Chapter 4

Herpes Meningoencephalitis: Causes, Diagnosis, and Treatment

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.68553

Abstract

Meningoencephalitis also known as encephalomeningitis is an inflammation of the brain and its surrounding protective membranes. It resembles both meningitis and encephalitis. Meningoencephalitis can be caused by bacteria, viruses, fungi, and protozoan or as secondary sequel of other inflammations like AIDS. The viral or aseptic meningoencephalitis is mainly caused by enteroviruses, varicella-zoster viruses, herpes simplex viruses, or measles viruses. Among the various causes of viral meningoencephalitis, herpes meningoencephalitis (HME), caused by herpes simplex virus type 1 and 2, is dreadful. It is a communicable infection spread through droplets, air, water, food, sexual intercourse, or effected mother to child. The symptoms of the disease resemble to common viral infections except few like nuchal rigidity, blurred vision, and purple body rashes. Diagnosis is carried out from body fluids like urine, saliva, blood, or cerebrospinal fluid using laboratory methods, imaging techniques, PCR or enzyme-linked immunosorbent assays. The causes, diagnosis, prevention, and treatments of HME are discussed detail in this chapter.

Keywords: encephalitis, encephalomeningitis, herpes meningoencephalitis, meninges, meningitis, meningoencephalitis

1. Introduction

Mammalian brain and spinal cords are covered by three membranous tissue layers pia mater, arachnoid mater, and dura mater (from inner to outer) forming meninges. Infection in these layers is known as meningitis. An inflammation or infection in the brain tissue is known as encephalitis [1]. The infection in the brain and meninges together is known as meningoencephalitis or encephalomeningitis. This can be caused by either of the bacteria, fungi, viruses, or protozoans. Viral or aseptic meningoencephalitis, caused by herpes simplex

virus type 1 (HSV 1) and 2 (HSV 2), is known as herpes meningoencephalitis (HME) [2]. The direct infection in the brain or meninges is called primary HME, whereas if it spreads from other parts to the brain, then it is called secondary HME. Both the male and female are affected at an equal ratio with a higher mortality and morbidity rate (~50%) for infants. Like a communicable infection, spread through air, water, or close contact [3], the viruses after entering the patient through mouth, nose, or genital tract reach to the brain-crossing blood-brain barrier and cause infection.

The symptoms of this infection are a combinatorial effect of both the meningitis and encephalitis insisting the physicians to suspect meningoencephalitis [4]. Symptoms resemble to the common viral infections but may vary among the children and adults. Some of the typical symptoms of HME are nuchal rigidity, blurred vision, and purple body rashes. The infection can spread among people through droplets, foods, air, or close contact. There is always a need for early diagnosis of the infection followed by treatment. The disease can be suspected initially on the basis of the specific symptoms of the patients. This can be further confirmed by several laboratory-based, imaging, or advanced techniques [5]. Although the prevention of HME is not possible through vaccination, but proper precaution measures can reduce the risk of spreading and relapsing of the disease. Abstain or safety measures during sexual intercourse and proper management during pregnancy lessen the risk of contamination.

Mild infected persons may recover in few weeks but a severely infected person requires longer time and intense care. Early treatment of the patients with antiviral drugs may hugely reduce the risk of the contamination and death. Anticonvulsants or diuretics can minimize the inflammation, cranial pressure, or pain. In this chapter, we have discussed in detail about the symptoms, causes, diagnosis, prevention, and treatment of HME.

2. Symptoms

The symptoms of HME resemble to common flu and may vary among children, adults, and neonates. HME type 1 is more prominent at age below 20 years or over 40 years. The earlier symptoms shown in children and adults are fever, disorientation, or speech problem. At a later stage, headache, vomiting, fever, drowsiness, seizures, and unconsciousness also appear. Specific symptoms of this infection are nuchal rigidity, blurred vision, hallucinations, purple rashes or behavioral changes [4]. Infants are mainly infected by type 2, and the symptoms include high fever, bulging of forehead, poor feeding or constant sleepiness.

3. Causes

HME is mainly caused by HSV type 1, type 2 or as secondary squeal of other diseases like Crohn's disease [2, 6]. HME accounts for about 10% of the total meningoencephalitis cases with a effecting rate of about $2/10^6$. Most of the HME cases are seen in case of infants or children. The infection is contaminated through coughing, sneezing or close contact. Type 1

http://dx.doi.org/10.5772/intechopen.68553

viruses can spread through food, water, and air, whereas type 2 transmits mainly through sexual contact [3]. Sometimes, after complete treatment, also the viruses remain silently in the body and relapse at a later stage. AIDS, alcoholism, diabetes, immunosuppressant drugs, splenectomy, and other immunosuppressive factors increase the susceptibility of a person toward getting infected. The infection may cause partial or complete impairment of the brain or sensory organs, kidney failure or death [7]. Therefore, there is a compulsory need for an early diagnosis of the disease followed by treatment.

4. Diagnosis

On the basis of different symptoms seen in the suspected patients, physicians suggest different preliminary or confirmatory diagnostic tests [5]. Diagnosis of the HME involves several stages, initially differentiation from other closely related infections and then distinguishes between bacterial, fungal, and viral meningoencephalitis. The final step involves confirmation of HME from other forms of aseptic meningoencephalitis. Diagnosis can be carried out from blood, saliva, urine or cerebrospinal fluid (CSF) of the patients with the CSF being preference. Diagnosis of HME is done as below:

4.1. Laboratory methods

4.1.1. Body fluid test

Different types of body fluids like urine, blood, or saliva of the suspected patients can be tested for antigens, antibodies, level of WBCs, proteins, procalcitonin, or glucose. These components are mainly detected through biochemical analysis or immunological assays. Increase in the WBC count in the CSF or the presence of IgM antibodies in the serum confirm HME. The level of these components confirms pathogenic condition of a person and differentiates between bacterial, fungal, and aseptic meningoencephalitis. The presence of WBCs or microorganisms turns the CSF from transparent to cloudy in color. Increase in the lymphocyte count is a characteristic of viral infection. Increase in the amount of proteins or decrease in the glucose in CSF also confirm viral infection. But biochemical analysis may be inconclusive or misleading. Therefore, further tests like PCR or blotting must be carried out for further confirmation of the specific infection. Sometimes, the samples from the patients are cultured and sensitivity tests carried out for confirmation of the pathogen [8–10]. But this consumes 2–3 days for confirmation. Microscopic analysis of the patient samples is also another alternative diagnostic method. But this is a preliminary mode of diagnosis and nonspecific.

4.1.2. Spinal tap

Diagnosis using CSF through spinal tap or lumbar puncture is one of the most preferable methods to distinguish meningoencephalitis from blood toxicity or sepsis. This technique involves extraction of about 0.5–1.0 ml of CSF from the subarachnoid space between lumbar (L) vertebrae L3/L4 or L4/L5 [8]. The change in the composition of CSF, presence of

pathogens or their by-products, presence of lactic acid, lactate dehydrogenase, or C-reactive proteins or increase in the white blood cells (WBCs) count of CSF can be detected by various methods [9, 10]. CSF-based detection is one of the traditional methods used for the diagnosis of several disorders associated with the central nervous system. Although the method is less time consuming, it is low sensitivity and nonspecific.

4.2. Non-laboratory tests

4.2.1. Electroencephalography

This is a noninvasive electrophysiological technique which analyze the electrical signals or ionic current within the neurons of the brain. Any abnormalities or functional changes in the brain cause change in neural oscillation or brain waves over a period of time which can be detected [11]. The pattern of the waves in an electroencephalogram signifies the specific type of seizure or viral infection [12]. Despite its low resolution, it is still used as one of the pioneer diagnostic tool. This method consumes several hours for complete detection of the pathogen.

4.2.2. Neurological examinations

HME may cause partial or complete impairment of the brain and the sensory system in the patient. Therefore, physician carries out neurological examinations to confirm the infection. Neurological examination is carried out through series of tests to detect neurological disorders, mental status, strengths of sensation, and behavioral changes. Simple instruments like forks, reflex hammer, or small pins are used by the physicians to detect the strength of the neurological response. But this test is nonspecific and misleading because it cannot discriminate between HME and meningocephalitis due to other causes.

4.3. Radiological methods

4.3.1. CT scan

Use of CT scan has gained preference over other methods during last few decades for diagnosis [13, 14]. CT scan or X-ray CT involves two dimensional X-ray images of the brain from several possible angles and computer-based analysis for any deformities. Sometimes, dyes are also used to differentially highlight the different parts of brain [15]. This technique clearly visualizes any type of blood hemorrhage, clot, swellings, infections, or inflammations in the brain or the meninges. The dark areas signify for edema, whereas bright areas signify calcification or hemorrhage of the brain tissue. Although the high resolution of CT scan proved it to be better diagnostics method over others conventional methods but is associated with several side effects like damaging tissue and cancer. Therefore, is less preferred in the case of infants or children.

4.3.2. MRI-based detection

Since 1970, after discovery, MRI is used as one of most versatile and prominent diagnostic tool in biomedical research. MRI or NMRI uses magnetic fields, radio waves, and field gradients

to image the anatomy or physiological structure of brain [16]. A clear image obtained there of reveals any infection or inflammation in the brain or meninges. Since, this technique does not use any ionizing radiations and has a higher sensitivity, therefore, preferred over CT scan. This method is sometimes time-consuming, expensive, and cumbersome [17].

4.3.3. Brain biopsy

This technique involves digging a hole at a point in the skull identified through CT scan or MRI, collection of small tissue using sterilized needle, and then observation under microscope [18]. The status or condition of the brain and its surrounding tissue can be analyzed through this method. HME is detected depending upon the swelling or damage of the tissue. This method although is highly sensitive but painful and associated with several complications. Therefore, this method was slowly replaced by other methods.

4.3.4. Ultrasound

Ultrasound or sonography is a nondestructive method uses sound wave of >20 kHz to study the structure and secretions from brain. These wave with very short wavelength and low power density resolute every change in the brain without heating or cavitations effect [19]. Infection, swelling, lesions, or inflammation of the brain or the associated tissue can be clearly imaged. Despite these, over exposure to this wave may cause side effects like hearing loss and organ dysfunction.

4.4. Future directions

A quick and specific diagnosis of any disease is necessary to initiate an early treatment against it. Present diagnostic methods for HME are inconclusive, time-consuming, misleading, non-specific, or complicated. Therefore, there is a need for a quick, simple, sensitive, and specific method for diagnosis of HME. Nowadays, several advanced methods have been developed for the diagnosis of different types of diseases. The principles of these methods can be used to develop a quick, simple, and reliable diagnostic method in future. Detection of any pathogen based on the analysis of partial or complete genome is one of the most preferred techniques nowadays. The genome of HSV is approximately of 152 kb which can be very easily analyzed as below:

4.4.1. PCR

Since the discovery of PCR, it is used as quick, specific, and sensitive method for diagnosis of several diseases. Several researchers proposed PCR-based detection of HSV from patient samples through designing specific primers and found higher sensitive than other conventional methods [5, 20–22]. The PCR amplicons can be analyzed which is an agarose gel electrophoresis with or without Southern blotting [23], although Southern blotting increases the sensitivity of a PCR but increase the time taken. Therefore, some researchers replaced it with enzyme-linked inmmunosorbent assay. Recently, we have reported very less time-consuming direct PCR for detection of *Neisseria meningitidis* from the CSF samples (**Figure 1**) [24, 25]. The same procedure may be followed to detect HSV in future.

4.4.2. Biosensors

Biosensors are replacing the traditional diagnostic methods because of their sensitivity, specificity, simplicity, and economical value [26–29]. A biosensor contains a biotransducer or bioreceptor which interact with the analyte, and the signal released is detected by a detector. At a low analyte concentration, electrochemical sensor is more favorable than the others (**Figure 2**) [28, 29]. For construction of an electrochemical sensor, ionic bonding between the gold and thiol-group can be used for immobilization. Which can be further hybridized with the complementary analyte and detected electrochemically (**Figure 3**) [28, 29]. Metallic nanoparticles and carbon nanotubes can also be used to increase the surface of immobilization and sensitivity of the sensor for quick, sensitive, and specific diagnosis of large number of HME suspected samples at a time [30, 31].

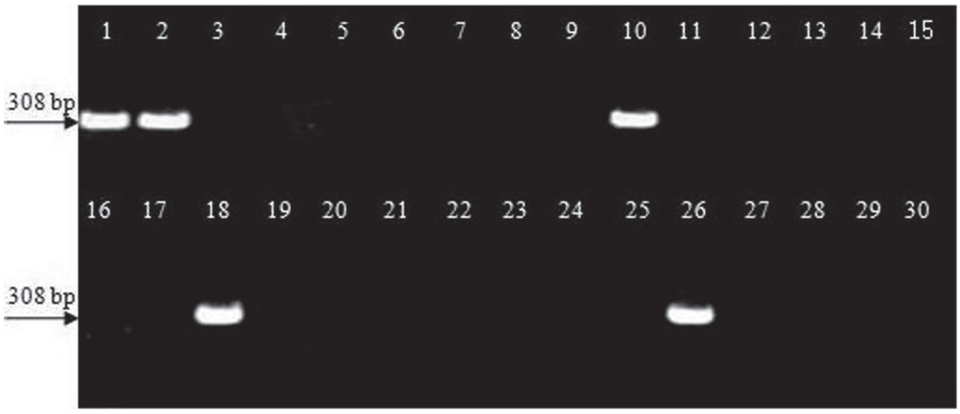

Figure 1. PCR-based diagnosis of bacterial meningitis Lane 1 and 2: control, lane 10, 16, and 26: infected patients, and lane 3-9, 11-15, 17-25, and 12-20: negative [25].

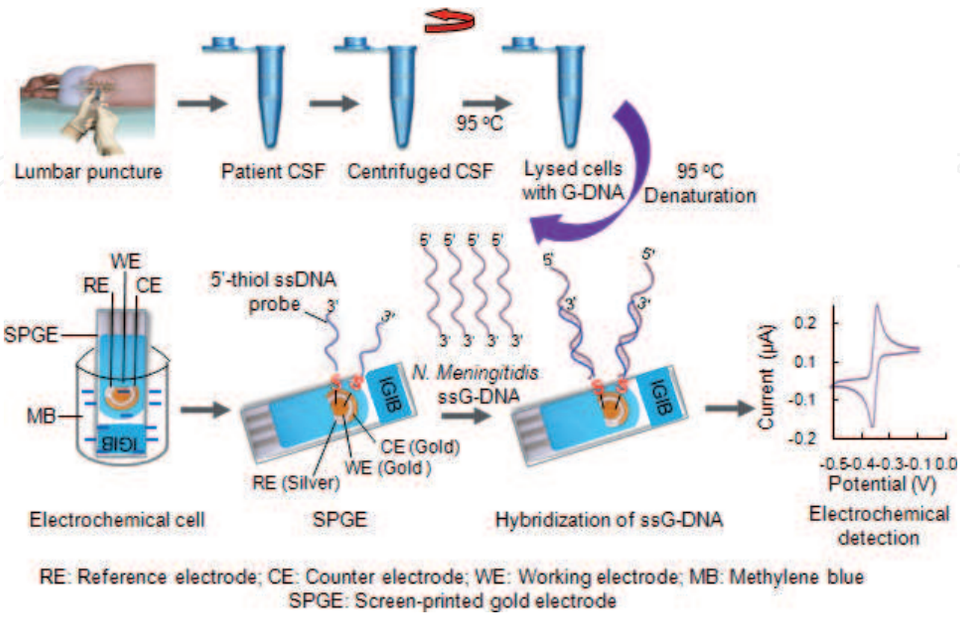

Figure 2. Schematic representation of immobilization of thiol-labeled probe onto gold electrode and detection of *N. meningitidis* from patient CSF [29].

http://dx.doi.org/10.5772/intechopen.68553

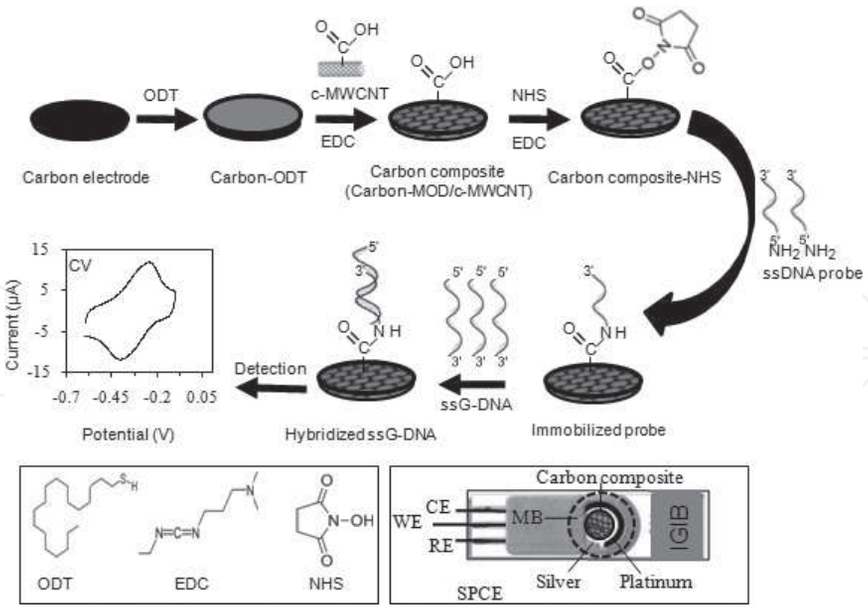

Figure 3. Schematic representation of immobilization of probe on nanocomposite and diagnosis of bacterial meningitis from patient CSF [30].

4.4.3. Microarray

Microarray involves immobilization of an array of single or multiple types of ssDNA probes onto a surface and then hybridization with complementary ssDNA followed by detection through LASER scanning. Microarray is an advance and promising technique for diagnosis of any disease [32]. Tong et al. first time used 16S microarray for detection of neonatal bacterial meningitis using patient's blood [33]. Nowadays, DNA microarray is used for detection of large number of suspected samples of different diseases at a time. DNA microarray can either be constructed by direct synthesis of oligonucleotide on the solid surface (affymetrix microarray) or by immobilization of earlier synthesized oligonucleotides onto a substrate [34]. The second one remains as choice of preference for the researchers because of its flexibility regarding the surface and ligand used for construction of microarray [35]. Glasses are preferred over other platforms due to their low-cost, intrinsic fluorescence, and superior optical properties. 3′-modified probe is preferred over the 5′-modified probe because the later requires phosphoramidite reagents of the modifier in strictly anhydrous condition [36]. Surface of the substrates can be coated with polylysine or aminopropyle to increase the immobilization. The noncovalent attachments used for immobilization of the ssDNA probe onto an electrode are epoxide-amine, epoxide-thiol, epoxide-aminooxyalkyl, aldehyde-amine, and semicarbazide-aldehyde. Carboxyl-amine, thiol-disulfide, biotin-streptavidin, gold-thiol, zirconylated-surface-phosphate, and epoxide-amine are some of the covalent linkage used often for the probe immobilization (**Figure 4**) [34]. The immobilization of the probe is optimized for time, pH, temperature, and concentration in order to obtain maximum immobilization efficiency. The array of immobilized oligomers can be hybridized with the genomic DNA of pathogen in patient sample. Several researches have been reported by our lab to detect the presence of *N. meningitidis* from the CSF samples using microarray [35, 36]. The same principle can be used to develop a microchip in future for diagnosis of large number of HME suspected samples at a time.

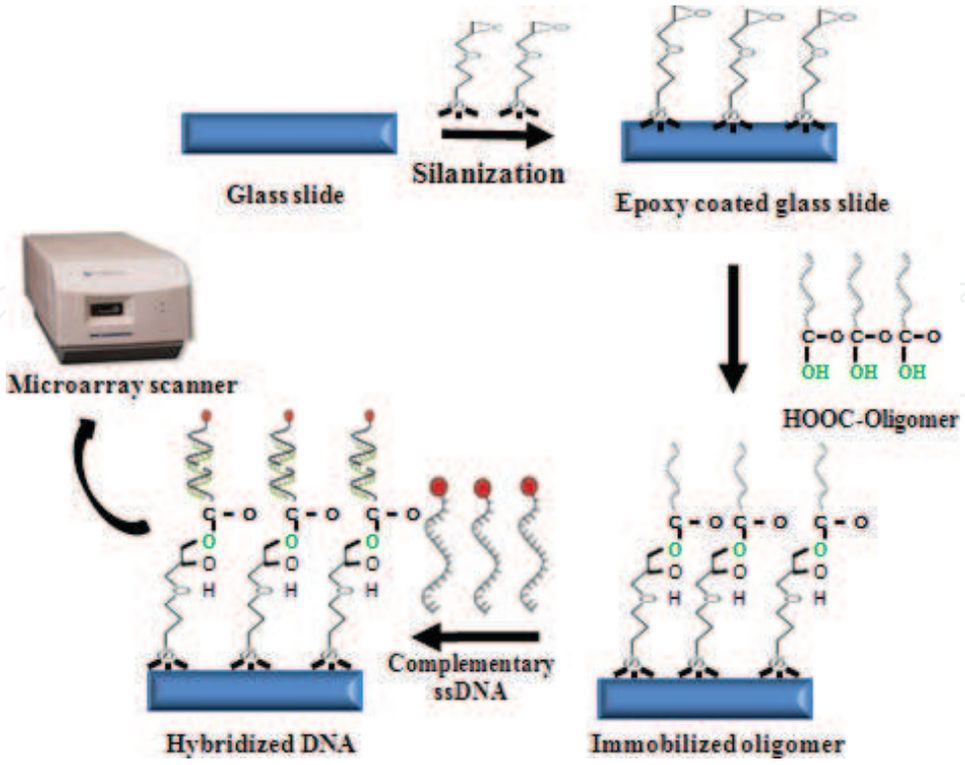

Figure 4. Schematic presentation of microarray-based detection of bacterial meningitis [35].

5. Prevention

It has always been said that prevention is better than cure. There is no effective vaccine available against HME, but prevention lies primarily in the management of genital infections in pregnant women [37]. Avoiding of sharing of food, beverages, and other objects in between the infected and healthy persons prevent the contamination of HME. Proper cleaning, sterilization, sanitation, and isolation also help to prevent spread of the infection [38]. Regular monitoring and health checkups are necessary for the people living in mass, working together, or pilgrims to avoid the risk of contaminations. Abstain from sex or protected sexual relation through latex condoms can reduce the risk of sexual transmission.

6. Treatment

Patients suffering with mild infection recover within few weeks of treatment, whereas severe cases may require longer period. About 50–70% of the HME patients suffer from secondary sequel-like brain damage, neurological disorders or comma. Therefore, an early treatment of the HME is necessary [39]. A dramatic improvement in the HME patient health can be achieved by treating at an earlier stage with antiviral drugs like acyclovir, vidarabine, or famciclovir. At a later stage, the treatment becomes ineffective. Anticonvulsants such as dilantin or phenytoin prevent HME seizures [40]. Corticosteroids or diuretics such as prednisone, furosemide, or mannitol can relieve the skull pressure, reduce swelling due to inflammation,

http://dx.doi.org/10.5772/intechopen.68553

and prevent hearing loss. In the case of severe inflammations, pain suppressors or sedatives may be prescribed. Complete rehabilitation, rest, regular monitoring, balanced nutrition, and occupational therapy are necessary for preventing relapse of the infection.

7. Conclusions

HME is one of the most dreadful forms of aseptic meningoencephalitis caused by HSV 1 and 2. It has a high mortality and morbidity rate especially in infants. The fail to accurate diagnosis and complete treatment has raised the risk of disease. Therefore, a rapid and accurate diagnosis is essential for early treatment of the infection and effective public health management. The inefficacy for eradication of any disease is equally shared by ignorance of the people and fail of early treatment. Therefore, the dreadful impact of this disease should be made aware to the common people. Recent advances in the field of diagnosis such as PCR, microarray, and nanosensors may help for early diagnosis. Still, there is a high demand on the research regarding early treatment of the infection to save the life of people.

Acknowledgements

I would like to thank Mrs. Sanjukta Satapthy, Principal, Chikiti College, Ganjam for her suggestions and advises.

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