MATTERS ARISING

MRI in monitoring the treatment of multiple sclerosis: concerted action guidelines

We would like to comment on the article by DH Miller *et al.*[1]

At the University of British Columbia, (UBC) we have been involved in serial MRI evaluations of multiple sclerosis (MS) since 1985. We originally did our serial MRI evaluations without the use of gadolinium and at present we are using gadolinium in selected cases. Dr Miller and his colleagues at Queen Square have done elegant studies both with and without gadolinium to detect activity of MS lesions by using MRI.

There is no doubt that gadolinium can show breakdown of the blood brain barrier (BBB) in new and enlarging MS lesions. Gadolinium may even show BBB impairment in some old lesions in which no changes can be seen on the standard unenhanced scans. In Dr Miller's experience this occurred in 10% of the instances. Conversely, the percentage of active lesions seen on serial unenhanced scans, but missed on gadolinium enhanced scans, is higher. Dr Miller *et al* have shown that in patients with a secondary progressive and early relapsing remitting MS, about 20% of new lesions did not enhance. In patients with benign MS and primary progressive MS, this percentage is even higher (67% and 95% respectively). They have also shown that in 25% of enhancing lesions the enhancement persisted for less than 4 weeks. Therefore one might miss detecting activity in up to 25% of lesions with a 4 weekly scanning interval. We have found using a low field strength unit at UBC (0·15 Tesla), and without gadolinium, that only 67% of active lesions were identified if the scanning interval is 4 weeks rather than 2 weeks. If the scanning interval is 6 weeks, only 40% of the active lesion is identified. Our experience therefore suggests to us that to maximise detection of MS lesions on MRI, scanning at shorter intervals will allow for a higher detection rate. The savings in time and cost incurred by not doing gadolinium enhanced scans could then be applied to scanning the patient more frequently, obviously within the limits of patient tolerance. A single set of multi-echo T2 weighted transverse images carefully repositioned is all that is required to monitor the morphological changes that we see. To perform gadolinium studies, two additional T1 weighted spin echo sequences are required. The imaging time is therefore increased at least two fold.

The addition of gadolinium on a routine basis also increases the invasiveness of the procedure. Not only must material that is potentially harmful be injected (there are rare reports of anaphylaxis) but patients also report discomfort from the injection. Our patients in Vancouver have complained of headaches and other transient symptoms related to the injection of gadolinium. Fortunately we have not had any serious side effects. Nevertheless, patients are probably more willing to be scanned at more frequent intervals if an injection is not required.

Those of us at UBC who have been doing serial MRI evaluations for many years feel therefore that for routine clinical trial evaluation purposes, frequent unenhanced scans will suffice. However, if one is doing a study in which evaluation of the immediate therapeutic effect on leakage of the BBB is an important endpoint, then gadolinium must, of course, be used.

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1 Miller DH, Barkhof F, Berry I, *et al.* Magnetic resonance imaging in monitoring the treatment of multiple sclerosis: Concerted Action Guidelines. *J Neurol Neurosurg Psychiatry* 1991;54:683–8.
2 Paty DW. Trial measures in multiple sclerosis: the use of magnetic resonance imaging in the evaluation of clinical trials. *Neurology* 1988; 38(suppl 2):82-3.

Miller et al reply:

We welcome the comments of Professor Paty and his colleagues, whose MRI studies have contributed much to our understanding of the natural history of MS and of the use of MRI in diagnosing and monitoring the disease. We agree with Paty that frequent serial unenhanced T2-weighted brain MRI is a powerful tool in monitoring MS treatment trials, and we also recommend that it is performed on every occasion.[1]

Nevertheless, MRI monitoring has its limitations. One is the marked variation in MRI activity both between and within patients over time, implying that substantial numbers may have to be studied. It is therefore appropriate to develop strategies which maximise the information gained. The addition of gadolinium enhancement to unenhanced MRI substantially increases the amount of MRI-detected activity in early relapsing-remitting and secondary progressive MS.[2–4]

Another limitation is the low pathological specificity of MRI. On unenhanced scans, oedema, inflammation and gliosis all produce similar signal changes. An added benefit of gadolinium enhancement is that it identifies the active, inflammatory MS lesion, and may give some indication of the mode of action of the drug under study. The risk of anaphylaxis from gadolinium-DTPA, although remote (about 1/100 000), should always be discussed with patients when obtaining informed consent. In our experience, the minor side effects referred to by Paty have been both rare and nontroublesome.

Finally, we agree that patient compliance is essential to a successful study, and it might be argued that a 40 minute monthly scan is more acceptable than a 20 minute fortnightly scan.

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1 Miller DH, Barkhof F, Berry I, *et al.* Magnetic resonance imaging in monitoring the treatment of multiple sclerosis: Concerted Action Guidelines. *J Neurol Neurosurg Psychiatry* 1991;54:683–8.
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3 Bastianello S, Pozzilli C, Bernadi S, *et al.* Serial study of gadolinium-DTPA MRI enhancement in multiple sclerosis. *Neurology* 1990; 40:591–5.
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The prognosis of primary intracerebral tumours presenting with epilepsy: the outcome of medical and surgical management.

We welcome the paper by Smith *et al*[3] which attempts to address the question of effectiveness of resective surgery in intrinsic brain tumours presenting with epilepsy as the first symptom. We agree that it is important to consider the timing of surgery in this group of patients, but definitions of "early" and "late" in this context have not yet been agreed. There are, however, a number of methodological problems posed in this paper, which we think do not allow the correct comparisons to be made.

First, a definition of "resective surgery" is not provided, consequently, no distinction is made between "total" versus "subtotal" resection. This comparison was a significant prognostic factor reported by Laws *et al.*[1] Thus, it is not the extent of surgery which is important as suggested in the author's discussion, but whether the tumour is considered to be totally removed or not. Unfortunately, the authors fail to make this important distinction.

Second, no direct comparison of duration of survival is made between "resective" surgery versus "non-resective" surgery in the first symptom epilepsy group, who demonstrated a non-enhancing CT scan lesion associated with a low grade tumour at the time of surgery. This is an important comparison, because it is likely that patients presenting with epilepsy who are found to have non-enhancing lesions on CT scan will have low grade tumours.[4] Depending on their site in the brain, some non-enhancing CT, low grade tumours are likely to be totally resectable. Previous studies of low grade tumours have demonstrated that non-enhancing CT lesions and total resection both carry a better prognosis.[1 2]

Presumably these important comparisons were not made, because the number of first symptom epilepsy group undergoing any form of surgery was 65, and only 20 had any type of resection. Subdivision into patient's suffering from low-grade tumours demonstrated as a non-enhancing lesion on CT scan, who had surgery compared with those that did not; and those that had "total" versus "subtotal" resection with this type of lesion, would probably have resulted in numbers too small for statistical comparisons to be made.

This paper illustrates the problem of trying to use data from a single centre in order to make definitive management policies. It emphasises the importance of considering collecting a national data base to pose the important questions raised by the authors of this paper.

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1 Laws ER, Taylor WF, Clifton MB, Okazaki H. 61. Neurosurgical management of low grade

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3 Smith DF, Hutton JL, Sandermann D, Foy PM, Shaw MDM, Williams IR, Chadwick DW. The prognosis of primary intracerebral tumours presenting with epilepsy: the outcome of medical and surgical management. *J Neurol Neurosurg Psychiatry* 1991;**54**:915–20.
4 Wilden JN, Kelly PJ. CT computerised stereotactic biopsy for low density CT lesions presenting with epilepsy. *J Neurol Neurosurg Psychiatry* 1987;**50**:1302–5.

D Smith et al reply:

We thank Mr Wilden for his interest in this article. Whilst recognising minor problems with some of our definitions, we would like to emphasise that this was a retrospective study which generates a simple hypothesis demanding prospective testing.

We agree that definitions of "early" and "late" surgery have not been agreed upon and that our own definitions, of necessity, are somewhat arbitrary. They do, however, allow the essential differentiation between those patients receiving surgery soon after diagnosis and those in whom surgery is delayed until a change in clinical status occurs. Furthermore, by using an intention to treat analysis, we avoided bias against the effectiveness of surgery as a whole by excluding patients whose surgery was performed because of neurological deterioration.

With regard to the type of surgery—resective surgery refers to procedures which involve debulking of the tumour and non-resective to biopsy or drainage of cysts. As Mr Wilden states, we have not subdivided resective surgery according to whether or not the surgeon considered the resection to be complete or partial. However, this information is difficult to obtain from a retrospective review of case notes and is not likely to be reliable. Furthermore, whilst accepting that this issue may be relevant in a minority of patients, with well circumscribed temporal or frontal lobe tumours, it is well recognised that resections "considered" to be total macroscopically are rarely confirmed on histopathological specimens, and many pragmatic neurosurgeons would concede that total excision of infiltrative gliomas, often involving more than one lobe, is not possible.

Mr Wilden has answered his second query himself. We would, however, like to emphasise that it was never our intention to conduct sub-group analyses, in small numbers of patients, and it is well known that such analyses on retrospective data yield unreliable results that are very difficult to interpret.

His final remarks merit two comments. Firstly, we would like to reiterate that we made every effort not to over-interpret our data and our intention was simply to generate a testable hypotheses and certainly not the development of "definitive management policies". Secondly, we must take issue with Mr Wilden's comments on the need for a national database derived from individual centres inevitably employing different treatment regimens. Data collected in this way would not allow development of satisfactory management policies and the necessary information can only be obtained, as we state clearly in our final paragraph, from a well designed, multi-centre, prospective randomised trial comparing conservative and aggressive management policies.

Extracranial vertebral artery dissection

We would like to make several comments about the recent report by Hinse *et al*[1] on extracranial vertebral artery (VA) dissection:

1) This article is based on 4 personal cases and a review of 53 published cases. However, several published reports, including 2 recent studies[2 3] on a total of 38 cases, are not quoted, which may give the impression that VA dissection is rare. In 1988, Hart[4] estimated that nearly a hundred cases of VA dissections had appeared in the English language literature in the past decade and that between 0·5 and 2·5 cases per year were reported from large referral-based hospitals.

2) We have come to similar conclusions in our own work on the subject[2] regarding symptoms and prognosis of this disorder. The authors, however, do not mention in their discussion that VA dissection may be asymptomatic and possibly discovered when exploring a concomitant carotid artery dissection.[2] They point out that there is a high incidence of bilateral VA dissection but do not mention the possibility of simultaneous occurrence of vertebral and internal carotid artery dissections, which is not infrequent particularly in patients with spontaneous dissection.[2 3] The frequency of multivessel dissection implies that four-vessel exploration (by angiography or other method) should always be attempted if a VA dissection is demonstrated.

3) The diagnosis of dissection relies classically on angiography, which reveals irregular stenosis, pseudoaneurysm, occlusion, or double-lumen. Of these features, the only pathognomonic one (but also the rarest) is the double lumen. Occlusion which can be due to thrombosis of any cause is the least specific. We think that the diagnosis of probable occlusive form of VA dissection can only be made when there is angiographic evidence of dissection in the other VA or in the internal carotid artery. In this respect, the diagnosis of dissection in patients 2 and 3 of Hise *et al*[1] who had VA occlusion should only be regarded as possible.

4) Normalisation or improvement of angiographic abnormalities is frequent in this condition and is an excellent argument in favour of the diagnosis. In one of our cases,[2] marked improvement was observed as early as 7 days after the first angiogram, which stresses the point that the first angiography should be performed as early as possible so that the diagnosis should not be overlooked. We also concluded that control angiography could be performed around the third month, a time by which most dissected vertebral arteries had returned to normal.

5) In our opinion, ultrasound examination

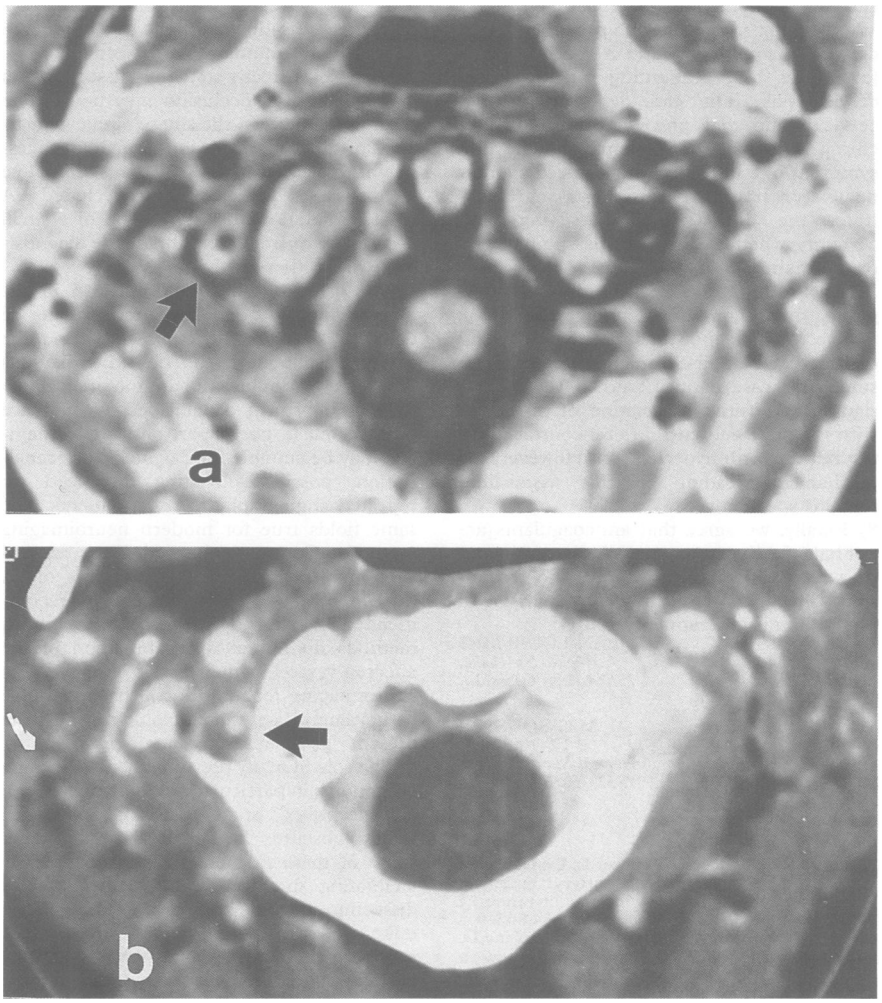

Figure Dissection of the third segment of the right vertebral artery.
a) T1-weighted axial MRI (SE 500/25): Central hyposignal (flow void in the residual lumen of the vertebral artery) surrounded by hypersignal (parietal haematoma).
b) Thin section contrast-enhanced dynamic CT scan: Eccentric hyperdensity (injected residual lumen) surrounded by isodense haematoma and peripheral ring enhancement.

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