Cognitive Impairment Among Patients with Multiple Sclerosis. Associations with Employment and Quality of Life.

J Campbell [1], W Rashid [2], M Cercignani [1], D Langdon [3].

1 Clinical Imaging Sciences Centre, Brighton and Sussex Medical School, Falmer, United Kingdom.
2 Department of Neurology. Brighton and Sussex University Hospitals NHS Trust.
3 Department of Neuropsychology. Royal Holloway. University of London

Abstract

Objectives

To explore the relationship between cognitive impairment and conventional measures of disability in multiple sclerosis (MS), quality of life (QOL) and employment status using the Brief International Cognitive Assessment for MS (BICAMS) in the routine outpatient clinic.

Methods

62 patients with MS were assessed on the Brief International Cognitive Assessment for MS (BICAMS) test battery for cognitive impairment. Data was obtained on employment status and a number of questionnaires completed including; Fatigue Severity Score (FSS), Multiple Sclerosis Neuropsychological Questionnaire (MSNQ), Hospital Anxiety and Depression Scale (HADS) the Functional Assessment of MS (FAMS) as well as on the EuroQOL five dimension questionnaire (EQ-5D). Other assessments include the Patient Activation Measure (PAM-13) and Unidimensional Self-Efficacy scale for MS (USE-MS).

Results

Cognitive assessment revealed 44 subjects (65%) had evidence of cognitive impairment on formal testing. In comparison with patients without evidence of cognitive impairment, cognitively impaired patients exhibited significantly higher rates of unemployment (p = 0.009). The SDMT was the most significant predictor of unemployment.

Cognitive impairment was associated with lower QOL scores on the FAMS (p = 0.001) and EQ-5D (p <0.001).

Conclusion

BICAMS provides a sensitive and easy to administer screening test for cognitive impairment within the outpatient setting. Cognitive impairment is common in our cohort of MS patients attending outpatients and appears to be associated with increased rates of unemployment and lower measures of quality of life.

Introduction:

Multiple sclerosis (MS) is a common inflammatory condition affecting the central nervous system (CNS) and is the most common cause of acquired, non-traumatic disability in young adults [1]. As well as the physical disability associated with MS there exist significant non-motor manifestations. Rates of depression and cognitive dysfunction are higher among patients with MS than the general population [2]. Of these, cognitive dysfunction is particularly under recognised and currently, presents limited opportunity for intervention or treatment. Studies have revealed that cognitive impairment is present in 40-65% of individuals with clinically definite MS on neuropsychological testing [2]. Cognitive impairment has been identified at all stages and affects all subtypes of MS. Studies have shown cognitive deficits, (in particular deficits in information processing speed, concentration and working memory) to be present in the early stages of MS including clinically isolated syndrome (CIS) [3] [4]. The presence of cognitive impairment may therefore provide a measure of diffuse brain pathology early in the course of MS.

Cognitive impairment has a broad negative impact on the lives of people with MS independent of physical symptoms [5]. Perhaps the most severe and far-reaching effect is unemployment, which results in extensive personal, social and financial costs. Cognition has been linked to unemployment in many countries [6] [7]. Cognition has been shown to mediate the effects of disability on employment status [8]. Within 10 years of diagnosis, about 50% of people with MS are unemployed [9].

It is clearly important to identify people with MS who may be at risk of unemployment so that appropriate management strategies can be put in place [10]. There are a number of cognitive test batteries that can be used to identify cognitive impairment in MS [11] [12]. The Brief International Cognitive Assessment for MS (BICAMS) is a brief (15-minute) screening tool for health care professionals to identify cognitive impairment in MS [13]. BICAMS comprises the first five learning trials of the California Verbal Learning Test II (CVLT-II), the first three recall trials Brief Visuospatial Memory Test Revised (BVMT-R) and the Symbol Digits Modalities Test (SDMT) [14].

This study was designed to explore the utility of BICAMS in the outpatient clinic to identify cognitive impairment and examine how cognitive impairment relates to disability, employment and quality of life measures in our patient population. It provides the first UK data on the application of BICAMS in relation to many of these measures including employment status.

Subjects and Methods

Participants

Sixty-two patients (43 female, 19 male) were included in the study between February 2014 and February 2015. Participants were recruited through outpatient clinics while attending for routine Neurology outpatient appointments at Brighton and Sussex University Hospitals NHS Trust (BSUH). Those with cognitive impairment went on to participate in a study cognitive rehabilitation. We report here the baseline data of all patients screened.

All participants signed informed written consent before undergoing testing. The study was approved by the Northern Ireland Research Ethics Committee. Inclusion criteria were as follows: (a) age between 18 and 65, (b) clinically definite MS, according to the McDonald criteria [15]. All participants underwent a detailed neurological assessment including Kurtzke Expanded Disability Status Scale (EDSS) [16] scoring by an EDSS certified neurologist (http://www.neurostatus.net).

Patients were excluded if they had a history of significant psychiatric disorders, alcohol or drug abuse, visual acuity less than 6/18 corrected, oscillopsia or diplopia that would interfere with testing. Patients were also excluded if they had a MS relapse, received corticosteroids, or had changes made to antidepressants or psychoactive medications within the previous month.

Cognitive and Behavioural Assessment

Participants underwent neuropsychological assessment and were defined as having cognitive impairment if they scored below the 5th centile for normative data (adjusted for age, sex and years of formal education) on one or more of the BICAMS tests [17].

Patients also completed the following assessments: EuroQOL five dimension questionnaire (EQ5D-5L), a generic health-related quality of life scale [18], Functional Assessment of MS (FAMS) (an MS specific quality of life scale) [19], Patient Activation Measure (PAM-13) (a 13 item generic scale for chronic illness management), and a measure of patient empowerment in MS [20], Unidimensional Self-Efficacy scale for MS

(USE-MS) [21], the Hospital Anxiety and Depression Scale (HADS) [22], Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (a patient self-reported measure of cognitive function) [23], and the Fatigue Severity Scale [24].

Statistical Analysis

Descriptive statistics for normally distributed continuous variables are expressed as mean and standard deviation. Skewed continuous variables were summarised using median and interquartile range (IQR). Categorical variables are summarised by frequencies and percentages.

Those patients with cognitive impairment were compared to those without cognitive impairment across a number of variables.

Normality of continuous variables was assessed using the Kolmogorov-Smirnov test.

Categorical variables were compared by the Pearson χ^2 test. The means of continuous variables were compared using the independent samples t-test or the Mann-Whitney *U* test for skewed data.

All tests were two-tailed; p-values less than 0.05 were considered significant.

Analyses were performed using SPSS version 21 (Armonk, NY: IBM Corp).

Results

Demographic and Cognitive Outcomes

62 patients underwent clinical and neuropsychological assessment. 40 patients (65%) showed evidence of cognitive impairment, as defined as scoring below the 5th centile for normative data on one or more of the BICAMS scales [17].

At entry, 44 patients (71%) had relapsing remitting MS (RRMS) and 18 patients (29%) had secondary progressive MS (SPMS). Participants were aged between 31 and 63 years of age. The mean (SD) age of participants was 49.35 (8.88) years, range was 31 to 63 years. The mean (SD) duration of MS from diagnosis to enrolment was 12 (8.0), range 1 to 40 years. Median EDSS was 4.0 (range 1.0–6.5). Thirty-one participants (50%) were on disease modifying therapy (DMT) at enrolment (natalizumab n=7, beta-Interferon n=9, glatiramer acetate n=2, fingolimod n=11 and teriflunomide n=2).

Among the cognitively impaired patients, 21 (53%) failed one test, 11 (28%) failed two tests and 8 (20%) failed all three tests of the BICAMS test battery. The most frequently failed exam was the SDMT with 56% of all patients scoring below the 5th centile, 29% failed the CVLT-II and 23% failed the BVMT-R.

Baseline and demographic characteristics of the two groups (cognitively impaired versus non-cognitively impaired) are shown in table 1. Gender, age, education, duration of illness, treatment with disease modifying therapy and EDSS did not differ significantly between the groups. Overall 27 (44%) of patients were in employment however, patients with cognitive impairment on one or more tests were significantly more likely to be unemployed with an OR (95% CI) of 4.5, (1.5 to 13.6). Greater rates of unemployment were associated with increased number of tests failed (p=0.011) (see figure 1). The odds ratio of being unemployed with patients failing on 1, 2 and 3 tests increased to 4.3, 5.7 and 6.4 respectively.

The SDMT score was found to be the most significant predictor of unemployment (table 2). The strength of association did not change significantly when adjusting for other variables.

Rates of unemployment were seen to increase with lower performance on the SDMT (figure 2).

Table 1: *Characteristics by group*

	Normal Cognitive Performance (n=22)	Cognitively Impaired (n=40)		
	Mean (SD)	*Mean (SD)*	*Mean difference (95% CI)*	*p*
Age (years)	51.27 (9.70)	48.30 (8.33)	2.97 (-1.72 to 7.66)	0.210
Disease duration (years)	10.77 (7.30)	12.65 (8.21)	2.10 (-6.07 to 2.32)	0.375
EDSS	3.48 (1.74)	4.34 (1.70)	-0.86 (-1.77 to 0.05)	0.065
Education (years)	14.05 (2.34)	13.80 (2.78)	0.25 (-1.15 to 1.64)	0.614
	N/22 (%)	*N/40 (%)*	*Odds ratio (95% CI)*	*p*
Gender (female)	15 (68.2)	28 (70)	1.09 (0.35 to 3.35)	0.882
Unemployed	7 (31.8)	28 (70)	5.00 (1.63 to 15.38)	0.009
Disease subtype:				
Relapsing-remitting	17 (77.3)	27 (67.5)	0.61 (0.19 to 2.02)	0.417
Secondary-progressive	5 (22.7)	13 (32.5)		
On treatment at enrolment to study	12 (54.5)	19 (47.5)	0.75 (0.266 to 2.14)	0.596
Interferon *	3	6		
Glatiramer Acetate	2	0		
Fingolimod	6	5		
Natalizumab	0	7		
Teriflunomide	1	1		

*Includes Interferon (IF)-1b SC, IF-1A IM and IF-1A SC

Table 2: Univariate analysis of employment status vs cognitive impairment.

	Employed (n=27)	Unemployed (n=35)		
	Mean (SD)	*Mean (SD)*	*Mean difference (95% CI)*	*p*
SDMT	53.3 (10.4)	39.5 (9.5)	13.79 (8.72 to 18.86)	<0.001
CVLT	52.5 (12.6)	46.2 (9.6)	6.28 (0.65 to 11.91)	0.029
BVMT	24.9 (6.9)	19.4 (6.8)	5.51 (2.02 to 9.02)	0.03

SDMT: Symbol Digits Modalities Test; CVLT: California Verbal Learning Test; BVMT-R: Brief Visuospatial Memory Test Revised.

When adjusting for potential confounding variables (age and years of formal education) the strength of association did not change significantly ($p < 0.01$).
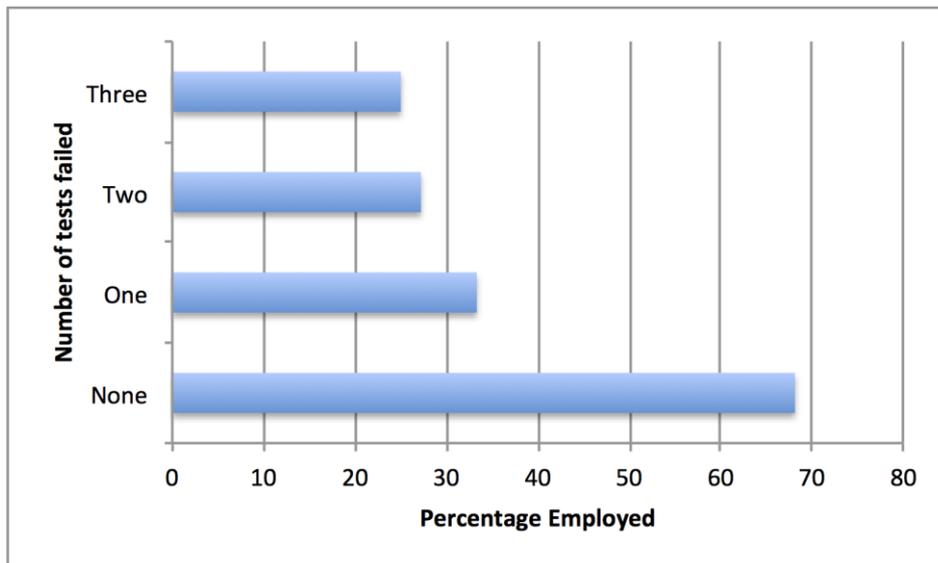
Figure 1: BICAMS performance and employment

Rates of employment versus number of tests failed showing increasing rates of unemployment the more BICAMS tests that are impaired.

Quality of life and behavioural data

Patients with cognitive impairment had significantly lower FAMS scores (p=0.001) (indicating lower QOL), higher EQ-5D scores (p<0.001) (indicating lower QOL) and higher MSNQ (p=0.004) scores in keeping with a greater subjective perception of cognitive impairment. Quality of life and behaviour outcome measures are shown in table 3. Quality of life measures were seen to improve with increasing performance on the SDMT (figure 3).
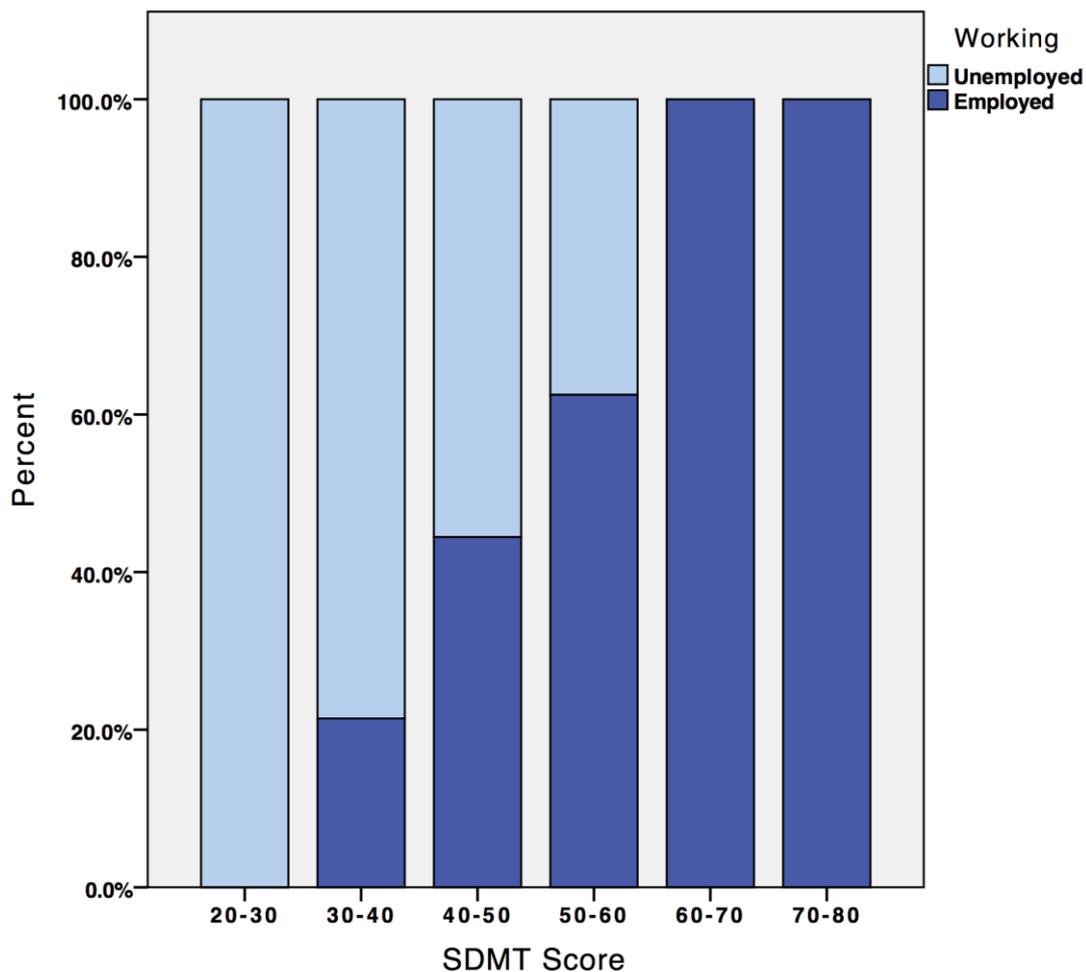

Figure 2: Rates of employment with increasing performance on SDMT

SDMT score versus rate of employment showing increasing rates of employment with higher SDMT scores.

Table 3: *Quality of life and behavioural measures*

	Normal Cognitive Performance (n=22)	Cognitively Impaired (n=40)		
	Mean (SD)	*Mean (SD)*	*Mean difference (95% CI)*	*p*
FAMS	117.1 (23.7)	90.9 (30.9)	26.12 (10.95 to 41.29)	0.001
PAM-13	64.9 (13.1)	61.8 (17.0)	3.04 (-5.35 to 11.44)	0.471
EQ5D	8.6 (2.6)	11.8 (3.3)	-3.18 (-4.82 to -1.55)	<0.001
USE-MS	20.3 (5.2)	17.4 (6.8)	2.86 (-0.45 to 6.18)	0.089
MSNQ	27.1 (10.5)	35.6 (12.2)	-8.56 (-14.73 to -2.38)	0.007
HADS-D	7.2 (3.6)	9.0 (3.3)	-1.80 (-3.60 to 0.01)	0.050
HADS-A	7.5 (5.2)	9.2 (4.7)	-1.65 (-4.24 to 0.94)	0.208
FSS	45.81 (9.5)	50.4 (11.9)	-4.54 (-10.54 to 1.46)	0.136

FAMS: Functional Assessment of MS; PAM-13: Patient Activation Measure; EQ5D: EuroQOL five dimension questionnaire; USE-MS: Unidimensional Self-Efficacy scale for MS; MSNQ: Multiple Sclerosis Neuropsychological Questionnaire; HADS-D: Hospital Anxiety and Depression Scale (depression); HADS-A: Hospital Anxiety and Depression Scale (anxiety); FSS: Fatigue Severity Scale;
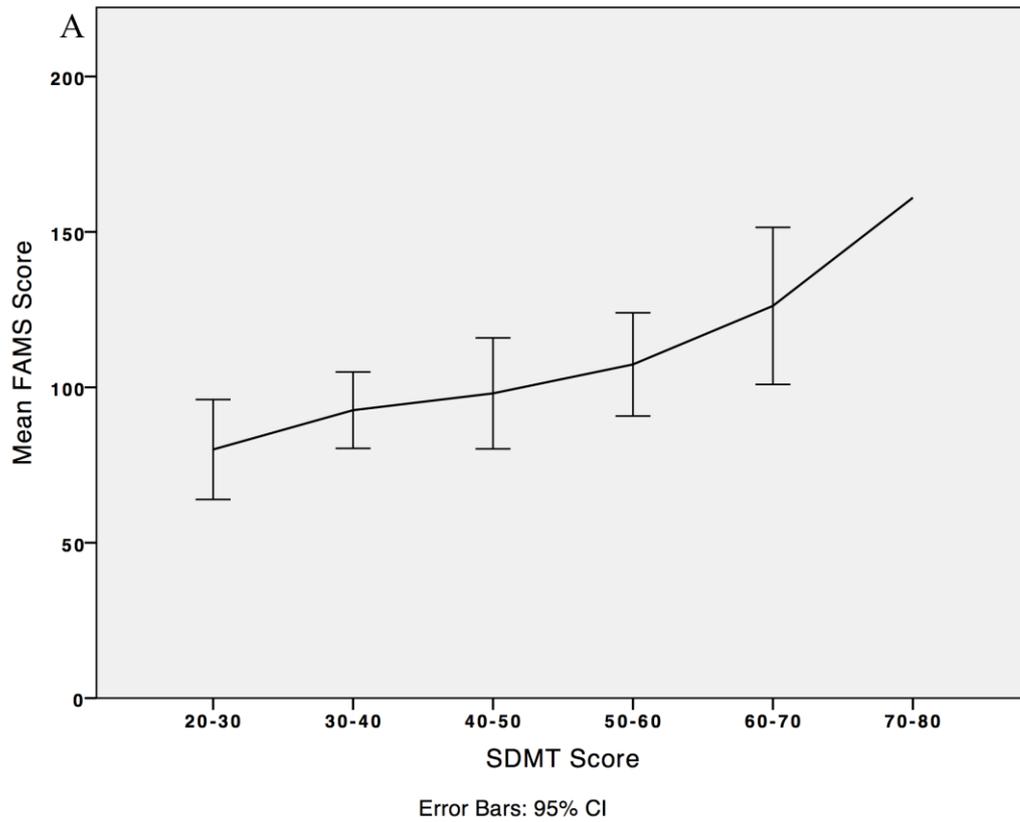
Figure 3: Relationship between SDMT score and QOL measures

Graph showing increase mean (95% CI) FAMS score (indicating better QOL) with increasing SDMT performance.

Discussion

Cognitive impairment is common among patients with MS. The incidence of cognitive impairment in our cohort of MS patients attending outpatients at 65% was similar to that previously reported elsewhere [2].

Rates of unemployment have been shown to increase over time in patients with MS and presents significant cost implications to the individual and society [25]. Various risk factors for unemployment in MS have been identified including, low education level, extent of disability, progressive subtype and personality as well as cognitive impairment [7][26].

BICAMS provides a sensitive and easy to conduct means of identifying cognitive impairment in the outpatient setting and may provide a means for identification of patients with other, more complex psychosocial needs. This study provides the first UK data pertaining to the use of BICAMS in assessing employment status within a UK cohort. Factors linked to unemployment in our study were advanced age and disease duration, increased disability and cognitive impairment. Of these, the SDMT was the most significant predictor of unemployment. The strength of association did not change significantly when adjusting for other variables.

Of the tests utilised within BICAMS, the SDMT may provide among the most sensitive measures of cognitive impairment in MS [27]. Previous work examining cognitive impairment in relation to employment in MS had identified the SDMT to also be one of the main predictors of employment status [6][7][28]; the CVLT-II has also predicted reduced employment status in a longitudinal study [7]. Although simple strategies may overcome memory deficits, at least when they are mild, the "bandwidth" limitations of reduced information processing speed are less easy to manage.

Patients with MS have consistently been shown to have a reduced quality of life with multiple factors related to the disease such as disability, pain, fatigue, personality, depression and unemployment likely to be implicated [28] [29]. Cognitive impairment has been shown to negatively impact upon QOL independent of physical disability [5] and employment status has been more closely linked to QOL than EDSS [30].

In our study there was a statistically significant difference in QOL between those patients with cognitive impairment compared to those without as measured on both the MS specific QOL scale, (FAMS) as well as a generic QOL scale (EQ-5D). A better understanding of the specific cognitive deficits in MS has led to more sensitive patient reported measures being developed in which relatively close correlation is seen between subjective measures of cognitive impairment and objective outcomes [23]. Recent work has also suggested that patient reported perceptions of cognitive difficulties may be predictive of unemployment status independent of mood and objective memory performance [6]. This finding may reflect a relative insensitivity of standard tests to subtle cognitive impairments at a time when "sub-clinical" cognitive impairment is beginning to cause difficulties with work.

To explore this, we utilised the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ), a patient self-reported measure perceived competency with activities of daily living and day-to-day cognitive tasks [23]. Cognitively impaired patients had significantly lower MSNQ scores than patients without cognitive impairment.

How best to manage cognitive impairment is, at present, far from clear. However on a clinical basis, early identification of cognitive impairment allows identification of patients who are at risk of employment difficulties, which may enable support to be put in place that enables them to continue in their current employment with accommodations [10]. This will extend their time in employment and potentially allow them to avoid having employment terminated for poor performance. Instead individuals might achieve medical retirement, a better personal and financial outcome in most countries. More broadly, by identifying patients who may struggle with disease management, more optimal communication strategies and monitoring protocols can be adopted to reduce the morbidity associated with cognitive impairment [5].

Limitations of this current study are that it involved a relatively small cohort and was cross-sectional in nature. Through recruiting patients from a specialist clinic there does exist the potential for selection bias (possibly reflecting more complex or patients with more highly active disease).

Other limitations include the retrospective acquisition of the employment data, a lack of descriptive data pertaining to employment status such as full-time versus part-time employment and details pertaining to when an individual ceased to be in employment and how this relates to duration of illness. The type of employment (e.g. professional versus manual occupations) may also be impacted upon differently by cognitive impairment. Future work might examine these factors in detail.

Current research questions:
- What is the pathophysiology of cognitive impairment in multiple sclerosis?
- What is the relationship between cognitive impairment and employment status in multiple sclerosis?
- What are the optimum interventions to ameliorate the negative impact of cognitive impairment in multiple sclerosis?

Main messages:
- Cognitive impairment is common in patients with multiple sclerosis
- Cognitive impairment is associated with increased rates of unemployment
- Cognitive impairment is associated with lower measures of quality of life and may be partly independent of physical disability.

References

1. Mapping Multiple Sclerosis Around the World. . Multiple Sclerois International Federation 2013;**http://www.msif.org/wpcontent/uploads/2014/09/Atlas-of-MS.pdf**.
2. Benedict RH, Zivadinov R. Risk factors for and management of cognitive dysfunction in multiple sclerosis. Nature reviews Neurology 2011;**7**(6):332-42.
3. Potagas C, Giogkaraki E, Koutsis G, et al. Cognitive impairment in different MS subtypes and clinically isolated syndromes. Journal of the neurological sciences 2008;**267**(1-2):100-6.
4. Amato MP, Ponziani G, Pracucci G, et al. Cognitive impairment in early-onset multiple sclerosis. Pattern, predictors, and impact on everyday life in a 4-year follow-up. Archives of neurology 1995;**52**(2):168-72.
5. Langdon DW. Cognition in multiple sclerosis. Current opinion in neurology 2011;**24**(3):244-9.
6. Honan CA, Brown RF, Batchelor J. Perceived Cognitive Difficulties and Cognitive Test Performance as Predictors of Employment Outcomes in People with Multiple Sclerosis. Journal of the International Neuropsychological Society : JINS 2015:1-13.
7. Morrow SA, Drake A, Zivadinov R, et al. Predicting loss of employment over three years in multiple sclerosis: clinically meaningful cognitive decline. The Clinical neuropsychologist 2010;**24**(7):1131-45.
8. Cadden M, Merritt V, Ukueberuwa D, et al. B-59Comprehensive Examination of Factors Contributing to Employment Status in Multiple Sclerosis. Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists 2014;**29**(6):559.
9. Kobelt G, Berg J, Lindgren P, et al. Costs and quality of life of patients with multiple sclerosis in Europe. Journal of neurology, neurosurgery, and psychiatry 2006;**77**(8):918-26.
10. Doogan C, Playford ED. Supporting work for people with multiple sclerosis. Multiple sclerosis 2014;**20**(6):646-50.
11. Benedict RH, Fischer JS, Archibald CJ, et al. Minimal neuropsychological assessment of MS patients: a consensus approach. The Clinical neuropsychologist 2002;**16**(3):381-97.
12. Rao S. A manual for the Brief Repeatable Battery of Neuropsychological Tests in multiple sclerosis. New York: National MS Society 1991.
13. BICAMS. Brief International Cognitive Assessment for MS. https://wwwbicamsnet 2013.
14. Langdon DW, Amato MP, Boringa J, et al. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). Multiple sclerosis 2012;**18**(6):891-8.
15. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Annals of neurology 2001;**50**(1):121-7.
16. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;**33**(11):1444-52.
17. Parmenter BA, Testa SM, Schretlen DJ, et al. The utility of regression-based norms in interpreting the minimal assessment of cognitive function in multiple sclerosis

(MACFIMS). Journal of the International Neuropsychological Society : JINS 2010;**16**(1):6-16.

18. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Annals of medicine 2001;**33**(5):337-43.

19. Cella DF, Dineen K, Arnason B, et al. Validation of the functional assessment of multiple sclerosis quality of life instrument. Neurology 1996;**47**(1):129-39.

20. Stepleman L, Rutter MC, Hibbard J, et al. Validation of the patient activation measure in a multiple sclerosis clinic sample and implications for care. Disability and rehabilitation 2010;**32**(19):1558-67.

21. Young CA, Mills RJ, Woolmore J, et al. The unidimensional self-efficacy scale for MS (USE-MS): developing a patient based and patient reported outcome. Multiple sclerosis 2012;**18**(9):1326-33.

22. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta psychiatrica Scandinavica 1983;**67**(6):361-70.

23. Benedict RH, Cox D, Thompson LL, et al. Reliable screening for neuropsychological impairment in multiple sclerosis. Multiple sclerosis 2004;**10**(6):675-8.

24. Amtmann D, Bamer AM, Noonan V, et al. Comparison of the psychometric properties of two fatigue scales in multiple sclerosis. Rehabilitation psychology 2012;**57**(2):159-66.

25. Pfleger CC, Flachs EM, Koch-Henriksen N. Social consequences of multiple sclerosis (1): early pension and temporary unemployment--a historical prospective cohort study. Multiple sclerosis 2010;**16**(1):121-6.

26. Strober LB, Christodoulou C, Benedict RH, et al. Unemployment in multiple sclerosis: the contribution of personality and disease. Multiple sclerosis 2012;**18**(5):647-53.

27. Parmenter BA, Weinstock-Guttman B, Garg N, et al. Screening for cognitive impairment in multiple sclerosis using the Symbol digit Modalities Test. Multiple sclerosis 2007;**13**(1):52-7.

28. Benedict RH, Wahlig E, Bakshi R, et al. Predicting quality of life in multiple sclerosis: accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. Journal of the neurological sciences 2005;**231**(1-2):29-34.

29. Miller DM, Rudick RA, Baier M, et al. Factors that predict health-related quality of life in patients with relapsing-remitting multiple sclerosis. Multiple sclerosis 2003;**9**(1):1-5.

30. Kwiatkowski A, Marissal JP, Pouyfaucon M, et al. Social participation in patients with multiple sclerosis: correlations between disability and economic burden. BMC neurology 2014;**14**:115.