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Research Article

BACTERIAL EXPEDITION INTO BRAIN

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ABSTRACT

Infections of the Central nervous system (CNS) account for significant morbidity and mortality. Most of the infections present as a medical emergency; need prompt treatment. The CNS consistes of brain and spinal cord; covered by three layers of meninges-duramater (outermost) arachnoid and piamater (latter two are called leptomeninges). Meningitis is an inflammation of leptomeninges surrounding the brain and spinal cord, with involvement of the subarachnoid space. The agents implicated in pyogenic meningitis may vary according to age. Meningitis in neonates and infants caused by *E.coli, Group B Streptococci (Streptococcus agalactiae), Streptococcus pneumoniae, Listeria monocytogenes.* In children, *Haemophilus influenzae, Neisseria meningitidis, Streptococcus pneumoniae,* where as in *adults Neisseria meningitidis, Streptococcus pneumoniae* produce meningitis. The most common meningitis causing bacteria are, *Haemophilus influenzae*, *Streptococcus pneumoniae, Neisseria meningitidis.* The bacteria enter into the body through throat. The infection is transmitted from person- to- person through droplets of respiratory sections from cases or nasopharyngeal carriers. Organisms may gain access to the meninges by several routes such as hematogenous, direct spread from an infected site or anatomical defect in central nervous system causing causing fever, chills and rash, soon these bacteria settle in meninges causing inflammation. This causes pressure in head, and the patient feels severe headache. Neck becomes stiff. The patient often becomes confused or even unconscious the patient may have convulsions which are twitching and jerking of the body that cannot control.

INTRODUCTION

The most common meningitis causing bacteria are, Haemophilus *influenzae*, *Streptococcus pneumonia, Pneumococcal pneumonia represents 15%–50% of all episodes of community-acquired pneumonia.* (1)
Addressing the issue of morbidity and mortality with this disease, The World Health Organization recommend routine childhood pneumococcal vaccination (2)
Pneumococcal vaccines can prevent some cases of pneumonia, meningitis, and sepsis (3) *Neisseria meningitides* is an exclusively human pathogen it is the main cause of bacterial meningitis in children and young adults. (4)
Symptoms of *Meningococcal meningitis* are easily confused with *Haemophilus influenza and Streptococcus pneumonia* (5)

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Current guidance in the United Kingdom is that if a case of meningococcal meningitis or septicaemia (infection of the blood) is suspected, intravenous antibiotics should be given and the ill person admitted to the hospital (6)

H. influenzae type b (Hib) causes bacteremia, pneumonia, epiglottitis and acute bacterial meningitis. On occasion, it causes cellulitis, osteomyelitis, and infectious arthritis. It is one cause of neonatal infection (7)

The latex particle agglutination test (LAT) is a more sensitive method to detect H. influenzae than is culture (8)

Haemophilus influenzae produces beta-lactamases, and gained resistance to the penicillin family of antibiotics. (9)

Meningitis is an acute inflammation of the protective membranes covering the brain and spinal cord, known collectively as the meninges. The most common symptoms are fever, headache, and neck stiffness. Other symptoms include confusion or altered consciousness, vomiting, and an inability to tolerate light or loud noises. (10)

Meningitis caused by meningococcal bacteria may be accompanied by a characteristic rash (11)

Diagnosis of TB meningitis is made by analysing cerebrospinal fluid collected by lumbar puncture (12)

Acid-fast bacilli are sometimes seen on a CSF smear, but more commonly, M. tuberculosis is grown in culture (13)

A spider web clot in the collected CSF is characteristic of TB meningitis, but is a rare finding (14)

Studies suggest up to 10% of human gastrointestinal tracts may be colonized by L. monocytogenes. Nevertheless, clinical diseases due to *L. monocytogenes* are more frequently recognized by veterinarians, especially as meningoencephalitis in ruminants (15)

Chronological record of significant events

The pneumococcus that cause of pneumonia, was first isolated imultaneously and independently by the U.S. Army physician George Sternberg and the French chemist Louis Pasteur (16)

The organism was termed Diplococcus pneumoniae from 1920 because of its characteristic appearance in Gram-stained sputum.

It was renamed *Streptococcus pneumonia* in 1974 because it was very similar to *streptococci* (17)

H. influenza was first described in 1892 by Richard Pfeiffer during an influenza pandemic.(18)

This species was the first free-living organism to have its entire genome sequenced (19)

The World Health Organization recommends a pentavalent vaccine, combining vaccines against diphtheria, tetanus, pertussis, hepatitis B and Hib (20)

In 1884 Ettore Marchiafava and Angelo Celli first observed the bacterium inside cells in the cerebral spinal fluid (CSF) (21)

In 1887 Anton Weichselbaum isolated the bacterium from the CSF of patients with bacterial meningitis. He named the bacterium Diplococcus intracellularismeningitidis. (22)

Research without Boundaries

Cerebrospinal Meningitis

The problem of main concern in pathogenesis is the occurrence of cerebrospinal meningitis among only a limited proportion of the population at risk.

Recent studies have confirmed some early observations that the absence of bactericidal antibody in the blood is the factor most closely related to susceptibility to clinical infection. Evidence in support of this relationship is, the age distribution of meningococcal disease, which has its highest incidence in infants and young children, from three months to three years of age, amongst whom humoral meningococcal antibodies are rarely found the analogy with haemophilus meningitis is obvious. The reciprocal relationship in the appearance of these bactericidal antibodies in older children and adults with the decreasing incidence of cerebrospinal meningitis, except when it occurs in outbreaks among adults brought together for special reasons.

Tuberculous Meningitis

Although tuberculous meningitis occur characteristically as an early extension of a primary lung infection in very young children, it may also develop as an apparently primary infection in older children and young adults. In such cases, as in many instances of renal, bone and joint tuberculosis, there has presumably been an early seeding of tubercle bacilli, blood borne from the primary lesion in the lung or elsewhere, which has lain latent until some factor has encouraged fresh activity. Sometimes too, an active lesion in one area may help to reactivate a latent infection in another organ or tissue Epidemic meningitidis Meningococcus, an obligate human bacterial pathogen, remains a worldwide and devastating cause of epidemic meningitis and sepsis (23)

Encephalo meningitidis

Meningitis and encephalitis already present in the brain or spinal cord of an animal may form simultaneously into meningoencephalitis (24)

Chorio meningitides

It is caused by arena virus. The condition mainly occurs in children and young adults. The CSF is under increased pressure.

Syphilitic meningitis

In meningo vascular syphilis, basalgummatous meningitis may present with cranial nerve palsies. meningitis over the surface of the hemispheres may give rise to headaches and fits in addition to focal signs cortical dysfunction. Pathology of Bacterial meningitis the pia-arachnoid is congested and unfiltered with inflammatory cells. A thin layer of pus forms and this may later organize to form adhesions. These may cause obstructions to the free flow of CSF leading to hydrocephalus, or may damage the cranial nerves at the base of the brain. The CSF pressure rises rapidly, the protein content increases and there is a cellular reaction which varies in type and severity according to the nature of the inflammation and the causative organism. The sugar content of

the CSF is decreased in bacterial infections and in carcinomatosis of the meninges. Diagnosis Meningitis ranks high among medical emergencies and early, rapid, and precise diagnosis is essential.

Diagnosis of meningitis

Depends upon maintaining a high index of suspicion, securing adequate specimens properly, and examining the specimens promptly. Because the risk of death or irreversible damage is great unless treatment is started immediately, there is rarely a second chance to obtain pre treatment specimens, which are essential for specific etiologic diagnosis and optimal management. The immediate decision is usually based on the cell count and the glucose and protein content of cerebrospinal fluid and the result of microscopic search for microorganisms. The initial impression is modified by the results of culture, serological tests and other laboratory procedures (25)

Chemical examination of Cerebrospinal fluid

In addition to cell count, bacterio logical examination, the following chemical tests are commonly carried out on cerebrospinal fluid; determination of glucose, chloride and protein, qualitative test for globin. Normal cerebrospinal fluids are clear and colorless and give no coagulum or sediment on standing. The sugar content of normal lumbar fluid is usually between50 to 80 mg per 100 ml. The most important pathological change is the decrease occurs in meningitis. In meningitis due to various cocci-meningococci, pneumococci, streptococci, staphylococci. The glucose often disappears completely from the fluid. In TB meningitis is reduced. And rarely absent In benign lymphocytic choriomeningitis the sugar is often normal, or decreased to 20 mg %In syphilitic meningitis it is almost always within normal limits .Small increase is found in encephalitis. Considerable increase is found in diabetes mellitus when the blood sugar is increased. Low fluid sugar is found in hypoglycaemia. Chloride content of normal CSF lies between 120 and 130 m Eq. per litre. (700-760mg) NaCl per100mlThe reduction generally more marked in TB meningitis than cocci meningitis. In benign choriomeningitis chlorides are usually normal. An increase is sometimes found in hypertension and in renal disease. The protein content in normal lumbar fluid lies between 15 to 45 mg.per 100ml. An increase in the total protein is the commonest abnormality (26)

Etiology of bacteria Neonates and infants E.coli, Group B Streptococci *(Streptococcus agalactiae), Streptococcus pneumoniae, Listeria monocytogenes*

Children

Haemophilus influenzae, Neisseria meningitidis, Streptococcus pneumoniae

Adults

Neisseria meningitidis, Streptococcus pneumoniae Pathogenesis Transmission- direct contact, respiratory droplets from nose and throat of infected persons, most infections subclinical. Incubation period:2- l0 days. Winter-spring - temperate zones. Dry season in tropical countries.

Highest rates -in young children, during epidemics- older children, teenagers and young adults are also affected. Endotoxin bound to a circulating plasma protein called endotoxin binding protein. This interaction alters the conformation of endotoxin - enable increased binding to and activation of macrophages and other inflammatory cells cytokines including TNFa, IL-1ß, IL-6, IL-8, IL-10. Clinical manifestations Fever and chills, Mental status changes, Nausea and vomiting, Purple, bruise-like areas (purpura),Rash, pinpoint red spots (petechiae) Sensitivity to light (photophobia) Severe headache Complications Meningococcemia & widespread dissemination-Bleeding complications & coagulopathies. Purpurafulminans-tissue destruction. Hydrocephalus, Seizures, Fulminant meningococcal Shock- absence of superficial & deep tendon reflexes. Waterhouse Frederickson Syndrome- haemorrhagic necrosis of adrenal glands, DIC induced micro thrombi, hemorrhage, Myocarditis Microbiological laboratory diagnosis of Meninges causing bacteria Smears are made from fresh uncentrifuged cerebrospinal fluid that appears cloudy or from sediment of centrifuged cerebrospinal fluid. Smears are stained with Gram's stain and occasionally with ZiehlNeelsenstain. Studyoo stained smear under the oil immersion objective may reveal intracellular Gram negative diplococcic *(Meningococci*) intra and extra cellular lancet shaped gram positive diplococci, or small gram negative rods *(H.influenzae* or enteric gram negative rods) *Streptococcus pyogenes* is aerobic facultative anaerobe growing best at temperatures of 37 degrees C. On blood agar, after incubation 24 hours, the colonies are small, circular, semitransparent, low convex discs with an area of clear hemolysis around them. On fresh isolation from lesions, produce a ' matt' colony, whileavirulent strains form glossy colonies. Strains with well marked capsules produce mucoid colonies (27)

Neisseria meningitidisorganisms are Gram negative, ovalcocci. The organisms require an enriched medium like lysed blood or chocolate agar for growth .The inoculated medium is incubated in a moist aerobic environment containing 5-10 % co2 at a temperature of 35-36 degrees C.

Enriched agar medium with lysed blood and antibiotics (Vancomycin, Colistin, nystatin and trimethoprim) is used as popular selective medium (Thayer-Martin medium).These antibiotics inhibit other bacteria but not gonococcus. *Haemophilus influenzae*, is gram negative rod but often show pleomorhism. It requires enriched media such as blood or chocolate agar because they need growth factors, X and V *Mycobacterium tuberculosis*, is a slender bacterium They are acid fast due to presence of mycolic acid in cell wall and weal gram positive. With Ziehl-Neelsenstain, *M.tuberculosis* look slender, straight, or slightly curved rod appearance. The growth is slow. They grow in enriched media containing egg, asparagine, potatoes, serum and meat extracts .The solid medium contain egg (Lowenstein Jense or Dorset.

L J medium is the most widely use solid medium Bacterial meningitis. Bacterial meningitis must be the first and foremost consideration in the differential diagnosis of patients with headache, neck stiffness, fever, and altered mental status. (28)
Lumbar puncture is contraindicated if there is a mass in the brain (tumor or abscess) or the intracranial pressure (ICP) is elevated, as it may lead to brain herniation. (29)

The most important test in identifying or ruling out meningitis is analysis of the cerebrospinal fluid through lumbar puncture (LP, spinal tap) this applies in 45% of all adult cases (30)

Special conditions

Increased ICP- Papilledema.Do CT scan rather than LP.Patient presents with severe HA,altered sensorium,blurred vision need to repeat LP- Relieve ICP.Recurrent meningitis-Immunological etiology. Def of C5-C8 factors Hiking and camping- No neck stiffness,No photophobia.RMSF,Lymes diseases-Ceftriaxone.Serology IgM,IgG, Enzyme substrate tests –specific biochemical substrates hydrolysed by enzymes yield coloured product. Molecular methods –PCR amplifications.Use of biological safety cabinet is a must CNS Infections

Meningitis

Fever, Headache, lethargy, vomiting, stiff neck, photophobia

Interleukin-6 in cerebrospinal fluid as a biomarker of acute meningitis

Bacterial meningitis in adults is a rapid progressive and life threatening condition.

Monitoring of cytokine interleukin (IL) 6 by automated chemilumine scence poses an alternative to monitoring of conventional biomarkers. Low concentrations of CSF IL6 do not exclude viral meningitis but might be a helpful biomarker to exclude acute bacterial inflammation of the central nervous system (31)

CSF IL-6 was shown to be elevated in various types of central nervous diseases such as subarachnoid hemorrhage (32, 33) , traumatic brain injury(34), cerebral ischemia (35,36) and meningitis and encephalitis (37,38)

High concentrations of cytokines, namely tumor necrosis factor-a, IL-1 and IL-6, are correlated with disease severity in meningococcal disease (39,40) and high concentrations of CSF IL-6 were a negative prognostic marker in herpes simplex (HSV) encephalitis (41)

Microbiological culture of cerebrospinal fluid is the gold standard to differentiate between aseptic and bacterial meningitis, but this method has low sensitivitye.(42)

Role of Cerebrospinal Fluid Lactate Dehydrogenase in meningitis

Lactate dehydrogenase (LD) catalyses the reaction CH3.CO.COO- (Pyruvate) +NADH2-----CH2.CHOH.COO- (Lactate) +NAD Lactate dehydrogenase is widely distributed, being found in all cells in man, but is specially plentiful in cardiac, skeletal muscle, liver, kidney, brain and red blood cells.

An increase in cerebrospinal fluid lactate dehydrogenase activity has been reported in the presence of tumours of the central nervous system. The normal range has been given as 10-25IU.per litre by King and as 3-20 by Wroblewski. Enzymes level in CSF like CK, LDH are significantly raised in the meningitis and accessing its value can be an important diagnostic and prognostic marker. (43)

Acid phosphatase activity of cerebrospinal fluid cells in bacterial and a bacterial meningitis

Acid phosphatase activity of cerebrospinal fluid is strongly positive in the early samples of bacterial meningitis, as far as the patients had not received a pretreatment with antibiotics for more than 24 h. Acid phosphatase activity is positive in some cases of Cryptococcus meningitis. It is negative in all cases of aseptic and Mycoplasma pneumonia meningitis. (44)

Encephalitis

Fever, HA, Confusion

Brian Abscess

Fever, HA, Focal neurological deficit, Stiff neck Risk factors Smoking, Viral coinfections, Congenital/acquired Complement deficiencies- C5,6,7,8,9,Crowding,close contacts, Hepatic failure and Multiple Myeloma, Asplenia Teens Are at Increased Risk Transmitted through saliva, the bacteria that cause meningococcal meningitis can spread from one teen to another.

Break through treatments in management of Bacterial meningitis

Pneumonia and Tuberculosis are classified as Lower Respiratory Tract Infections and hence require a strong antibiotic therapy with proper regimen. Almost 80% of meningitis is bacterial. Treatment with antibiotics is very much essential beside corticosteroids. Wherever the history of anaphylaxis to Beta Lactam antibiotics is noticed, Chloramphenicol is considered as an alternative choice. The following antibiotics are used either in single or in combination.

I) CEPHALOSPORINS Ex: Ceftriaxone Cefotaxime II) PENCILLINS Ex: Benzyl Penicillin III) SEMISYNTHETIC AMINOGLYCOSIDES Ex: Chloramphenicol IV) GLYCOPEPTIDES Ex: Vancomycin When the cause is unknown, Benzyl Penicillin sodium injection 600mg is given intravenous every 6 hourly. Dexamethazone is suggested as adjunctive therapy for reducing inflammation. However the use of this steroid should be limited to 2 days in case of children.

Streptococcus pneumoniae Treatment

If the cause is known and if it is *S.pneumoniae*, Ceftriaxone sodium injection 500mg is given every 6 hourly or Cefpotaxime sodium injection 500mg is given every 6 hourly for 10 to 14 days. If the infection is resistant, Vancomycin along with Rifampicin is taken up as next regimen for 10 to 14 days.

Alternatively Chloramphenicol can also be used.

Neisseria meningitidis Treatment

If the infection was identified as *N.meningitidis*, regimen of choice contains Benzyl Penicillin injection 600mg and it is given intravenous every 4 hourly for 5 to 7 days. Alternatively Cefuroxime, Ampicillin & Chloramphenicol can also be used.Cefotaxime or ceftriaxone ? DOC,Rifampicin or ciprofloxacin – for carriers & prophylaxis

Haemophilus influenza Treatment

If the infection was identified as *H.influenza*, the regimen of choice is Cefotaxime 500mg injection or Ceftriaxone sodium injection 500mg given intravenous every 6hourly for 10 to 14 days. If the infection is found to be resistant Ampicillin along with Sulbactam can be switched as other regimen.

Alternatively Chloramphenicol can also be used. 4. Listeria monocytogenes Treatment: If the infection was identified as L.monocytogenes, the regimen of choice is Ampicillin

injection 500mg given intravenous every 4hourly along with Gentamycin injection in the dose of 5mg/kg body weight for 10 to 14 days. Alternatively co-trimoxazole in the dose of 50mg/kg body weight can also be used.

Prevention

Prevention process is common for all meningitis of all etiologies. Casual contacts like professional and school are non contagious. Close contacts of infected patients are likely to get infected.

The disease is transmitted through cough, sneeze & saliva. The following precautions with infected ones will prevent infection. Washing hands often, especially in public places. Not sharing items like toothbrushes, eating utensils, or lipstick. Not sharing food or drinks with infected ones. Covering the mouth and nose while coughing or sneezing. Eating a healthy diet, with good exercise, and rest practice. It suggested avoiding use of unpasteurized milk.

Vaccination

Real prophylactic protection to the entire disease forms is not available. But vaccines are available for meningitis that usually occur in children. The first vaccine was invented in 1981.

Some vaccines are included in National immunization programs. 1.Meningitis B vaccine (Meningococcal group B vaccine) Meningococcal group B vaccine is given to new born at the age of 8weeks, 16weeks and 1year. This vaccine will take care of 90% infections in young children. Bivalent (groups A and C), trivalent (groups A, C and W), or tetravalent (groups A, C, Y and W135),For group B -due to antigenic mimicry with polysaccharide in human, neurologic tissues. Outer membrane proteins (OMP) and strain-specific to control specific epidemics. Additional universal group B protein vaccines are in late stages of development. Overseas travellers should check to see if meningococcal vaccine is recommended for their destination. Travelers should receive the vaccine at least 1 week before departure, if possible. 2.

Pneumococcal Vaccine Pneumococcal vaccine offers protection against meningitis due to *S.pneumoniae.* Children born after January 2020 can have this vaccine as two separate injections, one at 12weeks and the other as a booster at 1 year. Babies born before this date were asked to have 3 doses. 3. *H.influenzae* Vaccine (Hib Vaccine) *H influenzae* vaccine gives protection against H.influenzae. The schedule is 2, 4, 6, & 15 months of age. Side effects include fever, redness at the site of injection. 4.Meningitis C Vaccine *Neisseria meningitides* has around 8 serotype forms among which 5 forms A, b, C, Y & W135 can be controlled with this Men-C Vaccine.

Babies around 1 year of age are required to take this vaccine. 5. Meningitis ACWY Vaccine This vaccine protects against *N.meningitides* A, C, Y & W vaccine. This vaccine is intended for teenagers and university students for getting protected from a, b, C & Y serotype forms pertaining to *N.meningitides.*

Current debate

Currently, the Meningitis B vaccine is available on the NHS for babies aged 2 months, followed by further doses at 4 months and a booster at 12 months. This is part of the childhood immunisation programme (since 1/9/2015). The new meningococcal B vaccine has been licensed in many jurisdictions in the past 2 years. Since 2014, national health authorities have implemented regionally focused campaigns to respond to either outbreaks of Men B invasive disease (e.g. In 2 American Universities) or durable high incidence of Men B disease in some countries (e.g. Quebec hyper-endemic regions). As of September 2015, more than 100,000 doses of the Men B vaccine have been administered - surveillance has confirmed the safety profile and vaccine acceptance in targeted populations has been high. The control of the outbreaks, with large reductions in the incidence of Men B disease, suggests the vaccine is effective against Men B.

Disease control

1. Getting vaccinated is the best method to control meningitis. 2. Vaccination at the age of 11-12 Yrs with a booster at 16-18 years will give protection from meningitis. 3. Following prevention guidelines will control the spread of this disease. 4. Community is suggested to have a diet with immunity boosters for control of this disorder. Cases of bacterial meningitis should be reported to state or local health authorities so that they can follow and treat close contacts of patients and recognize outbreaks. Chemoprophylaxis In close contact with patients in the endemic situation. Not an effective means of interrupting transmission during an epidemic. Antimicrobials - rifampicin, minocycline, ciprofloxacin and ceftriaxone. Sulfonamides are only useful when circulating meningococci are identified as susceptible.

Shortened version of large work

Bacterial meningitis is very serious and can be deadly. Leading causes in the United States include *Streptococcus pneumonia, Group B Streptococcus, Neisseria meningitidis, Haemophilus influenza and Listeria monocytogenes* (45)

Vaccination has greatly decline in the number of cases for the three most common meningeal pathogens *(Haemophilus influenzae, Neisseria meningitides, and Streptococcus pneumoniae)* (46)

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