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NEUROPSYCHOLOGICAL EFFECTS OF COMORBIDITY IN MULTIPLE SCLEROSIS PATIENTS

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ABSTRACT

Introduction: Multiple sclerosis (MS) is a progressive demyelinating and degenerative neurological disease. The degree of disability increases along with pathological damage, especially in cases with comorbidity.

Methodology: The objective of this study was to analyze the influence of MS alone and with comorbidity on some neuropsychological patterns. Individual quality of life of 80 MS patients at a mean age of 49 years, 56 females and 24 males, was examined by means of Multiple Sclerosis Quality of Life-54 Questionnaire (MSQOL-54) in 2002-2015. Forty patients presented with MS alone and 40 with MS and comorbidity. The frequency of troubles of mental concentration/thinking, fixation of attention, and memory as well as of difficulty at work and other activities were examined.

Results: Statistically significant differences were observed between patients with MS alone and those with MS and comorbidity concerning troubles of mental concentration/thinking ($t=4.822$; $p<0.0001$), and of memory ($t=4.020$; $p<0.0001$). Gender correlated negatively with troubles of memory ($R=-0.343$; $r<0.05$), while EDSS scores did with troubles of memory ($R=-0.346$; $p<0.05$) and with troubles of attention

RÉSUMÉ

Effets neuro-psychologiques de la comorbidité chez les patients avec de la sclérose en plaques

Introduction: La sclérose en plaques (SEP) est une maladie neurologique dégénérative et démyélinisante progressive. Le degré d'invalidité augmente avec les atteintes pathologiques, en particulier en cas de comorbidité.

Méthodologie: L'objectif de cette étude était d'analyser l'influence de la SEP seule et de la comorbidité sur certains indices neuro-psychologiques. La qualité de vie individuelle de 80 patients atteints de SEP à l'âge moyen de 49 ans, 56 femmes et 24 hommes, a été examinée au moyen du questionnaire MSQOL-54 entre les années 2002 et 2015. Quarante patients se sont présentés avec SEP seulement et 40 patients, avec SEP et comorbidités. La fréquence des problèmes de la concentration/ réflexion mentale, de la fixation de l'attention et de la mémoire ainsi que de la difficulté au travail et d'autres activités ont été examinées.

Résultats: Il y avait des différences significatives entre les patients atteints de SEP seulement et ceux avec SEP et comorbidité, concernant les problèmes

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($R=-0.330$; $p<0.05$). The accompanying diseases additionally worsened the components of health-related quality of life.

Conclusions: Common comorbidity in MS patients requires careful clinical examinations and proper management in order to reduce the neuropsychological burden and assure a better individual quality of life for the patient.

Key words: multiple sclerosis, quality of life, comorbidity, neuropsychological impairment

Abbreviations: Co: comorbidity; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; MSQOL-54: Multiple Sclerosis Quality of Life-54 Questionnaire.

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory and neurodegenerative disease of the central nervous system of potential autoimmune origin that is frequently associated with psychological disorders and cognitive deficits as well as with fatigue and stress, being a psychosocial burden. Most common psychological impairments include cognitive and memory deficits, depression, and insufficient social communications. Such unfavorable factors often cause decreased quality of life, social withdrawal, and unemployment¹. Because of the high prevalence of comorbidity in MS and the potential for its prevention or treatment, comorbidity is of rising interest as a factor that could explain the heterogeneity of outcomes². A rapidly growing body of evidence suggests that comorbidity adversely affects outcomes throughout the disease course in MS, including diagnostic delays from symptom onset, disability at diagnosis and subsequent progression, cognition, mortality, and health-related quality of life.

The results from a population-based, nationwide cohort study showed a total of 8947 incident MS cases in Denmark, with first MS symptom between 1980 and 2005³. There were statistically significant odds ratios for longer diagnostic delays with cerebrovascular (2.01; between 1.44 and 2.80; $p<0.0005$), cardiovascular (4.04; between 2.78 and 5.87; $p<0.0005$), lung (1.93; between 1.42 and 2.62; $p<0.0005$), diabetes mellitus (1.78; between 1.04 and 3.06; $p=0.035$),

de la concentration/ réflexion mentale ($t = 4.822$; $p < 0.0001$) et concernant les troubles de la mémoire ($t=4.020$; $p < 0.0001$). Le sexe du patient est en corrélation négative avec les troubles de la mémoire ($R = -0.343$; $r < 0.05$), et les scores EDSS, avec les troubles de la mémoire ($R = -0.346$; $p < 0.05$) et les problèmes de fixation de l'attention ($R=-0.330$ $p<0.05$). Les maladies accompagnantes aggravent en outre les composantes de la qualité de vie liée à la santé des patients.

Conclusions: La présence de comorbidités chez les patients atteints de SEP nécessite des examens cliniques minutieux et une prise en charge appropriée afin de réduire les troubles neuro-psychologiques et de garantir une meilleure qualité de vie individuelle du patient.

Mots-clés: sclérose en plaques, qualité de vie, comorbidité, détérioration neuro-psychologique.

Abréviations: Co: comorbidité, EDSS: Échelle élargie de l'invalidité, SEP: sclérose en plaques, MSQOL-54: Questionnaire sur la qualité de vie de la sclérose en plaques-54.

and cancer comorbidity (2.10; between 1.20 and 3.67; $p=0.009$). Besides, MS patients with somatic comorbidity presented with increased odds of low incomes both five (1.41; between 1.19 and 1.67; $p<0.0005$) and ten years (1.37; between 1.17 and 1.60; $p<0.0005$) after MS onset (4). The odds of a low income with psychiatric comorbidity increased ten years after MS onset (3.06; between 1.47 and 6.37; $p=0.003$).

THE OBJECTIVE OF THE STUDY was to evaluate the MS influence on hospitalized patients' neuropsychological characteristics either alone, or in the presence of accompanying diseases.

MATERIAL AND METHODS

Individual quality of life of 80 MS patients at a mean age of 49 years, 56 females and 24 males, was examined by means of Multiple Sclerosis Quality of Life-54 Questionnaire (MSQOL-54) in 2002-2015. The respondents were divided into two equal groups: 40 MS patients with at least one and 40 with no accompanying diseases.

The gender distribution of both groups is summarized on Table 1, while patients' distribution according to gender and age is illustrated on Figure 1.

Comorbidity was divided into 19 groups according to different systems. Neurological (in 29.16%), cardiovascular (in 17.28%), gastrointestinal (in 6.91%) and endocrine accompanying diseases (in 5.83% of the cases) occurred most commonly. These patients

presented with similar Expanded Disability Status Scale (EDSS) scores of 2.0 or 2.5.

The influence of MS and comorbidity during the preceding four weeks on four symptoms of health-related quality of life, troubles with mental concentration/thinking, fixation of attention, and memory, as well as difficulty at work and other activities were examined.

Statistical data processing was performed by means of correlation analysis (Pearson's coefficient) and *t*-test, using SPSS software, version 19 (IBM Corp., Armonk, NY). Statistical significance was considered at *p*-value less than 0.05.

RESULTS

The frequency of these symptoms in males and females with MS and with MS and comorbidity are demonstrated in Table 2 and Table 3.

The comparison of two parameters of health-related quality of life between the patients with MS alone and those with MS and comorbidity, by means of *t*-test, revealed the following statistically significant differences: concerning the troubles of mental concentration/thinking ($t=4.822$; $p<0.0001$) and concerning the troubles of memory ($t=4.020$; $p<0.0001$).

There were statistically significant negative correlations between patient's gender and troubles of memory ($R=-0.343$; $r<0.05$), as well as between EDSS scores and troubles of memory ($R=-0.346$; $p<0.05$) and of fixation of attention ($R=-0.330$; $p<0.05$).

The difficulty at work and other activities was less common in male and female patients with MS alone than in those with MS and comorbidity (Table 4).

The substantial differences between MS patients without and with comorbidity concerning these MSQOL-54 scores indicated that the accompanying diseases additionally worsened these components of patients' health-related quality of life (mental concentration and thinking, attention, memory capacity and coping with everyday activities).

DISCUSSION

Recently, a series of publications reported comprehensive investigations of neuropsychological effects of MS on individual quality of life.

Health-related quality of life of a total of 1220 MS patients in Germany was examined by means of Multiple Sclerosis International Quality of Life questionnaire and the short form of the Fear of Progression Questionnaire⁵. Multiple regression analyses identified disease severity and comorbidity – in different directions (positive and negative) – as

the strongest factors in predicting activities of daily living, symptoms, sentimental and sexual life, and reject. The demographic variables sex, age, education, and employment status exerted different impact on the health-related quality of life.

An expert committee of twelve members representing the main cultural groups that have contributed to considerable data about MS cognitive dysfunction recommended a brief cognitive assessment for MS that is optimized for small centers, with one or few staff members, who may not have neuropsychological training and constructed to maximize international use⁶.

Diffusion tensor imaging metrics from 3T magnetic resonance imaging of deep grey matter nuclei were assessed in the caudate, putamen, and thalamus of 30 MS patients and 10 controls⁷. Their potential association with mobility and neuropsychological function was analyzed. Fractional anisotropy of the caudate and putamen was higher in MS patients compared to controls. Caudate fractional anisotropy correlated with EDSS score, Ambulation Index, and severity of depressive symptomatology while putamen and thalamus fractional anisotropy correlated with deficits in memory tests.

Cognitive impairment is a common feature of MS that has a sophisticated neuroanatomic and pathophysiologic background and disturbs several vital cognitive domains such as information processing speed, memory, attention, executive functions and visual perceptual functions⁸.

Recent multicentre studies in Latin America showed that 43% of the patients presented with cognitive impairment and 34.5% of them were in the early stages of the disease⁹. The profile of cognitive impairment corresponded to alterations in visual and verbal memory, attention, information processing speed and verbal fluency.

The time course of decline of different cognitive domains was assessed in 514 MS patients by means of the Neuropsychological Screening Battery for MS and the Symbol Digit Modalities Test¹⁰. Survival curves of tests focusing on information processing speed declined statistically significantly faster than tests with less specific demands of information processing speed. Median age for pathological decline was 56.2 years (between 54.4 and 58.2 years at 95% confidence interval) on the Symbol Digit Modalities Test and 63.9 years (95% CI: between 60 and 66.9 years at 95% confidence interval) on the memory task.

Neurological and psychiatric evaluation of 31 MS patients and 31 age, sex, and education-matched healthy controls was performed by using Structured Clinical Interview for Axis I Disorders and cognitive

functions were assessed using Mini Mental, Serial Digit Learning, Verbal and Nonverbal Cancellation, Stroop and Rey Auditory Verbal Learning tests¹¹. Retrieval from long-term memory and psychomotor speed were statistically significantly worse in MS group. Cognitive impairment correlated with disease duration, number of attacks, and physical disability.

Memory, information-processing speed, attention and executive functions are mainly involved in cognitive impairment in MS¹². Advanced neuroimaging has helped to increase knowledge about structural and functional mechanisms responsible for cognitive decline in MS. Early detection of cognitive impairment is essential to provide appropriate therapeutic intervention.

An exploratory hypothesis whereby working memory capacity could mediate the relationship between intellectual enrichment and verbal long-term memory decline in MS patients was tested¹³. Intellectual enrichment, verbal long-term memory, and working memory capacity were estimated with the Wechsler Test of Adult Reading and Peabody Picture Vocabulary Test, delayed recall of the Hopkins Verbal Learning Test-Revised and Logical Memory of the Wechsler Memory Scale, and Digit Span Total, respectively. Intellectual enrichment predicted long-term memory ($B=0.54$; $p=0.003$) and working memory capacity ($B=0.91$; $p<0.001$). Working memory capacity predicted long-term memory ($B=0.44$; $p<0.001$) and fully mediated the relationship between intellectual enrichment ($B=0.24$; $p=0.27$) and long-term memory ($B=0.33$; $p=0.03$; Sobel test, $Z=3.31$; $p<0.001$). Working memory capacity was an underlying mechanism of cognitive reserve.

The evaluation of 32 MS patients and 32 matched healthy controls indicated that 19 patients presented with episodic memory impairment¹⁴. Only these individuals showed deficits in working memory capacity leading to difficulty in encoding, and/or retrieving information from episodic memory.

A computer-based method, the memory and attention test, was applied in 531 MS outpatients and in 84 age-, sex- and education-matched healthy subjects in Germany¹⁵. Episodic short-term memory was substantially decreased in MS patients. About 20% of them reached a score of only less than two standard deviations below the mean of the control group. The episodic short-term memory score negatively correlated with the EDSS one. There were minor statistically significant impairments of verbal short-term memory, episodic working memory and selective attention in MS patients.

The Attention Network Test assesses attention in terms of discrepancies between response times to

items that differ in the burden they place on attention. Attention networks were examined in 20 patients with relapsing-remitting MS, 20 patients with secondary progressive MS, and 40 healthy controls¹⁶. There were substantial differences between patients and controls concerning all the measures of processing speed. When deficits in information processing speed were adequately controlled using proportional or residualized score, deficits in the alerting network emerged. These deficits were more prominent in MS than those involving attention.

CONCLUSION

Based on the recent literature review and our own results we could draw the conclusion that common comorbidity in MS patients requires careful clinical examinations and proper management in order to reduce the neuropsychological burden and warrant a better individual quality of life.

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