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The association of insular stroke with lesion volume

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ABSTRACT

The insula has been implicated in many sequelae of stroke. It is the area most commonly infarcted in people with post-stroke arrhythmias, loss of thermal sensation, hospital acquired pneumonia, and apraxia of speech. We hypothesized that some of these results reflect the fact that: (1) ischemic strokes that involve the insula are larger than strokes that exclude the insula (and therefore are associated with more common and persistent deficits); and (2) insular involvement is a marker of middle cerebral artery (MCA) occlusion. We analyzed MRI scans of 861 patients with acute ischemic hemispheric strokes unselected for functional deficits, and compared infarcts involving the insula to infarcts not involving the insula using t-tests for continuous variables and chi square tests for dichotomous variables. Mean infarct volume was larger for infarcts including the insula ($n = 232$) versus excluding the insula ($n = 629$): 65.8 ± 78.8 versus 10.2 ± 15.9 cm^3 ($p < 0.00001$). Even when we removed lacunar infarcts, mean volume of non-lacunar infarcts that included insula ($n = 775$) were larger than non-lacunar infarcts ($n = 227$) that excluded insula: 67.0 $cm^3 \pm 79.2$ versus 11.5 $cm^3 \pm 16.7$ ($p < 0.00001$). Of infarcts in the 90th percentile for volume, 87% included the insula ($\chi^2 = 181.8$; $p < 0.00001$). Furthermore, 79.0% infarcts due to MCA occlusion included the insula; 78.5% of infarcts without MCA occlusion excluded the insula ($\chi^2 = 93.1$; $p < 0.0001$). The association between insular damage and acute or chronic sequelae likely often reflects the fact that insular infarct is a marker of large infarcts caused by occlusion of the MCA more than a specific role of the insula in a range of functions. Particularly in acute stroke, some deficits may also be due to ischemia of the MCA or ICA territory caused by large vessel occlusion.

1. Introduction

The insula, also known as the insular cortex, is the small part of the brain that lies deep within the lateral sulcus. It is a triangular region, covered by the fronto-parietal and temporal opercula (Varnavas and Grand, 1999). The insula has bidirectional connections with most of the brain, including the frontal, temporal, parietal, cingulate, subcortical structures (basal ganglia and thalamus), and limbic structures (amygdala, periamygdaloid areas, and entorhinal cortex) (Augustine, 1996). The arterial supply of the insula is complex: arteries supplying the insula arise from the middle cerebral artery (MCA), with predominance from the M2 segment and a small contribution from the insular branches of the M1 segment (Türe et al., 2000). Because it receives blood supply from both M1 and M2, complete MCA occlusion may be necessary to produce a substantial insular infarct.

The insular cortex has been implicated in viscerosensory, visceromotor, and interoceptive functions (Augustine, 1985), and also in complex processes such as emotions, music, and language (Shura et al., 2014). It has been reported that stroke-induced insular damage is associated with a variety of deficits, including disrupted autonomic nervous system (Augustine, 1985; De Raedt et al., 2015; Inamasu et al., 2013), emotion (Calder, 1996; Ibanez et al., 2010), pain functions (Cattaneo et al., 2007; Cereda et al., 2002), apraxia of speech (Dronkers, 1996), other aspects of speech production such as respiration (Ackermann and Riecker, 2010), auditory processing (Bamiou et al., 2003), gustatory functions (Flynn, 1999; Small, 2010), and somatosensory function (Stephani et al., 2011). Insular stroke has been associated with cardiac arrhythmias and cardiac death after stroke (Oppenheimer, 2006; Seifert et al., 2015; Tokgozoglu et al., 1999) as well as hospital acquired pneumonia (Kemmling et al., 2013). It is possible that the frequent association between insular damage and at least some of the post-stroke sequelae that have been attributed to the insula can be explained by the fact that patients with strokes involving the insula have larger volume strokes (and are therefore less likely to recover from

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any sequelae), compared to patients with stroke with no insular involvement (Hillis et al., 2004). Previous studies have shown that the insula is frequently involved in any large MCA territory infarct (Nakano et al., 2001; Truwit et al., 1990). However, it has not been shown that strokes involving the insula are larger than other hemispheric strokes. The goal of this study is to test the hypotheses that: (1) ischemic strokes including the insula are larger in volume than other hemispheric strokes; and (2) insular infarct is a marker of MCA occlusion. We tested these hypotheses in a series of 861 patients with acute ischemic hemispheric stroke, unselected for clinical deficits. This study was a retrospective analysis of prospectively collected data.

2. Methods

2.1. Participants

Patients were identified from a prospective database of patients who presented with acute ischemic hemispheric stroke to the Johns Hopkins Medical Institutions stroke service (East Baltimore campus or Johns Hopkins Bayview Medical Center) and consented for a study of language or cognitive deficits associated with areas of acute ischemia. All participants gave informed consent (if they demonstrated intact comprehension), or their closest relative or legal representative consented (if the patient had impaired comprehension) to the study according to according to the Declaration of Helsinki. The study was approved by the Johns Hopkins Medicine Institutional Review Board

Inclusion criteria were: (1) symptoms of acute ischemic hemispheric stroke; (2) age 18 or older; (3) able to complete testing within 48 h from onset of symptoms. Exclusion criteria included: (1) contraindication for MRI; (2) premorbid dementia or other neurological disease; (3) impaired level of consciousness or need for ongoing sedation; (3) hemorrhage; and (4) stroke limited to the brainstem or cerebellum. For this study we also excluded patients who were found to have: (1) chronic stroke; (2) no lesion on diffusion-weighted image (DWI); (3) other (non-stroke) lesions on MRI, such as tumor; and (4) poor quality DWI, preventing reliable measurement of lesion volume. From the database we identified 861 patients with acute strokes unselected for functional deficits. The mean age of participants was 61.1 years (SD of 15.5 years).

2.2. Imaging

MRI scans were obtained within 48 h of symptom onset. Participants underwent the following imaging: T2, fluid attenuation inversion recovery (FLAIR; to evaluate for old lesions), susceptibility weighted images (to evaluate for hemorrhage), PWI (to evaluate for areas of hypoperfusion), and DWI (to evaluate for acute ischemia). DWI scans were 5 mm in thickness and provided whole-brain coverage. MR/CT angiography (to evaluate for stenosis or occlusion) was obtained for 620 patients. Acute DWI scans were evaluated by a technician blinded to clinical data (including MRA/CTA) for presence or absence of involvement of the insula. A neurologist, also blinded to clinical data evaluated a subset of 50 scans for inter-rater reliability. For those 50 scans there was 96% point-to-point percent agreement on involvement of the insula. Stroke laterality was determined based on the DWI image and was categorized as left hemisphere, right hemisphere or bilateral. Volumes of tissue dysfunction on DWI were calculated using Image J (http://imagej.nih.gov/ij/;(Schneider et al., 2012).

2.3. Data analysis

Volume of infarct and demographics were compared for lesions involving the insula and those not involving the insula, using unpaired t-tests (STATA, version 16). The association between lesions involving the insula and (1) MCA occlusion and (2) MCA stenosis or occlusion (and other dichotomous variables) were evaluated by chi-square tests.

3. Results

3.1. Analysis of all strokes

A total of 861 patients were included in the study. Mean age of the study group was 61.1(±SD 15.5); 49.6% were men (see Table 1 for additional demographics). Analysis of the DWI images revealed that 414 (48.1%) had acute right hemisphere infarcts, 417 (48.4%) had acute left hemisphere infarcts and 30 (3.5%) patients had bilateral acute infarcts. Among the 861 patients, 232 (27%) had insular involvement and 629 (73%) had no involvement of the insula. Mean infarct volume was larger for infarcts including the insula versus excluding the insula: 65.8 ± 78.8 cm^3 versus 10.2 ± 15.9 cm^3; $t = -16.8$; $p < 0.0001$. Moreover, among infarcts in the 90th percentile for volume, 87% included the insula ($\chi^2 = 181.8$; $p < 0.0001$). Not surprisingly, because larger strokes are associated with more severe neurological deficits, patients with insular involvement had higher National Institutes of Health Stroke Scale (NIHSS) scores than those without insular involvement (7.1 ± 4.3 versus 2.8 ± 2.2; $t = -14.9$; $p < 0.0001$).

3.2. Subanalysis excluding lacunar infarcts

We repeated analyses after excluding lacunar infarcts, defined as, "round or ovoid lesion of increased signal relative to white or deep gray matter on DWI and hypointense on the apparent diffusion coefficient map, in the cerebral hemispheric white matter or basal ganglia or in the brain stem with greatest diameter < 20 mm" (from Potter et al., 2011, but without T2, FLAIR, or CT criteria). There were 85 patients with lacunar infarcts, who did not differ significantly from the total group with respect to age (mean age 61.4 ± 15.9) or other demographics, although there was a trend for lacunar infarcts to be more common among men ($\chi^2 = 3.2$; ns) and African Americans ($\chi^2 = 3.9$; ns; see Table 1). Of the 775 patients with non-lacunar stroke, 227 (29.3%) had insular involvement and 548 (70.7%) had no insular involvement. Mean infarct volume was larger for non-lacunar infarcts including the insula versus excluding the insula: 67.0 cm^3 ± 79.2 versus 11.5 cm^3 ± 16.7; $t = -15.8$; $p < 0.00001$. Still, among non-lacunar infarcts in the 90th percentile for volume, 87% included the insula ($\chi^2 = 137.5$; $p < 0.0001$).

3.3. Subanalysis of patients with vessel imaging

Data from the subset of 620 participants with magnetic resonance angiogram (MRA) or computed tomography angiogram (CTA) revealed that 62 (10.0%) patients had MCA occlusion and 63 (10.2%) had MCA stenosis. Among the 62 patients with occlusion of the MCA, 49 (79%) had insular infarcts and 13 (21%) had infarcts not involving the insula ($\chi^2 = 93.1$, df1, $p < 0.0001$; Table 2). Among the 63 patients with MCA stenosis, 29 (46.0%) had infarcts involving the insula and 34 (54.0%) had infarcts not involving the insula. Insular cortex involvement was also strongly associated with the presence of either MCA occlusion or stenosis ($\chi^2 = 114.7$, df2, $p < 0.0001$) (Table 3, Fig. 1).

Interestingly, the volume of infarcts was larger for patients with MCA occlusion compared to those without MCA occlusion, but *only* in patients with insular infarcts (Table 3). This finding should be considered preliminarily because there were only a small number of patients without insular infarcts who had MCA occlusion. But there was no trend for their infarcts to be larger than those of other patients without insular involvement. We can speculate that cases of MCA occlusion without acute insular stroke are those cases in which the occlusion has been gradual, and thus does not cause a large stroke.

We also evaluated whether or not there was any difference in the relationship between volume of infarct and MCA occlusion in left versus right hemisphere stroke, because earlier research has demonstrated a higher frequency of left MCA occlusion relative to right MCA occlusion (Hedna et al., 2013). Among left hemisphere strokes, 26/308 (8.4%)