

## Brain Abscess Due to *Streptococcus MG-intermedius* (*Streptococcus milleri*)

JULIO C. MELO<sup>1\*</sup> AND MARTIN J. RAFF<sup>1,2</sup>

Section of Infectious Diseases, Departments of Medicine<sup>1</sup> and Microbiology and Immunology<sup>2</sup>, University of Louisville School of Medicine, Louisville, Kentucky 40232

Received for publication 26 January 1978

Three cases of brain abscesses due to *Streptococcus MG-intermedius* are reported, and the literature pertaining to this subject is reviewed. The importance of careful and complete identification of these etiological agents of infection is stressed. The clinical presentation, the origin of *S. MG-intermedius* producing brain abscess, and its relation to hepatic abscesses and endocarditis are discussed.

Brain abscesses are localized infections of the brain substance, produced by a variety of pyogenic organisms. They are characterized by progressive stages of purulent exudate formation and encapsulation. Infection originates via extension from adjacent foci or by metastasis through the blood stream. This may occur due to episodes of bacteremia or through septic emboli from other sources of intravascular infection.

Although both aerobic and anaerobic streptococci account for the majority of cases of brain abscess (4, 8, 10, 13, 14, 20, 23-25), the true incidence of each type of streptococcus causing brain abscess is not known. Most reports mention only major groups of streptococci and go no further in their identification. Three cases of brain abscesses due to *Streptococcus MG-intermedius* are presented here, and their clinical significance is discussed.

### CASE REPORTS

**Patient 1.** A 69-year-old white male, with known arteriosclerotic heart disease and mild hypertension, was hospitalized on 10/30/75 after 3 days of fever, chills, and epigastric pain. He had had a lumbar laminectomy 2 weeks previously. On physical examination, he was in acute distress. Blood pressure was 140/90 mm of Hg, temperature was 101°F, and pulse was 110/min. There was no nuchal rigidity; heart sounds were normal except for an S<sub>4</sub> gallop, and lungs were clear. There was epigastric tenderness without organomegaly. The hepatic vertical span was 15 cm. The leukocyte count was 11,300/mm<sup>3</sup>, with 80% neutrophils, 18% lymphocytes, 1% monocytes, and 1% eosinophils. The hematocrit was 37.3%. Sequential multiple analyzer 12 (SMA-12) showed the following: serum glutamic oxalacetic transaminase, 60 IU; alkaline phosphatase, 120 IU; lactic dihydrogenase, 240 IU; total bilirubin, 1.2 mg/100 ml; direct bilirubin, 0.9 mg/100 ml; and blood urea nitrogen, 16 mg/100 ml. Urinalysis revealed a pH of 6.5, a trace of albumin, 50 to 60 erythrocytes per high-power field, and 10 to 20

leukocytes per high-power field, and the culture was negative. Extensive X-ray examinations were within normal limits. Three blood cultures were positive for *S. MG-intermedius*. In view of persistent abdominal pain and fever, an abscess of the left lobe of the liver was drained on 11/6/75. Gram stain of purulent exudate showed many leukocytes and gram-positive cocci in pairs and small chains. Culture grew *S. MG-intermedius*. He was treated with intravenous chloramphenicol, and on 11/13/75 oral penicillin was substituted. The liver scan was normal, and he was discharged on 11/20/75. He was readmitted 11/26/75 with photophobia, ophthalmalgia, and severe frontal and occipital headaches. He had no nausea, vomiting, or abdominal pain, but was acutely ill. Blood pressure was 130/80 mm of Hg, pulse was 110/min, and temperature was 99°F. He was confused, with an expressive aphasia, but followed simple verbal commands. Ophthalmoscopic examination was normal, the neck was supple, and there were no heart murmurs or other focal neurological signs. The hematocrit was 34%, and the leukocyte count was 10,300/mm<sup>3</sup>, with 82% neutrophils, 15% lymphocytes, and 3% monocytes. Urinalysis had 8 to 10 erythrocytes per highpower field, no leukocytes, and no casts. The latex fixation titer was 1:32. SMA-12 revealed an alkaline phosphatase of 120 IU and was otherwise normal. Electroencephalogram showed diffuse encephalopathy. Blood and urine cultures were negative. Brain scan revealed two focal areas of increased activity in the left occipital region. On 12/27/75 he was started on intravenous aqueous penicillin G, and on 12/30/75 several brain abscesses were surgically drained. Purulent material was aspirated into a glass syringe directly from the abscess cavity, sealed from the external environment, and taken directly to the laboratory for aerobic and anaerobic cultures. Gram stain revealed many leukocytes and gram-positive cocci in pairs and small chains. *S. MG-intermedius* grew aerobically, but anaerobic cultures showed no growth. Chloramphenicol was added, but the patient expired on 12/31/75. Permission for postmortem examination was denied.

**Patient 2.** A 27-year-old white male became ill 12/25/75 with fever and chills. After 2 days dysuria developed, and he was begun on tetracycline for a

urinary tract infection. No cultures were taken. He did well until 1/6/76 when severe frontal headaches began, with flashing lights in the right visual fields. He had no fever or chills. He was hospitalized on 1/10/76 after a grand mal seizure. On physical examination he was alert and oriented. Blood pressure was 110/80 mm of Hg, temperature was 98.8°F, and pulse was 90/min. The examination was normal except for a right homonymous hemianopsia. The hematocrit was 39%, and the leukocyte count was 16,000/mm<sup>3</sup>, with 82% neutrophils, 1% bands, and 11% lymphocytes. Urinalysis and SMA-12 were normal except for a uric acid of 11.5 mg/100 ml. Chest X-ray and electrocardiogram were normal. Blood and urine cultures were negative. Brain scan showed increased activity in the left posterior parieto-occipital area. Arteriography suggested a neoplasm in the same region. On 1/14/76 a brain abscess was drained, and Gram stain of the exudate showed many leukocytes and gram-positive cocci in pairs and chains. Cultures obtained as for patient 1 grew *S. MG-intermedius*. Intravenous chloramphenicol was begun. Severe nausea and vomiting developed along with a nonpruritic maculopapular vesicular eruption on the upper extremities, trunk, and back, with a few lesions on the upper third of both thighs. Gram stain and culture of these lesions were negative for bacteria and viruses. Viral serologies were also negative. Chloramphenicol was discontinued, and he was treated with intravenous aqueous penicillin and gentamicin for a total of 4 weeks. He was discharged 2/10/76 with a minimal right homonymous hemianopsia. On 2/26/76 he again developed fever, severe headaches, and a sensation of flashing lights in the right side of the visual field. A computerized axial tomographic brain scan showed abscesses in the left occipital region. He was started on intravenous aqueous penicillin G, and on 3/17/76 the abscess was drained. Gram stain did not show organisms, but the culture grew staphylococcal species. He gradually improved, and penicillin was discontinued on 4/12/76. During his hospitalization, multiple laboratory and X-ray procedures performed to find the origin of the brain abscess or underlying disease or malignancy were not revealing. He was discharged 4/15/76 with a minimal visual defect and has continued to do well.

**Patient 3.** An 18-year-old white male with minimal brain dysfunction developed grand mal seizures in September 1975. He was begun on Dilantin and phenobarbital until 1/16/76, when he complained of substernal and epigastric pain, anorexia, nausea, fever, and chills but no headaches. On 1/17/76 the patient was begun on oral penicillin. Throat culture did not grow group A beta-hemolytic *Streptococcus*. On 1/28/76 he awoke with severe headache, nausea, vomiting, and confusion. These symptoms worsened, and he was hospitalized on 1/31/76. On physical examination he was poorly responsive, confused, and disoriented. Blood pressure was 90/60 mm of Hg, pulse was 120/min, and temperature was 101°F. Ocular examinations were normal, the neck was not rigid, and the chest was clear. There was a systolic thrill over the third left intercostal space and a high-pitched early systolic murmur grade III/VI over the third left intercostal space and a grade II/VI holosystolic murmur over the apex without radiation. S<sub>1</sub> and S<sub>2</sub> were nor-

mal, and no gallops or diastolic murmurs or pericardial friction rubs were heard. The liver was 14 cm in total span; there was no splenomegaly. A mild left facial weakness was noted without other neurological abnormalities. The hematocrit was 41%, and the leukocyte count was 9,200/mm<sup>3</sup>, with 94% neutrophils, 1% bands, 4% lymphocytes, and 1% monocytes. Urinalysis was normal. Electrocardiogram showed sinus tachycardia. SMA-12 showed the following: alkaline phosphatase, 270 IU; lactic dihydrogenase, 200 IU; serum glutamic oxalacetic transaminase, 125 IU; and bilirubin, 1.6 mg/100 ml (direct, 1.0 mg/100 ml); it was otherwise normal. Electroencephalogram indicated diffuse encephalopathy. Brain scan showed multiple areas of increased activity in both cerebral hemispheres, and cerebral arteriogram was suggestive of multiple brain abscesses. Liver scan revealed a focal defect in the upper portion of the left lobe of the liver. Latex fixation was positive at a titer of 1:64. Blood and urine cultures were negative. On 2/2/76 several brain abscesses were drained. The Gram stain of the purulent exudate showed many leukocytes and gram-positive cocci in pairs and small chains. Cultures taken as in patient 1 grew *S. MG-intermedius*. The patient was initially begun on chloramphenicol, but 3 days later was switched to oxacillin and gentamicin. After surgery he had decerebrate posturing and required a permanent tracheostomy. Mental status improved only to the point where he was intermittently able to follow simple verbal commands. Hepatic scan was repeated after 3 weeks of therapy, and the filling defect had resolved. During hospitalization, exploratory laparotomy for massive upper gastrointestinal bleeding revealed no evidence of hepatic abscesses. Antibiotic therapy was discontinued on 3/2/76; he was discharged to a rehabilitation center and is currently well and without evidence of infection.

## RESULTS

**Bacteriology.** The Gram stain of the purulent exudate in each case showed gram-positive cocci in pairs and small chains; many leukocytes were also seen. All cultures grew only a single organism. No hemolysis was seen on blood agar plates. One of the three organisms isolated reacted with Lancefield type F antiserum; the other ones were not groupable. They were bacitracin insensitive and failed to grow on 4.0 and 6.5% NaCl or on bile-esculin media. Catalase was negative, and acid was produced from trehalose, lactose, and sucrose but not from mannitol or sorbitol. Arginine and esculin were hydrolyzed. The organisms were identified as *S. MG-intermedius* by the Staphylococcus and Streptococcus Unit, Clinical Bacteriology Section, Center for Disease Control, Atlanta, Ga.

## DISCUSSION

Brain abscesses produce a significant degree of morbidity, and mortality varies from 17 to 65% (1, 3-5, 8, 10, 12, 14, 23). Although mortality is usually related to the extent of clinical disease

(13, 25), some authors have pointed out that it may also be dependent upon the organism involved (14). Anaerobic streptococci have been associated with greater mortality (4, 14, 21), although other authors do not agree with this concept (5, 10).

Although there seem to be some difficulties in the classification of the viridans streptococci, it is believed that physiological differentiation of species offers the best method of grouping human clinical isolates (7). *S. MG-intermedius* is an aerotolerant, slow-growing, nonhemolytic streptococcus, often requiring either the addition of carbon dioxide or anaerobic conditions for its initial isolation. These organisms are mannitol, sorbitol, and inulin negative and hydrolyze both esculin and arginine. Lactose-positive strains with these characteristics are classified as *S. MG-intermedius* to differentiate them from the lactose-negative *Streptococcus anginosus-constellatus* (7). These two groups of organisms are synonymous with what has been termed *Streptococcus milleri* in the United Kingdom (6, 17). *S. milleri* was initially described by Guthof in 1956 (9) when he isolated nonhemolytic streptococci from infections of the mouth and gave the name *S. milleri* to strains which grew in 40% bile agar and at 45°C and hydrolyzed arginine and esculin but did not ferment mannitol, sorbitol, or glycerol. Colman and Williams (6) found that the strains isolated by Guthof and by Otens and Winkler (16) were similar to each other and to strains of *Streptococcus MG*. Some of these organisms can be grouped with Lancefield antisera types A, C, F, and G. The strain isolated from patient 3 was typable with antiserum to group F. Data from the Streptococcus Reference Laboratory, London (2), showed that *S. milleri* accounted for only 4% of 175 streptococci isolated from the blood in cases of endocarditis or suspected endocarditis, but accounted for 21% of 75 strains of streptococcus isolated from pus in the viscera or the central nervous system. More recent data show that *S. milleri* accounted for only 5.4% of cases of streptococcal endocarditis but was the most commonly isolated organism in clinically recognized purulent disease (28.3%). It was also isolated from 13 of 16 streptococcal brain abscesses (81.3%) and from 8 of 65 cases (12.3%) of streptococcal meningitis (17). In Facklam's study (7), *S. MG-intermedius* was isolated in 20 of 28 cases of brain abscesses (71.4%) and with *S. anginosus-constellatus* accounted for 69.1% of all abscesses caused by viridans streptococci. The natural habitat of *S. MG-intermedius* is not well known, but *S. milleri* has been isolated from dental root canals (16), and Roger (19) isolated it from 11% of 170 appendixes.

Our cases represent the first three cases of brain abscesses in our hospitals recognized as due to this organism. It is of interest to note that two of these patients also had hepatic abscesses with this organism, case 1 proven by laparotomy and culture. Case 3 was suggested by clinical presentation, laboratory data, and liver scan. After antimicrobial therapy, the hepatic filling defect resolved. Bateman et al. (2) recently described three cases of hepatic abscesses due to this organism. This suggests that *S. MG-intermedius* may have a propensity for the production of abscesses in the hepatic parenchyma as a part of the natural history of the disease process. Physicians dealing with diseases caused by this organism should be aware of this fact. The two patients described here with hepatic abscesses were also suspected of having had endocarditis. Patient 1 had multiple positive blood cultures, hematuria, and positive latex fixation tests, but no heart murmurs were auscultated. Unfortunately, no autopsy was performed, and the diagnosis remains a presumptive one. Patient 3 had negative blood cultures but had received oral penicillin before admission, and significant heart murmurs that had not been heard on previous examination were present. In addition, his latex fixation tests were positive. No source or predisposing factors for the brain abscess were found in patient 2, although the presence of occult malignancy or another underlying disease was strongly suspected. The inability to locate a primary source for the etiological agent of brain abscesses is not uncommon. In fact, the origin is unknown in 8 to 29% of cases (4, 11-14, 20, 23). The natural habitat of the particular organism causing the brain abscess may provide a clue as to the origin of the infection (4). This can only be done if the organisms are identified carefully and thoroughly. In two of our patients, gastrointestinal symptomatology was the initial complaint, and hepatic abscesses were found in both of them. It is therefore possible, if not probable, that the gastrointestinal tract may have been the initial source of the organism.

The patients described here all presented with headaches, which is the universal symptom for brain abscess (10, 11), but none of the patients presented with hemiparesis, which is the commonest physical finding (20, 22). Therapy of brain abscess consists of adequate surgical drainage combined with prolonged systemic antimicrobial therapy (4). The duration of therapy necessary for cure has not been well defined, but a minimum of 4 weeks of intravenous therapy has been recommended (4).

Aerotolerant organisms are reported as being sensitive to penicillin (15, 18), and this would appear to be the drug of choice. All three isolates

in this series were quite sensitive to both penicillin and chloramphenicol. Chloramphenicol becomes a good alternative for the therapy of brain abscess due to this organism in patients who are allergic to penicillin.

In summary, we have presented three cases of brain abscess due to a recently renamed group of organisms, *S. MG-intermedius*. Although this organism may have been one of the streptococci previously described by other authors as being responsible for brain abscesses, it has not been specifically identified as such until now. Its predilection for the hepatic parenchyma and its ability to produce hepatic and other abscesses have been described previously (2, 7, 17) and appear to be reaffirmed by this report. Possible sources of the organism are discussed, and brief therapeutic recommendations are made.

#### ACKNOWLEDGMENTS

We thank Robert Facklam of the Staphylococcal and Streptococcal Unit, Center for Disease Control, for his assistance in identifying the strains of organisms reported here. We also thank Stuart Urbach, John Guarnaschelli, and Bernard Rand, Jewish Hospital, Louisville, Ky., for their encouragement and support.

#### LITERATURE CITED

- Ballantine, H. T., and J. C. White. 1953. Brain abscess. Influence of the antibiotics on therapy and mortality. *N. Engl. J. Med.* **248**:14-19.
- Bateman, N. T., S. J. Eykyn, and I. Phillips. 1975. Pyogenic liver abscess caused by *Streptococcus milleri*. *Lancet* **i**:657-659.
- Black, P., J. R. Graybill, and P. Charache. 1973. Penetration of brain abscess by systemically administered antibiotics. *J. Neurosurg.* **58**:705-709.
- Brewer, N. S., C. S. MacCarty, and W. E. Wellman. 1975. Brain abscess: a review of recent experience. *Ann. Intern. Med.* **82**:571-576.
- Carey, M. E., S. N. Chou, and L. A. French. 1972. Experience with brain abscesses. *J. Neurosurg.* **36**:1-9.
- Colman, G., and R. E. O. Williams. 1972. Taxonomy of some human viridans streptococci, p. 281-299. In L. W. Wannamaker and J. M. Matsen (ed.), *Streptococci and streptococcal diseases*. Academic Press Inc., New York.
- Facklam, R. R. 1977. Physiological differentiation of viridans streptococci. *J. Clin. Microbiol.* **5**:184-201.
- Garfield, J. 1969. Management of supratentorial intracranial abscess: a review of 200 cases. *Br. Med. J.* **2**:7-11.
- Guthof, O. 1956. Ueber pathogene "vergrünende Streptokokken." Streptokokken Befunde beim dentogenen Abszessen und Infiltraten im Bereich der Mundhöhle. *Zentrabl. Bakteriolog. Parasitenkd. Infektionskr. Hyg. Abt. 1* **166**:553-564.
- Heineman, H. S., and I. B. Abraham. 1963. Anaerobic infections of the brain. Observations on 18 consecutive cases of brain abscess. *Am. J. Med.* **35**:682-697.
- Kapsalakis, Z., H. C. Askitopoulou, and A. Gregoriades. 1972. Analysis of the treatment of 12 consecutive cases of brain abscess. *J. Neurosurg.* **37**:82-84.
- Karandanis, D., and J. Shelman. 1975. Factors associated with mortality in brain abscess. *Arch. Intern. Med.* **135**:1145-1150.
- Krayenbuhl, H. A. 1967. Abscess of the brain. *Clin. Neurosurg.* **14**:25-44.
- Liske, E., and N. J. Weikers. 1964. Changing aspects of brain abscesses. *Neurology* **14**:294-300.
- Moore, W. E. C., E. P. Cato, and L. V. Holdeman. 1969. Anaerobic bacteria of gastrointestinal flora and their occurrence in clinical infections. *J. Infect. Dis.* **119**:641-649.
- Ottens, H., and K. C. Winkler. 1962. Indifferent and haemolytic streptococci possessing group antigen F. *J. Gen. Microbiol.* **28**:181-191.
- Parker, M. T., and L. C. Ball. 1975. Streptococci and aerococci associated with systemic infection in man. *J. Med. Microbiol.* **9**:275-302.
- Pien, F. D., R. L. Thompson, and W. J. Martin. 1972. Clinical and bacteriologic studies of anaerobic gram positive cocci. *Mayo Clin. Proc.* **47**:251-257.
- Roger, K. B. 1957. The association of acute appendicitis with infective diarrhea. *Proc. R. Soc. Med.* **50**:1025-1026.
- Samson, D. S., and K. Clark. 1973. A current review of brain abscess. *Am. J. Med.* **54**:201-210.
- Sperl, M. P., Jr., C. S. MacCarty, and W. E. Wellman. 1959. Observations on current therapy of abscess of the brain. *Arch. Neurol. (Chicago)* **81**:439-441.
- Wise, G. R., and T. W. Farmer. 1971. Bacterial cerebral vasculitis. *Neurology* **21**:195-200.
- Wright, R. L., and H. T. Ballantine. 1967. Management of brain abscess in children and adolescents. *Am. J. Dis. Child.* **114**:113-122.
- Yates, C., and R. Tompsett. 1971. Reliability of brain scans in diagnosis, p. 112-113. *Antimicrob. Agents Chemother.* 1970.
- Yoshikawa, T. T., and S. J. Goodman. 1974. Brain abscess—Teaching Conference, University of California, Los Angeles, and Harbor General Hospital. *West. J. Med.* **121**:207-219.