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Pathogenesis and Pathophysiology of Acute Bacterial Meningitis

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ABSTRACT

Bacterial meningitis is a serious medical disorder that requires a timely diagnosis and immediate treatment as soon as it is suspected. Meningitis is typically caused by two strains of bacteria that are extremely dangerous to humans: streptococcus pneumoniae and neisseria meningitidis. Antibiotic resistance is quickly becoming a problem that will need to be addressed. Researchers have developed a more comprehensive understanding of the particular mechanisms that contribute to brain damage, following problems, and cognitive deficits as a result of both clinical and experimental studies. We present a succinct summary of the current understanding of the underlying mechanisms of acute bacterial meningitis and detail the most up-to-date ways for its treatment. In addition, we discuss the implications of this understanding for future research. These infections multiply by taking advantage of the unique properties that the immune system possesses in the central nervous system (CNS), which then leads to inflammation. In bacterial meningitis, the recruitment of leukocytes that have been intensely stimulated into the cerebrospinal fluid (also known as CSF) is a crucial component of the disease. Inflammation of the meninges can be brought on by a wide variety of factors, including microorganisms such as bacteria, viruses, and fungi, as well as non-infectious factors such as systemic and neoplastic illnesses. In most cases, the inflammatory process affects not only the meninges that surround the brain but also the parenchyma of the brain (meningoencephalitis), the ventricles (ventriculitis), and spreads throughout the spinal cord. This condition is referred to as meningoencephalitis. Neuronal damage, namely in the areas of the hippocampus, has been identified as a potential cause of long-term cognitive problems in survivors of traumatic brain injuries.

KEYWORDS: Bacteria, Meningitis, inflammation, CSF

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INTRODUCTION

1.1 Meningitis

The term "meninges" refers to the membranes that cover the brain and spinal cord. The meninges consist of three layers that cover the brain and get their names in order from the outside in: the dura mater, the arachnoid mater, and the pia mater. The meninges are also known as the membranes that surround the brain and spinal cord. Acute inflammation of the membranes that surround and protect the brain and spinal cord are the symptoms of meningitis [1]. These membranes are referred to as the meninges. Infection with viruses, bacteria, or other microbes, as well as, less frequently, with some drugs, can all lead to inflammation. However, this condition can be caused by a wide variety of factors. Meningitis is another possibility. Because of how close it is to the brain and the spinal cord, it poses a significant risk to life [2].

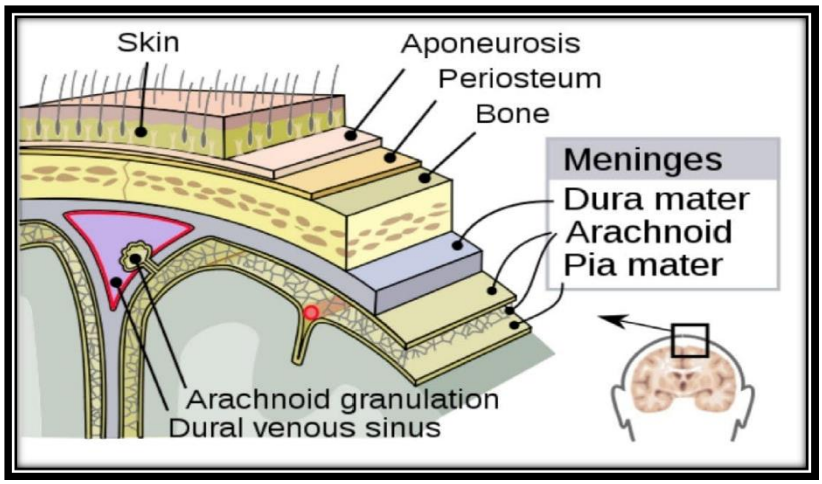

Figure 1. Layers of meninges

1.2 Pathophysiology

Bacterial meningitis is distinguished by the introduction of bacteria into the cerebrospinal fluid (CSF) and the subsequent proliferation of bacteria in this compartment, which leads to inflammation both within the CSF and in the brain tissue that is next to it.The following elements, when combined, are responsible for the development of long-term neurological sequelae and death: (1) The host's systemic inflammatory response causes leukocyte extravasation into the subarachnoid space, an increase in the impedance of the CSF outflow, and brain edema. The increased intracranial pressure that results from this is a significant contributor to mortality during the acute phase and to long-term complications. Vasculitis, cerebral venous thrombosis, and secondary ischemia are among possible complications that can arise from systemic inflammation. (2)The stimulation of immune cells within the brain parenchyma, in particular microglia, by proinflammatory bacterial chemicals can directly lead to damage to the brain's neurons. (3) Certain bacterial chemicals, such as pneumolysin, have the ability to directly cause toxicity in neuronal cells. The release of reactive oxygen intermediates, proteases, cytokines, and excitatory amino acids, as well as the activation of transcription factors, caspases, matrix metalloproteases, and other proteases, all contribute to the mechanism that initiates neuronal injury [3]. The cerebrospinal fluid can be sterilized and the risk of dying from bacterial meningitis is decreased if appropriate antibiotic treatment is started quickly. In industrialized countries, the addition of dexamethasone to antibiotic treatment improves the prognosis of bacterial meningitis, particularly meningitis caused by Streptococcus pneumoniae. In experimental meningitis, the use of dexamethasone as an addition to antibiotic treatment results in an increase in neuronal damage in the dentate gyrus of the hippocampus formation. This finding suggests that corticosteroids may not be the most effective supplemental therapy. Several methods that interfere selectively with the mechanisms of neuronal injury have been shown to be effective in animal models. These methods include the use of non-bactericidal bactericidal proteinsynthesis-inhibiting antibiotics, antioxidants, and inhibitors of transcription factors, matrix metalloproteinases, and caspases. Other methods include the use of neuroprotective agents. Nevertheless, there is a dearth of sufficient clinical investigations.A recently conducted randomized clinical research [4] suggests that supplementary oral glycerol may have a positive effect.

1.3 Signs and symptoms

Early symptoms of meningitis may be confused with those of the flu (influenza). It could take a few hours or it could take a few days for symptoms to appear. There is a possibility that anyone over the age of 2 could display the following signs and symptoms [5].

- **Sudden high fever**
- **Stiff neck**
- **Severe headache that seems different from normal**
- **Headache with nausea or vomiting**
- **Confusion or difficulty concentrating**
- **Seizures**
- **Sleepiness or difficulty waking**
- **Sensitivity to light**
- **No appetite or thirst**
- **Skin rash (sometimes, such as in meningococcal meningitis)**
- **Signs in newborns**
- **Newborns and infants may show these signs:**
- **High fever**
- **Constant crying**
- **Excessive sleepiness or irritability**
- **Difficulty walking from sleep**
- **Inactivity or sluggishness**
- **Poor feeding**
- **Vomiting**

- **A bulge in the soft spot on top of a baby's head (fontanel)**
- **Stiffness in the body and neck**

1.4 Clinical features

The most frequent symptom of meningitis in adults is a severe headache, which is present in over 90% of cases of bacterial meningitis. The next most common symptom is neck stiffness, which is the inability to flex the neck forward passively due to increased neck muscular tone and stiffness. The classic triad of diagnostic indications includes stiffness in the neck, sudden high fever, and altered mental status; however, only 44–46% of cases with bacterial meningitis have all three of these criteria present at the same time. In the event that none of these three symptoms are present, acute meningitis is a very unlikely diagnosis. In addition to these symptoms, meningitis is frequently accompanied by photophobia (an aversion to bright light) and phonophobia (an intolerance to loud noises). Small children frequently may not exhibit the symptoms described above; instead, they may just be irritable and appear to be sick. Up until the age of six months, an infant's fontanelle, which is the soft region on the top of their skull, may protrude. Leg pain, cold extremities, and an odd skin tone are some of the other symptoms that set meningitis apart from other, less serious infections that can affect young children [6]. In adults with bacterial meningitis, nuchal stiffness is present in approximately 70 percent of cases. In addition to it, the existence of a positive Kernig's sign or Brudziski sign is another indicator. When evaluating a patient for Kernig's sign, the patient is required to be in the supine position with the hip and knee bent to a 90-degree angle. A person who has a positive Kernig's sign will have difficulty passively extending their knee because of pain. When bending of the neck generates an involuntary bending of the knee and hip, this is referred to as a positive Brudzinski's sign. In spite of the fact that both Kernig's sign and Brudzinski's sign are frequently used to screen for meningitis, neither of these tests has a particularly high sensitivity. They do, however, have an extremely high degree of specificity for meningitis, as the symptoms are quite uncommon in the context of other disorders. The "jolt accentuation maneuver" is an additional test that helps evaluate whether or not meningitis is present in those who have reported having fever and headache. It is recommended to urge the individual to quickly swivel their head to the side; if this does not make the headache worse, meningitis is probably not the problem.Other conditions can result in symptoms that are comparable to those described above, but these conditions are not caused by meningitis. Meningism or pseudomeningitis are the terms used to describe this condition [7].

A fast developing petechial rash, which may precede other symptoms, can be used to differentiate meningitis caused by the bacterium Neisseria meningitidis (also known as "meningococcal meningitis") from meningitis caused by other organisms. This type of meningitis is referred to as "meningococcal meningitis." The rash can appear anywhere on the body, including the trunk, lower extremities, mucous membranes, conjunctiva, and (rarely) the palms of the hands or soles of the feet. These spots are called "petechiae" and can be either red or purple in color. The rash is often one that does not blanch when it is touched with a finger or a glass tumbler; this means that the redness does not fade. Despite the fact that this rash may or may not be present in meningococcal meningitis, it is considered to be a fairly reliable indicator of the disease. Meningitis caused by other types of bacteria may on occasion also cause this rash to appear. The skin indications of hand, foot, and mouth disease and genital herpes, both of which are associated with various kinds of viral meningitis [8], may provide further information that can help determine the origin of meningitis.

1.5 Early complications

In the early stages of the illness, there is a possibility that further complications will emerge. These can call for a very specific therapy, and they frequently point to a severe sickness or a worse prognosis. Sepsis is a systemic inflammatory response syndrome that can be caused by an infection. Symptoms of sepsis include dropping blood pressure, fast heart rate, high or unusually low fever, and rapid breathing. An extremely low blood pressure can occur at an early stage, particularly but not solely in meningococcal meningitis; this can lead to an inadequate blood supply being delivered to other organs [9]. Disseminated intravascular coagulation, also known as the overactivation of blood clotting, can paradoxically increase the risk of bleeding while at the same time obstructing blood flow to organs. Gangrene of the limbs is a possible complication of meningococcal illness. Hemorrhaging of the adrenal glands is a potential complication of severe meningococcal and pneumococcal infections, which can lead to Waterhouse-Friderichsen syndrome, a condition that is frequently deadly. The tissue of the brain may enlarge, the pressure inside the skull may grow, and the brain may herniate through the base of the skull if it has swollen. This can be recognized by a decline in the patient's state of consciousness, the absence of the pupillary light reflex, and inappropriate posturing [10].

The inflammation of the brain tissue may also restrict the natural flow of cerebrospinal fluid (CSF) around the brain, which is known medically as hydrocephalus. Seizures can be brought on by a number of different factors; among children, seizures are common in the early stages of meningitis (in thirty percent of cases), but they do not necessarily point to an underlying cause. Increased pressure and inflammatory regions in the brain tissue both have the potential to bring on seizure activity. A poorer long-term result is indicated by epileptic symptoms such as focal seizures (seizures that only affect one limb or area of the body), persistent seizures, late-onset seizures, and seizures that are difficult to control with medication. Inflammation of the meninges can cause anomalies in the cranial nerves,

which are a set of nerves that arise from the brain stem and feed the head and neck region. Cranial nerves are responsible for a variety of tasks, including hearing, eye movement, and facial muscle function, amongst others. After an incident of meningitis, you may still experience visual problems and a loss of hearing **[11].**

1.6 Causes

In most cases, an infection with microorganisms will be the root cause of meningitis. [12] Viruses are the most prevalent cause of infections; bacteria, fungi, and protozoa are the next most common culprits in that order.Additionally, it may be the result of a variety of factors that are not infectious. Meningitis is referred to as "aseptic" when there is no evidence of a bacterial infection in the patient's body at the time of diagnosis. When bacteria disappear from the meninges or pathogens infect an area close to the meninges (for example, sinusitis), this type of meningitis is typically brought on by viruses; nevertheless, it is possible that it was brought on by a bacterial infection that had previously been cured in part, as described above. Aseptic meningitis is sometimes brought on by endocarditis, an infection of the heart valves that can spread through the circulation in the form of tiny clusters of bacteria. Infection with spirochetes, a group of bacteria that includes Treponema pallidum, which is the cause of syphilis, and Borrelia burgdorferi, which is recognized for causing Lyme disease, can also result in aseptic meningitis. Meningitis can be a complication of cerebral malaria, which is an infection of the brain caused by malaria, or amoebic meningitis, which is meningitis caused by an infection with amoebae such as Naegleria fowleri and is contracted via freshwater sources [13].

1.7 Bacterial meningitis

Bacterial meningitis can be caused by a wide variety of bacteria, and the types of bacteria that are present depend on the age group of the person who is sick. Group B streptococci (subtypes III, which normally inhabit the vagina and are primarily a cause during the first week of life) and bacteria that normally inhabit the digestive tract, such as Escherichia coli (carrying the K1 antigen), are common causes of strep throat in premature babies and newborns up to three months old. This condition can also occur in newborns older than three months. Inadequately prepared foods, such as dairy products, fruit, and deli meats, can transmit the Listeria monocytogenes (serotype IVb) bacteria, which can lead to meningitis in newborns. This bacteria can also cause diarrhea in adults. Children under the age of five are more likely to be afflicted by Haemophilus influenzae type B (in nations that do not offer immunization), whereas older children are more likely to be infected with Neisseria meningitidis (meningococcus) and Streptococcus pneumoniae (serotypes 6, 9, 14, 18, and 23).Together, the microorganisms Neisseria meningitidis and Streptococcus pneumoniae are responsible for approximately 80% of all occurrences of bacterial meningitis in humans. People over the age of 50 have a significantly higher likelihood of becoming infected with Listeria monocytogenes [14]. The development of a vaccination against pneumococcal disease has resulted in a decline in the incidence of pneumococcal meningitis in both children and adults. Recent trauma to the skull makes it more likely that germs from the nasal cavity will enter the meningeal space.

Meningitis is also more likely to occur in patients who have medical devices implanted in their brains or meninges, such as cerebral shunts, extraventricular drains, or Ommaya reservoirs. In situations like these, the individuals have an increased risk of being infected with Gram-negative bacteria like Staphylococci and Pseudomonas, amongst others. Meningitis is another condition that can be caused by these viruses in those who have a weakened immune system. Meningitis can be contracted by a very tiny percentage of persons who have an infection in the head and neck region, such as otitis media or mastoiditis, for example. People who have had cochlear implants as a treatment for hearing loss are at an increased risk of pneumococcal meningitis. People who originate from nations in which tuberculosis is endemic are more likely to contract tuberculosis meningitis, which is meningitis caused by Mycobacterium tuberculosis. However, tuberculosis meningitis can also be seen in people who have difficulties with their immune systems, such as AIDS [15]. In some cases, recurrent bacterial meningitis can be traced back to persistent anatomical anomalies that were either congenitally present or acquired over time. In other cases, immune system problems are to blame. Defects in anatomical structure allow for uninterrupted communication between the nervous system and the surrounding environment. Skull fractures are the most prevalent cause of recurrent meningitis. In particular, fractures that impact the base of the skull or extend into the sinuses and petrous pyramids are more likely to induce this type of meningitis. Approximately 59% of recurrent meningitis cases are due to such anatomical abnormalities, 36% are due to immune deficiencies (such as complement deficiency, which predisposes especially to recurrent meningococcal meningitis), and 5% are due to ongoing infections in areas adjacent to the meninges [16]. These percentages are based on studies that have been conducted.

a) Haemophilus influenzaetype b (Hib)

H influenzae infections, while traditionally less common than many viral infections, cause a variety of childhood diseases, a number of which give rise to considerable morbidity and mortality. The bacterium Haemophilus influenzae has been historically common as a cause of infection in human populations. H influenzae type b is a gram-negative bacterium that can be found in the normal flora of the human respiratory tract. Of the six types of H. influenzae that have been identified (a to f), Hib is the most virulent of the six. H. influenzae type b (Hib) has in the past been responsible for a large proportion of the most severe forms of H. influenza disease [17]. Vaccination is now the

primary method for preventing hib infections. More than 90 countries throughout the world include the vaccine as a required component of their immunization programs; consequently, the Hib illness has been brought to the brink of elimination in many developed nations. Non-type b H. influenzae, for which there are no vaccinations yet available, will be responsible for an increasing share of H. influenzae infections as more countries establish vaccination programs. Hib is a disease that primarily affects young children, with 80 percent of all cases occurring in children younger than five years old around the world. The transmission of hib requires respiratory secretions: As a direct consequence of this, interaction with other children, whether in large homes or in care centers, has been recognized as the primary risk factor for the development of Hib disease **[18].**

b) Neisseria meningitides

Neisseria meningitides is an aerobic gram-negative diplococcus that can be classified into 13 different serogroups according to the antigenic properties of its capsular polysaccharide (these serogroups include A, B, C; D, 29E,H;I, K,L, W-13S,X; Y, and Z). YA has been most commonly associated with epidemics in sub-Saharan Africa and also in Asia, but serogroup C is also an important cause of outbreaks in Africa, and serogroup W-135 and X have emerged as causes of significant epidemics in selected African countries. The strains A, B, C, W-135, and X are the most commonly implicated in systemic disease around the world. The microvillous surface of nonciliated columnar mucosal cells in the nasopharynx is a typical location for the colonization of Neisseria meningitidis in the upper respiratory tract. Carriage prevalence of meningococcal disease rises steadily during childhood, from roughly 5% in infants to maximum of 24% at 19 years of age, and then falls steadily throughout adulthood, reaching 8% by the time a person reaches the age of 50. Infectious meningococci that are associated with invasive illness have a capsule that shields the germs from drying out. Phagocytosis and host-mediated, complement-dependent bacteriolysis also contributed to the group peak. Only humans serve as a natural reservoir for the bacterium that causes meningitis: The vast majority of N. meningitidis infections result in harmless nasopharyngeal colonization rather than invasive illness, and the bacterium has never been identified from animals because it can only obtain iron from human sources [19]. N. meningitidis is essentially a human commensal.

c) Streptococcus pneumoniae

Community-acquired pneumonia, which can have mortality rates of more than 20% in patients with concurrent pneumococcal septicaemia, is frequently caused by Streptococcus pneumoniae, which is often referred to as the pneumococcus. Streptococcus pneumoniae is the most common bacterial respiratory pathogen in the United Kingdom and other countries. S pneumoniae is a member of the family Streptococcaceae, which contains shaped cocci that are frequently arranged in pairs and are classified as family-gram-positive in short chains. It is one of the most common causes of Streptococcus pneumoniae in adults and young adults, along with Neisseria bacterial meningitis of bacterial meningitis in adults in the meningitidis, and it is the leading cause of bacterial meningitis in the United Significant human pathogenic bacterium, according to Dagan (2000), S. pneumoniae has been the focus of a great deal of research on humoral immunity since it was identified in the late 9th century as a major contributor to the development of pneumonia. S. pneumoniae can be found living in the nasopharynx of healthy carriers without causing any symptoms. However, the infection can spread to other areas and cause sickness in susceptible individuals, such as the elderly, persons with compromised immune systems, and children. Clinical manifestations of S. pneumoniae include meningitis, acute sinusitis; otitis media, conjunctivitis; bacteremia; sepsis osteomyelitis; arthritis endocarditis, peritonitis; pericarditis; cellulitis; and brain abscess [20]. S. pneumoniae is the most common cause of meningitis in children and the elderly. Other types of microorganisms, such as Staphylococcus aureus, Staphylococcus epidermidis, and Escherichia coli, can also be the cause of acute meningitis.

1.8 Aseptic meningitis

Aseptic meningitis is the inflammation of the meninges, a membrane covering the brain and spinal cord, in patients whose cerebral spinal fluid test result is negative with routine bacterial cultures. Aseptic meningitis is caused by viruses, mycobacteria, spirochetes, fungi, medications, and cancer malignancies. The testing for both meningitis and aseptic meningitis is mostly the same **[21].** A cerebrospinal fluid sample is taken by lumbar puncture and is tested for leukocyte levels to determine if there is an infection and goes on to further testing to see what the actual cause is. The symptoms are the same for both meningitis and aseptic meningitis but the severity of the symptoms and the treatment can depend on the certain cause **[22].**

a) Viral meningitis

Also known as aseptic meningitis is a type of meningitis due to a viral infection. It results in inflammation of the meninges, viruses are the most common cause of aseptic meningitis. Most cases of viral meningitis are caused by enter viruses (common stomach viruses). However, other viruses can also cause viral meningitis, such as West Nile virus, mumps, measles, herpes simplex types I and II, varicella and lymphocytic choriomeningitis (LCM) virus. Based on clinical symptoms, viral meningitis cannot be reliably differentiated from bacterial meningitis, although viral meningitis typically follows a more benign clinical course. Viral meningitis has no evidence of bacteria present in cerebral spinal fluid (CSF). Therefore, lumbar puncture with CSF analysis is often needed to identify the disease. In most cases, there is no specific treatment, with efforts generally aimed at relieving symptoms (headache, fever or nausea). A

few viral causes, such as HSV, have specific treatments **[23].**

b) Fungal meningitis

Refers to meningitis caused by a fungal infection. Symptoms of fungal meningitis are generally similar to those of other types of meningitis, and include: a fever, stiff neck, severe headache, photophobia (sensitivity to light), nausea and vomiting, and altered mental status (drowsiness or confusion).Fungal meningitis may be caused by the following (and also other) types of fungi Candida - C. albicans is the most common Candida species that causes infections of the central nervous system. Coccidioides - it is endemic to southwestern United States and Mexico. A third of patients presenting with disseminated coccidioidomycosis have developed meningitis. Histoplasma - occurs in bird and bat droppings and is endemic to parts of the United States, South, and Central America. Involvement of the central nervous system occurs in about 10-20% of cases of disseminated histoplasmosis. Blastomyces - occurs in soil rich in decaying organic matter in the Midwest United States. Meningitis is an unusual manifestation of blastomycosis and can be very difficult to diagnose. Cryptococcus (Cryptococcal meningitis) - it is thought to be acquired through inhalation of soil contaminated with bird droppings. C. neoformans is the most common pathogen to cause fungal meningitis.Aspergillus - Aspergillus infections account for 5% of fungal infections involving the central nervous system **[24]. c) Parasitic**

A parasitic cause is often assumed when there is a predominance of eosinophils (a type of white blood cell) in the CSF. The most common parasites implicated are Angiostrongylus cantonensis, Gnathostoma spinigerum, Schistosoma, as well as the conditions cysticercosis, toxocariasis, baylisascariasis, paragonimiasis, and a number of rarer infections and no infective conditions **[25]. d) Non-infectious meningitis**

Meningitis may occur as the result of several non-infectious causes: spread of cancer to the meninges (malignant or neoplastic meningitis) and certain drugs (mainly non-steroidal anti-inflammatory drugs, antibiotics and intravenous immunoglobulins). It may also be caused by several inflammatory conditions, such as sarcoidosis (which is then called neurosarcoidosis), connective tissue disorders such as systemic lupus erythematosus, and certain forms of vasculitis (inflammatory conditions of the blood vessel wall), such as Behçet's disease. Epidermoid cysts and dermoid cysts may cause meningitis by releasing irritant matter into the subarachnoid space. Rarely, migraine may cause meningitis, but this diagnosis is usually only made when other causes have been eliminated **[26][27].**

Investigation of meningitis

Lumbar puncture (LP)

A medical operation that is also known as a spinal tap is one in which a needle is placed into the spinal canal. The purpose of this treatment is most usually to collect cerebrospinal fluid (CSF) for diagnostic testing. The primary objective of a lumbar puncture is to assist in the diagnosis of disorders affecting the central nervous system, which includes the brain and the spine. Meningitis and subarachnoid hemorrhage are two examples of conditions that fall under this category. In certain circumstances, it also has a potential medicinal application. Increased intracranial pressure, also known as pressure inside the skull, is not allowed because of the potential for brain tissue to get squeezed and pushed in the direction of the spine. In certain cases, a lumbar puncture cannot be performed safely (for instance, when there is a high propensity for serious bleeding). Although it is generally viewed as a risk-free treatment, a post-dural-puncture headache is a typical side effect [32], especially if a short, non-traumatic needle is not utilized.In most cases, the treatment is carried out under local anesthesia utilizing a method that is completely sanitary. In order to enter the subarachnoid region and collect fluid from there, a hypodermic needle is utilized. It is possible to send fluid out for analysis using biochemical, microbiological, and cytological methods. There is a possibility that using ultrasound to landmark will boost success. In 1891, a German physician by the name of Heinrich Quincke [33] was the first person to perform a lumbar puncture

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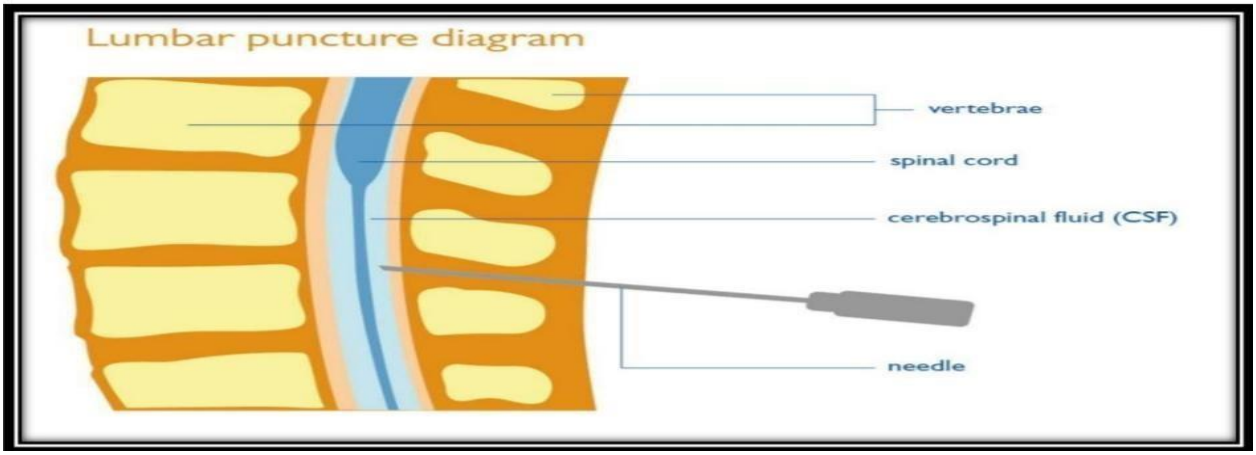

(Fig. 2) Lumber of puncture 1.11.2 Biochemical analysis

a) CSF Protein

Cerebrospinal fluid, often known as CSF, is a bodily fluid that is transparent and colorless. It is located in the tissue that surrounds the brain and spinal cord in all vertebrates. At any given time, there is around 125–150 mL of cerebrospinal fluid (CSF) [34]. The ventricular system of the brain contains this CSF, which circulates throughout the system. A series of cavities that are all filled with cerebrospinal fluid make up the ventricles. The majority of cerebrospinal fluid (CSF) is generated within the two lateral ventricles of the brain. From this point, CSF travels down the cerebral aqueduct to the third ventricle, where it subsequently goes through the interventricular foramina to reach the fourth ventricle. The fluid travels into the subarachnoid space from the fourth ventricle through four openings: the central canal of the spinal cord, the median aperture, and the two lateral apertures. These openings are located on opposite sides of the spinal cord. There is cerebrospinal fluid (CSF) present in the subarachnoid space, which surrounds the brain and spinal cord and extends from the bottom of the spinal cord to the sacrum. In 93% of persons, the cerebrospinal fluid is continuous with the perilymph because there is a connection from the subarachnoid area to the bone labyrinth of the inner ear.When leaving the ventricles, cerebrospinal fluid travels only in one direction, but once it reaches the subarachnoid region, it goes in multiple directions. Fluid movement is pulsatile and corresponds to the pressure waves that are produced in blood vessels as a result of the beating of the heart. Some writers disagree with this and claim that there is no unidirectional circulation of CSF, but rather cardiac cycle-dependent bidirectional systolic-diastolic movement of CSF to and from the craniospinal region [35].

Doctors can use samples of CSF to find out if a person has a brain infection, like meningitis, encephalitis, or syphilis. CSF samples can also show bleeding from certain parts of the brain. Swelling in the brain, caused by some inflammatory diseases like multiple sclerosis, can show in a CSF sample as well. Usually, doctors take samples of CSF by doing a lumbar puncture (spinal tap).Normal CSF should be clear and colorless, with no red blood cells, and very few white blood cells**[36].**

Signs of a brain infection include:

- **CSF that is cloudy, yellow, or pink**
- **More protein in the CSF than normal**
- **More white blood cells in the CSF than normal**
- **Less glucose (sugar) in the CSF than normal**
- **Bacteria, viruses, fungi, or other pathogens in the CSF**

Protein levels that are higher than normal can be a sign of inflammation in the brain. However, they can also be a sign of other problems, like a bleed in the brain; a brain tumor; epilepsy; and "acute alcoholism."Cancer cells in the CSF are a sign that a person has brain cancer, or has cancer that started somewhere else and spread to the brain **[37].**

b) CSF Glucose

CSF glucose or glycorrhachia is a measurement used to determine the concentration of glucose in cerebrospinal fluid (CSF)

In Low CSF glucose levels

Hypoglycorrhachia (low CSF glucose levels) can be caused by CNS infections, inflammatory conditions, subarachnoid hemorrhage, hypoglycemia (low blood sugar), impaired glucose transport, increased CNS glycolytic activity and metastatic carcinoma.CSF glucose levels can be useful in distinguishing among causes of meningitis as more than 50% of patients with bacterial meningitis have decreased CSF glucose levels while patients with viral meningitis usually have normal CSF glucose levels. Decrease in glucose levels during a CNS infection is caused due to glycolysis by both white cells and the pathogen, and impaired CSF glucose transport through the blood-brain barrier **[38].**

In High CSF glucose levels

Because there is no pathogenic mechanism that directly leads to hyperglycorrhachia (high CSF glucose levels), high CSF glucose levels have no special diagnostic value. This is because hyperglycorrhachia is a symptom of hyperglycorrhachia.However, elevated blood sugar levels (also known as hyperglycemia) lead to elevated amounts of glucose in the cerebrospinal fluid (CSF). This is because the level of glucose in the CSF is proportional to the level of glucose in the blood, and glucose can either be actively transported or just diffuse down the concentration gradient from blood to CSF. In addition, causing injury to smaller blood vessels during a lumbar puncture (traumatic tap) can result in an increased amount of glucose in the CSF. This is because the blood that enters the obtained CSF sample carries higher concentrations of glucose [39]. In most cases, the glucose concentration in the CSF does not go over 16.7 mmol/L (or 300 mg/dL).

1.11.3 Culture the CSF

The fluid that travels in the region around the spinal cord is called cerebrospinal fluid (CSF), and a cerebrospinal fluid culture is a laboratory test that looks for bacteria, fungi, and viruses in that fluid. The brain and spinal cord are shielded from harm by the cerebrospinal fluid (CSF). It is necessary to obtain a sample of CSF. This is typically accomplished by the use of a lumbar puncture, which is also referred to as a spinal tap.The specimen will be analyzed in the laboratory. After that, it is put in a unique dish that is referred to as a culture medium. The employees of the laboratory check to see if any bacteria, fungus, or viruses have grown in the dish. The presence of growth indicates the presence of an infection [40].If your primary care physician suspects that you have an illness that is affecting your brain or nervous system, he or she may recommend that you undergo this test. The test

provides assistance in determining the source of the infection. Your healthcare professional can use this information to choose the most appropriate treatment for you. A normal result indicates that the laboratory dish did not support the growth of any bacteria, viruses, or fungi. This kind of outcome is referred to as a negative result. However, a normal result doesn't mean that an infection is present. There is a possibility that another spinal tap and CSF smear will need to be performed [41]. There is a possibility that meningitis is present if the sample contained bacteria or other pathogens. The membranes that cover the brain and spinal cord have become infected as a result of this condition. It's possible that bacteria, fungi, or viruses are to blame for this sickness.

1.11.4 Polymerase Chain Reaction

In light of the high mortality rate and the long-term effects that meningitis can have, early diagnosis and timely treatment have a significant bearing on the overall prognosis of the patient. In this study, we created a multiplex-PCR that enables simultaneous identification of the four bacterial infections that are most commonly found directly in CSF samples. The multiplex-PCR was developed with the intention of identifying the following genes: fbsA (Streptococcus agalactiae), lytA (Streptococcus pneumoniae), crtA (Neisseria meningitidis), p6 (Haemophilus influenzae), and 16S rRNA (any bacterial agent). The DNA detection threshold for the multiplex PCR was determined to be 1 pg/L. There were 447 CSF samples that were analyzed, and 40 of them were positive for multiplex-PCR. Of those 40, 27 had positive bacterial culture, and 13 had negative bacterial culture. When it comes to the confirmation of bacterial meningitis in patients who have already begun antibiotic treatment, our multiplex PCR is a method that is quick, reliable, and simple to include into standard laboratory procedures. Our molecular method has the potential to significantly enhance clinical diagnosis as well as epidemiological measurements of the burden of meningitis [42].

1.12 Treatment

The production of novel cephalosporin antibiotics has resulted in the development of medications that are capable of curing an impressive proportion of the myriad subtypes of meningitis. There is not a single cephalosporin from the first generation that may be recommended for use as a treatment for meningitis. Cefuroxime is an antibiotic that is effective in treating meningitis in children that is caused by Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis.In the treatment of meningitis caused by E. coli, Klebsiella pneumoniae, and Proteus species, the antibiotics cefotaxime, ceftizoxime, ceftriaxone, and cefzidime have proven to be successful. In general, cephalosporins are now able to be considered a significant component of the treatment of acute bacterial meningitis. This is true regardless of the age group that is going to be administered treatment. Penicillin is also utilized in the treatment of meningitis, particularly meningitis caused by streptococci, pneumococci, and some strains of streptococci [43]. There has not been a lot of research done on the effectiveness of vancomycin in treating bacterial meningitis in clinical settings. The data that are currently available indicate that when vancomycin is delivered intravenously in the treatment of meningitis, it is able to permeate into the cerebrospinal fluid, and levels that are often therapeutically efficacious are attained. Vancomycin has been shown to be an effective treatment for meningitis in clinical circumstances in which the use of regularly administered medicines has been rendered impossible; for example, in infections caused by resistant strains or atypical organisms, as well as in individuals who are allergic to penicillin [44].

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