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NEUROLOGY

COMMENTARY

Approximately 15% of ischemic strokes are preceded by a transient ischemic attack (TIA). The early estimated risk of stroke after a TIA is 8-12% at seven days and 11-15% at one month. A study from California done on the short-term prognosis of transient ischemic attacks revealed that in a 90-day period after a TIA, one in nine patients had a stroke and half of all the strokes occurred in the first 2 days. TIAs should be considered a neurologic emergency and a harbinger of stroke.

The EXPRESS and FASTER studies have yielded some interesting insights in the treatment of transient ischemic attacks. The EXPRESS study is a sequential population-based interventional study nested in the population of the OXVASC study such that the case ascertainment, investigation and follow-up were complete and identical in both cases. There were 1278 patients that were studied, those in the first phase had a delay in seeking medical care and those in the second phase were referred to a study clinic and received immediate attention and preventive care. The 90-day risk of recurrent stroke dropped from 10.3% to 2.1%. This reduction was independent of age and sex, and early treatment did not increase the risk of intracerebral hemorrhage. Although the second study FASTER - a 4x4 factorial design testing the intervention of clopidrogel loading plus simvastatin after TIA - failed to reach statistical significance of efficacy due to poor enrollment, it did demonstrate the safety of early treatment.

These two studies together demonstrate a relative risk reduction of 80-90% in the emergent risk of stroke by the prompt treatment of TIA. They merit our attention and a paradigm shift in our strategy for treating transient ischemic attacks is called for.

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Lancet. 2007 Oct 20;370(9596):1432-42.

Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JN, Lovelock CE, Binney LE, Bull LM, Cuthbertson FC, Welch SJ, Bosch S, Alexander FC, Silver LE, Gutnikov SA, Mehta Z; Early use of Existing Preventive Strategies for Stroke (EXPRESS) study.

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EFFECT OF URGENT TREATMENT OF TRANSIENT ISCHAEMIC ATTACK AND MINOR STROKE ON EARLY RECURRENT STROKE (EXPRESS STUDY): A PROSPECTIVE POPULATION-BASED SEQUENTIAL COMPARISON.

BACKGROUND: The risk of recurrent stroke is up to 10% in the week after a transient ischaemic attack (TIA) or minor stroke. Modelling studies suggest that urgent use of existing preventive treatments could reduce the risk by 80-90%, but in the absence of evidence many health-care systems make little provision. Our aim was to determine the effect of more rapid treatment after TIA and minor stroke in patients who are not admitted direct to hospital. **METHODS:** We did a prospective before (phase 1: April 1, 2002, to Sept 30, 2004) versus after (phase 2: Oct 1, 2004, to March 31, 2007) study of the effect on process of care and outcome of more urgent assessment and immediate treatment in clinic, rather than subsequent initiation in primary care, in all patients with TIA or minor stroke not admitted direct to hospital. The study was nested within a rigorous population-based incidence study of all TIA and stroke (Oxford Vascular Study; OXVASC), such that case ascertainment, investigation, and follow-up were complete and identical in both periods. The primary outcome was the risk of stroke within 90 days of first seeking medical attention, with

independent blinded (to study period) audit of all events. **FINDINGS:** Of the 1278 patients in OXVASC who presented with TIA or stroke (634 in phase 1 and 644 in phase 2), 607 were referred or presented direct to hospital, 620 were referred for outpatient assessment, and 51 were not referred to secondary care. 95% (n=591) of all outpatient referrals were to the study clinic. Baseline characteristics and delays in seeking medical attention were similar in both periods, but median delay to assessment in the study clinic fell from 3 (IQR 2-5) days in phase 1 to less than 1 (0-3) day in phase 2 (p<0.0001), and median delay to first prescription of treatment fell from 20 (8-53) days to 1 (0-3) day (p<0.0001). The 90-day risk of recurrent stroke in the patients referred to the study clinic was 10.3% (32/310 patients) in phase 1 and 2.1% (6/281 patients) in phase 2 (adjusted hazard ratio 0.20, 95% CI 0.08-0.49; p=0.0001); there was no significant change in risk in patients treated elsewhere. The reduction in risk was independent of age and sex, and early treatment did not increase the risk of intracerebral haemorrhage or other bleeding. **INTERPRETATION:** Early initiation of existing treatments after TIA or minor stroke was associated with an 80% reduction in the risk of early recurrent stroke. Further follow-up is required to determine long-term outcome, but these results have immediate implications for service provision and public education about TIA and minor stroke.

Lancet Neurol. 2007 Nov;6(11):961-9.

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FAST ASSESSMENT OF STROKE AND TRANSIENT ISCHAEMIC ATTACK TO PREVENT EARLY RECURRENCE (FASTER): A RANDOMISED CONTROLLED PILOT TRIAL.

BACKGROUND: Patients with transient ischaemic attack (TIA) or minor stroke are at high immediate risk of stroke. The optimum early treatment options for these patients are not known. **METHODS:** Within 24 h of symptom onset, we randomly assigned, in a factorial design, 392 patients with TIA or minor stroke to clopidogrel (300 mg loading dose then 75 mg daily; 198 patients) or placebo (194 patients), and simvastatin (40 mg daily; 199 patients) or placebo (193 patients). All patients were also given aspirin and were followed for 90 days. Descriptive analyses were done by intention to treat. The primary outcome was total stroke (ischaemic and haemorrhagic) within 90 days. Safety outcomes included haemorrhage related to clopidogrel and myositis related to simvastatin. This study is registered as an International Standard Randomised Controlled Trial (number 35624812) and with ClinicalTrials.gov (NCT00109382). **FINDINGS:** The median time to stroke outcome was 1 day (range 0-62 days). The trial was stopped early due to a failure to recruit patients at the prespecified minimum enrolment rate because of increased use of statins. 14 (7.1%) patients on clopidogrel had a stroke within 90 days compared with 21 (10.8%) patients on placebo (risk ratio 0.7 [95% CI 0.3-1.2]; absolute risk reduction -3.8% [95% CI -9.4 to 1.9]; p=0.19). 21 (10.6%) patients on simvastatin had a stroke within 90 days compared with 14 (7.3%) patients on placebo (risk ratio 1.3 [0.7-2.4]; absolute risk increase 3.3% [-2.3 to 8.9]; p=0.25). The interaction between clopidogrel and simvastatin was not significant (p=0.64). Two patients on clopidogrel had intracranial haemorrhage compared with none on placebo (absolute risk increase 1.0% [-0.4 to 2.4]; p=0.5). There was no difference between groups for the simvastatin safety outcomes. **INTERPRETATION:** Immediately after TIA or minor stroke, patients are at high risk of stroke, which might be reduced by using clopidogrel in addition to aspirin. The haemorrhagic risks of the combination of aspirin and clopidogrel do not seem to offset this potential benefit. We were unable to provide evidence of benefit of simvastatin in this setting. This aggressive prevention approach merits further study.

NEURORADIOLOGY

COMMENTARY

The first of this issue's selections tries to answer a seemingly unanswerable question. What to do with unruptured, incidentally-diagnosed intracranial aneurysms? There is general consensus that lesions greater than 10 mm should be treated but what of the smaller aneurysms? Gallas et al report their experience of endovascularly treating 321 unruptured aneurysms, the majority (76%) of which were under 10 mm in diameter. Although they conclude that endovascular treatment is "an attractive option for treatment of unruptured aneurysms," this is not supported by their reported morbidity of 14.4% with five deaths due to aneurysm perforation during the procedure. Of the 302 aneurysms for which follow-up was available, 85 were deemed either to be subtotally (n=80) or incompletely (n=5) treated. Even after this article the question of what to do with small incidental aneurysms remains unanswered.

Bendel et al writing in Radiology, on the other hand, provide yet more data that points to endovascular treatment having benefits over surgical options in aneurysmal subarachnoid hemorrhage. In a randomized cohort, the patients undergoing endovascular treatment had fewer MR abnormalities at one year, as compared to those having surgery. These changes correlated with performance on neuropsychological tests.

Laslo et al have pointed to the potential use of perfusion imaging in prognostication following subarachnoid hemorrhage. Using transit time analysis they were able to predict development of vasospasm in an animal model. If these data can be replicated in humans then this will be a novel way to assess vasospasm. And as opposed to transcranial doppler, there is low inter-observer variability with a high degree of reproducibility.

The final abstract also refers to the high degree of inter-observer reproducibility in most multi-detector CT studies. This time the target is carotid disease. Using standardized reporting, the authors were able to achieve a high degree of inter-observer agreement.

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FEASIBILITY, PROCEDURAL MORBIDITY AND MORTALITY, AND LONG-TERM FOLLOW-UP OF ENDOVASCULAR TREATMENT OF 321 UNRUPTURED ANEURYSMS

BACKGROUND AND PURPOSE: The purpose of our study was to evaluate the technical feasibility, morbidity and mortality, and durability of occlusion of unruptured aneurysms treated with Guglielmi detachable coils (GDCs) with a long-term follow-up. **MATERIALS AND METHODS:** Between January 1998 and January 2005, we treated 321 unruptured aneurysms with GDCs in 5 neuroradiologic institutions. During this period, 63% of unruptured aneurysms were treated by endovascular technique. Procedural feasibility, technical complications, morbidity and mortality, and acute and long-term angiographic occlusion were assessed. **RESULTS:** Overall technical feasibility of

coiling treatment was 94%; 302 aneurysms were treated by endovascular technique. At the end of the initial procedure, acute occlusion was classified as complete in 207 cases (70%), subtotal in 84 cases (26.1%), and incomplete in 11 cases (3.9%). Ischemic complications were observed in 28 patients (9%); 8 patients (2.6%) had perforation of their aneurysms. Treatment-related morbidity was 14.4%, and morbidity with clinical complications was evaluated at 7.7% (n = 23 patients). Five patients (1.7%) died as a result of aneurysm perforation. Final follow-up angiograms, after 9 secondary treatments, demonstrated complete occlusion in 193 patients (69.5%), subtotal in 80 aneurysms (28.5%), and incomplete occlusion in 5 (1.8%). Nineteen patients were lost to follow-up (6.3%). **CONCLUSION:** Endovascular coiling with detachable coils is an attractive option for treatment of unruptured aneurysms. This method of treatment is safe with a low rate of complications. Prospective studies with longer follow-up periods are needed to assess the long-term durability of occlusion in unruptured aneurysms.

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MR IMAGING OF THE BRAIN 1 YEAR AFTER ANEURYSMAL SUBARACHNOID HEMORRHAGE: RANDOMIZED STUDY COMPARING SURGICAL WITH ENDOVASCULAR TREATMENT

Purpose: To prospectively evaluate, with magnetic resonance (MR) imaging, long-term outcome of the brain after endovascular versus neurosurgical treatment for aneurysmal subarachnoid hemorrhage (aSAH). **Materials and Methods:** Institutional review board approval and informed consent were obtained. One hundred sixty-eight (77 men, 91 women; mean age ± standard deviation, 51 years ± 13) patients were randomly assigned to surgical versus endovascular treatment of the ruptured aneurysm with 138 (67 endovascular, 71 surgical) MR examinations 1 year after aSAH. The presence, localization, volumes, and cause of lesions were analyzed with 2, Mann-Whitney U, and Student t tests. Furthermore, correlation between MR-detectable brain parenchymal high-signal intensity (SI) lesions on T2- and intermediate-weighted MR images and neuropsychologic outcome was evaluated by using Spearman correlation coefficient. **Results:** Only 44 (31.9%) of 138 patients had no lesions associated with aSAH. According to intention to treat, lesions were more frequent after surgical rather than endovascular treatment, predominating in the frontal (surgical: n = 50, [70.4%] vs endovascular: n = 34 [50.7%], P = .018) and temporal (n = 34 [47.9%] vs n = 15 [22.4%], P = .002) lobes. Only endovascular patients had subtentorial lesions (n = 4 [6.0%], P = .037). Ischemic lesions in the parental artery territory were more frequent in surgical (n = 33 [46.5%]) than in endovascular (n = 15 [22.4%], P = .003) patients, with corresponding mean lesion volumes of 20.9 cm3 ± 46.5 versus 17.6 cm3 ± 35.8 (P = .209). Ischemic lesions in remote vascular territories were equal in frequency and size. Retraction injuries were common in the surgical (n = 40, [56.3%]) treatment group. Ischemic lesion volumes correlated with neuropsychologic test scores. **Conclusion:** Parenchymal high-SI lesions on T2- and intermediate-weighted MR images are more frequent after early surgical rather than endovascular treatment of the ruptured aneurysm, and lesion volumes correlate with the neuropsychologic test performance.

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CT PERFUSION-DERIVED MEAN TRANSIT TIME PREDICTS EARLY MORTALITY AND DELAYED VASOSPASM AFTER EXPERIMENTAL SUBARACHNOID HEMORRHAGE

BACKGROUND AND PURPOSE: There are limited indicators available to predict cerebral vasospasm in patients with subarachnoid hemorrhage (SAH). The purpose of this study was to determine if CT perfusion-derived hemodynamic parameters are predictors of vasospasm severity and outcome after experimental SAH. **MATERIALS AND METHODS:** SAH was induced in 25 New Zealand white rabbits. Cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) were measured with CT perfusion before SAH, within 1 hour after SAH, and on days 2, 4, 7, 9, and 16 after SAH. Basilar artery diameter, measured with CT angiography and neurologic scoring, was also obtained on the same days. Differences between animals with moderate-severe delayed vasospasm (24% basilar artery narrowing) and mild delayed vasospasm (<24% basilar artery narrowing) were investigated with repeated measures analysis of variance. Multiple linear regression analysis was used to investigate the relationship between CT perfusion parameters (CBF, CBV, MTT), basilar artery diameter, and neurologic score. **RESULTS:** MTT increase <1 hour after SAH independently predicted mortality within 48 hours of SAH ($P < .05$). MTT and neurologic deficits were significantly greater with moderate-severe than with mild vasospasm ($P < .05$). MTT on day 2, but not CBF or CBV, was a significant predictor of subsequent moderate-severe delayed vasospasm ($P < .05$). **CONCLUSION:** In the rabbit model of experimental SAH, the CT-derived hemodynamic parameter MTT on day 0 predicted early mortality, and MTT on day 2 predicted development of moderate-severe delayed vasospasm. MTT was also significantly correlated with arterial diameter and neurologic score.

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MDCTA OF CAROTID PLAQUE DEGREE OF STENOSIS: EVALUATION OF INTEROBSERVER AGREEMENT

OBJECTIVE. Atherosclerotic disease of the carotid arteries is one of the most important causes of stroke. Our objective was to evaluate the interobserver agreement in the measurement of the degree of carotid plaque stenosis by using MDCT angiography (MDCTA) and the effects produced using different window parameters and by the different types of plaque. **MATERIALS AND METHODS.** From June 2005 to June 2006, we retrospectively evaluated 215 patients (151 men, 64 women) who underwent MDCTA for the study of carotid arteries. In all patients we measured degree of stenosis, applying the criteria of the North American Symptomatic Carotid Endarterectomy Trial (NASCET). Each patient was studied independently by two observers. We used three window settings for the measurements. We grouped the measurements according to the type of plaque. Obtained data were then analyzed to calculate the interobserver agreement and the kappa value. **RESULTS.** Kappa values for the degree of stenosis evaluation were 0.696, 0.79, and 0.775 for window settings 1, 2, and 3, respectively. The best agreement was observed in the assessment of fatty plaque, whereas the presence of calcification produced disagreement. **CONCLUSION.** We observed a very good interobserver agreement in the evaluation of degree of stenosis using MDCTA with the application of specific visualization parameters. Our data suggested that MDCTA can provide reproducible values.

PSYCHIATRY

COMMENTARY

It is well known for some time that depression in the elderly increases the risk of mortality. Ryan et al have further explored this issue in terms of gender and antidepressant use. They showed that depressed males using antidepressants are at the highest risk of dying - the greater the severity of depression the higher the risk. In women severe depression was significantly associated with dying in the absence of treatment. This highlights the importance of treating depression in this age group.

Placebo and nocebo effects, the therapeutic and adverse effects, respectively, of inert substances, are of great interests to psychiatrists as several psychiatric illnesses have a placebo response rate as high as 40 % in randomized clinical trials. It has long been suspected that placebo response is not just a psychological phenomenon but has a neural basis. Scott and colleagues demonstrate that high placebo responses were associated with greater dopaminergic and opioid activity in the basal ganglia while nocebo responses were associated with a deactivation of dopamine and opioid release.

While the discovery of anti-dementia drugs has brought some temporary relief to some of the patients with dementia, by and large dementia remains a relentlessly progressive disease with death as the final outcome. Xie and colleagues show that after the onset of dementia the median survival time is 4.5 years. The survival time is slightly longer for women and is positively correlated with the age of onset of dementia, the earlier the onset the longer the survival time.

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LATE-LIFE DEPRESSION AND MORTALITY: INFLUENCE OF GENDER AND ANTIDEPRESSANT USE

Background Depression may increase the risk of mortality among certain subgroups of older people, but the part played by antidepressants in this association has not been thoroughly explored. Aims To identify the characteristics of older populations who are most at risk of dying, as a function of depressive symptoms, gender and antidepressant use. Method Adjusted Cox proportional hazards models were used to determine the association between depression and/or antidepressant use and 4-year survival of 7363 community-dwelling elderly people. Major depressive disorder was evaluated using a standardised psychiatric examination based on DSM-IV criteria and depressive symptoms were assessed using the Center for Epidemiological Studies-Depression scale. Results Depressed men using antidepressants had the greatest risk of dying, with increasing depression severity corresponding to a higher hazard risk. Among women, only severe depression in the absence of treatment was significantly associated with mortality. Conclusions The association between depression and mortality is gender-dependent and varies according to symptom load and antidepressant use.

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PLACEBO AND NOCEBO EFFECTS ARE DEFINED BY OPPOSITE OPIOID AND DOPAMINERGIC RESPONSES

CONTEXT: Placebo and nocebo effects, the therapeutic and adverse effects, respectively, of inert substances or sham procedures, represent serious confounds in the evaluation of therapeutic interventions. They are also an example of cognitive processes, particularly expectations, capable of influencing physiology. **OBJECTIVE:** To examine the contribution of 2 different neurotransmitters, the endogenous opioid and the dopaminergic (DA) systems, to the development of placebo and nocebo effects. **DESIGN AND SETTING:** Using a within-subject design, subjects twice underwent a 20-minute standardized pain challenge, in the absence and presence of a placebo with expected analgesic properties. Studies were conducted in a university hospital setting. PARTICIPANTS: Twenty healthy men and women aged 20 to 30 years recruited by advertisement. **MAIN OUTCOME MEASURES:** Activation of DA and opioid neurotransmission by a pain stressor with and without placebo (changes in the binding potential of carbon 11 [11C]-labeled raclopride and [11C] carfentanil with positron emission tomography) and ratings of pain, affective state, and anticipation and perception of analgesia. **RESULTS:** Placebo-induced activation of opioid neurotransmission was detected in the anterior cingulate, orbitofrontal and insular cortices, nucleus accumbens, amygdala, and periaqueductal gray matter. Dopaminergic activation was observed in the ventral basal ganglia, including the nucleus accumbens. Regional DA and opioid activity were associated with the anticipated and subjectively perceived effectiveness of the placebo and reductions in continuous pain ratings. High placebo responses were associated with greater DA and opioid activity in the nucleus accumbens. Nocebo responses were associated with a deactivation of DA and opioid release. Nucleus accumbens DA release accounted for 25% of the variance in placebo analgesic effects. **CONCLUSIONS:** Placebo and nocebo effects are associated with opposite responses of DA and endogenous opioid neurotransmission in a distributed network of regions. The brain areas involved in these phenomena form part of the circuit typically implicated in reward responses and motivated behavior.

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SURVIVAL TIMES IN PEOPLE WITH DEMENTIA: ANALYSIS FROM POPULATION BASED COHORT STUDY WITH 14 YEAR FOLLOW-UP.

OBJECTIVES: To provide estimates of survival after onset of dementia by age, sex, self reported health, disability, and severity of cognitive impairment. DESIGN: Analysis of participants from prospective population based cohort study in 1991-2003, with follow-up of dementia status in all individuals after two and six years (in one centre) and 10 years and in subsamples additionally at six and eight years and mortality until 2005. **SETTING:** Multicentre population based study in England and Wales: two rural and three urban centres. PARTICIPANTS: 438 participants who developed dementia from a population based study of 13 004 individuals aged 65 years and over drawn from primary care population registers. **MAIN OUTCOME MEASURES:** Sociodemographic factors, cognitive function, specific health conditions, and self reported health collected at each interview. Cox's proportional hazards regression models were used to identify predictors of mortality from the selected variables in people who received diagnosis of dementia according the study's criteria. **RESULTS:** By December 2005, 356 of the 438 (81%) participants who developed dementia during the study had died. Estimated median survival time from onset of dementia to death was 4.1 years (interquartile range 2.5-7.6) for men and 4.6 years (2.9-7.0) for women. There was a difference of nearly seven years in survival between the younger old and the oldest people with dementia: 10.7 (25th centile 5.6) for ages 65-69; 5.4 (interquartile range 3.4-8.3) for ages 70-79; 4.3 (2.8-7.0) for ages 80-89, and 3.8 (2.3-5.2) years for ages > or =90. Significant factors that predicted mortality in the presence of dementia during the follow-up included sex, age of onset, and disability. **CONCLUSION:** These analyses give a population based estimated median survival for incident dementia of 4.5 years. Such estimates can be used for prognosis and planning for patients, carers, service providers, and policy makers.