

CLINICAL RESEARCH

Variation in the Clinical Manifestation of Rheumatoid Arthritis Based on the Residence Areas

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Abstract

The study included rheumatoid arthritis patients from three regions of Uzbekistan, viz., Tashkent city - zone I (n=144), Khorezm region – zone II (n=112) and the Namangan region – zone III (n=104). Comparative clinical and laboratory analyses showed the clear evidence of aggressive joint syndrome dominance in zone II (71.4%), which was higher than those of the patients in zone III ($P<0.05$), as well as the development of severe destructive lesions of the joints, even up to the joints ankylosing. Also, zone II was dominated by the visceral forms of the disease, up to 52.7%, whereas in zone I this value was 31.3%, while zone III was characterized by the low rates of extra-articular manifestations, at 11.5% ($P<0.05$). Moreover, the zone II patients in comparison with zone I patients more frequently required hospitalization and ambulant therapy ($P<0.05$). A retrospective study of the genetic aspects of rheumatoid arthritis patients had established the fact that in zone I, 52.14% of the patients' family history was burdened with rheumatoid arthritis (28.6% in zone II and 24.1% in zone III); while in zone II - there was an upward trend in the incidence of the disease among the descendants of the rheumatoid arthritis patients, at 55.4% (27.8% in zone I and 23.1% in zone III). Thus, a comparative analysis demonstrated that the clinical and epidemiological parameters of rheumatoid arthritis were different in all the three areas of Uzbekistan, which did not exclude the probability of the influence of climatic and geographical factors on the course of the rheumatoid arthritis.

Keywords: *rheumatoid arthritis; aggressive joint syndrome; extra-articular manifestations; climatic areas of Uzbekistan.*

Introduction

Rheumatic diseases (RD), in particular rheumatoid arthritis (RA) is one of the most common [1] and serious health as well as social problems, and therefore, is in the spotlight of not only health care managers, but also of physicians themselves. Despite the fact that the prognosis of RA has been constantly improved due to modern therapy, the morbidity and mortality rates remain highly substantial [2].

However, by far, statistics do not reveal the true picture of the morbidity, because they consider mainly only the severe forms of the disease. Now, apparently, the organization of high quality care to the RA patients and preventive measures regarding the disease are impossible

without the knowledge and consideration of the environmental factors and living conditions of the population. This, in turn, demonstrated the need to address the problem of using the experience drawn from many other fields of science, including medicine, ecology, demography, health and epidemiology. Over the recent years, importance is being increasingly paid to the area of residence of the patients, i.e. considering the impact of the climatic and geographical factors on the course of the disease. According to the literature data [2], the course of rheumatoid arthritis depends upon certain environmental factors, which also determines the further disease outcomes [3]. Therefore, studying the influence of environmental factors is becoming increasingly essential to find a solution for the patients' issues, which could help to identify a large group of cause-and-effect relationships, and spatial analysis of epidemiological phenomena [4]. Under the impact of the complex environmental factors, lesions are occurring in various organs and systems, accompanied by functional, morphological and genetic alterations as well, within the whole organism. Deterioration of the disease occurs under the

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simultaneous influence of a myriad climatic and geographical factors, viz., solar radiation, atmospheric circulation and several local climatic features [5].

Currently, Uzbekistan has become the focus of many medical and geographical studies because of the Republic's distinctive geographical location, climatic factors and industrial as well as agricultural development. Moreover, special attention should be paid to the environmental problems in certain areas of the Republic. As it is known, deterioration in nature does not occur immediately or instantly. This process takes a much longer time. In other words, an environmental situation is normally one that is gradually accumulated. Uzbekistan's biggest environmental challenge is the high degree of soil salinity. The real threat is the intensive soil pollution resulting from the various types of industrial and household wastes. One of the major problems is the water resource quality, an issue of the Aral Sea, while another threat for ecological security in the country is air and space pollution. For the Republic of Uzbekistan - located in the arid zone - the presence of large natural sources of atmospheric dust, such as the Kara-Kum and Kyzyl Kum deserts, with frequent dust storms, are characteristic. Therefore, we believe that this study is topical with regard to environmental rheumatology, particularly regarding the problem of RA in the various climatic and geographical zones of Uzbekistan. It is interesting for us to study the features of the development and the course of the RA in association with the environmental factors.

The purpose of this study was based on the comparative analysis of the clinical features of rheumatoid arthritis in a random sample of inhabitants of the various regions of Uzbekistan.

Material and Methods

A comparative analysis was conducted on the basis of a comparison of the clinical, radiological and laboratory findings in patients with RA, living in the different regions of the country. Disease activity and severity of the articular syndrome were determined by the number of tender and swollen joints, DAS (*Disease activity score*) and HAQ (*Health Assessment Questionnaire*) indexes and the evaluation of pain intensity, which were conducted according to VAS (*Visual analog scale*). Also, the following indicators were used for the analysis: the percentage of cases with positive clinical dynamics, the percentage of patients with long-term remission (more than 6 months), the percentage of patients requiring hospitalization, the percentage of frequently admitted patients (2 times or more per month in a year), and the percentage of patients with comorbid conditions.

The study included 360 patients with a valid diagnosis of RA, ranging in age from 20 to 66 years (mean age 51.58 ± 8.2 years), with an illness duration of 9.7 ± 4.8 years.

The studies were conducted in three regions of Uzbekistan, viz., Tashkent city - zone I (n=144), Khorezm region - zone II (n=112) and the Namangan region - zone III (n=104).

In 25% of the patients, the I degree activity of the

pathological process was ascertained; in 50% - II and in 25% - III. The I radiographic stage of RA is set to 9% of cases, II - in 39%, III - in 30.5% and IV - in 19%.

Statistical analysis was performed using the statistical software «Statistica». The mean (M) and standard error of the mean (SEM) were deduced. Analysis of the distribution of values obtained was performed using the Kolmogorov-Smirnov test. For data with normal distribution, significance was assessed using Student's *t*-test corrected for multiple comparisons using Bonferroni criterion. A value of $P < 0.05$ was considered statistically significant.

Results and Discussion

Women were the dominant group among the patients observed, at 336 (93.3%). The disease duration ranged from 4 months to 36 years (mean 9.7 ± 4.8 years). Of these, 75 patients (20.8%) were ill for less than 5 years, 195 (54.2%) from 5 to 10 years, and 90 patients (25%), for more than 10 years. Pharmacological remission was detected in 72 patients (20%); the current activity was being maintained in 288 patients (80%). Disability was detected in the majority (77.8% or 280 patients) of patients and polyarthritis was documented in 355 patients (98.6%). Systemic manifestations were observed in 228 patients (63.3%). In addition to the main complaints, such as pain in the joints (98.6%) and morning stiffness (94.4%), the most frequent complaints were general weakness (62.5%), irritability, sleep and attention disorders (51.7%), restlessness and anxiety (63.9%), and subfebrile temperature (33.3%). Virtually all the patients with RA, regardless of the type of therapy, demonstrated signs of anemia and chronic inflammation.

The prospective studies conducted show that the course of the RA in the three different climatic and geographical zones reveals certain distinctions. Therefore, in zone II, there is certainly a dominance of a rapidly progressive start in 71.4% of the cases (in zone I - 24.3%, zone III - 18.3%). Moreover, as evident from Table 1, a more aggressive joint syndrome is characteristic for the patients in this zone. This trend is confirmed by the average values of the number of swollen and tender joints in zone II patients, and among those of zone I as well, which are higher in number than those in zone III ($P < 0.05$). While discussing the significance of these figures, it must be emphasized that the articular index of 28 joints and the degree of functional impairment of the joints (HAQ, Ritchie index) ended-up being very significant in the patients with RA in zone II in comparison with those in zone I ($P < 0.05$). A comparative analysis of the laboratory and radiological data of the patients in the three zones highlighted some differences, especially in the patients between zones I and II, although the high activity of the disease (by DAS index) is almost the same in those zones, at 72.2% and 80.4%, respectively. However, the development of severe destructive lesions of the joints until the total ankylosing was considerable in zone II, i.e. stage III radiological was detected in 49.1% and stage IV in 26.8% patients, whereas for zone I these figures were 24.3% and 11.8%, respectively. Characterizing the articular syndrome, it should be stated that in the zone III patients,

unlike those in the other zones, the presence of sacroiliitis was predominant in 21.2% of the cases. These experiments allow the determination of the predominant form of RA depending on the residence in a particular climatic zone and geographical area. As the research conducted reveals, in western Uzbekistan (zone II) the visceral form of the disease dominated, at 52.7%; in zone I it was 31.3%, while zone III was characterized by low rates of extra-articular manifestations, i.e. in 11.5% of the cases.

Table 1

The comparative analysis of clinical and laboratory parameters in patients with RA from various regions of Uzbekistan

Indicators	Zone I (n=144)	Zone II (n=112)	Zone III (n=104)
Rheumatoid factor, U/l	105.6±24.3	551±23.5**	93.6±4.5
Stiffness, hours	2.02±1.7	3.9±1.35**	1.01±1.8
Pain, VAS	6.52±1.72 ⁰	7.75±1.52**	3.12±1.22
APJ	13.1±3.7 ⁰	19.3±8.5**	7.72±2.28
ASJ	7.6±1.86 ⁰	14.8±5.58**	4.6±0.67
Ritchie index	7.65±3.03 ⁰	12.55±3.2**	4.54±1.1
VAS	55.32±16.6	67.8±12.1**	33.31±13.2
Activity (Astapenko & Otto)	1.34±0.09	2.21±0.12**	0.77±0.24
Activity, SDAI	43.07±9.3	66.26±13.6**	35.06±7.46
HAQ	10.5±5.4	15.0±2.6**	7.5±1.94
CRP, mg/l	14.8±5.8 ⁰	27.9±8.43**	7.07±0.1
ESR, mm/hour	30.3±14.67	31.4±13.69	29.3±12.67

*- $p < 0.05$ between zones II and I; ⁰- $p < 0.05$ between zones I and III; ** - $p < 0.05$ between zones II and III. APJ – an amount of painful joints; ASJ – an amount of swollen joints; SDAI- the simplified disease activity index.

On comparison of these zones by assessing the extra-articular manifestations (Table 2), it is important to note that there is an increase of nearly 4 times in the occurrence of systemic vasculitis, polyneuropathy and lymphadenopathy in zone II when compared with zone I ($P < 0.05$), which is apparently connected with the presence of more environmental hazards in the Khorezm region.

Table 2

Comparative data on extra-articular manifestations of RA in various regions (results are shown in percentage)

Extra-articular manifestations	Zone I (n=144)	Zone II (n=112)	Zone III (n=104)
Rheumatoid nodules	33.4 ⁰	22.3**	8.7
Generalized amyotrophy	47.9 ⁰	55.4**	9.6
Lymphadenopathy	14.9*	61.6**	10.6
Subfebrile fever	37.5 ⁰	58.9**	0
Hepatosplenomegaly	7.6	11.6	9.6
Sensitive polyneuropathy	8.3 ⁰ *	32.1**	0
Systemic vasculitis	6.3 ⁰ *	25.9**	0
Pleuritis (exudative)	0	0.9	0
Lung lesions	0.7	2.7	0
Kidney lesions	4.2 ⁰	6.3**	1.9
Heart lesions	10.4	8.9	7.7
Sjogren syndrome	1.4*	5.4**	0
Still's syndrome	3.5	5.4**	0.9

*- $p < 0.05$ between zones II and I; ⁰- $p < 0.05$ between zones I and III; ** - $p < 0.05$ between zones II and III.

As far as the other extra-articular manifestations, such as subfebrile fever, weight loss, amyotrophy around the affected joints, the presence of rheumatoid nodes, heart disease, kidney disease, and other relevant significant differences between zones I and II, they were absent. The rheumatoid factor (especially with high titer) is of high diagnostic value, as its presence is the predictor of the systemic lesions in RA, because a significant majority of the seropositive patients, are from the western region-zone II (Table 1).

Valuable data on the predisposing factors among those patients with RA were extracted, as in zone I, and the rates of psycho-emotional stress were significantly more frequent, at 45.8% (9.6 % in zone II and 7.7 % in zone III), whereas the physical exertion figure was at 35.7% in zone II (10.4% in zone I and 8.7% in zone III). In turn, among the factors predisposing towards the development of the disease in zone III, hypothermia and acute respiratory infections were the dominant ones, at 66.3% (30.6 % in zone I and 26.8 % in zone II).

By studying certain indicators, it has been revealed, as seen in Table 3, that among the zone II patients, the dominant factors were, the frequency of the need for hospitalization treatment, frequent visits to a doctor regarding the problems associated with the disease during one year, while in this region the long-term remission rates were low in comparison with the other zones. Besides, zone II dominated with such parameters as a tendency towards progression of the disease over the past three years (82.1%), and the manifestation of the disease at an early age, in 57.4% of the cases. In turn, zone III distinguished itself by the relatively low (positive) figures compared with the other zones.

However, the data presented in Table 3 shows that in all the zones, in most patients, the manifestation of the disease was characterized by a gradual deterioration of the patient's condition against the background of accompanying diseases.

Table 3

Comparative data of indicators in patients with RA from various regions (results are shown in percentage)

Indicators	Zone I (n=144)	Zone II (n=112)	Zone III (n=104)
Positive clinical changes	61.1	26.7**	56.7
Long-term remission	40.3* ⁰	18.8**	59.6
Need hospitalization	31.3	50.0**	20.2
Frequently visiting a doctor	40.9 ⁰	68.8**	27.9
Co-morbid conditions	61.1	67	52.9

*- $p < 0.05$ between zones II and I; ⁰- $p < 0.05$ between zones I and III; ** - $p < 0.05$ between zones II and III.

A retrospective study of the genetic aspects of RA patients had established the fact that in zone I, 52.14% of the patients' family history was burdened with rheumatoid arthritis (28.6% in zone II and 24.1% in zone III); while in zone II - there was an upward trend in the incidence of the disease among the descendants of the rheumatoid arthritis patients, at 55.4% (27.8% in zone I and 23.1% in zone III).

Conclusion

In conclusion, the retrospective analysis demonstrated that the clinical and epidemiological parameters of RA are different in all the three areas of Uzbekistan, which did not exclude the probability of the influence of climatic and geographical factors on the course of the disease. The comparative analysis of the genetically-effect relationships in the three zones of Uzbekistan allows the inclusion of the significant role played by the genetic alterations in the human organism due to environmental factors. The facts mentioned above call for a more focused and detailed study of the influence of the environmental factors on the development and progression of RA, which enables outlining the many possible ways to influence the progress of the disease, i.e. to develop a more rational basis for providing adequate therapies in order to improve the course of the disease and thus enhance the patient's quality of life.

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