Clinical Neurology and Neurosurgery 115 (2013) 1032–1035

Contents lists available at SciVerse ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Cognitive impairment and optic nerve axonal loss in patients with clinically isolated syndrome

C.F. Anhoque[a], L. Biccas-Neto[b], S.C.A. Domingues[c], A.L. Teixeira[a,c], R.B. Domingues[a,d,*]

[a] Neuroscience Postgraduation Program, Federal University of Minas Gerais, Belo Horizonte, MG, Brazil
[b] Surgery Department, Santa Casa, School of Health Sciences, Vitória, ES, Brazil
[c] Department of Internal Medicine, Federal University of Minas Gerais, Belo Horizonte, MG, Brazil
[d] Department of Pathology and Internal Medicine, Santa Casa School of Health Sciences, Vitória, ES, Brazil

ARTICLE INFO

Article history:
Received 22 May 2012
Received in revised form 16 August 2012
Accepted 25 October 2012
Available online 20 November 2012

Keywords:
Cognition
Clinically isolated syndrome
Neuropsychological tests
Optic nerve
Axonal loss
Optical coherence tomography

ABSTRACT

Objective: To investigate cognitive impairment, to assess optical nerve axonal loss, and to determinate whether there is correlation between optical nerve axonal loss and cognition impairment in Clinically Isolated Syndrome (CIS).
Methods: Fifteen CIS patients and 15 controls were submitted to Wechsler memory scale, Rey Auditory Verbal Learning, Rey Complex Figure, Paced Auditory Serial Addition, Digit Span, verbal fluency, stroop color, D2, and Digit Symbol tests. CIS patients were evaluated by optical coherence tomography (OCT) (23 eyes).
Results: CIS patients had worse performance in Paced Auditory Serial Addition Test (PASAT) 2 seconds ($P=0.009$) and fluency tests ($P=0.0038$). Optical nerve axonal loss was found more frequently in eyes with previous optic neuritis (ON) (85.7%) than in those without previous ON (21.7%) ($P=0.0146$). There were no significant correlations between optical nerve axonal loss and cognitive findings.
Conclusions: CIS patients had worse cognitive performance than controls. OCT can detect axonal loss resulting from optical neuritis and subclinical axonal loss in eyes without previous optical neuritis. Optical nerve axonal loss was not correlated with cognition.

1. Introduction

Cognitive impairment is present in 40–65% of patients with multiple sclerosis (MS) [1] and it is correlated with the number and localization of the demyelinating plaques, axonal loss, and brain atrophy [2]. 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) [3,4]. Patients with the first demyelinating episode may already be diagnosed as having MS if both gadolinium-enhancing and nonenhancing lesions on the baseline magnetic resonance imaging (MRI) are found [5]. Some studies have shown that cognitive deficits may be detected in patients with CIS [1,6–10].

Progressive brain atrophy is a well-known feature of MS and is considered as a marker of irreversible tissue damage of both gray matter and white matter [11]. Brain damage and brain atrophy reflect axonal loss and are correlated with cognitive outcome in multiple sclerosis [12,13]. Recently, measures of retinal nerve fiber layer thickness (RNFL) by optical coherence tomography (OCT) showed to be a potentially reliable predictor outcome in MS and optic neuritis [14–16]. Some studies have demonstrated correlation between optical nerve atrophy measured by RNFL and the degree of brain atrophy in patients with MS [16]. However, there are still concerns about the use of OCT for measuring global axonal injury in MS [18].

Taking into account the correlation between cognitive impairment and brain atrophy and the correlation between brain atrophy and optical nerve atrophy it is reasonable to hypothesize a correlation between cognitive decline and optical nerve atrophy measured by OCT. In fact, a correlation between optical nerve atrophy measured by OCT and cognitive impairment was shown in patients with MS [19]. However, it is not known whether such correlation occurs at all stages of disease and if it can already be observed in patients with CIS. The aim of the present study was to investigate the presence and frequency of cognitive impairment, to assess optical nerve atrophy with OCT, and to assess the correlation between optical nerve atrophy and cognitive deficits in patients with CIS.

* Corresponding author at: Rua Prof. Almeida Cousin, 125, sala 1310, Bairro Enseada do Suá, CEP 29.055-565, Vitória, ES, Brazil. Tel.: +55 27 3345 7056; fax: +55 27 3315 4620.
E-mail address: contato@renandomingues.med.br (R.B. Domingues).

0303-8467/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.clineuro.2012.10.025

2. Materials and methods

2.1. Subjects

Subjects aged 19–48 with CIS were recruited during 2 years in the Multiple Sclerosis Clinic of Santa Casa School of Health Sciences, Vitória, Espírito Santo, Brazil. The control group was composed of selected healthy subjects paired by age, gender, and education level. The study was approved by the Research Ethics Committee of the Federal University of Minas Gerais, Belo Horizonte, Brazil, and informed consent was obtained from each participant. CIS patients were submitted to neurologic examination, neuropsychological evaluation, magnetic resonance imaging (MRI), and spectral domain optical coherence tomography (SD-OCT). Patients with severe cognitive impairment defined as score bellow 24 points in the Mini-Mental State Examination [20], severe psychiatric illness, or using psychotropic drugs were not included.

2.2. Neurologic and neuropsychological evaluation

The diagnosis of CIS was done according to the following criteria: one isolated neurological episode lasting at least 24 h compatible with demyelination of the central nervous system and magnetic resonance imaging showing at least two lesions similar to those seen in MS [3]. Patients fulfilling diagnostic criteria of dissemination in time with baseline MRI were excluded. The neurologic evaluation included neurologic examination and determination of current disability using the *Expanded Disability Status Scale* (EDSS) [21].

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); visuo-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 color test), and attention (D2 test; Digit Symbol).

2.3. Optical coherence tomography

CIS subjects, with or without optic neuritis history, underwent measurement of RNFL thickness for both eyes by Spectral Domain Optical Coherence Tomography (SD-OCT) using High Definition optical coherence tomography (HD-OCT) (Cirrus, Carl Zeiss Meditec, Dublin, CA, USA).

For each eye, the OCT software used an automated, computerized algorithm to determine retinal nerve fiber layer (RNFL) thickness. The RNFL values were compared with normative values derived from the database of age-matched controls (internal Cirrus normative database, according to the manufacturer's recommendations), so that these measurements were designated into the following categories: normal (5–95th percentile), below normal (<5th percentile), markedly below normal (<1% percentile) or supra-normal (>95th percentile).

SD-OCT scanning was performed by trained technicians, who monitored scans to ensure fixation was reliable. Mydriatic drops were administered for scan acquisition with 3 doses of topical tropicamide (MydriaCyl®). OCT images were obtained with the Optic Disc Cube 200×200 protocol, which consists of 200 horizontal scan lines (each composed of 200 Å scans) that form a $6\,mm \times 6\,mm \times 2\,mm$ volume cube. Segmentation software determines the location of the inner limiting membrane and the outer boundary of the RNFL at each A-scan to create a 2D map of the thickness of the RNFL in this peripapillary region. Software automatically determines the center of the optic disc and samples the RNFL thickness in a circumpapillary circle of 1.73 mm radius around the optic disc.

Each CIS patient had both eyes examined. The eyes were divided in two categories: symptomatic and non-symptomatic. Symptomatic eyes were those with history of optic neuritis (ON) and non-symptomatic eyes those without history of ON. The time between ON symptoms and OCT was at least 3 months. Patients in whom another ocular abnormality was found were excluded from the OCT analysis. The average RNFL thickness of symptomatic eyes was compared with RNFL thickness of asymptomatic eyes.

We measured the intraocular pressure using the Goldmann applanation tonometry through a Haag-Streit tonometer (Haag-Streit, Bern). We excluded patients with personal history of glaucoma or whose single tonometry values were above 20 mmHg. To rule out normal tension glaucoma, patients whose cup-to-disc excavation ratios were above the normal threshold determined by the Cirrus normative database were also excluded.

2.3.1. 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 cognitive tests between CIS patients and controls. Mann-Whitney test was used to compare the RNFL thickness of symptomatic and non-symptomatic eyes. The correlation between retinal fiber thickness and cognition was evaluated with Spearman correlation test. The proportions of impaired and not impaired cognitive tests were compared with Fisher's exact two-tailed test. The level of significance was set at $P < 0.05$.

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

	Groups	*N*	Mean (±SD)	*P*-value
Age	Patients	18	35.6 (9.3)	
	Controls	18	35.5 (9.2)	
Female	Patients [age 37.5 ± 7.7]	13		
	Controls [age 37.4 ± 7.4]	13		
Male	Patients [age 30.6 ± 12.3]	5		
	Controls [age 30.6 ± 12.4]	5		
EDSS	Patients	18	0.8 (0.5)	
Time between symptom and first assessment (years)	Patients	18	2.09 (2.6)	
Education (years)	Patients	18	14.1 (4.3)	
	Controls	18	14.2 (4.2)	
MEEM	Patients	18	28.4 (1.3)	0.18
	Controls	18	29.1 (0.9)	
Wechsler Adult Intelligence Scale (WAIS)	Patients	18	113.3 (10.1)	0.36
	Controls	18	115 (9.1)	
CIS symptom localization	Lobar	2		
	Brainstem	1		
	Spinal cord	5		
	Optic neuritis	10		

SD: standard deviation.

3. Results

Demographical and clinical data of patients and controls are shown in Table 1. Eighteen CIS patients were included, 13 female and 5 male. The mean ± SD age was 35.5 ± 9.1 years. The mean ± SD EDSS score of patients with CIS was 0.8 ± 0.5. In Table 2 the median