Penetration of brain abscess by systemically administered antibiotics

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In six consecutive patients treated with systemic antibiotics for brain abscess, chloramphenicol, methicillin, and penicillin were found capable of penetrating the abscess in therapeutic concentration. Nafcillin, a fourth antibiotic tested, failed to penetrate. While on antibiotics, all six patients continued to deteriorate neurologically until needle aspiration of the abscess was carried out, after which recovery began promptly. Organisms were found in the pus despite the presence of therapeutically effective antibiotic levels, and despite the fact that the organisms were sensitive, in vitro, to the antibiotics used. These observations confirm that antibiotics alone are insufficient and that surgical evacuation of the abscess is essential. The need for local instillation of antibiotics directly into abscesses is questionable since penetration following systemic administration of three antibiotics tested was adequate when blood levels were high. It is suggested that the instillation of penicillin or its derivatives be avoided in view of their potential epileptogenicity as well as the questionable value of this method.

Key Words: brain abscess • antibiotic concentration in abscess • chloramphenicol • methicillin • nafcillin • penicillin

Antibiotics vary widely in their ability to penetrate the blood-brain barrier. Penetration, particularly by the penicillins, is known to be increased in the presence of meningitis. Little is known, however, regarding the diffusibility of systemically administered antibiotics into brain abscesses. In order to achieve effective antibiotic levels in abscess cavities, local injection of antibiotics after needle aspiration or surgical excision is widely practiced.

The purpose of the present study was to evaluate the ability of antibiotics to penetrate brain abscess cavities in order to determine if effective intra-abscess antibiotic concentrations can be achieved by systemic administration, without direct instillation of antibiotics. The evaluation included a consideration of whether treatment failure in undrained abscesses can be attributed to inadequate drug penetration. In six patients, determinations were made of 1) antibiotic activity in brain abscess fluid against the patient’s pathogen, 2) microbial persistence in the abscess fluid in the presence of high-level systemic antibiotic therapy, 3) anti-
TABLE 1

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Underlying Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>F</td>
<td>congenital heart disease</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>M</td>
<td>congenital heart disease</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>F</td>
<td>endocarditis</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>M</td>
<td>congenital heart disease</td>
</tr>
<tr>
<td>5</td>
<td>33</td>
<td>M</td>
<td>endocarditis</td>
</tr>
<tr>
<td>6</td>
<td>47</td>
<td>F</td>
<td>pyarthrosis; septicemia</td>
</tr>
</tbody>
</table>

bacterial concentration in the circulating blood, and 4) the patient's clinical response.

Materials and Methods

Clinical Data

The age, sex, and the underlying pathology in six patients with brain abscesses are summarized in Table 1. Table 2 lists the type and amount of antibiotics received by each patient prior to abscess aspiration; in all cases, the antibiotics were administered intravenously in high dosage.

Isolation of Bacteria

Blood Cultures. Venous blood samples were inoculated into trypticase soy broth and thioglycollate broth media. Gram stains and subcultures were made at 24 to 48 hours, the trypticase soy broth being subcultured on chocolate agar plates. The thioglycollate medium was subcultured into thioglycollate broth at 1 week. All cultures were subcultured and negative cultures were discarded at 14 days.

Brain Abscess Cultures. In each case, material aspirated from the brain abscess at the time of surgery was inoculated into thioglycollate broth and onto blood agar, chocolate agar, and McConkey's agar plates. An additional 1 to 2 ml of the material was incubated directly. Gram-stain slides were made of the original fluid, and of subcultures on days 2, 7 and 14. In addition, cultures from four of the six patients were processed for cell-wall defective bacterial variants. These cultures were inoculated into three hypertonic media in addition to routine media.

Antibiotic Sensitivity Testing

Tube Dilution Sensitivity Test. Serial twofold tube dilution antibiotic sensitivity measurements were made, using nutrient broth for S. aureus; trypticase soy broth plus serum were used for microaerophilic streptococci. Minimal inhibitory concentration (MIC) was defined as that concentration at which no turbidity occurred within 48 hours.

Antibiotic Levels. Antibiotic levels in serum and in the abscess cavity were determined by serial twofold tube dilution, using a standard S. aureus reference organism in nutrient broth. The dilution endpoint for 48-hour inhibition was employed. To calculate antibiotic level, the MIC

TABLE 2

Antibiotic therapy and bacterial persistence

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Initial Blood Culture</th>
<th>Antibiotic (Dose/day)</th>
<th>Days on Antibiotic Before Aspiration</th>
<th>Organism Recovered from Abscess</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>negative</td>
<td>chloramphenicol (0.9 gm)* penicillin (8 M.U.)</td>
<td>½</td>
<td>microaerophilic Streptococcus</td>
</tr>
<tr>
<td>2</td>
<td>negative</td>
<td>chloramphenicol (3 gm) penicillin (16 M.U.)</td>
<td>1</td>
<td>microaerophilic Streptococcus</td>
</tr>
<tr>
<td>3</td>
<td>positive</td>
<td>chloramphenicol (4 gm) methicillin (24 gm)</td>
<td>4</td>
<td>S. aureus</td>
</tr>
<tr>
<td>4</td>
<td>negative</td>
<td>chloramphenicol (3 gm) penicillin (20 M.U.)</td>
<td>10</td>
<td>microaerophilic Streptococcus</td>
</tr>
<tr>
<td>5</td>
<td>positive</td>
<td>nafcillin (18 gm) penicillin (20 M.U.)</td>
<td>15</td>
<td>Staphylococcus†</td>
</tr>
<tr>
<td>6</td>
<td>positive</td>
<td>chloramphenicol (4 gm) methicillin (16 gm)</td>
<td>2</td>
<td>S. aureus‡</td>
</tr>
</tbody>
</table>

* Child, age 3 yrs, body weight 9 kg.
† Seen on smear but no growth on routine culture.
‡ Seen on smear, negative on routine culture, but positive for cell-wall defective S. aureus.
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endpoint was multiplied by the MIC of the test strain, and was expressed in micrograms per milliliter.

Results

Bacterial Persistence

As shown in Table 2, the patients were on antibiotics for a period ranging from 12 hours to 15 days. Despite intensive systemic antibiotic therapy, a striking feature in all cases was the persistence of organisms within the brain abscess as indicated by the recovery of organisms in the aspirate at the time of surgical intervention. In two patients (Cases 5 and 6), the aspirate had the gross appearance of blood, suggesting the possibility of infected intracerebral hematoma.

Antibiotic Penetration

In view of the persistence of organisms in the abscess aspirate at a time when each patient was on a high dosage of systemic antibiotics, several questions may be raised. Either penetration of antibiotic into the brain abscess was inadequate, or it was ineffective in eradicating the organisms. Table 3 presents data addressed to these questions. In each case, antibiotic concentration in the blood and abscess are compared. The concentrations are expressed as a multiple of the Minimal Inhibitory Concentration (MIC) which is the smallest concentration of the antibiotic, *in vitro*, effective against the patient’s own organism. Thus, any value over 1 should theoretically be effective against the organism. In all instances where data were available, the blood concentration was higher than that found in the abscess, indicating a declining gradient from blood to abscess. In one instance (Case 3), in which the blood concentration of chloramphenicol was 2 times the inhibitory concentration, no activity was present in the abscess. In contrast, in Case 6, the chloramphenicol blood-level of 8 was associated with an effective abscess concentration of 2. These observations suggest that, given a high blood level of chloramphenicol, methicillin, or penicillin, brain abscess penetration is likely to be adequate. The antibiotic, nafcillin (Case 5), proved a striking exception to this generalization in that no abscess penetration could be shown even in the presence of a high blood level.

Clinical Response

In all cases the differential diagnosis prior to surgical intervention included brain abscess, although the clinical picture was indefinite in most instances. A characteristic feature noted in all patients was that of progressively increasing neurological deficit despite high-level systemic antibiotic therapy. Although intracranial mass lesion was suspected, diagnostic studies early in the course of hospitalization sometimes failed to reveal any abnormality. Repeated testing, particularly brain scan and arteriography, over the course of 7 to 10 days resulted in localization of the mass, after which surgical intervention was promptly undertaken. A burr hole was placed over the site of the lesion, and the brain abscess was aspirated with a brain cannula and irrigated with saline. A small quantity of barium sulfate suspension was instilled as a radiographic marker. Postoperatively, the patients were maintained on systemic antibiotic therapy, selected on the basis of the gram stain and culture characteristics of the aspirated pus. In general, the patients improved promptly neurologically, with considerable resolution of their neurological deficits continuing over
the course of several weeks. Three patients required re-aspiration of the abscess cavity during the first week after initial aspiration when their condition showed signs of deterioration.

Discussion

All antibiotics tested, except for nafcillin, penetrated in concentrations effective against the patients' pathogen. The limiting factor in the three antibiotics (chloramphenicol, methicillin, and penicillin) that diffused readily into the abscess cavities seemed to be the concentration of the antibiotic in the blood. Abscess penetration appeared to be effective, providing the blood level was sufficiently high.

These data suggest that the failure of antibiotics to control the infection prior to surgery was not a consequence of inadequate penetration, or insensitivity of the organism, but to poor antibacterial activity within the abscess. Although the antibiotics were generally present in the abscesses at therapeutically effective levels, their failure to eradicate the local infection was presumably related, in part, to the protection afforded the organism by the purulent milieu of the abscess contents. This possibility is supported by the finding of organisms in the abscess aspirate of all cases, although these organisms, in vivo, had been exposed to bactericidal or bacteriostatic antibiotic concentrations. Similar observations have been made in experimental animals concerning the pathophysiology of abscesses elsewhere in the body. 16, 17, 21

The question may be raised as to whether antibiotics have a place in the management of brain abscess. Experimental evidence regarding abscesses in general suggests that antibiotics are effective in the early stage of parenchymal infection, prior to the development of frank suppuration. 17, 21 In the case of infection in the brain, the early stage would probably represent a cerebritis. That antibiotics may be of prophylactic value in the stage of cerebritis is supported by the clinical observations of Heineman, et al., 7 who have suggested that antibiotics can abort the development of an abscess.

Once an abscess has become established, a high concentration of antibiotics in the parenchyma surrounding the lesion might also be expected to prevent spread of the infection. With respect to the role of antibiotics within the suppurative focus, namely, the abscess cavity, antibiotics may suppress the local infection but are probably incapable of eradicating it. The suggestion by Heineman, et al., 7 that systemic antibiotics may reverse an established abscess without surgical intervention is not supported by experimental evidence, 16, 17, 21 nor by the present clinical study. After aspiration of the pus, however, it seems likely that antibiotics can become effective in controlling the residual local infection.

The experience of most neurosurgeons supports the view that antibiotics have improved the outlook of the patient with intracranial abscess. Garfield, 4 however, points to a continuing mortality rate of 40% during the past 20 years despite the use of antibiotics, and attributes this to the "inadequate use of antibiotics," in terms of low dosage or inappropriate selection of drugs.

It appears that local instillation of antibiotics directly into the abscess cavity is not necessary, since penetration following systemic administration of properly selected antibiotics is adequate, providing that the blood levels are sufficiently high. The addition of local injection of antibiotics does not offer any advantage over systemic therapy. Instillation of penicillin derivatives, moreover, presents the possibility of local toxicity; there is a well-known propensity for their inducing epileptogenic foci when experimentally injected into cerebral tissue, or to produce seizures when systemically administered in high dosage. 14 Independent of the question of penicillin epileptogenicity, the 55% incidence of early and late epilepsy after surgery for brain abscess emphasizes the serious incidence of this complication. 5, 10, 13 When the penicillin is locally injected into a brain abscess, some outward diffusion into the surrounding parenchyma seems likely, since systemically administered penicillin can diffuse readily into the abscess. Therefore, it would seem advisable to avoid local instillation of penicillin or its derivatives.
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Acknowledgments

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