(RESEARCH ARTICLE)

Updates and perspectives on the genetic markers in Rheumatoid Arthritis

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Abstract

The research was carried out on a representative group of patients diagnosed with rheumatoid arthritis (RA). We studied the distribution of patients by sex, age group, and disease stage, and we also tried to identify a genetic marker. In this sense, the blood groups of all RA patients were determined. In the study group, the frequency of patients with blood group B was much increased (47%), compared to the frequency of patients with blood group B in the control group (12%). Calculating the relative risk Rr for the disease, of the patients with blood group B, we found that it was 6.5, which indicated a positive association between RA and the blood group B marker. As a result, individuals belonging to blood group B are much more susceptible to RA compared to those who belong to other blood groups. Another genetic aspect of the research was the familial genetic study of RA. Using the family investigation as a method of investigation, we found that the incidence of family cases of RA in the studied group was 13%. RA, being a condition with the polygenic hereditary transmission, it is difficult to calculate the risk of recurrence, however, we found that, in affected families, the genes with "risk" for RA are much more frequent than in families where they were not observed, in the direct or collateral ancestry, other subjects diagnosed with RA. These observations are of particular importance in the prophylaxis of this condition.

Keywords: Genetic markers; Rheumatoid arthritis; Blood group; Genetic susceptibility

1. Introduction

Rheumatoid Arthritis (RA) is an autoimmune systemic disease of inflammatory type, that affects approximately 0.5 to 1% of the general population [1, 2]. The cause of RA is unknown [3]. At present, it is admitted that it is a multifactorial determined condition, in which both genetic and environmental factors are involved [4].

The genetic component with a different weight in each individual is represented by the predisposition to this condition [5, 6]. Genetic factors are represented by several risk genes, with minor but additive effects, individuals prone to RA inherit several "risk" genes that, under certain environmental conditions, can turn the predisposition into disease [7-9].

The fact that RA has a hereditary component is proved by the familial character of the disease and by the higher incidence in monozygotic twins (who have identical heredities) [10, 11].

Another argument is the increased risk of RA in individuals with serotypes HLA-DR4 and HLA-DR1 compared to other serotypes that do not develop RA [12-14].

The genetic predisposing field can also be searched by researching the genetic markers of blood group Rh, MNSs, etc [15].

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In this research, we aimed to investigate the families of patients with RA to detect the existence of a hereditary predisposing field, as well as the analysis of the possibility of involvement of a certain blood group as a marker of genetic susceptibility to RA.

2. Material and methods

The study was performed on a representative group of 100 Caucasian patients, of Romanian nationality, diagnosed with RA in stages I, II, and III of the disease. The diagnosis of RA was made based on clinical, radiological, and laboratory examinations. Serum values of various types of immunoglobulins and rheumatoid factor (RF) were determined using the following methods:

- Mancini's test (simple radial immunodiffusion method) - used to determine plasma immunoglobulins;
- Waaler-Rose reaction - used to determine the RF.

In this investigation we followed:

o Age, sex, onset, stage of the disease;
o The association of RA with a genetic marker - ABO group antigens;
o The genetic susceptibility;
o The hereditary-collateral antecedents.

3. Results and discussion

The investigated group includes 74 women and 26 men with RA in stages 1, 2, and 3 of the disease (American College of Rheumatology standardization).

- 13 patients (11 women and 2 men) were diagnosed with RA stage 1 (early RA). These patients lacked specific RA radiological lesions.
- 60 patients (49 women and 11 men) were diagnosed with RA stage 2 (moderate RA). These patients showed radiographic lesions of osteoporosis, but without bone deformities.
- 27 patients (15 women and 12 men) were diagnosed with RA stage 3 (severe RA). These patients showed bone and cartilage lesions with obvious osteoporosis, joint deformities (ulnar deviation), and muscular atrophy.

The investigated patients ranged in age from 20 to 82 years. Regarding the age of patients affected by RA, there is an increased number of those aged 40-60 years in women and 50-60 years old in men. Most cases of RA were in women, RA being about three times more common in women compared to men.

The distribution of RA by stages of the disease highlights stage 2 as the most frequently diagnosed, followed by patients with RA in stage 3 of the disease (Table 1).

Table 1 RA distribution by age, stages, and seronegative/seropositive RA tests

Age interval	RA Stage 1				RA Stage 2				RA Stage 3			
	women		men		women		men		women		men	
	SN	SP	SN	SP	SN	SP	SN	SP	SN	SP	SN	SP
20-29	-	1	-	-	-	1	-	1	-	-	-	-
30-39	1	1	-	1	3	7	2	1	1	3	-	-
40-49	-	2	-	-	11	7	-	1	1	1	-	1
50-59	2	1	-	1	3	10	1	2	2	1	1	8
60-69	-	2	-	-	2	3	1	1	-	3	-	-

SN - seronegative; SP – seropositive

To highlight the association with a genetic marker, we determined the blood group of patients with RA, which we compared with a control group (Table 2).

Table 2 Frequency of the ABO blood group marker in RA patients compared to the control group

Group	A=blood group	B= blood group	0= blood group	AB= blood group
RA	35.7	47.6	9.5	7.2
Control	40.6	12.2	39.0	8.2

Analyzing these results, we find an increased frequency of patients with RA belonging to the B blood group.

In order to evaluate the intervention of some genetic factors in the etiopathogenesis of RA, we resorted to the association of a normal monofactorial character (ABO blood group) with a multifactorial pathological one (RA). In this way, "suspicious loci" which contribute to the genetic susceptibility of the disease, can be identified and expressed by the relative risk of disease (Rr):

Rr > 1 indicates a positive association
Rr <1 indicates a negative association

The relative risk is expressed using the formula:

$$Rr = (P \times c) / (p \times C)$$

Where;

P = number of patients (with RA) in which the chosen marker is present
p = number of patients (with RA) in whom the marker is missing
C = number of witnesses in which the chosen marker is present
c = number of witnesses in which the chosen marker is missing

The marker we chose was blood group B, which occurs with an increased frequency among those with RA.

For the studied group we have:

P = 47
p = 53
C = 12
c = 88

$$Rr = (47 \times 88) / (53 \times 12) = 6.5$$

This specifies that people with blood group B are approximately 6.5 times more susceptible to RA, compared to people with another blood group.

The gene for antigen B is placed on chromosome 9q34 and can be considered as the gene that contributes to the genetic predisposition for RA, along with genes from the HLA system (HLA-DR1, and HLA-DR4) and others, as "risk genes" [16].

Regarding the hereditary-collateral antecedents of the analyzed patients, we found that in 13 situations and other family members were affected by RA (Table 3).

In 11 cases was affected the mother of the proband and in 2 cases was affected the father of the proband. In 6 cases we found RA patients among siblings, in 4 cases we found affected maternal or paternal grandparents and in 7 families we found affected collateral relatives (cousins, aunts, uncles).

The heredo-collateral antecedents in the 13 families suggest that they concentrate more "risk" genes than the other 77 families in which no other cases of RA have been reported and that certain favorable environmental conditions may transform the genetic predisposition to RA in the disease, confirming the multifactorial polygenic determinism of this disease.

Table 3 The heredo-collateral antecedents in patients with RA

No.	Case	Age interval	Gender	Parents		Brothers/ Sisters	Grandparents	Other relatives
				Mother	Father			
1	AB	30-39	B	+	-	-	-	cousin
2	BC	60-69	w	+	-	-	maternal grandmother	-
3	CD	30-39	w	-	-	2 sisters	-	-
4	DE	60-69	w	+	-	-	-	Uncle
5	EF	50-59	m	+	-	1 sister	-	-
6	FG	60-69	w	-	+	-	-	cousin
7	GH	30-39	m	+	-	-	maternal grandmother	aunt
8	HI	30-39	m	+	-	1 sister	-	-
9	IJ	40-49	w	+	-	1 sister	-	-
10	JK	60-69	w	+	-	-	maternal grandmother	cousin
11	KL	60-69	w	+	-	1 brother	-	-
12	LM	30-39	m	-	+	-	paternal grandfather	aunt
13	MN	30-39	m	-	-	1 sister	-	cousin

w – woman; m – male

4. Conclusion

RA is a disease that presupposes the existence of a hereditary predisposition that causes a certain immune response to an unusual antigenic stimulation, probably of an infectious nature.

Genetic predisposition to RA can be demonstrated by:

- The existence of family forms in 13% of cases;
- Hereditary polygenic transmission with a degree of heritability of approximately 60-70%;
- The association between RA and blood group marker (Rr = 6.5).

In conclusion, the results of this investigation have both theoretical and especially practical importance, because it facilitates the early diagnosis of the disease, allows the identification of subjects at high risk of disease, especially in families where there is already a proband and, through it, an evaluation of the prognosis of the disease and the prevention measures that are required in each given situation.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest.

Statement of informed consent

Informed consent was obtained from the patient included in the study.

Authors' contributions

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