Acute necrotising encephalopathy (ANE)

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Background

Acute necrotising encephalopathy (ANE) is a rare type of brain condition that occurs after a viral infection. 'Encephalopathy' is a general term referring to acute or chronic disturbance in brain function and structure leading to confusion causing acute or chronic dysfunction of the brain. 'Necrotising' refers to the death of brain tissue.

ANE as a distinct syndrome was first documented by Masashi Mizuguchi in 1995.

How is it caused?

ANE usually starts during or shortly after a viral infection, usually influenza A or B. Other viral triggers have been reported, including SARS-CoV-2 and other respiratory viruses. ANE is generally considered to be caused by the immune system's response to the infection, rather than the virus itself which distinguishes it from viral encephalitis.

The exact mechanism is not fully understood but an overreaction by the body's immune system to the infection whereby it releases a flood of inflammatory chemicals known as cytokines is thought to play a key role. This excess of cytokines can directly damage brain cells, but injury also occurs because of the brain cells inability to keep up with the increased energy demands needed to manage this "cytokine storm."

ANE usually happens only once and is not passed down in families. However, there has been documentation where more than one person in a family has developed the condition. Most of these cases have been associated with mutations in the RANBP2 gene. Patients with familial ANE can experience a recurrence of the disease.

What are the symptoms?

ANE predominantly affects children under the age of five. However, although very rare, it is being increasingly reported in adults. People with this condition usually exhibit symptoms of an infection, such as a fever, cough, congestion, vomiting, and diarrhoea, for a few days.

Shortly after, or in tandem with these flu-like symptoms, neurological problems develop, such as seizures, altered sensorium, speech changes, weakness or difficulty coordinating movements.

People with ANE develop areas of damage in certain regions of the brain. As the condition progresses, these regions develop swelling, bleeding, and then tissue death (necrosis). Eventually, this may lead to a coma which can last days to weeks in severe cases. In addition to convulsive seizures, patients with ANE can develop nonconvulsive seizures which manifest primarily as altered sensorium and can only be detected with an encephalogram (EEG).

How is it diagnosed?

The condition is not diagnosed with a single test. It's a combination of clinical symptoms, imaging, lab tests, and ruling out other causes.

A nasopharyngeal swab can be done to confirm viral infection.

An MRI (magnetic resonance imaging) can support diagnosis of ANE by showing characteristic lesions, often involving both thalami, with swelling (oedema), haemorrhage or necrosis (tissue death).

A lumbar puncture (LP; spinal tap) may be conducted. The CSF (cerebrospinal fluid) often shows normal white cell count with raised protein, helping differentiate ANE from viral encephalitis.

A blood test may also be conducted to check for indicators such as high inflammatory markers and metabolic abnormalities.

Finally, in some cases where ANE is recurrent or occurs without a strong viral trigger, doctors may test for gene mutations.

How is it treated?

As of the most recent reviews, there are currently no evidence-based guidelines, approved medications, or randomised trials for ANE treatment.

The main method of treatment includes immunotherapy and supportive care. The former primarily consists of high-dose steroids (e.g. glucocorticoids) and plasma exchange (PLEX). Sometimes intravenous immunoglobulin (IVIG) is used, though evidence remains limited. Early steroid treatment (within 24-48 hours) is sometimes associated with better outcomes in some studies.

Antiseizure drugs are usually started to manage seizures. Continuous EEG monitoring to detect nonconvulsive seizures may help in the management of ANE.

What are the outcomes?

Around a third of people affected do not survive their illness and subsequent neurological decline.

Of those who do survive, about half have permanent neurological impairment due to tissue necrosis. This results in impairments in walking, speech, and other motor functions. Over time, many of these skills may be regained functionally, but the loss of brain tissue is permanent. Other individuals who survive appear to recover completely.

To reduce the risk of recurrence, influenza vaccination and vigilant monitoring during flu season are advised.

Can it be prevented?

Vaccination reduces risk indirectly. Annual influenza vaccination is recommended for children aged 6 months or older. This prevents influenza and its associated complications such as ANE and influenza-associated encephalitis.

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