SHORT REPORT

Assessing the risk of early multiple sclerosis in patients with clinically isolated syndromes: the role of a follow up MRI

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Abstract

Objectives—With increasing evidence that permanent tissue damage occurs early in the course of multiple sclerosis, it is important that treatment trials include patients in the earliest stages of the disease. For many patients with multiple sclerosis the first presentation is a clinically isolated syndrome. Not all patients with a clinically isolated syndrome develop multiple sclerosis, however, and treatment of all such patients would be unwarranted. A single abnormal brain MRI identifies patients at a higher risk for the early development of multiple sclerosis, but current criteria are limited by either poor specificity (T2 lesions) or sensitivity (contrast enhancing lesions). The aim of the study was to assess the positive predictive value, sensitivity, and specificity of MRI indices for the development of multiple sclerosis after 1 year from two MRI examinations obtained 3 months apart.

Methods—MRI examinations were performed in 68 patients with a clinically isolated syndrome, with a clinical assessment after 1 year.

Results—Contrast enhancing lesions at both time points were the most predictive indices for developing multiple sclerosis (positive predictive value 70%) but had low sensitivity (39%). The combination of T2 lesions at baseline with new T2 lesions at follow up had the best overall positive predictive value (53%), sensitivity (83%), and specificity (76%). In patients with T2 lesions at baseline, the presence or absence of new T2 lesions at follow up significantly altered the risk of multiple sclerosis within 1 year (55% and 5% respectively, p<0.001). Multiple sclerosis also developed in 10% of patients with a normal baseline MRI.

Conclusions—Serial imaging in patients with clinically isolated syndromes improved the positive predictive value, sensitivity, and specificity of MRI for the development of early multiple sclerosis and also identified patients at a lower risk of early multiple sclerosis than would have been expected from their abnormal baseline MRI. Selection of patients with clinically isolated syndromes for therapeutic intervention or clinical trials may benefit from serial MRI, to target those at greatest risk of early development of multiple sclerosis.

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Several recent studies indicate that permanent tissue damage occurs early in the course of multiple sclerosis.[1 2] It is therefore important that trials of disease modifying drugs include patients at the earliest stages of the disease. In most cases the first clinical episode in multiple sclerosis is a clinically isolated syndrome involving CNS white matter. Not all patients with clinically isolated syndromes will develop multiple sclerosis and so treatment of all such patients would be unwarranted. In 50%–80% of patients, focal areas of high signal, identical to those seen in patients with established multiple sclerosis, have been found on T2 weighted MRI.[3–5] The presence of these "T2 lesions" significantly increases the risk that a patient will have a relapse leading to a diagnosis of multiple sclerosis over subsequent years.[6–8] These abnormalities are, however, relatively nonspecific and are often found in patients who do not have further symptoms. Contrast enhancing lesions, when found in patients presenting with a clinically isolated syndrome, have been found to be more predictive MRI indices for the development of multiple sclerosis within 3 years.[9] However, one or more enhancing lesions are seen in only a third of patients with a clinically isolated syndrome at presentation[5 9 10] meaning that many patients at risk of relapses are not identified.

Our aim was to assess the relative predictive value, sensitivity, and specificity for the development of multiple sclerosis after 1 year of several MRI indices in a cohort of patients presenting with clinically isolated syndromes from two MRI examinations, one performed at presentation, and the second 3 months later.

Early MR findings in 68 patients with clinically isolated syndromes of whom 18 developed multiple sclerosis (MS)* within 1 year

MRI index	Cut off point	Prevalence n (%)	MS n	PPV %	Sensitivity %	Specificity %
Baseline MRI:						
Lesions on T2 weighted imaging	1	48 (71)	16	33	89	36
	4	37 (54)	14	38	78	54
	9	25 (37)	11	44	61	72
Contrast enhancing lesions	1	21 (31)	11	52	61	80
Baseline and follow up MRI:						
Lesions on T2 weighted imaging at baseline and new lesions at follow up	1	27 (40)	15	55	83	76
Contrast enhancing lesions at baseline and new contrast enhancing lesions at follow up	1	10 (15)	7	70	39	94

*Clinically probable or definite MS.

Methods

Patients were recruited from the wards and clinics of The National Hospital for Neurology and Neurosurgery and from the physicians' clinic at Moorfields Hospital, London, UK. A clinically isolated syndrome was defined as the occurrence of a presumed inflammatory demyelinating event of acute onset in the CNS in a patient with no history suggestive of an earlier demyelinating episode. In all patients appropriate investigations were carried out to exclude alternative diagnoses. Only patients between the ages of 16 and 50 years were included. The study had received approval from local ethics committees. Informed consent was obtained from all patients before entry into the study.

MAGNETIC RESONANCE IMAGING

Brain imaging was performed at presentation and again after 3 months. All imaging was performed on a 1.5 Tesla Signa (General Electric, Milwaukee, WI, USA) imager. Before imaging an intravenous bolus of 0.1 mmol/kg gadolinium-DTPA was administered. Proton density (PD) and T2 weighted images were acquired using a duel echo fast spin echo (FSE) sequence with a repetition time (TR) of 3200 ms and effective echo time (TE) of 15/95 ms. A T1 weighted spin echo image (TR=600 ms, TE=14 ms) was acquired 15 minutes after the injection of the gadolinium-DTPA. For each sequence, 46×3 mm contiguous axial slices were acquired. The field of view=24 cm, matrix=256^2, and number of excitations=1.

CLINICAL ASSESSMENT

All patients were assessed clinically after 1 year. They were classified according to the criteria of Poser *et al*[11] as having clinically probable or definite multiple sclerosis or remaining as a clinically isolated syndrome, using only clinical information. Although the criteria of Poser *et al* for diagnosis of multiple sclerosis requires 1 month between relapses, we stipulated a 3 month interval to reduce the chance of including patients with a slowly evolving acute disseminated encephalomyelitis. In practical terms, acute disseminated encephalomyelitis rarely proves to be the diagnosis in this adult clinically isolated syndrome cohort.

IMAGE ANALYSIS

The images were reviewed by an experienced neuroradiologist, blinded to the clinical state. The number of high signal lesions on T2 weighted images and contrast enhancing lesions on each examination were recorded. Images were reported as normal if they had no lesions compatible with demyelination, or if only the symptomatic lesion, as determined by a separate unblinded observer, was visible. They were reported as abnormal if one or more asymptomatic lesions compatible with demyelination was present.

STATISTICAL ANALYSIS

Based on clinical outcome at 12 months the number of true positives (TP: test abnormal, multiple sclerosis diagnosed), true negatives (TN: test normal, no multiple sclerosis), false positives (FP: test abnormal, no multiple sclerosis) and false negatives (FN: test normal, multiple sclerosis diagnosed) were calculated for each parameter and used to determine its positive predictive value: (TP/(TP+FP)), sensitivity: (TP/(TP+FN)), and specificity: (TN/(TN+FP)).

Results

We recruited 81 patients with a clinically isolated syndrome into the study (60 of whom were the subject of an earlier report on multisequence MRI in clinically isolated syndromes[5]). Of these, 68 (84%) attended all three visits and were the subject of this analysis. There were 39 women and 29 men. The mean age at presentation was 31 years (range 17–50 years). The presenting symptom was optic neuritis in 45, a brain stem syndrome in 16, a spinal cord syndrome in six, and an optic tract lesion in one case.

The first MRI (baseline) was performed a median of 5 weeks (range 1–12 weeks) after the onset of symptoms, the second after a further 13 weeks (range 8–20) and the clinical assessment after a median of 12 months (range 11–19 months) from baseline. Of the 68 patients, 48 (71%) had an abnormal baseline MRI (median number of T2 lesions five, range 0–76); 18 (26%) developed clinically definite (14) or probable (four) multiple sclerosis after 1 year.

The most predictive index from the baseline images alone was the presence of one or more contrast enhancing lesions (positive predictive value 52%, table 1). This had high specificity (80%) but a relatively low sensitivity (61%) for the development of multiple sclerosis. A single lesion on the baseline T2 weighted images was very sensitive, being present in 16 (89%) of the patients who subsequently developed multiple sclerosis, but had a poor specificity (36%); increasing the number of T2 lesions required improved specificity but at the expense of sensitivity. Two (10%) patients with a normal baseline MRI examination developed multiple sclerosis.

The combination of baseline lesions on T2 weighted images with new T2 lesions at follow up seemed to give the most robust overall prognostic data with a positive predictive value of 55% and both high sensitivity (83%) and specificity (76%). The presence or absence of new T2 lesions at follow up in patients with abnormal baseline T2 weighted MRI examina-

tions significantly altered the risk of developing multiple sclerosis (55% and 5% respectively; p<0.001 (χ^2 test)). The median number of T2 lesions at presentation in the first group was 20 (range 1–76) and in the second it was five (range 1–20).

The combination of enhancing lesions on the T1 weighted images of both examinations had the highest positive predictive value (70%) and specificity (94%), but had a very low sensitivity (39%) for the development of multiple sclerosis. All patients with new enhancing lesions at follow up also exhibited new T2 lesions.

Discussion

This study has shown that the predictive value of MRI in determining the risk of a patient presenting with a clinically isolated syndrome developing clinically definite or probable multiple sclerosis within a year can be improved by a second MRI performed several months after presentation. Thus, the presence of an abnormal baseline image combined with new T2 lesions at follow up had a better combination of positive predictive value, sensitivity, and specificity than any lesion parameter obtained from a single MRI examination. Such a combination is desirable for optimal patient selection for treatment trials aimed at preventing the development of multiple sclerosis. The high positive predictive value—that is, risk for multiple sclerosis, in untreated patients means that a placebo controlled trial will have a good power to show a reduction in the proportion developing multiple sclerosis in the active treatment arm. A high sensitivity means that few patients who will go on to develop multiple sclerosis would be excluded from the trial. A high specificity means that few of the patients not developing multiple sclerosis would be included in the study.

Abnormalities on MRI based on a single scan have been recently used to select patients for clinical trials of β-interferon aimed at delaying the conversion from a clinically isolated syndrome to clinically definite multiple sclerosis.[10 12] Our new serial MRI data suggest that it may be possible to identify a subgroup of patients with a low risk for early multiple sclerosis despite an abnormal baseline T2 weighted MRI examination—only 5% who did not develop new lesions at 3 months went on to develop clinical multiple sclerosis at 1 year. Serial MRI criteria may thus identify patients with an abnormal baseline scan who are less suitable for early treatment or clinical trial participation. However, the follow up period needs to be extended before the risk for multiple sclerosis can be more accurately determined.

As with previous studies,[9] the presence of contrast enhancement was the most predictive parameter from a single image. The presence of contrast enhancing lesions at both baseline and follow up further improved positive predictive value and specificity. Contrast enhancement reflects a defect in the blood-brain barrier, which occurs early in inflammatory demyelinating lesions[13] and usually lasts for 4–6 weeks.[14] This combination almost certainly reflects new lesion formation at different time points, strongly suggesting multiple sclerosis as the underlying pathology. The usefulness of such a combination for selection of patients for clinical trials is limited, however, by its low sensitivity—that is, it would exclude many patients who would go on to develop early clinical multiple sclerosis. It might have a role in identifying a subgroup who seemed to have a particularly high risk for the early development of multiple sclerosis (70% did so in this study).

Two (10%) patients with normal baseline and follow up imaging did develop multiple sclerosis during this study. Both presented with optic neuritis, one then developing a spinal cord and one a brain stem syndrome. This emphasises the fact that patients with normal brain MRI examination at presentation are still at risk from relapses, although numerous studies have shown that this risk, even in the long term, is substantially less than for those who have abnormal imaging at presentation.[6–9]

Our study investigated the predictive value of only two serial scans. It is possible that more extensive serial MRI (for example, monthly for 6 months, or 3 monthly for 1 year) will provide better prognostic data. Further studies using such protocols are required.

Although this cohort of patients has been followed up for only 1 year, a large prospective study of patients with relapsing-remitting multiple sclerosis has found that relapsing disease activity within the first 1–2 years has a major influence on future disability.[15] More accurate identification of such a subgroup from early serial MRI studies therefore has potential long term relevance although further follow up is necessary to clarify the long term risk for multiple sclerosis and disability. In the meantime, the evidence that serial MRI has advantages over a single examination in identifying patients at greatest risk of developing early clinical multiple sclerosis, suggests a role for this approach in the selection of patients with clinically isolated syndromes for clinical trials, or for early therapeutic intervention.

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NEUROLOGICAL STAMP

Paul Emilio Roux (1853–1933)

The French microbiologist Emilio Roux obtained his MD in 1881. He then joined the newly created Pasteur Institute and in 1904 became its director; he remained in this post until his death in 1933. Roux worked with Pasteur with many of his medical discoveries. He assisted in his work with anthrax vaccination and did much of the early work
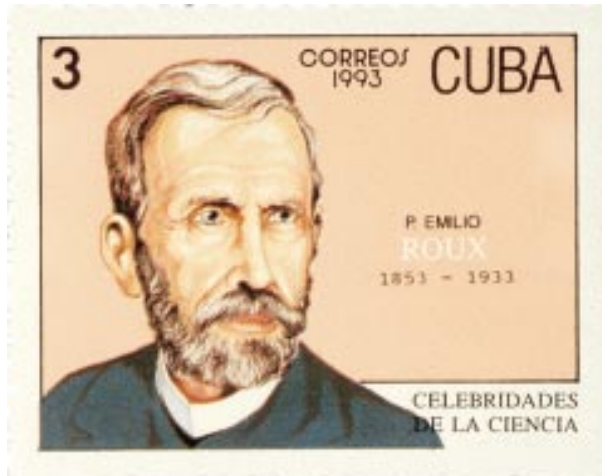
on the development of a rabies vaccine. Later he disagreed with Pasteur on the speed with which the vaccine was applied to humans and withdrew from the project.

His most important work was his discovery in 1885 with the Swiss bacteriologist Alexandre Yersin of diphtheria toxins and that the menace of diphtheria lay not in the bacteria themselves, but in the lethal toxin produced. Later he inoculated horses with the toxin and collected the serum, which contained an antitoxin. By 1894 he had tried this serum on patients in the Enfants Maladies Hospital in Paris. Within 4 months the mortality from diphtheria fell from 51% to 24%.

In 1903 Roux, with Elie Metchnikoff, achieved some success in transmitting syphilis to a chimpanzee. This facilitated the laboratory investigation of syphilis and the search for a cure.

He suffered in the last 30 years of his life from chronic tuberculosis. Roux never married and lived in the hospital. He gave all his money to the Pasteur Institute and after a national funeral was buried in the garden of the institute. The institute is situated on the Rue de Docteur Roux.

Roux was postally honoured by France in 1954 (Stanley Gibbons 1219, Scott B289) and again by Cuba in 1993 (Stanley Gibbons 3806, Scott 3484).

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