British Isles survey of multiple sclerosis in twins: MRI

J W Thorpe, C J Mumford, D A S Compston, B E Kendall, D G MacManus, W I McDonald, D H Miller

Abstract

64/105 subjects who have a twin with multiple sclerosis included in a study of clinical concordance also underwent MRI of the brain. 8/23 monozygotic and 1/41 dizygotic co-twins from this subgroup were clinically concordant of whom 8/9 had MRI appearances typical of multiple sclerosis. Of the 48 clinically discordant twins aged less than 60, abnormalities on MRI were detected in 6/15 (40%) monozygotic and 13/33 (39%) dizygotic twins compared with 7/37 (19%) healthy age-matched controls. Abnormalities on MRI typical of multiple sclerosis (defined by the Fazekas criteria) were, however, present in only 2/15 (13%) monozygotic and 3/33 (9%) dizygotic twins and 0/37 controls. These results suggest that about 10% of monozygotic and dizygotic twins have "subclinical multiple sclerosis". It is likely that most of the MRI abnormalities seen in clinically discordant twins, however, represent incidental pathology.

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For a given disease, the determination of concordance rates in twins permits an estimation of the aetiological contribution made by genetic factors.¹ Higher concordance rates in monozygotic than dizygotic twins indicate a genetic contribution, but if the monozygotic concordance rate is less than 100%, genetic factors alone, or at least those determined by the germ cell line, are not of themselves sufficient to cause the disease.

Several large studies of clinical concordance for multiple sclerosis in twins have been published.²⁻¹² Despite considerable methodological differences, a consistent pattern has emerged; most but not all studies have identified a higher concordance rate in monozygotic twins, and all are in accord that the monozygotic concordance rate falls well short of 100%. Two of the largest population based surveys^{2,11} produced remarkably similar results (25% monozygotic and 2-3% dizygotic concordance) although the recent French study¹² found low concordance rates that were independent of zygosity.

It might be concluded from the current twin data that although genetic factors make an important contribution to the aetiology of multiple sclerosis, additional environmental factors are probably needed to produce the

disease. An important question in multiple sclerosis twin studies is the reliability of concordance rates that have been determined by an assessment of clinical features alone. The certainty of clinical diagnosis varies especially in the early stages, and this is reflected in the use of criteria that allow for definite, probable, and possible categories. Furthermore, and potentially of much greater importance, the disease may run an extremely benign course¹³⁻¹⁵ and indeed may first be discovered only at necropsy.¹⁶⁻²¹ One postmortem series¹⁹ identified multiple sclerosis that had not been suspected in life with a frequency of 1 in 500, which suggests that completely asymptomatic disease may be as common as the clinically expressed form. Additional suggestive evidence for clinically silent multiple sclerosis during life comes from the finding of CSF oligoclonal bands in clinically unaffected twins²² and abnormalities of evoked potentials in healthy siblings of patients with multiple sclerosis, especially those who are identical at the HLA-A and HLA-B loci.²³ Taken together, the evidence suggests that clinical ascertainment alone fails to detect an appreciable number of cases who actually have multiple sclerosis.

MRI now provides a sensitive means for detecting, in vivo, the characteristic cerebral lesions of multiple sclerosis.^{24,25} White matter lesions, most of which are asymptomatic, are seen in well over 90% of patients with clinically definite multiple sclerosis.²⁶ Furthermore, multiple asymptomatic white matter lesions are already visible in 50%-70% of patients at presentation with a first episode of suspected demyelination²⁷⁻³¹ and have also recently been reported in healthy first degree relatives of patients with multiple sclerosis.^{32,33} MRI should therefore be of value in a multiple sclerosis twin study by detecting subclinical disease in clinically normal twins, leading to a more reliable estimate of concordance than that obtained from clinical criteria. It would also be useful in clarifying the diagnosis in clinically possible cases. A major limitation to using MRI to detect multiple sclerosis in asymptomatic subjects, however, is that the abnormalities seen are not specific; there are many causes of multifocal white matter lesions,³⁴⁻³⁶ of which the most frequent is age-related changes, most likely due to small vessel disease.³⁷⁻⁴¹ This produces abnormalities of white matter in a large proportion of healthy controls over the age of 60, and in smaller numbers of younger age groups.⁴²⁻⁴⁵ To determine the significance of

Multiple Sclerosis NMR Research Group, Institute of Neurology, Queen Square, London WC1N 3BG, UK

J W Thorpe
B E Kendall
D G MacManus
W I McDonald
D H Miller

University of Cambridge Neurology Unit, Addenbrooke's Hospital, Hills Road, Cambridge, UK
C J Mumford
D A S Compston

Correspondence to:
Dr D H Miller.

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abnormalities seen in asymptomatic twins, it is therefore crucial to obtain MRI scans from age matched controls and to use criteria that improve the specificity of abnormalities detected by MRI in multiple sclerosis. We now report the brain MRI findings obtained in 64 co-twins of patients with multiple sclerosis and 40 healthy controls.

Methods

TWINS

The group consisted of 64 of the 105 co-twins interviewed and examined as described elsewhere.² Briefly, recruitment (over a period of 28 months) was predominantly via members of the Association of British Neurologists, who were asked to ascertain of all patients with multiple sclerosis seen by them whether they were a twin. Index cases and co-twins were all assessed by one of us (CJM) who used a standardised questionnaire to obtain clinical details followed by a full neurological examination. All 105 co-twins were requested to attend for MRI: of the 64 who were scanned 23 were monozygotic aged 21–53 (mean 37.5) years (four men) and 41 dizygotic aged 24–67 (mean 44.3) years (22 men). There were 21 monozygotic and 20 dizygotic (31 women) twins who were not scanned.

CONTROLS

The control group consisted of 40 healthy volunteers aged 18–72 (mean 41.3) years (20 men). They were recruited from hospital staff and friends of patients attending the unit. Relatives of patients with multiple sclerosis were excluded. All filled in a general health questionnaire seeking evidence of previous neurological illness, hypertension, cerebrovascular or cardiovascular disease, and diabetes.

MRI

Most twins were imaged at the National Hospitals for Neurology and Neurosurgery (NHNN) on a Picker 0.5 T (24 subjects) or General Electric 1.5 T Signa system (28), provided by The Multiple Sclerosis Society of Great Britain and Northern Ireland. Smaller numbers were scanned in other centres in the United Kingdom on 0.15T (2), 0.5T (4), or 1.5T (6) systems.

Moderately T2-weighted 5 or 10 mm axial images of the brain were obtained in all cases and more proton density-weighted images in some subjects. For example, the imaging

parameters for the Picker 0.5 T scanner, NHNN, were SE_{2080/60}, 5 mm contiguous slices, field of view 30 cm, 2 excitations, 128 × 256 matrix and for the GE Signa 1.5 T scanner, NHNN, SE_{2700/32,80}, 5 mm slices with 2.5 mm interslice gap, field of view 24 cm, 1 excitation, 192 × 256 matrix.

All the controls were imaged on the GE 1.5 T Signa scanner. In 21 T2 and proton density-weighted axial spin echo were obtained as described but in the remaining 19 fast spin echo images (either FSE_{3500/19,95} or FSE_{3100/76}) were obtained instead.

All images, with controls and twins interdigitated, were interpreted by one of us (BEK) without reference to the clinical history. A scan was judged to be abnormal if there were one or more areas of unequivocal high signal in the brain parenchyma compatible with demyelination. The site and size of every such lesion was noted. Abnormalities on MRI that were obviously not due to demyelination (for example, incidental arachnoid cysts) were ignored. To improve the specificity of MRI for detecting multiple sclerosis, those with an abnormal scan were classified separately according to whether or not they fulfilled the criteria of Fazekas *et al.*⁴⁶ With this system, MRI diagnosis of multiple sclerosis requires the presence of any two out of three abnormalities: (a) a lesion adjacent to the body of the lateral ventricles; (b) an infratentorial lesion; (c) a lesion greater than or equal to 6 mm in diameter. Previous evaluation of these criteria in 1500 consecutive patients reported a sensitivity of 81% and specificity of 96% for the diagnosis of multiple sclerosis.⁴⁷

Results

CLINICAL FEATURES

The mean age of the twins scanned was 41.8 (SD 10.4) and of the controls 41.3 (SD 13.2). The mean age of the twins not scanned was 44.2 (SD 12.9). Nine of the twins who were imaged (eight monozygotic and one dizygotic) were classified on clinical criteria alone as having possible, probable, or definite multiple sclerosis (table 1). There were two men and seven women. There were no significant differences in the demographic features of the 64 twins who were and the 41 who were not scanned. The most common reason given for refusal to be scanned was unwillingness to travel.

There were no differences between the 55 clinically unaffected co-twins and controls for frequency of hypertension or other cardiovascular disease, migraine, or cerebrovascular disease and none gave a history of neurological episodes suggestive of demyelination.

MRI FINDINGS

Clinically affected twins

There was good agreement between clinical and MRI findings (table 1). All nine twins had an abnormal scan (fig 1), and six fulfilled the criteria of Fazekas *et al.*⁴⁶ (four definite, one probable, and one possible multiple sclerosis).

Table 1 MRI findings in clinically concordant twins

Zygosity	Age (y)	Clinical classification	Criteria of Fazekas <i>et al.</i> ⁴⁶	Comments
Monozygotic	38	Definite	Met	
Monozygotic	43	Definite	Met	
Monozygotic	40	Definite	Not met	Many small lesions
Monozygotic	34	Possible	Not met	Single lesion only
Monozygotic	47	Probable	Not met	Many small lesions
Monozygotic	36	Definite	Met	
Monozygotic	35	Probable	Met	
Monozygotic	21	Possible	Met	
Dizygotic	40	Definite	Met	

Figure 1 MRI of 21 year old monozygotic twin with clinically possible multiple sclerosis showing multiple periventricular lesions.

One twin with definite and one with probable multiple sclerosis displayed multiple small ($\leq 5\text{mm}$) cerebral white matter lesions characteristic of multiple sclerosis, but there were no infratentorial or larger lesions to satisfy the criteria. One twin with clinically possible multiple sclerosis showed a single lesion in the cerebral white matter. Eight of nine therefore had an abnormal scan typical of multiple sclerosis.

In three twins, MRI increased the diagnostic

certainty. Multiple white matter lesions were seen in two monozygotic twins, aged 35 and 47, with probable multiple sclerosis and in a 21-year-old monozygotic twin with possible multiple sclerosis based on clinical criteria alone; using the criteria of Poser *et al*,⁴⁸ these patients were reclassified as having definite and probable multiple sclerosis respectively after including the MRI result.

Clinically unaffected twins

MRI was obtained in 55 asymptomatic twins, 15 monozygotic (aged 30–53, mean 37.9 y), and 40 dizygotic (aged 24–67, mean 44.4). Overall, lesions were detected in 6/15 (40%) monozygotic and 20/40 (50%) dizygotic twins (fig 2) and in 8/40 (20%) controls (table 2). The difference between dizygotic twins and controls was significant ($p < 0.01$, Fisher's exact test). This difference was, however, largely due to a group of elderly (age ≥ 60) dizygotic twins, all of whom had an abnormal scan. When the analysis was confined to those aged less than 60, MRI showed abnormalities in 6/15 (40%) monozygotic twins, 13/33 (39%) dizygotic twins and 7/37 (19%) controls, and the difference between dizygotic twins and controls was no longer significant.

All lesions detected in controls were small and none of the control subjects fulfilled the criteria of Fazekas *et al*⁴⁶ whereas eight clinically unaffected twins did. Three of these eight were older than 60. When the analysis was confined to those younger than 60, the criteria were satisfied in only 2/15 (13%) monozygotic twins, 3/33 (9%) dizygotic twins, and 0/37 controls, whereas minor MRI abnormalities not fulfilling the criteria were seen in 4/15 (27%) monozygotic twins, 10/33 (30%) dizygotic twins, and 7/37 (19%) controls.

Figure 2 Criteria of Fazekas *et al*⁴⁶ met in a 41 year old clinically normal dizygotic twin showing two periventricular white matter lesions. The subject also had a brainstem lesion.

Table 2 MRI findings in clinically discordant twins and controls

Age (y)	Normal MRI	MRI + (Faz-)	MRI + (Faz +)	Total	No (%) of abnormal scans
Controls:					
< 60	30	7	0	37	7 (19)
≥ 60	2	1	0	3	1 (33)
Total	32	8	0	40	8 (20)*
Monozygotic (all < 60 years)	9	4	2	15	6 (40)
Dizygotic:					
< 60	20	10	3	33	13 (39)
≥ 60	0	4	3	7	7 (100)
Total	20	14	6	40	20 (50)*

* $p < 0.01$ (Fisher's exact test).

MR+ = any abnormality present on MRI; Faz- = criteria of Fazekas *et al*⁴⁶ not satisfied; Faz+ = criteria of Fazekas *et al*⁴⁶ satisfied.

There was no significant effect of magnet field strength on the number of lesions detected.

Discussion

MRI was used in the present study to ascertain the frequency of clinically silent abnormalities thought likely to be due to multiple sclerosis and thereby to consolidate and extend the concordance rates that had already been calculated from clinical criteria alone.

One limitation is that we were only able to obtain MRI on 9/11 (82%) clinically affected and 55/94 (59%) of the clinically unaffected co-twins of index cases included in the clinical study.² Twins who were scanned had demographic characteristics similar to the entire cohort, however, and it seems reasonable to regard them as representative of the larger group. In particular, it should be emphasised that the 55 clinically unaffected co-twins who participated in the MRI study had all been screened by a clinician and did not have neurological symptoms or signs; this cohort was therefore unlikely to be biased through willingness to undergo MRI as a result of personal anxiety about disease.

The MRI was diagnostically useful in the 8/9 clinically affected twins of patients with multiple sclerosis who were examined. It displayed one or more lesions compatible with multiple sclerosis, however, in all nine, and in none did it reveal alternative diagnoses to account for the symptoms. In three, the diagnostic category of multiple sclerosis was made more certain after the MRI result was taken into account.

In evaluating the significance of abnormalities on MRI in the clinically unaffected twins, it is necessary to consider their age. Numerous surveys on healthy subjects aged over 60 have revealed a high frequency

(40–100%) of multifocal abnormalities of white matter.^{37 38 41–46} Such MRI findings have been correlated pathologically with cerebral small vessel disease.^{39 40} Because MRI is so often abnormal in this age group, the finding that all seven dizygotic twins aged over 60 had an abnormal MRI should be interpreted cautiously. Even criteria that are more specific for multiple sclerosis than simply the presence of an abnormality of white matter have been shown to be at their least specific among the elderly subjects.⁴⁷ It is likely that most of the MRI abnormalities seen in these seven elderly dizygotic twins are due to incidental age-related vascular disease, but the possibility that some are due to multiple sclerosis cannot be excluded. To achieve a reasonable degree of specificity for multiple sclerosis, however, it is wise to confine the analysis to younger adults (aged less than 60).

If it is assumed that all twins aged less than 60 with an abnormal scan actually have multiple sclerosis, the overall (clinical plus radiological) concordance rate would be 55% for monozygotic and 41% for dizygotic twins. If the stricter criteria of Fazekas *et al*⁴⁶ are applied for MRI diagnosis, the overall concordance rates are 34% and 12% for monozygotic and dizygotic twins respectively.

Several previous studies have reported MRI findings in clinically unaffected twins of patients with multiple sclerosis. Kinnunen *et al*⁴⁹ found no abnormalities on low field strength MRI in five monozygotic and six dizygotic clinically unaffected twins, McFarland *et al*⁵⁰ in 1/3 monozygotic and 0/1 dizygotic (MRI was also normal in the clinically affected member of the dizygotic pair) and Uitdehaag *et al*⁵¹ in 3/4 monozygotic and 0/3 dizygotic. These are small numbers, and the last two studies recruited subjects by public appeal, which introduces an important ascertainment bias. The recent French¹² and Canadian update¹¹ studies provide MRI data on 42 and 32 clinically unaffected co-twins respectively. The first used the criteria of Paty and associates³¹ for the MRI diagnosis of multiple sclerosis, the second criteria of Fazekas *et al*.⁴⁶ The MRI findings in these two studies are in agreement with our results (table 3) with less than 20% of asymptomatic subjects having scans suggestive of demyelination; neither were there significant differences between monozygotic and dizygotic co-twins.

Even if the presence of any MRI abnormality is taken for the purposes of this study to indicate multiple sclerosis in clinically unaffected twins under the age of 60, the concordance rate in monozygotic twins falls well short of the 100% needed to support a necessary genetic aetiology for multiple sclerosis; about one third are both clinically unaffected and have a completely normal MRI. It could be argued, somewhat improbably, that some of the remaining discordant monozygotic twins have purely spinal multiple sclerosis (a region not examined by MRI in this study), or that the disease has yet to express itself although the mean age of the cohort (42 years) is already beyond the age at which most

Table 3 MRI findings in healthy co-twins

	Monozygotic		Dizygotic	
	n	Multiple sclerosis criteria satisfied	n	Multiple sclerosis criteria satisfied
Alperovich <i>et al</i> ¹³	13	3	29	6
Sadovnick <i>et al</i> ¹²	21	4	11	1
United Kingdom study	15	2	33	3
Total	49	9 (18.4%)	73	10 (13.7%)

patients first develop clinical symptoms of multiple sclerosis. What seems more likely is that these figures are in fact an overestimate of the true pathological frequency of the disease. The abnormalities shown with MRI were usually few in number and small in size (fig 2), and it is notable that minor abnormalities not fulfilling the criteria of Fazekas *et al*⁴⁶ were only slightly more frequent in both categories of twins than in healthy singleton controls (monozygotic = 4/15, 27%; dizygotic = 10/33, 30%; controls = 7/37, 19%; NS). It is also possible that such minor differences as exist could be due to being a twin per se—twins are more liable than singletons to perinatal trauma and prematurity, which might conceivably produce non-specific MRI abnormalities.

The nature and frequency of the abnormalities in our 20–60 year old controls are similar to those reported in other series.^{36–45} Although definitive pathological correlation is not available, several lines of evidence favour a vascular process: (1) the lesions are predominantly punctate, and discretely placed in the deep cerebral or subcortical white matter, similar to the pattern in elderly controls where the lesions have been correlated with vascular disease, and unlike classical multiple sclerosis in which periventricular lesions predominate; (2) the lesions are more often seen in the presence of risk factors for cerebrovascular disease such as hypertension^{37 38 41 45} or with a history of frequent classical migraine attacks³⁶; (3) such lesions are seen in 20% or more of healthy adults aged less than 60, and it is inherently unlikely that multiple sclerosis approaches anything close to this frequency in the general population. Given the frequency of abnormalities on MRI, it would seem wise to develop MRI criteria that are more specific for multiple sclerosis, even in this younger age group. Several criteria for diagnosis of multiple sclerosis by MRI have been devised.^{26 31 52 46} None is absolutely specific. The most thoroughly validated criteria are those of Fazekas *et al*,⁴⁶ which in a study of 1500 consecutive cases had a 96% specificity and an 81% sensitivity for multiple sclerosis.⁴⁷ Most of the false positive diagnoses were found in older patients suggesting that the specificity was nearer 99% in those under 60 years old. It is notable that none of 37 healthy controls in the present study had abnormalities that fulfilled the criteria of Fazekas *et al*.⁴⁶ Although multiple sclerosis can undoubtedly be present without these criteria being met, their application will only exclude a few genuine cases and the use of less rigorous criteria will undoubtedly lead to significant overascertainment by including those with minor, non-specific, age-related vascular changes.

We therefore conclude that the true pathological concordance for multiple sclerosis in this twin series aged less than 60 is probably around 35% for monozygotic and 10% for dizygotic twins. The frequency of MRI abnormality is no greater in the clinically unaffected monozygotic than dizygotic twins, and MRI only increases the concordance rate in either

group by about 10% over that obtained through clinical assessment alone. Whereas the higher overall concordance in monozygotic twins confirms a contribution of genetic factors to the aetiology of multiple sclerosis, the lack of clear clinical or MRI evidence for multiple sclerosis in about two thirds of monozygotic twins suggests that environmental factors are also relevant.

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