Diagnostics in infectious encephalitis

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What is infectious encephalitis?

Infectious encephalitis is an inflammation of the brain caused by an infection invading the brain. Viruses are the most common cause of infectious encephalitis. Some of the viruses that can cause encephalitis include herpes viruses, enteroviruses, insect-borne viruses (e.g., Japanese encephalitis virus, West Nile virus) and tick-borne viruses. Bacteria, fungi and parasites can cause infectious encephalitis more rarely. Encephalitis can also be caused by the body's immune system attacking the brain, which is known as autoimmune encephalitis.

Why is a diagnosis of infectious encephalitis important?

Encephalitis is a neurological emergency which needs to be diagnosed as soon as possible to avoid severe after-effects such as disability or death. If a doctor suspects that a patient may have encephalitis, they need to act quickly. First of all, they need to stabilise the patient and then they need to look for a cause of the brain inflammation. Sometimes, they may start treatment even before an exact cause is found.

The diagnosis of infectious encephalitis aims to establish that there is inflammation within the brain, and secondly to find the cause of the inflammation. Finding the exact cause of inflammation is important as various types of encephalitis have different treatments. Although the identification of the pathogens causing encephalitis remains challenging, and in many cases the cause is still unknown, there have been many advances in the diagnosis of encephalitis over the past few years. Now, tests take much shorter time to get results (an hour in some instances), they are more reliable, and they look for a much larger number of pathogens than before.

Overview of diagnostics in infectious encephalitis

Not one test/symptom is enough for making a diagnosis of encephalitis, but rather a combination of tests and assessments. Initially, the doctor will try to:

- Get a thorough history of the illness (e.g., when did it start, what symptoms were experienced).
- Get any travel history (if there was travel any contact with animals, mosquito, ticks, fresh water).
- Examine the patient, looking for signs of brain inflammation, signs of infection and signs of specific causes of encephalitis

Based on the information from the above assessments, the doctor will perform various diagnostic tests to confirm the diagnosis and find the cause of encephalitis. They will also try to eliminate other illnesses with similar symptoms such as: bacterial meningitis, strokes, brain tumours, and other causes of brain damage.

Diagnostic tests

Diagnostic tests used in encephalitis can be split into two broad categories:

1. Laboratory tests, which analyse samples from patients such as cerebrospinal fluid, blood, urine and other body fluids.

2. Neuroimaging, including scans such as CT and MRI or special tests such as EEG which record brain waves. For an overview of neuroimaging in encephalitis please see the **Neuroimaging** factsheet.

Cerebrospinal fluid (CSF) analysis

This is the vital test to establish a diagnosis of encephalitis. The CSF is produced within the brain and flows out at the base of the brain to surround and cushion the brain and spinal cord. Cerebrospinal fluid is collected from patients via a lumbar puncture (spinal tap). All patients suspected of encephalitis should have a lumbar puncture as soon as possible unless there is a clear reason preventing it from taking place.

A lumbar puncture involves passing a needle, under local anaesthetic, between two of the backbones at the base of the spine to access the fluid that bathes the spinal cord. Lumbar punctures are common procedures in hospital, but there are some risks. Approximately 10% of adult patients suffer a headache after this procedure. This headache is typically mild and worse upon being upright and better lying flat. It usually improves with simple painkillers and good hydration. Some doctors advocate caffeine, from tea or coffee. Much more rarely, a lumbar puncture can cause nerve damage, long term back pain, bleeding and infection.

Various laboratory tests are performed on CSF. Some tests give results within hours whereas others can take days. Immediate tests performed on CSF include analysis under the microscope to assess the number and type of white blood cells present. A raised number of white blood cells in CSF can indicate inflammation within the brain, spinal cord or lining of the brain (meninges). Other parameters including the opening pressure of CSF, its appearance, CSF protein content and ratio of CSF to blood glucose level can also be helpful in distinguishing between different types of brain infection or conditions that might have similar symptoms to encephalitis.

Other CSF tests are more complicated and include

- Culture for microbes (bacteria)
- Antibody studies (if autoimmune encephalitis is suspected)
- Conventional microbiological tests to detect viruses or bacteria such as polymerase chain reaction (PCR) or high-throughput sequencing (HTS) of CSF. These are much quicker than trying to culture (grow) the pathogen
- Metagenomic next generation sequencing (mNGS) (not available as a routine test) aimed at identifying a broad range of pathogens in a single test.

Some of these tests may be negative in the first few days after the onset of the illness. In this case, an LP may have to be repeated during an individual's illness.

Other laboratory screening

Blood, urine, as well as other body fluids can help detect and identify brain and/or spinal cord infection especially when CSF analysis is not possible, or it is negative. These tests can also exclude other causes of encephalitis' mimics.

Brain biopsy

A brain biopsy can be considered when the cause of encephalitis remains unknown despite extensive investigations and the patient condition does not improve. However, often in cases where the cause of encephalitis is unknown, a brain biopsy is not performed as it is so invasive. It is very rare these days when a biopsy is performed, and it would only ever be performed at a specialist centre.

Diagnosing encephalitis can be challenging and there is no single test which will give patients and doctors an answer. Sometimes doctors must treat the patient based on what the most likely cause is, while accepting that they are not certain. Doctors continuously monitor a patient's response to treatment and if the patient fails to improve or the

diagnosis remains unclear, they may do extra tests, ask specialists or transfer to a hospital which specialises in encephalitis.

The journey of the sample

After the sample (CSF, blood) is collected from the patient, it is transported to the laboratory. There, it is stored and analysed by laboratory professionals using various machines and equipment. The results are logged into computer and/or sent to the doctor who treats the patient.

Please see our animation on the **Journey of a Sample** for more information

(www.encephalitis.info/the-journey-of-a-sample)

Diagnostic test results

The doctor will analyse the laboratory results as well as considering the results of other tests (imaging, EEG), the patient's condition and the response to treatment. Even negative results are important as the doctor can eliminate some of the possible causes which means they can stop the treatment they have initiated, and they can look somewhere else.

The diagnostic test can help to confirm a diagnosis when a direct cause is found (there is evidence the pathogen has caused the inflammation), can make a probable diagnosis (when all tests and clinical features suggest a cause and treatment seems to be efficient) or a diagnosis of encephalitis with an unknown cause. In some cases, the encephalitis is not confirmed, and an alternative diagnosis is made.

The results of the tests may depend on the time they were performed and are correlated with the evolution of the illness. It is not unusual for the results of some tests to be 'normal' at the beginning of the illness but then change during the illness. In some cases where the CSF is obtained very early in the disease course, the tests can be falsely negative. So, if the doctor still suspects encephalitis, some tests will need to be repeated.

The challenges of diagnostics in encephalitis

There are many factors which make establishing an encephalitis diagnosis challenging. Some of the challenges are associated with the nature of the condition or the patient and others with diagnostic tests and methods.

- Patient's symptoms and signs can be non-specific, which means that they are common in various other conditions.
- The variety and multitude of possible causes. There are over 100 pathogens that can cause infectious encephalitis.
- Encephalitis is a condition that can start suddenly and rapidly worsens; patients often require intensive supportive management as they can be severely ill.
- Lack of encephalitis specialists. Patients with encephalitis are not usually looked after by specialist teams such as what happens with stroke patients.
- Establishing that a specific pathogen found in the brain/spinal fluid has caused that encephalitis. Sometimes, pathogens may contaminate the CSF and not actually be the cause of encephalitis.
- As mentioned above, some tests, such as lumbar puncture, may be negative early on in encephalitis
- Not having access to specific diagnostic test in the local hospital. Sample will need to be sent to other hospitals which requires time.
- Reluctance of professionals to perform certain diagnostics tests such as an LP, as it can be a challenging procedure that requires training

- Encephalitis is rare, and other more common conditions can have similar symptoms. This means some doctors may fail to spot it and the need to carry out appropriate tests.
- Costs of diagnostic testing not covered by the patient's insurance.

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Thank you!

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