Studies on regional cerebral oxygen utilisation and cognitive function in multiple sclerosis

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SUMMARY Regional cerebral oxygen utilisation ($rCMRO_2$), oxygen extraction ($rOER$), blood flow ($rCBF$), and blood volume ($rCBV$) have been determined for fifteen patients with multiple sclerosis in remission using positron emission tomography (PET). Cerebral oxygen utilisation and blood flow were significantly reduced in both white matter and peripheral cortical grey matter in the multiple sclerosis patients compared to a group of normal controls. No evidence of regional cerebral ischaemia in the multiple sclerosis group was found. Lowest levels of cerebral oxygen utilisation were found in patients with cerebral atrophy, and in patients in whom a significant fall in present full-scale IQ from estimated pre-morbid levels had occurred. No correlation was found between $rCMRO_2$ values and severity of locomotor dysfunction or clinical disease duration.

The primary pathology of multiple sclerosis consists of plaques of demyelination distributed about the central nervous system.^{1,2} These plaques range from 1 mm–4 cm in size and initially form as perivenular sleeves of demyelination.³ The lesions contain macrophages, lymphocytes and plasma cells and characteristically consist of breakdown of the myelin sheath with axonal sparing.⁴ Occasionally Wallerian degeneration of the axon is seen. The plaques tend to be symmetrically distributed with a predilection for the spinal cord, cerebellum, and periventricular regions. At necropsy, however, numerous plaques may be found in clinically silent areas of central white and cortical grey matter.⁵

Gyldensted has reviewed 110 CT brain scans of multiple sclerosis patients and found a 36% incidence of intracerebral plaques and a 79% incidence of generalised central white matter atrophy and/or widening of the cortical sulci.⁶ Forty five per cent of his group had evidence of generalised cerebral atrophy in the absence of demonstrable focal plaques. It is likely that a higher incidence of plaques would have been found had brain scans been performed with a nuclear magnetic resonance (NMR) rather than a CT scanner.^{7,8}

A number of studies have been carried out on levels of cognitive function in multiple sclerosis. Peyser *et al*⁹ studied 55 multiple sclerosis patients and found a 55% incidence of impaired cognitive function. Impairment of general cognitive function correlated significantly with clinical disease duration but not with the degree of neurological disability. Several studies have shown a selective impairment of performance IQ relative to verbal IQ in multiple sclerosis.^{10–12} Jambor¹³ has examined cognitive function of specific cortical regions in a group of 103 multiple sclerosis patients and again demonstrated a significant impairment. None of these studies however compared CT brain scan findings with levels of cognitive function.

Claims have been made for the efficiency of hyperbaric oxygen in ameliorating symptoms of multiple sclerosis.^{14,15} In one of these studies,¹⁵ a double-blind controlled study, significant though transient improvements in mobility, fatigability, and balance were noted in patients treated with hyperbaric oxygen compared to those given a placebo. The mechanism of action of hyperbaric oxygen is uncertain. One possibility is that it acts as an immunosuppressive agent.^{16,17} A second possibility that has been suggested¹⁵ is that regions of ischaemia exist in perivenular plaques due to an associated venous back pressure, and that such ischaemia is transiently relieved by hyperbaric oxygen.

The purpose of this study was two-fold. Firstly, we

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Table 1 Clinical details of multiple sclerosis patients

Patient	Age at onset	Disease duration (yr)	Locomotor dysfunction	MS ¹⁸ classification	CSF	VEP latency
1	34	24	+	CDMS A1	—	—
2	35	3	+	CDMS A1	—	—
3	26	28	+	CDMS A2	OB	—
4	17	3	+	LSDMS B1	OB	↑↑
5	40	14	++	LSDMS B1	IgG↑	↑↑
6	29	15	+	CDMS A1	IgG↑	↑↑
7	53	14	++	CDMS A1	Normal	—
8	32	4	+	CDMS A2	—	↑
9	30	18	++	CDMS A1	Paretic	—
10	34	16	+	CDMS A1	IgG↑	Normal
11	20	6	++	CDMS A1	OB	↑↑
12	33	14	++	CDMS A1	OB	↑↑
13	29	8	+	LSDMS B1	OB	Normal
14	47	7	+	LSDMS B1	IgG↑	—
15	24	3	++	CDMS A1	OB	↑
Mean	32	12				

OB = Oligoclonal bands. Paretic = Paretic Lange curve. IgG↑ = IgG:protein ratio >13%. ↑ = prolonged VEP latency. CDMS = Clinical definite multiple sclerosis. LSDMS = Laboratory supported multiple sclerosis.

wished to measure levels of cerebral oxygen utilisation in multiple sclerosis and to correlate these with neurological and cognitive function, and the presence of cerebral atrophy. Secondly we wished to investigate whether a rationale exists on metabolic grounds for raising the level of the oxygen content of arterial blood supplying the cerebral tissues of multiple sclerosis patients by administering hyperbaric oxygen.

Methods and patient selection

The fifteen multiple sclerosis patients selected for this study had either clinically definite (CDMS) or laboratory-supported definite (LSDMS) multiple sclerosis according to criteria recently laid down.¹⁸ Clinical details of the fifteen patients studied are shown in table 1.

Age of clinical onset of disease ranged from 17–53 years and clinical disease duration from 3–28 years. All patients studied had evidence of spasticity on clinical examination. Severity of locomotor dysfunction was graded (+) if the patient could walk without aids, and (++) if crutches or a wheelchair were required for locomotion.

The cerebrospinal fluid (CSF) was examined in twelve patients. In eleven of these the CSF was abnormal with either oligoclonal banding on immunoelectrophoresis, a paretic Lange curve, or an IgG:total protein ratio greater than 13%. Seven out of nine patients who had their visual

evoked potentials (VEPs) assessed had prolonged latencies of these in one or both eyes.

Thirteen of the fifteen patients had CT brain scans performed as part of this study. The presence or absence of plaques and cerebral atrophy was decided by a panel of neuroradiologists from the National Hospital for Nervous Diseases, London, UK, with a prior knowledge of the patients' ages but not of their clinical condition.

Psychometric tests of general and specific cognitive function were carried out on thirteen of the fifteen patients by a clinical psychologist (GH) who had no prior knowledge of the results of clinical examination or physical investigations. Present IQ (post-morbid IQ) was assessed with seven sub-tests of the Wechsler Adult Intelligent Scale (WAIS):¹⁹ Arithmetic, Similarities, Digit Span, Vocabulary, Picture Completion, Block Design, and Picture Arrangement. One patient (GL) was physically unable to perform the Block Design subtest and in his case the IQ was prorated from six sub-tests. Pre-morbid IQ was estimated from combined scores on the National Adult Reading Test (NART) and Schonell Graded Word Reading Test^{20,30} which were standardised against those WAIS subtests listed above. Tests of specific functions listed below were also administered. Verbal and visual memory (forced-choice recognition of words and faces), object recognition (unusual views test), visual perception (fragmented letters test) are as described by McKenna and Pratt.²¹ Frontal function was sampled with a work-fluency test (number of words beginning with S produced by the patient in two minutes—see Benton²²), the Weigl Colour Form Sorting Test,²³ and a tapping test to examine verbal control of motor acts.²⁴

Scores were classified as abnormal if they fell below the 5th percentile for normal subjects. A fall in present full-scale IQ of twelve points or greater from estimated pre-morbid levels was taken as a significant deterioration, as such a discrepancy was found in 4% only of normal subjects.

The thirteen normal controls selected for this study (eight males and five females) were healthy, normotensive volunteers with ages ranging from 26–63 years. Table 2

Table 2 A comparison of age range, arterial oxygen content, haemoglobin and pCO₂ between the multiple sclerosis and normal control groups

	Multiple sclerosis (15) mean ± SD	Normals (13) mean ± SD
Age	44 ± 13	39 ± 11
Haemoglobin (g/dl)	13.6 ± 1.3	13.3 ± 1.2
Arterial oxygen content (mls O ₂ /ml)	0.19 ± 0.016	0.18 ± 0.016
Arterial pCO ₂ (kPa)	5.2 ± 0.48	5.5 ± 0.13

compares ages, haemoglobin levels, arterial $p\text{CO}_2$ levels, and arterial oxygen contents of the multiple sclerosis and normal control groups. No differences between the groups were found.

Regional cerebral blood flow and oxygen extraction were measured using positron emission tomography during steady-state inhalation of C^{15}O_2 and $^{15}\text{O}_2$, an EG and G Ortec ECAT II scanner with a full-width-half-maximum height (FWHM) resolution of 17 mm being employed.²⁵ Corrections for the tissue attenuation of 511 keV γ -irradiation were carried out by obtaining transmission scans at the same axial tomographic level as emission scans using a ^{60}Co ring source as previously described.²⁵ Arterial plasma and whole-blood ^{15}O concentrations were measured during PET scanning by withdrawing multiple arterial samples via an indwelling 22-gauge teflon radial artery cannula, and well-counting. These data, combined with the regional tissue concentrations of ^{15}O measured using PET scanning, enabled absolute values of rCBF and rOER to be obtained from tracer equations.²⁵ rCMRO₂ values were derived from values of rCBF, rOER, and the oxygen content of arterial blood using the relationship:

$$\text{rCMRO}_2 = \text{rCBF} \times \text{rOER} \times \text{arterial oxygen content} \quad (1)$$

Regional cerebral blood volume (rCBV) was measured by labelling red cells via inhalation of ^{11}CO as detailed by Phelps *et al.*²⁶ This information was used to correct for errors in rOER and rCMRO₂ measurements arising from the superimposition of signal from ^{15}O contained within the cerebral blood pool onto the metabolic ^{15}O signal due to uptake of tracer by cerebral tissue.²⁷ Patients and normal controls were scanned with the single-slice ECAT II PET scanner so as to produce transaxial tomographic images 2.5 cms and 6.5 cms above the orbitomeatal line (OM + 2.5, OM + 6.5). These tomographic planes correspond to the level of the cerebellum, and the top of the lateral ventricles and centrum semiovale respectively.

The purpose and nature of this study was approved by the Hammersmith Hospital Research Ethics Committee, London. The United Kingdom Administration of Radioactive Substances Advisory Committee has given permission for the administration of radioisotopes to perform these studies. The informed consent of the patient was obtained prior to the commencement of each study.

Data Analysis

Measurements of blood flow and oxygen consumption in cerebral white matter were taken from the left and right centrum semiovale at an axial tomographic level of OM + 6.5 cm. Regions of white matter clear of lateral ventricle were identified by overlaying patient CT brain scan images at an equivalent tomographic level onto the rCMRO₂ image for each subject. Two circular regions of interest (ROIs) radius 1 cm containing 49–2.5 mm × 2.5 mm pixels were used to sample white matter function in each centrum semiovale. The precise locations of these circular ROIs were defined by selecting the regions of white matter from the rCMRO₂ image which gave the minimum standard deviation between individual pixel readings for rCMRO₂ within the circular ROIs. In this way the homogeneity of the white matter being sampled was maximised.²⁵ The average of the mean pixel readings for rCMRO₂ in the two

ROIs representing white matter in the left and right centrum semiovale was then taken as the overall mean value for white matter rCMRO₂. These two white matter ROI positions defined from the rCMRO₂ image were stored and superimposed on rCBF, rCBF and rCBV images to provide mean white matter values of these variables.

Peripheral cortical grey matter blood flow and oxygen consumption were measured using a cortical plot technique.²⁸ Rectangular ROIs 1.5 cm × 0.75 cm containing 18 pixels were arranged contiguously around the peripheral ribbon of high oxygen utilisation evident on the rCMRO₂ image at a level of OM + 6.5 cm so as to produce the minimum standard deviation between individual pixel readings. In this way the homogeneity of the cortical tissue being sampled was maximised. Cortical plots prepared in this way contained approximately 900 pixels, and the mean pixel value for rCMRO₂ was taken as representing the rCMRO₂ value for peripheral grey matter at OM + 6.5 cm. The positions of the rectangular ROIs comprising the cortical plot as defined on the rCMRO₂ image were stored and superimposed on the rCBF, rOER and rCBV images to obtain mean peripheral grey matter values for these variables.

Blood flow and oxygen consumption in the cerebellum were measured at a level of OM + 2.5 cm. The rCMRO₂ image at this level shows regions of high oxygen utilisation corresponding to cerebellar cortex and dentate nuclei. An elliptical ROI containing 267 pixels was positioned over cerebellar territory on the rCMRO₂ image so as to produce a maximum mean rCMRO₂ value per pixel. The position of this elliptical ROI representing cerebellar function as defined from the rCMRO₂ image was then stored and superimposed on rCBF, rOER and rCBV scans at OM + 2.5 cm to provide mean cerebellar values of these variables.

Results

The clinical details of the fifteen multiple sclerosis patients studied are shown in table 1. Locomotor dysfunction was graded as outlined in the *Methods* section. Figure 1 shows similarly scaled PET images of cerebral function at OM + 6.5 cm for a patient and a normal control. At this level a peripheral rim of high oxygen utilisation and blood flow is evident, corresponding to peripheral cortical grey matter, with lower rCMRO₂ and rCBF values being seen for the white matter in the left and right centrum semiovale. Figure 2 shows the CT brain scan of the patient, generalised cerebral atrophy and periventricular lucencies being present. Compared to the PET images of the normal subject, those of the patient show a generalised coupled reduction in both cerebral oxygen utilisation and blood flow. The oxygen extraction image of the patient is uniform and similar to the rOER image of the normal subject, both yielding mean rOER values of around 40% for central white and peripheral grey matter. Regions of ischaemic tissue in which blood flow is

Fig 1 PET images of regional cerebral blood flow, oxygen extraction fraction and oxygen utilisation for a multiple sclerosis patient and normal control.

inappropriately low in relation to cerebral metabolic demands are characterised by high fractional oxygen extractions.²⁸ No such regions with raised rOER can be seen in the multiple sclerosis OER image, cerebral blood flow being coupled to cerebral oxygen utilisation in all areas.

Tables 3 and 4 detail respectively the mean white and peripheral cortical grey matter values of rCBF, rOER, rCMRO₂ and rCBV for the group of fifteen multiple sclerosis patients and thirteen age-matched normal controls. Using an unpaired *t* test to compare the two groups, the multiple sclerosis group was found to have significantly lower mean rCMRO₂ and rCBF values for both white and peripheral grey matter compared to the normal controls. Mean white and grey matter oxygen extraction however were similar for both groups, no regions of ischaemic tissue with raised oxygen extraction being found in the multiple sclerosis group.

Figure 3 shows the correlation between mean white and peripheral grey matter rCMRO₂ in the combined group of individual patients and normal controls. A reduction in oxygen utilisation by both white and grey matter of patients compared to white and grey matter of normal controls is evident. The relationship between mean grey and white matter oxygen utilisation however remains similar for both groups of subjects, stressing the coupled nature of the rCMRO₂ reduction in the white and grey matter of the multiple sclerosis group.

Cerebellar oxygen consumption appeared to be little affected in the multiple sclerosis group. Table 5 shows that although mean rCBF was significantly lower for the cerebellum in the multiple sclerosis group, this was balanced by a slight rise in mean rOER. Mean cerebellar oxygen utilisation, while lower for the multiple sclerosis group, did not significantly differ between the two groups at a 5%

Fig 2 CT Scan of the patient with multiple sclerosis whose PET images are shown in fig 1.

level of significance.

Of the thirteen patients who had CT brain scans performed as part of this study, eight (62%) had evidence of either generalised central white matter and peripheral grey matter atrophy, or generalised white matter atrophy alone—see table 6. Four of these eight also had evidence of plaques. Figure 4

shows a comparison of mean rCMRO₂ for grey and white matter of individual normals, multiple sclerosis patients with cerebral atrophy, and multiple sclerosis patients with normal CT scans. Using an unpaired *t* test to compare the groups, both grey and white matter rCMRO₂ were found to be significantly reduced in the multiple sclerosis atro-

Table 3 White matter function in multiple sclerosis

	Multiple sclerosis (15) mean ± SD	Normals (13) mean ± SD	p value
rCBF (mls/100 ml/min)	21 ± 4	27 ± 5	<0.05
rOER	0.39 ± 0.07	0.38 ± 0.06	NS
rCMRO ₂ (mls O ₂ /100ml/min)	1.4 ± 0.3	1.8 ± 0.2	<0.01
rCBV (mls/100ml)	2.7 ± 0.4	2.4 ± 0.8	NS

NS = Non-significant

Table 4 Cortical grey matter function in multiple sclerosis

	Multiple sclerosis (15) mean ± SD	Normals (13) mean ± SD	p value
rCBF (ml/100 ml/min)	38 ± 5	45 ± 10	<0.05
rOER	0.42 ± 0.06	0.40 ± 0.06	NS
rCMRO ₂ (ml O ₂ /100ml/min)	2.9 ± 0.3	3.2 ± 0.3	<0.01
rCBV (ml/100ml)	4.0 ± 0.4	4.1 ± 0.6	NS

NS = Non-significant

Table 5 Cerebellar function in multiple sclerosis

	Multiple sclerosis (15) mean $\pm$ SD	Normals (13) mean $\pm$ SD	p value
rCBF (ml/100 ml/min)	41 $\pm$ 8	47 $\pm$ 5	<0.05
rOER	0.39 $\pm$ 0.08	0.37 $\pm$ 0.04	NS
rCMRO ₂ (ml O ₂ /100ml/min)	2.9 $\pm$ 0.7	3.1 $\pm$ 0.3	NS
rCBV (ml/100ml)	4.5 $\pm$ 1.4	4.3 $\pm$ 0.7	NS

NS = Non-significant

phy group compared to normal controls. Those patients with normal CT scans however had cerebral oxygen utilisation values within the normal range.

Thirteen of the fifteen patients underwent detailed psychometric assessment. The results of

Fig 3 The correlation between cortical and white matter oxygen utilisation in multiple sclerosis patient and normal subject.

Fig 4 Cerebral atrophy and regional oxygen utilisation in multiple sclerosis.

tests of general cognitive function are detailed in table 6. Mean estimated pre-morbid IQ levels and present full-scale IQ levels for the multiple sclerosis group were not significantly different from normal populations. Using Nelson's methods of assessment,³⁰ a fall in present full-scale IQ of twelve points or more from estimated pre-morbid levels is considered pathological. Four of the thirteen patients tested (31%) fell into this category and all four had evidence of generalised cerebral atrophy on CT scan

Table 6 General cognitive function in the multiple sclerosis group

Patient	Pre-morbid IQ (NART/Schonell)	Present full-scale IQ (WAIS)	IQ difference	CT scan
5	105	92	-13	CSP
2	114	106	-8	C
7	91	98	+7	CSP
11	117	102	-15	CSP
13	119	126	+7	N
12	108	88	-20	CSP
3	110	114	+4	CSP
9	119	137	+18	N
4	96	79	-17	C
8	94	95	+1	C
1	121	116	-5	C
10	112	105	-7	N
6	120	124	+4	N
Mean	110	106		

NART: National Adult Reading Test.
 Schonell: Schonell Graded Word Reading Test.
 CT Scans: C = Generalised central atrophy.
 S = Generalised widening of sulci.
 P = Plaques.
 N = Normal.

Fig 5 Correlation between pre- and post-morbid IQ change and CT scan atrophy in multiple sclerosis.

(fig 5). When the fall in functional IQ from estimated pre-morbid levels was plotted against mean cortical rCMRO₂ values for individual patients, a significant correlation was found (fig 6), those patients with the greatest deterioration in IQ having lowest levels of cortical oxygen utilisation.

Table 7 details the results of psychometric tests of specific cerebral function for thirteen of the patients. Seven of the thirteen patients tested (54%) had selective defects in cortical function. Six of these seven patients had current CT brain scans available and all six showed evidence of generalised cerebral atrophy.

Fig 6 Correlation between cerebral cortical oxygen utilisation and the difference in pre- and post-morbid IQ levels in multiple sclerosis.

Figure 7 shows the relationship between white and peripheral grey matter rCMRO₂ values and severity of locomotor dysfunction for individual patients. No significant correlation was found between these quantities, or between levels of cerebral oxygen utilisation and clinical disease duration (fig 8).

Discussion

The fifteen patients with multiple sclerosis in remission had a lower level of oxygen utilisation by both central white and peripheral cortical grey matter than an age-matched normal control group. The reduction in rCMRO₂ was generalised rather than focal and correlated well with the presence of generalised cerebral atrophy on examination of the CT brain scans of the multiple sclerosis group. In individual patients a correlation was found between the depression in levels of mean white and mean peripheral grey matter oxygen utilisation.

Table 7 Tests of specific cortical function in multiple sclerosis

Patient	Forced-choice faces non-dominant temporal	Unusual views non-dominant parietal	Weigl frontal	Verbal fluency frontal
5	↓	N	↓	↓
2	↓	N	N	↓
7	↓	N	N	↓
11	N	N	N	N
13	N	N	N	N
12	N	N	N	N
3	N	N	N	N
9	N	N	N	N
4	N	N	N	N
8	N	N	N	N
1	N	N	N	N
10	N	N	N	N
6	N	N	N	N

↓ = deficit. N = normal.

All patients scored normally on the following tests: forced choice words (dominant temporal); fragmented letters (non-dominant parietal); tapping test (frontal).

Fig 7 Relationship between regional cerebral oxygen utilisation and severity of locomotor dysfunction in multiple sclerosis.

Fig 8 Relationship between regional cerebral oxygen utilisation and clinical disease duration in multiple sclerosis.

This depression in cerebral function found for the multiple sclerosis group as assessed by PET is likely to reflect the volume of increased non-exchanging tissue produced by cerebral atrophy rather than a

decrease in actual oxygen utilisation by those neurones still remaining intact.³¹ Cerebral function per unit volume of viable brain tissue, rather than per unit total volume as measured by PET, probably remains similar for both the multiple sclerosis and the normal groups. Mean cortical rCMRO₂ was reduced by 9% from normal values in the multiple sclerosis group as opposed to a 22% reduction in mean rCMRO₂ for white matter. Within the 1.7 cm resolution of our PET scanner, peripheral cortical grey matter regions of interest contain at least a 50% contribution from surrounding white matter, the cortical ribbon being only 5 mm in width. As a result the depression in cortical function found for the multiple sclerosis group could probably be explained entirely in terms of a partial volume effect of the surrounding white matter, where function is more seriously affected.³¹ This is unlikely however to be the sole explanation for the measured cortical hypofunction, as occasionally multiple sclerosis patients are found with evident widening of their sulci on CT brain scans in the absence of central white matter atrophy.⁶ Such a CT scan finding implies that cortical atrophy can be a feature of multiple sclerosis in the absence of obvious white matter lesions.

The measurement of regional fractional oxygen extraction by PET is free from problems due to partial volume effects when cerebral atrophy is present, and reflects the oxygen extraction of remaining viable tissue.³² This is because the ratios of regional cerebral H₂¹⁵O uptake when ¹⁵O₂ and C¹⁵O₂ are inhaled are used to derive rOER values, and so effects of non H₂¹⁵O exchanging regions are eliminated.

The relative sparing of cerebellar oxygen utilisation in the multiple sclerosis group compared to the reduction in central white and peripheral grey matter rCMRO₂ is difficult to explain. The cerebellum is a reported site of predilection for demyelination.¹ No cerebellar plaques however were evident on the CT scans of our group of patients.

Eight out of thirteen (62%) of the patients had evidence of cerebral atrophy on their CT scans, and in all cases the atrophy was generalised involving either central white matter alone or both central white and peripheral grey matter. Four of the thirteen patients CT scanned had evidence of focal plaques, all four falling into the atrophy group. These data suggest that focal plaques of demyelination, generalised cerebral hypofunction, and generalised cerebral atrophy all form a part of the disease process of multiple sclerosis. In his review of 110 CT brain scans of multiple sclerosis patients,⁶ Gyldensted found a 45% incidence of generalised cerebral atrophy in the absence of any demonstrable

focal plaques, supporting this concept, although more plaques may have been demonstrated had NMR rather than CT imaging been used.^{7,8}

Studies of cognitive function in multiple sclerosis also support the concept that cerebral function becomes generally impaired as part of the disease process. In a series of 55 patients, Peyser *et al*⁹ showed a significant fall in general cognitive function from estimated pre-morbid levels in 55% of their multiple sclerosis group. In our study, using the NART/Schonell tests to estimate pre-morbid IQ levels, we found a significant deterioration in general cerebral function in 31% of our multiple sclerosis patients, all of whom had evidence of generalised cerebral atrophy on their CT brain scans. Falls in present IQ from estimated pre-morbid levels correlated well with present levels of mean cortical oxygen utilisation. Interestingly Frackowiak *et al*²⁹ reported a similar correlation between degree of dementia and levels of cortical rCMRO₂ in a group of dementia cases.

Psychometric testing of specific rather than general cerebral functions in our group of patients proved a more sensitive method of detecting cognitive impairment. Seven out of thirteen (54%) had significant impairment of cognitive function using such tests, as opposed to 31% when assessment of general IQ was used. Using similar tests Jambor¹³ demonstrated a significant impairment of cognitive function in his group of 103 multiple sclerosis patients. There were no obvious regions of cortical hypofunction or atrophy which corresponded with specific regions of cortical impairment revealed by psychometric testing, all our affected patients having generalised disturbances on PET and CT scanning. It must be remembered however that focal multiple sclerosis plaques may only be 1–2 mm in length and as such are beyond the resolution of PET and CT scanners currently available.

We found no correlation between levels of cerebral oxygen utilisation and clinical disease duration of multiple sclerosis. Gyldensted⁶ in his series of 110 CT scans was also unable to demonstrate a correlation between degree of cerebral atrophy and clinical disease duration. This finding is surprising and presumably reflects the wide range of disease activity that individual multiple sclerosis patients exhibit on clinical follow-up. Less surprising was the lack of correlation found between levels of cerebral oxygen utilisation and locomotor dysfunction. rCMRO₂ values reflect intracerebral disease whereas locomotor dysfunction frequently reflects the presence of brain-stem and spinal cord plaques. Peyser *et al*⁹ were also unable to demonstrate any correlation between impairment of cognitive function and degree of neurological impairment.

The low levels of cerebral oxygen utilisation found for our group of multiple sclerosis patients were matched by coupled reductions in cerebral blood flow, mean oxygen extraction by central white and peripheral cortical grey matter in our multiple sclerosis group being similar to that of normal controls. No regions of cerebral tissue with significantly raised oxygen extraction (implying focal tissue ischaemia) were found either in plaques or white matter within the 1.7 cm resolution of our PET scanner. We were thus unable to find any metabolic grounds for raising the oxygen content of arterial blood supplying the cerebral tissue of multiple sclerosis patients by administering hyperbaric oxygen.

The cause of the generalised cerebral hypofunction and atrophy in multiple sclerosis remains unclear. Numerous submicroscopic plaques leading to Wallerian degeneration of neurons is one possibility. A second possibility is suppression of neuronal activity by a toxic product of myelin breakdown. What is clear is that psychometric evaluation when combined with a conventional neurological examination provides a far more sensitive way of assessing the severity of intracerebral disease than conventional neurological examinations alone, and that levels of cognitive impairment correlate well with the presence of cerebral atrophy and levels of cerebral oxygen utilisation. Ideally multiple sclerosis patients should be reviewed both neurologically and psychometrically, as in this way a truer measure of the extent of the disease is likely to be obtained.

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