Palindromic rheumatism

Clinical and serum complement study

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SUMMARY A review of 39 patients diagnosed as suffering from palindromic rheumatism showed that 17 cases had evolved into typical rheumatoid arthritis (RA), while 22 had remained palindromic. The pattern of palindromic attacks in the two groups gave no grounds for regarding palindromic rheumatism as a separate condition from RA with palindromic onset. At the first attendance minor clinical or radiological changes, raised erythrocyte sedimentation rate, and positive serology were more common among those patients who were about to develop the picture of RA. Rheumatoid disease developing in patients with a palindromic onset was at least as severe as that among other patients with RA. 5 patients gave a history suggestive of fluid retention during the palindromic episodes, suggesting that attacks might be related to circulating immune complexes and altered vascular permeability. However, samples of blood obtained from 6 patients both during and between attacks showed no reduction in any of a variety of complement components tested.

Since Hench and Rosenberg (1944) first clearly described palindromic rheumatism, this acute episodic form of arthritis has become widely recognized. The accuracy of the original clinical description has been confirmed, although most authors writing subsequently (Ropes and Bauer, 1945; Ansell and Bywaters, 1959; Mattingly, 1966) found a closer relationship with rheumatoid arthritis (RA) than suggested by Hench and Rosenberg. Apart from this there have been no more definite pointers to the pathogenesis.

We studied the pattern of disease in a series of patients diagnosed as suffering from palindromic rheumatism, and attempted to determine whether any early features have predictive value as to which cases may develop into definite RA. A few patients had noted symptoms (see below) suggestive of fluid retention during the painful episodes. This raised the possibility that the attacks might represent intravascular formation of immune complexes, with complement fixation and increased vascular permeability. We therefore carried out serum complement determinations (when the opportunity arose) in the same patients both during and between acute attacks.

Materials and methods

PATIENTS

All patients attending the London Hospital Department of Rheumatology are entered by the clinician into a Diagnostic Index. During the 5-year period 1969-1974, 57 patients were indexed as suffering from palindromic rheumatism. These included both patients seen for the first time during this period and also patients who were first seen before 1969, but who reattended during this period. The notes of these 57 patients were reviewed and letters were sent to all requesting them to attend for follow up. In the end 39 patients (68.7%) reattended and were fully reviewed. Of the 18 patients who were not followed up, the notes of 2 could not be traced, 2 had moved to unknown addresses, and 14 failed to respond to our letter. Each was questioned, examined, and had a blood count, erythrocyte sedimentation rate (ESR), and latex test performed. Further x-rays of joints were obtained only when it was felt that these were likely to be contributory.

COMPLEMENT DETERMINATIONS

Six patients were seen during acute attacks. From each a sample of blood was obtained during the attack, allowed to clot at room temperature, and the serum separated and frozen immediately.

Accepted for publication May 22, 1976
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Samples were subsequently obtained from each of these patients between acute attacks. Sera were kept at -70°C until tested.

CH₅₀ (total haemolytic complement)

CH₅₀ determination was carried out by the method of Lachmann *et al.* (1973). Briefly, sheep red cells (E) were presensitized with rabbit IgM anti-sheep antibody (A) for 15 minutes at 4°C . The EA was washed in complement-fixing diluent, then added to 1/40 dilutions of the patients' sera at 37°C , and the lysis of the reaction mixture was plotted in a Unicam SP 500 spectrophotometer at 600 nm. Lysis was continuously plotted against time to give an S-shaped curve and the time to 50% lysis measured. This value in minutes was converted to CH₅₀ units/ml by reading it against a standard curve plotted on log-log paper of dilutions of normal serum in μl against time in minutes.

C3 levels

C3 was measured immunochemically by the 'rocket' technique. Dilutions of the test sera and appropriate dilutions of control sera were electrophoresed into agarose plates containing anti-C3 serum. The precipitation rockets developed to completion in 5–6 hours at 7V/cm. C3 values were expressed as a percentage of the normal pool by plotting the rocket heights of the test sera against a standard C3 dose response curve.

C1-esterase inhibitor levels

C1-est INH levels were measured by the method of Lachmann *et al.* (1973). Briefly, the synthetic ester acetyl tyrosine ethyl ester (ATE) was added to the test serum at 37°C in minimally buffered saline (containing just enough phosphate buffer pH 7.2 to raise the pH of the saline to 7.2). Active C1 (C1) was then added in 50 μl aliquots until the C1-esterase inhibitor was stoichiometrically saturated and neutralized. At this point free C1 attacks the substrate ATE and releases H^{+} ions. The released H^{+} ions were detected and neutralized by addition of M/40 NaOH from an autoburette attached to a pHstat titrator. The amount of C1 added before autotitration begins is a measure of the C1-esterase inhibitor activity. Results are expressed as a per cent of a normal pool.

Factor B levels

Factor B was measured by a 'haemolytic plate' technique. Agarose 1.2% made isotonic with phosphate-buffered saline pH 7.2 also contained 10 mmol/l EDTA, 7 mmol/l MgCl_2 , and 1/10 v/v human serum preheated to 50°C for 15 minutes to destroy factor B. Guinea pig red cells were added to

this mixture just before pouring the plate to give a final red cell concentration of 1%.

Results

At the time of review it was possible to divide the 39 patients into two distinct categories (Table 1): 17 cases had evolved into definite or classical RA, while 22 had remained palindromic. In no instance had the disease gone into complete remission. Of the 17 patients whose condition evolved into RA, 15 became seropositive and erosive, and 7 of these developed subcutaneous nodules. One (Case 11) developed the typical picture of rheumatoid polyarthritis with positive serology, but we failed to obtain follow-up x-rays, so it is not known whether he became erosive. One patient (Case 1) developed a polyarthritis of rheumatoid type, but after 5 years was still seronegative and nonerosive, although synovial histology showed typical rheumatoid changes. The disease in these 17 patients as a whole appeared to us to be at least as severe, and possibly more severe, as that among other hospital outpatients with RA at a comparable stage.

Of the 22 patients who remained palindromic, all had continued to experience episodic attacks separated by symptom-free intervals. In some the attacks had become milder or less frequent. None had evidence of permanent joint damage. Generally the pattern of attacks was similar to that described by Hench and Rosenberg (1944). The incidence of certain clinical features was as follows. Visible swelling of painful area 21/22; morning stiffness of affected joint during attack 14/22; skin colour change over painful area (red, purple, or bluish) 16/22; unrelated urticarial attacks 1/22; attacks related to menses 3/11; fever during attacks 6/22; concentrated urine at onset of attacks 4/22; transient finger nodules 4/22.

Symptoms suggestive of fluid retention during attacks were first noted in Case 14 (Table 1). He gave a history of oliguria and dark urine for some hours before an attack, followed by diuresis at the end of the attack. Daily weight and urinary output records kept by the patient at home gave some evidence of fluid retention during attacks, without however being conclusive. This patient's disease evolved into typical polyarticular RA before the complement study was started. On direct questioning, 4 other patients (Cases 19, 27, 31, 37) admitted to symptoms suggestive of fluid retention during attacks. The patients from whom we managed to obtain specimens of blood for complement determinations both during and between attacks are indicated in Table 1.

The time scale of the disease in all patients is

Table 1 Clinical details of 39 patients, 17 of whom developed RA and 22 of whom remained palindromic

Case no.	Sex	Age at first attack (yr)	Length of history (yr)	Family history of RA?	Joints affected*	Duration of attack† (d)	No. attacks per year	Severity of pain‡	Joint abnormality at first visit? §	ESR (mm/h)	Latex test titre	Erosions on initial x-ray? ¶	Duration of follow-up (yr)	Interval between first visit and diagnosis of RA(m)**	Status at follow-up††
Definite RA															
1	F	34	1	—	WH	14	1	++	+	6	—	—	6	6	RA (—NE; histology)
2	M	43	4	—	HK	2	4	++	+	8	>1/320	—	2	5	RA (+, E, N)
3	M	62	8m	—	SHHp	3	3	++	+	56	1/160	—	3	3	RA (+, E, N)
4	F	18	22	+	HW	14	V	++	+	40	>1/320	+	1	—	RA (+, E)
5	M	40	7	—	HWKS	3	V	++	+	15	>1/320	—	2	0	RA (+, E)
6	M	57	2	—	WH	2	V	++	+	10	>1/320	—	2	1	RA (+, E)
7	M	53	1	—	H	17	V	++	+	4	>1/320	—	2	6	RA (+, E)
8	M	38	1m	—	WS	2	V	++	+	40	1/80	—	5	1	RA (+, E, N)
9	F	49	1½	—	H	2	V	++	+	54	1/80	—	3	1	RA (+, E)
10	F	34	2	+	HSF	1½	100	++	—	8	>1/320	—	15	3 yr	RA (+, E, N)
11	F	54	6w	+	H	1	V	++	—	71	>1/320	—	3	1	RA (+, ?)
12	F	36	14	+	WHK	2	2	++	+	20	1/80	+	1	—8 yr	RA (+, E)
13	F	43	1	—	HF	1	V	++	+	16	—	—	5	4	RA (+, E, N)
14	M	63	6m	—	HWF	2	8	++	+	26	>1/320	+	1	6	RA (+, E)
15	F	32	6m	—	HF	½	V	++	+	26	—	—	5	2	RA (+, E)
16	M	46	5m	—	HF	1	20	++	+	5	—	—	3	3 yr	RA (+, E, N)
17	F	40	4	—	HF	10	1	++	+	28	—	+	5	1	RA (+, E, N)
Palindromic															
18	M	23	1	—	HKEA	3	3	++	+	15	—	—	3	—	P
19	F	22	1½	+	KEH	3	4	++	—	8	—	—	4	—	P
20	F	33	20	—	K	5	25	+	—	8	—	—	1	—	P
21	F	22	1½	—	W	11	6	++	+	5	—	—	7	—	P (C)
22	F	11	21	+	WHS	4	30	+	+	10	—	—	1	—	P
23	F	21	6	—	KW	4	9	++	—	6	—	—	3	—	P
24	F	24	1	—	HJ	20	6	++	—	11	—	—	3	—	P
25	F	20	1	—	WS	2	7	++	—	5	—	—	1	—	P
26	F	9	9	—	WKH	4	12	++	—	26	—	—	7	—	P (C)
27	F	21	1	—	HWK	3	12	++	—	10	—	—	5	—	P
28	F	43	4	+	HWS	7	12	++	+	14	—	—	5	—	P (C)
29	F	20	3m	—	HsK	2	6	++	—	20	—	—	1	—	P
30	M	42	6	—	HWAKE	5	V	++	+	17	—	—	1	—	P (Latex 1/320)
31	M	30	2	—	HSE	5	3	++	—	0	—	—	1	—	P
32	M	36	2	+	WH	3	4	++	—	6	1/160	—	5	—	P (Latex 1/160)
33	M	43	5	—	F	14	4	++	+	?	—	—	1	—	P
34	M	31	4	—	KSW	5	4	++	—	18	—	—	2	—	P (C)
35	M	34	9	—	HKEA	8	7	++	—	12	—	—	2	—	P
36	M	52	3m	—	HS	10	V	++	+	15	—	—	2	—	P
37	M	33	2	—	SKWA	1	12	++	—	8	—	—	1	—	P (C)
38	M	31	6m	—	KW	7	1	++	—	3	—	—	3	—	P (C)
39	M	28	4m	—	HW	2	V	++	—	10	—	—	1	—	P

*W = wrist; H = hand; K = knee; S = shoulder; Hp = hip; F = foot; E = elbow; J = jaw; A = ankle.

†Figures are only approximate. V = variable.

‡++ = very severe; + = moderately severe; + = mild.

§+ = any joint abnormality recorded, including affected joint during an acute episode and sometimes very minor changes.

¶Interval between first attendance and clinicians recording of diagnosis as RA. A negative value indicates that this diagnosis was established before first attendance.

set out in the Fig. Both this and Table 1 show that a number of patients had developed RA within a short time of their first attendance, and 2 actually before they were first seen although both had been clearly palindromic for a number of years before this change occurred. Cases 1–17 are thus patients with RA whose disease had a palindromic onset, while Cases 18–39 are those in whom the disease had remained palindromic up to the time of review. Cases 4 and 5 illustrate the fact that even after many years (20 and 7, respectively) typical palindromic rheumatism can evolve into classical seropositive erosive RA.

Fig. Time scale of disease pattern. Each horizontal bar represents one patient. Above: 17 patients who developed rheumatoid arthritis; below: 22 patients who were still palindromic at time of review. Within each group patients are ranked according to duration of palindromic rheumatism. For each patient the left hand end of the bar represents the onset of palindromic rheumatism, the right hand end represents the time of follow-up. The first attendance at The London Hospital is indicated by a vertical line.

We studied the information available to the clinician at the time when the patient was first seen in the outpatient clinic, to determine whether there were any indications as to which patients were going to develop RA within the period of follow-up. Some aspects of this analysis are set out in Table 2 (Cases 4 and 12 are excluded as they had already developed rheumatoid polyarthritis when first seen). Patients developing RA tended to be older and gave a shorter history. More of them showed some joint abnormality on examination than the group who remained palindromic, but the changes tended to be relatively insignificant in both groups. However, of the 15 patients who developed RA, 7 had an ESR >20 mm/h, 9 had a positive latex test, and 3 had radiological changes which in retrospect were probably early erosions. There were no significant differences in the characteristics of the episodic attacks, and it was noteworthy that features such as marked skin erythema and localized para-articular swelling occurred in both groups. We were not able to detect any differences between the two groups in the pattern of joints involved, and in both groups a family history of a close relative with RA was obtained in about one-quarter of the patients.

COMPLEMENT STUDIES

Table 3 shows the result of the complement studies in the 6 patients in whom specimens were obtained both during and between acute attacks. No evidence was obtained of any depression of complement activity either during or between attacks.

Discussion

The patients discussed here were selected on the basis that the diagnosis 'palindromic rheumatism' was applied by the clinician whom they first saw in the outpatient clinic. At that stage, 2 were already seen to have RA, and a number of others showed this within the next few months. Thus, these are instances of RA presenting with a palindromic onset. Other cases 'converted' to RA after remaining palindromic for as long as 7 and 20 years. 22 patients remained palindromic at the time of review. Clearly, with the duration of follow-up being relatively short in relation to the overall length of disease in many of these patients, this finding alone does not provide grounds for regarding these latter patients as suffering from a separate disorder: some or all of them might turn into cases of RA if followed-up long enough.

We attempted to find out whether among these patients as a whole there were clinical or investigative findings which separated those who did or would

Table 2 Characteristics of patients with palindromic rheumatism (at time of presentation)

	Patients who subsequently developed typical RA (n=15)		Patients who remained palindromic (n=22)	
Mean age at onset of symptoms (yr) (range)	45.9	(32-62)	28.6	(9-52)
Sex (M:F)	8:7		11:11	
Family history of RA	4/15	(26%)	5/22	(23%)
Mean duration of complaints (yr) (range)	1.7	(1 m-7 yr)	4.5	(3 m-21 yr)
Duration of attacks				
<24 h	3	(20%)	2	(9%)
24-48 h	7	(47%)	2	(9%)
2-7d	3	(20%)	13	(59%)
>7d	2	(13%)	5	(23%)
Severity				
Mild	0		3	(14%)
Moderate	6	(40%)	7	(31%)
Marked	9	(60%)	12	(55%)
Joint abnormality on examination	10	(67%)	7	(31%)
Raised ESR (>20) between attacks	7	(47%)	1	(4.5%)
Latex test $\geq 1/80$	9	(60%)	1	(4.5%)
Radiological erosions	3	(20%)	0	

Table 3 Results of serum complement determinations. A: sample obtained during attack; R: sample obtained during remission; C: control value; spaces indicate test not performed

Case no.	CH ₅₀ (units/ml)	C3 (%)	C1 esterase inhibition level (%)	Factor B (%)
21	A-1368 (C-1360) R-1278 (C-1000)	A-100 R-100	A-200 R-266	R-158 (total alternative pathway level)
26	A-967 } (C-1000) R-1000 }	A-100 R-100	A-125 R-100	A-88 R-130
28	A-1228 } (C-1000) R-1228 }	A-100 R-100	A-125 R-125	A-140 R-171
34	A-2560 } (C-1344) R-2260 }	A-100 R-60	A-125 R-150	
37	(1)A-2240 } (C-1344) (2)A-1960 }	(1)A-100 (2)A-55	(1)A-150 (2)A-125	
	R-2240 }	R-100	R-50	
38	A-1056 (C-1000) R-2400 (C-1600)	A-100 R-75	A-100 R-100	A-107 R-120 (total alternative pathway level)

develop RA from those who remained palindromic. No clear differentiation emerged. The difference in mean age at the onset of symptoms (46.9 years in those who became palindromic, 28.6 years in those who developed RA) might reflect some difference in tempo related to age. Hench and Rosenberg (1944) recorded a mean age of 34.9 years among their patients. There were no clear differences between the two groups in duration, severity, frequency, or distribution of the attacks, and it was notable that features regarded as being characteristic of palindromic rheumatism (dramatic acute onset, and redness and swelling occurring some distance away from a joint) were seen also among patients who subsequently developed RA. Certain findings recorded at the first visit (slight abnormality of a joint on examination, raised ESR, positive test for rheumatoid factor, and radiological joint abnormality) were more common among patients in whom frank RA was about to show itself (or had already begun to show itself). Other

cases provided no clues of this sort. Case 16, for example, continued to experience palindromic attacks for a further 3 years with complete clinical and laboratory normality between these episodes before developing classical seropositive, erosive nodular RA.

These case histories therefore do not provide grounds for separating patients who present with palindromic rheumatism into those who will and those who will not develop RA. However, the length of time before some cases do 'convert' is variable, and clinical and laboratory abnormalities may provide clues that this change is about to take place. Our data are in keeping with the findings and conclusions of Ansell and Bywaters (1959).

It is difficult to understand why Hench and Rosenberg (1944) did not observe the conversion to rheumatoid arthritis noted by subsequent authors. They found palindromic rheumatism to be 'rare'. During the period covered by the present study approximately 21 new cases of RA were

indexed for each new case of palindromic rheumatism. Hench and Rosenberg emphasize that palindromic rheumatism is not a variant of RA, and point out that in their group of 'atypical RA' the attacks lasted weeks or months. In our patients the attacks tended, if anything, to be shorter among those who subsequently developed RA. Mattingly (1966) noted that a number of his patients developed into RA, but the disease was mild and carried a good prognosis. This was not our experience. Among the rheumatoid patients who had a palindromic onset we found the disease to be at least as severe as that among patients lacking an episodic onset. A number of our patients received gold therapy. Our impression is that this treatment was perhaps less effective than Mattingly recorded, but our data are inadequate to draw firm conclusions about this. In his review, Lamont-Havers (1966) suggested that the relationship between palindromic rheumatism and RA was in doubt, but pointed out that the differentiation should be attempted because of the more favourable prognosis in the former disorder.

The complement screening tests were carried out to see if the local acute changes in vascular permeability around joints in palindromic rheumatism could be related to changes in serum complement levels. Increased vascular permeability can be produced by at least two products of complement activation. The first is generated during the fluid phase activation of C1 in hereditary angio-oedema and the second is produced during the activation and cleavage of C3 and C5 with release of anaphylatoxin peptides C3a and C5a.

The complement screening tests used in this study were sufficiently sensitive to have detected minor changes in serum levels though they may not have shown more subtle changes occurring at an extravascular site and in a limited anatomical area. It can only be concluded from this study that attacks of palindromic rheumatism are not precipitated by systemic activation of the complement system. Further studies may show the relationship between complement and acute fluid retention at a tissue level, though at present the attacks remain unexplained.

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