ORIGINAL ARTICLE

Cognitive Assessment in Pakistani Rheumatoid Arthritis Cohort: CAP-RA: cross sectional study

ABRAR AHMED WAGAN[1], SULTAN AHMED CHANDIO[2], SADIA NASIR[3], *ABDUL RHIM[4], DAIM KHAN[5]*
[1]Assistant Professor Rheumatology, Central Park Medical College/Hospital, Lahore
[2]Assistant Professor Medicine, Shaheed Mohtarma Benazir Bhuto Medical College, Larkana
[3]Assistant Professor Medicine, Central Park Medical College/Hospital, Lahore
[4]PGR Medicine, Central Park Medical College/Hospital, Lahore
[5]Senior Registrar Medicine, Central Park Medical College/Hospital, Lahore
Correspondence to Dr. Abrar Ahmed Wagan, Email: bestabrar2002@yahoo.com cell: 0331-3406174

ABSTRACT

Aim: To determine the frequency of cognitive dysfunction in pts of rheumatoid arthritis at tertiary care hospital.
Methods: This study was conducted from 30-09-2017 t0 30-09-2018, total 127 patients of Rheumatoid Arthritis were enrolled from outpatient department of rheumatology division of department of medicine central park medical college Lahore, after demographic parameters, Montreal objective cognitive assessment questionnaire (MoCA), urdu version was filled, participants were asked in detail about the smoking, diabetes mellitus, blood pressure and body mass index were measured, current and past use of DMARD's were noted.
Results: In this study, females were 101 (77%), with mean age of 47.7 (±6.49) years, and disease duration of 11 years. Cognitive dysfunction was present in 42(33.1%) with mean MoCA score of (22.3±2.08) in cognitive dysfunction group and (28.6±1.34) in cognitively normal RA group (p-value <0.01). There was significant association of hypertension, smoking and use of DMARD's with cognitive dysfunction (p-value <0.5).
Conclusion: There is significant prevalence of cognitive dysfunction in rheumatoid arthritis and it remains a neglected aspect of management plan and aggravates the already existing psychosocial problems of RA patients. Montreal objective cognitive assessment questionnaire (MoCA) Urdu version is easy to understand, could be a useful tool for cognitive assessment in RA patients and modifiable cardiovascular risk factors contributes to cognitive dysfunction.
Keywords: Rheumatoid Arthritis, Montreal objective cognitive assessment (MoCA), Body Mass Index,

INTRODUCTION

Rheumatoid arthritis is inflammatory arthritis which affects (0.5 to 1%) general population worldwide[1]. RA patients had a shorter median survival than expected for general population[2]. The disease interferes with normal daily activities and contributes to a decline in the quality of life[3].

Recently there has been tremendous research carried out to know about the involvement of the central nervous system (CNS) and to assess its ability to work and adapt in rheumatic diseases[4]. The loss of physical and emotional skills in daily living assumes a social relevance in rheumatoid arthritis (RA), chronic progressive, persistent evolution of pain and morning stiffness is often associated with deterioration in psychological wellbeing, majorly due to chronic distress and deterioration in one's functional abilities, which ultimately results in decreased ability to cope up with the disease, its outcomes an impaired quality of life[5].

Cognitively impaired persons have increased functional difficulties and reduced sense of well-being[6]. In RA, intact cognitive function is critical for the successful daily living ,treatment, and planning for future .[7] In RA and general population mechanisms linked to cognitive impairment are persistent systemic inflammation and cardiovascular diseases[8-9]. Bartolini et al, observed that cognitive dysfunction was common in RA patients, with prevalence rates ranging from 38% (divided/sustained attention and mental flexibility) to 71% (visuo-spatial and planning functions), changes were seen on neuroimaging as well like hypo perfusion on brain single-photon–emission computed tomography and increased white matter alterations on magnetic resonance imaging[10]. Appenzeller et al found cognitive impairment in 30% of the RA cohort in comparison to 8% of healthy controls[11].

Disease not only affects joints, muscles, bones but various other body organs as part of disease process, leading to very subtle changes to catastrophic outcomes. Out of many extra-articular manifestations, cognitive dysfunction is one of them which are least explored and least discussed by the patients and treating physicians.

There is very limited information available about the potential factors leading to cognitive dysfunction in autoimmune diseases, and absolute lack of uniform tools to assess cognitive functions.

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METHODOLOGY

This cross sectional study was conducted after IRB approval in outpatient department of Rheumatology division of medicine department at central park medical college hospital Lahore. Each study participants written and informed consent was sought. Rheumatoid arthritis was diagnosed as per 2010 American College of Rheumatology criteria. Sample size was estimated using openepi sample size calculator with 30%[11] prevalence and 8% margin of error at 95% confidence interval, total sample size of127.

Rheumatoid arthritis patients who were seropositive for either Rheumatoid factor or Anti citrillinuted peptides or both were taken into study, demographic data, disease duration and number of disease modifying anti rheumatoid

drugs use noted. Sero-negative rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematous, scleroderma, primary osteoarthritis, mixed connective tissue diseases, current or past use of biological disease modifying anti rheumatoid medcines, primary and secondary fibromyalgia were excluded from study and, those patients who have not completed primary school level education were excluded from study.

Acute psychosis, post-traumatic stress disorder, diagnosed cases of depression, dementia, parkinsonism, Alzheimer's, multiple sclerosis, delirium, presence of end organ failure like (cardiac, renal and liver), stroke, significant mental impairment from other systemic illnesses (hypothyroidism, malignancy), chronic use of opioids, history of chronic hepatitis and its treatment with interferon ,antipsychotics, RA with CNS vasculitis, cranial nerve palsies, partial or complete blindness, those who can't read and write, brain surgery in last six months, Hakeem medication in last six months, alcoholics and those with any type of illicit drug addiction, currently on anxiolytics and narcotic analgesics, on dialysis ,refusal to participate were used as exclusion parameters for this study. Current depression was assessed by Primary health assessment questionnaire, study participants with score of < 4 were labeled as not suffering from depression included in study. A senior physician examined all study participants for other coexisting comorbid illness.

Body mass index (weight measured using a beam balance scale and height measured by a stadiometer) was calculated by dividing weight (in kilogram) by square of height (in meters). Hypertension was diagnosed (blood pressure measurements with mercury sphygmomanometer carried out in sitting position after 5 minutes mandatory rest, three readings were done and mean of two last readings was noted) level of >140mmHg systolic or 90mmHg diastolic pressure , or self-reported diagnosis or any patient who was taking anti-hypertensive. Smoking habit was evaluated about years since smoking, number of cigarettes per day. Diabetes mellitus was diagnosed with fasting blood glucose level of >126mg/dl, and patients self-reported or were using insulin and/oral hypoglycemic drugs.

Cognitive assessment was done for all selected participants by using validated Urdu version of MoCA questionnaire (Montreal objective cognitive assessment questionnaire) with prior permission for its use (annexure1). All patients having scored less than 26 were labeled as having cognitive dysfunction, and 1 point was added to total score if any study participant's level of education was less than 12 years. Data were stored and analyzed using IBM SPSS version 23.0, mean and standard deviation were reported for age, BMI, duration of disease, SBP , DBP and MoCA test scores, count and percentages were reported for Sex, BMI levels, Education, smoking, Hypertension, diabetes mellitus, and DMARDS, independent sample t-test was used to compare mean differences between two groups of cognitive dysfunction and Pearson chi square test was done to see the association of cognitive dysfunction with different study parameters. P-values less than 0.05 were considered significant.

RESULTS

In this study total 127 RA patients were enrolled, out of which females were 101(77%) and 26 (33%) with mean age of 47.7 years±6.49 and mean disease duration of 11 years. Cognitive dysfunction was present in 42(33.1%) of RA patients (Fig.1) out of which 35(83.5%) were females and 7(16.7%) were males. There was significant difference of age between cognitive dysfunction (53 years) present and those who didn't had cognitive dysfunction (p value <0.1).Significant difference of systolic blood pressure was observed between in cognitive dysfunction positive and absent group (p-value<0.01), The mean MoCA test scores were also different between both groups (22.3) in cognitive dysfunction present, and (28.6) in cognitive dysfunction absent group (p-value<0.1) (Table 1). There was significant association of hypertension, smoking and use of DMARD's with cognitive dysfunction (p-value <0.5), while diabetes, gender, and level of education didn't have significant association with cognitive dysfunction in RA (Table 2).

RA patients with cognitive dysfunction (n=42) majority had modifiable cardiovascular risk factors like smoking, diabetes mellitus, obesity and hypertension (Table 3).

Fig..1: Prevalence of Cognitive dysfunction in rheumatoid arthritis

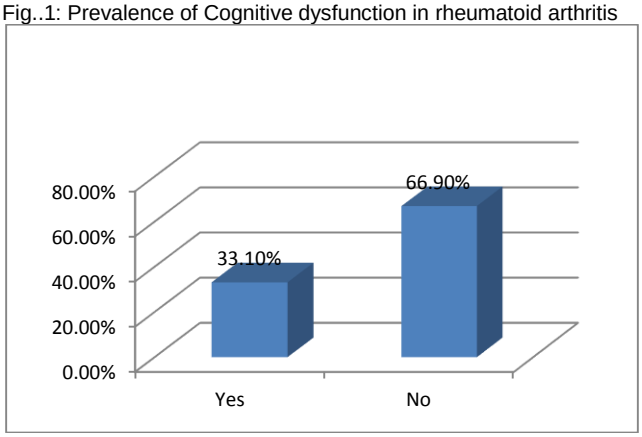


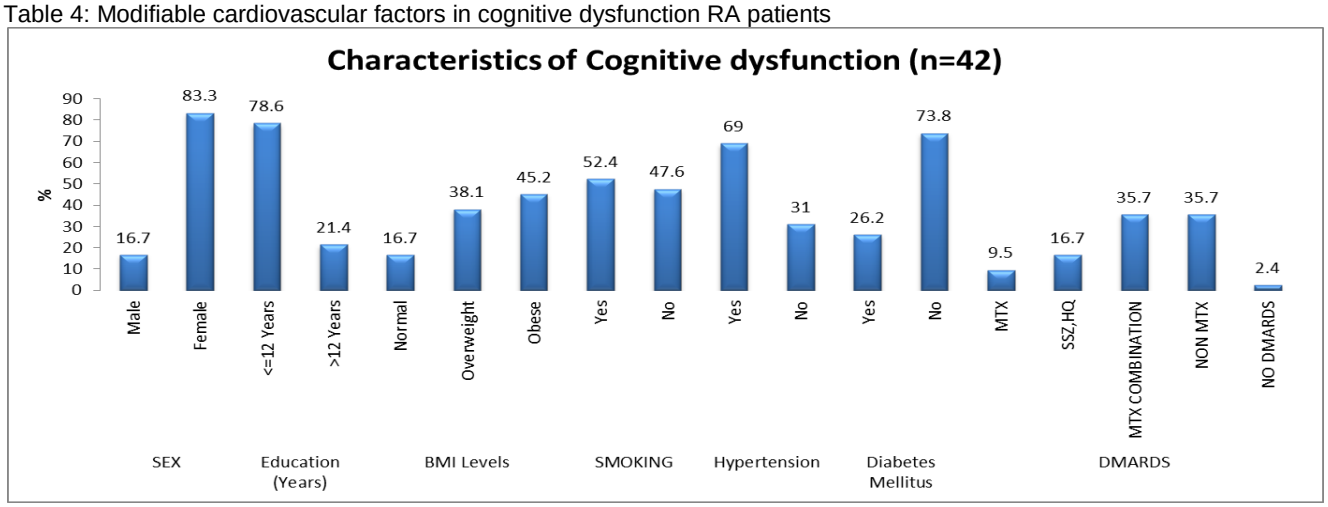
Table 1: Mean comparison of baseline parameters

Variables	cognitive Dysfunction				p-value
	Yes (n=42)		No (n=85)		
	Mean	SD	Mean	SD	
Age	53.91	5.74	44.69	4.35	<0.01*
Bmi	29	4.54	27.72	4.15	0.11
Sbp	130.67	10.35	122.71	10.41	<0.01*
Dbp	86.15	8.11	80.13	7.52	<0.01*
Disease duration	11.17	5.47	7.4	4.45	<0.01*
MoCA test Score	22.34	2.08	28.68	1.34	<0.01*
*p<0.05 was considered significant using independent sample t-test					

Table 2: Chi Square Association with Cognitive Dysfunction

Variables		cognitive Dysfunction				p-value
		Yes (n=42)		No (n=85)		
		n	%	n	%	
Gender	Male	7	16.7	19	22.4	0.45
	Female	35	83.3	66	77.6	
Education (Years)	<=12 Years	33	78.6	66	77.6	0.90
	>12 Years	9	21.4	19	22.4	
BMI Levels	Normal	7	16.7	24	28.2	0.35
	Overweight	16	38.1	29	34.1	
	Obese	19	45.2	32	37.6	
Smoking	Yes	22	52.4	16	18.8	<0.01*
	No	20	47.6	69	81.2	
Hypertension	Yes	29	69.0	14	16.5	<0.01*
	No	13	31.0	71	83.5	
Diabetes Mellitus	Yes	11	26.2	12	14.1	0.09
	No	31	73.8	73	85.9	
DMARDS	MTX	4	9.5	11	12.9	<0.01*
	SSZ,HQ	7	16.7	10	11.8	
	MTX combination	15	35.7	55	64.7	
	NON MTX	15	35.7	4	4.7	
	NO DMARDS	1	2.4	5	5.9	
*p<0.05 was considered significant using Pearson Chi Square test						

Table 4: Modifiable cardiovascular factors in cognitive dysfunction RA patients



DISCUSSION

Rheumatoid arthritis exerts wide spectrum of effects over a human body from physical and emotional aspects of life. Disease control is essential for the physical and cognitive wellbeing, poor control will not only leads to functional disability but also predisposes to psycho-social issues, leading to vicious circle of poor disease control, physical disability, poor cognition and poor adherence to treatment plan. Till now in rheumatoid arthritis assessment of cognitive functions remains neglected area and reason for this is lack of laid down tools, protocols and guidelines. So Young Shin et al in their study carried out for assessment of cognitive decline by using battery of tests and found that 8-29% had cognitive decline in each test[12].

Apart from cognitive dysfunction, prevalence of depression is very high in patient of RA and again this is multifactorial due to effects of chronic systemic inflammation, physical disability and psychosocial pressures. In a recently conducted meta-analysis by XIN FU et al for the prevalence of depression in Chinese population with RA, found that 48% patients were suffering from depression.[13] Another Meta-analysis by Tanya Meade et al, reported significant cognitive dysfunction in RA, disturbances were noted in verbal function, memory and attention[14].

In our study we used this MoCA questionnaire for the assessment of cognitive function and found that (33.1%) had cognitive dysfunction, results showed that hypertension, smoking and use of DMARD's have significant association with cognitive dysfunction. Pamuk et al and Peterson et al also noted similar results like our study, that use of DMARD's and cardiovascular risk factors were associated with cognitive decline[15,16]. Eman Khedr et al also found that patient suffering from RA had low IQ (54%) along with other neuropsychiatric problems[17].

As many factors have been related with cognitive dysfunction in RA, TNF has a definitive role in various neuropsychiatric manifestation like excessive fatigue and cognitive impairment and depression[18]. Study carried on wistar rats found that single bolus of TNF resulted in

significant decrease in cerebral blood flow (15-30%) through type 2 TNF receptor activation[19].

Graham Raftery et al, in a pilot study noted that successful treatment with Anti-TNF therapy with (adalimumab) has resulted in significant improvement in cognitive functions and clinical improvement in disease activity[20].

Neuroimaging studies carried out on RA and SLE patients have found that there is decreased blood flow to parietal and frontal lobes of RA patients, while similar changes were only observed in frontal lobes of SLE patients leading to cognitive dysfunction[21]. Hamed et al, and Bekkelund in their neuroimaging studies from RA patient noted that there was no difference present on T2w MRI study of WM lesions between RA patient and control cases but very importantly they noted that WM lesions were associated higher levels of protein S100B a potential biomarker of blood brain barrier disruption and neurodegeneration[22,23]. P. Simos et al, found poor performance in various psychometric test indices in 20% of RA study participants and cognitive decline was weakly related with disease activity[24]. In a Brazilian cross sectional and case control study, which used multiple tests for cognitive assessment MMSE (Mini mental state examination) and MoCA found that, patients with RA presented significant lower MMSE (21.9±3.9) and MoCA (17.0±4.4) scores ($p<0.05$), and cognitive dysfunction was associated with prolonged disease duration and poor functional outcomes[25].

Limitations: This was a cross sectional study, small sample size so results can't be generalized, association with disease activity wasn't assessed, needs more studies for the efficacy of MoCA questionnaire utility in assessment of cognitive dysfunction with larger sample size in RA, while the strong point of this study is this is first study which assessed cognitive function on local population which used this novel assessment tool.

CONCLUSION

Cognitive assessment in RA part of examination at the start of treatment and on subsequent visits, treating Rheumatologists take cognitive involvement as extra articular involvement. RA patients should be encouraged to adopt healthy life style, stop smoking, control weight and associated comorbid conditions.

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