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Diagnosis and treatment of bacterial meningitis

Research presented

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بِسْمِ اللَّـهِ الرَّحْمَـٰنِ الرَّحِيمِ

{قُلْ هَلْ يَسْتَوِي الَّذِينَ يَعْلَمُونَ وَالَّذِينَ لا يَعْلَمُونَ إِنَّمَا يَتَذَكَّرُ أُولُو الْأَلْبَاب}

صدق الله العظيم

الزمر : 9

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Content:

Abstract:

Background: Worldwide, acute bacterial meningitis is a major cause of high morbidity and mortality especially in children under ages of five years old, particularly in settings where vaccination for *Haemophilus influenzae* type b, *Streptococcus pneumoniae* and *Neisseria meningitis* is yet to be introduced in the national immunization programs. Estimation of disease burden of bacterial meningitis associated with these pathogens can guide the policy makers to consider inclusion of these newer vaccines in the immunization programs. The diagnosis of the bacteria that cause meningitis is essential to treat this dangerous infection and reduce the complications and death rate. Therefore, the main objectives of this review is to explain the best methods for diagnosis and treatment of bacterial that cause meningitis in Diyala governorate, Iraq.
Objectives: To determine the diagnosis and treatment of bacterial meningitis

Key words: Meningitis, bacteria, diagnosis, treatment.

Introduction:

Meningitis was first described in the 1020s in Avicenna's the Canon of Medicine (1) and again more accurately by Avenzoar of al-Andalusia in the 12th century (2). The symptoms of the disease were also noted in 1805 by the Swiss GabinettoVieusseux (a scientificliterary association) during an outbreak in Geneva- Switzerland in 1887 and Dr. Anton Weichselbaum (1845- 1920) of Vienna became the first to isolate the specific germ meningococc (3).

Meningitis is an infection of the subarachnoid space and leptomeninges caused by a variety of pathogenic organisms and continues to be an important source of morbidity and mortality. (4)

Meningitis may develop in response to number of causes most prominently bacterial as *Streptococcus pneumoniae*, *Neisseria meningitides*,

Haemophilus Influenzae, *Escherichia coli*, Group B *Streptococcus* or viruses, physical injury, cancer and drugs. (5)

Acute bacterial meningitis remains an important cause of death and neurological sequelae in children, the clinical features of meningitis are often non-specific and may overlap with those of other infections (Figure 2). Early diagnosis and appropriate treatment are perhaps the most important steps in management, but published data suggested that fewer than half of the cases of meningitis are identified at first assessment (6,7).

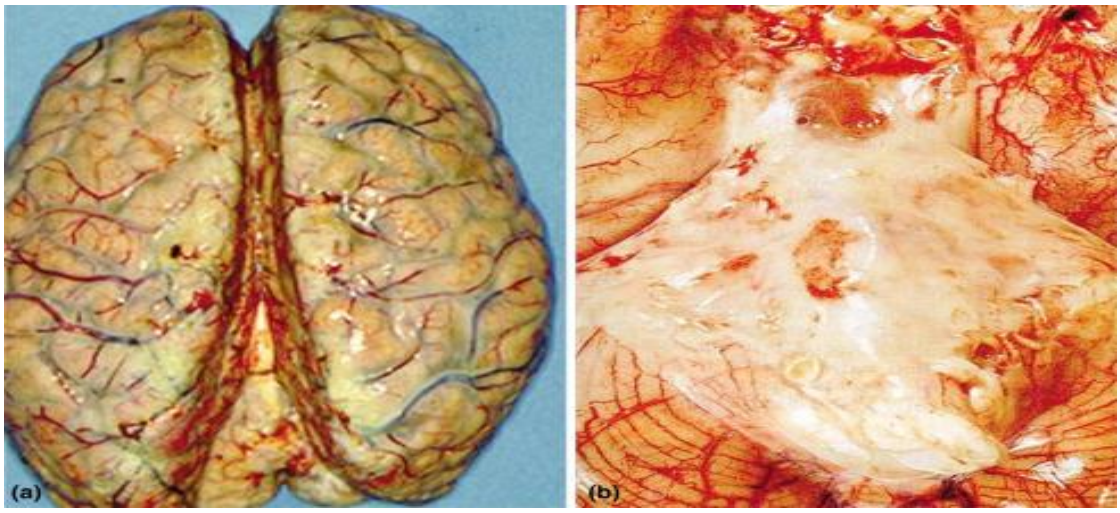

Figure 2. Bacterial meningitis: presence of exudate over convexities and base of the brain.

Literature review:

Diagnosis

1. Symptoms and signs

Symptoms and signs Bacterial meningitis can be difficult to diagnose as the symptoms and signs are often non-specific, especially in young children. The symptoms may include high temperature, poor feeding, vomiting, lethargy, and irritability. The clinical signs include bulging fontanelle, fever, drowsiness, apnoeas, convulsions, and purpuric rash. In older children the more classic signs of neck stiffness, headache, and photophobia are more common. The specific signs of Kernig, Brudzinski, and nuchal stiffness are often absent in children (8). These signs are poorly sensitive in adults, let alone children. In one study in adults, both Kernig

and Brudzinski signs had a sensitivity of only 5%, while sensitivity of nuchal rigidity was 30% (9). The non-specific nature of the symptoms and clinical signs means that we often over treat and look to other investigations to confirm the diagnosis. The 'glass test' can be used to determine if a rash is or is not a symptom of meningitis (Figure 1).

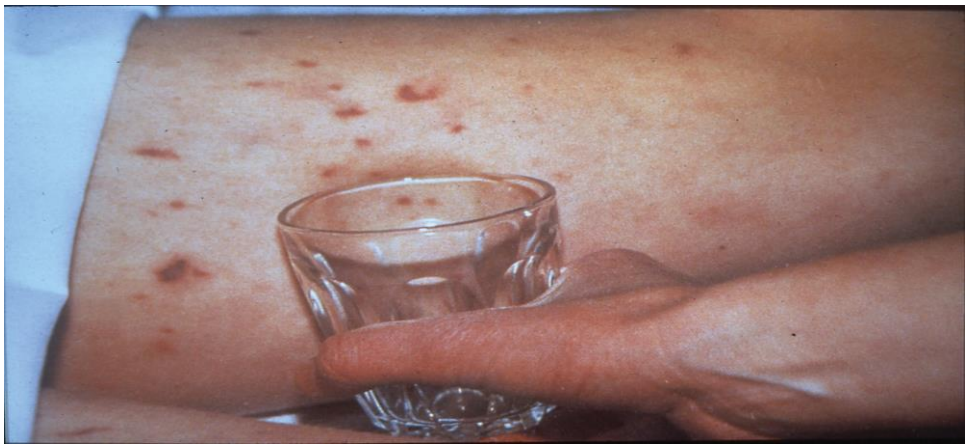

Figure 1: The 'glass test' for diagnosis.

Investigations

Lumbar puncture

Cerebrospinal fluid (CSF) analysis and culture remains the definitive method for diagnosis of meningitis. Issues in respect of indications, contraindications, and safety of lumbar puncture have been covered recently.(10-11) Whether to perform lumbar puncture (LP) in a child with petechial rash is still a matter of debate. Some in the UK hold that an unwell child with petechial rash is pathognomonic of meningococcal disease and so a lumbar puncture would add very little in terms of diagnosis and carries a high risk of making the haemodynamically unstable child worse.(12-13) Others contend that identification of the organism in the CSF is important for treatment, prophylaxis, and epidemiological studies.(14) We side with the latter view but recognise that there are reasons for delaying LP until it is safe. (12-14) Whether the decision is to perform LP or not, antibiotic treatment should not be delayed.

CSF sterilization following antibiotic use occurs rapidly. “Sterilization” of meningococci may occur within two hours, whereas for pneumococci at least four hours of antibiotic therapy is needed.(15) If live bacteria are to

be cultured, the LP must be performed before or, if that is not possible, immediately following the administration of antibiotics.

The introduction of molecular techniques has, however, meant that live organisms are not required for identification, so there is less need for an early CSF. Blood polymerase chain reaction (PCR) may be negative, whereas PCR performed on CSF collected after treatment and stabilisation can still be informative (see below for further discussion of molecular techniques). Traditional teaching holds that when white cells found in CSF are primarily polymorphs, meningitis is bacterial in origin. However, viral infections, especially those caused by enterovirus, may initially cause a predominant polymorph response in the CSF, which may persist throughout the illness.(16)

The rapid antigen latex agglutination test on CSF or blood has the benefit that it can be done locally and rapidly, but its lack of sensitivity can limit its clinical use (17).\ Ultrasonic enhancement has increased the sensitivity of these tests.(18) Commercial kits are available that cover *Neiserria meningitidis* serogroup B, a combination of meningococcal serogroups (W135, A, C, and Y), *Streptococcus pneumoniae*, *Haemophilus influenza* type b, *Escherichia coli* K1, and group B streptococcus. Where specimen volume is limited, guiding the microbiology laboratory as to what the clinician thinks is the presumptive infecting organism is important in prioritising the tests.

2. Cranial computed tomography

Cranial computed tomography (CT) is of limited use in acute bacterial meningitis. It has been used mistakenly to exclude raised intracranial pressure.(19) CT in cerebral oedema may show slit-like lateral ventricles, areas of low attenuation, and absence of basilar and suprachiasmatic cisterns. However, there is considerable variation in the size of normal lateral ventricles, which makes interpretation of the CT scan difficult. There are case reports of cerebral herniation following an LP with a normal CT scan.(20) In a prospective Canadian study of 41 children, clinical management was not influenced by CT findings; those abnormalities detected were already suspected on neurological examination.(21) The main indication for a CT scan in meningitis is when the diagnosis is uncertain and other possible causes of meningism are being considered, for

example, posterior fossa tumours or if complications of meningitis are suspected, for example, cerebral abscess. Any decision to perform a CT should not delay the use of antibiotics.

Other investigations

All children admitted to hospital with suspected meningitis should have a blood culture, a throat swab, a blood EDTA (ethylenediaminetetra-acetic acid) specimen for PCR studies\ and baseline clotted blood for serology. Full blood count, C\ reactive protein (CRP), clotting studies, and urea and electrolytes should also be routinely performed. A trap to watch for is a low or normal CRP that may occur early in severe infection. Meningococci can be isolated from the throat in about half\ the patients with meningococcal disease; this figure is not affected by antibiotic treatment.(22) Aspiration of petechiae in meningococcal disease is a neglected investigation. One study found that petechiae from\ two thirds of patients contain meningococci, which could be seen on Gram stain or cultured.(23) Antibiotics do not affect the visualisation of meningococci in the skin aspirates.(24) This investigation is particularly useful in that a definitive diagnosis of meningococcal disease can be made when clinical signs\ preclude lumbar puncture.

3. Molecular techniques

PCR for *Neisseria meningitidis* and *Streptococcus pneumoniae* using either blood or CSF can be obtained in the UK from several public health laboratories. In the case of meningococcus, the introduction of a new extraction method from whole blood has improved sensitivity and specificity of PCR; in a recent study from Liverpool a sensitivity of 87% and a specificity of 100% were reported in children with probable meningococcal disease.(25) The clinical distinction of probable from possible meningococcal disease is important, as the yield from patients described as “possible” cases is very low. Requesting PCR tests on samples from every patient with the remotest chance of meningococcal disease would lead to inundation of the diagnostic service with very little benefit.(26) It may be argued that if the clinician is already certain that he or she is dealing with meningococcal disease, why the need for further tests? However, confirmation is important at an epidemiological and public health level, especially as PCR techniques can be used to further

characterise meningococci, for example, by serogroup and serotype.(27) Furthermore, not all ill children with haemorrhagic rash have meningococcal disease. While the test itself can be done quickly in the UK (and elsewhere) on the same day of receipt, the centralised nature of the service in the UK at the Meningococcal Reference Unit means that, once transport time is factored in, the turnaround may be several days before a result is available. PCR may in the future be used to determine prognosis. A recent study using quantitative PCR on blood revealed that meningococcal bacterial DNA load correlates with disease severity and that the maximum load is highest in those who die.(28) For the diagnosis of pneumococcal disease, using PCR may be problematic. Its role in diagnosis is at present not as well established as for meningococci. Most commonly, the technique involves the amplification of the pneumolysin gene common to all pneumococci. On CSF, the test is both sensitive and specific (29). However on blood, false positive results may be obtained due to the high nasopharyngeal carriage rate in young children (30).

Treatment:

The choice of antibiotic depends on the organism isolated. In most cases the initial treatment has to be empirical, but nonetheless based on epidemiological knowledge of the commonest organisms for each age group and local antibiotic resistance patterns. The chosen antibiotic should have bactericidal activity in the CSF. Patients with pneumococcal or Gram negative bacillary meningitis who are treated with bacteriostatic antibiotics may have a poor clinical outcome.(31) Animal studies have shown that a bactericidal effect is necessary for sterilisation of the CSF and survival.(32)

There are three factors affecting antibiotic activity: ability to penetrate the CSF, concentration, and intrinsic activity in infected fluid.(33-34) When the blood-brain barrier is intact, penetration is limited, because transport across cells is minimal and the junctions between endothelial cells of the cerebral microvasculature are tight. In meningitis, the integrity of the barrier is altered, resulting in increased permeability and enhanced CSF penetration of most antibiotics. The antibiotic concentration in CSF needed for optimal bactericidal activity is uncertain. However, in experimental studies, maximal bactericidal activity occurs when the concentration of an antibiotic is approximately 10–30 times the minimal bactericidal concentration against the organism in vitro.(35-36)

Partially treated meningitis

As the early symptoms and signs of bacterial meningitis are non-specific, up to 50% of cases may initially receive oral antibiotics. This partial treatment may delay the child's presentation to hospital and result in a diagnostic dilemma. The CSF findings may be altered; Gram stain and growth of organism may be negative, however antibiotics rarely interfere with CSF protein or glucose. In this situation CSF should be sent for both PCR and bacterial antigen detection, as these are not affected by prior antibiotic administration.(37)

Duration of treatment and choice of antibiotic

The duration of antibiotic therapy depends on the organism isolated. For *S pneumoniae* and *H influenzae*, 10–14 days treatment is generally recommended while for *N meningitidis* a seven day course is sufficient. In *Listeria monocytogenes* and group B streptococcal meningitis, antibiotics should be given for 14–21 days. For Gram negative bacilli a minimum of three weeks is needed.(38)

In most cases of bacterial meningitis a broad spectrum cephalosporin (cefotaxime or ceftriaxone) is the most appropriate empirical choice in children over 3 months old. These cover Neisseria meningitides, *Streptococcus pneumoniae*, and *Haemophilus influenzae*, and penetrate CSF well. Ampicillin should be added in young infants (less than 3 months old) to cover *Listeria monocytogenes*. The treatment of choice for Gram negative bacillary meningitis is cefotaxime or ceftriaxone. Aminoglycosides are sometimes used in addition, but not alone as they often do not exceed the minimum inhibitory concentrations (MIC) for Gram negative bacteria and may not be successful in eradicating the pathogen.

Antibiotic resistance

There has been a worldwide increase reported in infection with penicillin and cephalosporin resistant strains of *S pneumoniae*, for example in Europe, South Africa, Asia, and the United States.41–45 The rate in the UK remains low but has increased.(39) Such meningitis may not respond to high dose penicillin therapy and those resistant to cephalosporin may not respond to the standard dose (40). The resistance of S pneumoniae to

penicillin and other β lactam antibiotics is caused by either alteration in the penicillin binding proteins involved in the synthesis of bacterial cell wall or the production of β lactamase.48 In view of the increasing reports of resistant strains of S pneumoniae in the United States, the American Academy of Pediatrics recommended combination therapy, initially with vancomycin and either cefotaxime or ceftriaxone for all children 1 month of age or older with definite or probable bacterial meningitis.

Use of intravenous fluids

In general, most children admitted with meningitis are given intravenous fluids. A common practice has been to restrict fluids to two thirds or three quarters of the daily maintenance: the reasoning is that this reduces the likelihood of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). The incidence of SIADH reported in studies varies considerably, from 4% to 88%, which can be attributed to the different criteria used in its definition. SIADH leads to hyponatraemia and fluid retention, which may worsen cerebral oedema. However, a significant proportion of meningitis cases present with dehydration or hypovolaemia and are in clinical need of fluid resuscitation (41).

Use of dexamethasone

Steroids have anti-inflammatory effects and decrease the release of various cytokines. They inhibit the transcriptions of mRNA for TNF-α and IL-1, and the production of prostaglandins and PAF, reduce vasogenic cerebral oedema, and reduce the production of inducible nitric oxide synthase.(42)Inflammatory changes in meningitis may ultimately lead to nerve damage and deafness. The use of corticosteroids in bacterial meningitis has been debated for more than 40 years. Recent meta-analyses of steroid use in bacterial meningitis have reached different conclusions, perhaps because of the difference in their eligibility criteria (43).

Treatment of raised intracranial pressure

Raised intracranial pressure (ICP) is a well recognised complication of meningitis. The signs of raised ICP include altered level of consciousness, bradycardia, hypertension or hypotension, and altered respiratory pattern. A normal fundoscopy examination does not rule out a raised ICP, as papilloedema is a late sign. Osmotic diuretics such as 20% mannitol,

glycerol, and hypertonic saline are used in the treatment of cerebral oedema and raised ICP. Their action is through shifting fluids from the extravascular to the intravascular space, resulting in a reduction of intracranial pressure. Mannitol is given as an infusion in a dose of 0.25–1 g/kg. Mannitol is not without side effects; a hyperosmolar state may follow repeated doses, worsening cerebral oedema and impairing cardiac output (44,45).

Conclusion:

Bacterial meningitis is a medical emergency which requires a high index of clinical suspicion, prompt diagnosis, and early, aggressive protocolized management. New vaccination programs have led to a change in epidemiology of the disease; however, it remains prevalent worldwide. Advances in clinical and investigation techniques are aiding the diagnosis of bacterial meningitis, and a combination of techniques is useful to confirm or exclude the diagnosis. While antibiotics, steroids, and supportive therapy remain the mainstay of treatment, further research should be performed into the roles of adjuvant therapy.

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