Cranial computed tomography in the diagnosis of multiple sclerosis

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SUMMARY A group of 202 patients with suspected, probable or definite multiple sclerosis was studied, using cranial computed tomography (CT). Atrophy alone, or in combination with white-matter and periventricular lucencies, and areas of contrast enhancement, were the main abnormal findings in 52% of patients. Atrophy was detected in 44% of patients, and its frequency and severity correlated with disease duration up to 10 years, age, and disease category. Atrophic changes in the brainstem and cerebellum could be correlated with clinical data more often than supratentorial atrophy could be correlated with features such as dementia or mood changes. Lucencies in the white matter, thought to represent areas of demyelination, were noted in 21% of patients, and only a proportion of these lesions could be correlated with clinical data, the others being clinically silent. Contrast enhancement was seen in a small proportion of white-matter lesions, and was independent of disease activity and steroid medication. Electrophysiological tests and cerebrospinal fluid analysis showed a higher yield of abnormality than CT scanning in cases with suspected or possible multiple sclerosis, though in such patients CT scanning excluded alternative cerebral atrophy. Modifications of the technique of CT scanning may improve the detection rate of white-matter lesions, thereby enhancing the value of CT as a diagnostic tool in the study of patients with multiple sclerosis.

Cranial computed tomography (CT) has been used in the investigation of patients with diseases of the white matter, including multiple sclerosis.1-7 The main abnormalities detected in CT scans of patients with multiple sclerosis are atrophy and areas of low attenuation, with or without enhancement, interpreted as plaques. The results of the series reported so far have been rather variable, and the diagnostic usefulness of CT has been questioned, especially in the early or suspected cases of multiple sclerosis. The enhancement characteristics of “plaques” have been reported in a small number of patients only, again with variable and conflicting results. The present investigation was undertaken both as a retrospective and prospective assessment of the value of CT in the management of patients with multiple sclerosis. The various types of abnormality were identified and correlated with the clinical data at the time of CT scanning. The specificity of these abnormalities was assessed, and their usefulness was compared with other standard investigations, namely cerebrospinal fluid analysis, and visual and auditory evoked potentials.

Patients and methods

All 202 patients in this study had been investigated as in-patients at the neurological units of the Queen Elizabeth Hospital, Birmingham, and the Midland Centre for Neurosurgery and Neurology, between 1977 and 1980. There were 129 female (63.8%) and 73 male (36.2%) patients, classified on clinical criteria alone into four groups, as described by McDonald and Halliday:8 clinically definite (81 patients), probable (80), possible or suspected multiple sclerosis (41). Cerebrospinal fluid (CSF) and electrophysiological results (visual and auditory evoked potentials) were available in most patients, but were not used in the diagnostic criteria. The course of the disease (acute, relapsing, chronic progressive) and its activity at the time of CT scanning (stable, remission, exacerbation) were
assessed, as described by Hershey et al. Functional impairment of patients was graded into severe (bedridden or totally dependent), moderate (chairbound or other disability interfering with work and social life), mild, and no impairment.

CT scans were performed using an EMI head-scanner with a 160 × 160 matrix (126 patients) or an EMI body-scanner with a 160 × 160 matrix. Fifty-five patients had unenhanced CT scans only; 70 had the CT scan repeated after contrast infusion of 40 ml to 70 ml sodium meglumine diatrizoate (Urografin 370); and 77 patients had a post-contrast infusion CT scan only. CT scans were taken initially on polaroid films, but the vast majority were printed on transparencies. CT scans were examined for the presence of atrophic lesions: namely, ventricular dilatation, widening of the sulci and of the basal cisterns with concomitant shrinkage of the brainstem (and cerebellum); an Evans ratio was calculated for each scan as a measure of ventricular size, but this was not found to be as useful as visual inspection in assessing cerebral atrophy. In addition, periventricular and white-matter lesions of low attenuation (PVL and WML) were looked for, and abnormal contrast enhancement noted. No systematic attempt was made to measure white-matter attenuation figures from computer printouts. The CT scans of 325 consecutive patients investigated for complaints such as headache, migraine, vertigo, single seizures, facial neuralgia, possible cerebellopontine angle or pituitary tumour, served as controls. Statistical analysis was carried out using the Student’s t test or the χ² test.

Results

At the time of CT scanning the age range of the 202 patients with multiple sclerosis was 13–70 years. The mean age of males in the three disease categories of suspected, probable and definite multiple sclerosis was 40·1 ± 10·5, 39·2 ± 13·6, and 39·5 ± 11·3 respectively; for females the corresponding figures were 32·6 ± 9·4, 42 ± 12·6, and 42·4 ± 11·8 respectively. Seventy-seven per cent of all patients examined were under 50 years of age, reflecting the age at onset of the disease, as shown in table 1. In 10% the age at onset of the disease was before the age of 20 years; in 63% between 20 and 40; and in 27% between 41 and 70 years. In the possible multiple sclerosis group the age at onset was lower in females, the difference being significant (p < 0·02). There was no sex difference in the incidence of the disease after the age of 40. Analysis of the mode of clinical presentation showed that the spinal cord was involved in 72%, the brainstem in 68%, the optic nerves in 33% and the cerebral hemispheres in 9% of all patients.

CT scan abnormalities

CT scan abnormalities consisted of atrophy, periventricular lucencies, lucencies elsewhere in the white matter, and areas of abnormal enhancement (table 2).

(a) Atrophy

There was an increase in the incidence of atrophy with age, disease category, and disease duration (tables 3 and 4). Supratentorial atrophy alone was present in 31 patients; infratentorial atrophy alone in six patients; while supratentorial and infratentorial atrophy were combined in 51 patients. There was a tendency, therefore, for supratentorial atrophy to be seen more frequently. Sulcal enlargement was present in 78 patients; ventricular dilatation in 59; and brainstem/cerebellar atrophy in 53 patients. Infratentorial atrophy showed correlation with clinical features, for example ataxia, nystagmus and dysarthria, in 72% of patients, while supratentorial atrophy correlated with features such as memory deficit, and mood changes in only 17% of patients, the difference being significant (p < 0·001) (fig 1).

(b) Periventricular lucencies (PVL)

Areas of low attenuation in the periventricular region were identified in only 10 patients (two in “probable” and eight in “definite” multiple sclerosis category). Four patients were in exacerbation, and six were in chronic progression of their disease, and none

Table 1  Age at onset of multiple sclerosis

<table>
<thead>
<tr>
<th>Age group</th>
<th>Multiple sclerosis category</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Possible/Suspected</td>
<td>Probable</td>
</tr>
<tr>
<td>0–10</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>11–20</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>21–30</td>
<td>15</td>
<td>23</td>
</tr>
<tr>
<td>31–40</td>
<td>41</td>
<td>50</td>
</tr>
<tr>
<td>41–50</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>51–60</td>
<td>38</td>
<td>3</td>
</tr>
<tr>
<td>61–70</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

Mean ± SD: M 38·3 ± 9·56; F 35 ± 12·2; M 30·4 ± 11·2; F 39 ± 11·1; F 30·7 ± 9·9

*Differs from males, p < 0·02.

Table 2  Number of patients showing CT scan abnormalities

<table>
<thead>
<tr>
<th>CT scan abnormality</th>
<th>Multiple sclerosis category</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Possible/</td>
<td>Probable</td>
</tr>
<tr>
<td>Atrophy</td>
<td>4</td>
<td>29</td>
</tr>
<tr>
<td>Atrophy + WML</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Atrophy + PVL</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Atrophy + PVL + WML</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>WML</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>39</td>
</tr>
</tbody>
</table>

PVL = periventricular lucencies.
WML = white-matter lucencies.
* Differs from Possible + Probable groups, p < 0·001.
† Differs from Probable, p < 0·01.
‡ PVL in one patient.
Table 3  Relationship of atrophic changes to age at CT scanning and category of multiple sclerosis (Number of patients with atrophy expressed as percentage of age group total)

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Possible/ Probable/ Definite/ Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Suspected</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>10–20</td>
<td>—</td>
</tr>
<tr>
<td>21–30</td>
<td>7</td>
</tr>
<tr>
<td>31–40</td>
<td>6</td>
</tr>
<tr>
<td>41–50</td>
<td>—</td>
</tr>
<tr>
<td>51–60</td>
<td>33</td>
</tr>
<tr>
<td>61–70</td>
<td>83</td>
</tr>
<tr>
<td>Total</td>
<td>9·8</td>
</tr>
</tbody>
</table>

* Differs from controls, p < 0.001.
† Differs from controls, p < 0.02.
‡ Differs from Probable group, p < 0.01.
§ Differs from Possible group, p < 0.001.

Table 4  Relationship of atrophy to disease duration

<table>
<thead>
<tr>
<th>Disease duration (years)</th>
<th>Patients</th>
<th>Percent showing atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–5</td>
<td>137</td>
<td>28</td>
</tr>
<tr>
<td>6–10</td>
<td>24</td>
<td>62*</td>
</tr>
<tr>
<td>11–15</td>
<td>11</td>
<td>81-8†</td>
</tr>
<tr>
<td>16–20</td>
<td>20</td>
<td>75</td>
</tr>
<tr>
<td>21–25</td>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td>26–30</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>2</td>
<td>100</td>
</tr>
</tbody>
</table>

* p < 0.01 compared to 0–5 year group.
†, ‡, not different compared to 6–10 year group.

showed correlation between clinical data and location of lucencies. PVL were mostly seen in older patients with longer disease duration. Contrast enhancement was not noted.

(c) White-matter lucencies and areas of contrast enhancement

White-matter lucencies were seen in two patients with suspected multiple sclerosis, eight patients with probabile, and 25 patients with definite multiple sclerosis. Single lucencies were seen in 24 patients; nine patients had two lucencies; one patient showed three lucencies; and another patient showed four lucencies. The location of these lesions was as follows: parietal 15; frontal 11; occipital 10; capsular 7; brainstem 3; temporal lobe 3. Only 10 patients showed correlation between location of WML and clinical data (fig 2).

Contrast enhancement was noted in white-matter areas in seven patients; in three there were no unenhanced scans for comparison; in the others, low attenuation areas showed uniform or peripheral contrast enhancement; in two of the latter patients, radionuclide scans showed increased uptake of technetium in areas corresponding to the enhancing lesions. There was no correlation between contrast enhancing lesions and disease activity; six patients with enhancing WML were in exacerbation, compared with 15 others who did not show enhancement of their WML. Complete resolution of a contrast-enhancing lesion was noted in one patient.

The incidence of white-matter and/or periventricular lucencies in patients in clinical exacerbation was 23%, compared with 18% for patients in remission or stable disease activity: the difference is not significant. The incidence of lucencies in patients over the age of 40 was 31%, compared with 13-5% for patients under the age of 40, the differences being significant (p < 0.01). A significant difference (p < 0.01) was also found in the incidence of WML and PVL in patients with disease duration over five years. In the 56 patients with moderate or severe disability, the incidence of

Fig 1a, b  Unenhanced scan of a 23-year-old female with a seven-year history of vertigo, nystagmus, bilateral limb and trunk ataxia; normal myelogram and vertebral angiogram; abnormal CSF, VEP and AEP. There is atrophy of the brainstem, cerebellar vermis, and dilatation of the third ventricle and Sylvian fissures.
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Fig 2a-c  (a) Contrast-enhanced CT scan of a 35-year-old female patient with a two-year history of definite multiple sclerosis; recent episode of slowly evolving right sensory and motor paresis, with dysphasia, followed by spontaneous resolution. CT scan taken during this phase shows an enhancing low-attenuation lesion in the left fronto-parietal white matter. (b) Technetium isotope brain scan shows increased uptake in corresponding area, confirmed to be located in the white matter by the reconstructed section scan.
Angiography was normal. (c) Delayed high-dose contrast-enhanced CT scan seven months later. There is almost complete resolution of the lesion.

Lucencies was 29%, compared with 17% in patients with no or mild disability; the difference did not reach statistical significance. There was no difference in the incidence of abnormal scans (atrophy ± lucencies) in these two groups either (table 5). In patients with four to 10 relapses the incidence of lucencies was 41% compared with 16% in those with one to three relapses (p < 0.02). No lucencies were seen in 32 patients with purely spinal presentation.

Effect of steroids
Medication with ACTH had been used in 14 patients with definite multiple sclerosis at the time of CT scan. Of these patients, two had normal scans, six showed

Table 5 Disability rating by disease category. (Number of patients with abnormal scans, in brackets)

<table>
<thead>
<tr>
<th>Disability</th>
<th>Multiple sclerosis category</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Suspected</td>
<td>Probable</td>
<td>Definite</td>
</tr>
<tr>
<td>Nil</td>
<td>9 (0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mild</td>
<td>32 (6)</td>
<td>58 (26)</td>
<td>47 (41)</td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
<td>22 (13)</td>
<td>24 (10)</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0</td>
<td>10 (9)</td>
</tr>
</tbody>
</table>

Table 5 Disability rating by disease category. (Number of patients with abnormal scans, in brackets)
atrophy, and six showed PVL or WML, three of which showed contrast enhancement. The remaining 147 patients in the probable and definite multiple sclerosis categories were not receiving ACTH, and in four of these there was contrast enhancement in white-matter lesions. Thus steroid medication did not alter the detection rate of abnormalities.

Comparison of CT scan with other investigations
Visual and auditory evoked responses were carried out in just over 50% of the patients. Abnormal responses were recorded in 66% of patients with possible multiple sclerosis; in 57% with probable multiple sclerosis; and in 78% with definite multiple sclerosis. The CSF was examined in 84% of all patients; it was abnormal (showing raised cell count, total protein, immunoglobulin or combination of these) in 42% of patients with suspected, 63% with probable, and 70% with definite multiple sclerosis. Statistical analysis showed that both the evoked responses and CSF examination were more sensitive in detecting abnormalities than the CT scan in the possible multiple sclerosis group (p < 0.001 and p < 0.02 respectively), but all three investigations were comparable in the clinically probable and definite groups.

Discussion
This study has established that the cranial CT features of multiple sclerosis are atrophy, areas of white-matter low attenuation, and areas of abnormal contrast enhancement. It has also provided some epidemiological data on a large hospital group of multiple sclerosis patients. Cerebral atrophic changes, occurring alone or in combination with other lesions, were seen in 44% of our patients. It was established that the incidence of atrophy is greater in all age groups of multiple sclerosis patients compared with controls; that there is an increase in the incidence of atrophy with advancing disease category; that most atrophic changes occur during the first 10 years of the disease; and that thereafter the increased incidence of atrophy does not reach statistical significance within the multiple sclerosis group. Cala et al² observed the same positive relationship between atrophy and age, disease duration and category, in their 100 patients, their overall figure for the incidence of atrophy being 44%. Other authors ¹ on the other hand did not find such a correlation, most probably because they confined their studies to patients with long-standing “definite” or “highly probable” multiple sclerosis. The incidence of atrophy as reported in other series ranges between 21% and 72%, reflecting either the relatively small number of patients studied, or the predominance of patients with definite multiple sclerosis in the series. ¹ ⁵ ⁶ ⁹–¹²

Atrophic changes alone were seen in 64 patients in this series, while atrophy in combination with white-matter and periventricular lucencies was present in 25; in the latter patients—21 of whom had definite multiple sclerosis, the extent of atrophy was greater, supporting the neuropathological findings of Brownell and Hughes¹³ that there is a close association between ventricular dilatation and the number and size of multiple sclerosis plaques. Infratentorial atrophic changes were found to correlate with clinical data of brainstem or cerebellar dysfunction in a significant proportion of our patients: this is a reflection of the close relationship between structure and function in these areas of the brain, and of their frequent involvement in multiple sclerosis (68% of all patients in this series). Cortical atrophy with ventricular dilatation has been reported to correlate with dementia in a small group of multiple sclerosis patients studied by CT;²相似 observations were made by Barnard and Triggs¹⁴ in their neuropathological study of 20 multiple sclerosis patients. Such correlation was also seen in the present study, in that all the 14 patients who had dementia or mood changes showed supratentorial atrophy on CT, while no patients with mental changes were found in the group with normal CT scans. In general the presence of atrophic changes is a significant diagnostic observation in patients with a clinical profile suggestive of multiple sclerosis, although such changes are in no way qualitatively different from those found in patients with other disease processes.¹⁵–¹⁷ The discriminant value of atrophy is, however, increased in the presence of white-matter lucencies and areas of contrast enhancement.

In the present series more lucencies were encountered in the central white matter than in the immediate periventricular region (49 vs 15, in 41 patients).¹³ The white-matter lucencies occurred both as acute symptomatic and as silent lesions, while the periventricular lucencies were all clinically silent.²⁶ Lucencies were found mainly in patients with definite multiple sclerosis occurring either alone (16 patients), or in combination with atrophy (25 patients).¹³ ⁶ ¹⁸ The relatively low incidence of lucencies in the present series may be due to the routine use of 13 mm or 10 mm cuts; whereas because of their mainly small size, white-matter lucencies are better seen in 8 mm or 5 mm cuts.¹³ ¹⁹–²¹

Enhancement of the CT scan did not result in demonstration of a substantially greater number of abnormal areas in the white matter. Only seven of 149 patients who were given contrast showed enhancing lesions; in four, the lesions were detectable in the unenhanced scans; in the other three, unenhanced
scans were not available. Other authors found no enhancing lesions,\textsuperscript{16} or only a few.\textsuperscript{3 5 9 12 22} By contrast, 30\% of patients in a recent study\textsuperscript{11} showed enhancing lesions, and in another study\textsuperscript{18} enhancement was found in 16 low-attenuation and 15 isodense lesions, representing 65\% of all lesions seen in 14 patients with definite or probable multiple sclerosis. Enhancement is thought to be due to leakage of contrast material through a damaged blood brain barrier in multiple sclerosis lesions.\textsuperscript{18 19 24--28} In favour of this view is the observation that such lesions may also show increased uptake of isotope on radionuclide scans,\textsuperscript{29--34} as observed in two patients in this series, and in two others subsequently. Such lesions are, however, angiographically negative. They may show easier detection if CT scanning is delayed for about two hours after contrast injection, and if a higher than normal dose of contrast is used.\textsuperscript{33--36} It has been suggested that enhancement is only seen in patients who are in acute exacerbation.\textsuperscript{9 24} A case has been reported, however, with biopsy-proven acute multiple sclerosis, in whom the white-matter lesion did not show contrast enhancement,\textsuperscript{31} and a further case with biopsy-proven multiple sclerosis showed enhancement in a lesion, while in clinical and pathological regression.\textsuperscript{34} Some of the patients in this series showed contrast enhancing lesions while stable or in remission. Thus, contrast enhanced CT may not always give an accurate indication of disease activity.\textsuperscript{37} The influence of steroids on contrast enhancement has been rather controversial. It has been suggested that by re-establishing the blood-brain barrier, steroids reduce contrast enhancement in white-matter lesions.\textsuperscript{19 23} In the present series, three out of seven patients with enhancing lesions were receiving steroids at the time of scanning.

Enhancing lesions in multiple sclerosis should be differentiated from other pathologies, for example, glioma, metastases, arteriovenous malformation, and infarcts.\textsuperscript{38 39} A characteristic feature of the lesions in multiple sclerosis is their localisation in the white matter, and their lack of space-occupation (with the notable exception of the one well documented case in the literature\textsuperscript{40}). On subsequent examinations, white-matter lucencies may resolve to isodensity, or new ones may appear—a further diagnostic point.\textsuperscript{38}

It was noted that the overall mean age at onset of the disease in this series was identical in the two sexes (33.8 years), but significantly earlier in females in the suspected/possible categories. There was no greater incidence of the disease in females over the age of 40 years, in contrast to the findings of a recent study.\textsuperscript{41} There was a preponderance of females (63.8\%) and in 73\% of patients the onset of the disease was before the age of 40 years: figures comparable with the 60\% and 80\% respectively in the latter study.\textsuperscript{41} The classification of patients according to clinical criteria alone resulted in the relatively lower figure (39\%) for the definite category compared with the 50\% figure in the French study,\textsuperscript{41} which took into consideration laboratory results. The majority of our patients had no or only mild disability (5\% and 67\% respectively), moderate disability affecting 23\%, and severe disability 5\% of patients. The percentage of abnormal scans in these four functional groups was 0\%, 53\%, 50\% and 90\% respectively. It was interesting to note that within the definite multiple sclerosis category there were more abnormal scans in patients with mild disability than in patients with moderate and severe disability combined (87\% vs 56\%, p < 0.01). At present, therefore, the CT scan can only discriminate between patients with no disability, some disability, and severe disability, but cannot be used reliably as an indicator of prognosis.

Comparison of the standard CT scan with CSF examination and electrophysiological tests showed that the latter investigations were superior in detecting abnormalities in the possible or suspected cases of multiple sclerosis. This is at variance with the results of another study\textsuperscript{11} on 33 patients, 10 of whom had the diagnosis of possible multiple sclerosis supported by CT. In this category, the value of CT scanning lies in the fact that it excludes alternative structural pathology, and may also demonstrate relevant white-matter lesions in individual patients. In patients with probable or definite multiple sclerosis, the CT scan provides as much information as the CSF analysis and electrophysiological tests, but in addition it provides direct evidence of dissemination of lesions in various parts of the neuraxis.\textsuperscript{4} A similar conclusion could be drawn from a study of 72 patients with chronic progressive myelopathy investigated by CSF analysis, neurophysiological tests, and CT.\textsuperscript{42}

Further improvements in the resolution of CT scanners may make it possible to detect lesions in the brainstem, optic nerves, and spinal cord\textsuperscript{44} with greater accuracy, thus enhancing the value of CT as a diagnostic tool in multiple sclerosis, though it may be supplanted by nuclear magnetic resonance imaging, when this facility becomes widely available.\textsuperscript{44}

We gratefully acknowledge the co-operation of our clinical colleagues at the Midland Centre for Neurosurgery and Neurology and the Queen Elizabeth Hospital, Birmingham. Invaluable secretarial assistance was provided by Miss S Alexander and Miss M Smith; radiographic assistance by Miss E Kirkwood and Mrs R Tyler, and photographic assistance by Mr S Thomas.
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