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A Novel form of Dementia: Limbic-predominant Age-related TDP-43 Encephalopathy

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Abstract

Limbic-predominant age-related TDP-43 encephalopathy (LATE) is a recently identified new form of dementia. It is characterized by problems with memory, thinking, and reasoning, primarily due to the accumulation of the protein TDP-43 in the brain's limbic system. Whereas its symptoms are like Alzheimer's disease, LATE has different underlying causes, involving abnormal clusters of TDP-43. Also, while this protein is also involved in frontotemporal dementia, LATE exhibits a different pattern of brain changes and tends to affect people over the age of 80. This article will present this novel form of dementia, identifying its key characteristics, clinical presentation, risks, signs and symptoms. Its etiology, differential diagnosis, current symptoms management, and aims of current research will also be discussed. In sidebars, the limbic system, the TAR DNA-binding protein TDP-43, and encephalopathies will be reviewed for a greater understanding of LATE.

Abbreviations

AD: Alzheimer's disease; ADRC: Alzheimer's Disease Research Centers; ALS: Amyotrophic lateral sclerosis; CSF: Cerebrospinal fluid; CTF: (Alzheimer's) Clinical trials finder; EEG: Electroencephalography; FDG: Fluorodeoxyglucose; FTLD: Frontotemporal lobar degeneration; LATE: Limbic-predominant Age-related TDP-43 Encephalopathy; MRI: Magnetic resonance imaging; lncRNA: long non-coding RNA; mRNA: messenger RNA; miRNA: microRNA; NES: Nuclear export signal; NIA: (U.S.) National Institute on Aging; NLS: Nuclear localization signal; PET: Positron emission tomography; RNA: Ribonucleic acid; RRM: RNA recognition motif; TAR: Trans-activation response; TDP-43: TAR DNA-binding protein 43.

Keywords

Amyotrophic lateral sclerosis; dementia; limbic-predominant age-related TDP-43 encephalopathy; TAR DNA-binding protein.

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Researchers investigating changes inside the brain after death recently identified a new form of dementia: Limbic-predominant Age-related TDP-43 Encephalopathy (LATE). The term limbic comes from the Latin limbus for "border" or "edge"; in medical terminology, it is a border of an anatomical component. The limbic system (see Sidebar 1), including the hippocampus and the amygdala, is the brain's center of emotions responsible for the cortical representation of emotions, the neocortex being responsible for cognition. However, cognition depends on acquisition and retention of memories, in which the hippocampus, a primary limbic interacting structure, is involved; hippocampus damage causes severe cognitive (memory) deficits. More important, the "boundaries" of the limbic system have been repeatedly redefined because of advances in neuroscience. Therefore, while it is true that limbic interacting structures are more closely related to emotion, the limbic system itself is best thought of as a component of a larger emotional processing plant. LATE has been predominantly attributed to the limbic system. In humans, TDP-43 (see Sidebar 2) is a protein that is encoded by the TARDBP gene. It has been shown to bind both DNA and RNA and have multiple functions in transcriptional repression, pre-mRNA splicing, and translational regulation. Encephalopathy (/ɛnˌsɛfəˈlɒpəθi/; from Ancient Greek (enképhalos) 'brain' and πάθος (athos) 'suffering') means any disorder or disease of the brain, especially chronic degenerative conditions (see Sidebar 3). In modern usage, encephalopathy does not refer to a single disease, but rather to a syndrome of overall brain dysfunction; this syndrome has many possible organic and inorganic causes.

LATE is thus a type of dementia characterized by problems with memory, thinking, and reasoning, primarily due to the accumulation of the protein TDP-43 in the brain's limbic system. [Note: TDP-43 is involved in other brain disorders, including amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD).]

When thinking about memory problems, Alzheimer's disease (AD) comes to mind. But LATE is a different disease with its own characteristics. Nonetheless, sometimes, signs and symptoms of both LATE and AD may be present.

Whereas its symptoms are like AD, LATE has different underlying causes, involving abnormal clusters of TDP-43. Also, while this protein is also involved in FTD, LATE exhibits a different pattern of brain changes and tends to affect people over the age of 80.

Key characteristics

The key characteristics of LATE are:

• **TDP-43 accumulation:** LATE is defined by the presence of abnormal clumps of the TDP-43 protein, specifically in the limbic regions of the brain, including the hippocampus and amygdala (Figure 1).
• **Progressive amnestic dementia:** The primary clinical manifestation is memory loss, particularly difficulty remembering recent events and conversations. This is similar to AD, but with a focus on memory loss, particularly delayed recall.
• **Age-relation:** LATE most commonly affects individuals over 80 years old.
• **Overlap with other conditions:** LATE can occur alongside other brain pathologies like AD or arteriosclerosis.
• **Diagnostic challenges:** LATE is often difficult to diagnose clinically, as the symptoms can mimic other types of dementia. A definitive diagnosis usually requires autopsy to examine brain tissue for TDP-43

accumulation.

Clinical presentation

The clinical presentation of LATE is as follows:

• **Memory problems:** Difficulty remembering facts, conversations, and recent events.
• **Language difficulties:** Trouble finding the right words or understanding others.
• **Cognitive decline:** Problems with decision-making, orientation, and spatial awareness.
• **Behavioral changes:** Potential for wandering, repetitive behaviors, and personality changes.
• **Slower progression:** Slower rate of clinical progression compared to AD.

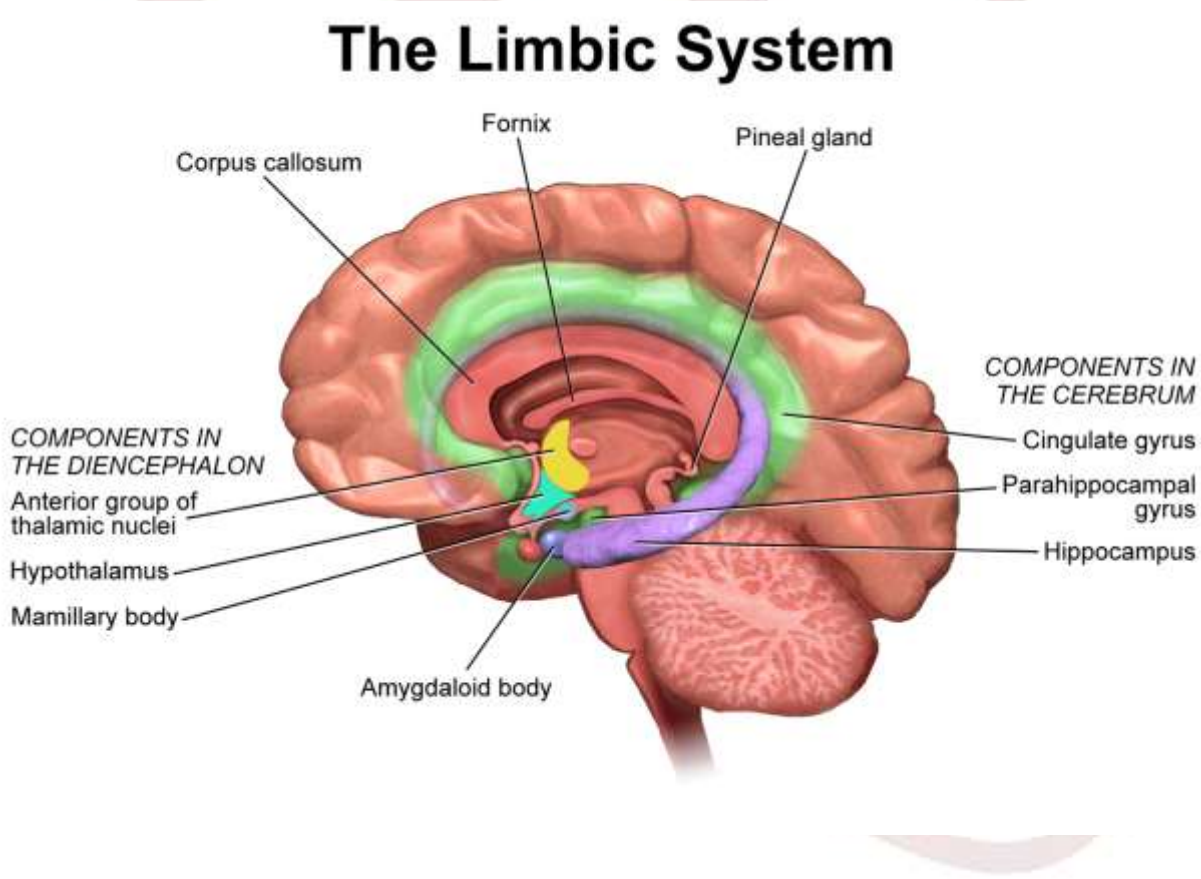


Figure 1: The human limbic system

Risks

The risks for contracting LATE are limited and include:

• **Age:** LATE usually affects older individuals, particularly those over age 80. Although advancing age is a risk factor, dementia is not part of the typical aging process.

• **Genetics:** Genetics can also increase a person's risk of developing this disease. At least five genes are associated with the risk of LATE. These same genes may also increase the likelihood of other forms of dementia.

Signs and symptoms

People with LATE have problems with memory but, often, have a slower rate of clinical change than people with AD. They may notice that over time it is more difficult to remember facts, conversations, and events. People with LATE may repeat themselves often, be forgetful and have trouble finding the right words during conversations. They may also have difficulty understanding words.

Individuals with LATE may:

• Wander or get lost.
• Make poor decisions.
• Misplace things.
• Have trouble driving.
• Have difficulty keeping up with personal hygiene.

Other signs include:

• Brain atrophy: Shrinkage and thinning of the parts of the brain responsible for memory formation: These changes can be seen on MRI examination and on autopsies. Thinning seems to be a stronger indicator of how severe the disease is compared with atrophy.

• TDP-43 protein buildup: This naturally occurring protein helps with nerve development. Its buildup is usually found in the part of the brain that supports memory, emotion, behavior, and mood (limbic system). There is not a simple test to see whether a person has an excessive amount of TDP-43. This would be discovered only with an autopsy.

• Arteriosclerosis: Hardening and thickening shrinkage of the walls of the arteries is common in people with LATE.

Eventually, someone with LATE has trouble with daily living activities such as dressing, cooking or paying bills. The mental decline in LATE is slower than in other forms of dementia. This causes a slow, rather than a rapid, worsening of symptoms.

The symptoms of LATE are like those of AD and include:

• Problems with memory.
• Difficulty thinking and making decisions.
• Trouble finding the right words.
• Wandering or getting lost.

Etiology

The TDP-43 protein normally helps to regulate gene expression in the brain and other tissues. Deposits of this protein have been associated with deterioration of parts of the brain involved in memory, such as the hippocampus, resulting in cognitive impairment.

Recent autopsy studies examining tissue from donated brains found that certain patterns of misfolded TDP-43 proteins may be common in older adults. As indicated earlier, researchers characterized this pattern of misfolded protein deposits as LATE.

For example, results from autopsy studies of more than 6,000 people with an average age at death of 88 years found that 40% had TDP-43 protein deposits associated with LATE and that LATE was associated with deficits in memory and thinking in approximately 25% of the donors. Those same studies also suggest that LATE can

contribute to cognitive decline alone or in combination with other types of dementia. Just over half of those with signs of LATE also had evidence of Alzheimer's-related proteins, suggesting that having more than one of these brain disorders may contribute to a more rapid decline than either disease alone.

It remains to establish whether these TDP-43 deposits and misfoldings are the cause of LATE or merely its hallmarks – an issue that seems to pervade most neurodegenerative diseases. In his several publications, this author has advocated for the position that such observed protein characteristics are merely symptoms of a causal runaway brain autoimmune disease (Fymat, 2017-2025).

Differential diagnosis

There is currently no possibility to diagnose LATE in living people. It can only be definitively diagnosed after death through an autopsy. But for people with symptoms, a diagnosis of LATE can be suggested through:

• Clinical history,
• MRI or fluorodeoxyglucose (FDG)-positron emission tomography (PET) findings, and
• Ruling out other causes.

If LATE is suspected, a mental status examination may be recommended to ascertain how severe the cognitive impairment is.

Researchers are working to find a simpler way to diagnose LATE and other forms of dementia, and to quickly identify these diseases. They are working to develop a simple blood screening test for dementia, including LATE, but that is still under study.

Distinction from other dementia types

Dementia is the result of changes in certain brain regions that cause nerve cells (also known as neurons) and their connections to stop working properly. Researchers have connected changes in the brain to certain forms of dementia. For example, the hallmark brain changes associated with Alzheimer's are the buildup of amyloid plaques and tau tangles. Compared to other types of dementia, LATE can be distinguished as follows:

• **Alzheimer's disease (AD):** While LATE can mimic Alzheimer's, the primary focus of LATE is memory loss, whereas Alzheimer's can also involve language and executive function problems.
• **Frontotemporal lobar dementia (FTLD):** FTLD is characterized by personality changes and language difficulties, whereas LATE is primarily an amnestic dementia.

Current symptoms management

There is not a definitive treatment or cure for LATE, yet. To help improve overall health and manage the symptoms of dementia, the World Health Organization (WHO) has made recommendations that include:

- Increasing physical activity.
- Maintaining a healthy diet.
- Decreasing alcohol intake.
- Avoiding smoking.
- Treating chronic conditions such as hypertension, high cholesterol, depression, obesity and diabetes.

The WHO also suggests increasing accessibility of health care and social workers to people with dementia and their caregivers.

More studies are under way to discover better ways to diagnose and possibly treat LATE.

Research aims

Researchers continue to investigate the causes of and risk factors for LATE and ways to diagnose this disease in living people. For example, they are currently examining data to explore whether LATE has a unique pattern of brain degeneration and memory loss that could help further distinguish it from AD. They are also exploring whether there are unique molecular signatures for LATE that might be used to create a blood or spinal fluid diagnostic test.

Research into LATE and the underlying causes of dementia would not be possible without volunteers who donate their brains after death. (Additional information about participating in research to discover new ways to potentially diagnose, treat, and prevent dementia can be found through the National Institute on Aging (NIA)-funded Alzheimer's Disease Research Centers (ADRC) and by visiting the Alzheimer's.gov Clinical Trials Finder (CTF).

Conclusions and take-aways

- Researchers investigating changes inside the brain after death recently identified a new form of dementia: Limbic-predominant Age-related TDP-43 Encephalopathy (LATE). The limbic system, including the hippocampus and the amygdala, is the brain's center of emotions responsible for the cortical representation of emotions, the neocortex being responsible for cognition. LATE has been predominantly attributed to the limbic system.

- TDP-43 is a protein that in humans is encoded by the TARDBP gene. It has been shown to bind both DNA and RNA and have multiple functions in transcriptional repression, pre-mRNA splicing, and translational regulation.

- Encephalopathy does not refer to a single disease, but rather to a syndrome of overall brain dysfunction; this syndrome has many possible organic and inorganic causes.

- LATE is thus a type of dementia characterized by problems with memory, thinking, and reasoning, primarily due to the accumulation of the protein TDP-43 in the brain's limbic system.

- LATE is a different disease than Alzheimer's. Whereas the symptoms of both diseases may look alike or even be present at the same time, LATE has different characteristics and underlying causes, involving abnormal clusters of TDP-43. Also, while this protein is also involved in frontotemporal dementia, LATE exhibits a different pattern of brain changes and tends to affect people over the age of 80.

- The key characteristics of LATE are: TDP-43 accumulation; progressive amnestic dementia; age-relation; overlap with other conditions and diagnostic challenges.

- The clinical presentation of LATE is: Memory problems; language difficulties; cognitive decline; behavioral changes; and slower progression compared to Alzheimer's.

- The risks for contracting LATE are limited and include: Age and genetics.

- Signs and symptoms of LATE include brain atrophy, TDP-43 protein buildup, and

arteriosclerosis. Eventually, someone with LATE has trouble with daily living activities. The mental decline in LATE is slower than in other forms of dementia. This causes a slow, rather than a rapid, worsening of symptoms.

- The symptoms of LATE are like those of AD and include: Problems with memory, difficulty thinking and making decisions, trouble finding the right words, and wandering or getting lost.

- The TDP-43 protein normally helps to regulate gene expression in the brain and other tissues. Deposits of this protein have been associated with deterioration of parts of the brain involved in memory, such as the hippocampus, resulting in cognitive impairment. Recent autopsy studies examining tissue from donated brains found that certain patterns of misfolded TDP-43 proteins may be common in older adults.

- There is currently no possibility to diagnose LATE in living people. It can only be definitively diagnosed after death through an autopsy. Compared to other types of dementia, LATE can be distinguished from Alzheimer's and frontotemporal lobar dementia.

- There is currently not a definitive treatment or cure for LATE.

- Researchers are currently examining data to explore whether LATE has a unique pattern of brain degeneration and memory loss that could help further distinguish it from AD. They are also exploring whether there are unique molecular signatures for LATE that might be used to create a blood or spinal fluid diagnostic test.

Sidebar 1 – The limbic system

The limbic system is where the subcortical structures meet the cerebral cortex. It is a set of brain structures located on both sides of the thalamus, immediately beneath the medial temporal lobe of the cerebrum, primarily in the forebrain (see Figure 1). Its various components support a variety of functions including emotion, behavior, long-term memory, and olfaction. It is also involved in lower-order emotional processing of input from sensory systems and relays that processed information to a collection of other structures.

Structure

The limbic system was originally defined by the French physician Pierre Paul Broca (1824-1880) in 1878, as a series of cortical structures surrounding the boundary between the cerebral hemispheres and the. brainstem. Further studies began to associate these areas with emotional and motivational processes and linked them to subcortical components that were then grouped into the limbic system. In recent years, using diffusion-weighted MRI, multiple additional limbic fiber connections have been revealed. Currently, it is not considered an isolated entity responsible for the neurological regulation of emotion, but rather one of the many parts of the brain that regulate visceral autonomic processes. Therefore, the set of anatomical structures considered part of the limbic system is controversial.

Function

The structures and interacting areas of the limbic system are involved in motivation, emotion, learning, and memory. These interactions are closely linked to olfaction, emotions, drives, autonomic regulation, memory, and pathologically to encephalopathy, epilepsy, psychotic symptoms, cognitive defects. They also interact with the basal ganglia - a set of subcortical structures that direct intentional movements. The basal

ganglia are located near the thalamus and hypothalamus. The limbic system receives input from the cerebral cortex, which sends outputs to the motor centers in the brainstem. The limbic system is also tightly connected to the prefrontal cortex.

The functional relevance of the limbic system has proven to serve many different functions such as emotions, memory, sensory processing, time perception, attention, consciousness, instincts, autonomic/ vegetative control, and actions/ motor behavior. Some of the disorders associated with the limbic system and its interacting components are epilepsy and schizophrenia.

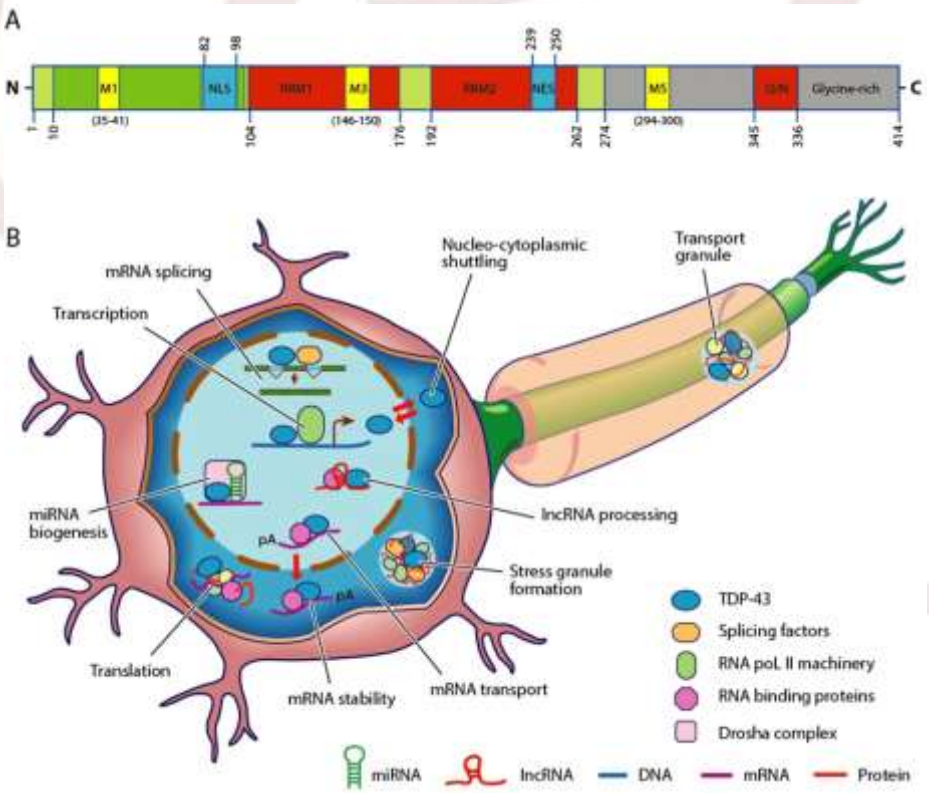
Sidebar 2 - TAR DNA-binding protein TDP-43

Transactive response (TAR) DNA binding protein 43 (or TDP-43) is a protein that in humans is encoded by the TARDBP gene.

Structure

TDP-43 is 414 amino acid residues long. It consists of four domains (an N-terminal domain, two highly conserved folded RNA recognition motifs, and an unstructured C-terminal domain).

Mutations within the TDP-43 proteins glycine rich region have recently been identified as associates that can contribute to various neurodegenerative diseases (NDD), with the most notable and common NDD being amyotrophic lateral sclerosis (ALS); about 10% of the mutations causing familial ALS are accredited with the TDP-43 protein (Figure 2).



Source: Eva Maria Johanna de Boer et al. (2020) - https://jnnp.bmj.com/content/92/1/86.full Based on PYMOL, rendering of PDB and Wikipedia

Figure 2: Structure of the TAR DNA binding protein

Figure 3(A) illustrates the TheTDP-43 protein containing 414 amino acids and consisting of an N-terminal region with a nuclear localization signal (NLS). In addition, the protein consists of two RNA recognition motifs (RRM1 and RRM2), a nuclear export signal (NES) and a C-terminal domain with a glutamine/asparagine-rich (Q/N) and glycine-rich regions. Mitochondrial localization motifs (M1; M3; M5) are also evident. Pathogenic mutations are predominantly located within the C-terminal region which can exhibit prion-like properties. The numbers represent amino acid lengths. On the other hand, Figure 3(B) shows the TDP-43 protein as critical for mediating RNA metabolism. In the nucleus, TDP-43 is important for transcription and splicing of messenger RNA (mRNA), as well as maintaining RNA stability (pA) and transport to nucleus. In addition, TDP-43 regulates biogenesis of microRNA (miRNA) and processing of long non-coding RNA (lncRNA). Although predominantly located within the nucleus, TDP-43 shuttles between the nucleus and the cytoplasm. In the cytoplasm, TDP-43 participates in mRNA stability, translation, formation of stress and ribonucleoprotein (RNP) transport granules.

Function

TDP-43 is a transcriptional repressor that binds to chromosomally integrated trans-activation response (TAR) element DNA and represses HIV-1 transcription. It has been shown to bind both DNA and RNA and have multiple functions in transcriptional repression, pre-mRNA splicing and translational regulation.

Sidebar 3 - Encephalopathies

Encephalopathy means any disorder or disease of the brain, especially chronic degenerative conditions. It does not refer to a single disease, but rather to a syndrome of overall brain dysfunction, having many possible organic and inorganic causes.

Types

There are many types of encephalopathy, including particularly in the brain:

- **Mitochondrial encephalopathy:** A metabolic disorder caused by dysfunction of mitochondrial DNA. It can affect many body systems, particularly the brain and nervous system.
- **Hashimoto's encephalopathy:** It arises from an auto-immune disorder.
- **Anti-NMDA receptor encephalopathy:** An auto-immune encephalitis.
- **Chronic traumatic encephalitis:** A progressive degenerative disease associated with repeated head trauma, often linked to contact sports.
- **Toxic metabolic encephalopathy:** A catch-all for brain dysfunction caused by infection, organ failure, or intoxication.
- **Transmissible spongiform encephalopathy:** A collection of diseases all caused by prions and characterized by "spongy" brain tissue (riddled with holes), impaired locomotion or coordination, and a 100% mortality rate. Includes bovine spongiform encephalopathy ("mad cow disease"), scrapie, and kuru among others.
- **Neonatal encephalopathy (hypoxic-ischemic encephalopathy):** An obstetric form, often occurring due to lack of oxygen in blood flow to brain-tissue of the fetus during labor or delivery.
- **Salmonella encephalopathy:** A form of encephalopathy caused by food poisoning (especially out of peanuts and rotten meat) often resulting in permanent brain damage and nervous system disorders.

Signs and symptoms

The hallmark of encephalopathy is an altered mental state or delirium. Characteristic of the altered mental state is impairment of the cognition, attention, orientation, sleep orientation, sleep-wake cycle, and consciousness. Depending on the type and severity of

encephalopathy, common neurological symptoms are loss of cognitive function, subtle personality changes, and an inability to concentrate. Other neurological signs may include dysarthria, hypomimia, problems with movements, ataxia, tremor.

Diagnosis

Blood test, cerebrospinal fluid (CSF) examination by lumbar puncture (also known as spinal tap), brain imaging studies, electroencephalography (EEG), neuropsychological testing and similar diagnostic studies may be used to differentiate the various causes of encephalopathy. The diagnosis is frequently clinical, i.e., no set of tests give the diagnosis, but the entire presentation of the illness with nonspecific test results informs the experienced clinician of the diagnosis.

Treatment

Treatment varies according to the type and severity of the encephalopathy. It may include anticonvulsants and sympathomimetic drugs to increase motivation, cognition, motor performance, and alertness in persons with encephalopathy caused by brain injury, brain tumors, chronic infections, or strokes.

Prognosis

Treating the underlying cause of the disorder may improve or reverse symptoms. However, in some cases, the encephalopathy may cause permanent structural changes and irreversible damage to the brain. These permanent deficits can be considered a form of stable dementia. Some encephalopathies can be fatal.

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