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THE INCIDENCE OF GENERALIZED ANXIETY DISORDER IN PATIENTS WITH RHEUMATOID ARTHRITIS AND ITS RELATIONSHIP TO DISEASE ACTIVITY

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Abstract:

Background: *Rheumatoid arthritis (RA) is a life-long disease with progressive disability, and people with RA experience higher levels of mental stress than the general population.*

Aim: *The aim of this study was to assess the prevalence of generalized anxiety disorder (GAD) in RA patients and to determine its relationship to disease activity.*

Place and Duration: *In the Rheumatology department of Jinnah Hospital, Lahore for one-year duration from April 2019 to April 2020.*

Patients and Methods: *The study included 200 cases of RA. Psychiatric examinations of all cases were performed according to the Hamilton scale. Patients suspected of having GAD were further assessed against the latest diagnostic criteria for GAD in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) and the Psychiatric Assessment Sheet (PAS).*

Results: *The incidence of GAD in RA was 38.5% (n = 77), as assessed on the basis of the Psychiatric Assessment Chart (PAS). RA patients with GAD showed significantly higher measures of disease activity than patients without GAD (p-value 0.05) or positive RF (r = 0.058; p-value> 0.05).*

Conclusion: *Generalized anxiety disorder (GAD) is common in cases of RA. Disease activity was significantly higher in RA with GAD than in RA without GAD. GAD was found not to be associated with disease duration.*

Key words: *rheumatoid arthritis, generalized anxiety disorder.*

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INTRODUCTION:

Rheumatoid arthritis (RA) is a systemic, chronic and inflammatory disease of probable autoimmune etiology and predominant joint involvement, characterized by symmetrical peripheral polyarthritis causing deformation of the joints. In addition to causing chronic inflammation, the disease generally has many detrimental psychosocial consequences for the patient; also, the patient with this chronic disease faces an unpredictable course and a painful progression marked by seizures.

The persistent pain, functional disability, fatigue, inability to work, economic constraints, and the side effects of therapeutic drugs that RA can trigger can ultimately reduce the quality of life of these patients. In addition, psychiatric symptoms in RA patients increase pain perception, the use of analgesics, and make work more difficult and lead to a reduction in adherence to medical recommendations.

One of the factors that is believed to play a role in the initiation, persistence, and worsening of RA is mental stress. The diagnosis of RA can cause stress and uncertainty in patients and their relatives, and a higher stress at the onset of the disease is indicative of a worse prognosis.

It is hypothesized that chronic pain, joint deformities, loss of function and inability to work lead to social stress and contribute to the development of psychiatric disorders in RA patients, and numerous research lines suggest that stress plays an important role in shaping the cause of inflammation. diseases such as RA; stress activates a cascade of neurohumoral events, many of which may be deregulated in RA patients, including aspects of the hypothalamic-pituitary-adrenal (HPA) axis, the autonomic nervous system and proinflammatory processes, so this means that the endocrine stress response system may be a target stress management interventions in patients with immune related diseases such as RA.

People with RA tend to experience more anxiety and other emotional problems than others in the general population, and anxiety has been found to have a direct impact on pain, and this effect was much greater than with depression. Previous research has shown that a common time sequence is anxiety first, followed by depression. Therefore, screening for anxiety symptoms in people with RA can help identify depression early and help prevent future depressive episodes.

One of the most common types of anxiety disorders in RA is generalized anxiety disorder (GAD). GAD is characterized by excessive anxiety and worry about various topics (such as health, work, family ... etc) that last for more than at least six months and are accompanied by physical symptoms.

Research objectives:

The purpose of this study was to evaluate:

1. The prevalence of generalized anxiety disorder (GAD) in RA patients using the Hamilton Anxiety Scale (HAM-A), the Diagnostic and Statistical Manual of Mental Disorders (DSM5), diagnostic criteria for GAD and a clinical psychiatric assessment card (PAS)
2. Differences in disease activity parameters between patients with RA with GAD and without GAD.

PATIENTS AND METHODS:

Study design: cross-sectional descriptive study of patients with RA.

Patients:

This study was held in the Rheumatology department of Jinnah Hospital, Lahore for one-year duration from April 2019 to April 2020. Two hundred patients diagnosed with RA who came to the outpatient clinic of Rheumatology were included in the study. RA patients were recruited over a six-month period, and data analysis and explanations were performed over a further six-month period.

Admission Criteria:

1. Age> 17 years.
2. Can and willing to provide written informed consent and to comply with the requirements of the study protocol.
3. Patients with RA diagnosed according to the criteria of the European League Against Rheumatism / American College of Rheumatology (EULAR / ACR 2010) and / or ACR from 1988.
4. Symptoms of post-RA generalized anxiety disorder.

Exclusion criteria:

1. Defiant autoimmune rheumatic disease other than RA, including systemic lupus erythematosus, mixed connective tissue disease, scleroderma, seronegative spondyloarthropathies and polymyositis ... etc.
2. History or current history of inflammatory disease of the joints (eg, gout).
3. Patients with fibromyalgia syndrome.
4. History of prior mental disorders.
5. Chronic disorders other than RA (eg Diabetes mellitus, chronic liver disease, chronic renal failure… etc).

Recruitment and counseling for patients:

Patients were recruited from the Sohag University Department of Rheumatology and Rehabilitation.

METHODS:

After taking an anamnesis, complete general and musculoskeletal examination of RA patients; RA patients underwent the following assessment tools:

1. Demographic data, including name, age, gender, occupation, marital status, education, disease duration, and morning stiffness were recorded for each RA patient.
2. Rheumatoid factor (RF).
3. Erythrocyte sedimentation rate (ESR).
4. Visual analog scale (VAS).
5. DAS-28
6. Hamilton Anxiety Rating Scale (HAM-A) and HAMA rating in Arabic translation.

This scale consists of the following 14 assessment elements:

1. Restless worries, anticipating the worst, fearful anticipation, irritability.
2. Tension Feeling tense, tired, surprised, moving easily to tears, trembling, anxiety, inability to relax.
3. Fear of the dark, strangers, being left alone, animals, traffic, crowds.
4. Insomnia Difficulty falling asleep, interrupted sleep, unsatisfactory sleep and fatigue upon waking, dreams, nightmares, nightmares.
5. Intellectual (cognitive): difficulty concentrating, poor memory.
6. Depressed mood: loss of interest, lack of pleasure from hobbies, depression, waking up early, daily swing.
7. Somatic (muscular): Pain and aches, tremors, stiffness, myoclonic convulsions, teeth grinding, shaky voice, increased muscle tension.
8. Somatic (sensory): Tinnitus, blurred vision, hot and cold flushes, feeling weak, stinging feeling.
9. Cardiovascular symptoms: tachycardia, palpitations, chest pain, pulsation of blood vessels, fainting, no beating.
10. Respiratory symptoms: chest tightness or tightness, choking, gasping, shortness of breath.
11. Gastrointestinal symptoms: difficulty swallowing, wind, abdominal pain, burning sensation, abdominal fullness, nausea, vomiting, weight loss, constipation.
12. Symptoms of the genitourinary system: frequency of urination, urgent urge to urinate, amenorrhea, menstrual bleeding, development of coldness, premature ejaculation, loss of libido, impotence.
13. Autonomic symptoms: dry mouth, redness, pale skin, a tendency to sweat, dizziness, tension headaches, rising hair.
14. Interview behavior: shaking hands, frowning, facial tension, sighing or rapid breathing, pale face, swallowing, belching, jerking tendons, dilated pupils, bulging eyes.

Each of these 14 items is rated as follows: NONE = 0, MENT = 1, MODERATE = 2, SERIOUS = 3, SERIOUS, COMPLETELY OFF = 4

This calculation will give a comprehensive score ranging from 0 to 56. It was predetermined that the evaluation results could be interpreted as follows. A score of 17 or less indicates mild anxiety. A score of 18 to 24 indicates mild to moderate anxiety severity. Finally, a score of 25 to 30 indicates a moderate or severe severity of anxiety. 7. Diagnostic and statistical manual of mental disorders, ed. 5. (DSM-5) GAD diagnostic criteria They include:

A. Excessive anxiety and worry (fearful anticipation) for more than 6 months related to multiple events or activities (such as work or school performance).

B. The person has difficulty controlling worry.

C. Anxiety and worry are related to three (or more) of the following six symptoms (with at least some symptoms lasting for more than the last 6 months):

1. Anxiety or feeling agitated or nervous.
2. It is easy to tire.
3. Difficulty concentrating or empty mind.
4. Irritability.
5. Muscle tension.
6. Sleep disturbances (difficulty falling asleep or falling asleep, restless, unsatisfactory sleep).

D. Anxiety, worry, or physical symptoms cause clinically significant stress or impairment in social, work, or other important areas of functioning.

E. The disorder cannot be ascribed to the physiological effects of a substance (eg, intoxicating drug, drug) or any other disease (eg, hyperthyroidism).

F. The disorder cannot be better explained by another mental disorder (e.g., anxiety or fear of panic attacks in panic disorder, negative evaluation of social anxiety disorder [social phobia], infection or other obsessions with obsessive compulsive disorder, separation from attachment character in separation anxiety syndrome, recall of traumatic events in post-traumatic stress disorder, weight gain in anorexia nervosa, physical ailments related to somatic symptoms, perceived appearance defects in organism dysmorphia, having severe illness, anxiety disorders or schizophrenia or delusional disorders).

8. Psychiatric evaluation card for patient evaluation and diagnosis:

The scales in this study were carefully explained to illiterate patients to give accurate answers to each item.
Patients in this study were informed about the study and obtained their consent.

Analysis:
Data was calculated and analyzed with IBMSPSS software version 22.

RESULTS:

Patient demographics: Two hundred patients were enrolled in the study, and the age distribution ranged from 18 to 70 years, mean 42.34 ± 11.99 years. One hundred and sixty-six patients are 83% female and 17% male. Disease duration ranged from 2 months to 35 years, as reflected in a very high standard deviation (6.2 years) compared to the mean (7.67 years). The classification of patients according to the duration of the disease was as follows: 5 (2.5%) patients were very early, 38 (19.0%) were early, 157 (78.5%) were diagnosed.

Table (1) shows the disease activity scores according to morning stiffness ranging from 0 to 150 minutes with a mean of 36.98 ± 36.69, a visual analog scale (VAS) ranging from 0 to 100 with a mean of 29.43 ± 28.06 , the number of swollen joints ranged from 0 to 8 with a mean of 1.50 ± 1.97, the number of painful joints ranged from 0 to 10, mean 2.43 ± 2.81.

Table 1: Clinical evaluation of disease activity

	Morning stiffness (Min)	VAS (0-100)	Swollen joints	Tender joints
Mean	36.98	29.43	1.50	2.43
Median	20.00	20.00	0.00	1.50
Std. Deviation	36.69	28.06	1.97	2.81
Minimum	0	0	0	0
Maximum	150	100	8	10

The rheumatoid index (RF) value ranged from 4.8 to 2048 IU / ml with a mean of 213.46 ± 337.69, and the ESR ranged from 9 to 110 with a mean of 35.43 ± 19.91 mm / h. for rheumatoid factor, 145 (72.5%) had RF + ve, and the remaining 55 patients (27.5%) had RF-ve. With regard to ESR, 98 patients (49.0%) were normal, while in the remaining 102 patients (51.0%), ESR was elevated. The DAS-28 ranged from 1.82 to 6.07 with an average of 3.69 ± 1.22. Disease activity measured by DAS-28 is presented in the table below as follows: 85 patients (42.5%) had mild disease activity, another 85 (42.5%) patients had moderate disease activity and the remaining 30 (15.0%) %) had high disease activity.

For Hamilton's anxiety score, it ranged from 0 to 35, with a mean of 13.28 ± 9.28. The frequency and grades of Hamiltonian anxiety were as follows: 124 (62.0%) patients with suspected mild anxiety, 46 cases (23.0%) had moderate anxiety, 28 cases (14.0%) had severe anxiety and 2 cases (1.0%) have very severe anxiety.

Regarding the correlation between the Hamilton scale, age, disease duration and measures of disease activity in RA patients: there was no significant correlation between the Hamilton scale and; age, disease duration, RF positive (p-value> 0.05). On the other hand, there was a very significant correlation between the Hamilton scale and morning stiffness, VAS, number of swollen joints, number of painful joints, ESR and DAS-28 (p value <0.001) (Table 2).

Table 2: Correlations between Hamilton score and each of age, disease duration and severity of RA patients

	Pearson correlation (r)	P value
Age (years)	0.013	0.858
Disease duration (years)	0.036	0.617
Morning stiffness (minutes)	0.772	<0.001
VAS (0-100)	0.841	<0.001
Swollen joints (number)	0.751	<0.001
Tender joints	0.816	<0.001
RF (IU/mL)	0.058	0.416
ESR (mm/hr)	0.752	<0.001
DAS28	0.904	<0.001

It turned out that there was no significant difference in anxiety as measured by the Hamilton scale between male and female genders (p-value> 0.05). There was also no significant difference in the Hamilton scale between the positive and negative RF events (p-value> 0.05). On the other hand, the mean Hamilton scale among patients with increased ESR was 19.55 ± 7.67 and was significantly higher than among patients with normal OB (6.76 ± 5.58); p-value was highly significant (<0.001).

A comparison of the Hamilton index with disease activity using DAS28 showed that the mean Hamilton score increased from 4.61 ± 3.1 in patients with low disease activity, to 17.39 ± 6.02 in patients with moderate disease activity, to 26.2 ± 3.99 in patients with high disease activity. The difference was very significant. All 85 patients with mild disease activity had mild anxiety suspicion, patients with moderate disease activity had the following suspicions of anxiety: 38 (44.7%) of them suspected mild anxiety, 41 (48.2%) of them suspected moderate anxiety, and 6 (7.1%) of them suspected severe anxiety. In addition, people with high disease activity had the following suspicions of anxiety: one (3.3%) suspected mild anxiety, 5 (16.7%) suspected moderate anxiety, 22 (73.3%) suspected severe anxiety, and 2 (6.7%) suspected very strong anxiety (Fig. 1).

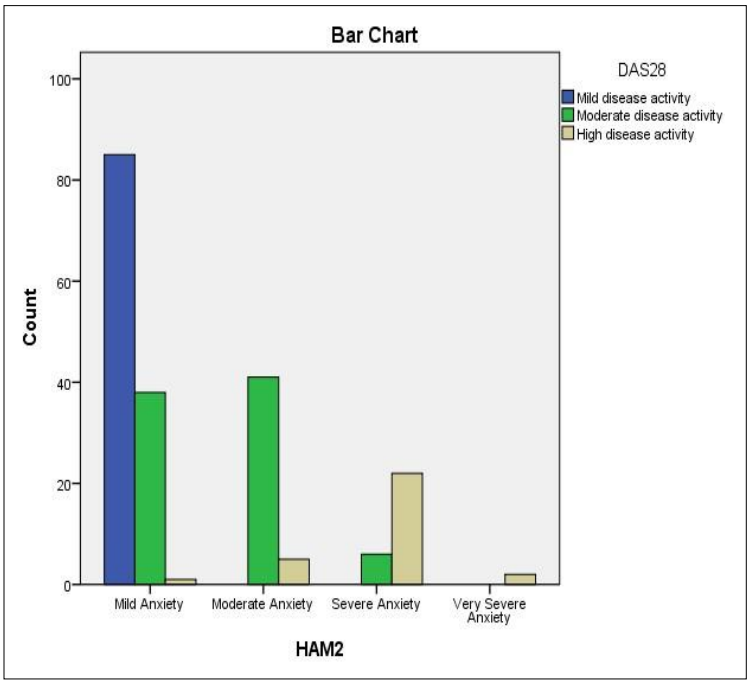

Figure 1: Relation between disease activity and degree of anxiety

The incidence of generalized anxiety disorder (GAD) among selected RA patients assessed according to the DSM diagnostic criteria for fifth edition GAD (DSM-5) was as follows: patients not meeting the GAD 117 criteria (58.5%) and patients who met the GAD diagnostic criteria 83 (41.5%). Table 3 shows that there is a significant difference in measures of disease activity between RA patients with and without GAD assessed by the DSM-5 as follows: morning stiffness, VAS, painful joint count, swollen joint count, ESR and DAS-28 are higher in RA patients with positive generalized anxiety disorder compared with patients without (p-value <0.001).

Table 3: Comparison of disease activity measures between male and female RA patients with and without generalized anxiety disorder assessed by DSM-5

		DSM-5		Chi square*/ t test** MW test***	P value
		Patients without Anxiety	Patients with Anxiety		
Sex	Male	19	15	0.116*	0.734 (NS)
	Female	98	68		
Age (mean±SD)		42.52±11.49	42.07±12.72	0.260**	0.795 (NS)
Disease duration (years)		7.92±5.91	7.623±6.60	4418.5***	0.277 (NS)
Duration of RA	Very early RA	1	4	3.393*	0.183 (NS)
	Early RA	24	14		
	Established RA	92	65		
Morning stiffness (min)		16.79±25.47	65.42±30.80	1036.0***	**<0.001 (HS)**
VAS (0-100 scale)		12.39±16.43	53.43±23.05	791.0***	**<0.001 (HS)**
No. of tender joints		0.72±1.14	4.83±2.70	1136.0***	**<0.001 (HS)**
No. of swollen joints		0.39±0.80	3.05±2.08	792.5***	**<0.001 (HS)**
RF		183.03±34.96	256.35±36.81	4230.5***	0.120 (NS)
RF positivity	Negative RF	34	21	0.344*	0.558 (NS)
	Positive RF	83	62		
ESR		24.79±1.41	50.41±19.71	10.642**	**<0.001 (HS)**
ESR	Normal	87	11	77.550*	**<0.001 (HS)**
	Raised	30	72		
DAS-28		2.91±0.78	4.79±0.81	16.527**	**<0.001 (HS)**
DAS-28 group	Mild disease activity	81	4	98.817*	**<0.001 (HS)**
	Moderate	36	49		
	Severe	0	30		
Hamilton Score(anxiety)		6.82±1.63	22.39±5.95	20.809**	**<0.001 (HS)**
Anxiety by HAM	Mild anxiety	117	7	172.794*	**<0.001 (HS)**
	Moderate	0	46		
	Severe	0	28		
	Very severe	0	2		
Psychiatry case sheet	Negative anxiety	117	6	176.491*	**<0.001 (HS)**
	Positive anxiety	0	77		
Total		117	83		200

There was a significant difference between RA patients with positive generalized anxiety disorder as assessed by the DSM-5 and those assessed by the Hamilton Score as follows: Two hundred RA patients were suspected of having Hamilton's anxiety score compared with eighty-three of these RA patients suspected of generalized anxiety disorders according to DSM-5 (p value <0.001). Regarding the incidence of GAD as assessed by the Psychiatric Assessment Sheet (PAS), 77 (38.5%) of the 200 RA patients were approved as having GAD (p-value <0.001). Table 4 shows that there are significant differences in disease activity measures for morning stiffness, VAS, painful joint count, swollen joint count, ESR, and DAS-28 between RA patients with and without GAD assessed on the psychiatric scorecard (p-value < 0.001). Regarding gender, age, disease duration, and RF positivity, there is no statistical difference (p-value> 0.05) between RA patients with and without GAD assessed on the psychiatric evaluation sheet.

Table 4: Comparison between Psychiatry assessment sheet positive and negative cases for anxiety

		Psychiatry Assessment Sheet		Chi square*/ t test** MW test***	P value
		Patients without Anxiety	Patients with Anxiety		
Sex	Male	23	11	0.654*	0.419 (NS)
	Female	100	66		
Age (mean±SD)		42.41±11.74	42.21±12.45	0.118**	0.906 (NS)
Disease duration (years)		7.92±5.94	7.49±6.62	44.83.5***	0.526 (NS)
Morning stiffness (min)		16.63±24.87	69.48±28.13	784.0***	**<0.001 (HS)**
VAS (0-100 scale)		12.64±16.26	56.23±21.28	570.0***	**<0.001 (HS)**
No. of tender joints		0.73±1.15	5.13±2.54	497.5***	**<0.001 (HS)**
No. of swollen joints		0.43±0.93	3.19±1.99	920.5***	**<0.001 (HS)**
RF		184.67±308.29	259.46±377.54	4003.0***	0.065 (NS)
ESR		24.54±9.47	52.82±18.10	12.258**	**<0.001 (HS)**
ESR	Normal	92	6	85.076*	**<0.001 (HS)**
	Raised	31	71		
DAS-28		2.91±0.80	4.93±0.58	20.872**	**<0.001 (HS)**
Hamilton Score(anxiety)		6.79±4.61	23.65±3.79	25.500***	**<0.001 (HS)**
Total		123	77	-	-

DISCUSSION:

A chronic disease such as RA can be an emotional challenge. In fact, when patients are diagnosed with RA, the first thing they may come across is dealing with any strong feelings that arise, including anxiety, insecurity, and fear. After overcoming your initial reaction, the daily challenges of RA increase your risk for emotional problems such as depression, anxiety and stress. It was shown that people with RA quit or change jobs within 2 years, 33% and 16%, respectively. Chronic and clinical fluctuation of the disease, as well as the ubiquitous possibility of the patient experiencing pain, are possible causes of psychiatric disorders in RA. Most studies of disease activity in RA have focused on the severity of clinical pain, while recent studies have found a complex association between pain, inflammation and mental stress in RA patients. A study by Murphy and her colleagues on the prevalence of anxiety and depression in patients with chronic arthritis such as RA found that more than a third of the study participants had at least one of two mental health conditions: anxiety and depression. Anxiety was much more common than depression, twice the proportion of depression, but the researchers found this was unexpected as much more attention was paid to depression. Radanov et al. found that individuals with RA had mean scores for anxiety as a trait that were similar to the normative data for the general population.

Tamiya and Vaeroy found a positive link between RA pain and anxiety, Tamiya found a 30% variation in pain explained by anxiety. In our study, we found that there was a correlation between pain (VAS) and GAD in RA patients, and this correlation was highly significant (r = 0.841 and p-value <0.001). In our study, we found that there was no significant difference in age, sex, rheumatoid factor positivity in patients with and without GAD (p-value> 0.05), which was consistent with other studies. The recent assessment of patients using the Psychiatric Assessment Sheet has helped us identify high-risk patients. It was found that patients with financial difficulties and weaker social interactions are at risk of anxiety, however, as a causal relationship cannot be implied from a statistical relationship, it may be due to different mechanisms and was consistent with Soderlin et al and Lok et al. The use of corticosteroids, especially large and long-lasting corticosteroids, and NSAIDs has been reported to have led to psychiatric side effects. On the other hand, corticosteroids and DMARDs used in RA did not contribute to anxiety and had an impact on physical health. In our study, patients were treated with DMARDs as monotherapy or in combination, and some in combination with low-dose corticosteroid or leflunomide.

CONCLUSION:

Generalized anxiety disorder (GAD) is common in RA patients. After assessing the accompanying factors in RA, its association with disease activity remained statistically significant in patients without GAD. Identifying the factors associated with mental

disorders in patients with RA may contribute to the development of possible preventive measures.

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