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Original article

Relapsing polychondritis: prevalence of cardiovascular diseases and its risk factors, and general disease features according to gender

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ABSTRACT

The comorbidities in relapsing polychondritis have been scarcely described in the literature. Moreover, apart from a few relapsing polychondritis epidemiological studies, no studies specifically addressing relapsing polychondritis distribution according to gender are available. Therefore, the objectives of the present study were: (a) to analyze the prevalence of cardiovascular diseases and its risk factors in a series of patients with relapsing polychondritis; (b) to determine the influence of gender on relapsing polychondritis. A cross-sectional tertiary single center study evaluating 30 relapsing polychondritis cases from 1990 to 2016 was carried out. To compare comorbidities, 60 healthy individuals matched for age-, gender-, ethnicity- and body mass index were recruited. The mean age of relapsing polychondritis patients was 49.0 ± 12.4 years, the median disease duration 6.0 years, and 70% were women. A higher frequency of arterial hypertension (53.3% *vs.* 23.3%; $p = 0.008$) and diabetes mellitus (16.7% *vs.* 3.3%; $p = 0.039$) was found in the relapsing polychondritis group, compared to the control group. As an additional analysis, patients were compared according to gender distribution (9 men *vs.* 21 women). The clinical disease onset features were comparable in both genders. However, over the follow-up period, male patients had a greater prevalence of hearing loss, vestibular disorder and uveitis events, and also received more cyclophosphamide therapy ($p < 0.05$). There was a high prevalence of arterial hypertension and diabetes mellitus, and the male patients seemed to have worse prognosis than the female patients in the follow up.

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Policondrite recidivante: prevalência de doenças cardiovasculares e seus fatores de risco e características gerais da doença de acordo com o gênero

Palavras-chave:
Doença autoimune
Doenças cardiovasculares
Gênero
Policondrite recidivante

RESUMO

Há escassez de estudos na literatura sobre as comorbidades na policondrite recidivante. Além disso, exceto por alguns estudos epidemiológicos sobre a policondrite recidivante, não existem trabalhos que analisem especificamente a distribuição da policondrite recidivante de acordo com o gênero. Portanto, os objetivos do presente estudo foram: (a) analisar a prevalência de doenças cardiovasculares e seus fatores de risco em uma série de pacientes com policondrite recidivante; (B) determinar a influência do gênero na policondrite recidivante. Fez-se um estudo transversal unicêntrico que avaliou 30 casos de policondrite recidivante entre 1990 e 2016. Para comparar as comorbidades, foram recrutados 60 indivíduos saudáveis pareados por idade, gênero, etnia e índice de massa corporal. A idade média dos pacientes com policondrite recidivante foi de 49,0 ± 12,4 anos. A duração média da doença foi de 6,0 anos e 70% eram mulheres. Foi observada uma maior frequência de hipertensão arterial (53,3% *vs.* 23,3%, p = 0,008) e *diabetes mellitus* (16,7% *vs.* 3,3%; p = 0,039) no grupo policondrite recidivante em comparação com o grupo controle. Em uma análise adicional, os pacientes foram comparados de acordo com a distribuição de gênero (nove homens *versus* 21 mulheres). As características clínicas iniciais da doença foram comparáveis em ambos os sexos. No entanto, durante o período de seguimento, os pacientes do sexo masculino tiveram maior prevalência de perda auditiva, envolvimento vestibular e eventos de uveíte e também receberam mais tratamento com ciclofosfamida (p < 0,05). Houve uma alta prevalência de hipertensão arterial e *diabetes mellitus* e os pacientes do sexo masculino apresentaram pior prognóstico do que as pacientes do sexo feminino no seguimento.

Introduction

Relapsing polychondritis (RP) is a rare systemic autoimmune disease characterized by recurrent inflammation of cartilaginous structures (*i.e.*: ears, nasal bridge, peripheral articulations and tracheobronchial tree) and/or tissues with high proteoglycan concentrations (*i.e.*: eyes, heart, kidneys and blood vessels).[1–3] Systemic manifestations can also involve the eyes, skin, joints, heart valves and blood vessels.[1,2]

RP has an annual incidence around of 3.5 cases per million, and affects all ethnic groups, but a predominate white population.[4,5] The female to male ratio is 0.7–2.9:1[6–13] and disease onset occurs typically in the fourth and fifth decades.[14]

The few RP epidemiological studies conducted to date showed that the most prevalent RP clinical symptoms are auricular chondritis (65–98% of cases) followed by peripheral arthritis (36–81%) and nasal chondritis (29–54%).[6–13] Mortality in RP is more than twice of the general population and the most frequent causes of death are respiratory disease, heart conditions and cancer.[11]

However, the comorbidities in RP have been scarcely described in the literature. Notably, there is currently only one prospective cohort study, reporting the incidence of cardiovascular diseases and their risk factors (coronary heart disease, stroke and diabetes mellitus) in a series of 117 patients with RP.[11] However, the authors did not specifically describe the prevalence of these comorbidities.

Moreover, expect for a few RP epidemiological studies,[6–13] no studies specifically addressing RP distribution according to gender are available. Therefore, the objectives of the present study were: (a) to analyze the prevalence of cardiovascular diseases and its risk factors in a series of patients with RP; (b) to determine the influence of gender on RP.

Materials and methods

The present study is a single center retrospective cohort that included 30 consecutive patients with RP. To improve the homogeneity of the sample under study, we include only patients followed up at our tertiary service from April 1990 to April 2016.

All patients met at least three of the 6 criteria established by McAdam et al.[6] Patients with age <18 years, overlapping syndrome, cancer or infections were excluded.

The study was approved by the local Ethics Committee.

Demographics data (age at onset of symptoms and diagnosis of RP, gender), clinical manifestations including fever, fatigue, nasal involvement (saddle nose), auricular chondritis, hearing loss, ocular problems (uveitis, episcleritis, scleritis, keratitis or conjunctivitis), vestibular disorder, articular (arthralgia or arthritis), neurological disorder (mainly optic neuropathy, headache, seizures, hemiplegia, organic brain syndrome, aseptic meningitis, meningoencephalitis or cerebral aneurysms), costochondritis, subglottic stenosis, laryngotracheitis, cardiac disorder (mitral or aortic valve diseases), renal involvement (glomerulonephritis), body mass index, weight, disease duration, and laboratory data were obtained from a systematic review of the medical records.

The clinical and laboratory manifestations considered were those presenting at disease onset and during follow-up

(cumulative manifestations). Data on body mass index and weight were obtained at the last outpatient visit.

The patients were initially treated with glucocorticoid (prednisone 0.5–1.0 mg/kg/day) with subsequent tapering of the dose according to clinical and laboratory stability. In the case of severe manifestations (*i.e.*: acute hearing loss, uveitis, scleritis, vestibular disorder, neurological disorder, subglottic stenosis, laryngotracheitis), pulse therapy with methylprednisolone (1 g/day for three consecutive days) was administered. For glucocorticoid tapering, different immunosuppressives were used, alone or in combination therapy, azathioprine (2–3 mg/kg/day), methotrexate (20–25 mg/week), cyclosporine (2–4 mg/kg/day), mycophenolate mofetil (2–3 g/day), leflunomide (20 mg/day), dapsone (100 mg/day), thalidomide (50–100 mg/day), cyclophosphamide (0.5–1.0 g/m^2 of body surface area), intravenous human immunoglobulin (1 g/kg/day, during two consecutive days) or biological (tocilizumab 8 mg/kg, every 4 weeks; abatacept 500–1000 mg at weeks 0, 2 and 4, then every 4 weeks) and non-steroidal anti-inflammatory. Drugs used throughout the course of the disease, as well as those prescribed in the last outpatient visit of each patient, were evaluated.

RP disease status was established under three groups, based the last outpatient visit: (a) RP disease activity was defined as the presence of any symptoms and/or signs associated with RP, after exclusion of infections and/or neoplastic causes, and of patients using immunosuppressives and glucocorticoid; (b) RP disease remission was defined as no symptoms either signs associated to RP and without glucocorticoid/immunosuppressives preceding six consecutive months; (c) RP disease controlled was defined as patients with no symptoms or signs associated with RP, but using immunosuppressives and tapering glucocorticoid.

Surgical intervention (tracheotomy, cochlear implant) for RP and mortality were also evaluated.

The following conditions were evaluated: (a) the cardiovascular diseases (acute myocardial infarction, stroke and congestive heart failure), and (b) cardiovascular risk factors (arterial hypertension, type 2 diabetes mellitus, dyslipidemia, smoking).

Dyslipidemia was defined as plasma total cholesterol >200 mg/dL, HDL-cholesterol <40 mg/dL (male) or <50 mg/dL (female), LDL-cholesterol >130 mg/dL, triglycerides >150 mg/dL or drug treatment for evaluated LDL-cholesterol or triglycerides.[14] Arterial hypertension was established when the patients were receiving antihypertensive medication or when systolic pressure was ≥140 mmHg and/or diastolic pressure was ≥90 mmHg. Diabetes mellitus was based on the results of plasma glucose measurement.[15]

To assess the prevalence of comorbidities in patients with RP, 60 consecutive healthy subjects (control group) were included. Controls were recruited from April 2013 to April 2016, and matched for age, sex and body mass index (BMI) (kg/m^2) at RP disease onset.

Statistical analysis

The Kolmogorov–Smirnov test was used to evaluate the distribution of each parameter. The data were expressed as a mean ± standard deviation or median (25th–75th interquartile) for continuous variables or as frequencies (%) for categorical variables. The median (25th–75th interquartile) was calculated for continuous variables not normally distributed. Comparisons between the patients and the controls and between the patients (female vs. male) were made using Student's t-test or the Mann–Whitney test for continuous variables. Pearson's chi-squared test or Fisher's exact test was used to evaluate the categorical variables. The measurements were expressed as an odds ratio (OR) with 95% confidence interval (CI). Values of $p < 0.05$ were considered significant. All of the analyses were performed with the SPSS 15.0 statistics software (Chicago, USA).

Results

Initially a total of 30 consecutive patients with RP were compared with 60 healthy individuals (Table 1). As expected, current age, gender, ethnicity and BMI were comparable between both groups ($p > 0.05$). However, the average BMI in patients with RP was 28.0 kg/m^2 and, therefore, they were overweight. The median RP disease duration was 6.0 (2.8–15.0) years.

There was higher prevalence of arterial hypertension (53.3% *vs.* 23.3%; $p = 0.008$, respectively) and diabetes mellitus (16.7% *vs.* 3.3%; $p = 0.039$) in patients with RP, when compared to controls. The dyslipidemia and smoking distribution were similar in both groups, whereas heart failure was found only in patients with RP. There were no cases of myocardial infarction or stroke events in either of the groups.

On multivariate analysis, after adjusting for gender, age and BMI, both arterial hypertension (OR 5.45; 95% CI 1.72–17.28) and diabetes mellitus (OR 6.67; 95% CI 1.12–39.89) were associated with RP.

Table 1 – General features and comorbidities of patients with relapsing polychondritis and healthy individuals (control).

Parameters	RP ($n = 30$)	Control ($n = 60$)	p
Current age (years)	49.0 ± 12.4	48.1 ± 11.3	0.753
Age at disease onset (years)	40.9 ± 12.4	–	–
Disease duration (years)	6.0 (2.8–15.0)	–	–
Female gender	21 (70.0)	42 (70.0)	1.000
White ethnicity	29 (96.7)	58 (96.7)	1.000
Body mass index (kg/m^2)	28.0 ± 4.9	27.4 ± 5.2	0.623
Weight (kg)	72.4 ± 15.3	72.9 ± 16.2	0.893
Comorbidities			
Arterial hypertension	16 (53.3)	14 (23.3)	0.008
Diabetes mellitus	5 (16.7)	2 (3.3)	0.039
Dyslipidemia	16 (53.3)	26 (43.3)	0.382
Cardiac insufficiency	1 (3.2)	0	–
Myocardial infarction	0	0	1.000
Stroke	0	0	1.000

RP, relapsing polychondritis.
Results expressed as percentage (%), mean ± standard deviation, median (25th–75th interquartile range).

As an additional analysis, patients with RP were compared according to gender distribution (9 men *vs.* 21 women) as shown in Table 2.

Current patient age, age at disease onset, time between diagnosis and symptom onset, and disease duration were comparable between the gender groups. All initial clinical manifestations were also similar in the RP and control groups. However, for follow up clinical manifestations, there was a higher prevalence of hearing loss, vestibular disorders and uveitis in males, compared to females.

On univariate analysis, after adjusting for gender, age and BMI, the hearing loss (OR 11.76; 95% CI 1.84–76.12), uveitis (OR 15.16; 95% CI 2.20–104.83) and vestibular disorder (14.70; 95% CI 1.59–136.14) were more frequently associated with RP in male patients than female patients.

Concerning cumulative treatment, there was a greater tendency for methylprednisolone pulse therapy in male, compared to female patients with RP (55.6% *vs.* 19.0%; $p = 0.082$) (Table 3). Male patients use significantly more cyclophosphamide than female patients (66.7% *vs.* 23.8%; $p = 0.042$). Use of other immunosuppressives was comparable in the male and female groups ($p > 0.05$). Moreover, there was no statistical different in current treatment (glucocorticoid and immunosuppressives) between the two groups.

Surgical cochlear implant procedures were performed in 2 (22.2%) male patients with RP, whereas tracheotomy was carried out in 1 (11.1%) male and 4 (19.0%) female patients during the follow up (Table 4).

Disease status, remission, activity and control were equally distributed between genders.

Table 2 – General features and clinical manifestations of patients with relapsing polychondritis, according to gender.

Parameters	RP Total ($n = 30$)	RP Male ($n = 9$)	RP Female ($n = 21$)	p
Current age (years)	49.0 ± 12.4	46.9 ± 16.6	49.9 ± 10.4	0.629
Age at disease onset (years)	40.9 ± 12.4	38.1 ± 13.0	42.1 ± 12.3	0.283
Diagnosis – symptoms (months)	6 (4–21)	4 (2–16)	7 (5–24)	0.085
Disease duration (years)	6.0 (2.8–15.0)	5.0 (3.0–9.0)	8.0 (2.0–17.0)	0.563
Initial clinical manifestations				
Fever	10 (33.3)	5 (55.6)	5 (23.8)	0.104
Fatigue	15 (50.0)	6 (66.7)	9 (42.9)	0.427
Auricular chondritis	30 (100.0)	9 (100.0)	21 (100.0)	1.000
Hearing loss	3 (10.0)	1 (11.1)	2 (9.5)	1.000
Vestibular disorder	0	0	0	1.000
Septum nasal chondrites	3 (10.0)	0	3 (14.3)	0.534
Laryngotracheitis	1 (3.3)	0	1 (4.8)	1.000
Subglottic stenosis	1 (3.3)	0	1 (4.8)	1.000
Bronchitis	1 (3.3)	1 (11.1)	0	0.300
Episcleritis	2 (6.7)	1 (11.1)	1 (4.8)	0.517
Uveitis	3 (10.0)	1 (11.1)	2 (9.5)	1.000
Costochondritis	2 (6.7)	0	2 (9.5)	1.000
Arthralgia	5 (16.7)	1 (11.1)	4 (19.0)	1.000
Arthritis	6 (20.0)	2 (22.2)	4 (19.0)	1.000
Cardiac disorder	0	0	0	1.000
Renal disorder	0	0	0	1.000
Neurological disorder	1 (3.3)	1 (11.1)	0	0.300
Follow up clinical manifestations				
Auricular chondritis	28 (93.3)	8 (88.9)	20 (95.2)	0.517
Hearing losing	9 (30.0)	6 (66.7)	3 (14.3)	0.008
Vestibular disorder	7 (23.3)	5 (55.6)	2 (9.5)	0.014
Nasal bridge	3 (10.0)	1 (11.1)	2 (9.5)	1.000
Tracheitis	8 (26.7)	3 (33.3)	5 (23.8)	0.666
Subglottic stenosis	4 (13.3)	1 (11.1)	3 (14.3)	1.000
Bronchitis	5 (16.7)	2 (22.2)	3 (14.3)	1.000
Episcleritis	5 (16.7)	4 (44.4)	3 (14.3)	1.000
Uveitis	11 (36.7)	7 (77.8)	4 (9.0)	0.004
Costochondritis	6 (20.0)	2 (22.2)	4 (19.0)	1.000
Arthralgia	18 (60.0)	6 (66.7)	12 (57.1)	0.704
Arthritis	11 (36.7)	4 (44.4)	7 (33.3)	0.687
Cardiac disorder	1 (3.3)	0	1 (4.8)	1.000
Renal disorder	0	0	0	1.000
Neurological disorder	4 (13.3)	2 (22.2)	2 (9.5)	0.563

RP, relapsing polychondritis.
Results expressed as percentage (%), mean ± standard deviation, median (25th–75th interquartile range).

Table 3 – Previous (cumulative) and current treatment of patients with relapsing polychondritis, according to gender.

Parameters	RP Total (*n* = 30)	RP Male (*n* = 9)	RP Female (*n* = 21)	*p*
Previous treatment				
Pulse therapy with MP	9 (30.0)	5 (55.6)	4 (19.0)	0.082
Prednisone	24 (80.0)	8 (88.9)	16 (76.2)	0.637
Cyclophosphamide	11 (36.7)	6 (66.7)	5 (23.8)	0.042
Azathioprine	14 (46.7)	6 (66.7)	8 (38.1)	0.236
Methotrexate	25 (83.3)	7 (77.8)	18 (85.7)	0.622
Cyclosporine	3 (10.0)	2 (22.2)	1 (4.8)	0.207
Mycophenolate mofetil	6 (20.0)	3 (33.3)	3 (14.3)	0.329
Leflunomide	1 (3.3)	1 (11.1)	0	0.300
Dapsone	2 (6.7)	0	2 (9.5)	1.000
NHAI	18 (60.0)	8 (88.9)	10 (47.6)	0.490
Talidomide	2 (6.7)	1 (11.1)	1 (4.8)	0.517
IVIg	4 (13.3)	2 (22.2)	2 (9.5)	0.563
Biological	5 (16.7)	2 (22.2)	3 (14.3)	0.622
Current treatment prednisone				
Current use	8 (26.7)	3 (33.3)	5 (23.8)	0.666
Dose (mg/day)	15.0 (8.2–20.0)	15 (15–20)	10 (6–30)	0.571
Immunosuppressives				
None	14 (46.7)	3 (33.3)	11 (52.4)	0.440
One	15 (50.0)	6 (66.7)	9 (42.9)	0.427
Two	1 (3.2)	0	1 (3.2)	–

IVIg, intravenous human immunoglobulin; MP, methylprednisolone; RP, relapsing polychondritis.
Results expressed as percentage (%), median (25th–75th interquartile range).

There was no statistical difference in cardiovascular disease and its risk factors distribution according to gender. The most common parameters in men were arterial hypertension and dyslipidemia, followed by diabetes mellitus and myocardial infarction, heart failure, and smoking. Among women, the most common parameters were arterial hypertension and dyslipidemia, following by diabetes mellitus and myocardial infarction, and smoking.

There were no cases of stroke or mortality in either of the groups.

Discussion

In the present study, a high prevalence of arterial hypertension and diabetes mellitus were observed in patients with RP. Moreover, the male patients appeared to have a worse prognosis than female patients in the follow up.

Although RP is a rare disease, we performed an analysis in a sample of 30 consecutive patients with defined RP. The patients were recruited from a single center, reducing inter-examiner follow-up variability. In addition, to evaluate the prevalence of cardiovascular disease and its risk factors, patients were matched with 60 healthy individuals for age, gender and body mass index.

The mean age of patients at disease onset was 49 years, comparable to patient age in the majority of other studies,[7–13] but contrasting with the studies of McAdam et al.[6] and Hazra et al.[11] that reported mean ages of 44 and 55 years, respectively (Table 5).

Although most studies show that RP affect both genders similarly,[6–9] our results found that RP predominantly affected women. Ethnicity distribution in RP remains controversial. Although RP affects all racial groups equally, some series studies have found predominance in the white population.[1] Our results corroborated this finding.

In the present study, no cases of myocardial infarction or stroke were found. However, there was a high prevalence of arterial hypertension and diabetes mellitus. In these conditions, the causes can be multi-factorial (*i.e.*: associated with RP, smoking and/or chronic use of drugs, particularly glucocorticoid). In fact, previous studies have shown that patients with chronic inflammatory rheumatic conditions, such as systemic lupus erythematosus, rheumatoid arthritis, spondyloarthritis (psoriatic arthritis and ankylosing spondylitis), inflammatory myopathies and juvenile idiopathic arthritis, are at increased risk of developing premature cardiovascular disease.[16–25]

The most common initial clinical manifestation of RP is the auricular condritis,[6–13] coinciding with our study, found in all patients without difference between genders. Of note, auricular chondritis could be mistaken by an infectious etiology or trauma. Other clinical manifestations are highly variable, in other series of case and our study found: nasal condritis, arthralgia with/without synovitis, laryngotracheitis, ocular inflammation. And the less common findings were: cardiac, renal and neurological involvement.[6–13]

In additional analysis, clinical course of the RP and theirs comorbities were evaluated, according to gender distribution. In our observation, male gender had worse prognosis when compared to female gender, with high prevalence of uveitis, hearing loss and vestibular disorder (55.6%). To corroborate these data, the male group had tendency to receive more

Table 4 – Surgery, disease status and comorbidities in patients with relapsing polychondritis, according to gender.

Parameters	RP Total (n = 30)	RP Male (n = 9)	RP Female (n = 21)	p
Surgery				
Cochlear implant	2 (6.6)	2 (22.2)	0	–
Tracheostomy	5 (16.7)	1 (11.1)	4 (19.0)	1.000
Disease status				
Remission	14 (46.7)	3 (33.3)	11 (52.4)	0.440
Activity	8 (26.7)	3 (33.3)	5 (23.8)	0.666
Controlled	8 (26.7)	3 (33.3)	5 (23.8)	0.666
Comorbidities				
Arterial hypertension	16 (53.3)	5 (55.6)	11 (52.4)	1.000
Dyslipidemia	16 (53.3)	5 (55.6)	11 (52.4)	1.000
Diabetes mellitus	5 (16.7)	2 (22.2)	3 (14.3)	0.622
Heart failure	1 (3.2)	1 (11.1)	0	1.000
Myocardial infarction	0	2 (22.2)	3 (14.3)	0.622
Stroke	0	0	0	1.000
Mortality	0	0	0	1.000

RP, relapsing polychondritis.
Results expressed as percentage (%).

Table 5 – Epidemiological studies analysing relapsing polychondritis.

	Authors [references]								
	Current study	McAdam et al.[6]	Michet et al.[7]	Chang-Miller et al.[8]	Zeuner et al.[9]	Trentham et al.[10]	Hazra et al.[11]	Lin et al.[12]	Shimizu et al.[13]
Year	2016	1976	1986	1987	1997	1998	2015	2015	2016
Study	Brazil	USA	USA	USA	German	USA	UK	China	Japan
Cases	30	159	112	129	62	66	106	158	239
Ratio (female:male)	2.3:1	0.9:1	1.0:1	1.0:1	0.7:1	2.9:1	NR	0.7:1	1.1:1
Age at disease diagnosis (years)	41	44	51	50	46.6	46	55	45.3	52.7
Auricular chondritis (%)		89	85	84	94	95	70	68	78
Auditory deficiency (%)		46	30	NR	19	42	NR	25	NR
Arthritis (%)		81	52	53	53	85	36	56	NR
Laryngotracheal involvement (%)		56	48	44	31	67	12	69	50
Eye inflammation (%)		65	51	51	50	57	20	44	NR
Cardiovascular involvement (%)		9	6	3.9	23	8	NR	10	7.1
Renal involvement (%)		NR	26	23	7	9	NR	3	NR
Nervous system involvement (%)		NR	NR	NR	8	8	NR	12	12
Cutaneous involvement (%)		17	28	NR	25	38	12	46	14

methyprednisolone pulse therapy and also received more cyclophosphamide pulses.

Conductive hearing loss develops in up to 46% of patients and sensorineural hearing loss and vestibular dysfunction may occur. It could be secondary to cartilage destruction with closure of the external auditory meatus, serous otitis media or eustachian tube obstruction, or serous otitis media.[4,26,27]

The etiology of sensorineural hearing loss and vestibular dysfunction may be due to conductive hearing loss, to vasculitis of the branches of the internal auditory artery[28] or to autoantibodies against labyrinthine binding sites with a local inflammatory response and subsequent apoptosis of labyrinthine cells.[29] The sensorineural hearing loss related to vascular mechanism generally is permanent, whereas peripheral vestibular dysfunction are generally reversible.[26]

Ocular inflammation in RP may affect any part of the eye and occurs between 20 and 60% of the cases.[27–30] In our study uveitis occurs in approximately 36.7% of patients with RP.

In the present study, 16.7% of patients were submitted to tracheotomy (11.1% male and 19.0% female). Respiratory tract involvement is seen in up to 38% of patients with RP at presentation, and in about one half to two thirds of patients throughout the course of the disease.[6,7,10] Airway involvement is generally considered ominous and has been reported to portend a poor prognosis.[7] Tracheobronchomalacia, due to loss of the supportive cartilaginous scaffolding of the upper respiratory airways, can be seen as a chronic sequelae of RP due to recurrent inflammation.[31,32] Respiratory compromise stemming from fixed airway obstruction or hyperdynamic collapse may cause significant morbidity and mortality.[33]

In the present study, comorbidity distribution and disease status were comparable between the gender groups. There are no data on the distribution of comorbidities between genders but our study found no difference between males and females. Data on disease status is also limited and in our sample 46.7% cases were in remission, 26.7% activity and 26.7% controlled. It is also difficult to determine the factors associated with this status, which may be attributable to disease severity, heterogeneity of clinical symptoms, absence of treatment protocols due to a lack of controlled clinical trials, adherence to treatment, or genetic components.

The leading cause of mortality in RP is airway obstruction secondary to pneumonia, respiratory failure or progressive cardiovascular involvement.[34] In the present study, no deaths occurred during patient follow-up.

This study has some limitations. The major limitations are a retrospective cohort study design. Additionally, the inclusion of patients solely from a tertiary care center may not represent the full RP spectrum and might have resulted in overestimation of disease or drug complications in these more severe cases. Finally, other cardiovascular risk factors were not analyzed, such as tobacco, unhealthy diet, physical inactivity, low socioeconomic status.

In conclusions, there was a high prevalence of arterial hypertension and diabetes mellitus in RP, and male patients appeared to have a worse prognosis during the follow up than female patients. Further epidemiological studies are needed to confirm our results.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Sharma A, Gnanapandithan K, Sharma K, Sharma S. Relapsing polychondritis: a review. Clin Rheumatol. 2013;32:1575–83.
2. Gergely P Jr, Poor G. Relapsing polychondritis. Best Pract Res Clin Rheumatol. 2004;18:723–38.
3. Ananthakrishna R, Goel R, Padhan P, Mathew J, Danda D. Relapsing polycondritis – case series from South India. Clin Rheumatol. 2009;28 Suppl. 1:S7–10.
4. Kent PD, Michet CJ Jr, Luthra HS. Relapsing polychondritis. Curr Opin Rheumatol. 2004;16:56–61.
5. Peebo BB, Peebo M, Frenneson C. Relapsing polychondritis: a rare disease with varying symptoms. Acta Ophthalmol Scand. 2004;82:472–5.
6. McAdam LP, O'Hanlan MA, Bluestone R, Pearson CM. Relapsing polychondritis: prospective study of 23 patients and a review of the literature. Medicine (Baltimore). 1976;55:193–215.
7. Michel CJ Jr, McKenna CH, Luthra HS, O'Fallon WM. Relapsing polychondritis: survival and predictive role of early disease manifestations. Ann Intern Med. 1986;104:74–8.
8. Chang-Miller A, Okamura M, Torres VE, Michet CJ, Wagoner RD, Donadio JV Jr, et al. Renal involvement in relapsing polychondritis. Medicine (Baltimore). 1987;66:202–17.
9. Zeuner M, Straub RH, Rauh G, Albert ED, Scholmerich J, Lang B. Relapsing polychondritis: clinical and immunogenetic analysis of 62 patients. J Rheumatol. 1997;24:96–101.
10. Trentham DE, Le CH. Relapsing polychondritis. Ann Intern Med. 1998;129:114–22.
11. Hazra N, Dregan A, Charlton J, Gulliford MC, D'Cruz DP. Incidence and mortality of relapsing polychondritis in the UK: a population-based cohort study. Rheumatology. 2015;54:2181–7.
12. Lin DF, Yang WQ, Zhang PP, Lv Q, Jin O, Gu JR. Clinical and prognostic characteristics of 158 cases of relapsing polychondritis in China and review of the literature. Rheumatol Int. 2016;36:1003–9.
13. Shimuzu J, Oka H, Yamano Y, Yudoh K, Suzuki N. Cutaneos manifestations of patients with relapsing polychondritis: an association with extracutaneous complications. Clin Rheumatol. 2016;35:781–3.
14. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, et al. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J. 2003;24:1601–10.
15. The Expert Committee on the diagnosis and classification of diabetes mellitus. Report of the Expert Committee on the diagnosis and classification of diabetes mellitus. Diabetes Care. 1997;20:1183–97.
16. Movahedi M, Beauchamp M, Abrahamowicz M, Ray M, Michaud K, Pedro S, et al. Risk of incident diabetes mellitus associated with the dosage and duration of oral glucocorticoid therapy in patients with rheumatoid arthritis. Arthritis Rheumatol. 2016;68:1089–98.
17. Di Dalmazi G, Pagotto U, Pasquili R, Vicennati V. Glucocorticoids and type 2 diabetes, from physiopatology. J Nutr Metab. 2012;2012:525093.
18. Walker BR, Edwards CR. New mechanisms for corticosteroid-induced hypertension. Br Med Bull. 1994;50:342–55.
19. de Moraes MT, de Souza FH, de Barros TB, Shinjo SK. Analysis of metabolic síndrome in adult dermatomyositis with a focus on cardiovascular disesase. Arthritis Care Res. 2013;65:793–9.
20. de Souza FH, Shinjo SK. The high prevalence of metabolic syndrome in polymyositis. Clin Exp Rheumatol. 2014;32:82–7.
21. Pereira RM, de Carvalho JF, Bonfa E. Metabolic syndrome in rheumatological diseases. Autoimmun Rev. 2009;8:415–9.
22. Bruce IN. 'Not only, but also': factors that contribute to accelerated atherosclerosis and premature coronary heart disease in systemic lupus erythematosus. Rheumatology (Oxford). 2005;44:1492–502.
23. Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a metaanalysis of observational studies. Arthritis Rheum. 2008;59:1690–7.
24. Peters MJ, van der Horst-Bruinsma IE, Dijkmans BA, Nurmohamed MT. Cardiovascular risk profile of patients with spondylarthropathies, particularly ankylosing spondylitis and psoriatic arthritis. Semin Arthritis Rheum. 2004;34:585–92.
25. Coulson EJ, Ng W-F, Goff I, Foster HE. Cardiovascular risk in juvenile idiopathic arthritis. Rheumatology (Oxford). 2013;52:1163–71.
26. Lahmer T, Treiber M, von Werder A, Foerger F, Knopf A, Heemann U, et al. Relapsing polychondritis: an autoimmune disease with many faces. Autoimmun Rev. 2010;9:950–6.

27. Isaak BL, Liesegang TJ, Michet CJ. Ocular and systemic findings in relapsing polychondritis. Ophthalmology. 1986;93:681–9.
28. Yu EN, Jurkunas U, Rubin PA, Baltatzis S, Foster CS. Obliterative microangiopathy presenting as chronic conjunctivitis in a patient with relapsing polychondritis. Cornea. 2006;25:621–2.
29. Chow MT, Anderson SF. Relapsing polychondritis. Optom Vis Sci. 2000;77:286–92.
30. Letko E, Zafirakis P, Baltatzis S, Voudouri A, Livir-Rallatos C, Foster CS. Relapsing polychondritis: a clinical review. Semin Arthritis Rheum. 2002;31:384–9.
31. Bachor E, Blevins NH, Karmody C, Kühnel T. Otologic manifestations of relapsing polychondritis. Review of literature and report of nine cases. Auris Nasus Larynx. 2006;33:135–41.
32. Suzuki S, Ikegami A, Hirota Y, Ikusaka M. Fever and cough without pulmonary abnormalities on CT: relapsing polychondritis restricted to the airways. Lancet. 2015;385:88.
33. Adliff M, Ngato D, Keshavjee S, Brenaman S, Granton JT. Treatment of diffuse tracheomalacia secondary to relapsing polychondritis with continuous positive airway pressure. Chest. 1997;112:1701–4.
34. Lee KS, Ernst A, Trentham DE, Lunn W, Feller-Kopman DJ, Boiselle PM. Prevalence of functional airway abnormalities in relapsing polychondritis. Radiology. 2006;240:565–73.