PAPERS AND ORIGINALS

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Bacteriology of abscesses of the central nervous system: a multicentre prospective study

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Summary

Pus from 46 patients with abscesses of the central nervous system (CNS) was examined for bacteria; bacteria were found in all patients. Streptococci were isolated from 36 patients and most isolates were Streptococcus milleri, Lancefield Group F, Ottens and Winkler type 0 III. Staphylococci were isolated from nine patients, organisms of the bacteroides group from 11, Proteus spp from seven, Klebsiella aerogenes from one, and Haemophilus aphrophilus from one. Pure cultures predominated over mixed cultures. Streptococci were isolated from abscesses of all types, and at all sites, but members of the Enterobacteriaceae and of the bacteroides group were isolated, in mixed cultures, principally from abscesses of the temporal lobe secondary to infection of the middle ear. Staphylococci predominated in abscesses that followed accidental or surgical trauma. Compared with fully sensitive control organisms, microbes infecting half the patients were resistant to penicillin.

The prognosis of abscess of the CNS is grave, and the microbiological findings have important consequences for treatment. Prompt inoculation of specimens to culture plates and prompt incubation are mandatory if bacteria are to be cultured. Inhibitors of antimicrobial agents should be added to culture media if antibiotics have been administered. Provided that the site of the abscess and the antecedent history are ascertainable, the neurosurgeon should be able to start appropriate treatment while awaiting the results of culture.

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Introduction

There have been many reports on the surgery and treatment of brain abscess. Some have included bacteriological findings, but, with few exceptions,[1 2] laboratory procedures have not been described. McFarlan[1] seems to be the only author to have written solely on the bacteriology of brain abscess. Reasoned use of antibiotics depends on knowledge of the causative microbes, but abscesses of the central nervous system (CNS) with negative cultures have been reported in 9-63% of published cases. The reasons for so high an incidence of negative culture are not clear.

We describe here a prospective study designed to establish the microbial causes of abscesses of the CNS and to seek methods of improving the yield from culture.

Methods

ORGANISATION OF THE STUDY

Surgeons and microbiologists at several English neurosurgical centres joined in a prospective study. The results obtained by the examining laboratory (Queen Charlotte's Hospital for Women) were forwarded to consultant microbiologists as well as to the appropriate surgeons.

Participating centres were issued with specimen collection kits designed to maintain samples at 4°C during transit. Pus from 46 patients was taken directly at operation and was sent to the examining laboratory by express road or rail services. It was transported in Brewer's thioglycollate medium with added β-lactamase (Whatman), and in plain sterile universal containers and was accompanied by a form identifying the patient and giving details of current and projected antibiotic treatment. Successive specimens of pus were examined from patients whose abscesses had to be aspirated more than once. No specimen was in transit more than 16 hours, and most were received within five hours. On completion of the study summaries of the clinical notes were forwarded for analysis to the examining laboratory.

BACTERIOLOGICAL INVESTIGATIONS

Examination of specimens—Pus was examined as soon as it was received, and details of the Gram-stained appearance and subsequent

microbial findings were telephoned to the surgeon in charge. The pus was inoculated on to plates of 6% horse blood agar incubated aerobically and anaerobically with added carbon dioxide; to horse blood agar with added crystal violet, nalidixic acid, or neomycin incubated anaerobically; to chocolated blood agar incubated in 10% carbon dioxide; and to MacConkey's medium. Plates were incubated at 37°C for up to seven days. Subcultures were made from Brewer's thioglycollate medium after preliminary incubation at 37°C for 48 hours. Antibiotic sensitivities were determined by the disc method by comparison with organisms of known sensitivity, and minimum inhibitory concentrations (MICs) were determined by a double-row tube dilution technique using indicator serum broth.[3] Concentrations of antibiotics in pus were measured by the method described previously.[4]

Identification of bacteria—Routine bacteriological procedures based on the methods and nomenclature of Cowan and Steel[5] were used to identify aerobic isolates other than the "green" (viridans) streptococci. Anaerobic organisms were identified using the API system with the API-20 A test kit (API Laboratory Products Ltd, Rayleigh, Essex). The identifying methods used for the green and indifferent streptococci were, in general, those described by Colman,[6] and the organisms were classified according to the scheme proposed by Colman[6] and Colman and Williams.[7] In cases of doubt, streptococci were not allocated to a species or to a specific group.

Anaerobic procedure—Anaerobic jars (BTL) with three catalysts[8] were used. The catalysts were changed weekly and were dried before use. The anaerobic environment was provided by Gaspaks (BBL), and *Pseudomonas aeruginosa* on nutrient agar and an anaerobic indicator strip (BBL) were used as controls of anaerobiosis. A carbon dioxide (10%) environment was produced by Gaspaks in anaerobic jars from which the catalyst had been removed.

Serological investigations of streptococci—Antisera were prepared, in rabbits, to the Ottens and Winkler types 0 I-0 IV of strains of *Streptococcus milleri*. These organisms lacked a Lancefield group antigen. Antisera to Lancefield's groups A, C, D, F, and G were obtained commercially (Burroughs Wellcome). Streptococcal type and group antigens were extracted by the acid method of Lancefield,[9] the enzyme method of Maxted,[10] and the pronase method of Edwards and Larson.[11] Countercurrent immunoelectrophoresis was used for all serological investigations.

Results and comment

The 46 patients were classified according to the nature of the infection and its site. Thirty-five patients had a defined brain abscess from which pus was aspirated, some also having subdural or extradural empyemata. In eight patients infection was intracranial but extracerebral, and three more had extradural spinal abscesses. The male:female ratio of the whole group was 3:2. The male:female ratio for the 35 patients with brain abscess was 5:4, but, except for one woman with postoperative infection, all the patients who had subdural or extradural empyema were men. There was no association between or infection and the age of the patient. Table II shows the predisposing causes of infection.

ORGANISMS ISOLATED AND SITE OF INFECTION

Sixty-three samples of pus were examined from the 46 patients. None of the primary samples were bacteriologically sterile; nor were 10 of the 17 samples that were taken at subsequent aspiration.

The most common organisms (isolated in 36 patients) were streptococci; the most common species was *Str milleri*, which was found in 20 patients. *Staphylococcus aureus* was isolated from nine patients, organisms belonging to the bacteroides group from 11 patients, and Enterobacteriaceae from eight patients (see table I).

Mixed bacterial populations were found in 14 patients, 12 of whom had brain abscesses. In seven of the 12 patients with brain abscesses a mixed bacterial population was associated with temporal lobe abscesses of otitic origin. In two patients, one with a subdural empyema and the other with a cerebral abscess, a mixed infection arose after neurosurgery. Both patients came from the same unit and were infected with *Staph aureus* and a Lancefield group C β-haemolytic streptococcus.

The relation between the site of infection and the micro-organisms isolated is shown in table I. Streptococci were isolated from 27 of the 35 patients with brain abscess and from all patients with subdural or extradural empyema. *Str milleri* was cultured from 14 patients with brain abscess and from six patients with subdural or extradural empyema. *Staph aureus* was rarely isolated from intracranial infections

TABLE I—*Relation between site of infection and micro-organisms isolated*

Organisms	No of isolates	Brain abscess				Subdural and extradural empyemata (n = 8)	Spinal extradural abscess (n = 3)
		Temporal lobe (n = 13)	Frontal lobe (n = 11)	Cerebral (n = 6)	Others (n = 5)		
Str milleri	20	2	7	3	2	6	
Str species	6	3	2				1
Str pneumoniae	1	1					
Str faecalis/faecium	3	1	1		1		
Str mitior	1					1	
Str mutans	1			1			
Streptococci Lancefield group C	2			1*		1*	
Peptostreptococci	3	2				1	
Staph aureus	9	1	2	2*	1	1*	2
Bacteroides group	11	6	3		1	1	
Proteus spp	7	6			1		
K aerogenes	1	1					
H aphrophilus	1		1				

*Mixed postoperative infection.

TABLE II—*Relation between site of infection and predisposing cause*

Predisposing cause	Brain abscesses				Subdural and extradural empyemata (n = 8)	Spinal extradural abscesses (n = 3)
	Temporal lobe (n = 13)	Frontal lobe (n = 11)	Cerebral (n = 6)	Others (n = 5)		
Sinusitis		4			5	
Influenza	1	2				
Otitis	9					
Metastatic lesions after:						
Empyema/chest infection		1	1			1
Abdominal surgery				1		
Dental surgery				1		
Recurrent abscess		1				
Congenital heart disease	1		1	1		
Head injury		1			1	
Penetrating head wound		1				
Postoperative infection (neurosurgery)			1	1	1	
Cryptogenic	2	1	3	1	1	2

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unless the abscess had arisen after accidental or surgical trauma but was isolated from two of the three patients with spinal abscesses.

Clearly various organisms were responsible for temporal lobe abscess, reflecting the wide range of bacteria found in the aural canal, especially in cases of chronic otitis media. With one exception, a woman who developed a parieto-occipital abscess after extensive bowel surgery, all the isolates of *Proteus* spp were found in temporal lobe abscesses. Organisms of the bacteroides group were also often isolated from abscesses in the temporal lobe while *Str milleri* and *Staph aureus* were rarely found. *Str milleri* was the predominant isolate in brain abscesses other than temporal lobe abscesses, being present in over half the cases. The cultural findings were confirmed by gas-liquid chromatography of the pus for the presence of fatty acids characteristic of anaerobic bacteria.

INFECTION AND PREDISPOSING CAUSE

The relation between site of infection and predisposing cause is shown in table II. Abscess formation in the temporal lobe was associated with otitis while frontal lobe infection was associated with sinusitis. *Str milleri* was isolated from 10 of the 12 lesions that had developed after an attack of sinusitis or influenza. Metastatic, haematogenous, and post-traumatic abscesses were found in different sites.

SENSITIVITY OF INFECTING ORGANISMS

Antibiotic sensitivity tests carried out on the 66 isolates showed that 25 of them (from 23 of the 46 patients) were resistant to penicillin. Most patients were receiving multiple antibiotic treatment and the infecting organism was sensitive to one of the other antibiotics being used. In five cases, however, the patients received antibiotics that were inappropriate for treating their infecting organisms as judged by in-vitro sensitivity testing using antibiotic discs of standard concentration. Four of these, who were treated initially only with penicillin, were found to be infected with strains of *Staph aureus* that were resistant to the drug. In the fifth case *Klebsiella aerogenes* was isolated from the repeated aspiration of a patient treated with penicillin for an abscess from which *Str milleri* and fusobacteria had been isolated. These organisms were not isolated from the second specimen and treatment was therefore changed to gentamicin. Four weeks later *Str milleri* was again isolated from the abscess.

No allowance was made, in determining antibiotic sensitivity, for high concentrations of drugs following direct instillation into an abscess cavity. Results on the penetration of antimicrobial drugs into intracranial pus will be reported elsewhere.

TABLE III—*Antibiotic treatment in 43 cases of intracranial abscess*

Drug	No of patients receiving drug	
	Alone	In combined treatment
Penicillin	18	14
Ampicillin	1	3
Cephaloridine	1	6
Cloxacillin	1	2
Sulphonamide co-trimoxazole	0	7
Chloramphenicol	0	4
Streptomycin	0	2
Gentamicin	0	2
Kanamycin	0	1
Others	0	3
No antibiotic treatment	2	

The MIC of the drug being used in treatment was determined for each isolate. In no case was the MIC higher than that expected for sensitive bacteria of the same species or group.

The antimicrobial drugs used for the primary treatment of 43 cases of intracranial suppuration are shown in table III, which shows the treatment started or continued by the neurosurgeons but does not include that which may have been undertaken by the patients' general practitioners or in the referring hospital. Twenty-one patients received treatment with a single antibiotic, used speculatively in 20. In the patient treated with cephaloridine alone sensitive bacteria had been isolated from the ear before operation, and this was used as a guide for initial treatment. One patient was treated conservatively with penicillin and co-trimoxazole. This was unsuccessful and the abscess was subsequently aspirated five times; culture of the pus yielded a mixed growth of *Proteus vulgaris* and a penicillin-sensitive streptococcus, both sensitive to co-trimoxazole.

The sensitivities of the 66 isolates to the antimicrobial drugs used most often for treating intracranial and intraspinal suppuration are shown in table IV. The results are expressed as the percentage of isolates found to be fully sensitive when compared with control organisms.

SEROLOGICAL RESULTS

All isolates of *Str milleri* reacted with Lancefield group F antiserum and with the Ottens and Winkler type 0 III serum but not with any of the other antisera. Since the Ottens and Winkler strain used to produce the serum lacked a Lancefield group antigen, the reaction was judged to be specific for the type 0 III antigen.

The three isolates of faecal-type streptococci all reacted specifically with the Lancefield group D antiserum. The two isolates of Lancefield group C streptococci produced classical β-haemolytic colonies on blood agar and were biochemically distinct from *Str milleri*.

TREATMENT AND OUTCOME

In 10 of the 35 patients with brain abscesses the lesion was demonstrably encapsulated, and eight were excised. Three abscesses that did not have a capsule were also excised with the adjacent brain tissue. Seven patients had multiple abscesses.

Altogether 11 of the 46 patients died during the 40-month study. Three women and four men died as a result of brain abscesses, while all four deaths resulting from subdural or spinal abscesses occurred in men. Nine patients died after neurosurgery (in five for brain abscesses), giving a treated mortality rate of 20%. Two patients' abscesses were diagnosed only at necropsy. Their deaths, with the other nine, made up the overall mortality of 24%.

There was no correlation between mortality and excision of the abscess, encapsulation, or multiplicity of abscesses. Survival time varied greatly. Six patients died within three weeks of operation and the remaining three survived for 10 weeks to six months.

Discussion

It has been reported that 9-63% of primary pus samples from abscesses of the CNS are sterile.[2 12 15] Some commentators have suggested that this is due to antecedent antimicrobial treatment.[13 14] Irrespective of treatment, however, we have found that pus from brain abscess is not sterile, provided that exacting

TABLE IV—*Percentage sensitivity of microbes isolated to major antibiotics used in treatment*

Organisms	No of isolates	Penicillin	Chloramphenicol	Cephaloridine	Co-trimoxazole	Aminoglycosides*
Streptococcus spp	37	94	100	94	96	
Staphylococcus spp	9		100	100	100	100
Enterobacteriaceae	8		88	25	88	100
Bacteroides group	11	36	100	66	100	
H aphrophilus	1	100	100	100	100	100
% Of patients with sensitive organisms		50	98	74	96	27

*Gentamicin, streptomycin, kanamycin.

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methods of culture are used and the cultures are incubated for over 48 hours if necessary. The methods used are standard microbiological techniques, well within the competence of any diagnostic laboratory accustomed to dealing with specimens from seriously ill patients. The specimen must, however, be inoculated and incubated promptly, since aliquots of pus left at room temperature for 12-18 hours failed to yield positive cultures. Thus, abscess of the CNS is no less an emergency for the microbiologist than for the surgeon.

Although bacteriological findings relating to abscesses of the CNS appear in several works,[1 2 12 15] only McFarlan[1] and Heineman and Braude[2] state the criteria of identification. During the pre-antibiotic and early antibiotic era, *Staph aureus* was the most common single isolate. *Str pneumoniae* was often found, usually in abscesses complicating pneumococcal meningitis.[16] McFarlan[1] found that other streptococci constituted 29 of the 62 isolates found in 21 out of 48 patients. He considered it unjustifiable to group the several species present together, and he regarded the statement that streptococci are the commonest organisms in brain abscess as misleading. The taxonomical criteria available to us[7] were not available to McFarlan, and he did not investigate the streptococci by Lancefield grouping.

Our observation that streptococci of defined species, Lancefield group, and serological subtype (*Str milleri*, Lancefield group F, Ottens and Winkler type 0 III) predominate in brain abscesses invites an epidemiological study of the source and pathogenesis of the disease. The habitat of *Str milleri* has not yet been fully explored, although the organism occurs in the mouth flora.[17] It has also been isolated from abdominal abscesses[18] and purulent lesions elsewhere.[19] We have shown experimentally that *Str milleri* shows a well-defined affinity for the CNS of young mice,[20] though its affinity is less than that of *Str agalactiae* (Lancefield group B). The species specificity of types and subtypes of streptococci is already well attested.[21]

Early workers did not always perform anaerobic culture, and when they did they made no special arrangements for rapidly transporting specimens to the examining laboratory under anaerobic conditions. Heineman and Braude[2] emphasised the importance of anaerobic culture, stressing that prompt inoculation of cultures was essential. They isolated anaerobic bacteria from 14 out of 18 patients, commenting that they believed them to be the causal agents in most cases of brain abscess. Our findings indicate that this is not so. The microbes isolated depend on the site of the abscess, which itself depends on the predisposing cause. Gram-negative non-sporing anaerobes can be expected in temporal lobe or other otogenous abscesses, where they often occur in mixed cultures. When only patients with similar antecedent histories are considered the isolation rates for non-sporing anaerobic bacteria reported by Heineman and Braude are very similar to those reported by us and by other workers.[22]

Although our isolates of *Str milleri* were sensitive to penicillin (MIC $<$ 0·05 μg/ml), table IV shows that half the patients were infected with microbes, often in mixed culture, that were resistant to moderate doses of the drug. This is an important finding, for penicillin has been regarded as the drug of choice in the treatment of brain abscesses.[23] Penicillin used alone is unlikely to succeed in the treatment of otogenous abscess, where mixed infection with penicillin-resistant bacteria is usual, or in abscesses after injury, where staphylococci predominate. In these circumstances other drugs should be used.

Except in highly selected series of patients the mortality from abscesses of the CNS is high, ranging from 23 to 45%,[24] and rising mortality rates have been reported.[14 25] Garfield[23] believed that inadequate or inappropriate use of antibiotics contributed to the 40% mortality rate in the 200 cases he studied.

In our study of 35 unselected cases of brain abscess the mortality rate was 20% overall and 14% among treated cases. These figures are considerably lower than those reported by other workers and further work is being undertaken to determine whether the factors affecting mortality can be more clearly resolved.

The centres participating in the study were: Atkinson Morley's Hospital, London; Frenchay Hospital, Bristol; Regional Centre for Neurosurgery, Romford; St Bartholomew's Hospital, London; Walton Hospital, Liverpool; Wessex Neurological Centre, Southampton; and Queen Charlotte's Maternity Hospital, London.

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