Observational Study

Medicine®

OPEN

Mild cognitive impairment in psoriatic arthritis

Prevalence and associated factors

Marco Di Carlo, MD[a,*], Andrea Becciolini, MD[b], Antonella Incorvaia, MD[a], Giacomo Beci, MD[a], Gianluca Smerilli, MD[a], Martina Biggioggero, MD[b], Marika Tardella, MD[a], Rossella De Angelis, MD, PhD[a], Fausto Salaffi, MD, PhD[a]

Abstract

To assess the prevalence and factors associated with mild cognitive impairment (MCI) in patients suffering from psoriatic arthritis (PsA).

A cross-sectional evaluation was conducted in consecutive PsA patients. Sociodemographic data and the clinimetric variables related to PsA and psoriasis were collected for each patient. MCI was assessed through the Montreal Cognitive Assessment (MoCA). The cognitive performance of PsA patients was compared to healthy subjects using one-way analysis of variance (ANOVA). The correlations among variables were studied by the Spearman rank correlation coefficient. A multivariate logistic regression analysis was carried out to establish the predictors of MCI.

The study involved 96 PsA patients and 48 healthy subjects. MCI (defined as a MoCA score $< 26/30$) was detected in 47 (48.9%) PsA patients. Compared to healthy subjects, the MoCA score resulted significantly lower in PsA patients ($P = .015$). The main differences involved the denomination and language domains. MoCA was negatively correlated with age ($r = -0.354$; $P < .0001$), HAQ-DI ($r = -0.227$; $P = .026$), and fatigue ($r = -0.222$; $P = .029$), and positively correlated with psoriasis duration ($r = 0.316$; $P = .001$) and DLQI ($r = 0.226$; $P = .008$).

The multivariate logistic regression analysis revealed the duration of psoriasis ($P = .0005$), age ($P = .0038$), PASI ($P = .0050$), and HAQ-DI ($P = .0193$) as predictors of the MoCA score.

MCI is present in a significant proportion of PsA patients, and is mainly determined by age, cutaneous variables, and disability.

Abbreviations: ANOVA = analysis of variance, CASPAR = ClASsification criteria for Psoriatic Arthritis, CRP = C-reactive protein, DAPSA = Disease Activity Score for Psoriatic Arthritis, DLQI = Dermatology Life Quality Index, EULAR = EUropean Leaugue Against Rheumatism, FM = fibromyalgia, HAQ-DI = Health Assessment Questionnaire-Disability Index, IQR = interquartile range, LEI = Leeds Enthesitis Index, MCI = mild cognitive impairment, MoCA = Montreal Cognitive Assessment, NRS = numerical rating scale, PASI = Psoriasis Area and Severity Index, PGA = patient global assessment of disease activity, PsA = psoriatic arthritis, PsAID-12 = Psoriatic Arthritis Impact of Disease 12-item, QoL = quality of life, RA = rheumatoid arthritis, SCQ = Self-Administered Comorbidity Questionnaire, SD = standard deviation, SJC = swollen joint count, SLE = systemic lupus erythematosus, TJC = tender joint count.

Keywords: disability, mild cognitive impairment, montreal cognitive assessment, psoriasis, psoriatic arthritis

1. Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory joint disease whose consequences extend beyond joint or skin problems. While associations with extra-articular inflammatory manifestations, such as anterior uveitis or inflammatory bowel diseases, have been well known,[1] on the other hand and more recently, research has begun on the association with manifestations that do not necessarily relate to well-documented organic causes. Conditions such as anxiety, depression, or fibromyalgia (FM)

Editor: Francesco Carubbi.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

The authors have no conflicts of interests to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] *Rheumatology Clinic, Università Politecnica delle Marche, "Carlo Urbani" Hospital, Jesi (Ancona),* [b] *Department of Rheumatology, "Gaetano Pini"-CTO Institute, Milan, Italy.*

[*] *Correspondence: Marco Di Carlo, Rheumatology Clinic, Università Politecnica delle Marche, "Carlo Urbani" Hospital, Via Aldo Moro, 25, Jesi (Ancona) 60035, Italy (e-mail: dica.marco@yahoo.it).*

How to cite this article: Di Carlo M, Becciolini A, Incorvaia A, Beci G, Smerilli G, Biggioggero M, Tardella M, De Angelis R, Salaffi F. Mild cognitive impairment in psoriatic arthritis: prevalence and associated factors. Medicine 2021;100:11(e24833).

Received: 28 July 2020 / Received in final form: 24 October 2020 / Accepted: 25 January 2021

http://dx.doi.org/10.1097/MD.0000000000024833

have a higher prevalence in patients with PsA than in the general population.[2–4]

The need to investigate comorbidities and all the aspects that impact patients' quality of life (QoL) is also recognized internationally. To date, a comorbidity poorly studied in PsA is mild cognitive impairment (MCI).

Cognitive function is a complex health domain, and involves multiple abilities such as orientation, concentration, attention, memory, verbal functions, problem solving, and visual/space functions.

The general concept of QoL includes cognitive performance. The integrity of cognitive performance is fundamental not only for QoL, but also for a subject to maintain his or her functional capacity intact, especially with advancing age,[5] and is reflected in areas that are necessary for therapeutic success, such as adherence to treatment.[6]

The presence of a cognitive deficit, however, is not exclusively the prerogative of elderly subjects.

Cognitive impairment has been demonstrated in systemic autoimmune diseases, mainly in systemic lupus erythematosus (SLE) and in rheumatoid arthritis (RA).[7]

It is known that a cognitive dysfunction can be considered among the neuropsychiatric manifestations of SLE, but it can still be present in patients without documented neurologic involvement at imaging. With regard to RA, a disease in which neurological manifestations are not frequent, a cognitive impairment can be documented in more than half of the subjects.[8,9]

The cognitive deficit in psoriasis has been investigated in several psoriasis studies documenting the presence of a cognitive impairment in a significant proportion of patients.[10,11] It is estimated that an MCI is present in 44% of patients with psoriasis, and that the predominantly altered cognitive domains are long-term verbal memory, executive functions, and attention.[10] However, in studies examining cognitive impairment in psoriasis, the presence of a PsA was a criterion for exclusion. To date, to the best of our knowledge, there is no study that has investigated MCI in patients with PsA.

In line with these assumptions, the objective of this study was to assess the prevalence and the clinical and demographic factors associated with the presence of MCI in patients with PsA.

2. Methods

2.1. Patients and setting

In this study, PsA patients diagnosed according to the ClASsification criteria for Psoriatic ARthritis (CASPAR)[12] and in stable treatment for at least 3 months were consecutively enrolled in the inpatients and outpatients clinics of 2 Italian third-level rheumatology centres (Rheumatology Clinic, Università Politecnica delle Marche, Jesi, Ancona, Italy and Rheumatology Department, ASST Gaetano Pini - CTO, Milan, Italy) with experience in PsA diagnosis and management. Patients between 18 and 70 years of age were included, with predominant peripheral joint involvement, excluding subjects with concomitant conditions that could interfere with cognitive assessment. Patients diagnosed with dementias or other neurological diseases, with depression or other psychiatric disorders, and patients with FM (diagnosed according to the 2016 American College of Rheumatology criteria)[13] were excluded. It was considered appropriate to exclude FM because it is a frequent comorbidity in patients with PsA, itself associated with the presence of a cognitive deficit that is part of the so-called fibrofog.[14] Patients with other conditions that could interfere with the clinical evaluation of PsA and psoriasis were also excluded, considering inflammatory joint conditions such as crystal arthropathies, symptomatic osteoarthritis, neuropathic conditions, active neoplasms, heart failure, chronic renal failure, liver failure, and the possible presence of diffuse skin diseases other than psoriasis.

A control group was also enrolled among the patients' partners, in order to include subjects with an age, schooling and socio-cultural background comparable to those of the patients. Healthy subjects in the control group were also assessed with the Montreal Cognitive Assessment (MoCA),[15] the tool used in this study to evaluate MCI, as detailed below. A normative study on the healthy Italian population showed how age and education influence the MoCA score, while gender does not seem to have an effect.[16] Subjects over 70 years of age were also excluded from the control group. Schooling was considered by counting the years of formal education from the first year of primary school onwards.

Both in the patient group and in the control group, subjects with behavioural habits capable of affecting cognitive abilities were excluded, in particular, current smokers (defined as subjects still smoking or with smoking cessation <5 years), those with estimated alcohol consumption above 2 units (20 g) per day, and those with a current or past personal history of substance abuse.

The study was conducted in accordance with the principles of the Helsinki Declaration and was approved by the local ethics committee (Comitato Etico Unico Regionale, number 0458 AS), and patients signed informed consent for anonymous data collection.

2.2. Psoriatic arthritis, psoriasis, and comorbidities assessment

The objective joint examination was conducted to assess the tender joint count (TJC, 0–68 joints), the swollen joint count (SJC, 0–66 joints), the number of digits with dactylitis, and enthesitis. As a laboratory parameter, the C-reactive protein (CRP, in mg/dl) was collected as a marker for systemic inflammation.

Disease activity was determined through the Disease Activity Score for PsA (DAPSA). DAPSA is a composite disease activity index represented by the algebraic sum of TJC, SJC, patient global assessment of disease activity (PGA, 0–10 numerical rating scale [NRS]), NRS pain (0–10), and CRP (in mg/dl). DAPSA is a specific index for PsA that has gained international recognition, and cut-offs have been established that distinguish disease activity (remission ≤ 4, low disease activity >4 and ≤ 14, moderate disease activity >14 and ≤ 28, high disease activity >28).[17]

The presence of dactylitis was recorded simply by counting the number of digits with dactylitis at hand and foot level. The simple finger count with dactylitis demonstrated good discriminatory and responsiveness properties.[18]

Enthesitis was evaluated in the 6 enthesial sites (lateral epicondyles, medial femoral condyles, Achilles tendon insertions) of the Leeds Enthesitis Index (LEI), whose score is given by the algebraic sum of the sites with enthesitis. LEI is considered an acceptable index for enthesitis as it is easily computable and correlated with disease activity.[19]

Functional capacity was estimated with the Health Assessment Questionnaire-Disability Index (HAQ-DI). As a clinimetric tool

used for several years in rheumatology, HAQ-DI assesses the degree of difficulty in performing common daily life activities in 8 areas, with the highest score considered for each area. The questions are answered on a four-point scale (from 0, without difficulty, to 3, impossible), and the final score is the arithmetic mean of the 8 functional areas.[20]

The Psoriatic Arthritis Impact of Disease 12-item (PsAID-12) was used as a patient-reported outcome to assess the overall PsA burden. Obtained with 12 NRS to 11 points aimed at investigating the impact of disease in different health domains (pain, fatigue, skin problems, work and/or leisure activities, functional capacity, sleep disorders, discomfort, coping, anxiety, embarrassment and/or shame, social participation, depression), PsAID-12 is quickly calculated and the final score ranges from 0 to 10, where higher scores indicate a more severe disease impact. The PsAID-12 is endorsed by the EUropean League Against Rheumatism (EULAR), and has also proven to be valid against the PsA's disease activity indices.[4,21]

The Psoriasis Area and Severity Index (PASI), the typical measure used in clinical trials, was used to assess the extent and severity of psoriasis.[22] The PASI considers 4 characteristics of PsA (surface involved, severity of the erythema, thickening, and desquamation of the lesions) evaluated considering the head, trunk, upper and lower limbs. The score ranges from 0 to 72, where higher scores indicate a higher severity of PsA, and can be calculated using online calculators. Although the PASI in this study was not performed by a dermatologist, it was obtained by rheumatologists with daily experience in the management of PsA patients and with experience scoring this clinimetric index.

The Dermatology Life Quality Index (DLQI) was used as an indicator of QoL related to psoriasis. Although it is a generic dermatological instrument and not exclusively dedicated to psoriasis, it is widely used for this disease.[18] It is a 10-item instrument that investigates the last 7 days, and the score ranges from 0 to 30, where higher scores indicate a worse QoL.[23]

The overall weight of the comorbidities was calculated on the Self-Administered Comorbidity Questionnaire (SCQ). The SCQ includes 13 common diseases, plus 2 blank lines potentially usable with non-listed diseases. The patient is asked to confirm whether he or she is suffering from the disease, whether he or she is currently being treated for that disease, and whether that disease limits activities. As previously done, in the SCQ used for PsA the possible presence of RA was changed with inflammatory bowel diseases.[4] The significance of assessing the impact of comorbidities, through a measurement of comorbidity, is increasingly considered important in PsA as it influences fundamental variables such as persistence in treatment with biological drugs.[24]

2.3. Mild cognitive impairment assessment

MCI was evaluated in each location by blinded physicians (AB and AI) with respect to the case/control status. If the case definition was not obscurable, for example, due to the presence of psoriasis in visible skin areas or the presence of joint deformities, the physician was still blinded with respect to the clinical evaluation of PsA and psoriasis. The presence of MCI was defined using the MoCA, both in study group and controls. MoCA is a relatively short and easy to administer screening tool, taking about 10 minutes to be completed. MoCA can unveil an MCI that can pass unnoticed at the Mini Mental Status Examination. MoCA investigates multiple cognitive domains, that is, visuo-spatial skills, short-term memory, executive functions, language skills, sustained attention, concentration, working memory, and orientation. The overall score ranges from 0 to 30, where higher scores indicate better performance. A score <26 indicates the presence of MCI.[15] The Italian version of the MoCA was used in this study,[25] and the 7 subscales composing the various tool blocks were calculated.

2.4. Statistical analysis

The variables studied are presented, where appropriate, as mean (± standard deviation) or median (and interquartile range). The total MoCA score and its sub-scales were compared between patients and healthy controls using one-way analysis of variance (ANOVA), as well as the presence of any differences in age or schooling.

Two correlation analyses were then conducted using the Pearson correlation. In the first one the main variables related to PsA, psoriasis, demographic variables, and MoCA were correlated. In a second correlation analysis the impact measures of PsA, namely the items of PsAID-12, were correlated with MoCA. Finally, a multivariate logistic regression analysis was performed including as covariates the variables related to PsA (PsA duration, DAPSA, HAQ-DI, LEI, PsAID-12, NRS pain, CRP), psoriasis (psoriasis duration, PASI, DLQI), comorbidity (SCQ), and 2 demographic variables related to MCI (age, schooling). In this analysis, those items of PsAID-12 that obtained a correlation with MoCA (fatigue, see below) were also considered. The MoCA score was used as a dependent variable.

The statistical analysis was conducted with MedCalc, version 18.0.0, setting P values <.05 for statistical significance.

3. Results

A total of 96 PsA patients (58 men, 38 women), and 48 healthy subjects (25 men, 23 women) in the control group, were included in the study. The mean age of the patients was 52.7 ± 11.7 years versus 49.2 ± 12.2 years in the control group, a not statistically significant difference (P = .12). With regard to schooling, the mean years of education in the patients were 13.06 ± 3.75 vs 13.85 ± 4.20 in the controls. The difference was not statistically significant (P = .25) for schooling between the 2 groups either.

Among the patients, by definition all had a current or anamnestic history of peripheral joint involvement, in 7 (7.3%) at least 1 finger with active dactylitis was documented, in 11 (11.5%) there was at least 1 clinical sign of active enthesitis, in 3 (3.1%) there was symptomatic axial involvement, while 21 (21.9%) had PsA sine psoriasis. The mean PsA duration was 9.61 ± 8.68 years, while psoriasis duration was 14.92 ± 13.67 years. A mean SCQ of 2.62 ± 2.79 was recorded.

For articular disease activity, the mean DAPSA was 10.72 ± 8.75, while the mean HAQ-DI was 0.48 ± 0.48, and the mean PsAID-12 was 2.67 ± 2.12. For psoriasis, the mean PASI was 0.90 ± 1.73, and the mean DLQI was 1.93 ± 3.29. Table 1 summarizes all the clinimetric characteristics of the patient group.

All the patients were taking a disease modifying anti-rheumatic drug (DMARD), represented by a biological DMARD in 61 subjects (63.5%) (respectively 14 with golimumab, 12 with ethanercept, 12 with adalimumab, 8 with infliximab, 6 with ustekinumab, 5 with secukinumab, 4 with certolizumab pegol).

In the patients group, 47 out of 96 (48.9%) subjects had a MoCA score <26, indicative of reduced cognitive performance.

Table 1

Clinimetric features of the group of 96 patients suffering from PsA.

	Mean	Median	SD	IQR
PsA duration (years)	9.61	6.50	8.68	3.00–14.00
Psoriasis duration (years)	14.93	13.75	13.67	1.75–23.25
SCQ	2.62	2.00	2.79	0.00–4.00
PGA	3.76	4.00	2.59	1.25–6.00
PhGA	1.99	1.00	2.05	0.00–3.00
NRS pain	3.41	3.00	2.72	1.00–5.00
TJC (0–68)	2.17	1.00	3.77	0.00–2.00
SJC (0–66)	0.71	0.00	1.35	0.00–1.00
Dactylitis (number of fingers)	0.12	0.00	0.46	0.00–0.00
LEI	0.19	0.00	0.55	0.00–0.00
CRP (mg/dl)	0.67	0.30	1.28	0.14–0.70
DAPSA	10.72	9.20	8.75	4.10–15.35
HAQ-DI	0.48	0.31	0.48	0.13–0.75
PsAID-12	2.67	2.30	2.12	0.83–4.25
PASI	0.90	0.00	1.73	0.00–1.00
DLQI	1.93	1.00	3.29	0.00–2.00

CRP = C-reactive protein, DAPSA = Disease Activity index for Psoriatic Arthritis, DLQI = Dermatology Life Quality Index, HAQ-DI = Health Assessment Questionnaire-Disability Index, IQR = interquartile range, LEI = Leeds Enthesitis Index, NRS pain = Numerical Rating Scale of pain, PGA = patient global assessement of disease activity, PASI = Psoriasis Area and Severity Index, PhGA = physician global assessment of disease activity, PsA = psoriatic arthritis, PsAID-12 = Psoriatic Arthritis Impact of Disease 12 items, PsO = psoriasis, SCQ = Self-Administered Comorbidity Questionnaire, SD = standard deviation, SJC = swollen joint count, TJC = tender joint count.

In contrast, in healthy subjects 18 out of 48 (37.5%) individuals had a MoCA score <26.

All the MoCA subscales showed a reduced score in patients with PsA compared to controls, except for the domain related to orientation where, as expected, performance was overlapping and optimal in groups. The memory domain, on the other hand, was the most compromised in both patients and controls. The statistically significant differences between the 2 groups were obtained in the domain denomination ($P=.0004$) and language ($P=.008$). The MoCA score as a whole was significantly reduced in PsA patients compared to healthy controls ($P=.015$) (Table 2).

The first correlation analysis (including demographic data and indices related to PsA and psoriasis) revealed significant negative correlations between MoCA and age ($r=-0.354$; $P<.0001$) and HAQ-DI ($r=-0.227$; $P=.026$), and positive correlations between MoCA and psoriasis duration ($r=0.316$; $P=.001$) and DLQI ($r=0.226$; $P=.008$) (Table 3). From the second correlation analysis (including the 12 items of PsAID-12), the only significant negative correlation emerged between MoCA and fatigue ($r=-0.222$; $P=.029$) (Table 4).

The multivariate logistic regression analysis revealed, among the covariates implicated as predictors of the MoCA score, the duration of psoriasis ($P=.0005$), age ($P=.0038$), PASI ($P=.0050$), and HAQ-DI ($P=.0193$) (Table 5).

4. Discussion

In this study we have shown that a significant proportion of patients with PsA have MCI, with MoCA scores statistically worse than healthy control subjects. The main differences emerged in the domains related to language. The main predictors of a reduced MoCA score are the duration of psoriasis, age, extent of skin disease (evaluated with PASI), and reduced functional capacity (evaluated with HAQ-DI).

To the best of our knowledge, this is the first study that has investigated the presence of an MCI in PsA patients. Although the evaluation of the MCI is not part of the Outcome Measures in Rheumatology (OMERACT) core,[26] it was important to investigate cognitive performance in PsA. Identifying the presence of an MCI at an early stage has become a challenge for clinicians and is essential to try to implement prevention strategies towards the evolution of an established form of dementia.[27] From a large survey of narrative medicine conducted in patients with PsA, it emerged that the problems related to the cognitive domain concern 20% of patients, in third position after the categories physical and emotional problems.[28]

Several studies have investigated the cognitive deficit in psoriasis, yet inflammatory joint involvement, i.e., the coexisting presence of PsA, represented a criterion for exclusion until now.[10,11] The presence of a chronic inflammatory joint disease, considering for example the large literature on RA, can itself determine a cognitive deficit.[29] Compared to RA, the cognitive performance assessed by the MoCA of PsA patients would seem to be better: a score <26 was documented in 63% of RA patients.

However, the case history of Olah and colleagues was about 10 years older and contained smokers.[30]

The results of this study should be analyzed on several levels. First, the strong correlation with age was somehow preventable. Changes in cognitive abilities with advancing age are well known and considered part of a normal aging process.[31]

Proceeding to then analyze the variables related to PsA, correlations and associations with skin variables emerge, in particular with the duration of psoriasis, DLQI, and PASI. PASI

Table 2

Differences of MoCA total score and subscales between the PsA patients and the controls.

	PsA patients				Controls				
	Mean	Median	SD	IQR	Mean	Median	SD	IQR	Significance, P^*
Visuospatial/executive	4.15	4.00	0.96	4.00–5.00	4.44	5.00	0.82	4.00–5.00	.074
Denomination	2.49	3.00	0.58	2.00–3.00	2.88	3.00	0.33	3.00–3.00	.0004
Attention	5.31	6.00	0.93	5.00–6.00	5.48	6.00	0.87	5.00–6.00	.3
Language	2.59	3.00	0.69	2.00–3.00	2.88	3.00	0.33	3.00–3.00	.008
Abstraction	1.82	2.00	0.41	2.00–2.00	1.88	2.00	0.33	2.00–2.00	.44
Memory	2.63	3.00	1.73	1.00–4.00	2.65	3.00	1.72	1.00–4.00	.94
Orientation	5.96	6.00	0.20	6.00–6.00	5.96	6.00	0.21	6.00–6.00	1
MoCA total	25.11	26.00	3.14	23.00–27.00	26.35	26.00	2.19	25.00–28.00	.015

IQR = interquartile range, MoCA = Montreal Cognitive Assessment, PsA = psoriatic arthritis, SD = standard deviation.
* One-way analysis of variance.

Table 3

Correlations (Pearson correlation coefficient) between the main demographic and clinical features of psoriatic arthritis and psoriasis associated with MoCA.

		LEI	Age	MoCA	NRS pain	PASI	CRP	PsAID-12	SCQ	DAPSA	DLQI	PsA duration (years)	PsO duration (years)	Dactylitis	Schooling
HAQ-DI	Correlation, *r*	0.167	0.297	−0.227	0.684	0.126	0.336	0.781	0.210	0.744	0.113	−0.102	0.038	0.215	−0.035
	Significance, *P*	.103	.003	0.026	<.0001	.222	.0008	<.0001	.039	<.0001	.273	.320	.714	.035	.734
LEI	Correlation, *r*		0.038	−0.031	0.200	0.197	0.053	0.268	0.087	0.133	0.179	−0.005	−0.099	−0.101	−0.207
	Significance, *P*		.715	.767	.050	.054	.606	.008	.401	.195	.081	.958	.336	.329	.042
Age	Correlation, *r*			−0.354	0.235	0.075	0.048	0.169	0.451	0.219	0.027	0.232	0.162	0.082	−0.434
	Significance, *P*			<.0001	.021	.469	.639	.100	<.0001	.031	.796	.023	.115	.429	<.0001
MoCA	Correlation, *r*				−0.193	-.039	−0.085	−0.163	−0.166	−0.198	0.266	0.127	0.316	−0.107	0.222
	Significance, *P*				0.059	.705	.413	.113	.105	.053	.008	.219	.001	.297	.007
NRS pain	Correlation, *r*					0.168	0.218	0.795	0.199	0.912	0.074	−0.044	−0.097	0.240	−0.050
	Significance, *P*					.102	.033	<.0001	.052	<.0001	.475	.671	.346	.018	.626
PASI	Correlation, *r*						0.094	0.255	0.058	0.109	0.640	0.029	0.106	0.057	−0.022
	Significance, *P*						.363	.012	.576	.291	<.0001	.780	.305	.581	.828
CRP	Correlation, *r*							0.170	−0.046	0.288	−0.017	−0.055	−0.074	0.155	0.039
	Significance, *P*							.096	.655	.004	.865	.594	.476	.130	.704
PsAID-12	Correlation, *r*								0.216	0.764	0.257	−0.112	−0.015	0.282	−0.058
	Significance, *P*								.034	<.0001	.011	.278	.888	.005	.573
SCQ	Correlation, *r*									0.183	0.092	0.183	0.036	0.084	−0.210
	Significance, *P*									.074	.372	.073	.729	.416	.040
DAPSA	Correlation, *r*										0.022	−0.038	−0.091	0.230	0.008
	Significance, *P*										.831	.713	.379	.023	.941
DLQI	Correlation, *r*											0.105	0.383	−0.063	−0.122
	Significance, *P*											.310	.0001	.540	.235
PsA duration (years)	Correlation, *r*												0.471	0.006	−0.146
	Significance, *P*												<.0001	.953	.154
Psoriasisduration (years)	Correlation, *r*													−0.099	−0.253
	Significance, *P*													.336	.013
Dactylitis	Correlation, *r*														0.094
	Significance, *P*														.363

CRP = C-reactive protein, DAPSA = Disease Activity index for Psoriatic Arthritis, DLQI = Dermatology Life Quality Index, HAQ-DI = Health Assessment Questionnaire-Disability Index, LEI = Leeds Enthesitis Index, MoCA = Montreal Cognitive Assessment, NRS = Numerical Rating Scale of pain, PASI = Psoriasis Area and Severity Index, PsA = psoriatic arthritis, PsAID-12 = Psoriatic Arthritis Impact of Disease 12 items, SCQ = Self-Administered Comorbidity Questionnaire.

Table 4

Correlations (Pearson correlation coefficient) between PsAID-12 items and MoCA.

		Embarrassment and/or shame	Social participation	Depression	Fatigue	Skin problems	Work and/or leisure activities	Functional capacity	Discomfort	Sleep problems	Coping	Anxiety	MoCA
Pain	Correlation, *r*	0.247	0.297	0.400	0.703	0.172	0.688	0.751	0.533	0.663	0.627	0.447	−0.196
	Significance, *P*	0.015	0.003	.0001	<.0001	.093	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	.055
Embarrassment and/or shame	Correlation, *r*		0.637	0.622	0.240	0.548	0.322	0.325	0.593	0.397	0.522	0.534	0.100
	Significance, *P*		<.0001	<.0001	.018	<.0001	.001	.001	<.0001	.0001	<.0001	<.0001	.334
Social participation	Correlation, *r*			0.748	0.337	0.324	0.519	0.454	0.674	0.529	0.636	0.509	0.045
	Significance, *P*			<.0001	.0008	.0013	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	.663
Depression	Correlation, *r*				0.380	0.332	0.564	0.493	0.721	0.564	0.614	0.693	−0.070
	Significance, *P*				.0001	.0009	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	.496
Fatigue	Correlation, *r*					0.237	0.648	0.676	0.457	0.653	0.549	0.413	−0.222
	Significance, *P*					.020	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	.029
Skin problems	Correlation, *r*						0.339	0.312	0.336	0.248	0.309	0.337	0.051
	Significance, *P*						.0007	.002	.0008	.014	.002	.0008	.619
Work and/or leisure activities	Correlation, *r*							0.877	0.610	0.698	0.719	0.485	−0.133
	Significance, *P*							<.0001	<.0001	<.0001	<.0001	<.0001	.197
Functional capacity	Correlation, *r*								0.612	0.758	0.726	0.528	−0.108
	Significance, *P*								<.0001	<.0001	<.0001	<.0001	.295
Discomfort	Correlation, *r*									0.661	0.688	0.621	−0.081
	Significance, *P*									<.0001	<.0001	<.0001	.431
Sleep problems	Correlation, *r*										0.741	0.599	−0.148
	Significance, *P*										<.0001	<.0001	.151
Coping	Correlation, *r*											0.621	−0.045
	Significance, *P*											<.0001	.659
Anxiety	Correlation, *r*												−0.081
	Significance, *P*												.431

MoCA = Montreal Cognitive Assessment, PsAID-12 = Psoriatic Arthritis Impact of Disease 12 items.

Table 5

Multivariate logistic regression analysis, using MoCA as dependent variable.

Independent variables	Coefficient	Standard error	*t*	*P*	$r_{partial}$	$r_{semipartial}$
(Constant)	27.4597					
SCQ	0.0207	0.1118	0.186	.8531	0.0206	0.0160
DAPSA	0.0976	0.0604	1.615	.1101	0.1767	0.1392
DLQI	0.2454	0.1344	1.826	.0715	0.1989	0.1574
PsA duration (years)	0.0064	0.0364	0.177	.8597	0.0196	0.0152
Psoriasis duration (years)	0.0883	0.0244	3.609	.0005	0.3722	0.3110
Age	−0.0903	0.0302	−2.982	.0038	−0.3145	0.2570
HAQ-DI	−2.5494	1.0682	−2.387	.0193	−0.2563	0.2057
LEI	0.0888	0.5814	0.153	.8790	0.0169	0.0131
NRS pain	−0.0488	0.2253	−0.217	.8290	−0.0240	0.0186
PASI	−0.6047	0.2096	−2.885	.0050	−0.3053	0.2487
PsAID-12	0.2622	0.3738	0.701	.4851	0.0776	0.0604
CRP	0.0707	0.2492	0.284	.7771	0.0315	0.0244
Fatigue (PsAID-12 item 2)	−0.1698	0.1580	−1.075	.2857	−0.1186	0.0926
Schooling	0.1091	0.0847	1.287	.2017	0.1416	0.1109

CRP = C-reactive protein, DAPSA = Disease Activity index for Psoriatic Arthritis, DLQI = Dermatology Life Quality Index, HAQ-DI = Health Assessment Questionnaire-Disability Index, LEI = Leeds Enthesitis Index, MoCA = Montreal Cognitive Assessment, NRS pain = Numerical Rating Scale of pain, PASI = Psoriasis Area and Severity Index, PsA = psoriatic arthritis, PsAID-12 = Psoriatic Arthritis Impact of Disease 12 items, PsO = psoriasis, SCQ = Self-Administered Comorbidity Questionnaire.

as an index of skin disease activity has been shown to be a predictor of MoCA score to multiple regression analysis, even though no correlation has emerged. This is the first demonstration of an association between PASI and MCI. Previously Marek-Józefowicz and colleagues investigated the association between PASI and neurocognitive tests, without being able to demonstrate a statistically significant association.[32] The positive association between the MoCA score with psoriasis duration and DLQI is difficult to interpret and controversial. It can be hypothesized that a long-standing skin disease, even if it has a negative impact on the QoL at the particular moment of the evaluation, does not represent an obstacle to cognitive performance for patients because it could be a more accepted condition by the patient. These 2 aspects should be the subject of further studies. Certainly, the relationship between the skin and brain has implications at multiple levels (immunological, endocrinological, psychological) and is extremely intricate.[33]

Investigating the components more closely related to the rheumatological aspects, this study also revealed an association between MCI and disability. Excluding the variables related to the skin component, the only articular factor related to MoCA was HAQ-DI. It is interesting to note that disability is associated with a cognitive deficit but also with neuropathic pain features, as demonstrated in a previous study by our group.[34] There is thus a common link between disability, MCI and neuropathic pain in PsA, likely the expression of a "central dysregulation." This pathway of central dysregulation may also include fatigue (considered as item 2 of PsAID-12), to which the MoCA score was found to be negatively correlated.

Generally speaking, the presence of a cognitive deficit during chronic diseases is a multifaceted aspect and several factors contribute to its genesis. While the relationship between cognitive deficit and neurological diseases, such as multiple sclerosis or Alzheimer disease, may be intuitive, reduced cognitive performance can be frequently documented during chronic diseases such as chronic renal failure or chronic obstructive pulmonary disease. Taking these 2 conditions as illustrative models, both laboratory (e.g., uremia or hypoxemia/hyperpercarbia) and non-laboratory variables (e.g., depression or insomnia) that can lead to a cognitive deficit can be recognized.[35,36] At the same time, inflammatory changes can be recognized in PsA and psoriasis, for example, high levels of interleukin 6 or TNF alfa that can cause microvascular and neuronal damage,[37] but also a psychological burden, for example, stress caused by a joint disease that can cause chronic pain and disability. In this study, as a laboratory variable we simply collected CRP as an indicator of systemic inflammation, which however showed no association with MoCA.

It must be mentioned that one of the limits of the case study is the low number of individuals involved, and the disproportion between patients and controls. However, the relatively small number of patients (and controls) was directly related to the fact that strict inclusion criteria were applied to avoid, as much as possible, the presence of confounding factors (e.g., the presence of a coexisting FM) with excessive influence on cognitive testing. On the other hand, a strong point is the case study from 2 different rheumatology centers. Another limitation may be that the majority of patients were treated with a bDMARDs and had relatively low activity indices of joint and skin disease as mean scores. However, despite this fact, PASI has proven to be one of the predictors of MCI at multivariate analysis. Lastly, the definition of MCI is an evolving construct. In this study we used that proposed by MoCA, which represents a test that is relatively fast to execute and has already been used in many areas of chronicity.

5. Conclusion

MCI is present in about half of patients with PsA without other apparent risk factors for cognitive decline. MCI is present more frequently, and in a statistically significant way, in patients with PsA than in healthy controls, considering similar features in age, schooling and socio-cultural background. From the articular point of view, one of the main predictors of MCI is the disability measured with HAQ-DI. Rheumatologists must be increasingly aware of this possibility in order to diagnose and treat MCI early in patients with PsA.

Author contributions

Conceptualization: Marco Di Carlo, Fausto Salaffi.
Data curation: Marco Di Carlo.
Formal analysis: Marco Di Carlo, Fausto Salaffi.
Investigation: Marco Di Carlo, Andrea Becciolini, Antonella Incorvaia, Giacomo Beci, Gianluca Smerilli, Martina Biggioggero, Marika Tardella, Rossella De Angelis.
Project administration: Marco Di Carlo.
Supervision: Fausto Salaffi.
Writing – original draft: Marco Di Carlo.
Writing – review & editing: Andrea Becciolini, Antonella Incorvaia, Giacomo Beci, Gianluca Smerilli, Martina Biggioggero, Marika Tardella, Rossella De Angelis, Fausto Salaffi.

References

[1] Moltó A, Dougados M. Comorbidities in spondyloarthritis including psoriatic arthritis. Best Pract Res Clin Rheumatol 2018;32:390–400.
[2] Kamalaraj N, El-Haddad C, Hay P, et al. Systematic review of depression and anxiety in psoriatic arthritis. Int J Rheum Dis 2019;22: 967–73.
[3] Zhao SS, Duffield SJ, Goodson NJ. The prevalence and impact of comorbid fibromyalgia in inflammatory arthritis. Best Pract Res Clin Rheumatol 2019;33:101423.
[4] Di Carlo M, Becciolini A, Lato V, et al. The 12-item psoriatic arthritis impact of disease questionnaire: construct validity, reliability, and interpretability in a clinical setting. J Rheumatol 2017;44:279–85.
[5] Shimada H, Makizako H, Doi T, et al. Cognitive impairment and disability in older Japanese adults. PLoS One 2016;11:e0158720.
[6] Chudiak A, Uchmanowicz I, Mazur G. Relation between cognitive impairment and treatment adherence in elderly hypertensive patients. Clin Interv Aging 2018;13:1409–18.
[7] Oláh C, Schwartz N, Denton C, et al. Cognitive dysfunction in autoimmune rheumatic diseases. Arthritis Res Ther 2020;22:78.
[8] Zabala A, Salgueiro M, Sáez-Atxukarro O, et al. Cognitive impairment in patients with neuropsychiatric and non-neuropsychiatric systemic lupus erythematosus: a systematic review and meta-analysis. J Int Neuropsychol Soc 2018;24:629–39.
[9] Vitturi BK, Nascimento BAC, Alves BR, et al. Cognitive impairment in patients with rheumatoid arthritis. J Clin Neurosci 2019;69:81–7.
[10] Gisondi P, Sala F, Alessandrini F, et al. Mild cognitive impairment in patients with moderate to severe chronic plaque psoriasis. Dermatology 2014;228:78–85.
[11] Colgecen E, Celikbilek A, Keskin DT. Cognitive impairment in patients with psoriasis: a cross-sectional study using the montreal cognitive assessment. Am J Clin Dermatol 2016;17:413–9.
[12] Taylor W, Gladman D, Heliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665–73.
[13] Wolfe F, Clauw DJ, Fitzcharles MA, et al. 2016 Revisions to the 2010/ 2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum 2016;46:319–29.
[14] Kratz AL, Whibley D, Kim S, et al. Fibrofog in daily life: An examination of ambulatory subjective and objective cognitive function in fibromyalgia. Arthritis Care Res (Hoboken) 2019;doi: 10.1002/acr.24089.
[15] Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment [published correction appears in J Am Geriatr Soc. 2019 Sep;67 (9):1991]. J Am Geriatr Soc 2005;53:695–9.
[16] Santangelo G, Siciliano M, Pedone R, et al. Normative data for the Montreal Cognitive Assessment in an Italian population sample. Neurol Sci 2015;36:585–91.
[17] Schoels MM, Aletaha D, Alasti F, et al. Disease activity in psoriatic arthritis (PsA): defining remission and treatment success using the DAPSA score. Ann Rheum Dis 2016;75:811–8.
[18] Mease PJ. Measures of psoriatic arthritis: Tender and Swollen Joint Assessment, Psoriasis Area and Severity Index (PASI), Nail Psoriasis Severity Index (NAPSI), Modified Nail Psoriasis Severity Index (mNAPSI), Mander/Newcastle Enthesitis Index (MEI), Leeds Enthesitis Index (LEI), Spondyloarthritis Research Consortium of Canada (SPARCC), Maastricht Ankylosing Spondylitis Enthesis Score (MASES), Leeds Dactylitis Index (LDI), Patient Global for Psoriatic Arthritis, Dermatology Life Quality Index (DLQI), Psoriatic Arthritis Quality of Life (PsAQOL), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Psoriatic Arthritis Response Criteria (PsARC), Psoriatic Arthritis Joint Activity Index (PsAJAI), Disease Activity in Psoriatic Arthritis (DAPSA), and Composite Psoriatic Disease Activity Index (CPDAI). Arthritis Care Res (Hoboken) 2011;63(Suppl 11):S64–85.
[19] Healy PJ, Helliwell PS. Measuring clinical enthesitis in psoriatic arthritis: assessment of existing measures and development of an instrument specific to psoriatic arthritis. Arthritis Rheum 2008;59:686–91.
[20] Fries JF, Spitz P, Kraines RG, et al. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137–45.
[21] Gossec L, de Wit M, Kiltz U, et al. A patient-derived and patient-reported outcome measure for assessing psoriatic arthritis: elaboration and preliminary validation of the Psoriatic Arthritis Impact of Disease (PsAID) questionnaire, a 13-country EULAR initiative. Ann Rheum Dis 2014;73:1012–9.
[22] Fredriksson T, Pettersson U. Severe psoriasis: oral therapy with a new retinoid. Dermatologica 1978;157:238–44.
[23] Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)–a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19: 210–6.
[24] lannone F, Salaffi F, Fornaro M, et al. Influence of baseline modified Rheumatic Disease Comorbidity Index (mRDCI) on drug survival and effectiveness of biological treatment in patients affected with Rheumatoid arthritis, Spondyloarthritis and Psoriatic arthritis in real-world settings. Eur J Clin Invest 2018;48:e13013.
[25] https://www.mocatest.org/pdf_files/test/MoCA-Test-Italian.pdf
[26] Leung YY, Orbai AM, Ogdie A, et al. The GRAPPA-OMERACT psoriatic arthritis working group at the 2018 annual meeting: report and plan for completing the core outcome measurement set. J Rheumatol Suppl 2019;95:33–7.
[27] Jack CRJr, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:257–62.
[28] Sunkureddi P, Doogan S, Heid J, et al. Evaluation of self-reported patient experiences: insights from digital patient communities in psoriatic arthritis. J Rheumatol 2018;45:638–47.
[29] Meade T, Manolios N, Cumming SR, et al. Cognitive impairment in rheumatoid arthritis: a systematic review. Arthritis Care Res (Hoboken) 2018;70:39–52.
[30] Oláh C, Kardos Z, Andrejkovics M, et al. Assessment of cognitive function in female rheumatoid arthritis patients: associations with cerebrovascular pathology, depression and anxiety. Rheumatol Int 2020;40:529–40.
[31] Petersen RC. Mild cognitive impairment. Continuum (Minneap Minn) 2016;22(2 Dementia):404–18.
[32] Marek-Józefowicz L, Jaracz M, Placek W, et al. Cognitive impairment in patients with severe psoriasis. Postepy Dermatol Alergol 2017;34:120–5.
[33] Chen Y, Lyga J. Brain-skin connection: stress, inflammation and skin aging. Inflamm Allergy Drug Targets 2014;13:177–90.
[34] Di Carlo M, Muto P, Benfaremo D, et al. The neuropathic pain features in psoriatic arthritis: a cross-sectional evaluation of prevalence and associated factors. J Rheumatol 2020;47:1198–203.
[35] Grzegorski T, Losy J. Cognitive impairment in multiple sclerosis - a review of current knowledge and recent research. Rev Neurosci 2017;28:845–60.
[36] Drew DA, Weiner DE, Sarnak MJ. Cognitive impairment in CKD: pathophysiology, management, and prevention. Am J Kidney Dis 2019;74:782–90.
[37] Siegel D, Devaraj S, Mitra A, et al. Inflammation, atherosclerosis, and psoriasis [published correction appears in Clin Rev Allergy Immunol. 2018 Mar 19]. Clin Rev Allergy Immunol 2013;44:194–204.