Original Article

Anticitrullinated Protein Antibodies: Biomarker of Diagnosis & Prognosis in Elderly Rheumatoid Arthritis Patient with and Without Cognitive Impairment

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ABSTRACT:

INTRODUCTION: *Cognitive impairment is one of the most common comorbidities in elderly rheumatoid arthritis patients (RA). Possible etiological mechanisms of cognitive decline in aged rheumatoid arthritis, including chronic systemic inflammation affecting all organs, increased dysfunction of decreased substance use, and poor quality of life. Old RAs are associated with falls, cognitive impairment, and frail geriatric syndrome. The challenge in managing older patients with RA is usually that older people have significant comorbidity. Cognitive screening may be a useful tool for identifying subgroups to be further investigated for comorbid cerebrovascular disease. Anti-citrullinated protein antibody (ACPA) is a serological biomarker associated with early, rapidly progressing rheumatoid arthritis.* ***AIM OF THE WORK:*** *To assess the role of ACPA in elderly rheumatoid arthritis patients, to describe clinical, laboratory characteristics of disease activity, functional status, to determine the prevalence of cognitive impairment and the association of the determinants with the ACPA status.* ***SUBJECTS****: Sixty elderly patients with rheumatoid arthritis of both sexes aged ≥ 65 years fulfilling the 2010 EULAR /ACR classification criteria for rheumatoid arthritis recruited from the geriatric outpatient clinics were included in a cross-sectional study, with exclusion of patients with severe life-threatening disease, dementia, cancer or viral hepatitis.* ***METHODS:*** *Full medical history taking and thorough comprehensive geriatric assessment (CGA). Laboratory tests include CBC, FBS, 2hr PP, thyroid function tests, lipid profile, kidney function tests, ESR 1st hour, CRP, RF, liver function tests, uric acid, BMI categorized as normal, overweight and obese. Anticitullinated protein antibodies (ACPA) measured by ELISA technique. Disease activity assessment using DAS-28 CRP. Functional status assessment using HAQ score. CGA including function, mobility, cognitive, depression, fall risk, nutrition, full medication review and frailty index assessment. Plain X-ray of both hands and knees as a part of comorbidity assessment.* ***RESULTS:*** *Sixty elderly rheumatoid arthritis patients with cognitive impairment showed elevated anti-CCP titer. There was a marked increase in the number of the adverse outcomes scores in the elderly such as pain, mobility disorders, increased risk of falls, fractures, impaired ability or disability to perform activities of daily living, risk of malnutrition, depression risk, frailty risk, mobility risk, and increased risk of comorbidities as elevated blood pressure, kidney, liver functions impairment, elevated ESR, CRP, ANA, FBS, 2hPP, uric acid and lipid profile.* ***CONCLUSION:*** *Since anti-CCP titre has a high specificity in the elderly, it can be used as a diagnostic and predictive biomarker in elderly rheumatoid arthritis patients with cognitive impairment.*

Keyword: Anti-cyclic citrullinated peptide CCP), Rheumatoid Arthritis, Cognitive dysfunction*.*

INTRODUCTION:

Rheumatoid arthritis (RA) is a chronic, inflammatory disease characterized by chronic inflammation of the synovial joints leading to a progressive joint destruction. RA may involve both the vascular and nervous systems.[1,2] There is an increased risk of cognitive dysfunction, especially in elderly RA patients with long-standing disease [3]. Depression and anxiety are present in two-third of RA patients [4-6]. Cognitive function includes orientation, attention, concentration, judgment, problem solving, memory, verbal, visual, spatial and executive functions.[7-8] RA patients may significantly underperform on cognitive function tests compared to controls.[7,9-13] Even mild cognitive impairment may influence the functional capacity and quality of life of RA patients.[7,11,14,15] It affects reactivity to pain, compliance to and effectiveness of therapy.[7] In general, inflammation itself may also affect the brain.[6,7,13] Accelerated atherosclerosis and increased cardiovascular pathology also driven by systemic inflammation [11,15-17] may cause cognitive impairment in RA. Elderly RA is associated with the geriatric syndromes of falls, cognitive impairment, and frailty. A challenge when dealing with an elderly patient with RA is that the elderly usually has a significant comorbidity. Cognitive screening might be a useful tool to identify subgroups to be further investigated for cerebrovascular comorbidities. Pain, stress, fatigue, sleep disturbances, depression and anxiety may also be involved in RA associated cognitive decline.[5,7,11] Methotrexate, corticosteroids and biologics have been associated with cognitive impairment [7,18,19] As inflammation is involved in cognitive dysfunction in RA , the control of disease activity may be beneficial for the patients.[20, 21]

AIM OF THE WORK:

General Objectives: The aim was to assess the role of ACPA in elderly rheumatoid arthritis patients., **Specific Objectives:** Was to describe clinical, laboratory characteristics as well as functional status in elderly RA patients according to ACPA status, to describe the clinical , laboratory indices of disease activity , functional health status , to determine the prevalence of cognitive impairment and concurrent geriatric syndrome as a comorbidity in the elderly and their association with the ACPA status.

SUBJECTS:

Inclusion criteria: Sixty elderly patients with rheumatoid arthritis of both sexes aged ≥65 years fulfilling the 2010 EULAR / American College of Rheumatology (ACR) classification criteria for rheumatoid arthritis recruited from the geriatric medicine unit and outpatient clinics of the main Alexandria university hospital were included in a cross-sectional study. **Exclusion criteria:** Patients with severe life-threatening disease, severe dementia, and those with past history of cancer or viral hepatitis. An informed consent was taken from all patients prior to connecting the study according to the Helsinki declaration. **Data collection:** Prior to baseline examination in the clinic each patient was interrogated thoroughly using a questionnaire. Data on extra-articular features, comorbid conditions and treatment records was collected Comorbid conditions, using the Charlson comorbidity index (CCI) to summarize the medical comorbidities. CCI sum is calculated according to the number of morbidities affecting the individual. For each morbidity, a number of points are allocated and the sum of these points gives an overall score. This sum can be used in conjunction with the patient's age as the Charlson score to calculate a probability of survival.[22]

METHODS:

1-Full medical history taking with specific stress on age, sex, duration of mourning stiffness, number of swollen and tender joints, history of smoking, drug history especially Methotrexate.[23]

2-General examination for detection of extra-articular manifestations associated with rheumatoid arthritis; as skin (rheumatoid nodules), nervous system, and cardiac examination for detection of any cardiac abnormalities as a part of comorbidity assessment.

3-Laboratory tests: Complete blood count and differential count,[24] fasting and 2 hours postprandial blood glucose, blood urea, serum creatinine,[25] ESR 1st hour, CRP,[26] SGPT, SPOT.[27]

4-Immunological Profile: Rheumatoid Factor (RF) titre [28], and Anticitrullinated Protein Antibody (ACPA) measured by ELISA technique.[29]

5-Determination of disease activity using disease activity score-28 (DAS-28) based on CRP (DAS-28-CRP) [30], Functional and Quality of Life (QoL) assessment scores using Health Assessment Questionnaire (HAQ) score. [31,32]

6-BMI assessment according to the WHO criteria and categorized as normal, overweight and obese

7-Comprehensive Geriatric Assessment (CGA): Functional assessment using Katz activities of daily living (ADLs),[33] Mobility assessment using the timed "Get up and Go Test ", Cognitive assessment using the Mini Mental State Examination (MMSE),[34] Depression assessment using the Geriatric Depression Scale (GDS-15),[35] Fall risk assessment using Fall Risk Checklist, Nutritional assessment using the Mini Nutritional Assessment (MNA), [36] Frailty assessment using Frailty Index Measurement,[37] and Full Medication Review

8-Ophthalmologic examination was performed for all elderly RA patients.

9-Echocardiography to detect any cardiac abnormalities in elderly RA patients.

10-Plain X-ray of both hands and knees joints as a part of comorbidity assessment.

Statistical Analysis of The Data: Data were fed to the computer and analyzed using IBM SPSS software package version 20.0, Armonk, NY: IBM Corp. Comparison between different groups regarding categorical variables was tested using Chi-square test . When more than 20% of the cells have expected count less than 5, correction for chi-square was conducted using Fisher's exact test or Monte Carlo correction. The distributions of quantitative variables were tested for normality. For normally distributed data, comparison between more than two populations were analyzed using F-test (ANOVA) and Post Hoc test (Scheffe).

For abnormally distributed data, Kruskal Wallis test was used to compare between different groups and pair wise comparison was assessed using Mann-Whitney test. Significance of the obtained results was judged at the 5% level. Differences of ($P < 0.05$) were considered statistically significant.

RESULTS: Table (I): Distribution of the studied cases according to demographic data. Table (II): Distribution of the studied cases according to musculoskeletal examination. Table (III): Distribution of the studied cases according to different disease comorbidities. Table (IV): Descriptive analysis of the studied cases according to neurological, cardiovascular and chest examination findings. Table (V): Distribution of the studied cases according to immunological and radiological findings. Table (VI): Distribution of the studied cases according duration of the disease symptoms. Table (VII): Distribution of the studied cases according to comprehensive geriatric assessment scores.

Table(I): Distribution of the studied cases according to demographic data (n=60).

Age (years)	
- Min-Max	62.00-72.00
- Mean ± SD	67.63±2.31
- 95% CI for mean	67.04-68.23
Sex	
- Males	26 (43.33%)
- Females	34 (56.67%)
Marital status	
- Married	40 (66.67%)
- Divorced	9 (15.00%)
- Widowed	11 (18.33%)
Residency	
- Alexandria	55 (91.67%)
- Kafr elshiekh	1 (1.67%)
- Kafr eldawar	3 (5.00%)
- Abo elmatameer	1 (1.67%)
Occupation	
- Not working	9 (15.00%)
- Worker	15 (25.00%)
- Professional	18 (30.00%)
- retired	3 (5.00%)
- Semiprofessional	4 (6.67%)
- Housewife	11 (18.33%)
Smoking status	
- Non smoker	34 (56.67%)
- Smoker	26 (43.33%)
Education	
- Illiterate	8 (13.33%)
- Primary School	1 (1.67%)
- Preparatory school	1 (1.67%)
- Secondary school	26 (43.33%)
- University	24 (40.00%)
WHO Classification	
- 18.5-24.9 (Normal weight)	15 (25.00%)
- 25.0-29.9 (Overweight)	25 (41.70%)
- 30.0-34.9 (class I Obesity)	18 (30.00%)
- 35.0-39.9 (class II obesity)	2 (3.33%)
- > 40.0 (class III Obesity)	0 (0.00%)

CI: Confidence Interval

Table (II): Distribution of the studied cases according to musculoskeletal system examination.

Joint pain	60 (100.00%)
Spinal pain	52 (86.67%)
Fatigue	14 (23.33%)
Stiffness	58 (96.67%)
Skin rash	3 (5.00%)
Hyperpigmentation	7 (11.67%)
Xanthelasma	2 (3.33%)
Musculoskeletal Swelling	
- MCP joints	7 (11.67%)
- PIP joints	3 (5.00%)
- Wrist joints	2 (3.33%)
- Elbow joints	2 (3.33%)
- Shoulder joints	1 (1.67%)
- Ankle joints	1 (1.67%)
Musculoskeletal Deformity	
- Knee deformity	1 (1.67%)
- Foot deformity	4 (6.67%)
- Hand deformity	12 (20.00%)
- Wrist deformity	1 (1.67%)
- Joint deformity	18 (30.00%)
Limited Movement	
- MCP	6 (10.00%)
- PIP	3 (5.00%)
- Hand	2 (3.33%)
- Elbow	4 (6.67%)
- Ankle	4 (6.67%)
- Wrist	6 (10.00%)
- Shoulder	1 (1.67%)
Stiffness	
- MCP	1 (1.67%)
- PIP	1 (1.67%)
- Hand	1 (1.67%)
- Wrist	1 (1.67%)
- Ankle	1 (1.67%)
Pain	
- MCP	1 (1.67%)
- Wrist	1 (1.67%)
- Ankle	1 (1.67%)
- Shoulder	1 (1.67%)
- Knee	1 (1.67%)
Tenderness	
- Wrist	1 (1.67%)
- PIP	1 (1.67%)
- Shoulder	1 (1.67%)

Table (III): Distribution of the studied cases according to different disease comorbidities

Diabetes mellitus	14 (23.33%)
Hypothyriodism	1 (1.67%)
Hypertension	25 (41.67%)
Pyelonephritis	1 (1.67%)
Recurrent UTI	4 (6.67%)
Eyes	
- Normal	30 (50.00%)
- Wearing glasses	30 (50.00%)

Table (IV): Descriptive analysis of the studied cases according to neurological, cardiovascular and chest examination findings

Neurological	
- Normal	48 (80.00%)
- Abnormal	12 (20.00%)
○ Numbness of one side	5 (8.33%)
▪ Left	3 (5.00%)
▪ Right	2 (3.33%)
○ Lower limb numbness	3 (5.00%)
○ History of stroke	7 (11.67%)
○ Side Weakness (left)	1 (1.67%)
Cardiovascular and Chest	
- Tachycardia	1 (1.67%)
- Palpitation	11 (13.33%)
- MI	3 (5.00%)
- Aortic stenosis	1 (1.67%)
- Dyspnea on excretion	8 (13.33%)
- COPD	2 (3.33%)

Table (V): Distribution of the studied cases according to immunological and radiological findings

APCA	
- Negative	0 (0.00%)
- Positive	60 (100%)
RF	
- Negative	4 (6.67%)
- Positive	56 (93.33%)
CRP	
- Normal	13 (21.67%)
- Elevated	47 (78.33%)
ESR	
- Normal	13 (21.67%)
- Elevated	47 (78.33%)
Hepatitis Marker	
- Negative	60 (100%)
- Positive	0 (0.00%)
Plain X rays	0 (0.00%)
CT Chest	0 (0.00%)
Echo/ ECG	
- Normal	55 (91.67%)
- Left Ventricular Hypertrophy	2 (3.33%)
- Sinus Tachycardia	3 (5.00%)
U/S Abdomen	0 (0.00%)
BMI (kg/m^2)	
- **Min-Max**	21.00-35.00
- **Mean ± SD**	27.18±4.10
- **95% CI for mean**	26.12-28.24

CI: Confidence Interval

Table (VI): Distribution of the studied cases according to duration of disease symptoms

Duration of stiffness score	
- Non specific	32 (5.33%)
- Less than one hour	28 (46.67%)
Duration of stiffness attack (hour)	
- Min-Max	0.25-1.50
- Mean ± SD	0.49±0.378
- 95% CI for mean	0.35-0.63
Morning stiffness	12 (20.00%)
Duration of suffering of stiffness (Months)	
- Min-Max	2.00-6.00
- Mean ± SD	4.00±1.83
- 95% CI for mean	1.09-6.91
Duration of suffering of diabetes (years)	
- Min-Max	10.00-15.00
- Mean ± SD	13.33±2.89
- 95% CI for mean	6.16-20.50
Duration of suffering of hypertensive (years)	
- Min-Max	3.00-10.00
- Mean ± SD	7.29±3.68
- 95% CI for mean	3.88-10.69
Duration of MI (years)	
- Min-Max	0.00-5.00
- Mean ± SD	0.63±1.77
- 95% CI for mean	-0.85 – 2.10
Duration of CHF (years)	
- Min-Max	0.00-3.00
- Mean ± SD	0.38±1.03
- 95% CI for mean	0.17 – 0.92

CI: Confidence Interval

Table (VI): Distribution of the studied cases according to CGA scores

Katz ADL index	
- Min-Max	2.00 – 12.00
- Mean ± SD	6.88±2.78
- 95% CI for mean	6.17-7.60
MNA Screening Score	
- Min-Max	4.00-16.00
- Mean ± SD	10.50 ± 2.19
- 95% CI for mean	9.93-11.07
Geriatric Depression Scale (GDS)	
- Min-Max	0.00 - 11.00
- Mean ± SD	9.00 ±1.80
- 95% CI for mean	8.54-9.46
MMSE (total points)	
- Min-Max	9.00-28.00
- Mean ± SD	18.03±5.10
- 95% CI for mean	16.71-19.38
FRF (total points)	
- Min-Max	0.00– 10.00
- Mean ± SD	5.78±1.914
- 95% CI for mean	5.29-6.28
CGA Katz ADL questionnaire out of 12	
- Min-Max	0.00– 6.00
- Mean ± SD	3.31±2.77
- 95% CI for mean	1.83-4.79
MMSE questionnaire out of 30	
- Min-Max	0.00-28.00
- Mean ± SD	16.93±12.46
- 95% CI for mean	10.03-23.84
GDS questionnaire out of 15	
- Min-Max	0.00-12.00
- Mean ± SD	5.79±4.58
- 95% CI for mean	3.14-8.43
MNA for nutrition questionnaire	
- Min-Max	0.00-13.00
- Mean ± SD	6.93±4.70
- 95% CI for mean	4.22-9.64
DAS measurement	
- Min-Max	3.75-5.22
- Mean ± SD	4.52±0.54
- 95% CI for mean	4.10-4.94
Mobility assessment Get and Go test (min)	
- Min-Max	0.00-20.00
- Mean ± SD	15.60±5.78
- 95% CI for mean	11.47-19.73

CI: Confidence Interval

DISCUSSION:

Cognitive decline is a deterioration of intellectual and learning abilities and related memory problems, and is often associated with behavioral alterations, which prevents patients from carrying out the most common daily activities, such as maintaining normal productive interpersonal relationships, communicating, and leading an autonomous life. The aim was to assess the role of ACPA in elderly rheumatoid arthritis patients, to describe clinical, laboratory characteristics as well as functional status according to their ACPA status, and to determine the prevalence of cognitive impairment and concurrent geriatric syndrome as a comorbidity in elderly rheumatoid arthritis patients. In this cross sectional study, sixty elderly patients with rheumatoid arthritis of both sexes aged ≥ 65 years fulfilling the 2010 EULAR/American College of Rheumatology (ACR) classification criteria for rheumatoid arthritis were included, with exclusion of patients with severe life-threatening disease, severe dementia, and those with past history of cancer or viral hepatitis. Screening for comorbidities was initially carried out as part of the interrogation. A questionnaire was used to assess functional disability, quality of life, visual analogue scale (VAS) for spinal pain, joint pain, global status, fatigue, duration of morning stiffness, review of the systems, falls and cardiovascular risks. Monitoring of comorbidities and risk factors as cardiovascular disease detected by blood pressure measurement, blood glucose, lipid profile, kidney and liver function assessment was performed. Monitoring for infections including Hepatitis B, C was done. Opthalmological examination, echocardiogram and X- ray of the affected joints was carried out for all elderly rheumatoid arthritis patients.

The emerging body of data suggests that clinical, psychological, and biological factors may contribute to the pathogenesis of cognitive decline in RA, including cardiovascular complications, chronic pain, depression, inflammatory factors, drug side effects, and genetics which also were documented by Van der Woude, et al.[38] Comprehensive geriatric assessment (CGA) is a multidisciplinary diagnostic and therapeutic process to determine the medical, psychological, and functional capabilities of an older person to develop a coordinated and integrated plan for treatment and follow-up[39]. CGA is the gold standard for the assessment and management of an elderly person with complex health and social care needs, and those living with frailty. Elderly people with multimorbidity or frailty may benefit from CGA.

Our results demonstrated that sixty elderly rheumatoid arthritis patients with cognitive impairment showed elevated anti-CCP titer. There was a marked increase in the number of the adverse outcomes scores in the elderly such as pain, mobility disorders, increased risk of falls, fractures, impaired ability or disability to perform activities of daily living, risk of malnutrition, depression risk, frailty risk, mobility risk, and increased risk of comorbidities as elevated blood pressure, kidney, liver functions impairment, elevated ESR, CRP, ANA, Anti-CCP Abs, FBS, 2hPP, uric acid and lipid profile.

The exact relationship between RA and cognitive impairment remains contentious [40]. Cognitive impairment is one of the most common comorbidities found in RA, ranging between 38 and 71% [41, 42]. The pathogenic mechanisms of cognitive decline in RA are unknown [43]. Elderly onset RA seems to have a characteristic clinical pattern and perhaps biological profile different to that of early onset RA.[44,45] Working ability is one of most important goals for RA and also non-frail status should be goal of elderly RA, since it is associated with health expectancy.[46] Anticitrullinated protein antibodies (ACPAs) are serological biomarkers associated with early, rapidly progressing rheumatoid arthritis (RA), including more severe disease and joint damage. ACPA testing has become a routine tool for RA diagnosis and prognosis reviewed by Brink M et al.[47] Disease activity, which is reflected by tender and swollen joint counts, levels of acute phase reactants, and patient's and physician's global assessments, is a good predictor of damage and physical disability, and an outcome measure, which is used to evaluate health outcome in clinical

studies of patients with RA reviewed by Balsa A et al,[48]. A number of mechanisms have been proposed for the pathogenesis of cognitive impairment in RA including a chronic systemic inflammatory process involving all organs. Intact cognitive function is important for executing several basic tasks in people with chronic diseases, including RA documented by Mueller R, et al.[49]

Michael J et al, documented no association between rheumatoid arthritis and cognitive impairment in a cross sectional large national probability sample in elderly patients [50]. High prevalence of cognitive impairment among elderly RA patients was observed. Systemic inflammation is a well-established risk factor for cognitive impairment, which is found to be a strong predictor of poor physical and mental outcomes in RA. Cognitive impairment was not related to clinical, treatment features or disability. More studies are necessary to determine the clinical impact of cognitive impairment in elderly RA patients.[51,52] Elderly RA patients are at a particular risk due to increased cardiovascular morbidity.[53,54] It has been suggested that RA therapy might have a predictive effect on cognitive function, further supported by a German study where effective treatment significantly improves the mental component of the Short Form 36 (vitality, social functioning , role-emotional and emotional well-being) [53,55]. However, cognitive impairment in RA could be underestimated in clinical practice and might undermine the efficacy of RA therapy in the elderly by affecting their compliance to therapy [56]

CONCLUSION:

During disease progression anti-CCP titer in elderly rheumatoid arthritis patients with cognitive impairment was elevated. It was expected since anti-CCP has a high specificity for rheumatoid arthritis and become positive in the elderly with a high predictive value. However, in early stages of cognitive impairment, we could not use this biomarker as a diagnostic test. It needs more studies to confirm the role of anti-CCP antibody production in elderly rheumatoid patients without cognitive impairment.

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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