PAPERS AND ORIGINALS

Haemophilus influenzae Meningitis in Adults

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British Medical Journal, 1974, 2, 463-465**Summary**

Haemophilus influenzae meningitis though common in childhood is rarely seen in the adult. During the past four years eight cases of *H. influenzae* meningitis have been seen in St. Thomas's Hospital and four of these were in patients over 20 years old. There was a possible predisposing condition in two patients. In each case there was difficulty in identification of the organism in the Gram-stained film of the cerebrospinal fluid deposit.

Introduction

The incidence of *Haemophilus influenzae* meningitis has increased considerably during the past 30 years, particularly in North America but also in Great Britain and other countries. It is now the commonest form of purulent meningitis in childhood in most reported series (Turk and May, 1967). Adult cases of meningitis caused by *H. influenzae* are rare, however: in a recent review of the world literature, Stein *et al.* (1969) found that only 2.7% of 2,162 patients with *H. influenzae* meningitis were aged 20 years or more. These cases were all from the U.S.A. with the exception of a small series from India (Grant *et al.*, 1965) which, curiously, reported nine adult cases out of a total of 25. It is difficult to assess from published work how often adult cases occur in the United Kingdom as, apart from an isolated case reported by Dolphin and Popham (1951), there seem to be no published reports. Data obtained from the Public Health Laboratory Service show that in 1971 2.5% of 354 reported cases of *H. influenzae* meningitis were stated to be over 20 years old and in 1972 2.4% of 410 cases were. (Public Health Laboratory Service, 1973).

During the past four years eight cases of bacteriologically proven *H. influenzae* meningitis have been seen in St. Thomas's Hospital and four of these occurred in adult men.

Case Reports

Case 1.—A 44-year-old man was admitted to St. Thomas's Hospital in March 1970 with a two-day history of headache followed by fever and vomiting. On admission he was drowsy with marked neck rigidity and a temperature of 40°C. Five years previously he had been treated for meningococcal meningitis in another hospital. The C.S.F. contained 2,000 white blood cells/mm³, of which 95% were polymorphonuclear leucocytes. The C.S.F. protein was 150 mg/100 ml and there was no detectable glucose present. A Gram-stained smear of the C.S.F. deposit showed numerous Gram-variable coccobacilli. Treatment was begun with intravenous penicillin and sulphadiazine. A moderate growth of *H. influenzae* was obtained on culture from the C.S.F., and when the organism was identified the treatment was changed to ampicillin 8 g and chloramphenicol 4 g daily. After ten days his temperature had returned to normal and he was clinically much improved. Antibiotic therapy was continued in reduced dosage by mouth for a further two weeks. A search was made for a possible predisposing cause but none was found.

Case 2.—A 36-year-old man presented at another hospital in December 1970 with rigors and a two-week history of sore throat. He was treated with oral penicillin but the sore throat persisted, and over the next three days he developed flitting joint pains, headache, and repeated vomiting. On admission to St. Thomas's Hospital he was confused and photophobic with a temperature of 37.8°C. Obvious meningism was present and both knee and elbow joints were swollen and tender. He had had a splenectomy fifteen years previously after a road accident, he suffered from frequent attacks of sinusitis, and for six weeks before his admission to hospital he had been unemployed and admitted to drinking heavily. The C.S.F. contained 11,000 white blood cells/mm³, of which 95% were polymorphonuclear leucocytes, and 330 mg/100 ml of protein. There was no detectable glucose present. A Gram-stained smear of the C.S.F. deposit showed very occasional Gram-negative diplococci and treatment was begun with intravenous penicillin on the assumption that this was meningococcal meningitis. *H. influenzae* was isolated from C.S.F. and blood. Pus from his right knee was sterile on culture but intravenous antibiotics had already been given for two days when the joint was aspirated. Treatment was changed to sulphadiazine 6 g and chloramphenicol 3 g daily which were given intravenously for nine days and by mouth for a further six days. He was then clinically better but remained febrile for a further two weeks. Further lumbar punctures yielded sterile C.S.F. with decreasing numbers of white blood cells. X-ray pictures of his left antrum suggested sinus infection and mucopus was obtained on antral washout. This was sterile on culture but his temperature then rapidly settled and he was discharged 38 days after admission.

Case 3.—A 23-year-old man was admitted to St. Thomas's Hos-

pital in February 1971 having had an upper respiratory tract infection in the previous week and headache and vomiting for 24 hours. In 1968 he had had pneumococcal pneumonia and septicaemia and had been found to have hypopituitarism. A chromophobe adenoma was then partially resected and 18 months later he developed C.S.F. rhinorrhoea which further surgery failed to correct. Nine months later, in September 1970, he developed *Streptococcus viridans* meningitis and two months after this pneumococcal meningitis and septicaemia. Further surgery to correct his C.S.F. rhinorrhoea was successful. On admission he was drowsy and had a temperature of 39.2°C. There was obvious meningism. The C.S.F. contained 2,800 white blood cells/mm³, of which 98% were polymorphonuclear leucocytes, and 800 mg/100 ml of protein. The C.S.F. glucose was 70 mg/100 ml but the blood glucose at the same time was 250 mg/100 ml. A Gram-stained smear of the C.S.F. deposit showed occasional Gram-variable coccobacilli. Treatment was begun with intravenous ampicillin, cloxacillin, and sulphadiazine. *H. influenzae* was grown from the C.S.F. but blood culture was sterile. After 48 hours cloxacillin was discontinued and intravenous ampicillin 15 g/day and sulphadiazine 4 g/day were continued. The patient became afebrile in five days and was clinically much improved.

Case 4.—A 59-year-old man was admitted to St. Thomas's Hospital in October 1973. He had been well until 24 hours before admission, when he had complained of upper respiratory symptoms and fever and later developed a severe headache with vomiting. When first seen he was semiconscious with a temperature of 38.9°C but there were no clinical signs of meningeal irritation. A lumbar puncture was performed within a few hours, and by this time he had developed a stiff neck and photophobia. The C.S.F. was turbid with 5,200 white blood cells/mm³, of which 90% were polymorphonuclear leucocytes, and 800 mg/100 ml of protein. There was no detectable glucose in the C.S.F. A Gram stain of the C.S.F. deposit showed very occasional Gram-negative diplococci thought to be meningococci, and treatment with intramuscular penicillin was started. Culture of the C.S.F. yielded a moderate growth of *H. influenzae*, and this organism was also grown from the blood and from a throat swab. After 24 hours the treatment was changed to intravenous ampicillin 18 g daily. The patient's clinical condition deteriorated appreciably after 24 hours of ampicillin treatment with increasing fever. A further specimen of C.S.F. contained increased numbers of polymorphonuclear leucocytes but was sterile. Treatment was then changed to intravenous chloramphenicol 4 g daily. The response to chloramphenicol was slow and his temperature continued to rise for three days but gradual clinical improvement then occurred. The *H. influenzae* was later found to be sensitive to ampicillin (minimum inhibitory concentration 0.25 µg/ml) and the C.S.F. level of the drug was 13 µg/ml. X-ray examination of the patient's sinuses showed nothing abnormal, his immunoglobulins were normal, and no evidence of underlying disease could be found. He was discharged 26 days after admission.

Discussion

In view of the apparent rarity of *H. influenzae* meningitis in adults it is interesting that we saw four cases in the past four years at St. Thomas's Hospital and only a further four cases in children. *H. influenzae* meningitis is usually a disease of children over the age of 2 months with most cases occurring in the first three years of life. The long-accepted explanation for this specific age incidence is that given by Fothergill and Wright (1933). They showed that the blood of most newborn and very young infants was bactericidal to a capsulated strain of *H. influenzae* recently isolated from a case of meningitis, suggesting that immunity was passively acquired from the mother. This bactericidal activity was not present in the blood of children aged between two months and three years but was again found in older children and in all the adults they investigated.

It is known, however, that not only does *H. influenzae* meningitis occur in the otherwise healthy adult but it has also been reported in the neonate (Davis, 1909; Mathies *et al.*, 1965). This would suggest either that bactericidal antibody for *H. influenzae* is only one of several factors determining susceptibility to infection with the organism or that there has been a

change in the age distribution of antibody since the work of Fothergill and Wright. Recent work has produced some interesting results: Norden *et al.* (1970) described a 33-year-old woman with *H. influenzae* meningitis whose serum on the day of admission did not contain bactericidal activity against *H. influenzae*. She had previously been entirely healthy. They also found no bactericidal activity for the same organism in the sera of eight out of 29 normal adults and suggested that perhaps early and frequent use of antibiotics in childhood might have been responsible for this lack of bactericidal activity in adults. Feigin *et al.* (1971) also investigated the role of bactericidal antibody in *H. influenzae* infection and found that 9 out of 30 newborn children, 27 out of 76 healthy adults, and 4 out of 25 paediatric hospital workers had no bactericidal antibody. This work together with that of Norden *et al.* (1970) would suggest a marked change in the susceptibility of neonates and adults to *H. influenzae* in comparison with the 1930's. There has been no change in the age-incidence of *H. influenzae* infection, however, only an increased overall incidence. Feigin *et al.* (1971) also mention two patients with *H. influenzae* meningitis, whose ages are not stated, who were found to have high bactericidal antibody titres to *H. influenzae* in their serum before antimicrobial therapy was started. It is therefore difficult to be sure of the role of bactericidal antibody in protecting man from serious infections with *H. influenzae*.

Of the 110 reported adult cases of *H. influenzae* meningitis reviewed by Stein *et al.* (1969) 66 had some underlying disease thought to have predisposed them to infection with the organism. The most frequent underlying conditions were otitis or sinusitis, head injury or cranial surgery, sometimes accompanied by C.S.F. rhinorrhoea, and concurrent pneumonia. But all these conditions are often found in other types of bacterial meningitis as well. Diabetes mellitus, agammaglobulinaemia, chronic alcoholism, and splenectomy have also been mentioned. A predisposing cause is not found in every case, however, and Grant *et al.* (1965) found no underlying disease in any of the nine cases they reported. One of our patients (case 2) was known to suffer from chronic sinusitis, had had a splenectomy in the past, and was a heavy drinker and the patient in case 3 had persistent C.S.F. rhinorrhoea after cranial surgery and had a history of meningitis on two previous occasions. For the other two patients (cases 1 and 4), however, no underlying cause could be found. In none of these four patients was the bactericidal titre to *H. influenzae* estimated.

In the preantibiotic era though *H. influenzae* meningitis was almost always fatal in children (Fothergill, 1937) adults often survived. Becker and Spingarn (1949) reviewed eight adults with *H. influenzae* meningitis before 1940, all but one of whom survived with non-specific therapy, and they suggested that the prognosis of the disease was better in adults than in children. Gladstone and Russell (1969) state that *H. influenzae* meningitis is less severe in the adult than in the child, and the mortality of *H. influenzae* meningitis in adults is low when compared with other forms of meningitis (Jervey and Charleston, 1963). Nevertheless, though all four of our patients recovered without overt neurological sequelae one patient (case 4) was critically ill for several days. Stein *et al.* (1969) point out that the clinical picture of adult *H. influenzae* meningitis is not particularly characteristic. It may present as an upper respiratory tract infection which gradually progresses to meningeal involvement as in case 2 or have a much more abrupt onset with headache, fever, and vomiting as in case 4. Arthritis has previously been described in patients with *H. influenzae* meningitis (Dyer *et al.*, 1958; Turk and Wynter, 1961). Patients with bacterial meningitis, whatever the aetiology, often have an accompanying bacteraemia; blood was cultured from three of our patients, and *H. influenzae* was grown in two cases.

Several authors have drawn attention to the difficulty experienced in identifying *H. influenzae* in the initial Gram stain of the C.S.F. deposit in adult cases of *H. influenzae* meningitis (Holdsworth, 1960; Merselis *et al.*, 1962; Jervey and Charleston, 1963; Gladstone and Russell, 1969; Stein *et al.*, 1969).

Haemophilus may show Gram variability in staining and often assumes coccal rather than bacillary forms. No other organism commonly seen in the C.S.F. exhibits such marked pleomorphism (Fothergill, 1937). It may readily be mistaken for meningococci or pneumococci. Furthermore, though a heavy growth of *H. influenzae* may be recovered on culture very few or no organisms may be seen in the smear. In none of our patients cases was *H. influenzae* identified in the Gram-stained smear of the C.S.F. deposit and in two (cases 2 and 4) therapy for meningococcal meningitis with penicillin was started on the basis of the appearance of the organism in the Gram-stained film.

There are two main lines of treatment for *H. influenzae* meningitis—either chloramphenicol or high doses of ampicillin given intravenously. Though chloramphenicol treatment is technically the easier it carries a small risk of marrow aplasia. Shackelford *et al.* (1972) in a comparison of ampicillin and chloramphenicol therapy in patients with *H. influenzae* meningitis found bacteriological relapse occurred in six out of 136 patients treated with ampicillin but in none of the 116 treated with chloramphenicol. They also found that fever was more prolonged and of a greater magnitude in the patients treated with ampicillin. Garrod *et al.* (1973) conclude that both forms of treatment are generally effective and acceptable.

One can draw few conclusions from the therapy given to our four patients, but it is tempting to speculate that the slow response in the patient in case 1 could have been brought about by possible antagonism between ampicillin and chloramphenicol. In one patient (case 4) high dose ampicillin was given for only 24 hours, and the response to intravenous chloramphenicol was very slow.

Cases of *H. influenzae* meningitis are undoubtedly occurring in adults in the United Kingdom and may not be as rare as was previously supposed. The role of bactericidal antibody in pre-

venting the disease is far from clear. Though predisposing causes are sometimes found in these patients this is by no means invariably so. Attention is drawn in particular to the difficulty so often experienced in identifying the organism in the Gram-stained deposit of the C.S.F.

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Assessment of Limulus Test for Detecting Endotoxaemia

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Summary

The occurrence of endotoxaemia in 46 surgical patients has been investigated using a sensitive preparation of limulus lysate. Altogether 23 patients with local and systemic Gram-negative infections were shown to have endotoxaemia. An overt infection is not a prerequisite for a positive limulus test result, since endotoxin can be absorbed via the peritoneal cavity in patients with "chemical" peritonitis. Over 70% of the tests performed during episodes of Gram-negative infection or peritonitis gave positive results. In 23 patients without clinical evidence of infection or peritonitis only 15% of the limulus test results were positive. The implications of these findings and the use of the test in clinical practice are discussed.

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Introduction

Endotoxin shock and Gram-negative septicaemia, terms often used synonymously, are increasingly being recognized as complications in both medical and surgical patients. A definitive diagnosis is usually made by obtaining bacteriological evidence of Gram-negative organisms on blood culture, the results of which may not be available for several days. It has become clear, however, that many of the features of shock associated with Gram-negative infections in both experimental animals and man may be produced by endotoxaemia (Cavanagh *et al.*, 1970; Nies *et al.*, 1968).

The limulus test has been suggested as a simple and rapid method of detecting endotoxin or endotoxin-like material (Levin *et al.*, 1970, 1972). The test depends on the ability of endotoxin to produce gelation of an extract of blood cells (amoebocytes) from the horseshoe crab *Limulus polyphemus* (Bang, 1956). The reliability of this test in clinical practice has been reported with variable results (Levin *et al.*, 1970, 1972; Caridis *et al.*, 1972; Das *et al.*, 1973; Stumacher *et al.*, 1973).

A recent modification of the limulus lysate preparation (Yin *et al.*, 1972) has been shown to be more sensitive in detecting small amounts of endotoxin, and we report here our experience with this lysate in vitro and in clinical practice.