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ORIGINAL ARTICLE

R. A. Luosujärvi · T. M. Husman · M. Seuri
M. A. Pietikäinen · P. Pollari · J. Pelkonen
H. T. Hujakka · O. A. Kaipiainen-Seppänen · K. Aho

Joint symptoms and diseases associated with moisture damage in a health center

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Abstract Rheumatic diseases do not usually cluster in time and space. It has been proposed that environmental exposures may initiate autoimmune responses. We describe a cluster of rheumatic diseases among a group of health center employees who began to complain of symptoms typically related to moldy houses, including mucocutaneous symptoms, nausea and fatigue, within a year of moving into a new building. Dampness was found in the insulation space of the concrete floor below ground level. Microbes indicating mold damage and actinobacteria were found in the flooring material and in the outer wall insulation. The case histories of the personnel involved were examined. All 34 subjects working at the health center had at least some rheumatic complaints. Two fell ill with a typical rheumatoid factor (RF)-positive rheumatoid arthritis (RA), and 10 had arthritis that did not conform to any definite arthritic syndrome (three met the classification criteria for RA). Prior to moving into the problem building one subject had suffered reactive arthritis, which had then recurred. Another employee had undiagnosed ankylosing spondylitis and later developed psoriatic arthritis, and another developed undifferentiated vasculitis. A total of 16 subjects developed joint pains, 11 of these after beginning work at the health center. Three subjects developed Raynaud's symptom. Fourteen cases had elevated levels of circulating immune complexes in 1998, 17 in 1999, but there were only three cases in 2001, when the health center had been closed for 18 months. The high incidence of joint problems among these employees suggests a common triggering factor for most of the cases. As some of the symptoms had tended to subside while the health center was closed, the underlying causes are probably related to the building itself and possibly to the abnormal microbial growth in its structures.

Keywords Disease clusters · Rheumatic diseases

Abbreviations *RF* rheumatoid factor · *RA* rheumatoid arthritis · *CFU* colony-forming units · *CRP* C-reactive protein · *DMARD* Disease-modifying antirheumatic drug

R. A. Luosujärvi (✉) · O. A. Kaipiainen-Seppänen
Kuopio University Hospital,
PO Box 1777, 70211 Kuopio, Finland
E-mail: riitta.luosujarvi@kuh.fi
Tel.: 358-17-172553
Fax: 358-17-172543

T. M. Husman
National Public Health Institute, Kuopio, Finland

M. Seuri
Kuopio Regional Institute of Occupational Health,
Kuopio, Finland

M. A. Pietikäinen
Health Care Unit of Kuopio, Kuopio, Finland

P. Pollari
Kuopio Health Center, Kuopio, Finland

J. Pelkonen · H. T. Hujakka
Kuopio University, Kuopio, Finland

K Aho
National Public Health Institute, Helsinki, Finland

Introduction

A large number of drugs and an increasing number of environmental agents have been related to a variety of immune-mediated clinical syndromes [1]. The symptoms are frequently somewhat milder than those seen in their idiopathic counterparts, and they can often be aborted by removing the putative offending agent. Usually, only a proportion of the exposed subjects are inflicted, suggesting a role played by genetic factors. On the other hand, there is evidence of environmental triggers in idiopathic diseases. In particular, smoking is an established risk factor for rheumatoid arthritis (RA) [2, 3].

Although damp housing conditions are popularly supposed to predispose to rheumatism, objective data are few. In studies carried out by the Field Unit of the

Arthritis and Rheumatism Council in England the only significant finding was a greater prevalence of knee pain in females living in damp houses [4]. No relationship to arthritis was found. A number of studies have examined weather sensitivity in patients with established RA; some of them found an association between pain and/or stiffness and weather, whereas others found no association [5, 6]. Arthralgias and myalgias have been associated with exposure to mold, both occupational [7, 8] and in buildings [9, 10], but frank arthritis is to our knowledge rare. A recent review on mycotoxin-producing molds and their potential role in human immunopathology with respect to wet building environments listed a large variety of symptoms, but arthritis was not mentioned [11].

We previously reported a cluster of rheumatic diseases in an office with an indoor air problem [12]. The purpose of this study was to describe another cluster of rheumatic diseases among the employees of a moisture-damaged workplace that was probably caused by environmental exposure. The clinical findings differ somewhat from those in the cluster described previously.

Materials and methods

Building

In 1995 a suburban health center was established in the ground floor of a new building consisting of two parts connected to each other. The higher part had five floors and a basement below ground level. The lower part had only a ground floor, with no basement or upper floors above it. The health center, which had a separate ventilation system, occupied the entire ground floor.

Within a year after moving into the new building, the employees began to complain of respiratory symptoms, fatigue and nausea. Minor renovations were performed in the summer of 1997. However, the symptoms continued and the health center was closed in August 1998 for drying of the concrete floors and renewing the flooring materials, and was reopened 1 year later. However, owing to the reappearance of symptoms the health center was again closed in March 2000.

The land fillings around the building were removed and the concrete slabs were made waterproof. The fine land fillings were replaced by gravel. Some damaged insulation material was renewed. Inside the building damp floors were dried once more and flooring materials were changed where necessary. The ventilation system was cleaned and balanced to avoid leakage through wall structures. After renovations the health center was reopened in April 2002.

The indoor air problem of the building had been examined by several expert organizations. It appeared that below the ground level the water insulation was insufficient and there was no seaming between the concrete elements, allowing water and damp to enter the insulation space. From there the damp could move by diffusion and capillary force to the concrete slabs, leading to a high relative humidity of up to 93% in the floors of the health center's rooms. In indoor air sampling low concentrations of volatile organic compounds, chemicals such as 2-ethyl-1-hexanol and TXIB were found, indicating the breakdown of polyvinyl chloride in the plastic flooring materials. Microbes indicating moisture damage and mold growth (*Chaetomium*, *Streptomyces* spp, *Aspergillus versicolor* and *Ulocladium*) were found under the flooring materials. However, in indoor air samples the concentrations of viable microbes were low (fewer than 10 colony-forming units (CFU)/m^3 in all samples), and no microbes indicating moisture damage were found. Tracer gas measurements showed that air leaked from the damaged and damp insulation space to the indoor air. Microbes indicating moisture damage (molds and yeast) were found in the ventilation ducts. A more detailed description of the findings will be reported elsewhere (to be published).

Personnel

The health center had rooms for general practitioners, a dental clinic and maternal and child welfare clinics. The total number of personnel was 34 (4 men and 30 women), including six physicians and three dentists. The mean age of the employees in 1998 was 39.9 years (range 27–57). There were two current smokers among them.

Diagnostic procedures

Three examinations were performed at the rheumatological clinic of Kuopio University Hospital (in 1998, 1999, 2001); all but one subject participated in at least two examinations. Additional information was obtained by telephone interview or questionnaires and from clinic records. The examination scheme for patients with peripheral arthritis consisted of routine blood tests, testing for rheumatoid factor (RF) with a sensitized cell agglutination test (prevalence in healthy subjects about 2%), X-rays of the hands and feet, ultrasonography of the hip joints, and registration of the duration of morning stiffness and the joints involved; X-rays and ultrasonography of other joints were taken when needed. For the testing of circulating immune complexes (CIC), the conglutinin-binding assay was used the first time (in 1998) and the platelet iodine-labeled staphylococcal protein A test later in another laboratory [13], because the performance of the former test had been discontinued (cut-off level of positive reactions was mean +3 standard deviations in healthy subjects).

The study plan was approved by the Ethical Committee of Kuopio University Hospital.

Results

A total of 34 subjects had been working at the health center and all had at least some rheumatic or related complaints (Table 1).

Two subjects developed typical RF-positive RA affecting the hands and feet. A male office clerk, 38 years of age, became ill 1 month after beginning work at the health center. His disease calmed down within 12 months. He is currently in remission without antirheumatic drugs, although still RF positive, but there are no erosions. A 43-yearold woman developed joint pain in 1997. In 2000, at 46 years of age, she developed RF-positive erosive peripheral arthritis; the diagnosis was confirmed as RA in 2001.

The male patient with RA was employed for only 3 months at the health center. All the other subjects continued working there until it was closed for the first time in August 1998 and for the second time in March 2000.

A total of 10 subjects had arthritis that did not conform to any definite arthritic syndrome (Table 2). The mean period from beginning work to the onset of joint symptoms was 1.8 years (range 0.5–3). One of

Table 1 Different rheumatic diseases and symptoms during 1998–2001 among the 34 employees of the health center

Disease or symptom	Number of cases			Mean age in 1998 (years)	Treatment with DMARDs			Disease active in	
	Men	Women	Total		1999	2000	2001	2000	2001
Rheumatoid arthritis (RA)	1	1	2	40.5	1	0	1	1	1
Undifferentiated arthritis	0	10[a]	10	46	7	8	8	7	5
Psoriatic arthritis	0	1[b]	1	29	1	1	1	1	1
Chronic reactive arthritis	0	1[c]	1	46	1	1	1	1	1
Vasculitis	0	1	1	57	1	0	0	0	0
Arthralgias									
Alone	1	10	11	38.5	0	0	0	3	1
With osteoarthritis	1[d]	2[d]	3	43	0	0	0	3	2
With Raynaud's symptom	1[d]	1[d]	2	45	0	0	0	0	0
Raynaud's symptom	0	3	3	43.5	0	0	0	1	1
Total	4	30	34	39.9	11	10	11	16	12

DMARD, disease-modifying antirheumatic drug
[a]One subject with previous back and hip pains
[b]Previous ankylosing spondylitis
[c]Activation of prior disease
[d]Prior to beginning work at the health center

the subjects (case 6) had previously had back pain and an episode of hip pain. The other subjects had no previous joint complaints. Three of the subjects (cases 6, 9 and 10) met four of the 1987 classification criteria for RA [8]. In addition to peripheral joints, two subjects (cases 5 and 7) had arthritis in the hip joint and two (cases 5 and 9) had arthritis in the knee. In all cases the joint swelling was confirmed by ultrasonography. All five subjects with arthritis of the finger joints showed impaired fist clenching and grip strength. One subject (case 1) had marked destruction in one proximal interphalangeal joint; no other radiographic changes were noted. Several features distinguished these cases from typical RA. Thus, only one of these 10 subjects was RF positive, and C-reactive protein (CRP) was in the normal range (< 10 mg/l) in all cases. The joint swellings were more migratory than in typical RA, and the joints were not hot and red as is usually seen in RA. Despite treatment with disease-modifying antirheumatic drugs (in most instances methotrexate) the disease in seven subjects remained active in 2000, and in five subjects in 2001, although these patients no longer worked in the problem building. On the basis of the clinic records the disease in the above five subjects continued active in 2002.

One nurse had previously had reactive arthritis in 1989, but at the time of employment in the building she had no symptoms. After 2.5 months her arthritis recurred. Another nurse who had previously had undiagnosed ankylosing spondylitis (based on radiographic findings) developed psoriatic arthritis affecting the wrist and hip; her disease continues to be active. One female dentist developed undifferentiated vasculitis at 57 years of age after working for 1 year at the health center; she was currently in remission at the end of follow-up.

A total of 16 subjects had experienced joint pains, and in 11 cases the symptoms developed after beginning work at the health center. Two subjects with arthralgias had previously had mild Raynaud's symptom, and three had osteoarthritis. Three additional subjects developed Raynaud's symptom after beginning work at the health center; in one of these patients the symptoms persisted at the end of follow-up.

Seven subjects were positive for the HLA allele B27 (Table 3). Eight subjects were RF positive at the first examination, only one (the one with RA) in 1999, but four subjects were again RF positive in 2001. A total of 14 cases showed elevated levels of CIC in 1998, 17 cases in 1999, but only three in 2001. No clear correlation existed between the cases positive for RF and those with elevated CIC levels.

Table 2 The American College of Rheumatology classification criteria in the 10 subjects with undifferentiated arthritis in 1998 (the first –, + or number), in 1999 (the second –, + or number), and in 2001 (the third –, + or number)

Criterion	Case number										
	1	2	3	4	5	6	7	8	9	10	Total number of criteria
1. Morning stiffness	- - -	+ - -	+ - +	- - -	- - +	+ + -	+ + -	+ - -	+ - -	+ + -	7/3/2
2. Arthritis of ≥ 3 joint areas	+ - -	- - -	+ - -	- - -	- - -	+ - -	- - -	- - -	+ + -	+ - +	5/1/1
3. Arthritis of hand joints	+ + -	+ - -	+ - -	+ - -	+ - -	+ - -	+ - -	+ - -	+ + -	+ - +	10/2/1
4. Symmetric arthritis	- - -	- - -	- - -	- - -	- - -	+ - -	- - -	- - -	+ + +	+ - -	3/1/1
5. Rheumatoid nodules	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	0/0/0
6. Rheumatoid factor	- - -	- - -	- - -	- - -	+ - +	- - -	- - -	- - -	- - -	- - -	1/0/1
7. Radiographic changes	- + +	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	0/1/1

Six of the original employees and 24 new employees started to work at the health center when it was reopened in April 2002. All six original employees were asymptomatic at that time (one had had reactive arthritis, one undifferentiated arthritis, and four arthralgias). None of the subjects working at the health center had developed any rheumatic complaints during a follow-up period of 6 months.

Discussion

The purpose of the work described here was to concentrate on the rheumatological aspects of the cluster. All subjects working at the health center had at least some rheumatic or related complaints. In the great majority of cases the symptoms had developed after beginning work at the health center. Such an accumulation of patients with rheumatic complaints cannot be due to change. This suggests that the symptoms in most of the subjects were, in one way or another, related to the working conditions in the building. Most subjects had developed either undifferentiated arthritis or arthralgias. In the arthritis cases the signs of inflammation were milder than those in typical RA, e.g. the joints were not as hot and tender as in a typical case, and CRP was not elevated, yet the subjects undoubtedly had synovitis, as substantiated by ultrasonographic findings as well as by impaired fist clenching and grip strength. It is probable that some subjects classified as having arthralgias had in fact displayed episodes of short-lived arthritis. Thus, there was a spectrum of symptoms, ranging from arthralgias to polyarthritis, that formally met the ACR classification criteria for RA. It appears prudent to assume that one and the same environmental factor was responsible for giving rise to these cases. If genetic factors were involved, they most likely determined the severity of the disease. No new cases emerged after the health center was reopened in 2002, but the follow-up period is too short for any definite conclusions.

About one-third of patients initially presenting with symptoms and signs compatible with RA are seronegative in conventional RF tests. Yet, RF-negative RA tends to run a more favorable course than its RF-positive counterpart, and many patients go on to develop complete remission. Regarding RF-negative oligoarthritis, a good prognosis is nearly always the rule [15]. Most patients with remittent disease will remit during the first 2 years [16]. We have now followed up our patients, including those with undifferentiated arthritis, for a mean of 4 years. Only by continuing the follow-up will we be able to show whether these patients will develop erosive disease. Green et al. [17] have drawn attention to a patient group with indolent, yet progressive and destructive, symmetric polyarthritis that begins in the small joints, often without an elevated acute-phase response and which is only partially responsive to conventional treatment. The other end of our disease spectrum, i.e. patients with mere arthralgias, are not usually seen at arthritis clinics.

Regarding the other cases, different mechanisms might have been involved. There were two cases of typical RF-positive RA. The first is of special interest, as quite rarely patients presenting with RF-positive RA will remit, although such cases do exist [16]. Our patient terminated his work at the health center soon after becoming ill, and this may be the reason why he has now been in remission without drugs for 3 years.

Certain immunological aberrations were frequently noted in subjects working at the health center, although their exact role in the pathogenesis of joint symptoms remains elusive. Thus, a quarter of the cases were RF positive in the first examination performed in 1998 at Kuopio University Hospital; later the frequency was lower. About half of the cases had elevated levels of CIC in the first and second examinations. However, the

Table 3 Occurrence of the HLA B27 allele, rheumatoid factor (RF) and circulating immune complexes (CIC) during 1998–2001 among the 34 employees of the health center

Disease symptom	Number of cases	HLA B27	RF			CIC		
			1998	1999	2001	1998	1999	2001
Rheumatoid arthritis	2	0	1	1	2	2	2	0
Undifferentiated arthritis	10	1	1	0	1	6	5	0
Psoriatic arthritis	1	1	0	0	0	0	0	0
Chronic reactive arthritis	1	1	0	0	0	0	1	0
Vasculitis	1	0	0	0	0	0	0	0
Arthralgias	16	3	4	0	0	6	7	3
Raynaud's symptom	3	1	2	0	1	0	2	0
Total	34	7 /34	8 /34	1 /33[a]	4 /30[b]	14 /34	17 /33	3/30[b]

[a]One subject did not participate
[b]Information on the RF status and on the level of CIC was missing for four cases: one with osteoarthritis and two with arthralgias no longer participated in the study; one patient with undifferentiated arthritis had moved abroad

correlation between the CIC findings in the two examinations was poor, at least partly because different test techniques had been used. The low frequency of positive reactions in the third examination may be associated with the cessation of the exposure. Elevated levels of CIC are seen in many different disease conditions, but only seldom in healthy subjects [18].

A variety of microbiological and toxicological studies were carried out to obtain etiological clues from the environment, but nothing straightforward resulted. Likewise, antibody studies against a number of arthritis-associated microbes revealed no evidence of recent infections (data not shown). Detailed findings concerning the structural damages of the building with a short note on rheumatological aspects will be reported elsewhere.

Most subjects working at the health center had been vaccinated in 1994–1996 against hepatitis B, using a recombinant vaccine. An array of rheumatic or related disease conditions, including RF-positive RA, reactive-type transient arthritides, arthralgias and vasculitis, have been described as occurring within a short period after hepatitis B vaccination [19, 20, 21]. The accumulating evidence favors a causal association, although this cannot yet be regarded as definite. If the interval after vaccination is longer, any cause-and-effect relationship remains virtually impossible to establish. Concerning our cases, there remains the theoretical possibility that the subjects had initially become sensitized against yeast proteins present as impurities in the recombinant vaccine, and were subsequently restimulated with yeast proteins in the indoor environment, and this would have contributed to the emergence of symptoms. However, IgE RAST for yeast protein was negative in all subjects.

Joint pains occur in subjects exposed to mold [22, 23, 24], but we are aware of only one epidemiological investigation dealing with mold exposure and overt arthritis [25]. The authors had collected data by a postal questionnaire from 422 RA cases and 859 referents and found a significantly increased risk of RA among men living in a moldy home; however, the inverse relationship was found among women. The authors did not report the overall risk, but it must have been close to 1 and not statistically significant.

We have earlier described another type of cluster comprising well-defined rheumatic diseases (RF-positive RA, ankylosing spondylitis and Sjögren's syndrome) occurring in a moisture-damaged office building [12]. The underlying reasons for the accumulation of the rheumatic diseases in the health center remain elusive. However, our findings call for new studies to look for similar type of clusters, and the possibility remains that some common environmental trigger may eventually be found.

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