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Background: In multiple sclerosis (MS), the prevalence of alexithymia, defined as an inability to identify and describe emotions, is close to 50% but the prevalence of this symptom in clinically isolated syndrome (CIS) is unknown. Characterizing alexithymia at an early stage of the disease can help to clarify psychobehavioural disturbances in CIS patients.

Methods: Forty CIS patients, who fulfilled the MRI criteria for dissemination in space, were matched with 40 healthy subjects. They completed self-assessment scales for alexithymia, depression, anxiety, apathy and empathy. Cognitive functions were assessed using a battery of neuropsychological tests.

Results: The mean delay (± standard deviation) between the occurrence of CIS and inclusion in the study was 3.9 (2.8) months. The frequency of alexithymia was higher in CIS patients than in controls, with a prevalence of 42% ($p<0.0001$). Alexithymia correlated with anxiety and depression but not with cognition. Alexithymia was dependent only on depression ($p=0.003$).

Conclusion: Alexithymia, characterized by difficulty identifying feelings, is present in patients in the early stage of MS, and seems to be strongly associated with depression. Difficulty in social interaction could be a risk of future affective disorders.

Key words: alexithymia; clinically isolated syndrome; psychobehavioural disturbances; cognitive impairment; multiple sclerosis

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system [1]. In MS patients, alexithymia is reported and is characterized by difficulty identifying their own feelings and describing feelings to other people, restricted imaginative processes and externally oriented cognitive style [2-3]. Alexithymia is mostly evaluated by the Toronto Alexithymia Scale (TAS-20) [4], which evaluates three dimensions of alexithymia: difficulty in identifying feelings (DIF), difficulty in describing feelings (DDF) and externally oriented thinking (EOT). In MS, alexithymia is characterized by DIF and DDF and these emotional disorders are being stable over time [5-6-7]. The prevalence of alexithymia in MS is of 50%, in contrast to 20% in the general population [8] and 30% in other chronic neurological disorders [9].

In MS, alexithymia is associated with depression and anxiety [7], with a prevalence of 50% and 30% respectively [10-11], but these findings are still discussed [5]. This correlation is not assessed in four studies with depression and in one study with anxiety [5]. Apathy is also frequently found in MS with a prevalence of 30% [12-13] and share core features with alexithymia [14] but studies have not yet focused on their relationship. Disturbances in social cognition have been emphasized in MS [15], and a correlation between alexithymia and empathy has been described [16]. Higher alexithymia scores are associated with poor recognition of others' mental states in MS [17].

Cognitive impairment is present in 40% to 65% of MS patients at any stage of the disease and may be associated with depression and anxiety [18]. Such cognitive impairment, specially a slower information processing speed, and psychobehavioural disorders have been also been reported in CIS patients [19]. However, the prevalence and characterization of alexithymia remains under-explored among CIS patients. Alexithymia seems to be a risk factor for affective disorders [5] and therefore needs to be considered in a multidisciplinary approach to the disease, in order to improve social interaction.

The objectives of the present study were (i) to define the prevalence of alexithymia in CIS patients, and (ii) to study its relations to psychobehavioural and cognitive disorders frequently encountered in MS.

2. Methods

2.1 Subjects

We recruited 40 CIS patients between May 2012 and May 2016 in our MS center. The inclusion criteria were: (i) age between 18 and 60 years, (ii) the presence of at least two subclinical lesions on brain MRI, (iii) right-handedness according to the Edinburgh Handedness Inventory [20], (iv) non-use of disease modifying drugs, and (v) non-use of steroids for at least four weeks. The exclusion criteria were: (i) history of any clinically relevant psychiatric disease or other neurological diseases, (ii) a history of drug or alcohol abuse and (iii) difficulty in understanding the French language.

CIS patients were matched with 40 healthy right-handed controls recruited from general population according to age, gender and level of education. The exclusion criteria for controls were identical to those of patients.

The study protocol was approved by the local independent ethics committee (CPP Nord Ouest IV, Lille, France; 2011-A00016-35) and all participants gave their written, informed consent to participation in the study. The trial is registered as NCT03796247 (clinicalTrials.gov).

2.2 Procedure

2.2.1 Alexithymia assessment.

The prevalence of alexithymia was assessed by the TAS-20, a self-reported scale [4]. The TAS-20 total score corresponds to the global level of alexithymia, and is defined by three subdomains (DIF, DDF and EOT).

2.2.2 Clinical assessment.

A standard neurological examination was performed by a neurologist using the Kurtzke Expanded Disability Status Scale (EDSS) [21].

2.2.3 Cognitive assessment.

A standardized neuropsychological battery, the BCcogSEP, was validated in a French version to evaluate cognitive functions in MS [22]. Fourteen scores were obtained from 8 tests: The selective reminding test (SRT) measures verbal episodic memory, with 3 scores considered: mean number of words in immediate recall, learning index and delayed recall. The 10/36 spatial recall test assesses visual learning (10/36).The symbol digit modality test (SDMT) measures information processing speed and selective attention. The crossed tapping test evaluates mental flexibility. The paced auditory serial addition task (PASAT) evaluates sustained attention, information processing speed and working memory. Memory span assesses immediate and working memory. The word list generation test measures semantic and phonemic verbal fluency. The GOnoGO test assesses response inhibition. A score was considered impaired when it was below the 5th percentile. A global cognitive damage is considered when at least 4 scores are below the 5th percentile.

2.2.4 Psychobehavioural assessments.

We mesured (a) depression according to the Beck Depression Inventory (BDI); (b) anxiety according to the State–Trait Anxiety Inventory (STAI); (c) apathy according to the Lille Apathy Rating Scale (LARS); and (d) empathy according to the Interpersonal Reactivity Index (IRI) [23-24-25-26]. These assessments are largely used in studies that have explored psychobehavioural disorders in MS [5].

2.3 Data analysis

All statistical analyses were performed with SAS software (version 9.3, SAS Institute Inc., Cary, NC). The threshold for statistical significance was set to $p < .05$. Quantitative variables were expressed as the mean ± standard deviation (SD), and qualitative variables were expressed as percentages (%). The normal distribution of data was tested by Kolmogorov-Smirnov normality test.

Demographic characteristics (age, gender, and education level), cognitive functioning (number of subjects with cognitive dysfunction) and psychobehavioural symptoms (as estimated by STAI, BDI-II, IRI, and LARS scores) were compared between patients with CIS and controls. These comparisons were performed using the Mann–Whitney U test or Student's t-test for quantitative variables and the chi-squared and Fisher's exact test for qualitative variables. The prevalence of cognitive decline was estimated using the BCcogSEP cut-off scores (i.e., ≥ 4 impaired scores). A deficit in information processing speed was estimated when SDMT scored below the 5th percentile.The prevalence of psychobehavioural symptoms was estimated by cut-off scores (i.e. BDI-II score ≥ 12, STAI score ≥ 39, and LARS score ≥ 22).

Alexithymic symptoms (as estimated by TAS-20 scores, DIF, DDS and EOT scores) were compared between CIS patients and controls using the Mann–Whitney U test or Student's t-test for quantitative variables. The prevalence of alexithymia was compared between CIS patients and controls using the chi-squared test; alexithymia was defined as a TAS-20 score of at least 56.

Only the measures that significantly differed between CIS and healthy controls ($p<0.05$) were further included in the subgroup analysis. We tested the association between alexithymia and other cognitive, psychobehavioural characteristics and EDSS. Correlation analyses (using Pearson's r for variables with a normal distribution or Spearman's rank correlation for non-parametric variables) and group comparisons (between patients with and without alexithymia, using the Mann–Whitney U test or Student's t test for quantitative variables and the chi-squared test for qualitative variables) were applied. Due to Bonferroni correction significant p value for correction tests were considered when $p < 0.01$. Additionally, variables with a p-value below 0.20 in a bivariate analysis were selected for multivariate stepwise linear regression analysis to explain alexithymic symptom.

3. Results

3.1 Characterization of patients with CIS

Among the CIS patients, 82.5% (n=33) fulfilled Barkhof's MRI criteria for dissemination in space at baseline [27]. After a mean follow-up time of five years, 87.5% (n=35) of patients fulfilled

the definition of MS according to McDonald criteria [28], 2 patients were lost of follow-up, 1 patient accidentally died and 2 still had CIS. The mean delay between the CIS and the inclusion was 3.9 (2.8) months. Median EDSS score was 1.5 [0-4].

CIS patients did not differ significantly from controls in terms of baseline demographic characteristics (Table 1).

3.2 Alexithymia in CIS patients

Alexithymia was found in 42.5% of CIS patients (n=17) compared with 15% on controls subjects (n=6) and the difference was significant (p=0.006). Relative to controls, CIS patients had a significantly higher mean global score of alexithymia (p<0.0001) and specifically had significantly more difficulties to identify emotions (DIF sub-score, p<0.0001) (Table 2).

3.3 Psychobehavioural and cognitive disorders in CIS patients

Relative to cognitive assessment, CIS patients present more significant cognitive decline than controls (p=0.0006) (Table 1).

Concerning psychobehavioural assessment, CIS patients had a higher mean depression score (p=0.02) and a higher mean anxiety-state score (p<0.0001) than controls (Table 1). Depressive symptoms occurred in 35% (n=14) of CIS patients, and 65% (n=26) were considered anxious (anxiety-sate). CIS patients and controls did not differ significantly in apathy or empathy.

3.4 Association of alexithymia with depression, anxiety, cognitive decline, and EDSS in CIS patients

In CIS patients, significantly higher depression scores were reported among alexithymic patients compared to those without alexithymia (p=0.04). Specifically, BDI score was correlated with TAS-20 score (r=0.47; p=0.003) and DIF sub-score (r=0.45; p=0.004).

Alexithymic patients were not more anxious than those without alexithymia (table 3), although a moderate correlation was found between alexithymia and anxiety-state scores (r=0.46, p=0.003).

Alexithymic symptom is equally distributed between cognitively impaired (n=8) and cognitively preserved patients (n=9) (p=0.9).

Alexithymic patients did not have more cognitive decline and were no more slower than those without alexithymia (table 3). Alexithymia didn't have any significant correlation with cognitive decline (r=0.064, p=0.69) and with information processing speed (r=0.28, p=0.77).

The degree of neurological impairment evaluated by EDSS score was not correlated with TAS-20 score (r=0.13, p=0.4).

Finally, regression analysis identified BDI score as the only predictor of overall alexithymia TAS-20 score (r^2=0.21, p=0.003).

4. Discussion

Our study highlighted that (i) 42% of CIS patients presented alexithymia, independently of cognitive decline or anxiety; (ii) alexithymia was associated with depression, and (iii) alexithymia in CIS was characterized by difficulty identifying feelings. Our findings at the earliest stage of MS is close to the findings in MS disease which is reported at 50% [7]. Moreover, alexithymia was found in 15% on controls subjects. This result is close to the findings in general population disease which is reported at 10% [8].

The strength of our study is to compare prospectively CIS patients with matched healthy controls for assessing alexithymia, after a very short delay of CIS onset (4 months). The main limitation of our controlled and prospective study was the limited size of the sample. However, our methodology did allow us to reveal that, in the early stage of MS and absence of steroid intake, alexithymia was significantly more common in CIS patients than in controls and was associated with depression but not cognitive function or anxiety. Another limit in our study was to not take into account the fatigue. However, the study of Hyncicova et al. [29] did not support the notion that fatigue is present in patients with CIS. Fatigue seems to be related to disease duration and is not usually considered shortly after diagnosis of CIS.

Patients in our study had a high level of alexithymia and presented more DIF, as found in other studies [6-30]. This factor, which refers to emotional awareness, is one of the essential steps in emotion processing. As alexithymia is not related to cognitive decline, DIF cannot be explained by a cognitive disturbance and represents a real emotional processing disorder. In contrast, the EOT factor, is comparable between CIS patients and controls, which suggests that the capacity of introspection is preserved. The ability to describe feelings is preserved in CIS patients.

A relation between alexithymia and depression in MS has been reported by several authors [7-30] and DIF dimension of alexithymia is a vulnerability factor to develop depressive symptoms in general population [31]. Our data show that this relation exists at the earliest clinical stage of the disease. The link between DIF factor of alexithymia and depression in our CIS patients, could explain, in part, the occurrence of depressive symptoms. Therefore, depression is expected to be more common in alexithymic than in non-alexithymic patients because of a confusion about the source of emotions [14]. As in the study of Chahraoui et al. [7], we found a similar degree of correlation between anxiety and alexithymia. However, our alexithymic patients are no more anxious than non alexithymic patients. In our study, we focused on CIS stage of the disease, contrary to Chahraoui's study [7] where all MS stage are represented. This conflicting result could suggest that the classification of alexithymia at CIS stage and during the further disease course is different. It could mean that alexithymia in the early stage of the disease could referred a response of the distress and maybe to personality construct at the further course of the disease [31]. Alltogether alexithymic CIS patients could be less anxious than alexithymic MS patients in further course of the disease.

Other studies have reported depression in 35% of CIS patients [7-32]. Bianchi *et al.* [33] found that 72% of CIS and MS patients presented symptoms of depression, using a different scale, which is twice the prevalence in our study. Approximately 65% of CIS patients presented anxiety-state, three times the prevalence in healthy controls, with no difference in anxiety-trait. In contrast to our study, Di Legge *et al.* [34] reported that CIS patients showed significantly higher scores in the STAI "trait' but not 'state'. This discrepancy can be explained by the different evaluation time in their study compared to ours (33 vs 3.9 months after CIS onset). Emotional disturbances occur shortly after

a first episode suggestive of MS because of the diagnosis period and the high prevalence of anxiety state seems to represent a normal psychological reaction.

In MS, a decrease of empathy and increase of apathy have been described: the prevalence of apathy in MS is estimated to 20 at 40% [12-13]. At CIS stage, we didn't find any difference between controls and patients concerning apathy symptom, evaluated by the LARS, a semi-structured assessment. This finding is consistent with the finding of Hyncicova et al. [29]. As in our study, apathy assessment (assessed by AES, Apathy Evaluation Scale [35]) was performed in their study between 1 and 12 months from the diagnosis of CIS (median 4 months). A meta-analysis showed that in others studies most of the patients had a relapsing-remitting course of the disease, with a median disease duration of 8.1 [2.6-12] years [12]. It could mean that at CIS stage, patients do not have loss of interest in activities.

As the study of Capet *et al*. [36] and Dulau *et al*. [37], alexithymia did not correlate with global cognitive decline. However, Capet *et al.* [36] suggested that alexithymic patients are slower than non alexithymic patients. Their results suggested a link between the information processing speed and alexithymia. Contrary to their result, our alexithymic patients are not slower than non alexithymic patients but maybe our study is underpowered.

In conclusion, alexithymia is still largely represented at the early stage of MS, at CIS stage, and is characterized by difficulty identifying feelings and seems to be related to depression. However, in contrast to depression, which is expected to be highest in this early stage of disease and decrease with time [33], alexithymia is described as stable overtime in the disease course [6].

In order to clarify whether alexithymia in MS is a factor of personality or a consequence of neuronal networks, longitudinal data need to be assessed over time during the MS disease course, through functional MRI studies. Alexithymia is hypothesized to be related to interhemispheric transfer dysfunction [5] and significantly correlated with a decrease of corpus callosum volume [36], but the relationship between the both needs to be evaluated using functional MRI.

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Table 1. Comparison of demographic, cognitive and psychobehavioural characteristics between CIS patients and controls

	Controls (n= 40)	**CIS patients** (n= 40)	**p-values**
Demographic characteristics			
Age in years, mean (± SD)	33.58 (9.13)	33.60 (9.58)	1
Gender ratio (F/M)	3/1	30/10	1
Percentage of patients with more than 12 years of full time education	70.00	70.00	1
Cognitive characteristics			
Number of subjects having at least 4 scores ≤ the 5th percentile	n=2	n=23	**0.0006**
Psychobehavioural characteristics			
BDI-II score, mean (± SD)	5.22 (5.19)	10.45 (10.30)	**0.02**
STAI			
STAI-State score, median [IQR]	30.85 [24; 37.25]	43.48 [34.25; 53]	**<0.0001**
STAI- Trait score, mean (± SD)	37.30 (9.27)	41.52 (10.64)	0.06
LARS score, median [IQR]	-36.00 [-36; -33]	-36.00 [-36; -35.25]	0.5
IRI			
Cognitive sub-score, median [IQR]	35.00 [29.25; 38]	31.50 [27; 35.25]	0.07
Affective sub-score, median [IQR]	33.50 [29; 39]	31.00 [26.75; 34.25]	0.07

IQR= interquartile range, SD = standard deviation, BCcogSEP = Batterie Courte d'Evaluation des fonctions Cognitives des patients ayant une Sclérose En Plaques, BDI = Beck Depression Inventory, CIS = Clinically Isolated Syndrome, IRI = Interpersonal Reactivity Index, LARS = Lille Apathy Rating Scale, STAI = State-Trait Anxiety Inventory

Table 2. Comparison of means TAS-20 scores between CIS patients and controls

	Controls (n = 40)	**CIS patients** (n = 40)	**p-values**
overall TAS-20 score, mean (± SD)	43.98 (11.43)	50.78 (12.54)	**<0.0001**
Difficulty Describing Feelings TAS-20 sub-score, mean (± SD)	13.65 (4.68)	13.98 (4.42)	0.06
Difficulty Identifying Feeling TAS-20 sub-score, mean (± SD)	14.48 (6.66)	17.98 (6.33)	**<0.0001**
Externally-Oriented Thinking TAS-20 sub-score, mean (± SD)	16.40 (4.69)	18.38 (5.47)	0.08

CIS = Clinically Isolated Syndrome; TAS-20 = Toronto Alexithymia Scale; SD = standard deviation

Table 3. Percentage of psychobehavioural and cognitive characteristics in CIS patients with and without alexithymia

	All patients (N=40)	**With alexithymia** (N=17)	**Without alexithymia** (N=23)	**p-values**
Depression[a]	35 (n=14)	22.5 (n=9)	12.5 (n=5)	**0.04**
Anxiety state[a]	47 (n=26)	12 (n=12)	35 (n=14)	0.5
Cognitive impairment	57.5 (n=23)	20 (n=8)	37.5 (n=15)	0.2
SDMT deficit	7.5 (n=3)	17.5 (n=3)	0	0.06

[a]indicate the parameters that were included in the multivariate stepwise logistic regression analysis because of their positive correlation ($p<0.005$) with alexithymia; CIS = Clinically Isolated Syndrome; SDMT= Symbol Digit Modality Test