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Rheumatological manifestations of infective endocarditis

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SUMMARY A retrospective study showed musculoskeletal manifestations in 32 of 108 patients treated for infective endocarditis in several departments at the Poitiers CHU. Such manifestations included articular pain or aseptic arthritis, typically involving the major joints, as well as vertebral osteomyelitis, low back pain (inflammatory or non-inflammatory), and myalgia. Patients showing such signs were generally younger than those without musculoskeletal involvement, diagnosis was made later, and prognosis was worse; streptococcus D was more often involved, and microscopic haematuria was more common. With the exception of vertebral osteomyelitis, the pathogenesis was not clear.

Key words: bacterial endocarditis, rheumatology, arthritis, arthralgia, low back pain, vertebral osteomyelitis.

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Musculoskeletal manifestations of infective endocarditis (IE) are particularly hard to diagnose, and until recently their frequency has been underestimated. Reviewing 108 cases of patients admitted to hospital for IE at the Poitiers CHU we sought to determine: (*a*) the type and frequency of rheumatological manifestations of IE; (*b*) the clinical and laboratory characteristics of IE with or without such manifestations.

Materials and methods

This study included 108 cases of infective endocarditis, 77 males and 31 females, treated between 1 January, 1966 and 30 September, 1983 at the Poitiers CHU in the Departments of Cardiology A, Infectious Diseases, Internal Medicine, and Rheumatology. This diversified recruitment prevented statistical bias from the specialisation of a single department. For patients to be included they had to have the following: (*a*) organic valvular (or prosthetic) involvement; (*b*) demonstration of pathogens by haemoculture or culture of valvular tissue, *or* clinical septicaemia with development or increase in organic murmur. Echocardiographic, surgical, or necropsy reports confirmed the diagnosis in all cases where they were available.

Assay of circulating immune complexes (CIC) was carried out by a modified polyethylene glycol (PEG)-precipitation technique.[1] C4 precipitated by PEG was expressed as a function of serum C4 concentration, with assay carried out by nephelometry and results expressed as percentage C4 precipitated. The percentage precipitation increases with increasing quantities of circulating immune complexes (normally less than 20%).

Statistical analysis was carried out by Student's *t* test, the χ^2 test with Yates's correction where the samples were less than or equal to 5, and Wilcoxon's non-parametric test.

Results

MUSCULOSKELETAL MANIFESTATIONS

Thirty-two of 108 (29·6%) patients had musculoskeletal manifestations (Table 1). Arthritis or arthralgia developed in the major joints of the arms and legs; while arthritis involved only one joint per patient, it was accompanied by arthralgia in 4 of 7 cases. There were no radiological signs, and in the two cases where synovial fluid was taken, though it

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Table 1 *Type of musculoskeletal manifestations in endocarditis patients: n=number of patients (32 of 108). The sum exceeds 32 owing to the presence of multiple symptoms in some patients*

	Number	
Arthritis alone	4	
Arthritis+arthralgia	4	
Oligoarthralgia	8	
Polyarthralgia	5	3 cases of mobile polyarthralgia
Diffuse back pain	1	
Lower back pain	6	2 with unilateral sciatica
Inflammatory neck pain	1	
Clinical sacroiliitis	1	
Vertebral osteomyelitis	4	
L3–L4 (streptococcus D)		
L4–L5 (*Staphylococcus aureus*)		
C4–C5 (*Staphylococcus aureus*)		
L2–L3 (no pathogen isolated)		
Myalgia	5	

was rich in granulocytes, it remained sterile. Arthralgia was generally stationary, but it was mobile in three cases of non-D streptococcus endocarditis. Arthritis and arthralgia particularly involved the major joints of the arms and legs (Table 2).

Spinal involvement (in four cases this was vertebral osteomyelitis) was noted in 13 patients (12%). Six patients reported low back pain without clear radiological signs: in three cases the frequency of the pain was poorly defined or permanent, while three others (including two with unilateral sciatica) reported aggravation by mechanical factors, including cough; this was suggestive of mechanical compression. Of the last three patients one each reported diffuse back pain without precise temporal distribution, continuous sacroiliac pain without *x*-ray signs, and inflammatory neck pain.

Table 2 *Localisation and type of musculoskeletal manifestations in endocarditis patients: n=number of times that a given joint was involved in this group of patients*

	Arthralgia, n=17	*Arthritis, n=7*
Knee	16	4
Shoulder	14	
Ankle	6	1
Wrist	5	1
Elbow	4	1
Metacarpohalangial	3	
Hip	1	

Pain involving the shoulder or hip was noted in five cases, in two together with arthralgia, and in one with both arthralgia and C4-C5 vertebral osteomyelitis.

All aseptic musculoskeletal manifestations were rapidly diagnosed and yielded easily to treatment. They resolved after several days (or at most, several weeks) of treatment with appropriate antibiotics, and there were no sequelae. A new episode of arthralgia during treatment occurred in only one case, with simultaneous recurrence of fever; death followed within a few days.

COMPARISON OF INFECTIOUS ENDOCARDITIS WITH OR WITHOUT MUSCULOSKELETAL MANIFESTATIONS

These two groups of patients did not differ in terms of portal of entry, cardiac history, age, sex, distribution, or clinical signs.

Laboratory values, including assay for cryoglobulins (negative in all cases studied) were quite similar. There was a slight difference in terms of two parameters: CIC *levels* (rather than presence in abnormal quantities, identical in both groups) were partially reflected in the percentage of C4 precipitation, which was higher in those patients with musculoskeletal signs (31·5, SD 8%, versus 26·8, SD 7%), and in the Waaler-Rose reaction, which was more frequently positive in the patients with such signs. Nevertheless, differences were not statistically significant. This is also the case for the frequency of streptococcal infection in patients with positive serology for rheumatoid factor.

Table 3 *Bacteriological data (blood culture); n=number of patients: n is greater than 32 in the first column owing to isolation of several pathogens in 2 cases of IE. p=Statistical significance, NS=not significant*

	Musculoskeletal signs present (n=32)		*Musculoskeletal signs absent (n=76)*		*p*
	Number	*%*	*Number*	*%*	
Non-D streptococcus	10	31	24	31	NS
Streptococcus D	9	28	10	13	0·01
Staphylococcus aureus	9	28	12	16	NS
Staphylococcus albus	0	0	3	4	NS
Other pathogens	4	12	11	14	NS
Blood cultures negative	2	6	16	21	0·01

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Table 4 *Initial diagnosis in endocarditis patients with musculoskeletal manifestations: n=number of patients*

	Number
Atypical polyarthritis	2
Low back pain	3
Sciatica	2
Vertebral osteomyelitis	1
Arthritis	1
Horton's disease	1
Influenza-like syndrome	4

On the other hand, patients with detectable rheumatoid factor (RF) had a significantly longer delay between first clinical manifestations and diagnosis (82 days, SD 43, versus 26, SD 14 for the seronegative subjects, $p<0.05$). Microscopic haematuria was more frequent in those with rheumatic signs: 15 out of 30 versus 14 out of 68 ($p=0.05$).

Comparison of causal pathogens in the two groups showed no significant differences except for streptococcus D, which was more frequently found in patients with musculoskeletal signs (Table 3).

For the patients showing musculoskeletal signs the diagnosis was more frequently tardy. Delay in diagnosis exceeded 15 days in 21 of 32 versus 28 of 76 ($p=0.01$). Early death was more frequent: 13 of 32 versus 18 of 76 ($p<0.05$). Errors in initial diagnosis (13 of 32), (Table 4), and inappropriate administration of corticosteroids (three cases) partly accounted for this difference.

Discussion

Recent studies[2–5] have shown an incidence of 19 to 28% of patients with IE have musculoskeletal manifestations, though this phenomenon was partly or completely overlooked in earlier studies.[6–8] We found the same predominance of male patients as did other authors[2 3 9] regardless of whether there were musculoskeletal manifestations and regardless of the aetiology.[7 8] On the other hand, unlike the report by Deshayes *et al.*,[9] in our group the patients with musculoskeletal signs were younger than those without.

The main peripheral manifestations were arthralgia,[2 3 9] sometimes sequentially affecting several joints,[10] and less often arthritis.[2–4] Both phenomena preferentially involved the major joints; they showed rapid and complete resolution with antibiotics. They appear to be responsible for diagnostic errors,[2 10] since such signs can motivate highly inappropriate therapeutic decisions or delay the start of appropriate treatment.[11] This would account for the high mortality in subjects with the rheumatic form of IE.

The pathogenesis of arthralgia and arthritis in infective endocarditis is somewhat obscure. The hypothesis of septic foci in the joints would appear to be contradicted by the usual presence of sterile synovial fluid[2 12] as well as by the rapid resolution of peripheral manifestations without radiological sequelae. Nevertheless, three cases of septic arthritis during IE were reported, two confirmed by examination of synovial fluid[10] and the other by culture of a biopsy fragment of synovium from a patient in whom the fluid was sterile.[12] Furthermore, in other situations synovial culture has allowed isolation of a pathogen which could not be isolated from the fluid,[13 14] and since biopsy was not always carried out in such cases we cannot formally exclude the hypothesis of sepsis.

Data concerning bacteriological results in the majority of cases, as well as progress under treatment, tend to suggest a 'reactive' arthritis.[15] This would be in keeping with the parallel development of musculoskeletal signs and clinical endocarditis, notably the relapse of joint involvement following failure of treatment of the IE, which was noted in one of these patients.

In such cases there is a latent period between infection and development of musculoskeletal signs. The absence of such signs does not exclude this diagnosis, since development of arthralgia and arthritis before or simultaneously with fever can occur when clinically silent infection has been present for some time. The absence of a high frequency of HLA-B27 antigen in those subjects in whom this was studied (results not presented) also does not contradict this hypothesis. While it has been shown that this histocompatibility antigen characterises patients with the best identified risk of reactive arthritis (associated with pathogens quite different from those giving rise to IE), we cannot exclude the possible development of arthritis by a similar mechanism, however triggered by other pathogens.

We have found 16 published cases of vertebral osteomyelitis in conjunction with IE (Table 5). Two cases[16 17] were of multiple vertebral osteomyelitis, a rare occurrence suggesting dissemination in the blood stream.[17 18]

Several recent publications cite the possible development of febrile lumbago along with IE, independently of any identifiable vertebral osteomyelitis[2 3 9 19–21]; pain may have an inflammatory component.[2 9] In other cases, in view of the aggravation of pain by mechanical factors or cough, as well as radicular irradiation, the symptomatology may suggest disc herniation.[2] We have observed

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Table 5 *Vertebral osteomyelitis and infective endocarditis. Note the frequency of vertebral osteomyelitis at multiple sites, streptococcus infection, and infrequency of negative blood cultures*

Authors	*Localisation*	*Pathogens isolated from blood cultures*
Allen *et al.*[30]	L2–L3	Enterococcus
Bontoux *et al.*[31]	L2–L3	Enterococcus
Boutelier *et al.*[16]	L1–L2–L3	Enterococcus
Churchill *et al.*[2]	Not cited	Enterococcus: 1 *Staphylococcus aureus:* 2 Non-D streptococcus: 2
Meyers and Commerford[3]	L1–L2	Enterococcus
De Seze	L3–L4 D6–D7–D8 L4–L5	*Staphylococcus aureus*
Unterreker and Hanna[32]	Not cited	*Aerococcus viridens*
Unpublished 1	L4–L5	*Staphylococcus aureus*
Personal 2	C4–C5	*Staphylococcus aureus*
Results 3	L3–L4	Enterococcus

three such cases, and this frequency would seem to exclude the possibility of coincidental development of IE and degenerative disc pathology.

Sacroiliitis has occasionally been reported,[2] and we did find one such case.

The pathogenesis of low back pain not attributable to clearly identifiable vertebral osteomyelitis remains obscure: multiple factors may be involved. While it is possible that it is attributable to minimal osteomyelitis resolving either spontaneously or under the effects of antibiotics, this cannot account for all such cases. Meyers and Commerford[3] reported that low back pain was always correlated with renal involvement. Though glomerulonephritis can cause a painful increase in pressure on the renal capsule, despite a significant increase in microscopic haematuria in the overall group of patients showing musculoskeletal involvement we did not find a clear correlation between this phenomenon and low back pain.

Low back pain could also be attributable to myalgia, especially when the pain is poorly systematised. Independently of spinal involvement, myalgia in IE tends to involve the shoulders and hips,[2] and has been attributed to vasculitis[2] or arterial emboli.[21] Like the other musculoskeletal manifestations with which it is frequently combined myalgia is common in forms of IE in which diagnosis tends to be late.[2 3]

The presence of rheumatoid factor (RF) is not correlated with musculoskeletal manifestations, regardless of the type. Like elevation in gammaglobulins, RF is a consequence of prolonged infection, and probably has no pathogenic role.[9] Development of mixed IgM-IgG cryoglobulins is possible, and such cryoglobulins have been reported during IE.[22 23] However, this condition was not seen in the present study.

The reasons for development of RF in infective endocarditis remain debatable. Modifications in IgG[22] could render them antigenic, while multiclonal activation of B lymphocytes[24] could also account for the presence of antinuclear antibodies. Like Messner *et al.*[25] we did not confirm the report of preferential development of RF in streptococcus D infective endocarditis.[7] Immunological abnormalities seen in IE are not specific to this disease, and their absence is thus not an exclusion criterion; the practical value of such tests is limited.

To the best of our knowledge the correlation between musculoskeletal manifestations and renal phenomena noted in this study has not been reported elsewhere. Renal immunofluorescence studies in IE have shown the presence of granular IgG and BIC deposits on the membranes,[26] possibly due to the presence of circulating immune complexes, which some authors have considered to be pathogenic for renal manifestations.[27 28] If the correlation between renal damage and musculoskeletal involvement is confirmed, it would probably indicate that immune complexes are also involved in development of the latter phenomenon. Despite the absence of significant changes in circulating immune complexes in this study we cannot exclude this hypothesis. Both renal involvement and musculoskeletal phenomena could be a function of prolonged infection.[29]

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