Haemophilus endocarditis

*A. M. EMMERSON
M.B. B.S., M.R.C.Path.

†R. M. PERINPANAYAGAM
M.R.C.Path.

†D. E. BARNADO
M.D., M.B. B.S., F.R.C.P.

*Department of Microbiology, *Whittington Hospital, and
Queen Mary's Hospital, London*

Summary

Two cases are presented of *Haemophilus* endocarditis in patients with presumed normal valves. One case was due to *H. influenzae* presenting as a typical case of infective endocarditis and the other was due to *H. parainfluenzae* presenting as an acute pyrexia of unknown origin.

The difficulties in making the diagnosis and the optimal treatment are discussed.

Introduction

Haemophilus endocarditis is an uncommon entity according to Keith and Lyon (1963), Weinstein and Rubin (1973) and, in a large series of 422 cases of endocarditis reported by Cates and Christie (1951), it occurred in less than 1%. Almost all cases are of subacute infections, commonly superimposed on rheumatic or congenital disease and rarely on prosthetic valves. Two cases are now described.

Case no. 1

A 57-year-old Caucasian woman was admitted with a 4-week history of general malaise, anorexia, loin pain, fever and rigors. One week before admission she had noted painful purple lesions on her fingers. There was no past history of rheumatic heart disease and she had not had any recent surgical or dental treatment. Perinatal examination 20 years before and subsequent routine medical examinations which included the cardiovascular system had all been regarded as normal.

Physical examination revealed pyrexia (38.8°C), mucosal pallor and a solitary Osler's node on her right fingertip. The pulse was regular (96/min) and BP normal (110/60 mmHg). The apex beat was displaced 2.5 cm lateral to the left mid-clavicular line and a grade 3/4 apical systolic murmur of mitral regurgitation was heard, the first and second sounds being normal. The jugular venous pressure was raised 3 cm.

Results of investigations on admission

Hb, 9.9 g/dl; WBC, $18.3 \times 10^9/l$ with 89% neutrophils; ESR, 67 mm/hr (Westergren) and microscopic haematuria. Further investigations showed a normal ECG (except for sinus tachycardia), slight radiographic cardiomegaly together with small bilateral pleural effusions and upper lobe blood diversion. Linear shadowing at the left lung base was present suggesting resolving consolidation in this region. An echocardiograph showed a non-rheumatic valve with thick vegetations on its under surface and normal left ventricle in all respects.

Bacteriology. Three sets of blood cultures (2 in Castaneda's and one in Brewer's medium in each set) yielded bacterial growth after 2 days' incubation; Gram stains of colonies visible on the Castaneda slopes showed long filamentous Gram-negative rods. Subculture and further testing identified the organisms as *H. influenzae*. This proved to be a non-typable strain (Standards Reference Laboratory, Central Public Health Laboratories, Colindale, London). The organism was sensitive to ampicillin, sulphonamide, trimethoprim, chloramphenicol and streptomycin by disc testing. Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) mg/l tested against ampicillin and streptomycin were as follows: ampicillin, MIC 0.25; MBC 0.25; streptomycin, MIC 4.0; MBC 8.0. Synergism between ampicillin and streptomycin was demonstrated *in vitro* by the technique described by Anand and Paull (1976). Serum bactericidal assays using the infecting strain a few days after combined therapy with ampicillin and streptomycin showed peak and trough titres of 1 : 64 and 1 : 8 respectively.

Treatment and progress were as follows

It was clinically evident that the patient had infective endocarditis and after 3 sets of blood cultures had been taken, treatment was commenced

with benzyl penicillin 12 Mu./day i.v., and streptomycin 750 mg/day i.m. When bacteriological evidence of culture and the identity of the organism and its sensitivities were available, ampicillin 12 g/day were substituted for benzyl penicillin, and streptomycin was continued. This combination therapy was given for 4 weeks. Cardiac failure was treated with diuretics. Considerable clinical and subjective improvement occurred after the institution of therapy; however, the patient later developed a deep venous thrombosis in the right calf which was treated with heparin, and features of worsening regurgitation which necessitated emergency mitral valve replacement (Starr-Edwards prosthesis). A para-prosthetic leak followed surgery; following surgical repair of the leak she developed cardiogenic shock and died.

Case no. 2

A 24-year-old electrical engineer was admitted with a 6-day history of nocturnal sweats, headache, vomiting and rigors. His initial illness was a rigor which had lasted 30 min. There was no significant past or family history and he had not been abroad. In particular, he had no history of heart disease and had not had recent dental treatment.

Examination revealed a dehydrated, well built man with a temperature of 39.5°C. There was no anaemia, cyanosis, jaundice or lymphadenopathy. There were 2 small dark brown splinter haemorrhages under the finger nails but these were not considered significant as there were signs of local trauma. There were no cardiac murmurs, the BP was 120/80 mmHg. The pulse rate was 120/min, regular, the jugular venous pressure was normal and the apex beat was in the 5th intercostal space. The lung bases were clear and there was no abnormality in the alimentary or neurological systems.

Results of investigations on admission

Hb, 14.4 g/dl; WBC, $8.3 \times 10^9/l$ with 73% neutrophils; ESR was 32 mm in the first hour (Westergren) and normal electrolytes. Microscopy and culture of several fresh urines revealed no abnormality and in particular microscopic haematuria was not detected. No abnormalities were detected in the chest X-ray, in the electrocardiogram or in the cerebrospinal fluid. Blood cultures taken on admission and serially during the first week showed no bacterial growth.

Bacteriology. The patient's venous blood was cultured in 50 ml digest broth containing cooked meat and 0.1% glucose, and these primary cultures were plated out on to horse blood agar, incubated aerobically and anaerobically, at intervals of 24 hr, 48 hr, 3 days and 7 days. These subcultures were incubated for 48 hr before being discarded.

Blood cultures collected on the first, 4th, 12th and

15th day of illness showed no growth after 7 days' incubation. From 2 blood culture bottles collected on the 7th day and one of 3 cultures collected on the 8th day of illness, a pleomorphic Gram-negative bacillus was isolated. Growth on solid medium occurred only after 48 hrs' incubation under anaerobic conditions and only on subcultures made after the primary medium had been incubated for 48 hr.

Morphologically the organism was a slender Gram-negative bacillus 2–3 μ long, somewhat pleomorphic but not showing any marked coccobacillary forms. On blood and chocolate agar incubated anaerobically, the organism produced a grey non-haemolytic colony approximately 2 mm in diameter after 3 days. No growth occurred on digest agar aerobically or chocolate agar and blood agar anaerobically. When the colony was scraped off the surface of the medium, a small pit was left. Since at this time the organism would only grow under anaerobic conditions (with added 5% CO₂), satellitism tests were done under anaerobic conditions using X, V, XV factor discs. Profuse growth occurred around the V and XV discs but not the X factor disc. However, since *H. influenzae* is capable of growing anaerobically without X factor this satellitism to the V factor alone was not a conclusive test. After daily subculturing for 8 days, the patient's organism gained the ability to grow aerobically and the test was repeated. Satellitism occurred around the V and XV discs to confirm that the organism was *H. parainfluenzae*.

When the organism was able to grow aerobically, a suspension was made in physiological saline and heated to 56°C for one hr. The patient's serum collected on the 2nd day of illness and another specimen collected on 17th day of illness were tested against this suspension at 37°C and the agglutination titres rose from 320 to 2560. A complement fixation test showed a rise from a titre of 40 to one of 320. The organism was sensitive to ampicillin (MIC 1.0 mg/l), gentamicin (MIC 0.5 mg/l), streptomycin and chloramphenicol.

Treatment and progress

Eight days after admission when investigations had revealed no cause for the illness, a diagnosis of pyrexia of unknown origin was made and he was started on ampicillin 500 mg i.m. 6-hourly. This treatment produced a fall in his temperature initially, but 3 days later he was again pyrexial. Gentamicin was therefore added to the regime at a dose of 80 mg i.m. 12-hourly.

There was subjective improvement of his symptoms for a period of approximately one week but on the 18th day after admission, for the first time, there appeared signs indicative of endocarditis – 2 splinter

haemorrhages and an Osler's node. Two days later he developed a right-sided hemiplegia with dysphasia. An EEG confirmed that a cerebral embolism had occurred in an area consistent with the distribution of the left middle cerebral artery. A pansystolic murmur became audible at this stage. By this time, laboratory results of blood culture were available and based on sensitivity results and MIC values, a regime of i.v. ampicillin 15 g/24 hr in divided doses was started. This was continued for 6 weeks, during which time the patient remained afebrile. There were no further embolic phenomena, and over the next few weeks his walking and speech continued to improve. He was discharged home on the 44th day after admission and has remained well.

Discussion

Endocarditis caused by *Haemophilus* spp. is uncommon and forms less than 1% of a series of cases reported by Morgan and Bland (1959) and Keith and Lyon (1963). Geraci *et al.* (1977) at the Mayo Clinic, recognized 14 cases of *Haemophilus* endocarditis (only one of which was *H. influenzae*) between 1963 and 1976 of which 10 were seen between 1972 and 1976 suggesting to them a possible rise in incidence, but improved culture techniques may have contributed to detection.

There appears to be a higher morbidity and mortality in *Haemophilus* endocarditis compared with other forms of bacterial endocarditis and since so few cases of endocarditis due to *Haemophilus* spp. have been reported the optimum treatment has still not been defined. A recent article (Editorial, 1977) recommended that treatment should be with a combination of ampicillin and gentamicin for 6–8 weeks although Garrod and O'Grady (1971) suggested that ampicillin and streptomycin could be a logical first choice and Geraci *et al.* (1977) claim that ampicillin alone in a dosage of 12 g/day for 3 weeks is adequate for ampicillin-sensitive organisms. This is borne out by the successful outcome in the present case no. 2,

but the importance of adequate therapy is well illustrated in this case when the initial lack of progress and indeed, deterioration while on 2 g/day were reversed only when high dose i.v. therapy, 15 g of ampicillin daily was instituted.

In case no. 1, despite appropriate and adequate antibiotic therapy (as evidenced by bactericidal levels of antibiotics), valvular destruction was such that early surgical intervention was imperative.

The experience with these 2 cases (one treated promptly as an endocarditis and the other treated initially as a pyrexia of unknown origin) highlights the difficulties in the initial management of *Haemophilus* endocarditis since at no time were there any predisposing features to suggest that either patient was at risk.

Acknowledgments

We thank Dr A. Bloom for permission to publish the second case and Professor K. Zinnerman for confirming the identification of the organism. We are grateful to Dr D. C. Turk for his assistance.

References

- ANAND, C.M. & PAULL, A. (1976) Technical methods. A modified technique for the detection of antibiotic synergism. *Journal of Clinical Pathology*, **29**, 1130.
- CATES, J.E. & CHRISTIE, R.A. (1951) Subacute bacterial endocarditis. A review of 422 patients treated in 14 centres appointed by the Penicillin Trials Committee of the Medical Research Council. *Quarterly Journal of Medicine*, **20**, 93.
- EDITORIAL (1977) *Haemophilus* endocarditis. *Lancet*, **i**, 1349.
- GARROD, P.L. & O'GRADY, F. (1971) *Antibiotic and Chemotherapy*, 3rd edn, p. 292. Churchill Livingstone, Edinburgh and London.
- GERACI, J.E., WILKOWSKA, C.J., WILSON, W.R. & WASHINGTON, J.A. (1977) *Haemophilus* endocarditis. Report of 14 patients. *Proceedings. Mayo Clinic*, **52**, 209.
- KEITH, T.A. & LYON, S.A. (1963) *Haemophilus aphrophilus* endocarditis. *American Journal of Medicine*, **34**, 535.
- MORGAN, W.L. & BLAND, E.F. (1959) Bacterial endocarditis in the antibiotic era, with special reference to later complications. *Circulation*, **19**, 753.
- WEINSTEIN, L. & RUBIN, R.H. (1973) Infective endocarditis – 1973. *Progress in Cardiovascular Diseases*, **16**, 239.