PAPERS AND ORIGINALS

Allergic Complications of Meningococcal Disease I—Clinical Aspects

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Summary

Out of 717 patients with meningococcal disease 53 showed one or more of the three allergic complications: 47 (6.6%) developed arthritis, 12 (1.7%) developed cutaneous vasculitis, and 6 developed episcleritis. These complications, which were often multiple, occurred six to nine days after the beginning of the illness and three to six days after the start of successful antibiotic therapy. Those patients with severe systemic disease were prone to the complications.

Histological and bacteriological study of the arthritis and vasculitis showed that these lesions were probably not due to persisting infection and suggested that they might be due to immune complex disease.

Introduction

The arthritis which complicates cerebrospinal fever occurs in about 4-10% of cases, often when the patient is recovering (Herrick and Parkhurst, 1919; Boger, 1944; Pinals and Ropes, 1964), and rarely leaves permanent damage. In an excellent paper, Herrick and Parkhurst (1919) described three types of arthritis in meningococcal infection. Type A was an acute polyarthritis appearing early in the disease in those with severe infections. It was accompanied by a profuse haemorrhagic rash and disappeared when this faded. Pain was great but signs were not marked and effusion was unusual. It was thought to be due

to haemorrhage into the articular and periarticular structures. Type B occurred later, about the fifth day, and usually affected only one joint, such as the knee, ankle, hip, wrist, or elbow. Swelling was great but pain and limitation of movement were slight. The fluid was purulent and meningococci were found in a third of the specimens. The process lasted one to four weeks, recovery being gradual but complete. Type C occurred even later; it was an aseptic serous meningitis forming part of the serum sickness resulting from serotherapy which was in use at that time. Later some clinicians remarked that it was not always easy to distinguish clearly between the types (Cattell, 1943; Fox and Gilbert, 1944).

There has been dispute over the pathogenesis of the arthritis. Keefer *et al.* (1934) concluded from a histological study that meningococcal arthritis was a metastatic acute synovitis. Others (Boger, 1944; Pinals and Ropes, 1964) questioned the infective theory, observing that it was uncommon to isolate meningococci from the joints. It is also of interest that Fox and Gilbert (1944) found meningococcal arthritis to be more common after the advent of sulphonamides than before.

The petechiae of spotted fever are found early in the disease. Meningococci can be isolated from the damaged small vessels, which are acutely inflamed and thrombosed (Hill and Kinney, 1947). A different type of rash occurs in chronic meningococcaemia. It is most frequently maculopapular although petechial, nodular, and ecchymotic lesions are also seen. This rash is often accompanied by fever and arthralgia and more rarely by arthritis, carditis, nephritis, and eye lesions (Benoit, 1963). Ognibene and Dito (1964) suggested that these skin lesions might be produced by soluble antigen-antibody complexes. Similar lesions accompanied by fever, arthralgia, and arthritis have been found after gonococcal infection (Abu-Nassar *et al.*, 1963; Barr and Danielsson, 1971). They are thought to be due to bacterial embolization, though in only a few cases have gonococci been isolated from the lesions or from the blood.

Episcleritis associated with arthritis has not been previously described after acute meningococcal infection, but pericarditis and arthritis are sometimes seen together. (Herrick, 1919; Morse *et al.*, 1971). Morse *et al.* (1971) suggested that the pericarditis may be due to a hypersensitivity response induced by preceding infection.

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In this paper we describe the features of 53 patients who developed either arthritis or cutaneous vasculitis or episcleritis during or after successful treatment of their acute meningococcal infection. On the basis of this information we suggest that these are allergic complications. In our second paper more direct evidence is provided for this concept.

Patients

In the period January 1970 to July 1972 762 cases of meningitis and five cases of meningococcaemia without meningitis were treated at the Ahmadu Bello University Hospital, Zaria. The organisms responsible were: *Neisseria meningitidis*, 470 cases (61.7%); *Streptococcus pneumoniae*, 32 (4.2%); *Haemophilus influenzae*, 11 (1.4%); and others, 7 (0.9%). The organism was not found in 247 (32.4%). Detailed immunological investigations, however, using an indirect haemagglutination test for the detection of antigen in cerebrospinal fluid and a direct haemagglutination test on paired sera of a sample of these patients showed that probably almost all were infected with group A meningococci (B. M. Greenwood and H. C. Whittle, unpublished). This is the only type responsible for meningococcal disease in this area (Lapeyssonie, 1963; Greenwood *et al.*, 1971). The "unknowns" have therefore been added to the *N. meningitidis* group, giving a total of 717 patients in this study.

The routine treatment of meningococcal meningitis was crystalline penicillin 250,000 to 500,000 IU/kg daily given every four or six hours for about five days; 61 of the patients were treated with chloramphenicol during a trial of that drug.

All patients with proved or presumed meningococcal disease who developed arthritis, cutaneous vasculitis, or episcleritis have been included in this study. These complications were not seen in other types of meningitis with the exception of one patient who presented with pneumococcal pneumonia, meningitis, and arthritis.

Methods

Clinical.—Patients were examined daily for evidence of cutaneous vasculitis and arthritis. The diagnosis of arthritis was accepted only if objective signs of inflammation such as swelling, tenderness, warmth, or limitation of movement were present.

Bacteriological.—Cerebrospinal fluid, synovial fluid, and aspirates from bullae were examined by Gram's stain and culture on chocolate agar shortly after collection. After 24 hours' incubation in 5% CO₂, organisms were identified from their morphology, by Gram's stain, and by the oxidase test. Blood was cultured in thioglycolate broth.

Histological.—Biopsy specimens were fixed in formol saline, cut, and a section from each was stained with haematoxylin and eosin and Gram's stain.

Patients with Complications

Of the 717 patients 53 (7.4%) had one or more of the three complications. Thirty-five developed arthritis alone, 5 cutaneous vasculitis alone, and 1 episcleritis alone. In the others complications were multiple; 7 developed arthritis and vasculitis, 4 arthritis and episcleritis, and 1 had all three complications.

Age and Sex.—Complications were more common in older people (fig. 1). Thirty-three males and 20 females were affected, which was the ratio found in our other patients with meningococcal meningitis.

Presenting Features.—These are shown in table I, and the findings in patients who did not have complications are given for comparison. Conjunctival petechiae and a positive blood culture were common in the group with complications. Five of these patients presented with hypotension, multiple petechiae, and no signs of meningitis.

FIG. 1—Incidence of allergic complications by age. Numerical incidence is shown above the bars.

TABLE I—Presenting Features of Patients with and without Complications

	Complications		No Complications	
	No.	%	No.	%
Meningitis	48/53	91	664/664	100
Meningococcaemia without meningitis	5/53	9	0/664	0
Conjunctival petechiae	43/53	81	139/416	33
Positive blood culture	11/38	29	23/154	15

Bacteriology.—On admission *N. meningitidis* was found by Gram's stain or culture in the cerebrospinal fluid or blood of 41 patients (77%). In 12 (23%) this was presumed to be the organism, as the meningitis was associated with conjunctival petechiae.

Treatment and Progress.—Thirty-seven patients were treated with penicillin, 4 received chloramphenicol, 7 were given both, and 5 had sulphadimidine in addition to the other two drugs. No drug was especially associated with complications. The response to treatment was rapid and did not differ from the group without complications. The mean period of disturbed consciousness was $1.3 \pm \text{S.D. } 0.5$ days, mean duration of fever 2.1 ± 1.4 days, and mean duration of neck stiffness 3.7 ± 1.5 days.

Timing of Complications.—The onset of the complications is related to the duration of disease and start of therapy in fig. 2. The duration of illness is dated from the first symptom. In most patients signs of meningitis had greatly improved and the petechiae had faded or were fading when the complications

FIG. 2—Time of onset of allergic complications. Fine arrow marks mean for start of treatment; thick arrow relates to onset of complications.

appeared. At that time mild fever was recorded in 51% (23 out of 45) of the patients as opposed to 6.1% (3 out of 49) of a sample of the group without complications ($P < 0.001$). Slight proteinuria (30–100 mg/100 ml) was noted in 26% (9 out of 35) of the patients tested and in 15% (7 out of 46) of the controls (P not significant). Red cells were found in five of the nine patients with complications. One out of 16 patients had a positive blood culture at that time.

ARTHRITIS

Forty-seven patients (6.6%) developed arthritis. The mean onset of the joint signs was 5.7 ± 2.7 days after the start of the illness and 3.3 ± 2.5 days after the beginning of therapy. Altogether 38.2% of these patients gave a history of joint pains compared with 19.8% (35 out of 177) of a sample of patients without complications ($P < 0.05$). Only eight patients had objective signs of arthritis on admission. Seventeen patients (36%) had monarticular arthritis which attacked large joints such as knee or wrist. Thirty patients (64%) had two or more joints affected. These were usually large joints such as knee, wrist, elbow, or ankle, which were often bilaterally involved. Occasionally smaller joints such as the metacarpophalangeal were affected. Effusions were most common in the knees but also occurred in elbow and wrist.

Typically the patient would experience pain and swelling in a large joint such as the knee about three days after the start of the illness. An effusion would develop within the next 24 hours but after three or four days signs and symptoms abated, leaving the joint slightly tender but mobile. Meanwhile arthritis might have developed in another joint or joints. Rarely was arthritis so painful that the joints needed to be immobilized. Aspirin usually relieved pain but antibiotics did not affect the course of events. The mean duration of arthritis was 6.3 ± 3.9 days. In no case was any residual effect noted in the short follow-up period of two to three weeks.

Synovial Fluid.—Ten samples of fluid were obtained from nine patients. Five specimens were obtained within 24 hours of the onset of arthritis; the interval in the rest varied from 36 to 200 hours. All the fluids were very turbid but in none were organisms seen on Gram's stain or grown in culture. The mean leucocyte count was $43,000 \pm 33,000/\text{mm}^3$ with a differential of $83 \pm 8\%$ polymorphonuclear cells, $12 \pm 6\%$ mononuclear cells, and $5 \pm 2\%$ lymphocytes. The mononuclear cells were often strikingly large, with vacuolated cytoplasm. Mean total protein was 6.2 ± 1.5 mg/100 ml. Variations in these findings were not related to the duration of arthritis.

Synovial Biopsy.—Specimens were obtained from the knee joints of four patients. The picture was one of inflammation with a mixed infiltrate of polymorphs and mononuclear cells in the absence of organisms.

CUTANEOUS VASCULITIS

Twelve patients (1.7%) developed cutaneous vasculitis. The mean onset was 7.1 ± 2.2 days after the start of the illness and 5.0 ± 1.5 days after the beginning of antibiotic treatment. The first sign was a single area of darkened skin some 2 by 1 cm ringed by a blistered edge (fig. 3). This was often triangular. It appeared on either the dorsum of the hand or the lower legs or the deltoid areas. The underlying tissue was usually slightly swollen, warm, and tender. Some 24 hours later a sterile bulla containing red cells and leucocytes formed (fig. 4). Two or three days later the skin broke, leaving a shallow, punched out ulcer (fig. 5) which soon healed. In two patients nodules as well as vesicles appeared in the area of darkened skin; later these coalesced and followed the typical course.

In five patients the cutaneous vasculitis consisted of a single lesion. In seven the lesions were multiple, cropping on the legs

FIG. 3—Early skin lesion (<24 hours) consisting of darkened skin with blistered edge. Underlying tissue is swollen.

FIG. 4—Later lesion (24–48 hours) on hand showing bullous formation.

FIG. 5—Ulcers healing at 10 days in patient with particularly severe cutaneous vasculitis.

TABLE II—*Histology of Cutaneous Vasculitis*

Case No.	Interval between Appearance of Lesion and Biopsy (Hours)	Microscopy						Remarks on Vasculitis
		Vessels				Cellular Infiltrate		
		Oedema	Thrombosis	Necrosis	Haemorrhage	Polymorpho-nuclear	Mononuclear	
1	<24	+	—	—	—	+	+	Mild, early
2	<24	++	+	+	—	++	++	Moderate, early
3	<24	+++	+	+	—	++	+	Moderate, early
4	<24	+++	+	++	++	+++	+	Severe, early
5	<24	+++	++	++	+++	+++	++	Severe, early
6	24	++	++	++	++	++	++	Severe, early
7	24-36	++	—	—	—	—	+++	Mild, late
8	24-48	+	+	+	—	+	++	Mild, late
9	72	++	++	++	++	++	+++	Severe, late

and arms at irregular intervals over two or three days. Two of these patients also developed a tender, warm nodule similar to an Osler's node. Three of the patients with widespread cutaneous vasculitis developed signs of heart failure at the same time. Seven of the 12 patients also had arthritis.

Histology.—Nine biopsy specimens were taken at varying intervals after the appearance of the lesion. The microscopic characteristics are summarized in table II. The vessels of both the superficial and deep dermis showed a spectrum of damage. The mild early lesions consisted of dilatation of small blood vessels with oedema of the coats and perivascular infiltration with polymorphs and mononuclear leucocytes. The severe early lesion showed marked oedema of both small vessel and arteriolar walls with thrombosis and sometimes necrosis (fig. 6). Some had ruptured, causing haemorrhage. The vascular coats and surrounding structures were infiltrated with polymorphs and mononuclear cells. The late lesions showed a similar spectrum of damage to the vessels but the cellular infiltrates were mainly mononuclear. Epidermal changes ranged from slight hyperkeratosis in mild cases to intense infiltration of the basal

EPISCLERITIS

Inflammation of one or both sclerae was seen in six patients. This occurred nine days after the start of the illness and six days after the start of treatment. The inflammation lasted about seven days and although uncomfortable left no permanent damage. No obvious uveitis or keratitis was seen but minor changes may have been missed as a slit lamp was not available. Local antibiotic therapy appeared to have no effect on the inflammation. Five of the six patients also had arthritis at that time.

Discussion

The incidence of arthritis in this series was similar to many reported before the advent of antibiotic therapy (Herrick and Parkhurst, 1919; Boger, 1944). Likewise the timing, distribution, and effects of the complications were similar to the type B arthritis of earlier reports. Antibiotics did not seem to prevent or modify the course greatly. Joint pains, however, were a common symptom and arthritis was seen from day 1 to day 12 of the illness. Thus it was not easy to draw a clear distinction between the three types of arthritis described by Herrick and Parkhurst.

The turbid fluid in the joints in the absence of organisms needs an explanation. Pinals and Ropes (1964) suggested that early in the disease during the septicaemia meningococci cause acute synovitis. In most joints this clears but in some such as knees or elbows the process progresses to infection of the joint space. They postulated that though the bacteria died inflammation continued owing to induction of hypersensitivity by bacterial, leucocytic, or tissue breakdown products. The findings in the synovial fluid and synovial biopsy specimens from our patients were compatible with a local Arthus reaction or deposition of antigen-antibody complexes in the joints.

Some authors have recorded the appearance of a papular (Cattell, 1943; Fox and Gilbert, 1947) or bullous (Pinals and Ropes, 1964) skin eruption around the time the arthritis appears. The coincidence of arthritis and these sterile bullous lesions which we have described could also be explained by an underlying allergic mechanism. Histologically the skin lesions showed a vasculitis similar in appearance to that caused by the deposition of antigen-antibody complexes or to an Arthus reaction (Cochrane and Wiegler, 1958). Cochrane and Wiegler (1958) showed that if antigen-antibody complexes were injected into the skin of guinea-pigs mild vascular damage occurred about 20-24 hours later; leucocytes were found in the surrounding tissues and in the vessels, which occasionally thrombosed or ruptured. They noted that in the direct Arthus reaction severe damage to vessels occurred at five to eight hours, when vessels and tissues were heavily infiltrated with polymorphs. The later stages of both these reactions were characterized by a mononuclear cell infiltrate. Our biopsies showed a spectrum of damage covered by both types of reaction. The mild early reaction fitted the picture of complex-induced damage; the severe damage looked like an Arthus reaction. In practice it was

FIG. 6—Histological appearances of moderately severe early lesion. Oedematous and thrombosed vessels are infiltrated with polymorphonuclear and mononuclear cells.

layer with mononuclear cells with overlying atrophy. At the stage of bullous formation parakeratosis and degeneration of the prickle layer preceded intraepidermal necrosis. In severe lesions dermal appendages were disorganized or destroyed by the heavy infiltration of leucocytes. Bullae contained erythrocytes, polymorphs, and eosinophils. No organisms were seen in or cultured from the aspirates of three bullae. Gram staining of six of the biopsy specimens showed no organisms in the tissue.

not possible to decide which of the mechanisms was responsible as the exact age of the lesions was not known and sequential specimens were not obtained from the same patient.

When antigen is injected into the vitreous body of a rabbit's eye an inflammatory response occurs in the uvea after about a week, when circulating antibodies appear (Silverstein *et al.*, 1961). Episcleritis is associated with arthritis which is produced by injecting rats with bacteria in adjuvants (Waksman and Bullington, 1956), and the complication is also well known in patients with rheumatoid arthritis (Boyle and Buchanan, 1971). In our patients petechiae, which presumably contained meningococcal antigen, were often seen in the conjunctivae and sclerae at the time of admission. About six days later episcleritis appeared, which may have been the result of a reaction between this depot of antigen and antibodies which were then in production (Artenstein *et al.*, 1971).

The incidence of proteinuria at the time of the complications did not differ significantly from the uncomplicated group. Thus we have no evidence of immune complex nephritis. Either proteinuria was coincidental and due to another cause, such as schistosomiasis, or there was slight transient renal damage related to the preceding infection in both groups.

The arthritis, cutaneous vasculitis, and eye lesions appeared three to five days after the start of therapy, when the patients were recovering from meningococcal infection. At that stage antibiotics had obviously been successful, as all blood cultures except one were sterile and no organisms could be found or cultured from the lesions. Thus we have little evidence that active and persistent infection was the cause of these complications. Penicillin allergy is not a likely explanation as the allergic complications were equally common in the penicillin and chloramphenicol groups during trials of these drugs and were well known before the days of penicillin.

Allergy to meningococcal antigen seems the most likely explanation. In general the patients who developed the lesions suffered severe systemic infection characterized by profuse petechial haemorrhages, joint pains, positive blood culture, and sometimes hypotension. They were also likely to have meningococcal antigen in their blood (Greenwood *et al.*, 1971). The complications occurred at a time when antibodies were being produced. The histological changes in joints and skin were in keeping with immune complex disease.

One odd feature of this group was the high incidence of people over the age of 30, an age when meningococcal meningitis is

uncommon in the meningitis belt (Lapeyssonie, 1963). Either these patients were unusually susceptible to the infection or, as Morse *et al.* (1971) suggested, the allergic reactions are a feature of an anamnestic response to past infection. This is not likely as patients who have high haemagglutinating antibody titres on admission have less severe disease, and in such cases meningococci or circulating antigens are rarely detected (B. M. Greenwood and H. C. Whittle, unpublished). It is known that patients with chronic meningococcaemia who also develop arthritis and skin lesions are unable to agglutinate the infecting organism (Benoit, 1963). Perhaps our group of patients had a defective or slow antibody response which allowed a more severe infection. Large amounts of antigen would then circulate in the blood and be deposited in synovia, skin, and the eye. Later, when antibodies are produced, antigen is still in excess and damaging complexes are formed either directly at these sites (Arthus-type situation) or in the blood, from which they are deposited in the vessels of these structures (serum sickness situation).

References

- Abu-Nassar, H., Hill, N., Fred, H. L., and Yow, E. M. (1963). *Archives of Internal Medicine*, 112, 731.
 Artenstein, M. S., *et al.* (1971). *Journal of Infectious Diseases*, 124, 277.
 Barr, J., and Danielsson, D. (1971). *British Medical Journal*, 1, 482.
 Benoit, F. L. (1963). *American Journal of Medicine*, 35, 103.
 Boger, W. P. (1944). *American Journal of the Medical Sciences*, 208, 708.
 Boyle, J. A., and Buchanan, W. W. (1971). *Clinical Rheumatology*. Oxford, Blackwell.
 Cattell, J. P. (1943). *New England Journal of Medicine*, 229, 49.
 Cochrane, C. G., and Wiegler, W. O. (1958). *Journal of Experimental Medicine*, 108, 591.
 Fox, M. J., and Gilbert, J. (1944). *American Journal of the Medical Sciences*, 208, 63.
 Greenwood, B. M., Whittle, H. C., and Dominic-Rajkovic, O. (1971). *Lancet*, 2, 519.
 Herrick, W. W. (1918). *Medical Clinics of North America*, 2, 411.
 Herrick, W. W., and Parkhurst, G. M. (1919). *American Journal of the Medical Sciences*, 158, 473.
 Hill, W. R., and Kinney, T. D. (1947). *Journal of the American Medical Association*, 134, 513.
 Keefer, C. S., Parker, F., and Myers, W. K. (1934). *Archives of Pathology*, 18, 199.
 Lapeyssonie, L. (1963). *Bulletin of the World Health Organization*, 28, Suppl.
 Morse, J. R., Oretsky, M. I., and Hudson, J. A. (1971). *Annals of Internal Medicine*, 74, 212.
 Ognibene, A. J., and Dito, W. R. (1964). *Archives of Internal Medicine*, 114, 29.
 Pinals, R. S., and Ropes, M. W. (1964). *Arthritis and Rheumatism*, 7, 241.
 Silverstein, A. M., Welter, S., and Zimmerman, L. E. (1961). *Journal of Immunology*, 86, 312.
 Waksman, B. H., and Bullington, S. J. (1956). *Journal of Immunology*, 76, 441.

Allergic Complications of Meningococcal Disease II—Immunological Investigations

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Summary

Immunological investigation of four patients with meningococcal meningitis who developed arthritis or cutaneous lesions showed circulating meningococcal antigen at the time of presentation in each patient. It was cleared from the circulation over the next few days.

Circulating antibody was detectable in three of the four patients about a week after the onset of the illness. A marked fall in the serum C₃ level occurred in two patients at about that time. Deposits of meningococcal antigen, immunoglobulin, and C₃ were detected in the synovial fluid white cells of the two patients studied and in one of three skin biopsies examined. These findings suggest that the arthritis and cutaneous lesions of meningococcal meningitis may be due to immune complex formation.

Introduction

Our previous paper showed how a proportion of patients with meningococcal meningitis developed arthritis and unusual

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