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Neurobehavioral Aspects of Different Forms of Multiple Sclerosis

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Abstract

Introduction: Multiple sclerosis (MS) is an inflammatory disease of the central nervous system in young adults. Cognitive impairment during MS has been overlooked for a long time and raises a renewed interest recently.

Objective: Determine prevalence of cognitive dysfunction in MS in a cohort hospital, particularities and factors affecting progression of cognitive dysfunction in individuals with MS.

Methods: Thirty patients (21 women and 9 men) with MS aged 18 to 43 years followed at the Neurology Department of Charles-Nicolle Hospital from 2008 to 2013 participated in this study. Patients participating in this study were chosen randomly without considering their cognitive status. Evaluation included a neuropsychological assessment, physical examination and brain and spine MRI.

Results: About 86% had cognitive impairment in at least one neuropsychological test. Predominant impaired domains were attention and information processing followed by verbal memory and executive functions. Depression was the most prevalent psychiatric disorder. Cognitive dysfunction was correlated with clinical form of MS, EDSS, radiological findings and disease's course.

Conclusion: Cognitive dysfunction might be more relevant to patients than mobility restrictions. Incorporating a systematic neuropsychological assessment in patients followed for MS allows psychosocial adaptation, monitoring disease activity and elucidating the effects of disease-modifying medications.

Keywords: Multiple sclerosis; Cognitive impairment; Tunisia

Introduction

Multiple sclerosis is an inflammatory disease of the central nervous system (CNS) in young adults with a presumed autoimmune origin. It affects more than 2.1 million people worldwide (National MS Society 2011) and is characterised by a heterogeneous broad spectrum and an unpredictable long-term outcome [1-2]. Cognitive impairment in MS has been underestimated. However, evidence emerging in the last 20 years suggests high prevalence rates of cognitive disturbances up to 70% when sensitive cognitive tests are applied. Attention, recent memory, information processing speed, executive functions, verbal intellectual ability, and visuospatial perception are the most involved [3-5].

Conflicting literature data report that cognitive impairment could be considered as an early feature of the disease or a consequence of its duration, course, and severity [6-8].Cognitive dysfunction has important clinical implications and might be more relevant to patients than mobility restrictions. Correlation between cognitive dysfunction and disease duration isn't clearly established. Recent studies have pointed out that it may affects patients at early stages of the disease. Cognitive impairment is detectable even in clinically isolated syndrome (CIS) and with increasing frequency in relapsing-remitting MS (RR-MS) and secondary progressive MS (SP-MS) [9]. Recent imaging and pathology studies have shown that MS affects white matter as well as grey matter. Unlike white matter lesion burden or distribution, grey matter atrophy has often been linked to cognitive impairment [10]. Nevertheless, relationship between cortical injury and diffuse white matter tracts damage and their respective contribution to cognitive dysfunction is still under investigations [11-12]. In this article we review cognitive profile in different forms of MS in a cohort hospital. Correlations with disability, clinical form, progression and imaging findings will be discussed.

Patients and methods

Study design

Thirty MS patients (21 women and 9 men) underwent the follow up study between 2008 to 2013. Patients were diagnosed with definite MS according to Macdonald criteria 2010 MS and gave informed consent before being included in the study. Physical disability was rated using Kurtzke's EDSS score. All patients participating in this study were chosen based on a clinical history of active MS and mild to moderate physical disability at disease's onset (EDSS 0–5.0), without considering their cognitive status. As a result, mean baseline neuropsychological test scores were within the normal range on all but one test (Word List Generation).Patients were in agreement with inclusion criteria such as age> 18 years, follow up > 1 year clinical. Exclusion criteria were no other neurological disease/head trauma, no known psychiatric illness, no alcohol/drug abuse and no medication which could influence cognition.

Demographic and clinical variables

Demographic and clinical variables were recorded for each patient. Involvement of the CNS at onset was categorized according to initial symptoms: visual, sensory, motor, brainstem/cerebellar, bladder or unclassified impairment. Patients were grouped according to overall disease course: RR-MS, SP-MS and primary progressive MS (PP-MS).

Neuropsychological assessment

Neuropsychological functioning was assessed by tests covering: general cognitive functioning (similarities/picture completion from the Wechsler Adult Intelligence Scale (WAIS-III), psychomotor speed (the barrage test of Zazzo]), selective attention (the Stroop Color Naming Test [13]), working memory (the block tapping test (BTT), verbal learning and memory (the California Verbal Learning Test (CVLT) [12]), visuo-spatial memory (the Subtest WMS-R [14]) and executive function (Frontal Assessment Battery (FAB) [15]), semantic memory (fluency), global intelligence (Raven's Progressive Matrice), language (Ducarne's Subtest), praxia (EMGD), visual gnosia (denomination) (Table 1).

Cognitive functioning

Global assessment of neuropsychological functioning based on the test results was made by a neuropsychologist. Some scores were graded as "no cognitive impairment present" and "cognitive impairment present". Criteria for "cognitive impairment" were a score of 1.5 standard deviations (SD) below the mean on at least one subtest in two of the four main functional areas (psychomotor speed, attention, learning/memory and executive functions).Deviations were based on norms, adjusted for age and educational level. Qualitative markers were consistent tendencies to perseverate or confabulate on learning and memory task, a clear impulsive response style with short performance time combined with many uncorrected false responses as well as inability to perform certain tasks.

All patients had a cerebral spinal MRI axial slices in sagittal and coronal T1, T2, FLAIR (Fluid attenuated inversion recovery), T2 * weighted images and gadolinium injection sequences.

Statistical methods

All statistical analyses were performed using SPSS for Windows version 15.0 (SPSS). We have calculated absolute frequencies and relative frequencies (percentages) for qualitative variables. We calculated averages, medians and standard deviations and determined extreme values for quantitative variables. Links between two quantitative variables were studied by the Pearson correlation coefficient. The Sig. (Significance) corresponds to the "p" if <0.05, then the "r" is significantly different from zero: therefore, as it is + or -, there is a positive correlation or a statistically significant negative correlation. In all statistical tests, significance level was set at 0.05.

Results

General data

Demographic data are summarized on Table 2. Mean age was 34.73 years; there were 21 women and 9 men. 17 patients (56.67%) had a relapsing-remitting (RR) disease course; 9 (30 %) a secondary-progressive (SP) disease course and 4 (13, 33%) a primary progressive form. Twenty-four patients (48%) received immunotherapy. Educational level was academic in 26 patients. Four patients were illiterate.

Age of onset

Age of onset was 29.26 years (range from 18 – 43). Age of onset was earlier on the relapsing remitting form (mean of 25,88yeras) comparatively with progressive forms of MS (32, 88 years for SP-MS and 35, 5 for the PP-MS).

Disability

Mean EDSS of total patients was 3, 02 ranging from 0,5 to 8. It varies according to the outcome type of MS: EDSS was 1, 64 for RR-MS, 4, 77 for SP-MS and 4,875 for the progressive form of MS.

Treatment

Treatment was based on immunomodulators (Interferon) and immunosuppressants (azathioprine and Natalizumab).

Neuropsychological profile of MS

About 86% had cognitive impairment in at least one neuropsychological test. The mean number of impaired tests per patient in the total population was 2.47 (range from 0 to 6 with an ecart type of 1.613). Predominant impaired domains were attention and information processing (73% abnormal), followed by verbal memory (53, 3%) and executive functioning (40%) (Figure1). 23 patients have depression (76, 6 %).

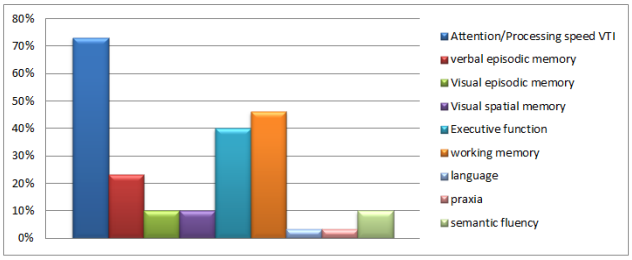

Figure 1: Neuropsychological profile of MS

Attention

21 Patients (70 %) with MS had impairment on complex attention tasks. The pattern of performance has been interpreted as evidence of a reduced capacity to hold and manipulate information in mind, processes commonly conceptualized as functions of either working memory or supervisory attention.

Memory

Mnestic function was disrupted, with impaired memory reported in 10 to 53.3 % of individuals with MS. Deficits in verbal memory may be more severe and appear earlier in the course of the disease ; observed in 53.3 % of patient with MS and followed by working memory impaired in 50%. Visuo-spatial functions appear to be impaired in 16.5 % of patient with MS. Other aspects of memory, including semantic knowledge (impaired in 10 %), short-term memory, implicit learning and recognition, are generally preserved.

Executive functions

Executive functions refer to such cognitive abilities as planning, problem-solving, and self-monitoring have frequently been found to be impaired in 40 %, conceptual reasoning appear to be a common feature of MS.

Depression

23 patients (76, 66%) had depression. Only 3 of them had a severe form (10%). Mild depression seems to be more frequently, observed on 40%.

Correlates of cognitive dysfunction

According to the type of MS, 100% of progressive form had cognitive impairment. The average number of tests impaired in the total population study was 2.47 (from 0 to 6) with an ecart type of 1,613 (Table 3). Otherwise, it differs if there is a progressive or remittent form of the disease with significant correlation if one variable is analysed (table 4, Figure 2). Depression was more frequent with progressive form of MS (88, 89% versus 64, 7 % on RRMS). A positive significant correlation was found between depression and severity of cognitive impairment (Figure 3). This average number varies according to the form of MS with statistically significant while between the progressive and the relapsing forms ((RR 1, 82; SP 3, 00; PP 4, 00) (Table 2).

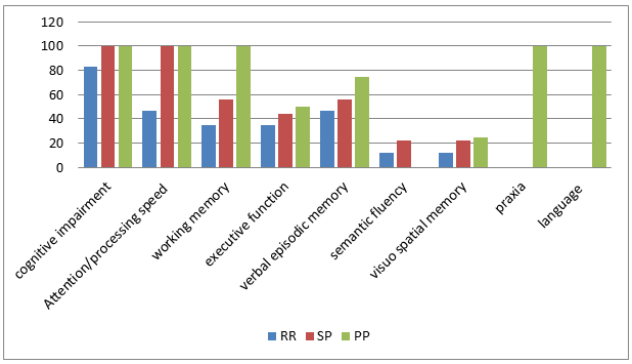

Figure 2: Cognitive impairment according to the form of MS

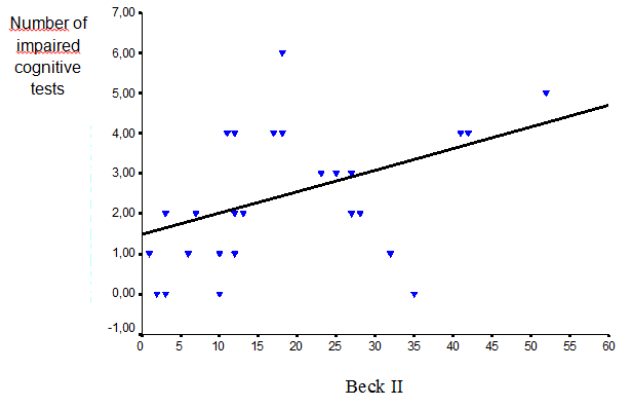

Figure 3: Correlation between depression and number of impaired tests

Correlations between any of the clinical data and cognitive function were observed. When investigating associations of markers that differ between cognitively impaired (CI) and cognitively preserved (CP) patients with cognitive function, a domain-specific pattern emerged. As expected from the lack of a group difference in disease duration, attention, the most frequent function impaired, significantly correlate with the duration, followed by visuo-spatial memory. Working memory correlates significantly with the form of MS, (SP= 55, 6%; PP= 100%; RR= 35, 3%; p= 0,012) but did not correlates with the EDSS or the disease duration (Table 6). Also, there is no correlation between verbal episodic memory and form of MS (RR= 47, 1%; SP= 55, 6%; PP= 75%); p= 0,594, neither between EDSS and verbal memory (p= 0, 98) or disease duration and verbal memory (p= 0, 18) (Tables 5, 7, 8). While measures of episodic memory were more strongly associated with the progressive form, memory tasks (CVLT) not showed closer associations with different form of disease. Controversially, the number of impaired function is significantly correlated with the duration of disease (Figure 4). EDSS and cognition showed the strongest associations with cognitive performance (Figure 5). A significant positive correlation was found between EDSS and number of impaired tests (r= +0,470 and p= 0,009) (Table 9). Another significant correlation was found between depression found in 87 % and number of impaired tests (Table 10).

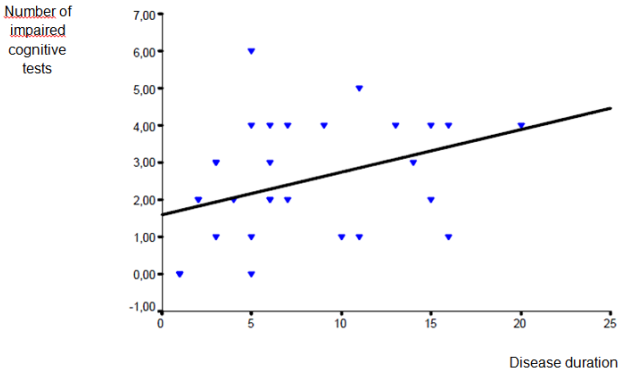

Figure 4: correlation between disease duration and cognitive impairment

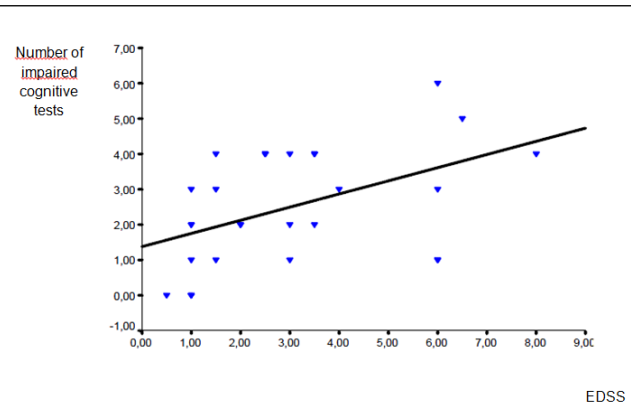

Figure 5: Correlation between EDSS and cognitive impairment

Brain and Spine MRI findings

Ten patients (33.3%) had cortical atrophy and 8 patients (26.7%) had atrophy of the callous cops. Average number of lesions was 22.5 (range 5 to 59). Lesions were located in: periventricular white matter (93.3%), corpus callosum (83.3%), semi oval center (80%), cervical cord (53.3%), cerebellar peduncles (53.3%), internal capsule (46.7%), protuberance, dorsolumbar cord (33.3%) and bulb (26.7%).

In our study, there is a significant correlation between cortical atrophy, corpus callosum atrophy and cognitive decline (respectively: $p < 0.05$ and $p = 0.049$). Moreover, number of lesions was significantly correlated with cognitive impairment ($p = 0.022$).

Discussion

Jean-Martin Charcot, the 19th-century neurologist who named multiple sclerosis, described cognitive and neuropsychiatric symptoms during this condition [19]. As neurologists stressed the white matter nature of multiple sclerosis, they further downplayed any cognitive or other "gray matter problems."

During the past two decades, there has been an increasing awareness of cognitive disturbances in MS which occur in about 35 to 70% of patients [1-5].

Cognitive impairment in early-onset MS has also been reported and has a major impact on social functioning [6,16]. It's a main cause of reduced work hours or unemployment in patients with MS [17].

In the world literature, data is based on studies from Western Europe, North America and Latin America. To our Knowledge, there are no available studies from other regions of the world, particularly from North Africa or the Maghreb.

Neurobehavioral aspects of MS include both cognitive disturbances and neuropsychiatric disorders. Cognitive impairment has been identified at all stages of the disease: clinically isolated syndrome (CIS), relapsing remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS) and primary progressive multiple sclerosis (PPMS). Cognition can also predict future disease progression and can be a risk factor of further physical disability [18].

Cognitive difficulties in MS involve memory retrieval, mental processing speed, reasoning and goal-oriented behavior, verbal fluency, and visuo-spatial skills. Neuropsychiatric disturbances are primarily mood disorders. Cognitive impairment occurs in 40-65% MS [19]. In our cohort, cognitive impairment was found in about 86% in at least one neuropsychological test. Cognitive deficits are most pronounced in secondary progressive disease, such as our population where 100% of progressive form had impairment.

Controversially, some data showed that cognitive profile did not correlate with physical disability. Karlińska I et al. concluded that correlation between physical disability and cognitive impairment was not significant, except for memory deficits and psychomotor speed [20].

Others demonstrate that cognitive deficits are more frequent and pronounced in chronic progressive MS and tend to worsen over time. Significant impairment occurs in almost all studied cognitive domains such as episodic memory, executive function, and processing speed [21]. For most cases, severity of cognitive impairment significantly correlates with physical disability and with depression severity [15,22,23].

In our study, EDSS showed the strongest associations with cognitive performance.

Moreover, it has been suggested that slowing velocity of information processing and, secondarily, deficient non speeded central executive skills may be core to the cognitive deficits characteristic of multiple sclerosis patients [15,24]. Memory is the most affected cognitive deficits in multiple sclerosis; impaired memory is reported in 40–60% of individuals and about 10 to 53.3 % in our study [25,26]. Furthermore, beginning during the early stages of the disease, memory impairments may be prominent [27].

Impairment appears to be characterized by deficits in retrieval from long-term storage. Free recall of verbal as well as visuo-spatial material appears to be impaired in MS [28]. Although, deficit in verbal memory may be more severe and appears earlier in the course of the disease. In contrast to secondary memory, primary memory, which is responsible for immediate recall, is generally intact. Multiple sclerosis patients perform comparable to normal on implicit memory tasks such as motor skill acquisition and priming. Primary problem in MS in memory functioning is in acquisition of new information. Verbal memory deficits is more associated with a progressive disease course, however, visuospatial memory deficits is more reported in RR MS. It has been suggested that automatic memory processing is intact in multiple sclerosis, but impairment in memory, in meta memory, and in other cognitive tasks becomes evident over time when patients rely on conscious processes [29].

Fatigue is a weakening symptom of MS ranging from 53 to 90% [30]. Degree of fatigue is related to processing speed impairment. Cognitive slowing has been observed to be significantly associated with the type of MS: secondary progressive forms show the most extensive range of deficits, closely followed by primary progressive forms; relapsing-remitting forms appear to be much less affected [31]. Our results also coincide with longitudinal studies showing that cognitive slowing reached the attention was found on 47.1% in our RR-MS group compared to 100% of patients with a progressive form. This significant difference ($p = 0.003$) was reported in several studies [19].

As previously mentioned, our results show a rate of executive dysfunction about 40 %. Working strategies seem to be the most frequent subtype of impaired executive dysfunction. According to Cerezo Garcïa M et al., cognitive flexibility, inhibition and abstraction ability were the most deficient components of executive functions [23]. A positive correlation was found between motor disability and severity of executive functions in our study and in the international literature: patients with the worst performance were those with progressive forms and a high EDSS. Given the complexity of executive functions, further studies are needed to clarify degree and types of executive difficulties experienced by those with MS and relation between executive dysfunction and other types of cognitive impairment.

Psychiatric disturbances are common in MS. Depression is frequent and is reported in up to 60 % of people with MS in our study (76, 6%) as well as in literature. Moreover, it's more common than in other chronic diseases [32]. Fatigue, anxiety, apathy are also prominent symptoms in MS and aggravate cognitive functioning [33].

Sleep disorders and high levels of sexual dysfunction are also common in patients with MS but often overlooked.

Information processing efficiency refers to the ability to maintain and manipulate information in the brain for a short time period and to the speed with which one can process that information [32]. The first

cognitive difficulty, in our study, refers to a processing speed. These data are consistent with world literature. Processing speed, visual learning and memory seem to be most commonly affected in MS [34].

Several studies, on this subject, have agreed that a close link is established between disease course and cognitive decline. When comparing subtypes of MS, patients with a PPMS or SPMS course have typically demonstrated a greater severity of cognitive impairment than patients diagnosed with a relapsing-remitting course. Furthermore, different subtypes of MS have also been associated with different cognitive profiles. PPMS and SPMS patients may be more likely than RRMS patients to suffer from attention, speed of processing, executive and abstraction deficits. Moreover, RRMS patients may be more likely than healthy controls to suffer from memory deficits. Relationship between cognitive impairment and MRI parameters is discussed in many studies. In our analysis and in other published data, cognitive impairment is correlated with brain atrophy and brain lesions' volume [5].

Atrophic frontal lobes and cognitive changes are frequently associated during MS. Gray matter demyelinating lesions (cerebral cortex, hippocampus, thalamus and basal ganglia) and white matter ones causing interconnectivity between structures highlighted are the major causes of neurobehavioral changes in MS [35]. MRI analysis seems to be insufficient. Studies based on functional neuroimaging are more reliable and needed.

Conclusion

Results of this study highlight ongoing need to perform more longitudinal studies of cognitive impairment in patients with relapsing and progressive forms of MS. Cognitive dysfunction in MS has a multi factorial etiology. It's a major source of vocational disability, social impairment, and impoverished quality of life during the course of MS.

Cognitive deficits may occur early in the course of the disease since first demyelinating episode that can precede clinically definite MS. Early cognitive dysfunction is a predicator of conversion to clinically definitive MS and possibly for further disabling evolution. As such, systematically assessment of cognitive function is strongly recommended in the first time examination. Regular monitoring of cognitive functioning is necessary.

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