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Pathophysiology and Molecular Mechanisms: Exploring the Underlying Mechanisms that Lead to the Development and Progression of Rheumatologic Diseases at the Cellular and Molecular Levels

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Abstract: This paper gathered 80 patients who were selected in a number of various hospitals in Iraq and had the intention of investigating the exact processes, which contribute to the formation and development of rheumatologic diseases, both on a cellular and molecular scale. Rheumatic illnesses are the most common chronic disease in humans and the most common cause of lifelong disability, complex diseases that are more best comprehended when enabled to apply molecular genetic analysis in rheumatology. They identify potential infectious factors, and the genetic factors influencing the determinants of the disease on an individual level. The knowledge of causation of illnesses, severity analysis, choice of therapy and classifications of data associated with a patient are enhanced by researching into the heterogeneity of genes. Clinical and pathological features of rheumatic diseases have heterogeneity predisposed to progression. This multifactorial aspect of the diseases determines the heterogeneity of the nature of rheumatic diseases because in some instances, the multifactorial nature of the environment and the polygenic background not only predisposes to the disease but also determines the severity and the outcome of the disease. Knowledge of the molecular genetic complexity and complexity of these disorders also remains unfinished and there is still no criteria to form subgroups that ought to be treated differently in patients. We have arrived at this research conclusion that as a result of genetic analysis approaches made it possible to demonstrate that the microbial factor and the genetic peculiarities of the person matters in the development of rheumatic diseases.

Keywords: Pathophysiology, Genetic, Multifactorial, Molecular, Heterogeneity, Patients.

INTRODUCTION

Some human leukocyte antigen (HLA) types, such as HLA-DRB1, are closely associated with the disorder. The effect of environmental factors, such as smoking and other diseases, increases the risk of a particular person having an illness [DeMik, D. E. *et al*., 2017]. The characteristic of rheumatoid arthritis is inflammation in the synovial tissue around the joints that triggers a series of processes. Upon the initial entry of the activated immune cells, particularly that of T cells, into the synovium, Tumor Necrosis alpha (TNF- 7), interleukin-1 (IL-1), interleukin- 6 (IL-6) are some of the pro-inflammatory cytokines that are produced. These cytokines among others assist in the recruitment and stimulation of macrophages, B cells [Curtis, J. R. *et al*., 2017; Rifbjerg-Madsen, S. *et al*., 2017; Davis, M. A. *et al*., 1992].

Essentially, rheumatic diseases are chronic immune diseases of the body involving joints, and other body organs. No obvious causes of RA are known in relation to one or another person; it is only important whether the patient is vulnerable to the disease or not, and a good number of factors increase the chances of catching the disease. Smoking or infections represented by a virus or bacteria are some of other diseases that may trigger the immune system and give rise to a variety of symptoms [Wang, K. *et al*., 2018].

Theories or hypotheses such as: the incidence of rheumatic diseases being more prevalent in women than in the male may be explained by the fact that hormones are of significant significance as part of an activating of the immune system. This is justified by the fact that women are seven to nine times more prone to lupus erythematosus as compared to men.

Macrophages that also destroy joint tissue and cause inflammation mainly cause rheumatoid arthritis. They cause pannus and synovial hyperplasia by the process of inducing the activation of synovial cells. B cells develop autoantibodies, which make inflammation and damage of the joints worse. The cause of autoimmune responses is a dysregulated immune response which is an imbalance between

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regulatory and effector T cells. One of the most prominent causes of years lived with disability globally is musculoskeletal diseases, including osteoarthritis and rheumatoid arthritis, with OA giving rise to 31.5 per cent increase in the years lived with disability over 2006-2016 and pain (especially knee pain) being one of its most prominent symptoms. [Jacobs, B. Y. *et al.*, 2019; Herold, S. *et al*., 2016]

The absence of effective pain management therapeutics is one of the causes of current opioid and narcotic abuse epidemics. One out of every 10 opioids dispensed in Australia is on OA and 12 out of every 100 incident opioid dispensing incidents can be attributed to both OA and comorbidities. Although there have been gains in the treatment of RA, pain experiences nearly one-third of early patients who respond to the treatment well. The nature of the processes that provide pain in these diseases is crucial in optimizing care [Gholami, M. *et al*., 2015; O'Callaghan, J. P. *et al*., 1975; Shiotsuki, H. *et al*., 2010].

The least amount of well-established animal models in OA and RA can be used to examine the mechanisms involved in the pathophysiology of degradation of joints and immune/inflammatory regulation. There is a wide range of behavioral and neurophysiological techniques that have been used to explore the concept of pain in arthritic animal models [Lynch, J. J. *et al*., 2011; Quinn, L. P. *et al*., 2003]. Nevertheless, because of certain technology-related constraints of the quantitative measure of pain in animal models, care should be taken when trying to generalize the results of the animal models, to a human patient. This article discusses the methods of study, as well as the biochemical and molecular mechanisms that underlie the pathophysiology of arthritic pain as revealed in animal models of RA and OA. [R. E. Miller and others, 2012].

PATIENT AND METHOD

Eighty patients were recruited in this research. They were allocated based on gender; 48 men and 32 women. Within a 1-year study period between March 2023 and, the patients were recruited in various hospitals in Iraq without any restriction to February 2024. The real value of the ages of the patients and the arithmetic mean of the latter were 45±. 7.2 years.

Preliminary data has been gathered about the patients and this consisted of (height, age, weight, body mass index, marital status of the patients, and leading causes).

The evaluation of the outcomes was based on complication. To the patients the scale at which the disease impacts the quality of life of the patients was evaluated based on the scale (WHOQOL-BREF).
It includes a statement of quality-of-life on 30 existing, member items and does not and I want to delete it on approximately 30 items. The Quality-of-Life Questionnaire scores are comprehensive items, which have a range of 0-30, with a lower score depicting a better life.

There is no doubt that the majority and most frequent symptom of rheumatic illnesses is pain, which is the outcome of alterations in the musculoskeletal systems structures due to various diseases, which is why the correlation between rheumatic patients and the duration of their sleep was investigated. A non-restorative sleep pattern and incredibly poor quality sleep can be associated with many of the symptoms of this particular disorder, such as those experienced during the day, such as morning stiffness, pains, and exhaustion. Studies that have examined the effects of pain and sleep on rheumatic diseases have found that insomnia is very prevalent.

Chronic pain is connected with sleep disorders which are caused by different mechanisms. Conversely, sleep disruption among healthy individuals results in pain and exhaustion of the body as a whole. Lastly, pain and sleep disturbance have a correlation where intense pain in the day triggers sleep disturbance and vice versa, where disturbed sleep raises more intense pain in the following day and psychological reasons also relate to pain and insomnia.

STATISTICAL ANALYSIS

The statistics analysis was performed based on the IBM SOFT SPSS 22 program and Microsoft Excel 2013 was used. The data was tabulated based on the mean and slandered division and acquired the percentages of Frequency value of the variable of the study.

This data was interpreted logistically, which implies the extraction of the statistical correlation and the establishment of its strength in the current study in the case when the B-value is less than 0.05.

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Table 1: Assessment outcomes according to factors

Variable	Value
Age	
Mean and SD	45±7.2
Sex	
Male f (p %)	48 (60)
Female f (p %)	32 (40)
Causes	
immune cells	20 (25)
cytokines and chemokines	17 (21.25)
Genetic factors	9 (11.25)
environmental stimuli	
Infections	9 (11.25)
smoking	9 (11.25)
hormonal changes	11 (13.7)
Chemicals	5 (6.3)
Education	
Low	20 (25)
Secondary	30 (37.5)
College	20 (25)
High	10 (12.5)
BMI	
Mean ±Sd	29±4.4

Table 2: Assessment outcomes according to complication

	Male	Female	P-value
joint damage	5 (10.4)	4 (12.5)	0.093
deformity	3 (6.25)	3 (9.3)	0.88
chronic pain	3 (6.25)	0	0.09
limited mobility	2 (4.1)	1 (3.1)	0.22
fatigue	2 (4.1)	3 (9.3)	0.892
muscle weakness	0	2 (6.2)	0.001
Disability in severe cases.	0	1 (3.1)	0.09
Total	15 patients	14 patients	

Table 3: Analysis of the impact of rheumatology on patients' quality of life (WHOQOL-BREF)

Variable	Mean ±SD
Sleep duration	10.22±2.2
Psychological fatigue	9.7±3.1
Physical fatigue	13.7±3.22
overweight	14.12±4.98
Perception of health	12.55±2.8
Social relationships domain	6.6±2.4

Table 4: The correlation between our outcomes and sleep

Factor	R correlation	SE	95%CI	β	*P*
Bad sleep	-3.2	1.11	2.23-5.5	−0.16	0.030
Normal sleep	3.8	0.982	1.1-3.83	0.17	0.020
Adequate sleep	11.1	3.02	4.3-11.98	0.19	0.001
Psychological counseling	12.65	4.13	7.7-13.93	0.12	<0.050

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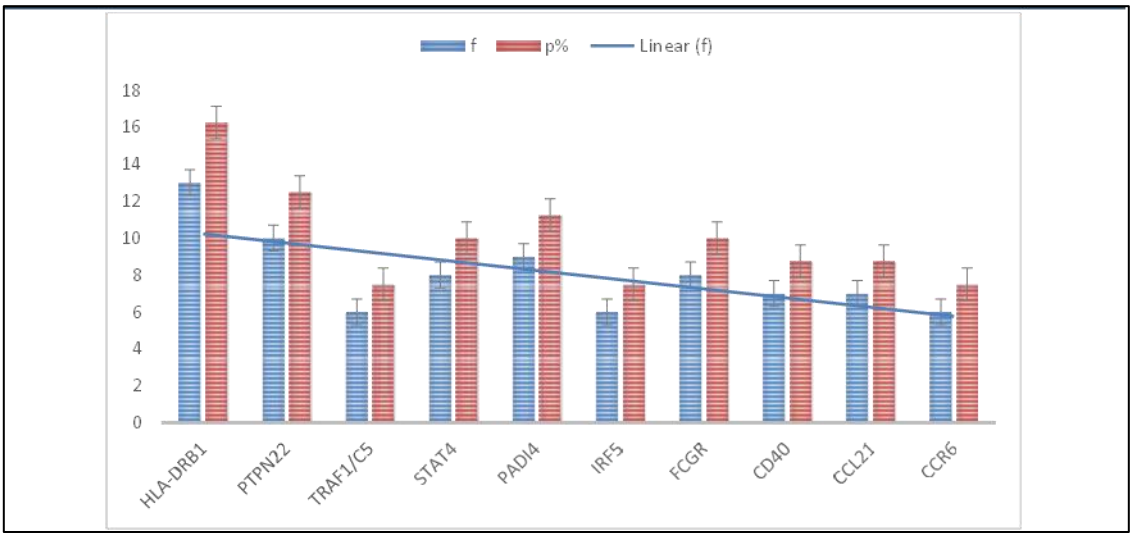

Fig 1: Distribution of genotypes among patients responsible for diseases

Table 5: Correlation between Causative factors with rheumatic diseases

	R correlation	**P-value**
Genetic factors	0.945**	>0.001
immune cells	0.848	0.034
cytokines and chemokines	0.06	0.33
hormonal changes	-0.45	0.55

Rheumatic diseases are complex and can involve multiple genes. Some of the most commonly associated genes in rheumatic diseases include

DISCUSSION

Rheumatoid arthritis (RA) is an inflammatory rheumatic disease with undetermined etiology, which is manifested by symmetrical chronic erosive arthritis (synovitis) of the peripheral joints, and systemic destruction of immunity to inner organs. The clinical picture is highly diverse and mainly depends on the localization predominance of inflammatory alterations of connective tissue of different organs. The WHO data illustrates that the incidence of rheumatoid arthritis in the population is between 0.6 and 1.3, and in relatives, it is 3-5 which implies the genetic predetermination of the pathology. In comparison to men, women become ill 2.5-3 times more frequently, particularly in the age group of 35-50 years, and during later age, the disease becomes more common [Nwosu, L. N. *et al*., 2016; Harvey, V. L. *et al*., 2009].

Several studies have found that the risk of developing rheumatoid arthritis is linked to carriage of major histocompatibility antigen class II HLA-DR4 and that one carrier HLA-DR1 has over 20 alleles. The activities of the other genetic factors which are not directly related to HLA-DR are also debated. These are a peptidyl arginine deaminase gene polymorphisms, protein tyrosine phosphatase N22 (PTPN22 C1858T), cytotoxic T lymphocyte-associated antigen (CTLA-4 A49G), chemokine receptor five gene (CCR5-Δ32) and NO synthetase ENOS 4 a /b MMP9-1562 C/T Matrix metalloproteinase (MMP) gene These are the least investigated genes with regard to being susceptible to rheumatic diseases [Ogando, J. *et al*., 2016].

Other researchers say that 70-80 percent of individuals affected by rheumatoid arthritis experience sleep problems. Although there is a higher level of disease incidence among women rather than men, sleep disorders are equally common among both sexes [Cheng, P. *et al*., 2020].

Studies on sleep disorders have been done most frequently in the case of fibromyalgia. Besides being another symptom, sleep disturbances can be involved as an etiological determinant of the disease, which is multifactorial and complicated. The diurnal variation in cortisol was linked to natural diurnal variation in cortisol and was modified in the biological temporal distribution of symptoms. [Cuppen, B. V. *et al*., 2016]

In over 75% of cases, sleep disorders are related

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and are characterized by fatigue and stiffness in the morning. The existence of spontaneous pains in the muscle masses, tendons and their insertions is attributed to poor restorative sleep. The sleep of fibromyalgic patients is shallow, readily disturbed by auditory stimuli and is slight or none restorative. Polysomnography-wise, there was an increase in the number of awakenings and the first stage, and a reduction in the amount of slow-wave and REM sleep, and sleep efficiency. Alpha delta activity is quite an ordinary observation at the EEG level. Patients have been observed to have sleep apnea and periodic limb movements during sleep. Antidepressants that are serotonin reuptake inhibitors, benzodiazepines and non-benzodiazepine hypnotics may be of limited value but it is extremely hard to get sleep improvement in such patients, particularly at the advanced stage of the disease.

There is a continuous increase in the level of Proinflammatory cytokines, TNF-alpha, IL 6, in response to the level of cortisol (a steroid hormone released by the adrenal gland in case of stress), and leads to a vicious circle of pain - Inflammation-insomnia-pain. Numerous interventions that aim at preventing this cytokine cascade exist today. Several studies have demonstrated that disease activity, sleep disturbances, inflammation mediators, pain, and psychological factors are all interrelated in patients with rheumatoid arthritis, therefore proper therapy to control disease activity and pain can increase sleep disturbances and may alleviate the symptoms associated with daytime such as fatigue and stiffness. We cannot overlook that to the agony brought by the disease, we should add the uncertainty, anxiety, and worry brought about by recent diagnosis of the disease.

Investigations of the activity of MMP-1, -3 and tissue MMP-1 inhibitors and concentration of C-reactive protein (CRP), and cytokines in patients with erosive and non-erosive rheumatic diseases showed a marked rise in proteinase activity in the blood serum of patients with erosive arthritis. Meanwhile, a direct correlation between CRP level and MMP-3 activity has been determined which is more in line with clinical manifestation of RA. Thus, one may say that establishing the MMP-3 activity and CRP level in the blood serum of rheumatoid arthritis patients is diagnostically significant. The findings of the study indicate that the activity of MMP-3, rather than cytokines is an indication of the extent of inflammation in rheumatoid arthritis. This operational capability enables us to view MMP-3 as being part of the primary proteins that are involved in the mechanisms of connective tissue destruction in rheumatoid arthritis.

CONCLUSION

To enhance the treatment results, it is crucial to conduct studies of the cellular and molecular components of rheumatologic disorders, which immune responses, environmental triggers, genetic variables, and cytokine signaling can help to identify therapeutic targets and develop personalized therapies, where new treatments and cures due to the current research, technological advances, and collaboration by millions of sufferers may lead to improvements.

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