INTRODUCTION

Meningitis is inflammation of the protective membranes covering the brain and spinal cord, known collectively as the meninges**.** The inflammation may be caused by infection with viruses, bacteria, or other microorganisms, and less commonly by certain drugs ***(Ginsberg, 2004)***. Most cases are due to infection with viruses ***(Attia et al., 1999).*** Bacteria, fungi, and parasites are the next most common causes ***(Ginsberg, 2004).***

Microorganisms reach the meninges either by direct extension from the ears, nasopharynx, cranial injury or congenital meningeal defect, or by blood- stream spread ***(Kumar and Clark, 2002).*** Host factors as lack of humoral immunity and lack of integrity of cerebrospinal fluid space may predispose to meningitis ***(Saif El-Din and Abdel-Wahab, 1995).*** Meningitis can be life- threatening because of the inflammation's proximity to the brain and spinal cord; therefore the condition is classified as a medical emergency **(*Sáez-Llorens and McCracken, 2003; Tunkel et al., 2004).***

The most common symptoms of meningitis are headache and neck stiffness associated with fever, confusion or altered consciousness, vomiting, and an inability to tolerate light (photophobia) ***(Van de Beek et al., 2006).*** The classic triad of diagnostic signs consists of nuchal rigidity, sudden high fever

and altered mental status; In infants up to 6 months of age, bulging of the fontanelle may be present ***(Theilen et al., 2008).***

Distinguishing acute, subacute, and chronic meningitis helps to identify the pathogen. Approximately 25% of patients with bacterial meningitis present acutely within 24 hours of onset of symptoms. Other patients with bacterial meningitis and most patients with viral meningitis present with subacute neurologic symptoms developing over 1-7 days. Chronic symptoms lasting longer than 1 week suggest meningitis caused by some viruses ***(Lippincott and Wilkins, 2006).***

Meningitis can lead to serious long-term consequences such as deafness, epilepsy, hydrocephalus and cognitive deficits, especially if not treated quickly **(*Sáez-Llorens and McCracken, 2003*; *van de Beek et al., 2006)***.

Cerebrospinal fluid (CSF) analysis is the cornerstone and diagnostic test of choice for suspected meningitis. Measure the opening pressure and send the fluid for cell count (and differential count), chemistry (ie, CSF glucose and protein), and microbiology (ie, Gram stain and cultures) ***(Razonable, 2007)***. However lumbar puncture is often delayed or deferred owing to concern about the risk of cerebral herniation, this risk is thought to be over emphasized ***(Scarborough and Thwaites, 2008)***.

Meningitis is defined as bacterial according to CSF laboratory findings [(increased protein > 100mg/dl, decreased

glucose < 40mg/dl, and leukocyte count 100-5000/mm3with polymorph nuclear leukocyte domination > 80%), identification of bacterial agents in Gram staining, and/or positive bacterial culture ***(Razonable, 2011)***]. Also, CSF/serum glucose ratio ≤ 0.4 is indicative of bacterial meningitis ***(Straus et al., 2006)***.

Meningitis is defined as viral if the viral culture, serological testing, pleocytosis, or reverse transcriptase polymerase chain reactions were positive, and the bacterial culture was negative ***(Dubos et al., 2008)***.

In practice, before definitive CSF bacterial cultures are available, most patients with acute meningitis are treated with broad spectrum antibiotics targeting bacterial meningitis. In general, this does not seriously harm the aseptic meningitis patient; however, it may enhance the local frequency of antibiotic resistance ***(Wise et al., 1998),*** and cause antibiotic adverse effects, nosocomial infections ***(Raymond, 2000),*** and high medical costs ***(Parasuraman et al., 2001).*** Thus, it is not only important to recognize bacterial meningitis patients who promptly need antimicrobial therapy but also aseptic meningitis patients who do not need antibiotics and/or hospital stays ***(Huy et al., 2010).***

Clinical criteria, Gram staining, and bacterial antigen testing of CSF as well as the classic biological markers in the blood (CRP level, white blood cell count, and neutrophil count) or CSF (protein level, glucose level, WBC count, and

neutrophil count) used alone do not offer 100% sensitivity with high specificity for distinguishing bacterial and aseptic meningitis ***(Dubos et al., 2008)***. Gram staining of the sample may demonstrate bacteria in bacterial meningitis, but absence of bacteria does not exclude bacterial meningitis as they are only seen in 60% of cases; this figure is reduced by a further 20% if antibiotics were administered before the sample was taken ***(Tunkel et al., 2004)***. Waiting for at least 2 days was recommended to identify bacterial growth in CSF cultures, whereas this period is 3-8 days for viral cultures ***(Cassady and Whitley, 1997)***. Moreover, identifying the frequently encountered viral agents via PCR is not always possible in every institution ***(Oberhoffer et al., 1999).***

Epidemiology is a good measure of understanding the significance of bacterial meningitis. Bacterial meningitis varies in terms of how it affects people on a global spectrum. Some age groups are more susceptible to contracting this form of meningitis in comparison to other age groups which makes it difficult to design different age-specific treatments. The most susceptible groups are children under the age of 5 years old and adolescents ***(Gold et al., 1999).*** It is more prevalent in developing countries with poor resources than developed countries that are more industrialized. Apart from actual epidemics, 1 million cases are observed every year out of which 170000 are life-threatening ***(Biaukula et al., 2012).***

AIM OF THE WORK

This study aims at:

Study the demographic, clinicoetiological and laboratory characteristics of acute meningitis in patients attending Embaba fever hospital.

Chapter (1)

ETIOLOGY, EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF MENINGITIS

Definition of meningitis

Meningitis is inflammation of the protective membranes covering the brain and spinal cord, known collectively as the meninges. The inflammation may be caused by infection with viruses, bacteria, or other microorganisms, and less commonly by certain drugs ***(Ginsberg, 2004).*** The most serious and the most difficult to treat types of meningitis tend to be those caused by bacteria ***(Klein et al., 2000)***.

Meningitis can be life-threatening because of the inflammation's proximity to the brain and spinal cord; therefore the condition is classified as a medical emergency ***(Sáez-Llorens and McCracken, 2003 & Tunkel et al., 2004).*** Despite advances in antimicrobial agents and intensive care management, case-fatality rates and long-term morbidity remain high ***(Dagbjartsson et al., 2000)***.

Definitions:

Suspected acute meningitis: sudden onset of fever (>38.5°C rectal or 38.0 axillary) and one or more of the following: stiff neck, altered consciousness, other meningeal

signs or petechial or purpural rash (in patients < 1 year of age, ever accompanied by a bulging fontanel).

Confirmed bacterial meningitis: a suspected case with turbid CSF and the following results: Meningococcal; gram stain showing gram-negative diplococcus, ongoing epidemic. Pneumococcal; gram stain with gram positive cocci. H. influenza; gram stain showing gram negative pleomorphic rods or acase with laboratory confirmation (either CSF culture or CSF antigen detection) ***(MOHP, 2000)***.

Aseptic meningitis: is defined as meningitis with a negative bacterial culture of the Cerebrospinal Fluid (CSF). Although viral meningitis is the most common type of aseptic meningitis, partially treated bacterial meningitis and other infectious agents not routinely cultured (e.g. tuberculosis and syphilis) can be also qualified as aseptic meningitis ***(Dodge et al., 2003)***.

Encephalitis: inflammation of the brain parenchyma; cerebral cortex causes altered mental status early in the course, and focal or diffuse neurological signs may be present ***(Heyderman, 2005).***

Classification

It can be useful to divide symptom onset into:

1- Acute

2- Subacute

3- Chronic categories.

Unlike subacute (1-7d) or chronic (>7d) meningitis, which have infectious and noninfectious etiologies, acute meningitis (<24h) is almost always a bacterial infection caused by one of several organisms. Subacute and chronic meningitis are more commonly caused by fungi, parasites, disseminated malignancy, tuberculosis, sarcoidosis, AIDS, Lyme disease, or syphilis ***(Schlech, 2002)***.

The meningitis according to etiology was classified by ***(Andreoli et al., 1990)*** into two major categories:

1- Infectious

2- Noninfectious meningitis.

The infectious group including bacterial, viral, spirochaetal, fungal and parasitic causes, while the non infectious causes involve the subarachnoid hemorrhage, collagen diseases, neoplasms, drugs and epidermoid cyst of the meninges.

This etiological classification has been modified by Zell and Richard, 1990 who considered the bacterial type of infectious group as (septic meningitis), while the other causes are collectively, known as (aseptic meningitis). Viral meningitis is the most common cause of meningitis and commonly presents with a less acute onset of signs and symptoms than does bacterial infection ***(Yogev, 2002).***

Bacterial (Septic) meningitis:

Common causative organisms in various age groups

1) Premature babies and newborn up to 3 months old:

- Group B streptococci (subtypes III which normally inhabit the vagina and are mainly the cause during the first week of life).
- Escherichia coli (carrying K1 antigen) that normally inhabit the digestive tract
- Listeria monocytogenes (serotype 1V-b) may affect the newborn and occurs in epidemics.

2) Infants and children:

- Neisseria meningitides.
- Streptococcus pneumoniae (serotypes 6,9,14,18,23).

- Haemophilus influenzae type B (under 5 years in countries that do not offer vaccination).

(Sáez-Llorens and McCracken, 2003 &Tunkel et al., 2004)

3) Adults:

- Neisseria meningitides and Streptococcus pneumoniae (together cause 80% of all cases of bacterial meningitis).

- Listeria monocytogenes (increased risk in those over 50 years old).

(Van de Beek et al., 2006)

Recurrent bacterial meningitis:

May be caused by persisting anatomical defects either congenital or acquired, or by disorders of the immune system, anatomical defects allow continuity between the external environment and the nervous system. The most common cause of recurrent meningitis is skull fracture particularly fractures that affect the base of the skull or extend towards the sinuses and petrous pyramids. A literature review of 363 reported cases of recurrent meningitis showed that 59% of cases are due to such anatomical abnormalities, 36% due to immune deficiencies (such as complement deficiency, which predisposes especially to recurrent meningococcal meningitis)

and 5% due to ongoing infections in areas adjacent to meninges ***(Tebruegge and Curtis, 2008).***

Tuberculous meningitis:

Meningitis due to infection with mycobacterium tuberculosis is more common in those from countries where tuberculosis is common, but is also encountered in those with immune problems, such as acquired immunodeficiency syndrome (AIDS) ***(Thwaites et al., 2000).***

Aseptic meningitis:

The term aseptic meningitisrefers loosely to all cases of meningitis in which no bacterial infection can be demonstrated ***(Ginsberg, 2004).***

A. Viral meningitis:

- Enteroviruses: such as coxsackie and echoviruses, comprise more than 80% of all episodes of aseptic meningitis and are the most commonly identified causes of CNS viral infections ***(Lee and Davies, 2007)***.
- Herpes simplex virus type 2 (and less commonly type 1).
- Varicella zoster virus (known to cause chicken pox and shingles).
- Mumps virus.

- HIV (Human immunodeficiency virus).
- LCMV (lymphocytic choriomeningitis virus). ***(Logan and MacMahon, 2008)***
- Adenoviruses, influenza types A and B, and Epstein-Barr virus ***(Nigrovic et al., 2007).***
- Cytomegalovirus
- Epstein-Barr virus ***(Tapiainen et al., 2007).***

B. Fungal meningitis:

Opportunistic fungi such as cryptococcus species, coccidioides species, and histoplasma species can cause meningitis ***(Tapiainen et al., 2007)***. Fungal meningitis due to Cryptococcus neoformanse is typically seen in people with immune deficiency such as AIDS ***(Ginsberg, 2004)***.

C. Some conditions of bacterial meningitis:

- Bacteria that do not grow on routine culture plates such as chlamydia species, mycoplasma species and rickettsia species ***(Tapiainen et al., 2007).***
- Bacterial infection that has already been partially treated with disappearance of the bacteria from the meninges.
- Infection in a space adjacent to meninges e.g. sinusitis.

- Endocarditis (infection of the heart valves with spread of small clusters of bacteria through the blood stream).
- Infection with spirochetes, a type of bacteria that includes Treponema Pallidum (the cause of syphilis) and Borrelia burgdurferi (known for causing Lyme disease) ***(Ginsberg, 2004).***

D. Protozoal meningitis:

- Cerebral malaria.
- Amoebic meningitis due to infection with amoeba such as Naegleria fowleri contracted from fresh water sources ***(Ginsberg, 2004)***.

E. Helminthic meningitis:

A parasitic cause is often assumed when there is a predominance of eosinophils in the CSF. The most common parasites implicated are:

- *Angiostrongylus cantonensis, Gnathostoma spinigerum and Schistosoma* species.
- Conditions such as cysticercosis, toxocariasis, and paragonimiasis ***(Graeff-Teixeira et al., 2009).***

F. Non-infectious:

1- Malignant meningitis: spread of cancer to meninges ***(Chamberlain, 2005).*** Meningeal carcinomatosis (MC) is the malignant infiltration of the meninges from a distant solid tumor, most commonly adenocarcinoma of the breast or lung and melanoma ***(Grossman and Krabak, 1999).*** MC also has been described infrequently in association with colon cancer ***(Kato et al., 1995).***

2- Drug induced: mainly non-steroidal anti-inflammatory drugs especially ibuprofen, Antibiotics especially cotrimoxazole, intravenous immunoglobulins and intrathecal agents ***(Jolles et al., 2000).*** Also, there have been reports of meningitis associated with immunizations such as the measles-mumps-rubella vaccine (MMR) ***(Miller et al., 2007).*** With a number of other agents reported less frequently as carbamazepine, azathioprine, anti-CD3 monoclonal antibodies ***(Jolles et al., 2000).***

3- Sarcoidosis, systemic lupus erythematosus and vasculitis such as Behcet's disease may cause meningitis ***(Ginsberg, 2004).***

4- Epidermoid cysts and dermoid cysts: may cause meningitis by releasing irritant matter into the subarachnoid space ***(Tebruegge and Curtis, 2008).***

5- Rheumatologic disorders, such as Sjogren's syndrome, can cause meningitis ***(Ishida et al., 2007).***

6- Rarely, migraine may cause meningitis, but this diagnosis is usually only made when other causes have been eliminated ***(Ginsberg, 2004).***

Mollaret's meningitis: is a syndrome of recurrent episodes of aseptic meningitis, it is now thought to be caused by herpes simplex virus type 2 ***(Gao et al., 2007).***

Epidemiology of Meningitis:

Although meningitis is a notifiable disease in many countries, the exact incidence rate is unknown ***(Logan and MacMahon, 2008).*** Bacterial meningitis occurs in about 3 people per 100,000 annually in Western countries. Population-wide studies have shown that viral meningitis is more common, at 10.9 per 100,000, and occurs more often in the summer ***(Attia et al., 1999).***

Mortality from meningitis was very high (over 90%) in early reports. In 1906, antiserum was produced in horses; this was developed further by the American scientist Simon Flexner and markedly decreased mortality from meningococcal disease ***(Swartz, 2004).*** The introduction in the late 20th century of haemophilus vaccines led to a marked fall in cases of meningitis associated with this pathogen ***(Peltola, 2000).*** Since the introduction of the conjugate vaccine in the United States in