Cognitive impairment in multiple sclerosis can be predicted by imaging early in the disease

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ABSTRACT

Background: Cognitive impairment is common in multiple sclerosis (MS) and adds significantly to the burden of the disease. The ability to predict future cognitive impairment from imaging obtained at disease onset has not been investigated.

Methods: 62 patients imaged within 3 months of a clinically isolated syndrome were assessed neuropsychologically 7 years later. Baseline and periodic MRI measures of lesions, atrophy and normal-appearing white and grey matter were regressed against neuropsychological scores to explore the best predictors of cognitive outcome.

Results: 28 patients had developed clinically definite MS at follow-up and a further nine met revised McDonald criteria for MS. Deficits in speed of information processing and executive function were the most common abnormalities. Poor performance correlated with high anxiety ratings. Baseline T_1 lesion metrics predicted executive deficits, and new T_2 lesions at the 3-month follow-up predicted slowed information processing. An increase in myo-inositol concentration in normal-appearing white matter over the first 3 years was associated with poor executive function.

Conclusions: MRI variables obtained at the onset of a clinically isolated syndrome can predict future development of cognitive abnormalities. Our findings may have implications in monitoring and treating patients.

Multiple sclerosis (MS) commonly presents as a clinically isolated syndrome (CIS). About 40% of cases of CIS convert into clinically definite MS (CDMS) in 5 years.[1 2] Early MRI abnormalities predict conversion into CDMS and disability,[3] but predicting subsequent cognitive deterioration from early imaging has not been fully explored. In our 5-year follow-up of patients with relapsing–remitting MS (RRMS),[4] we were able to predict cognitive impairment from baseline changes in normal appearing white matter (NAWM) and brain atrophy rate in the first year. Here we use imaging obtained early after the onset of a CIS to predict cognitive impairment 7 years later.

METHODS

Subjects

Sixty-two patients (36 female), part of a prospective cohort (mean (SD) age at baseline 32.5 (8.52) years (range 16–50); mean years of education 13.8 (2.93) (range 9–21)) recruited within 3 months (mean 5.6 weeks) of CIS onset participated; 48 had optic neuritis, 11 brain-stem and three cord syndromes. Clinical and neuropsychological assessments were conducted on average 7.2 years (range 4.8–9.8) later, and the revised McDonald criteria[5] were used for diagnosis. This study was approved by the local ethics committee, and patients gave written consent.

Clinical examination

The Expanded Disability Status Scale (EDSS)[6] and the Hospital Anxiety and Depression Scale (HADS)[7] were used. Scores of 11 or more in the HADS were considered to indicate anxiety or depression.

Neuropsychological assessment

Testing was performed (by MS) in one 2 h session.

1. General intellectual functioning: Wechsler Adult Intelligence Scale—Revised[8] (for current verbal, performance, and full-scale IQ); National Adult Reading Test[9] to estimate premorbid functioning. IQ decline was defined as $\geqslant$15 points difference between current and premorbid IQ.
2. Verbal and visual recall memory: Story and Figure recall subtests of the Adult Memory and Information Processing Battery.[10]
3. Attention/speed of information processing: Paced Auditory Serial Addition Test (PASAT)[11] (2-second and 3-second versions) and Symbol Digit Modalities Test (SDMT).[12]
4. Executive functions: Spatial Working Memory from the CANTAB[13] Hayling Sentence Completion Task (tests verbal response generation and inhibition); Brixton Spatial Anticipation Test[14]

Raw test scores were compared with those of published, age-adjusted healthy controls for all tests except the PASAT and SDMT.[15] As there were no gender differences or significant correlations with years of education in the patients' scores, comparisons with normative data were not adjusted for these variables. Scores at or below the 5th centile of published norms were considered to indicate impairment. For the PASAT and SDMT, age-standardised scores were normally distributed, and z-scores were calculated. Those falling $\leqslant$2 SD below the mean were considered to indicate impairment. Averaged z-scores from memory, attention and executive function tests were obtained and these were averaged to produce a composite z-score.

MRI

MRI performed on a 1.5 T GE Signa scanner at baseline and over the first 3 years was used.

Baseline imaging:

1. Hyperintense T_2 lesions identified on proton-density and T_2-weighted fast spin-echo images were contoured on the proton-density images

(fast spin-echo sequence: repetition time 3200 ms, echo time 15/95 ms, 46×3 mm contiguous axial oblique slices).

2. Hypointense T_1 and gadolinium (Gd) enhancing lesions identified and contoured[16] on post-contrast T_1-weighted spin-echo images (repetition time 600 ms, echo time 17 ms, 46×3 mm contiguous axial oblique slices) 5–7 min after intravenous 0.1 mmol/kg Gd.
3. Grey/white matter volumes. A mask of lesions in T_2-weighted images was created to avoid misclassification. The T_2 images were segmented using SPM99, and results expressed as fractions of total intracranial volume.

Imaging at 3 months:

1. Spectroscopic metabolites. Concentrations of N-acetyl aspartate plus N-acetylaspartyl glutamate, creatine, choline, glutamate plus glutamine, and myo-inositol were measured in a single voxel placed in the NAWM of the posterior parietal lobe and centrum semiovale using a point-resolved spectroscopy sequence.[17]

Longitudinal MRI data:

1. Changes over 3 months: number and volume of T_1, T_2 and Gd-enhanced lesions.
2. Changes over 1 year: volume of lateral ventricles at baseline and 1 year later on T_1-weighted spin-echo images using MIDAS,[18] and changes in NAWM metabolite concentration.
3. Changes over 3 years: changes in metabolite concentration and changes in the white and grey matter fractions from baseline to the 3-year follow-up.

Statistical analysis

t Tests and Mann–Whitney U tests were used to compare patients who had and had not developed MS, binomial single proportion exact tests to compare the proportions of expected and found to be cognitively impaired, and multiple linear regression to assess the variance in neuropsychological scores accounted for by demographic, clinical and MRI variables. Gender, age at onset, premorbid IQ, β interferon treatment, and HADS scores were entered in the first step, and only significant variables were retained in the second step when MRI variables were entered singly. No adjustment was made for multiple comparisons, as such adjustment would have incorrectly assumed that the various cognitive measures were independent.

RESULTS

At follow-up, 25 patients had CIS and 37 met revised McDonald criteria.[5] Of these, 26 had clinically definite RRMS, two had secondary progressive MS, and nine had no further relapses. The mean (SD) EDSS at follow-up was 1.61 (1.43) (range 0–7.5). Five patients were taking β interferon. There were no demographic, premorbid IQ, or baseline EDSS differences between CIS patients and the rest. The mean EDSS change during the follow-up was +0.15 (−3.0 to +5.0), and EDSS at follow-up differed significantly between patients with MS (1.5) and CIS (1.0) ($U = 159$, $p<0.001$). Fifty-seven patients were able to work. Four required substantial daily support. Twelve (27%) and four (9%) of 45 patients had abnormal anxiety or depression scores.

Patterns of cognitive impairment

More patients than expected were impaired on three tests of attention/speed of information processing (PASAT 3, 34% impaired, $p<0.001$; PASAT 2, 32% impaired, $p<0.001$; and SDMT, 14% impaired, $p<0.001$) and one of executive function (Brixton Spatial Anticipation Test, 14% impaired, $p = 0.007$). On the Hayling Sentence Completion Task, 10% were impaired ($p = 0.07$).

The most common impairment was in attention/speed of information processing (19.4%). IQ decline alone was present in five (8.1%), and a combination of attention/speed of information processing and executive deficits was present in five (8.1%). Conversion to CDMS had occurred in 16 of 29 patients (55%) without impairment, and also in 21 of 33 (64%) cognitively impaired ($\chi^2 = 0.136$, $df = 1$, ns).

Predicting cognitive performance at follow-up

Demographic and clinical variables

Women had a greater IQ deficit, but gender did not predict performance otherwise. Older age at onset and lower premorbid IQ predicted poor memory, executive function and overall cognitive scores. Low premorbid IQ also predicted poor performance in the PASAT 2 and 3 and SDMT. High EDSS at follow-up correlated with poor performance on the SDMT and the Hayling test.

High anxiety scores were associated with poor performance in the PASAT 2 and 3 and Brixton Spatial Anticipation Test and with poor memory, attention and overall cognitive scores. Anxiety scores were therefore retained in multiple regressions (table 1).

MRI variables

Number of T_1 lesions predicted overall cognitive score and failure in the Brixton Spatial Anticipation Test (60% sensitivity and 97% specificity), and volume of T_1 lesions predicted performance in the Hayling test. The number of Gd-enhancing lesions predicted memory, executive and overall cognitive scores.

The grey matter tissue fraction was the only measured volume that predicted poor executive function.

Increased T_2 lesions in the first 3 months predicted poor attention (SDMT) and executive function (Spatial Working Memory and Hayling test), and increased myo-inositol concentration in the first 3 years predicted poor executive function.

Metabolite concentrations, ventricular volume change in the first year, and changes in white and grey matter fractions over 3 years did not predict cognitive performance.

DISCUSSION

By 7 years after a CIS, only half of our patients had mild cognitive impairment, usually affecting attention, speed of information processing, and executive function—a pattern resembling that previously reported by ourselves in patients with optic neuritis[19] and RRMS[4] and by others.[20]

Age at onset was a robust predictor of subsequent cognitive impairment, independent of T_2 lesion metrics, in keeping with previous reports,[21] suggesting that, in addition to inflammation, an age-dependent "neurodegenerative" process causing diffuse axonal loss may contribute to cognitive disability.[22] Premorbid IQ also predicted cognition at follow-up, suggesting that "cognitive reserve" may influence the compensatory functional reorganisation of cognitive networks.

We found lesion metrics to be the best predictors. Regarding T_1 lesions, this was somewhat unexpected, as such lesions are few in CIS. Persistent non-enhancing T_1 lesions represent irreversible axonal and myelin damage, and their presence in CIS may be a harbinger of severe pathology. Baseline Gd-enhancing lesions and new T_2 lesions at 3 months were both associated with subsequent cognitive impairment, suggesting

Table 1 Neuropsychological testing at 7 years follow-up. Significant linear regression

Cognitive measure	Clinical/demographic predictors	Best MRI predictor	Next-best MRI predictor
Commonly failed neuropsychological domains and tests			
Overall attention score	Premorbid IQ ($\beta = 0.590$, 95% CI 0.345 to 1.800, $p<0.001$); anxiety ($\beta = -0.298$, 95% CI −0.544 to −0.073, $p = 0.012$)	–	–
PASAT 3	Premorbid IQ ($\beta = 0.479$, 95% CI 0.216 to 0.654, $p<0.001$); anxiety ($\beta = -0.419$, 95% CI −0.669 to −0.181, $p = 0.001$)	–	–
PASAT 2	Premorbid IQ ($\beta = 0.387$, 95% CI 0.132 to 0.637, $p = 0.004$); anxiety ($\beta = -0.500$, 95% CI −0.834 to −0.273, $p<0.001$)	–	–
SDMT	Premorbid IQ ($\beta = 0.492$, 95% CI 0.240 to 0.704, $p<0.001$)	New T_2 lesions at 3 months ($\beta = -0.390$, 95% CI −0.398 to −0.091, $p = 0.002$)	–
Overall executive score	Premorbid IQ ($\beta = 0.654$, 95% CI 0.385 to 0.750, $p<0.001$); age at onset ($\beta = -0.231$, 95% CI −0.406 to −0.026, $p = 0.027$)	Number of T_1 lesions ($\beta = -0.191$, 95% CI −0.501 to −0.037, $p = 0.09$)	–
Hayling test (errors)	Premorbid IQ ($\beta = 0.436$, 95% CI 0.175 to 0.636, $p = 0.001$)	Volume of T_1 lesions ($\beta = -0.418$, 95% CI −0.429 to −0.090, $p = 0.004$)	New T_2 lesions at 3 months ($\beta = -0.289$, 95% CI −0.342 to −0.013, $p = 0.035$)
Brixton test	Age at onset ($\beta = -0.368$, 95% CI −0.624 to −0.123, $p = 0.004$)	myo-Inositol increase ($\beta = -0.472$, 95% CI −0.601 to −0.137, $p = 0.004$)	Number of T_1 lesions ($\beta = -0.270$, 95% CI −0.568 to −0.072, $p = 0.013$)
Other neuropsychological domains			
Overall cognitive score	Premorbid IQ ($\beta = 0.685$, 95% CI 0.434 to 0.786, $p<0.001$); age at onset ($\beta = -0.193$, 95% CI −0.374 to −0.01, $p = 0.05$)	Number of Gd-enhancing lesions ($\beta = -0.258$, 95% CI −0.417 to −0.028, $p = 0.024$)	Number of T_1 lesions ($\beta = -0.226$, 95% CI −0.535 to −0.019, $p = 0.034$)
Overall memory score	Premorbid IQ ($\beta = 0.332$, 95% CI 0.079 to 0.535, $p = 0.012$); anxiety ($\beta = -0.292$, 95% CI −0.533 to −0.028, $p = 0.026$); age at onset ($\beta = -0.378$, 95% CI −0.570 to −0.112, $p = 0.005$)	Number of Gd-enhancing lesions ($\beta = -0.357$, 95% CI −0.617 to −0.072, $p = 0.015$)	–
Spatial working memory (accuracy score)	Premorbid IQ ($\beta = 0.488$, 95% CI 0.239 to 0.705, $p<0.001$)	Number of Gd-enhancing lesions ($\beta = -0.278$, 95% CI−0.509 to −0.030, $p = 0.048$)	–

Unless otherwise stated, all MRI variables reported are from baseline. Higher neuropsychological test scores indicate better performance.
β, standardised correlation coefficient; PASAT, Paced Auditory Serial Addition Test; SDMT, Symbol Digit Modalities Test.

that early inflammatory activity mediates cognitive impairment.

Contrary to previous reports,[23] early measures of progressive brain atrophy did not predict subsequent cognitive performance. Possible explanations are that our patients, in the early stages of disease, had mild cognitive and physical disability, and that the two-dimensional T_2-weighted sequence used to segment grey matter and white matter was suboptimal. Increased myo-inositol concentration probably reflects a glial/inflammatory response in the NAWM and predicted conversion to MS and clinical disability in our previous studies.[3 16 24] Together with the lack of correlation between cognitive performance and N-acetyl aspartate plus N-acetylaspartyl glutamate concentration, our findings suggest that a diffuse glial/inflammatory process, without significant axonal loss, may be sufficient to impair cognition.

Lack of baseline cognitive data is a limitation to our study and makes it impossible to ascertain the onset and course of cognitive impairment.

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