INTRODUCTION

Meningitis is inflammation of the protective membranes covering the brain and spinal cord, known collectively as the meninges **(Sáez-Llorens andMcCracken, 2003).** The inflammation may be caused by infection with viruses, bacteria, or other microorganisms, and less commonly by certain drugs **(Ginsberg, 2004).** 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 **(Tunkel, 2004).**

Meningitis is considered as an endemic disease in Egypt **(WHO, 2003).** Apart from endemicity, a violent periodic epidemic occurs every 6-12 years in the African meningitis belt; usually at the end of the dry season, peaking in April and declining with the start of the rainy season in May or June **(Tikhomirov and Santa, 1997).**Before the era of antibiotics, meningitis had a case fatality rate of almost 100% **(Pecoul and Varaine, 1991).** Today, despite the availability of nontoxic and affordable antibiotics worldwide, the case fatality rate and neurological sequelae among survivors are still high, ranging from 15 to 70% and 10 to 35%, respectively; depending on the interaction between multiple factors related to the causative agent, host, and management

(Carrol, 1994). In Egypt, case-fatality rate ranged from 8.5 to 55% **(Youssef and El-Sakka, 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) or loud noises (phonophobia). Children often exhibit only nonspecific symptoms, such as irritability and drowsiness. If a rash is present, it may indicate a particular cause of meningitis; for instance, meningitis caused by meningococcal bacteria may be accompanied by a characteristic rash **(Sáez-Llorens and McCracken, 2003).**

The classic triad of diagnostic signs consists of nuchal rigidity, sudden high fever, and altered mental status; however, all three features are present in only 44–46% of bacterial meningitis cases **(van de Beek, 2004).**

Meningitis is potentially life-threatening and has a high mortality rate if untreated; delay in treatment has been associated with a poorer outcome **(van de Beek, 2006)** Thus, treatment with wide-spectrum antibiotics should not be delayed while confirmatory tests are being conducted **(Heyderman, 2003).**

Untreated, bacterial meningitis is almost always fatal. Viral meningitis, in contrast, tends to resolve spontaneously and is rarely fatal. With treatment, mortality (risk of death) from

bacterial meningitis depends on the age of the person and the underlying cause. Risk of death is predicted by various factors apart from age, such as the pathogen and the time it takes for the pathogen to be cleared from the cerebrospinal fluid, the severity of the generalized illness, a decreased level of consciousness or an abnormally low count of white blood cells in the CSF. In children there are several potential disabilities which may result from damage to the nervous system, including sensorineural hearing loss, epilepsy, learning and behavioral difficulties, as well as decreased intelligence **(Sáez-Llorens and McCracken, 2003).**

In recent years, it has been proposed that CSF lactate may be a good marker that can differentiate bacterial meningitis, from partially treated meningitis and aseptic meningitis ***(Cunha, 2006).***

The differential diagnosis between bacterial and viral meningitis is based on CSF cellular and biochemistries characteristics, it is important for the adequate treatment and prognosis. CSF lactic acid determination is considered the best biomarker for this differential diagnosis **(De Almeida, 2008)**.

The CSF lactate concentration has been suggested as a useful parameter to differentiate bacterial from viral meningitis **(Tunkel, 2004).**

Lactate deyhydrogenase, a tetramer protein comprised of four monomer**,** it is intracellular enzyme and sensitive indicator of bacterial meningitis. It is more sensitive as early indicator of bacterial meningitis than is glucose, and appear to help to differentiate bacterial from non bacterialmeningitis **(Wellmer, 2001).**

AIM OF THE WORK

The aim of this work is to:

1. Correlate the clinical presentation and CSF analysis in childhood meningitis with special refrence to lactic acid and lactate dehydrogenase enzyme estimation.

2. Determine sensitivity analysis of LDH enzyme and lactic acid in CSF in early diagnosis of bacterial meningitis.

3. Evaluate the role of LDH enzyme and lactic acid in differentiation between bacterial and viral meningitis.

4. Detect the role of LDH enzyme and lactic acid in prognosis and response to treatment of meningitis.

I. MENINGITIS

Definition

Meningitis is an inflammation of the leptomeninges and underlying subarachnoid cerebrospinal fluid (CSF). The inflammation may be caused by infection with viruses, bacteria, other micro-organisms, or non-infective causes ***(Razonable, 2012).***

Bacterial meningitis is a medical emergency characterised by inflammation of the meninges in response to bacterial infection. Untreated, its mortality approaches 100%, and even with current antibiotics and advanced paediatric intensive care, the mortality rate of the disease is approximately 5–10%. Worldwide, the risk of neurological sequelae in survivors following hospital discharge approaches 20%. Early diagnosis and appropriate management of the child with meningitis is therefore critical **(Edmond, 2010).**

Viral meningitis is common and often goes unreported. In the absence of a lumbar puncture, viral and bacterial meningitis cannot be differentiated with certainty, and all suspected cases should therefore be referred. Lumbar puncture and analysis of cerebrospinal fluid may be done primarily to exclude bacterial meningitis, but identification of the specific viral cause is itself

beneficial. Viral diagnosis informs prognosis, enhances care of the patient, reduces the use of antibiotics, decreases length of stay in hospital, and can help to prevent further spread of infection **(Logan and MacMahon, 2008).**

Incidence

Bacterial meningitis remains a serious threat to global health, accounting for an estimated annual 170 000 deaths worldwide (**WHO, 2010)**. Every year, bacterial meningitis epidemics affect more than 400 million people living in the 21 countries of the "African meningitis belt" (from Senegal to Ethiopia). In this area over 800, 000 cases were reported in the last 15 years (1996–2010). Of these cases, 10% resulted in deaths, with another 10–20% developing neurological sequelae **(WHO, 2011).**

In a survey by the Haemophilus influenzae type b (Hib) and Pneumococcal Working Group, the incidence of meningitis in 2000 varied in different regions of the world. The overall incidence of pneumococcal meningitis was 17 cases per 100, 000, with the highest incidence in Africa, at 38 cases per 100, 000, and the lowest incidence in Europe, at 6 cases per 100, 000. The overall death rate was 10 cases per 100, 000. The death rate was highest in Africa, at 28 cases per 100, 000, and lowest in

Europe and Western Pacific regions, at 3 cases per 100, 000 **(O'Brien and Wolfson, 2009).**

Obtaining accurate international prevalence and incidence of this clinically heterogenous and often benign disease is difficult. Worldwide causes of viral meningitis include enteroviruses, mumps virus, measles virus, VZV, and HIV. Meningitis symptoms may develop in as few as 1 in 3, 000 cases of infection by these agents **(Wan, 2013).**

In a tertiary care children's hospital in Athens, Greece, 506 cases of aseptic or viral meningitis were reviewed from 1994 through 2002; the estimated annual incidence was 17 cases per 100, 000 children younger than 14 years.Most cases occurred during summer (38%) and autumn (24%), and 47 of 96 patients (48.9%) had positive results for enteroviral RNA on CSF polymerase chain reaction (PCR) assay of CSF **(Michos, 2007).**

Epidemiology

I.Bacterial meningitis

Bacterial meningitis remains a very important disease worldwide. In the United States, the epidemiology of bacterial meningitis has changed dramatically in the last 2 decades, primarily due to the introduction of vaccination against common meningeal pathogens. In the late 1970s, the overall annual rate

for bacterial meningitis was reported as 3.0 cases per 100 000 population **(Nudelman, 2009).**

Bacterial meningitis is still a major problem in many areas of the world, both in developing and underdeveloped countries. Data collected by the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) through the Pediatric Bacterial Meningitis (PBM) Surveillance Network in Sub-Saharan Africa demonstrated that between 2002 and 2008, the incidence of bacterial meningitis among children younger than 5 years was still very high, with about 75, 000 reported cases **(MMWR, 2009).** Of these, 47% of cases were due to *Streptococcus pneumoniae*, 34% due to *Haemophilus influenzae*, and 19% due to *Neisseria meningitides* **(MMWR, 2009).**

In Egypt, *S. pneumoniae* was recently described as the leading cause of bacterial meningitis ***(Afifi, 2007).***

II.Viral meningitis

Sex:

Depending on the type of viral pathogen, the ratio of affected males to females can vary. Enteroviruses are thought to affect males 1.3-1.5 times more often than females. Mumps virus is known to affect males 3 times more often than females. **(Wan, 2013).**

Age:

Viral meningitis can occur at any age but is most common in young children. In the largest reported study, a 1966 birth cohort of 12 000 children in Finland, the annual incidence of presumed viral meningitis was 219 per 100 000 in infants under 1 year and 27.8 per 100 000 overall in children under 14. In a smaller retrospective study, the incidence of aseptic meningitis in people aged 16 and over was lower at 7.6 per 100 000. **(Kupila, 2006).**

Etiology and causes:

I.Bacterial meningitis

The great majority of bacterial meningitis is caused by 3 main agents: N meningitides, S pneumoniae, and H influenzae. However, due to the introduction of conjugate vaccines to H influenzae type b (Hib) and S pneumoniae in many countries, there has been a shift in the causes of meningitis. Most of the recent surveillance studies in the US showed that the most common etiologic agents of bacterial meningitis were S pneumoniae (61%), N meningitides (16%), group B streptococcus (14%), H influenzae (7%), and Listeria monocytogenes (2%) **(Dery MA, 2007).**

Specific agents of bacterial meningitis also vary according to age group and host immunostatus. In the neonatal

period (newborn to 29 d), important pathogens are aerobic gram-negative bacilli, including Escherichia coli, group B-hemolytic streptococci, L monocytogenes, and Klebsiella species, among others. During childhood and adolescence, N meningitides and S pneumoniae are the most common agents in the community population **(Bilukha, 2005).**

Causative organisms

1.Streptococcus pneumoniae

S pneumoniae is a gram-positive, lancet-shaped diplococcus that is the leading cause of meningitis. Of the 84 serotypes, numbers 1, 3, 6, 7, 14, 19, and 23 are the ones most often associated with bacteremia and meningitis. Children of any age may be affected, but the incidence and severity are highest in very young and elderly persons ***(Muller, 2014)***.

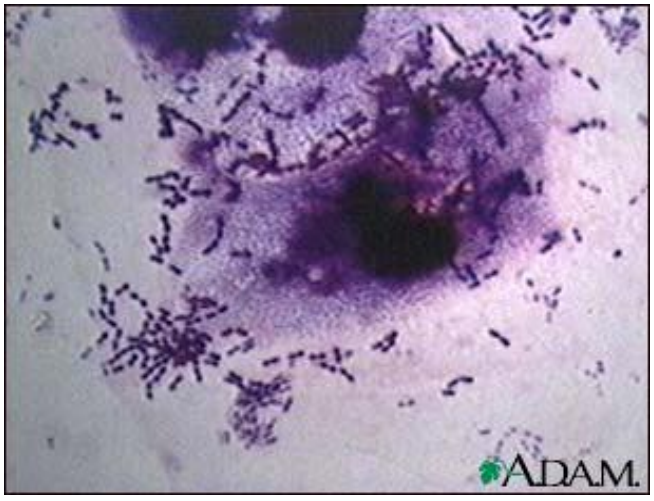

Fig. (1): Streptococcus pneumonia.

In patients with recurrent meningitis, predisposing factors are anatomic defects, asplenia, and primary immune deficiency. Often, the history includes recent or remote head trauma. This organism also has a predilection for causing meningitis in patients with sickle cell disease, other hemoglobinopathies, and functional asplenia **(Muller, 2014)**.

2. Neisseria meningitides:

N meningitidis is a gram-negative, kidney bean–shaped organism that is frequently found intracellularly. Organisms are grouped serologically on the basis of capsular polysaccharide; A, B, C, D, X, Y, Z, 29E, and W-135 are the pathogenic serotypes. In developed countries, serotypes B, C, Y, and W-135 account for most childhood cases. Group A strains are most prevalent in developing countries and have resulted in epidemics of meningococcal meningitis throughout the world, as well as outbreaks in military barracks **(Cohn, 2013)**.

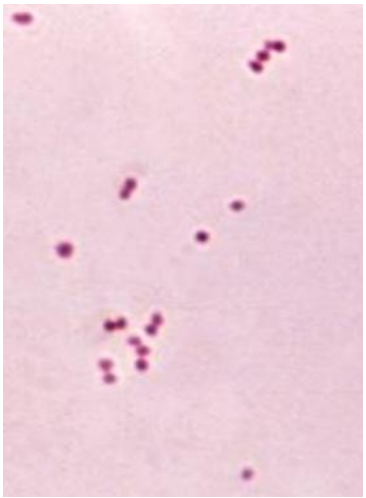

Fig. (2): Neisseria meningitides

3. Haemophilus influenzae type b:

Hib is a pleomorphic gram-negative rod whose shape varies from a coccobacillary form to a long curved rod. Hib meningitis occurs primarily in children who have not been immunized with Hib vaccine; 80-90% of cases occur in children aged 1 month to 3 years. By age 3 years, a significant number of nonimmunized children acquire antibodies against the capsular polyribophosphate of Hib, which are protective **(Watt, 2009)**.

The mode of transmission is person-to-person via direct contact with infected droplets of respiratory secretions. The incubation period generally is less than 10 days. Current mortality is less than 5%. Most fatalities occur during the first few days of the illness **(Watt, 2009)**.

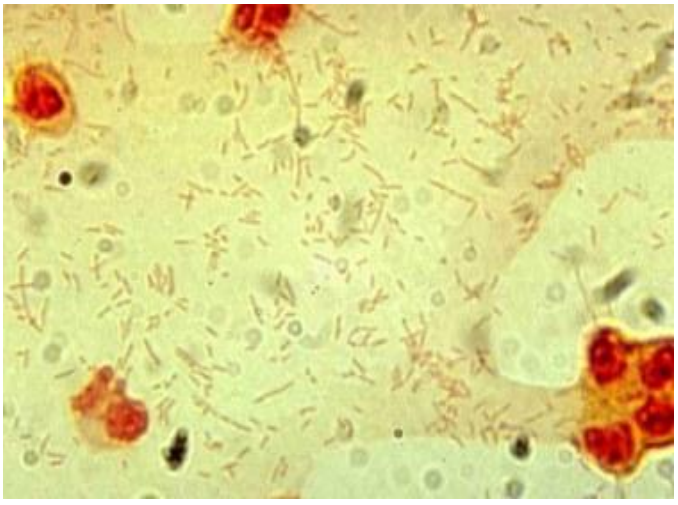

Fig. (3): Haemophilus influenzae type b.

II. Viral meningitis

Enteroviruses were most common, accounting for 46%, followed by herpes simplex virus type 2 (31%), varicella zoster virus (11%), and herpes simplex virus type 1 (4%) **(Kupila, 2006).**

Infants and young children with no immunity are most susceptible to enteroviruses, and the incidence decreases with age. Infection is seasonal in temperate climates—highest in summer and autumn—but high all year round in tropical and subtropical climates **(Sawyer & Rotbart, 2004).**

The incidence of viral meningitis drops with age, with the incidence during the first year of life being 20 times greater than it is in older children and adults. In neonates older than 7 days, enteroviruses are the most common cause of aseptic meningitis. Vaccination has greatly reduced the incidence of meningitis from mumps, polio, and measles viruses **(Wan, 2013).**

Enteroviruses are by far the most common cause of viral meningitis; they account for most cases, at all ages, in which the cause is identified **(Sawyer & Rotbart, 2004)**.

More than 80 serotypes of these small RNA viruses have been identified. The severity of infection caused by enteroviruses ranges from mild, self-limited illness with primarily meningeal

involvement to severe encephalitis resulting in death or significant sequelae **(Prober and Dyner, 2011).**

Herpes simplex virus now ranks second among the causes of viral meningitis in adolescents and adults in developed countries **(Kupilal, 2006)**. Herpes simplex virus type 1 (HSV-1) is an important cause of severe, sporadic encephalitis in children and adults. Brain involvement usually is focal; progression to coma and death occurs in 70% of cases without antiviral therapy. Severe encephalitis with diffuse brain involvement is caused by herpes simplex virus type 2 (HSV-2) in neonates who usually contract the virus from their mothers at delivery **(Prober and Dyner, 2011).**

The consequences of neonatal herpes simplex virus (HSV) infection can be severe. Disease can be localized to skin, eye and mouth (SEM disease), involve the central nervous system (CNS) or manifest as disseminated infection involving multiple organs. Most surviving infants in the latter two categories have neurological sequelae, and the mortality rate in the absence of therapy is very high (80%) for babies in the latter category. The International Herpes Management Forum (IHMF) has produced guidelines on the diagnosis, prevention and effective management of neonatal herpes **(Kimberlin, 2004).**