserver errors from 10 randomly chosen cases. Especially in the absence of a reference standard, reliability is an important indicator of the potential of the test to be accurate. Moreover, a sufficient description of the measurement process, including information regarding blinding, was missing in most studies.

Given the retrospective nature of our study, we had to apply a slice thickness of 5 mm as it was the standard in our department in the period of examination. Previous studies demonstrated that reduction of section thickness improves the detectability of a clot within the MCA. However, a slice thickness of 5 mm is used and recommended in clinical routine in non-enhanced CT imaging in most institutions [32, 34, 35].

Conclusion

Combining visual assessment and additional attenuation measurement with a cut-off value of 42.5 HU, the HMCAS becomes a highly sensitive and reliable indicator for MCAO.

Ethical standards and patient consent We declare that all human and animal studies have been approved by the Ethik-Kommission Ärztekammer Hamburg and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We declare that all patients gave informed consent prior to inclusion in this study.

Conflict of interest We declare that we have no conflict of interest.

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