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Pediatrics 1967;40;610

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PLAGUE MENINGITIS
A Report of Three Cases in Children and Review of the Problem

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In 1965, an outbreak of plague occurred among the Navajo Indians in New Mexico. There were seven cases of plague discovered, of which three developed a rare manifestation of plague infection, acute meningitis.

Cases of Pasteurella pestis meningitis were first described by the Austrian Plague Commission in 1898 and the German Indian Plague Commission in 1899, but since that time only a few sporadic case reports have appeared in the world literature. Acute plague meningitis has not been described previously in the United States, although in 1937 Meyer, et al. reported a patient with what was believed to be chronic meningal infection due to P. pestis. It is the purpose of this paper to describe three new cases of acute plague meningitis and to review some of the previous experience with this illness.

DESCRIPTION OF THE CASES
Case 1

P.N., a 33-year-old Navajo female, was first seen in the Out-patient Department of the U.S. Public Health Service Indian Hospital, Gallup, New Mexico, on June 21, 1965, with a temperature of 104°F and a sore throat. Her pharyngitis was treated with penicillin for 1 week with some improvement. On June 30, 9 days later, she became irritable, began vomiting, and cried, particularly when moved. She was admitted to the hospital the following day with a temperature of 104°F, her pulse was 132, her blood pressure was 120/70, and she weighed 31 lb. She was irritable and lethargic with definite signs of meningismus. No lymphadenopathy was noted. Her respirations were 44, and her blood cells per cubic millimeter, 36% and a white blood count of 18,850 with 63% neutrophils, 7% band forms, 25% lymphocytes, and 5% monocytes. Urinalysis was negative. A lumber puncture revealed cloudy cerebrospinal fluid with 196 white blood cells per cubic millimeter, 100% neutrophils. Cerebrospinal fluid protein was 158 mg per 100 ml and the cerebrospinal fluid glucose was 12 mg per 100 ml. Gram stain showed large gram-negative rods, which were also in the fluid culture. Aqueous penicillin (1 million units), sulfadiazine (150 mg), and chloramphenicol (100 mg), were administered intravenously every 6 hours. The patient’s temperature had gone down by the following day, and gradual but steady improvement ensued. She was treated by the same three drugs for a total of 13 days.

On July 14, a 3 x 3 cm node was detected in the left groin, and 2 cu cm of purulent material were aspirated from this node the following day. The smear was negative, but culture was positive for gram-negative rods. The cultures sent to reference laboratories at the Communicable Disease Center, Atlanta, Georgia, and the State of New Mexico Health Department for identification unfortunately contained no viable organisms when received.

Hemagglutination inhibition titration for P. pestis, performed at the U.S. Public Health Service Plague Laboratory, San Francisco, was negative on July 15 and 1:128 on August 15. The diagnosis of plague was suggested by the morphology of the organisms on smear and confirmed by the demonstration of a marked rise in the hemagglutination inhibition titer. Further investigation revealed that P.N. and her family lived in very primitive surroundings on the Navajo Reservation. Contact with animals was frequent, and of particular importance was the fact that this family hunted and ate prairie dogs found near their house.

The patient was discharged with no neurologic abnormalities on July 24.

Case 2

J.C., a 26-year-old Navajo male, had the sudden onset of fever, vomiting, and anorexia on July 9, 1965. He was admitted to the U.S. Public Health

(Received March 24; revision, with addendum, accepted for publication June 17, 1967.)

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Confirmed as virulent *P. pestis*.

Laboratory results were negative but rose to a peak of 1:64 on September 9. In this case, no definite history of animal contact could be obtained.

**Case 3**

B.M., a 33-year-old Navajo male, was admitted to the U.S. Public Health Service Hospital, Gallup, New Mexico, on August 19, 1965, with fever, vomiting, and diarrhea of 1 day's duration. His temperature was 104°F on admission, pulse was 152, blood pressure was 110/70, respirations were 42, and he weighed 32 lb. The child was lethargic, and his neck was found to be stiff on forward flexion. Healing, dried eschars were found on the skin of the left great toe and the dorsum of the left foot. There were no pustules or purulent material around these lesions, and no enlarged lymph nodes were found. The chest x-ray was normal. The white blood count was 17,400 with 93% neutrophils, 1% band forms, and 6% lymphocytes. The hemocrit was 34%; urinalysis was normal. Lumbar puncture revealed cloudy cerebrospinal fluid with 2,900 white blood cells per cubic millimeter, of which 79% were neutrophils and 21% were lymphocytes. Cerebrospinal fluid protein was 72 mg per 100 ml, and glucose was 30 mg per 100 ml. Gram stain of the fluid revealed no organisms, and cultures of both the blood and cerebrospinal fluid were negative.

Aqueous penicillin (1 million units), was given intravenously every 4 hours; sulfadiazine (400 mg), and chloramphenicol (500 mg), were given intravenously every 6 hours. The child’s condition improved greatly within 24 hours. He was afebrile and able to eat and walk without difficulty 2 days after admission. He was discharged on September 5 after 17 days in the hospital.

Initial hemagglutination inhibition titer performed on serum drawn August 22, 1965, was negative; a convalescent titer on serum taken September 2 was 1:16. The child lives in an area where a die-off of prairie dogs had occurred. Though his family did not hunt prairie dogs, animals were brought to his home from the fields by domestic dogs and cats. Diagnosis in this case rests on the epidemiologic history and a definite acute to convalescent phase titer rise.

**CLINICAL OBSERVATIONS**

The occurrence of three cases of meningitis in a total of seven plague patients is unusual and not readily explained. The possibility of a neurotropic strain of *P. pestis* has been considered, but there is no method at present by which this can be tested. The high incidence of meningitis might be related to the fact that the outbreak involved young children, five under 5 years of age...
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Though exact figures are not available, it does seem that a high proportion of the reported cases of plague meningitis are in children; but, childhood plague is common in endemic areas, and nothing approaching this incidence of meningitis has been seen before.

Of the three patients, Case 2 alone developed clear manifestations of bubonic plague prior to the development of meningitis. The tender, prominent node was at first thought to be due to streptococcal adenitis, a common problem among Navajo children. The other two children did not have symptoms characteristic of plague infection when admitted to the hospital. Case 1, actually diagnosed in retrospect, had no lymphadenopathy at the time of admission, and her symptoms were simply those of acute bacterial meningitis. The important history of animal contact could not be elicited until some time later. Case 3 also had no signs or symptoms suggestive of plague infection, but knowledge of the preceding two patients facilitated the acquisition of a complete history and the prompt institution of therapy.

The bipolar staining of this organism was helpful to the physicians caring for these patients. This feature of the plague organism is sometimes demonstrable by gram stain, but it is more reliably seen with Wayson or Giemsa stain. Material for staining and culture was obtained without difficulty from the patients by needle aspiration of involved lymph nodes and by lumbar puncture. The bacillus was grown on blood agar at its optimal growth temperature of 28°C, and colonies were often not visible until the plates had been incubated for 48 hours.

Treatment of all three patients included chloramphenicol and sulfonamides, both considered good agents for plague therapy. Chloramphenicol, sulfonamides, and the tetracyclines have all been employed successfully, but they have the theoretical disadvantage of being bacteriostatic rather than bacteriocidal agents. For this reason, most authors feel that streptomycin is the drug of choice for treatment of active plague infection, particularly when far advanced. It has been so successful an agent that some investigators consider excessively large initial doses dangerous. Such large doses might cause massive lysis of plague bacilli and result in fatal toxemia. In moderate amounts, streptomycin, in combination with a drug that effectively reaches the cerebrospinal fluid (such as chloramphenicol or a sulfonamide), would seem to be reasonable initial therapy for plague meningitis.

It is generally agreed that early treatment is essential. The rapidity with which this disease progresses to toxicity and death is striking, and early treatment of suspect cases is one of the most important factors in reducing mortality.

COMMENT

Human infection with *P. pestis* is not common in the United States. Though the disease is quite prevalent in wild rodents and rabbits, an average of only one or two cases of human illness has occurred each year since 1924.

In most instances, patients develop one of the more common forms of plague infection, and the disease is not difficult to recognize. Painful, enlarged lymph nodes, high fever, and prostration are well-known signs of infection with *P. pestis*. In contrast, meningitis is one of the least common manifestations of plague and one which might cause considerable diagnostic difficulty.

Plague meningitis is usually a secondary complication of bubonic plague. In seven of eight patients with plague meningitis in Landsborough and Tunnell’s series, the meningitis developed between the ninth and seventeenth days of illness. This experience is similar to that of most other authors. Since toxemia and death rapidly follow the development of plague septicemia, a meningeal focus probably develops during a period of intermittent bacteremia when infection is still localized principally in the lymph nodes.

It has been suggested that this is more likely to occur when treatment is
instituted with drugs of less than maximum effectiveness.\textsuperscript{10,17} Such treatment would supposedly prevent overwhelming septicemia but would allow the multiplication of organisms that had reached a protected site in the meninges. Landsborough and Tunnell indicated that the incidence of secondary meningitis had increased with the use of sulfonamides,\textsuperscript{10} and Feeley and Kriz postulate that treatment of their case with oral tetracycline and penicillin may have promoted the development of meningitis.\textsuperscript{37} It is noteworthy, in this regard, that the first and second cases presented in this paper were treated for 7 and 6 days, respectively, with penicillin before meningitis developed.

Evidence to substantiate this hypothesis is limited because of the small number of reported plague meningitis cases, and the reasoning is difficult to understand with regard to the sulfonamides, which are effective antiplague agents and do penetrate the blood-brain barrier. Inadequate drug dosage or delayed treatment might be more important factors in the development of meningitis, as suggested by Pollitzer.\textsuperscript{5}

A few reported cases have been called "primary meningitis."\textsuperscript{10,18-21} There is some doubt that the meninges can be the primary site of infection with \textit{P. pestis}, though without question the illness may be unnoticed prior to the development of meningeval symptoms.\textsuperscript{5}

With the exception of pneumonic plague, infection with \textit{P. pestis} is acquired by inoculation through the skin or mucous membranes; there the organism sets up a primary focus of infection before invading the bloodstream. Jawetz and Meyer showed that virulent \textit{P. pestis}, inoculated intracutaneously in sublethal doses into mice and guinea pigs, could be isolated sequentially from skin and lymph nodes before the occurrence of septicemia.\textsuperscript{22} The organism was occasionally found in the spleen or bone marrow before blood cultures became positive, indicating that intermittent bacteremia does occur before the development of septicemia, but this occurred after primary infection had been established in the lymph node.

In humans as well, primary infection seems to develop at the site of inoculation or in lymphatics before dissemination of the organism occurs. Occasionally patients develop septicemia before their lymph nodes are clinically enlarged, but it is generally believed that this septicemia is secondary bloodstream invasion from skin and lymph node infection too inconspicuous to be observed clinically.\textsuperscript{5} Pathologic examination in such cases usually reveals well developed lymph node infection. Theoretically, contact with a case of pneumonic plague could result in direct seeding of the bloodstream through the lungs and development of "primary meningitis," but this has never been reported.

None of the patients described as having "primary meningitis" have sufficiently detailed histories to show that meningitis was, in fact, the first manifestation of illness. In two instances\textsuperscript{18,19} the diagnosis of meningitis early in the illness was based on the presence of headache, which is a common early nonspecific manifestation of all types of plague infection. In both instances, meningitis was discovered by lumbar puncture after the development of neurologic signs some days after the headache was noted. Another reported case was in a patient who was found unconscious in the street and died without giving any history of his illness.\textsuperscript{20} A fourth patient had central nervous system symptoms but no laboratory evidence of meningitis.\textsuperscript{21} The best documented case is Landsborough and Tunnell's, but even there, signs of meningitis were not observed until 4 days after the onset of a febrile illness; lumbar puncture was not performed until 7 days after its onset.\textsuperscript{10} There was not sufficient information to rule out another focus of infection.

Case 3 reported here is similar to the above in that the patient presented to the physician with symptoms of meningitis. The information obtained in this case was incomplete, however, and suggested that the onset of illness might actually have preceded
the onset of meningitis. Case 1 was seen 1 week prior to her admission because of a febrile, respiratory infection, perhaps the first sign of *P. pestis* infection. Case 3 was allegedly ill only 1 day prior to admission, but details of the history were extremely scanty.

After reviewing the cases reported to date and considering the patients seen in this outbreak, it seems that "primary plague meningitis" is not a real entity. In most instances, plague meningitis develops in association with other signs of the disease, though occasionally these are not conspicuous. If other indications of *P. pestis* infection are present, they can be of considerable diagnostic help, particularly if associated with an appropriate history of animal contact. Case 2 in this report is a typical case of meningitis clearly secondary to bubonic plague.

One other form of plague meningitis was reported by Meyer in 1937. He described a case of chronic meningitis in a child who lived 123 days after the onset of illness. Headache and stiff neck associated with signs of meningismus developed almost 4 weeks after the onset of bubonic plague. Spinal fluid examination at that time revealed 105 white blood cells per cubic millimeter, of which 80% were polymorphonuclear cells. Smears and cultures of this fluid were negative. Without antibiotic or sulphonamide treatment, the patient lived 3 months from the onset of his central nervous system illness and showed sufficient improvement for him to be allowed to go home. On the one hundred ninth day of illness, his condition suddenly deteriorated, and signs of fulminant meningitis developed. He died 14 days later. A lumbar puncture 2 days before death yielded fluid that contained 425 white cells per cubic millimeter, with 84% lymphocytes. Direct smear of the fluid showed gram-negative rods, later identified by culture as *P. pestis*. Postmortem examination revealed extensive cellular infiltration of the meninges, ventricular ependyma, and moderate infiltration of the cortex. Internal hydrocephalus was present.

No abscess cavity was found on postmortem examination. The patient's benign course and period of improvement were unusual if active meningeal infection were continuously present. It is possible that the initial central nervous system infection became localized in the tissues. Rupture of a small abscess, perhaps unnoticed at postmortem examination, or spread of a focal process could explain the sudden deterioration 2 weeks prior to death. The survival of *P. pestis* for long periods of time in localized abscesses has been noted many times in the literature.

As an unusual entity, *P. pestis* meningitis will always cause difficulties in diagnosis. Awareness that plague meningitis can occur is, of course, essential to recognition and to the taking of an appropriate epidemiologic history. Simple laboratory procedures, outlined earlier in the text, were found extremely helpful in diagnosis. Other gram-negative organisms will occasionally resemble *P. pestis* morphologically; another pasteurella organism, *P. multocida*, often has bipolar staining and can cause meningitis in children and adults. Differentiation of these organisms from *P. pestis* would be difficult until cultures are available, but an epidemiologic history can be extremely helpful. Patients with plague almost always have a history of having been in an area where contact with wild rodents (squirrels, prairie dogs, field mice, chipmunks, etc.), rabbits, or their fleas is possible. Frequently, patients will have handled or skinned animals. Patients with *P. multocida* may have had contact with animals, but they would be dogs or cats. Geographically, plague has never been found in wild animals in the United States east of the 100th meridian, a line which passes through the center of the Dakotas, Kansas, and Texas. There is, of course, no such geographic limit to *P. multocida* or the other gram-negative organisms.

**ADDENDUM**

After submission of this paper we received a communication from Leo Kartman, Ph.D., Chief,
for recent or present Pasteurella infection, and was negative for plague organisms in a proven case.

On September 2, represents a non-specific agglutination. In which he stated, "a very critical examination of the serum from B.M. (Case 3) shows that the rise in titer from negative on August 22 to 1:16 on September 2, represents a non-specific agglutination."

A titer rise of 1:16 is usually considered positive for recent or present Pasteurella infection, and was noted in many contacts to the six confirmed cases. However, a diagnosis of plague cannot be made on this titer rise alone unless it is above 1:16 or other proof of active infection is obtained, e.g., positive culture from a node or cerebrospinal fluid. Also, it is very frequent for cerebrospinal fluid cultures to be negative for plague organisms in a proven case of plague infection in which there is a pleocytosis in the cerebrospinal fluid. It is also not unusual for a patient to develop plague meningitis without palpable lymphadenopathy, as noted in the discussion of the paper.

Therefore, Case 3 can be diagnosed as only presumptive. However, in view of the time of his illness, the fact that he was dwelling in an area where plague was discovered among wild rodents, and because of the neutrophilic nature of the pleocytosis, it is likely that this patient had plague infection. But, in face of the evidence by Dr. Kartman, Case 3 is only a presumptive case of plague meningitis. Finally, this situation exemplifies very vividly the problem clinicians run into when managing an outbreak such as occurred in the summer of 1965. There were many cases presenting with various, but suggestive, symptoms of plague infection during this time that were treated as presumptive cases until there was shown to be no rise in anti-Pasteurella antibody.

**SUMMARY**

Three cases of acute *Pasteurella pestis* meningitis occurred in a plague outbreak in New Mexico in 1965. Acute plague meningitis has occasionally been seen in other areas of the world. This entity almost invariably develops as a secondary complication of bubonic plague, and a critical review of the literature raises serious question about the existence of primary meningitis due to *P. pestis*. Treatment of these three cases and experience with plague therapy are discussed. Early recognition of plague infection, including its more unusual complications (such as meningitis), is essential for appropriate treatment and cure.

**REFERENCES**

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