Today's Treatment

Diseases of the central nervous system

Meningitis and encephalitis

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British Medical Journal, 1975, 4, 335-337

Common forms of bacterial meningitis

Acute bacterial meningitis results from invasion and subsequent inflammation of the meninges by bacteria. Early diagnosis, followed by appropriate antibacterial treatment, should result in cure—while late or inappropriate treatment ends in death or disablement. In spite of the ready availability of effective antibacterial agents the mortality and morbidity from this potentially curable condition remain unacceptably high, especially in neonatal meningitis and pneumococcal meningitis in people over 50.

In Britain most cases of bacterial meningitis are caused by the *Meningococcus*, *Pneumococcus*, and *Haemophilus influenzae*, other forms being relatively uncommon.

MENINGOCOCCAL MENINGITIS

Meningococcal meningitis is the commonest form of acute bacterial meningitis in Britain and affects all age groups, with a particularly high mortality at the extremes of life.

The onset of the disease may be remarkably sudden and the patient may die of the sequelae of meningococcaemic consumption coagulopathy before the full-blown meningitic picture arises. More usually the picture is one of acute meningeal irritation in a child or a young adult with fever, variable clouding of consciousness, and an associated petechial or purpuric rash, which is often sparse. Infants may present with grand mal seizures and fever without localising signs.

The clinical diagnosis should be confirmed by examination of the cerebrospinal fluid (CSF) and blood culture. Because of an increasing world-wide incidence of sulphonamide-resistant meningococci, treatment with benzylpenicillin should always be started except in the patient allergic to penicillin, when cephaloridine should be used 1 g six-hourly intravenously in the adult, perhaps with 50 mg intrathecally daily for 3 days. Four-hourly bolus intravenous pulse injections of 2-4 MU in the adult, for five days, should be followed by a further five days of phenoxymethyl penicillin 2 g daily with probenecid.

The pulse injections of potassium penicillin should be slow lest ventricular tachyarrhythmias are induced, while fluid retention may result with the sodium salt. Total daily doses greater than 25 MU of benzylpenicillin should be avoided because of the possibility of inducing encephalopathy. A definitive bacterial diagnosis is unlikely in patients who have received antibacterial treatment before admission. Most of the young patients will have meningococcal and many of the older pneumococcal meningitis, so that, if the clinical picture fits, benzylpencillin in full dosage should be given, except in children, when ampicillin should be used. For the patient in agony with headache, diamorphine or pethidine should be given as necessary.

Those patients who have fulminant meningococcaemia with shock should be given an initial bolus of 200 mg of hydrocortisone, followed by 500 mg-1 g hydrocortisone in each bottle of intravenous fluid, each being given over four to six hours. In the early stages of the consumption coagulopathy syndrome bolus injections of heparin 10 000 to 15 000 units four-hourly should be given, as this might prevent the development of the full-blown picture. The use of heparin in the later stages is, however, contentious and potentially dangerous although fresh frozen plasma and fibrinogen may be useful. Early penicillin treatment in the patient with meningitis without appreciable consumption coagulopathy cures without residua.

PNEUMOCOCCAL MENINGITIS

Pneumococcal meningitis is the next most common form in Britain and predominantly affects young infants and adults over the age of 40, in whom it is the commonest form of acute bacterial meningitis. The condition tends to recur especially if there is a local or systemic predisposition—the infection arising as an opportunistic infection. These background conditions include alcoholism, immunological dysfunction, skull fracture, operations on the nose or ethmoid sinuses, chronic otitis media, chronic sinusitis, and suppurative mastoiditis.

The prodromal illness may often be less acute than in meningococcal meningitis. A rash is unusual, and deep unconsciousness with fits and cranial nerve palsies are common. Treatment with benzylpenicillin should be started immediately after the CSF has been examined, and blood cultures have been taken. In the adult patient intrathecal injection of 10 000 units of benzylpenicillin should be given at the time of lumbar puncture if pneumococci are seen on the Gram-stained film of the purulent CSF and should be repeated daily for the next three days. Bolus intravenous injections of benzylpenicillin 2-4 MU should be given four-hourly for the first five to seven days, depending on the patient's progress. Thereafter oral phenoxymethyl penicillin therapy 2 g daily with probenecid should be given to a total of 14 days.

If the patient is allergic to penicillin, parenteral cephaloridine 1 g six-hourly and 50 mg daily intrathecally or chloramphenicol 1-2 g six-hourly should be given for not less than five days. In children the dose of chloramphenicol should not exceed 100 mg kg^{-1} day^{-1}, and half this dose should be used for neonates. This condition carries an overall mortality of some 15%, while in people over 50 the mortality is more than 50%,

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many of the survivors being left with permanent disability. If the response to full doses of penicillin is slow then oral prednisolone should be considered. The place of pancreatic desoxyribonuclease is not yet clear although early reports of its effect on viscous exudate are encouraging.

HAEMOPHILUS INFLUENZAE MENINGITIS

In America and Australia *H influenzae* is the most common cause of acute pyogenic meningitis, but in Britain the disease is largely confined to children, being uncommon after three and rare after five years. The disease carries a 10 to 12% mortality, serious damage often occurring because of late introduction of antibacterial treatment. The organism is sensitive to chloramphenicol and ampicillin, the former drug having distinct advantages in terms of diffusion rates into the CSF while ampicillin has the disadvantage of having to be given parenterally in doses of 150 to 200 mg kg^{-1} day^{-1} to attain adequate CSF concentrations. For adults the dose of chloramphenicol should never exceed 4 g/day, while 100 mg kg^{-1} day^{-1} is usually adequate in children, half that dose being employed for young infants or neonates. Treatment should be continued for five to ten days, depending on the clinical response, while persistent fever in these children often abates when antibacterial therapy ends.

NEONATAL MENINGITIS

Bacterial meningitis is comparatively uncommon but it appears in the first month of life more frequently than at any other time. It is especially common in premature infants, and in those with spina bifida, often after surgery. Most of these infections are caused by Gram-negative organisms, particularly *Escherichia coli*, *Proteus* sp and *Pseudomonas aeruginosa*, but are occasionally due to streptococci, staphylococci, or *Listeria monocytogenes*. Signs of bacteraemia usually dominate the clinical picture with minimal or absent neck stiffness in the early stages, when the child is irritable, febrile, and disinterested in feeding.

Once the clinical diagnosis has been confirmed by examination of the cerebrospinal fluid and blood cultures have been taken, antibacterial treatment should be started using intrathecal or intraventricular gentamicin in a dose of 1mg/day, the dose being prepared from preservative-free gentamicin powder. This procedure is repeated daily for five days and is given with parenteral gentamicin 4-8 mg kg^{-1} day^{-1} in two divided doses and continued for 10 to 14 days. For proved infections with streptococci, pneumococci, meningoccoci, and *L monocytogenes*, benzylpenicillin should be given as 1-2 MU/day in six divided doses with 1-3 daily intrathecal injections of up to 1000 units. Some paediatricians also favour the use of daily intrathecal injections of 10 mg cortisol. During treatment prolonged fever, fits, and subdural effusions may arise while blockage to CSF circulation should be largely prevented by the use of intrathecal corticosteroids. Even with prompt and effective antibacterial and supportive treatment this condition still carries a mortality of 20-30%.

RECURRENT BACTERIAL MENINGITIS

Recurrent bacterial meningitis is usually caused by pneumococci and arises particularly in patients with cranial defects, especially linear fractures of the anterior fossa across the cribriform plate, although it may arise with any abnormal communication between meninges and the environment. Common causes of such infections include congenital cranial defects; surgery on the nose and ethmoid sinuses; chronic suppurative mastoiditis and sinusitis; and occasionally as a sequel to splenectomy or as a result of agammaglobulinaemia or lymphoreticular disease with immunological dysfunction. Treatment is usually with benzylpenicillin by four-hourly pulse injections of 2-4 MU. Cephaloridine should be used for the penicillin allergic patient. In those occasional patients with persistent CSF otorrhoea, sinister opportunistic meningitic infections arise with streptococci, *Klebsiella pneumoniae*, *E coli*, staphylococci, and *Ps aeruginosa*. In these patients parenteral combination antibacterial treatment should be considered with cephaloridine, kanamycin, chloramphenicol, or lincomycin with benzylpenicillin. These infections carry a high mortality and often recur unless suitable surgical intervention is introduced.

RARER FORMS OF BACTERIAL MENINGITIS

Rare forms of bacterial meningitis occur not only in the neonatal period but also in later life as complications of congenital defects of the central nervous system or immune deficiency states.

Listeria monocytogenes meninigtis usually arises in patients with lowered resistance, especially infants and the elderly, but may arise in pregnancy or in apparently healthy adults. High-dose intravenous pulse injections of benzylpenicillin, ampicillin, cephaloridine, or chloramphenicol are generally effective.

Cryptococcus neoformans meningitis arises as an opportunistic infection in patients with lymphoreticular disease, diabetes mellitis, and sarcoidosis, although it may occur in otherwise apparently healthy people. The condition carries a high mortality, although amphotericin-B and flucytosine treatment have been used successfully. Prolonged treatment is necessary to prevent relapse and for this oral flucytosine is most suitable.

Amoebic meningitis is rare in temperate climates, but may occur in Britain during a hot summer. Children or young adults playing or swimming in dirty inland water are susceptible. The causative naegleria is sensitive to treatment with clotrimazole or amphotericin, though the condition carries a high mortality.

Streptococcal meningitis is rare except as an opportunistic infection in patients with head injury or after cranial surgery. It may, however, follow infection in the ear, nose, and throat or be a sequel to rupture of a cerebral abscess into the subarachnoid or ventricular space. Benzylpenicillin should be given intrathecally and by four-hourly pulse intravenous injections except in the patient who is allergic to penicillin when cephaloridine should be given.

Staphylococcal meningitis usually arises during fulminating staphylococcal bacteraemia or after cranial trauma but may occasionally be a sequel to sacral abscesses. Parenteral methicillin, lincomycin, or cephaloridine should be given.

Gram-negative bacterial meningitis

In the adult meningitis due to *E coli*, *Proteus* sp, *K pneumoniae*, *Ps aeruginosa*, or *Aerobacter aerogenes* are almost invariably opportunistic, arising from trauma, surgery, or background systemic disease (especially that associated with immunological dysfunction). The prognosis is usually grave because of the background disease and difficulty in getting bactericidal levels of appropriate antibiotics into the CSF. Combination treatment with ampicillin, cephaloridine, kanamycin, or chloramphenicol should be given and may occasionally save the patient.

Mima polymorpha meningitis usually arises in elderly or debilitated patients, although it has been described in infants and apparently fit adults. It mimics meningococcal infection with petechial rashes and shock. The diplococcus is easily mistaken for meningococci, but since the organism is resistant to penicillin and chloramphenicol correct diagnosis is vital. Parenteral tetracycline or kanamycin treatment should be given.

Tuberculous meningitis

Tuberculous meningitis is now comparatively uncommon in Britain but should always be remembered in the differential

diagnosis of the patient with atypical meningitis. The disease is most common in childhood or early adult life but may occur, and be missed, in the elderly. If diagnosed early and properly treated the condition is curable, but if left untreated is invariably fatal. Inadequate or late treatment results in permanent disablement or death.

Once the diagnosis is established, or even if it seems probable, treatment should be started with intramuscular streptomycin 3 mg kg^{-1} day^{-1} to a maximum of 1 g daily, with oral isoniazid 100 mg eight-hourly and pyridoxine 10 mg daily, with either ethambutol 20 mg kg^{-1} day^{-1} or rifampicin 450-600 mg/day. Daily intrathecal isoniazid 0·5 mg/kg to a maximum of 50 mg daily should be given for a fortnight. The value of corticosteroids is doubtful but many doctors still use daily intrathecal hydrocortisone in a dose of 1 mg/kg with oral prednisolone 40 mg daily. Some experts advocate purified protein derivative in advanced cases in which corticosteroids are of dubious value, except in those patients who develop cerebral oedema, which may be the result of an allergic reaction to tuberculin after treatment starts. Here corticosteroids may be life-saving. I believe that thev should be given in all cases at least for the first week. Oral chemotherapy should be continued for eighteen months.

Viral meningoencephalitis

Viral meningitis is common and, with the exception of mumps, is due largely to the enteroviruses, particularly the echovirus and Coxsackie viruses. No therapy is available, but antiviral chemotherapy is now available for some forms of meningoencephalitis—notably that due to herpes simplex and varicella herpes zoster.

HERPES SIMPLEX MENINGOENCEPHALITIS

The herpes viruses are among the few viruses influenced by antiviral chemotherapy. Meningoencephalitis is a serious disease with a 50% mortality, while most patients who survive the illness are left with some neurological disability. Eariy diagnosis is important for antiviral chemotherapy may positively influence the outcome. The diagnosis should be suspected from the clinical picture of fits, fever, personality change, and localised neurological signs. Once the diagnosis has been established treatment with idoxuridine or cytarabine should be started without delay. Both are toxic, causing neutropenia and thrombocytopenia. Cytosine arabinoside is the chosen drug at present, and is given by rapid daily bolus intravenous injections of 3-8 mg/kg for three to five days depending on the clinical response. Systemic corticosteroids, and in particular dexamethasone, should not be given. Neutrophil and platelet counts must be monitored daily.

VARICELLA HERPES ZOSTER MENINGOENCEPHALITIS

Occasionally herpes zoster encephalitis arises as part of an opportunistic generalised zoster infection in a patient with lymphoproliferative disease or on immunosuppressive treatment. Headache with a CSF pleocytosis is common in most cases of dermatomal zoster, expecially if the trigeminal nerve or the upper cervical segments are involved, but true encephalitis is much less common. It presents with variable and bizarre focal neurological signs and headache, often with clouding of consciousness or psychotic behaviour.

Early treatment should be started with cytarabine 3 mg/kg on the first day, followed by 2 mg/kg daily by bolus intravenous injections for a further three days given with zoster immunoglobulin. This latter treatment is particularly important in immunoincompetent patients where the zoster encephalitis is part of a generalised opportunistic infection.

Q-FEVER

This illness, caused by *Coxiella burneti*, often presents with headache and neck stiffness, but the CSF in these patients is often normal. Meningoencephalitis is, however, a well-described although rare complication of this febrile systemic illness. Treatment should be given with oxytetracycline 3 mg daily for 10-14 days, except in the seriously ill or semiconscious patient, when intramuscular tetracycline 100 mg four-hourly should be given for 5-7 days depending on the clinical response. Thereafter oral treatment may be introduced.

Toxoplasmosis

Meningoencephalitis with personality or psychotic changes is an uncommon complication of *Toxoplasma gondii* infection, which is often protracted but seldom fatal. When death does occur, however, it is usually due to meningoencephalitis associated with generalised infection. This is particularly likely to happen in laboratory workers exposed to virulent strains or in the immunoincompetent patient. Treatment should be started with sulphadimidine 3 g daily and pyrimethamine 50-100 mg initially and 25 mg daily, given together for four weeks. Spiramycin is less toxic to the marrow than pyrimethamine but is probably also less effective. If neutropenia or thrombocytopenia arise with the initial combination, then spiramycin 2 g daily should be introduced and continued for ten days with sulphadimidine 3 g daily.

The monthly *MIMS* index of proprietary preparations available in Britain includes the following trade names for the main drugs mentioned in this article (other than broad groups such as corticosteroids): amphotericin-B: Fungilin; ampicillin: Penbritin; benzylpenicillin: Crystapen, Eskacillin, Solvpen; cephaloridine: Ceporin; chloramphenicol: Chloromycetin, Kemicetine; cytarabine: Cytosar; gentamicin: Cidomycin, Genticin; kanamycin: Kannasyn, Kantrex; lincomycin: Lincocin; methicillin: Celbenin; oxytetracycline: Berkmycen, Clinimycin, Ethoxytet, Galenomycin, Imperacin, Oxydon, Oxymycin, Stecsolin, Terramycin, Unimycin; pancreatic desoxyribonuclease: Deanase; phenoxymethylpenicillin: Apsin, Co-Caps penicillin V-K, Compocillin V-K, Crystopen V, Distaquaine V-K, Econocil V-K, Econopen-V, Ethipen GPV, Icipen, Stabillin VK, Ticillin VK, V-Cil-K; rifampicin: Rifadin, Rimactane; spiramycin: Rovamycin; sulphadimidine: Sulphamezathine; tetracycline: Achromycin, Chymocyclar, Co-Caps Tetracycline, Economycin, Ethitet, Stedin, Sustamycin, Tetrabid, Tetrachel, Tetracyn, Tetrex, Totomycin.

Are any antibiotics secreted in tears and are the concentrations likely to be therapeutic?

Secretion of some antibiotic and chemotherapeutic agents, such as sulphonamides, may be demonstrated in animals. Lacrimal secretion of antibiotics, however, does not result in the appearance of levels of definite therapeutic value in man.

In the past patients with respiratory failure from obstructive airways disease used to become oedematous when they got better. Nowadays diuretics seem to mask this. What is the mechanism of the oedema?

The cause of oedema in patients with respiratory failure is not clear.[1] Anoxia may reduce renal blood flow and glomerular filtration rate, leading to retention of sodium, and chronic hypercapnia is accompanied by retention of sodium and bicarbonate ions. Both mechanisms could be responsible for oedema, but the fact that it may persist after recovery, in spite of improvements in renal haemodynamics and arterial blood gas tensions, suggests that other mechanisms are involved.

1 Aber, G M, and Bishop, J M, *Clinical Science*, 1965, **28**, 511.