Heterogeneity of Association Between MTHFR and Stroke Among European Regions: Additional Population Studies Are Needed in Italy

To the Editor:

The recent meta-analysis of Cronin et al examined the association between the MTHFR C677T polymorphism, the strongest genetic determinant of moderate hyperhomocysteinemia, and ischemic stroke. These authors considered 31 studies, including 15 from Europe, and concluded for the existence of an overall weak association, as recently suggested by Lewis et al. Pezzini et al found a significant association between the MTHFR C677T polymorphism and ischemic stroke in Northern and Central Europe, whereas the MTHFR C677T polymorphism was surprisingly a significant risk factor for ischemic stroke in Italy. The same authors suggested that it was important to investigate whether this finding was attributable to population differences in T allele frequency, folate status, or other genetic or environmental influences. In fact, the frequency of MTHFR 677T allele is higher in Italy than in Central and Northern Europe, and the same gradient is observed for the dietary intake and status of folate. Therefore, the significant association observed by Cronin et al in Italy should be regarded as paradoxical if one considers that adequate folate dietary intake neutralizes the phenotypic influence of MTHFR on homocysteine. In fact, 2 of the 4 Italian populations that were included in the meta-analysis of Cronin et al were different for age and cause of stroke from those recruited in the other areas of Europe; this makes the paradox reported by Cronin et al questionable. Pezzini et al found a significant association of MTHFR 677T with patients with spontaneous cervical artery dissection (CAD), a very particular cause of stroke, but not with those with non-CAD ischemic stroke, whereas Gallai et al found no association in younger patients with spontaneous CAD. A third study found no association between 677TT genotype and stroke, whereas in another study, Margaglione et al found only a weak association with premature stroke (age <50), after multivariate adjustment (P = 0.0486). We have evaluated the association between MTHFR 677TT and ischemic cerebrovascular disease in 131 patients from Southern Italy (Sicily) with a mean age of 76.2 years (51.9% males), compared with 118 sex- and age-matched controls (mean age 75.9 years, P = 0.6032, 50.8% males, P = 0.8672). The 677T allele frequency was comparable in both groups (patients: 0.439 [95% CI, 0.380 to 0.499], controls: 0.432 [95% CI, 0.371 to 0.496]; P = 0.8798) and no difference of the 677TT genotype frequency was observed (patients: 0.229 [95% CI, 0.165 to 0.308], controls: 0.169 [95% CI, 0.112 to 0.247]; P = 0.2418). In our opinion, the small number of studies on the association between homocysteine or MTHFR and stroke needs to be increased, taking into consideration other nutritional and genetic determinants of homocysteine, folate and vitamin B12 metabolism: a common pathway in neural tube defect and Down syndrome? (Clin Chem Lab Med. 2003;41: 1473–1477).


Response:

We thank Dr Bosco and colleagues for their interest in our study. Although subgroup analyses of meta-analyses of stroke risk associated with genetic polymorphisms may yield useful hypotheses-generating information for future studies, we again caution that such analyses should be considered exploratory and that the lower numbers within individual subgroups may lead to loss of power. As outlined in our original publication, our subgroup analyses further included studies which reported the association of MTHFR TT genotype only when compared with a combined CT and CC genotype control group, from which allele-specific information could not be gleaned for the overall allele-dose analysis. In addition to those 4 studies outlined above, our Italian group further included a population from Soriente et al. In total, there were 523 cases and 1507 controls from Italy. Of these cases, only 50 (9.5%) had spontaneous cervical artery dissection as the underlying stroke mechanism. When these are excluded,
the risk estimate for ischemic stroke associated with the MTHFR TT genotype in the Italian subgroup is 1.24 (95% CI, 0.96 to 1.61), which is consistent with our findings in the overall group. We agree that there is a need for further study in individual racial and ethnic subgroups.

We further suggest that future analyses of stroke risk associated with the 677T allele should detail their findings in the context of stroke mechanism and serum homocysteine and folate levels. Because of few reports of folate levels and stroke subtype, it was not possible from available data to fully examine their influence on individual populations under study. Our overall findings in almost 15 000 subjects suggest a modest elevation of risk for MTHFR T allele homozygotes and heterozygotes. We agree that large prospective population-based studies and clinical trials in homocysteine-lowering therapies are needed to definitively resolve the relationships between 677T allele, homocysteine, and vascular risk. Pending the availability of such data, meta-analyses remain a useful, albeit imperfect, approach to addressing some of the limitations of smaller retrospective studies. We await the results of ongoing trials with interest.

Simon Cronin, MB, MRCPI
Peter Kelly, MD, MS, MRCPI
Neurovascular Clinical Science Unit
Department of Neurology
Mater Misericordiae University Hospital
Dublin, Ireland

There Is More to it Than: The Greater the Infarction Volume, the More Probable Is a Malignant MCA Infarction

To the Editor:

In Stroke, we read with great interest the original article by Serena et al1 on prediction of malignant middle cerebral artery (MCA) infarction. As a group working experimentally and clinically on malignant MCA infarction,2–4 we would like to comment on their competent study on molecular brain barrier disruption markers in patients who developed a malignant MCA infarction, because their work establishes a new point of view in the understanding of this life-threatening disease.

The approach of Serena and colleagues to detect matrix metalloproteinases (MMPs) and basal lamina decomposition products like cellular fibronectin in plasma of patients allows a precise prediction of malignant MCA infarction.1 Cerebral ischemia leads to an up-regulation of MMPs, which degrade quite precise prediction of malignant MCA infarction.1 Cerebral ischemia leads to an up-regulation of MMPs, which degrade products like cellular fibronectin in plasma of patients allows a precise prediction of malignant MCA infarction. We should recognize, however, that in individual cases presented in these studies, a similar size of infarction resulted in completely different clinical courses highlighting the fact that a simple monoscalar relationship does not exist for the development of malignant MCA infarction and that inter- or even intra-individual variations need further mechanistic explanations. High levels of MMPs and of related substrates were thought to play a key role for such secondary deterioration,8 and in this respect, the work of Serena and colleagues is a promising step.

For a more comprehensive understanding of the pathophysiology of malignant MCA infarction, however, we think that direct, simultaneous measurements in extracellular fluid, cerebrospinal fluid and plasma are needed. In particular, the analysis of extracellular fluid would provide information about the extracellular matrix as the relevant location where MMPs generate their enzymatic activity. Furthermore, MMP-9 is produced by astrocytes as well as endothelial cells, and both glial and endothelial MMP-9 are thought to be responsible for BBB damage.13,14 Combination with microdialysis might provide the chance to get simultaneous information at the parenchymal and vascular side of the basal lamina.

We need longitudinal information on MMPs and related substrates. It is possible that processes at the parenchymal and at the vascular side of the basal lamina follow different time scales. Thus, the origin of substrate alterations detected in plasma remains unclear. The comparison with alterations in the extracellular fluid detected by cerebral microdialysis4,15 might help here, too. More importantly, longitudinal information on extracellular fluid and plasma concentration would also offer the chance to detect slower courses of malignant transformation in individual patients and thus provide the chance for treatment options like hemicraniectomy in these individuals. In this context, complementary translational research with animal models of malignant stroke would be valuable because we could compare with preschismic baseline levels of relevant substances.

Bert Bosche, MD
Max-Planck-Institute for Neurological Research
Cologne, Germany
Department of Neurosurgery
University of Cologne
Germany

Gerhard F. Hamann, MD
Department of Neurology
Dr.-Horst-Schmidt-Hospital
Wiesbaden, Germany

Ludwig-Maximilians-University
Munich, Germany

Christian Dohmen, MD
Rudolf Graf, PhD
Max-Planck-Institute for Neurological Research
Cologne, Germany


Response:
We are grateful to Drs Bosche, Graf, Dohmen and Hamann for the interest shown in our article. We agree that further studies focusing on both the comparison of molecular markers obtained simultaneously in extracellular brain tissue by microdialysis and peripheral blood samples as well as longitudinally obtained data regarding matrix metalloproteinases (MMPs) and related substrates are needed. We supply some information concerning this second point.
As in the studies cited by the authors, we too found that similar infarct volume resulted in very different clinical courses and so agree that better predictors of malignant MCA (m-MCA) infarction are needed. The analysis of extracellular fluid by microdialysis in experimental studies together with plasma samples would provide additional and useful information in clinical practice, particularly considering that microdialysis is not a suitable technique in clinical practice and could only be conducted in animal models or, possibly, after a hemicraniectomy has been performed with a prior decision, which rather defeats the object. Unfortunately, the study of cerebrospinal fluid before hemicraniectomy is not recommended in patients with massive brain infarction because of the risk of herniation.

Temporal profile of MMP-9 and its substrate c-Fn in the whole population with acute ischemic stroke of <12 hours evolution (upper graphs) and with massive MCA infarction (lower graphs) divided in those whose finale did or did not develop an m-MCA infarction.
Intra-arterial Thrombolysis in Late Pregnancy

To the Editor:

Johnson et al injected a limited amount of recombinant tissue plasminogen activator (r-TPA) in the middle cerebral artery of a 37-week pregnant woman with left acute ischemic stroke. The middle cerebral artery did not reopen. On the final angiogram, an efficient collateral circulation through posterior cerebral artery, not seen on the preoperative angiogram, filled the peripheral branches of the occluded middle cerebral artery. The patient rapidly improved, and no adverse effects of the procedure were observed.

We congratulate the authors for rapid diagnosis, excellent therapeutic approach and good final results, but we deeply disagree with the interpretation of angiographic pictures. Figure 1 (preoperative) and Figure 2A (postoperative) express exactly the same pattern of collateral circulation toward peripheral middle cerebral artery, the sole difference being the phase, early and late arterial, respectively. In effect, some thin branches of middle cerebral artery filled by leptomeningeal collaterals are already seen in Figure 1. In other words, collateral circulation may be similar pre- and postoperatively. In Figure 2B the main branches of the anterior cerebral artery are still injected, whereas posterior cerebral artery is not. This is the typical angiographic pattern of a posterior cerebral artery filled both from anterior and posterior circulation: the pressure wave of the contrast injection in carotid artery partially fills the posterior cerebral artery. Once the pressure wave of the injection is past, contrast is rapidly washed out from fresh blood of posterior circulation. Visualisation of the posterior cerebral artery depends on the pressure of the injection and on the position of the catheter. The alternative hypothesis suggested by Johnson et al of an asymptomatic thrombus occluding posterior communicating artery at its origin, dissolved by 15 mg of r-TPA injected in the middle cerebral artery, seems less realistic. Improvement may be explained by natural history of the middle cerebral artery occlusion, frequently going toward rapid improvement with limited basal ganglia infarctions, possibly helped by the systemic action of r-TPA. Anyway, the behavior of the authors was absolutely correct, because it was based on the clinical and not on the angiographic improvement. In similar cases a mechanical embolectomy may represent a less risky alternative.

Response:

I want to thank Drs Bergui and Bradac for their interest in our article and their kind words regarding our management. I am pleased to report the patient and her child continue to do well.

The writers suggest that the patient’s clinical improvement may have been an example of the natural history of resolving middle cerebral artery (MCA) occlusion with residual basal...

Figure 1. Angiogram. Right common carotid artery (RCCA) arterial phase. Lateral. Pretreatment RCCA angiogram shows nonfilling of the PCOM and nonfilling of the parietal and temporal MCA branches.
Hinchey and the Stroke Practice Improvement Network Investigators are to be commended for managing a major multi-site collaborative effort that has compiled a dataset demonstrating current practice in 15 institutions. However, this report is attended by all the usual limitations of this sort of study—dependence on routine documentation rather than evidence of actual practice, in some cases retrospective data extraction, pooling of data from diverse population groups, and an endeavor to identify significant factors among a host of variables which may potentially explain subgroup differences in outcomes.

In this instance, these problems are reflected in significantly different age and ethnicity profiles between clusters of sites, poor completion of key data fields, limited inter-rater reliability of data extraction for crucial variables, and presentation of selected information. Particular problems for this study included limited capture of stroke severity data, very broad definitions of what constitutes dysphagia screening, no information whether screening was performed before oral intake commenced in 25% of patients, and no data regarding duration for which patients were kept nil orally. There is also no consideration of the composite nature of the screened and nonscreened groups; both will have contained a mix of dysphagic and nondysphagic patients, and screening nondysphagic patients is unlikely to have affected pneumonia rates. Although many of these difficulties are acknowledged by the authors, they nonetheless claim a causal relationship, in the title and text, between use of dysphagia screening and reduced aspiration rates. This disregards their comparison of sites according to levels of guideline compliance (ie, a package of “best practice” care management). Given their reportage of only 1 of their 4 selected “quality indicators”, we have no idea of other, potentially equally significant discrepant aspects of care.

This study has much to commend it as a means to support local practice development, but its contribution to the body of knowledge is as further corroboration of the merits of adherence to evidence-based guidelines. It is neither unique in this field, (see for example Duncan et al3) nor this area (eg, Perry and McLaren4). What it does not do is demonstrate that formal dysphagia screening reduces incidence of pneumonia; there are many other aspects of care within guideline-compliant management that may contribute to this. Dysphagia screening is an essential yet not sole contributor to this outcome, but this study does nothing to unpack what other key components may be.

Once again, we have another study that shows much of current practice as substandard (for example, only 6 of 11 hospitals with Stroke Units had formal screening protocols), that indicates that we could achieve better outcomes for patients, including by use of dysphagia screening, but without fully investigating what may be required to accomplish this.

David M. Johnson, MD
David C. Kramer, MD
Mount Sinai Medical Center
Department of Anesthesiology
New York, NY

Formal Dysphagia Screening Protocols Prevent Pneumonia

To the Editor:

Hinchey and the Stroke Practice Improvement Network Investigators1 are to be commended for managing a major multi-ganglia infarction. They disagree with our interpretation that improved collateral circulation to the MCA territory accounted for the clinical improvement. These writers offer a valid criticism because the few images published do not clearly depict this change in circulation.

During the thrombolysis itself, we observed the first appearance of the posterior communicating artery (PCOM) and posterior cerebral artery (PCA), and, with that, we saw improved collateral circulation to the MCA via PCA-MCA leptomeningeal collaterals (Figures 1 and 2). The prethrombolysis image (Figure 1) shows nonfilling of the PCOM, with nonfilling of the parietal and temporal branches of the MCA. The postthrombolysis image (Figure 2), at comparable angiographic phase, using similar injection parameters, shows the first filling of the PCA with concurrent improved filling of additional parietal portions of the MCA territory.

These more complete images demonstrate that the differences in MCA collateral filling result from the improved PCA circulation, not from the differences in angiographic phase as suggested by the writers. One can never know whether the treatments given result directly in patient improvement, assist the patient in the natural process of healing, or occur contemporaneously with, but coincident to, spontaneous healing. We can only hope our efforts did contribute to the good outcome for this patient and her child.

Figure 2. Angiogram. RCCA arterial phase. Lateral. Postthrombolysis RCCA angiogram now shows filling of the PCOM, PCA and parietal branches of the MCA (arrows).
PUBLISHING REHABILITATION RANDOMIZED CONTROLLED TRIALS

To the Editor:

The Stroke Rehabilitation Evidence-Based Review (SREBR) is the most comprehensive and current review of the stroke rehabilitation literature. The website is www.ebrsr.com. Our systematic review found 452 randomized controlled trials (RCTs) of interventions directly related to stroke rehabilitation. We have listed the 10 journals with the most published RCTs in the area of stroke rehabilitation (Table). Stroke has the greatest number of RCTs directly related to stroke rehabilitation.

Robert W. Teasell, MD, FRCP C
Jeffrey Jutai, PhD
Katherine Salter
Norine Foley, MSc (Candidate)
Department of Physical Medicine & Rehabilitation
St. Joseph’s Health Care London
University of Western Ontario
London, Ontario

JournaLS PUBLISHING RCTs in STROKE ReHABILITATION

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Response:

We are delighted that Stroke leads in publishing randomized clinical trials in rehabilitation. This reaffirms our commitment of being a comprehensive stroke journal where the best in every discipline is published.

We continue to look forward to receiving the highest quality manuscripts, enabling Stroke to become the stroke journal of choice.

Vladimir Hachinski, MD, DSc
Editor-in-Chief
Stroke Editorial Office
London, Ontario, Canada

CATARACT SURGERY AFTER ACUTE STROKE: MAYBE MORE THAN A COINCIDENCE

To the Editor:

Cataract and stroke are 2 common pathologies in the elderly population. The need of cataract surgery in the UK approximates 200 000 a year, and >2.4 million people aged over 65 experienced cataracts with visual impairment in 1 eye or 2. This number increases by 1.1 million over a 5-year period.1 About 5% of patients undertaking cataract surgery reported a past history of stroke.2 Most stroke patients experience various levels of functional impairment which may, on the one hand, limit them from having cataract surgery, but, on the other hand, they may have a stronger drive to improve their visual acuity after stroke.

Liang-Kung Chen, MD
Department of Clinical Geratology
University of Oxford
Oxford, UK

Alastair Mitchell Buchan, MD
Department of Family Medicine
Taipei Veterans General Hospital
National Yang Ming University
School of Medicine
Taipei, Taiwan

Shinn-Jang Hwang, MD
Department of Family Medicine
Taipei Veterans General Hospital
National Yang Ming University
School of Medicine
Taipei, Taiwan
Potential Role for TCD-Directed Antiplatelet Agents in Symptomatic Carotid Artery Dissection

To the Editor:

We read with interest the debate regarding the role of anticoagulation in extracranial arterial dissection. We agree with Norris that arterial embolism is the most likely cause of stroke, and also agree with Lyer that there is no evidence supporting anticoagulation for extracranial internal carotid artery dissection (CAD). Donnan and Davis make a most important contribution when they differentiate between the use of antithrombotic agents and antiplatelet agents in CAD.

The commonest mechanism of stroke in carotid artery dissection is hypothesized to be artery to artery embolism. If this hypothesis is correct, then the situation would appear to be analogous to transient ischemic attacks arising from a critical internal carotid artery stenosis. Transcranial Doppler (TCD)-directed intravenous antiplatelet agents have been successful in treating these patients both before and after elective surgery. In further support of this hypothesis, we have recently reported a 45-year-old patient who was successfully treated with TCD-directed antiplatelet agents for recurrent focal deficits associated with an embolizing subintimal CAD.

Converging lines of evidence suggest that embolization from large arteries can cause focal cerebral symptoms and can be treated in the short-term with TCD-directed antiplatelet agents. TCD can rapidly and noninvasively assist both in identifying those patients at higher risk of a subsequent neurological event, and in assessing the efficacy of interventions. TCD emboli detection appears to offer an important advance, enabling the optimal integration of both medical therapy and the timing of any surgical intervention, in patients with symptomatic large-vessel disease. We advocate TCD interrogation of the middle cerebral artery for microemboli in symptomatic CAD, particularly where there are fluctuating neurological signs. TCD-directed antiplatelet agents could then be used to control cerebral microemboli and symptoms. Elective surgical or endovascular intervention can then be considered where appropriate.

Christopher H.E. Imray
Coventry and Warwickshire County Vascular Unit
Coventry and Warwickshire Hospitals
Coventry, UK

Magnetic Resonance Direct Thrombus Imaging in Moderate Carotid Artery Stenosis

To the Editor:

Wasserman et al prove a proof-of-concept case elegantly demonstrating that high-resolution MRI of carotid plaque can identify a lesion that was highly likely to be causing cerebrovascular symptoms even though it was not causing significant stenosis of the carotid lumen. The authors also acknowledge that acquiring high-resolution MR images is time-consuming and requires the injection of contrast.

We are interested in using MR techniques to find features of carotid artery plaque related to its biological behavior, rather than simply the degree of stenosis caused by it. We have explored magnetic resonance direct thrombus imaging (MRDTI) on the basis that thrombus associated with plaque is likely to be important in disease progression and not a crucial final step before plaques give rise to cerebrovascular symptoms. MRDTI takes only 5.5 minutes to acquire, and no contrast is required, making it potentially more easy to use than high-resolution MRI. MRDTI is sensitive and specific for complicated plaque in symptomatic patients with >70% stenosis coming to carotid endarterectomy. We are currently undertaking a longitudinal study of MRDTI in symptomatic patients with lesser degrees of carotid stenosis who, in our center, are not routinely offered carotid endarterectomy. We present the following case from our series which illustrates how this technique, like high-resolution MRI, can be clinically valuable.

Mr G was a 68-year-old man who had 2 episodes of loss of power affecting his right arm in September 2002. Duplex ultrasound (undertaken 10 days after the event) showed 30% to 50% stenosis of the right internal carotid artery. He was managed medically and commenced on an antiplatelet, a statin and an angiotensin-converting enzyme inhibitor. MRDTI was positive in the right internal carotid artery (Figure). In March 2004, he developed sudden weakness of the left arm and leg. An MRI scan the same day showed a stenosis of 60% to 70%, and the MRDTI was again positive in the right carotid artery.
He successfully underwent endarterectomy and has had no further symptoms to date. Histology of the endarterectomy specimen demonstrated a ruptured plaque with intraplaque hemorrhage.

We postulate that MRDTI of his carotid artery plaque identified symptomatic disease, even though the degree of intraluminal stenosis was below our usual threshold for surgery. MRDTI provides a feasible alternative to high-resolution MRI for this purpose, although we note that the findings of longitudinal studies such as ours are needed.

**Acknowledgments**

This study was supported by the Healthcare Foundation, UK.

Lucy R. Daniels, MRCP  
John R. Gladman, FRCP  
Department of Rehabilitation and Ageing  
University of Nottingham  
Queen’s Medical Centre  
Nottingham, UK

Nishath Altaf, MRCS  
Department of Vascular Surgery  
University of Nottingham  
Queen’s Medical Centre  
Nottingham, UK

Alan R. Moody, FRCR  
Department of Radiology  
Sunnybrook and Women’s College Health Sciences Centre  
Toronto, Ontario, Canada


Hyperintense signal in MRDTI scans of the right carotid artery. The coronal view (A) shows both carotid arteries (thin arrows) and a hyperintense signal (thick arrow) in the plaque of the right carotid artery. The axial view (B) orientated through the carotid bifurcation shows eccentric hyperintense signal (arrow) in the right internal carotid artery.
Cataract Surgery After Acute Stroke: Maybe More Than a Coincidence
Liang-Kung Chen, Alastair Mitchell Buchan, Shinn-Jang Hwang and Janice Hinkle

Stroke. 2006;37:766-767
doi: 10.1161/01.STR.0000204088.04384.74
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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