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# Cognitive impairment in newly diagnosed multiple sclerosis patients: A 4-year follow-up study

Agnete Jønsson [a,*], Jente Andresen [b], Lars Storr [a], Thomas Tscherning [a], Per Soelberg Sørensen [a], Mads Ravnborg [a]

[a] *Danish Multiple Sclerosis Centre, Department of Neurology, Section 6131, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark*

[b] *The Danish Psychological Publishers, Copenhagen, Denmark*

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**Abstract**

Cognitive impairment occurs in early multiple sclerosis (MS), may decline over time, and has major impact on social functioning. The objectives of this study were to examine cognitive functioning in newly diagnosed MS, and to follow up over a period of 5 years. The results of the first three yearly re-examinations are reported. Eighty newly diagnosed (<1 year) MS patients participated (male/female: 19:61, mean age: 35 years, mean EDSS 2.7, course: 75 relapsing–remitting, 3 primary progressive, 2 secondary progressive). Seventy-five healthy persons served as controls. The neuropsychological (NP) test battery comprised 30 test measures and was grouped into seven cognitive domains. A residual score of −1.5 SD as cut-off point was used to diagnose cognitive impairment. At the first examination, 44–48% had cognitive impairment. None of the patients were clinically depressed, 51% had no signs of depression on Beck Depression Inventory (BDI), and none had severe signs. Sixty-four patients completed four examinations, and a significant linear improvement over time was seen in three cognitive domains, no change in two domains, and deterioration in one domain. At the time of the fourth examination, 4.3 years since diagnosis, 33–34% of the patients had cognitive impairment. Thirty percent of the patients were on disablement pension, 34% received social services in relation to work and 13% had home care. Methodological problems are discussed, especially the practice effect and the importance of identifying sensitive and stable test measures.


*Keywords:* Multiple sclerosis; Early phase; Longitudinal; Cognitive impairment; Psychosocial impact

## 1. Introduction

During the past two decades, there has been an increasing awareness of cognitive disturbances in multiple sclerosis (MS). It is well documented that cognitive impairment occurs in about 40–60% of patients with MS [1–3], and that cognitive impairment has a major impact on social functioning including working abilities [4–6]. Cognitive impairment in early-onset MS has also been reported [6–8]. The results of longitudinal studies are inconsistent, either revealing progression of cognitive impairment over time [5–8] or no progression [9,10].

Frequency, type and severity of cognitive impairment found in the literature differ. This may be due to considerably differences with respect to materials, methods and type of patient recruitment used in the various studies. There are, for example, great differences with regard to patient recruitment, where patients may be randomly or consecutively recruited, in- or outpatients and sometimes have a definite diagnosis of MS and sometimes not. In some studies, a large test battery measuring a broad range of cognitive functions is used while others only use a screening battery or even a single test. Studies also vary with respect to inclusion of a control group. In some studies, the patient group is only compared with national normative data, which give rise to considerable differences with respect to the immediacy of the norms referred to in various studies.

* Corresponding author. Tel.: +45 3545 2487.
*E-mail address:* agnete.joensson@rh.hosp.dk (A. Jønsson).

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Furthermore, there is no general agreement of how to define or diagnose cognitive impairment. Some of the more important questions that ought to be discussed are the number of test measures needed to diagnose cognitive impairment, grouping of test measures into valid cognitive domains, and problems with defining reliable cut-off points for cognitive impairment. Factors concerned with the physical and emotional state of the patients may also affect the validity and precision of test results. Symptoms of MS such as upper limb sensory or motor dysfunction or disturbed vision may cause problems with interpretation of NP test results, the patient may be nervous, depressed or stressed or unable to cooperate fully, which also may make NP results less valid. The unstable nature of MS in itself is also a serious cause for misinterpretation of results on cognitive tests in MS patients. Finally and probably the most important problem when considering cognitive impairment in follow-up studies is the considerable practice effect found for many neuropsychological tests. This problem will be considered in more detail in this study.

The natural history of cognitive impairment in MS is not known and can no longer be truly investigated due to the fact that many MS patients receive disease-modifying drugs. Only a few studies have examined the general cognitive functioning in MS patients with short disease duration [5–7], while a few others examine specific cognitive functions such as attention or memory [11,12]. Correspondingly, not many longitudinal studies exist [6–10].

Great efforts have been made to investigate the relationships between cognitive impairment and other disease factors, such as physical impairment, disease duration, disease course, age at onset and MRI or PET parameters. So far, no unambiguous results have emerged. MRI total lesion burden and brain parenchymal volume seem to be the best predictors of cognitive impairment [8].

The aims of the present study were to evaluate cognitive functioning in a consecutive population of newly diagnosed MS patients, to follow-up over a period of 5 years with retesting once a year (resulting in six examinations altogether) and finally to analyse the relationship between cognitive dysfunctions, neurological impairment and psychosocial factors.

The study was approved by the Danish Ethical Committee (KF 01-129/99).

The study is still in progress, and in the present paper, we report the results of the first three yearly re-examinations.

## 2. Materials and methods

### 2.1. Patients

We studied 112 consecutive patients, who during a period of 4 years were either diagnosed with MS at the Danish Multiple Sclerosis Centre or referred to the centre shortly (<1 year) after being diagnosed elsewhere. The cohort represents 77% of the persons from the Copenhagen County registered in the Danish Multiple Sclerosis Register during that same period of time.

Patients were eligible if they had a definite diagnosis of MS according to the criteria of Poser et al. [13], and time since diagnosis of less than 1 year. Patients were excluded if they had other diseases that could cause cognitive impairment or psychiatric disease unrelated to MS. In all, 100 patients fulfilled the inclusion and exclusion criteria and were mailed a letter inviting them for an informative talk with the neuropsychologist. Nine persons never turned up, and 11 persons did not want to participate.

Seventy-five healthy Danish people served as normal controls. No significant differences were found between the normal controls and the patients with regard to gender, age and educational index (sum of years at school and educational status).

### 2.2. Neuropsychological measures

The neuropsychological test battery consisted of 21 tests resulting in 30 measures. From these 30 measures 7 cognitive domains were constructed, based on neuropsychological theory and an exploratory factor analysis and, furthermore, supported through an item analysis. The cognitive domains were Verbal Intelligence, Attentional Control, Mental Processing/Speed, Visuospatial Memory, Problem Solving, Visual Organization and Naming. Each cognitive domain contains a different number of test measures.

Verbal Intelligence contains two measures, WAIS Vocabulary and WAIS Similarities [14], and both measures are considered to be “hold” tests. The following 7 measures were included in Attentional Control: Serial Seven Subtraction Test [15], Arithmetical Operations [16], Digits Forward [17,18], Digits Backward [17,18], Design Fluency (errors/perseverations) [19], Stroop Colour Naming Test (simplified version) [20] and Raven Progressive Matrices, Section A (number correct) [21]. Mental Processing/Speed is the domain including the largest number of NP measures (11): SDMT [22], Raven Progressive Matrices (time to complete the task) [21], Rey Complex Figure (time to complete the task) [23], Design Fluency (number correct) [19], Tower of London (time to complete the task) [24], Selective Reminding Test (errors) [17,25], 7/24 Spatial Recall Test, Part A (learning) [26], 7/24 Spatial Recall Test, Part B [26], Animals in 1 minute [27], Mesulam Cancellation Test, random shapes (time to complete the task) [28]. Visuospatial Memory includes four measures: 7/24 Spatial Recall Test (immediate and delayed recall) [26], Rey Complex Figure (recall) [22] and Street Gestalt Completion Test [29]. Problem Solving contains only 2 measures, Tower of London (number of moves and rule breaks) [24], and so does Visual Organization: Mesulam Cancellation Test, random shapes (errors) [28] and Rey Complex Figure (copy) [23]. The last cognitive domain, Naming, includes 3 measures: Boston Naming (split