

# Cognitive impairment is correlated with reduced quality of life in patients with clinically isolated syndrome

Comprometimento cognitivo correlaciona-se com redução da qualidade de vida em pacientes com síndrome clinicamente isolada

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## ABSTRACT

**Objective:** To evaluate the quality of life (QoL) and potential QoL determinants in patients with clinically isolated syndrome (CIS). **Methods:** Eighteen CIS patients and eighteen controls were submitted to QoL evaluation with Functional Assessment of Multiple Sclerosis QoL instrument (FAMS). Cognition was evaluated with specific battery tests; Anxiety and depression with Beck Anxiety (BAI) and Depression (BDI) Inventories and Neurological disability with Guy's Neurological Disability Scale (GNDS). **Results:** There was a significant difference in QoL between CIS patients and controls. CIS patients had worse performance in Paced Auditory Serial Addition 2 seconds ( $p=0.009$ ) and fluency tests ( $p=0.0038$ ). There was a significant difference in BAI ( $p=0.003$ ), but no significant difference in BDI between patients and controls. There were significant correlations between QoL measure and verbal fluency and Stroop's test. **Conclusions:** Cognition, but not anxiety, depression and disability, was associated with reduced quality of life.

**Key words:** clinically isolated syndrome, quality of life, cognition, depression, anxiety.

## RESUMO

**Objetivo:** Avaliar a qualidade de vida (QoL) e seus potenciais determinantes em pacientes com síndrome clinicamente isolada (SCI). **Métodos:** Dezoito pacientes com SCI e 18 controles realizaram avaliação da QoL com Escala de Determinação da QoL na Esclerose Múltipla; cognição foi avaliada com bateria de testes específica; ansiedade e depressão com os Inventários de Beck de ansiedade (BAI) e de depressão (BDI) e a incapacidade neurológica com a Guy's Neurological Disability Scale. **Resultados:** Houve diferença significativa na QoL avaliada entre pacientes com SCI e controles. Pacientes com SCI apresentaram pior desempenho no Pased Auditory Serial Addition 2 segundos ( $p=0,009$ ) e na fluência verbal ( $p=0,0038$ ). Houve diferença no BAI ( $p=0,003$ ), entretanto sem diferença do BDI entre pacientes e controles. Houve correlações significativas entre QoL, fluência verbal e Stroop. **Conclusões:** Alterações cognitivas tiveram correlação com diminuição da QoL, o que não ocorreu com a depressão, ansiedade e incapacidade neurológica.

**Palavras-Chave:** síndrome clinicamente isolada, qualidade de vida, cognição, depressão, ansiedade.

Clinically isolated syndrome (CIS) is defined as the first episode of a demyelinating and inflammatory disease of the central nervous system (CNS), and most patients with CIS will convert to multiple sclerosis (MS)<sup>1,2</sup>. The most common CIS manifestations are optic neuritis, myelitis, brainstem,

and/or cerebellar syndromes<sup>2</sup>. Patients with the first clinical episode of demyelination may already be diagnosed as having MS if both gadolinium-enhancing and non-enhancing lesions on the baseline magnetic resonance imaging (MRI) are found<sup>3</sup>.

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Some recent studies have shown that CIS patients may present mild cognitive impairment, especially in processing speed and executive functions<sup>4,6</sup>. Depression and anxiety have also been found in patients with CIS but their precise prevalence in this population is still unknown<sup>6,9</sup>. Quality of life has been studied in patients with multiple sclerosis (MS) but there are no previous studies evaluating quality of life in patients with CIS.

Several studies have showed that cognitive dysfunction, anxiety, and depression impact significantly on the quality of life of MS patients<sup>10-12</sup>. Considering that CIS is associated with cognitive dysfunction, depression and anxiety, it is possible that it can affect quality of life in patients with CIS. However, quality of life in patients with CIS is still poorly understood<sup>6,9,13-15</sup>. The present study aimed to evaluate the quality of life of patients with CIS and to evaluate potential determinants of quality of life such as cognition, depression and anxiety in patients with CIS.

## METHODS

### *Subjects*

Subjects aged 19-48 with CIS were recruited in the Multiple Sclerosis Clinic of Santa Casa School of Health Sciences, Vitória, Espírito Santo, Brazil. The control group was composed of healthy subjects randomly selected and paired by age, gender, and education level. The study was approved by the ethics committees of Federal University of Minas Gerais and School of Health Sciences of Santa Casa, Vitoria. Informed consent form signature was obtained from each participant. The diagnosis of CIS was done according to the following criteria: one isolated neurological episode lasting at least 24 hours compatible with demyelination of the central nervous system and magnetic resonance imaging showing at least two lesions similar to those seen in MS<sup>1,3</sup>. Patients fulfilling diagnostic criteria of dissemination in time with baseline MRI were excluded<sup>3</sup>. Patients with severe cognitive impairment defined as score below 24 points in the Mini-Mental State Examination<sup>16</sup> or using psychotropic drugs were not included.

### *Quality of life, neurologic, neuropsychological, neuropsychiatric evaluation*

All patients and control subjects completed the Functional Assessment of Multiple Sclerosis quality of life instrument (FAMS)<sup>17</sup> which is validated in Portuguese language.

The neurologic evaluation included a complete history and determination of current disability using the Expanded Disability Status Scale (EDSS)<sup>18</sup>. Disability and activity limitations were assessed with Guy's Neurological Disability Scale (GNDS)<sup>19</sup>. Anxiety was evaluated with Beck Anxiety Inventory (BAI)<sup>20,21</sup>. The Beck Depression Inventory (BDI)<sup>22</sup> was used to evaluate depression.

CIS subjects and control group were submitted to neuropsychological evaluation which included: verbal learning and verbal retention (logical memory subtest from Wechsler memory scale-revised; Rey Auditory Verbal Learning Test); visual-spatial ability (Rey Complex Figure), information processing speed (Paced Auditory Serial Addition Test 3 and 2 seconds), working memory (Digit Span Test, Wechsler memory scale revised), executive functions (verbal fluency 'animals' and 'letter S' and Stroop's color test), and attention (D2 test; Digit Symbol).

### *Data analysis*

Analyses were performed using 'R' software, version 2.8.0. The normality of data distribution was assessed with the Shapiro-Wilk test. Mann-Whitney test was used to compare the results of quality of life, cognitive tests, anxiety and depression symptoms between CIS patients and controls. The correlations between quality of life parameters and potential quality of life determinants including neurological disability, depression, anxiety, and cognition were evaluated in patients with CIS using the Spearman correlation test. Significance level was set at  $p < 0.05$ .

## RESULTS

Eighteen CIS patients were included, 13 female. The clinical and demographical data of CIS as well as the mean  $\pm$  SD EDSS score of patients with CIS was  $0.8 \pm 0.5$  patients are shown in Table 1. Table 2 shows the comparison of quality of life, disability, depression and anxiety between patients and controls. The cognitive evaluation showed significant differences between patients and controls in the following tests: PASAT 2 ( $p = 0.0216$ ) and verbal fluency with letters ( $p = 0.0038$ ). No differences between CIS and controls were found in the other neuropsychological tests.

In patients with CIS, there are correlations between quality of life evaluated by FAMS with cognitive tests (verbal fluency with letters and stroop card test) (Table 3). FAMS is not correlated with neurological disability, activity limitations, depression and anxiety (Table 3).

## DISCUSSION

Our study demonstrated reduction in the quality of life of patients with CIS. Reduced quality of life was previously demonstrated in patients with MS<sup>23</sup>. Considering that CIS may be the first manifestation of MS and that the neuropathological abnormalities are the same only differing in intensity and distribution it seems reasonable that CIS may affect quality of life. It is possible that the impact of MS on quality of life is higher than in CIS since MS patients usually have higher

**Table 1.** Demographic and clinical data of CIS patients and controls.

	"n" and Mean ( $\pm$ SD)		p-value
	Controls	Patients	
Age	18;35.5 (9.2)	18;35.6 (9.3)	0.9747
Females	13	13	-
Males	5	5	-
EDSS	-	18; 0.8 (0.5)	-
Time between symptom and first assessment (years)	-	18; 2.09 (2.6)	-
Education (years)	18; 14.2 (4.2)	18; 14.1 (4.3)	0.9747
CIS symptom localization			
<i>Lobar</i>	-	2	-
<i>Brainstem</i>	-	1	-
<i>Spinal Cord</i>	-	5	-
<i>Optic neuritis</i>	-	10	-

SD: standard deviation; CIS: clinically isolated syndrome; EDSS: Expanded Disability Status Scale.

neurological disability and higher rates of depression and anxiety<sup>9</sup>; however, future studies are still needed to compare the reduction in quality of life in CIS and in MS patients.

Previous studies showed that CIS patients may have impairment in memory, information processing speed, attention, semantic verbal memory, and working memory. Our findings are in line with previous studies showing neuropsychological impairment in patients with CIS<sup>4-6,24</sup>. All previous studies of cognition in CIS as well as the present study showed changes in executive function evaluation, such as speed of information processing and verbal fluency<sup>5,6,24-26</sup>.

There was no significant difference between BDI score of patients and controls in the present study. Previous studies have reported depression in patients with CIS<sup>8,11</sup>. Di Legge et al.<sup>27</sup> reported depression in CIS patients with a tendency towards normalization after a relapse free period. A correlation between temporal lobe lesion load and depressive scores was previously found<sup>27</sup>. A possible explanation for the lack of significant reduction of CIS BDI scores compared to controls in the present study might be the low number of CIS patients not allowing a statistically significant difference to be demonstrated. Also, it was not possible to evaluate the MRI lesion sites and lesion load, and therefore it is not possible to rule out that the distribution of the lesions in this group of patients has not favored the emergence of depressive symptoms. It is also not possible to rule out that the low mean EDSS score of the CIS group explain the low depressive scores. In fact, previous studies presented a tendency to correlation between depression and disability<sup>9</sup>.

There were higher anxiety scores in CIS patients when compared with control group. Few studies explored anxiety in CIS patients. It was shown that the severity of anxiety symptoms are related with the EDSS score and time of disease, suggesting that anxiety worsens as the disease progresses<sup>28</sup>. Psychological aspects have been suggested to be

**Table 2.** GNDS and FAMS scale results and depression and anxiety scores of CIS patients and controls.

	Median		p-value
	Controls	Patients	
FAMS (total score)	168	149	0.000*
GNDS (total score)	0	2	0.000*
Depression symptoms (score BDI)	5.0	6.5	0.198
Anxiety symptoms (score BAI)	5.5	11.0	0.003*

\*Significant; GNDS: Guy's Neurological Disability Scale; FAMS: Functional Assessment of Multiple Sclerosis QoL instrument; CIS: clinically isolated syndrome; BDI: beck depression inventory; BAI: beck anxiety inventory.

**Table 3.** Correlation between quality of life (FAMS) with neurological disability (EDSS), activity limitations (GNDS), cognition, depression (BDI) and anxiety (BAI) correlations.

	FAMS p-value
EDSS	0.159
GNDS	0.444
BDI	0.324
BAI	0.451
COGNITION	
PASAT 3 Seconds (Correct responses)	0.102
PASAT 2 Seconds (Correct responses)	0.214
Fluency (Letter)	0.014*
Fluency (Animals)	0.153
Stroop (Time) (Card3)	0.020*
RALVT (Total)	0.272
Digit Symbol (Score)	0.414
Digit Span (Total)	0.050
D2 (Gross)	0.055

\*Significant; FAMS: Functional Assessment of Multiple Sclerosis QoL instrument EDSS: Expanded Disability Status Scale; GNDS: Guy's Neurological Disability Scale; BDI: beck depression inventory; BAI: beck anxiety inventory; PASAT: Paced Auditory Serial Addition; RALVT: Rey auditory Verbal Learning.

determinants of anxiety symptoms in patients with demyelinating diseases<sup>29</sup>, but there is no conclusive explanation for the causes of anxiety in CIS.

No previous studies explored quality of life determinants in CIS. In the present study we sought if neurological disability, activity limitations, cognition, depressive symptoms and anxiety had correlation with quality of life scores. Significant correlations were found between FAMS and verbal fluency with letters and Stroop's card test. Quality of life was not correlated with depression, anxiety, neurological disability and activity limitations. It has been previously shown that cognitive impairment affects quality of life in MS<sup>12</sup> but this is the first report showing that this occurs in CIS.

Our study has some limitations. The sample size may be considered small not allowing a definitive conclusions about the determinants of quality of life. Also, the diagnoses of anxiety and depression were not based on a strict and formal psychiatric evaluation. However, Beck inventories for anxiety

and depression have been used in all patients. These instruments are largely used, both in clinical practice and research.

It was not possible to correlate quality of life, cognition and neuropsychiatric findings with MRI evaluation and current treatment.

In conclusion, this study found reduced quality of life in patients with CIS. Our study suggests that cognitive impairment may be a more important determinant of impaired quality of life in CIS than neurological disability, depressive symptoms and anxiety.

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