SHORT REPORT

Insular cortical ischaemia does not independently predict acute hypertension or hyperglycaemia within 3 h of onset

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See Editorial Commentary, p 813

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Objectives: To test the hypothesis that insular cortical ischaemia is associated with acute hypertension and hyperglycaemia.

Methods: From the Canadian Activase for Stroke Effectiveness Study, which included only patients treated with thrombolysis hyperacutely (ie, within 3 h of onset of stroke), 966 patients were identified with ischaemia affecting (n=685), or sparing (n=281), the insular cortex. Demographic and clinical data, pretreatment indices of blood pressure, blood glucose, atrial fibrillation, and clinical imaging and outcome measures were compared between the two groups. Multivariable linear regression was used to assess predictors of systolic blood pressure and glucose levels before thrombolysis.

Results: Pretreatment hypertension (p=0.009), but not hyperglycaemia (p=0.32), was predicted by insular ischaemia in univariable linear regression analyses. After adjusting for other factors, however, insular cortical ischaemia was not found to be an independent predictor for acute hypertension or hyperglycaemia.

Conclusions: Raised blood pressure or serum glucose levels in hyperacute (<3 h) cerebral ischaemia is not independently predicted by insular involvement. Several hours are required for sympathetic manifestations of insular ischaemia to evolve.

Hypertension and hyperglycaemia are common manifestations of acute ischaemic stroke, affecting as many as 80% and 50% of patients, respectively, at the time of admission.¹ Although the aetiology of these changes is probably multifactorial, the insular cortex may have a role in the genesis of pathological sympathetic nervous system activation. Specific centres within the insula can alter blood pressure, heart rate and cardiac rhythm when stimulated,² transiently disabled with amobarbital,³ or lesioned experimentally.⁴ Patients with insular cortical infarcts subsequently have more frequent nocturnal rises in blood pressure, QT prolongations and cardiac arrhythmias, with concomitantly higher levels of norepinephrine compared with those with infarcts in other locations.⁵ Acute insular ischaemia, particularly right-sided ischaemia, has been associated with higher systolic and diastolic blood pressures, heart rate and plasma catecholamine levels at admission and over the subsequent 5-day period.⁶ Insular ischaemia may also be an independent predictor of acute stress hyperglycaemia.⁷ The timing of these changes is not entirely clear, as earlier investigations did not assess blood pressure and blood glucose levels hyperacutely (ie, <3 h from onset of stroke) in most patients.

We assessed whether insular cortical ischaemia was a predictor of elevated blood pressure and blood glucose levels within the first 3 h after onset of stroke in a large prospective cohort of patients with stroke who were subsequently treated with intravenous thrombolysis.

METHODS

Patients and study design

The Canadian Activase for Stroke Effectiveness Study was a prospective observational cohort study of all patients treated with alteplase at 60 centres in Canada between February 1999 and June 2001.⁸ In brief, baseline demographic characteristics, stroke characteristics and severity, interval times, baseline blood tests (including blood glucose levels), blood pressure and stroke risk factors were collected and outcome measures—modified Rankin Scale and the National Institute of Health Stroke Scale (NIHSS) score at discharge and at 90 days—were assessed. CT scans of the brain were graded at baseline and at follow-up by a three-person panel, according to a validated scoring system, the Alberta Stroke Program Early CT Score (ASPECTS).⁹ Insular ischaemia is one component of the ASPECTS (the “insular ribbon sign”) and corresponds to ischaemic oedema in any part of the insula. The whole insula may be affected, or simply a portion of the insular cortex. The diagnosis of insular ischaemia, for the purpose of this study, was based on the pretreatment CT scan and implies ischaemic change in any or all of the insular ribbon.

Statistical analysis

The data are illustrated by using descriptive statistics. Multivariable linear regression was used to assess the effect of insular ischaemia on pretreatment systolic blood pressure (SBP) and blood glucose levels. To identify predictors of SBP and glucose, a forward stepwise modelling approach was used, followed by confirmation with backwards elimination. The final model included all relevant variables, with the presence or absence of the insular ribbon sign and the pretreatment ASPECTS as forced variables. We assessed a potential interaction between insular ischaemia and side by using a simple interaction term. Univariable linear regression analyses were carried out using Fisher’s exact test and Student’s t test for binary and continuous variables, respectively. Traditional levels of significance were used at p<0.05. Statistical analyses were carried out with STATA V.8.0 software.

RESULTS

Data from 992 patients were available for study. We excluded 26 patients with bilateral or brain stem infarction. The insular ribbon sign was present in 685 (70%), and of those, 318 (46%) included the right hemisphere and 367 (54%) included the left hemisphere (table 1). No marked demographic or clinical differences were observed between those with and those without the insular ribbon sign, or between those with left-sided and those with right-sided involvement.

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; NIHSS, National Institute of Health Stroke Scale; SBP, systolic blood pressure

Table 1 Comparison between insular (right and left) and non-insular ischaemia

Variable	Hemisphere			Insular ribbon sign		
	Right (n = 318)	Left (n = 367)	p*	Present (n = 685)	Absent (n = 281)	p†
Demographic data						
Mean age (SD)	71 (13)	70 (13)	0.22	70 (13)	69 (14)	0.26
Sex (% male)	50.0	54.8	0.22	52.6	60.0	0.06
Caucasian (%)	84.0	82.8	0.42	83.4	89.0	0.42
Clinical data						
Diabetes (%)	17.0	15.4	0.59	16.1	12.7	0.22
Hypertension (%)	48.0	54.1	0.13	51.2	50.9	0.94
Ischaemic heart disease (%)	24.0	23.3	0.85	30.9	28.5	0.13
Baseline (pretreatment) data						
SBP (mm Hg)	159 (27)	159 (29)	0.87	159 (26)	154 (28)	0.009
DBP (mm Hg)	85 (16)	85 (18)	0.63	85 (17)	83 (15)	0.044
MAP (mm Hg)	110 (19)	109 (18)	0.70	110 (19)	106 (17)	0.010
Glucose (mmol/l)	7.7 (3.4)	7.3 (2.5)	0.08	7.5 (3.0)	7.3 (2.6)	0.32
Atrial fibrillation (%)	21.7	20.9	0.85	21.3	23.2	0.54
NIHSS score (median, IQR)	13 (9–17)	13 (8–19)	0.65	13 (8–18)	17 (13–21)	<0.001
ASPECTS >7 (%)	81.7	80.0	0.71	80.8	59.6	<0.001
Outcome data (90 days)						
Good outcome: mRS <2 (%)	34.9	44.7	0.01	40.1	25.9	<0.001

ASPECTS, Alberta Stroke Program Early CT Score; DBP, diastolic blood pressure; IQR, interquartile range; MAP, mean arterial pressure; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; SBP, systolic blood pressure.

Values are mean (SD) unless otherwise specified.

*Comparison between left and right insular ribbon signs.

†Comparison between patients with and without insular ribbon sign.

The insular ribbon sign was associated with significantly higher pretreatment systolic ($p = 0.009$), diastolic ($p = 0.044$) and mean arterial pressure ($p = 0.010$), but not pulse pressure or glucose level. Patients with insular infarcts had milder clinical deficits as assessed by the NIHSS, more favourable ASPECTS, and were more likely to be independent at 90 days ($p < 0.05$).

In multivariable analysis, the pretreatment NIHSS score principally confounded the association observed in univariable analysis. Age, history of hypertension and ischaemic heart disease were also confounders, but to a lesser degree. Age and history of hypertension were associated with higher pretreatment SBP. Ischaemic heart disease and higher NIHSS scores were predictors of lower pretreatment SBP. On excluding patients without a history of hypertension, ischaemic heart disease was no longer a predictor of the pretreatment SBP. The results for models examining diastolic and mean arterial pressures yielded similar findings. No interaction was observed between hemisphere side and the insular ribbon sign.

Neither univariable nor multivariable linear regression analyses disclosed a notable relationship between insular cortical ischaemia and pretreatment blood glucose levels, regardless of the hemisphere associated with it. Diabetes, pretreatment NIHSS score and pretreatment SBP were positive predictors of elevated blood glucose. No interaction was seen between hemisphere side and the insular ribbon sign. A trend toward higher glucose values was, however, seen among patients with right insular involvement ($p = 0.08$).

DISCUSSION

Insular cortical ischaemia was associated with raised blood pressure on univariable analysis but not on multivariable analysis, as the effect was confounded by age, history of hypertension and pretreatment stroke severity. Insular cortical ischaemia was also not a predictor of increased serum glucose levels. These results do not support earlier findings,^{6,7} despite attractive biological and anatomical reasons for such an association. Our findings suggest that sympathetic manifestations of insular ischaemia do not develop within the first 3 h poststroke but, rather, may require several hours to evolve.

One potentially important difference between our study and an earlier study showing an association with hyperglycaemia⁷ is the timing of glucose measurement. In our study, blood glucose was measured before alteplase treatment—that is, <3 h in most cases. By contrast, Allport and colleagues⁷ measured blood glucose later, with a median time of 7.5 h in those patients with insular infarcts and 13 h in those without. Blood glucose levels increase over the first 6–12 h after stroke and then gradually decrease.¹⁰ Insular ischaemia could conceivably potentiate this increase in blood glucose, peaking within several hours. Our blood glucose levels may have been relatively low, owing to earlier measurement.

Interestingly, insular cortical lesions were associated with better clinical (NIHSS score) and imaging characteristics (ASPECTS) before treatment as well as subsequent to outcome (modified Rankin Scale Score). One reason for this may be greater identification of isolated insular involvement compared with earlier studies.

Our study has important limitations. Because all patients were treated with alteplase, some patients with very high blood pressure refractory to treatment would have been excluded, potentially masking any association. Although we characterised parenchymal ischaemia by using ASPECTS, specific regional involvement of the insula was not described and may be relevant. Acute stress hyperglycaemia may result from involvement of the posterior or the entire insular cortex, but possibly not the anterior insular cortex.⁷

We conclude that insular involvement does not independently predict acutely raised blood pressure or serum glucose levels in hyperacute (<3 h) cerebral ischaemia.

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