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Determinants of mismatch in acute ischaemic stroke

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ABSTRACT

Background: Multimodal CT or MR imaging may be helpful in guiding reperfusion therapy for stroke. However, access to multimodal imaging may frequently be limited. We hypothesised that certain clinical and non-enhanced CT (NECT) findings at initial assessment can potentially predict mismatch on CT perfusion (CTP) in patients with acute ischaemic stroke.

Methods: We undertook an analysis of prospectively collected clinical and imaging data of consecutive patients with anterior circulation ischaemic stroke who underwent CTP during their initial assessment. NECT was read for early ischaemic change as measured by the Alberta Stroke Program Early CT Score (ASPECTS), and for hyperdense middle cerebral artery sign (HMCAS). CTP images were evaluated for mismatch. Independent clinical and imaging predictors of a CTP mismatch were identified using stepwise logistic regression.

Results: Of the 202 patients, 92 (46%) demonstrated a mismatch, 23 (11%) a matched deficit, and 87 (43%) no perfusion deficit. HMCAS on NECT (OR 13.65, 95% CI 6.04–30.81, $p < 0.001$), female gender (OR 2.37, 95% CI 1.19–4.72, $p = 0.015$), atrial fibrillation (OR 2.05, 95% CI 1.02–4.11, $p = 0.044$), and absence of a history of hypertension (OR 0.46, 95% CI 0.22–0.96, $p = 0.037$) were independent predictors of a CTP mismatch. HMCAS had 58% sensitivity, 91% specificity, 84% positive predictive value and 72% negative predictive value.

Conclusions: A HMCAS on the initial NECT is associated with a high probability of mismatch in acute ischaemic stroke, and may identify patients most likely to benefit from recanalisation treatments when access to multimodal CT or MR facilities is limited.

1. Introduction

The practice of thrombolysis in acute ischaemic stroke (AIS) is underpinned by the concept of penumbra. Although the penumbra may be highly variable in both volume and duration, one of the best predictors of functional outcome in clinical trials of intravenous thrombolysis using non-enhanced CT (NECT) has been the time since symptom onset [1]. Multimodal CT or MR imaging that provide an estimate of the penumbra have the potential not only to extend the time window for thrombolysis, but also to improve safety and clinical outcomes within approved time windows [2,3]. However, many centres lack equipment or expertise to operate multimodal imaging facilities 24 hours a day, and patient-related factors such as the presence of a pacemaker or contraindications to administer contrast media may also prohibit their application [4]. We hypothesised that certain clinical and non-enhanced CT (NECT) findings at initial assessment can predict mismatch on CT perfusion (CTP) in patients with AIS. Our objective was to identify such baseline clinical and NECT imaging markers of mismatch, a surrogate for penumbra, in a consecutive cohort of AIS patients.

2. Methods

This study is an analysis of prospectively collected baseline clinical and imaging data of consecutive patients with confirmed anterior circulation AIS admitted to an academic stroke centre during a whole calendar year. CTP was performed in 222 (24%) of the total 918 AIS patients. Seven patients were excluded because their CTP images were uninterpretable and a further 13 as having a posterior circulation stroke. This resulted in the inclusion of 202 patients. The study was approved by the East Midlands Research Ethics Committee (11/EM/0190).

Clinical information prospectively entered into the database included age, gender, hypertension, diabetes mellitus, hypercholesterolaemia, atrial fibrillation, previous stroke/TIA, and baseline blood pressure and blood glucose. The National Institutes of Health Stroke Scale (NIHSS) score was taken by certified assessors. The time of symptom onset and CT imaging were recorded. Stroke subtype was classified according to the TOAST criteria when a full diagnostic workup has been completed [5].

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CT examinations were performed on a 16-slice multidetector scanner (LightSpeed, GE Healthcare, USA). All patients underwent routine NECT, and the negative ordinal Alberta Stroke Program Early CT Score (ASPECTS) scale (range 10–0) was used to evaluate the extent of ischaemic change within the middle cerebral artery (MCA) territory [6]. The presence of an ipsilesional hyperdense middle cerebral artery sign (HMCAS) was identified on reconstructed thin (1.25 mm) axial slices [7]. A proximal HMCAS was defined as hyperattenuation of the horizontal part (M1 segment) of the MCA, whereas a distal HMCAS displayed hyperattenuation of the MCA in its Sylvian tract or more distally (M2 and/or M3 segment) [8]. Patients who had a HMCAS in both the proximal and distal MCA were classified as having a proximal HMCAS.

CTP was undertaken immediately following NCCT. Image acquisition was performed as a 50-sec cine series beginning 5 sec after a power injection (Medrad Power Injector, Medrad, USA) of 50 ml of a non-ionic iodinated contrast (Ominpaque 300 mg/mL, GE Healthcare, UK) at 4 ml/s. The imaging parameters were 80 kVp, 200 mAs, and a rotation time of 1 sec. Coverage consisted of two contiguous slices of 10-mm thickness positioned parallel and superior to the orbital roof, with the more caudal section at the level of the basal ganglia and internal capsule. The dynamic perfusion CT source images were analysed by using a semi-automated postprocessing software (CT Perfusion 2.6.9, GE Medical Systems, USA) that generated colour maps of cerebral blood volume (CBV), cerebral blood flow (CBF) and mean transit time (MTT) using deconvolution analysis. The colour scales were set at 0–10 ml/100 g for the CBV, 0–100 ml/100 g/s for the CBF, and 0–15 s for the MTT maps. The arterial and venous input functions were obtained automatically from the anterior cerebral artery and the superior sagittal sinus, respectively, following manual identification of relevant regions of interest.

A structured method of visual assessment, applying the semiquantitative ASPECTS technique, was used to read the CTP maps [9]. Areas showing normal CBV and MTT were scored as 1 and those demonstrating an impairment as compared to the contralateral hemisphere were rated as 0. A perfusion deficit was identified as areas with impaired MTT. ASPECTS mismatch was defined as the CBV ASPECTS minus the MTT ASPECTS. The ASPECTS mismatch is therefore a positive ordinal scale ranging from 0 to 10. A CTP ASPECT mismatch score of ≥ 2, found to be the optimum cut-off point for a volumetric mismatch of $\geq 150\%$, was used to define mismatch [10]. All NECT and CTP scans were masked and were read by two trained assessors not involved in the acute care of the patients, first independently and then in consensus in the event of a disagreement.

Categorical variables were compared using Chi-square tests. Continuous variables are presented as medians and interquartile range (IQR), and were compared with the Kruskal Wallis test as being non-parametric (Kolmogorov–Smirnov test). The independent determinants of a mismatch on CTP were identified using stepwise logistic regression analysis. This was performed by including all clinical and NECT parameters (with the exception of the TOAST classification frequently undetermined at initial presentation, and thrombolysis) in the model, and retaining those that were significant at $p < 0.10$. Two-sided p values are reported, with the level of significance set at <0.05. SPSS version 17.0 (SPSS Inc., USA) was used for analyses.

3. Results

Of the 202 patients with anterior circulation stroke included in this study, 92 (46%) demonstrated a mismatch, 23 (11%) exhibited a matched deficit, and 87 (43%) displayed no perfusion deficit. Clinical and imaging characteristics are shown in Table 1. When compared with those exhibiting no perfusion deficits, AIS patients with mismatched or matched deficits were more likely to be older, in atrial fibrillation, have more severe neurological deficits and a cardioembolic as opposed to a lacunar aetiology. More extensive early ischaemic changes and HMCAS on initial NECT were significantly more prevalent in patients with a perfusion deficit. The independent predictors of the presence of mismatch on CTP were HMCAS on initial NECT (OR 13.65, 95% CI 6.04–30.81, $p < 0.001$), female gender (OR 2.37, 95% CI 1.19–4.72, $p = 0.015$), atrial fibrillation (OR 2.05, 95% CI 1.02–4.11, $p = 0.044$), and absence of a history of hypertension (OR 0.46, 95% CI 0.22–0.96, $p = 0.037$). The adjusted ORs for proximal and distal HMCAS were 8.44 (95% CI 3.19–22.30, $p < 0.001$) and 8.33 (95% CI 2.66–26.09, $p < 0.001$), respectively. HMCAS had 58% sensitivity, 91% specificity, 84% positive predictive value and 72% negative predictive value in detecting CTP mismatch.

4. Discussion

This study shows that as many as 46% of anterior circulation AIS patients may have a CTP mismatch at the time of presentation, and that HMCAS on the initial NECT is highly predictive of a significant mismatch. HMCAS, whether proximal or distal, was the most important prognostic indicator of CTP mismatch suggestive of significant salvageable brain tissue, compared with other determinants, where the odds ratios were lower.

The high prevalence of mismatch in this study is consistent with other reports showing MR mismatch in 55%–70% of incident AIS patients [11]. Although the absence of HMCAS cannot reliably exclude a mismatch because of the moderate sensitivity (58%) of this marker, its high specificity (91%) suggests that a positive HMCAS on the initial NECT is highly predictive of a significant mismatch and potentially salvageable brain tissue. In our population of consecutive stroke patients, the likelihood of mismatch in the presence of HMCAS was 84% (i.e. the positive predictive value), whereas the probability of lack of mismatch in the absence of HMCAS was 72% (i.e. the negative predictive value). The HMCAS on reconstructed thin (1.25 mm) axial NECT slices, a method applied in this study, has been reported to have comparable sensitivity and specificity with CT angiography for the detection of an acute thrombus, although clot composition may well influence sensitivity [7,12]. HMCAS is an early marker of vessel occlusion, which has been associated with poor outcomes [13]. However it ceases to be an independent prognostic factor when initial neurological deficit and early parenchymal damage are also taken into account [14]. The disappearance of HMCAS after thrombolysis in nearly half of the patients was associated with favourable outcomes in a large registry, supporting the relationship between the HMCAS and the presence of salvageable tissue [15].

As concerns other predictors of mismatch, our results are in agreement with recent experimental studies reporting a negative impact of chronic hypertension on mismatch size in animal models of stroke, which is likely to be a consequence of impaired cerebral autoregulation [16]. Atrial fibrillation was a significant predictor of perfusion mismatch in our study, probably reflecting occlusion of the larger arteries and early recruitment of collaterals [17]. Mismatch was more likely to occur in women, which is in agreement with animal and human studies suggesting a more favourable response to brain ischaemia in females [18,19]. Interestingly, baseline blood pressure, blood glucose and onset-to-CT time were not significant predictors of mismatch in this study.

A potential limitation of this observational study is that it may not be absolutely free from a selection bias, although maximal care was taken to identify all consecutive patients at this single centre. Criteria for inclusion were pre-defined, and analyses were undertaken masked to patient identity. The limited volumetric coverage of the 20 mm PCT slab and its placement at the chosen levels may have introduced a bias towards association with HMCAS. The methodology to assess mismatch is open to debate because the definition of tissue states and tissue viability thresholds applied for CT and MR perfusion imaging have been derived from small numbers of patients and are further biased by differences in post-processing software and perfusion analysis methods [20]. Bias in our study was minimised by using the same pre-defined imaging protocol