Matters arising

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Disadvantages. As yet we do not have a way to subtract the area’s due to inertial effects without an estimate of the centre of gravity of the extremity. The patient’s tolerance of higher velocities of oscillating motion is less than linear motion at the same velocities. It is also harder for the patient to relax. These combined effects cause the measurement error to increase when compared to linear movement.

Fig 1 Length-tension plots of torque versus elbow flexion at 1, 2, 4, 6, 8, 10, 12, and 14 radians (A to D respectively) in a 46 year old healthy subject. Passive movements were continuous and oscillatory in which both extension and flexion were at the same velocity.

Fig 2 The relationship between the areas inscribed within the length-tension loop and the velocities of the passive movement.

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positive effects are the viscous forces as shown here in a 46 year old subject (fig 1) and can be represented by the progression in force-velocity areas (fig 2). We have found in an environment where acceleration is known and velocity is controlled during the motion, a highly linear increase in area with respect to velocity. And this effect is reproducible. It seems unreasonable to attribute the neural or reflex effect seen in the added force levels above 120°/s to changes in elasticity. This normal linear function (r = 0.99) from 90–220°/s represents a progression that includes the lumping of visco-elastic and inertial effects. But because limb mass and moment of inertia do not change, gravity correction is not necessary and qualitative statements can be made about the resistance to passive movements. This relationship is supported by earlier work in which a consistent linear relationship was found between reflex EMG and the velocity of stretch in the biceps over a wide range of velocities (0–500°/s).

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Blood brain barrier permeability in multiple sclerosis using labelled DTPA with PET, CT, and MRI

Sir: Pozzilli et al recently reported on the measurement of blood brain barrier (BBB) permeability in multiple sclerosis (MS) using 68-Ga-EDTA and positron emission tomography (PET). Their paper, however, contains some numerical inconsistencies and in some part the permeability measured is much smaller than that indicated by our MRI studies for the reasons discussed below. In their summary the authors quote blood to brain influx constant K, for Gallium EDTA of 12.5 ml g−1 min−1 in multiple sclerosis patients with a clinical exacerbation of their disease, and a K of 3.2 ml g−1 min−1 for normal tissue. The measurements of multiple sclerosis were made in areas of the brain judged abnormal by high volume delayed CT scanning (HVD-CT). These values are clearly too high and contradict their table 3 which shows K = 12.5 × 10−6 ml g−1 min−1 for multiple sclerosis patients and 3.2 × 10−6 ml g−1 min−1 for normal controls. Tables 3 and 4 also show for normal and multiple sclerosis brain the plasma volume (Vp) in the range 3–5 ml g−1. These values are clearly impossible since even pure blood contains only about 0.55 ml g−1 of plasma, and normal white matter only about 0.02 ml g−1 of blood.

The authors found BBB permeability in
the multiple sclerosis lesion increased only by a factor of 4 from normal. This contrasts with our MR findings using Gd-DTPA, in which signal enhancement is high (approximately 100%) in enhancing lesions, and negligible (<3%) in normal white matter. These MR findings suggest that the BBB permeability is enhanced by at least a factor of 30 in active multiple sclerosis. At 45 minutes after contrast injection MRI shows uniform enhancement, like HVD-CT. However, at shorter times (5–10 minutes) ring enhancement is usually seen in lesions >5 mm in diameter, which is consistent with pathological descriptions of active inflammation and demyelination at the perimeter of multiple sclerosis plaques. Later enhancement in the older, inner core of the lesion is probably caused by diffusion inwards from the ring enhancing edge. Using the CT scan to delineate the region of interest on the PET scan will produce a mean K, over the whole lesion, thus significantly underestimating the K, of the active ring-like part with defective BBB. The true K, will be greater by approximately the ratio of total lesion area to ring area, that is, as much as twenty times higher. Even if the correct region of interest was used, PET is intrinsically incapable of resolving the ring enhancement in multiple sclerosis because its spatial resolution is too poor (9 mm in the plane of a 16 mm thick slice). Our preliminary measurements of K, in the active part of the lesion using dynamic MRI scanning suggest values of K, in the range 0.012–0.06 ml g⁻¹ min⁻¹ (3 lesions) that is 10–50 times higher than in the authors' table 3.

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References


Pozzilli et al reply: We are grateful to Drs Tofts and Kermode for giving us the opportunity to rectify a typographical error in our article. In tables 2 and 3 the Vp should have been multiplied by 10², as correctly shown in our previous paper, and in the summary the values of Ki are ×10⁴. Clearly this omission solves a contradiction which is only too apparent. The values of Vp in the range of 3.3–4.5 × 10⁻³ ml g⁻¹ are in agreement with the values of CBV reported in the literature.

Drs Tofts and Kermode, on the basis of signal enhancement, reach the conclusion that BBB permeability should be increased by a factor of 30 in active multiple sclerosis. This, according to them is in contrast with the increase by a factor of four reported by us. We frankly have some difficulty in comparing the two sets of data since one originates from a signal enhancement ratio and the other from a numerical value of K calculated on the basis of a kinetic model for the passage of substances across the BBB.

Unfortunately we are unable to comment on the value of K measured with MRI since the underlying assumptions and the mathematical formulation of the method are neither reported in the letter, nor in the quoted reference. It should be pointed out, however, that K approaches in magnitude the permeability-surface area product (PS) only when PS ≈ F (where F = blood flow). Values of Ki as high as 0.06 ml g⁻¹ min⁻¹ would suggest that PS approaches F in magnitude. In these circumstances Ki is not only expression of PS, but would also depend upon blood flow. Thus for a correct evaluation of PS a measurement of local blood flow would be required.

Finally, our recent experience on Gd-DTPA suggest that ring enhancement in patients with multiple sclerosis is an uncommon finding. Moreover, none of the patients reported in our study showed a ring enhancement in the high volume delayed (HVD) CT scan.

References


Encephalopathy, deafness and blindness in young women: a distinct retinocochleoencephalopathy?

Sir: The recent paper by Bogousslavsky et al documenting three patients who developed progressive neuropsychiatric and neurological disturbances with hearing loss and multifocal retinal artery branch occlusions, requires some comment.

Their first patient demonstrated an abnormality of the helper/suppressor cells and blood suggesting an immunological disturbance. This patient also showed elevations in the CSF protein and erythrocyte sedimentation rate. Their third patient, in addition to an elevated ESR of 27 mm/hour, also demonstrated positive antinuclear antibodies (1:320) as well as positive rheumatoid factor (1:160), and low complement levels were later also discovered.

We would draw attention to the recently defined "primary" antiphospholipid syndrome. These patients may develop multiple infarct dementia, and vascular occlusions occur, involving both venous and arterial circulations. Indeed there appears to be a strong association between the retinal vascular occlusion and cranial disease. As many as 40% of these patients may be ANA negative, and there is only a 60–70% concordance between the "lupus anticoagulant" activity and the presence of antiphospholipid antibodies (aCL). The VDRL may only be positive in 20%–30% of patients. Other immunological disturbances are also commonly present.