Leukoencephalopathy

- Peripheral Neuropathy as an Early Marker in Newborn-Screened Krabbe Disease: The Value of Pre-Confirmatory Neurophysiological Testing
- Cerebellum-Predominant Progressive Multifocal Leukoencephalopathy: An Under-recognized Cause of Cerebellar Syndrome among People with Human Immunodeficiency Virus Infection
- A case report and review of the literature on hereditary diffuse leukoencephalopathy with spheroids presenting with stroke-like symptoms
- Genetic analysis of a child with gastrointestinal hemorrhage and Cerebroretinal microangiopathy with calcifications and cysts and a literature review
- Novel Cause of Reversible Leukoencephalopathy in an Infant Associated With Illicit Fentanyl Exposure
- Biomarkers for diagnosis and prognosis of myelin oligodendrocyte glycoprotein antibody-associated disease - review article
- The future of biomarkers for vascular contributions to cognitive impairment and dementia (VCID): proceedings of the 2025 annual workshop of the Albert research institute for white matter and cognition
- Targeting CD38 to alleviate brain endothelial cell dysfunction and cognitive impairment in vascular dementia

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The disease is largely confined to the white matter. Most of these lesions are caused by demyelinating disease.

Appear as white matter with low density on CT or low signal on T1WI MRI, and high intensity on T2 weighted image. Usually does not enhance. Unlike a stroke, changes tend to spare the cortex. Conditions such as metabolic derangements, leukoaraiosis, etc. tend to produce fairly symmetric findings.

The folate-antagonist methotrexate (HD-MTX) is integral to induction chemotherapy for Primary central nervous system lymphoma; however, it can be associated with leukoencephalopathy. Methylenetetrahydrofolate-reductase (MTHFR) is involved in intracellular folate depletion.

Karschnia et al. assessed whether MTHFR polymorphisms affect the risk for leukoencephalopathy.

They retrospectively searched the database at the Massachusetts General Hospital for newly diagnosed PCNSL treated with HD-MTX (without radiotherapy nor intrathecal chemotherapy).

Among 68 PCNSL patients, MTHFR polymorphisms were found in 60 individuals (88.2%) including a 677C→T genotype, a 1298A→C genotype, or a combined 677C→T/1298A→C genotype. Neither MTX clearance nor response to induction therapy was affected by specific genotypes, and complete response was achieved in 72.1% of patients by HD-MTX-based induction. However, the 1298A→C genotype was associated with increased frequency and severity of leukoencephalopathy over time (odds ratio: 4.0, CI 1.5-11.4). Such genotype predicted treatment-induced leukoencephalopathy with a sensitivity of 71.0% and a specificity of 62.2% (AUC: 0.67, CI 0.5-0.8; p=0.019). While progression-free survival did not differ in genotype-based subgroups, overall survival was lower for the 1298A→C

genotype.

The MTHFR 1298A→C genotype may serve to identify PCNSL patients at elevated risk for HD-MTX-induced leukoencephalopathy. This appears to translate into reduced survival, potentially due to decreased functional status [1)].

Clinical features

The clinical features of leukoencephalopathy can vary depending on the specific type of leukoencephalopathy, its underlying cause, and the areas of the brain affected. Here are some general clinical features that may be associated with leukoencephalopathy:

Neurological Symptoms: Leukoencephalopathy often presents with a range of neurological symptoms, which may include:

Cognitive Impairment: Memory problems, difficulties with attention, and other cognitive deficits.

Motor Dysfunction: Weakness, spasticity, difficulty coordinating movements, and changes in muscle tone.

Balance and Coordination Issues: Ataxia (uncoordinated movements) and problems with balance.

Behavioral and Psychiatric Symptoms: Some forms of leukoencephalopathy may manifest with behavioral or psychiatric symptoms, such as mood swings, depression, anxiety, or personality changes.

Speech and Language Difficulties: Changes in speech and language abilities, including slurred speech, difficulties articulating words, or language impairment.

Visual Disturbances: Visual symptoms may include changes in vision, optic nerve damage, or visual field defects.

Headache: Persistent or severe headaches may occur, although this is not a universal symptom.

Seizures: In some cases, individuals with leukoencephalopathy may experience seizures.

Progressive Symptoms: Many leukoencephalopathies are progressive, meaning that symptoms worsen over time. However, the rate of progression can vary.

Incoordination and Gait Abnormalities: Difficulties with walking, unsteady gait, and frequent falls may be observed.

It's crucial to note that the clinical features can be highly variable, and the specific manifestations depend on the underlying cause of the leukoencephalopathy. Some common causes of leukoencephalopathy include genetic disorders, metabolic conditions, autoimmune diseases, infections, and vascular abnormalities.

Diagnosis

Diagnosing leukoencephalopathy often involves a combination of clinical evaluation, neuroimaging studies (such as MRI or CT scans), and, in some cases, cerebrospinal fluid analysis.

Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is a key diagnostic tool used in the evaluation of leukoencephalopathy.

MRI provides detailed images of brain structures and can reveal changes in the white matter, helping in the diagnosis and characterization of leukoencephalopathy.

Here's how MRI is used in the context of leukoencephalopathy:

Detection of White Matter Changes:

MRI is highly sensitive in detecting changes in the white matter, including areas of demyelination, gliosis, or other abnormalities associated with leukoencephalopathy. The images obtained through MRI allow for a detailed examination of the brain's structure, helping to identify areas of abnormal signal intensity. Differentiation of Lesions:

MRI helps differentiate between various types of leukoencephalopathies and can assist in narrowing down potential underlying causes, such as genetic disorders, metabolic abnormalities, or inflammatory conditions. Assessment of Lesion Distribution:

The distribution and pattern of white matter lesions observed on MRI may provide clues about the specific leukoencephalopathy and its potential etiology. Quantitative MRI Techniques:

Advanced MRI techniques, such as diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI), can provide quantitative information about the microstructure of white matter tracts.

These techniques may help in assessing the extent of damage and the integrity of neural pathways.

Follow-up and Monitoring:

Serial MRI scans are often used to monitor disease progression over time. Changes in the appearance of white matter lesions on follow-up MRI can provide valuable information about the course of the disease.

It's important to note that while MRI is a powerful tool, the interpretation of images requires expertise, and the diagnosis of leukoencephalopathy is typically made in conjunction with clinical findings, patient history, and sometimes additional diagnostic tests, such as genetic testing or cerebrospinal fluid analysis.

Laboratory tests

While there is no specific laboratory test that can definitively confirm leukoencephalopathy, certain tests may be used to support the diagnosis and identify potential underlying causes. The specific tests ordered will depend on the suspected cause of leukoencephalopathy and the individual patient's symptoms. Here are some laboratory tests that may be considered:

Complete Blood Count (CBC): This test can help assess for anemia, infections, or other blood-related abnormalities.

Inflammatory Markers: Tests such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) may be used to evaluate signs of inflammation.

Basic Metabolic Panel: An assessment of electrolyte levels, kidney function, liver function, and other metabolic parameters.

Vitamin B12 Levels: Vitamin B12 deficiency can cause neurological symptoms, and checking B12 levels can be relevant, especially if a deficiency is suspected.

Autoimmune Markers: Depending on the clinical presentation, tests for autoimmune markers, such as antinuclear antibodies (ANA), may be considered.

Infectious Disease Markers: Specific tests for infections that can affect the central nervous system, such as JC virus (associated with progressive multifocal leukoencephalopathy), may be conducted.

Thyroid function test

Thyroid dysfunction can have neurological manifestations and thyroid function tests may be included in the evaluation.

Thyroid-Stimulating Hormone (TSH):

TSH is produced by the pituitary gland and stimulates the thyroid gland to release thyroid hormones (T3 and T4). High TSH levels may indicate hypothyroidism (underactive thyroid), while low levels may suggest hyperthyroidism (overactive thyroid).

Free Thyroxine (Free T4):

T4 is one of the primary thyroid hormones. Free T4 represents the portion of T4 that is not bound to proteins in the blood and is considered the biologically active form. Abnormal levels of Free T4 can indicate thyroid dysfunction. Total Thyroxine (Total T4):

Total T4 includes both the free and protein-bound forms of T4. It provides a broader view of the total amount of T4 in the blood. Free Triiodothyronine (Free T3):

T3 is another thyroid hormone, and Free T3 represents the unbound and biologically active form. Free T3 levels are important in assessing thyroid function. Total Triiodothyronine (Total T3):

Total T3 includes both the free and protein-bound forms of T3. Like Total T4, it provides a broader view of the total amount of T3 in the blood. Thyroid Antibodies:

Tests for antibodies such as anti-thyroid peroxidase antibodies (TPOAb) and anti-thyroglobulin antibodies (TGAb) help diagnose autoimmune thyroid disorders, including Hashimoto's thyroiditis and Graves' disease.

Genetic Testing

In cases where a genetic cause is suspected, genetic testing may be ordered to identify mutations associated with leukoencephalopathy.

Here are key points regarding genetic testing for leukoencephalopathy:

Indications for Genetic Testing:

Genetic testing may be considered when there is suspicion of an underlying genetic cause based on clinical symptoms, family history, or specific features observed through neuroimaging. Types of Genetic Testing:

Targeted Gene Testing: Analyzes specific genes known to be associated with leukoencephalopathy. This approach is suitable when there is a clear suspicion based on clinical features. Panel Testing: Examines a set of genes associated with leukoencephalopathy or related neurological conditions. This broader approach is useful when the specific gene is not known. Whole Exome Sequencing (WES) or Whole Genome Sequencing (WGS): Comprehensive testing that analyzes the entire exome or genome, respectively. These approaches are considered when there is a high degree of clinical and genetic heterogeneity. Hereditary Leukoencephalopathies:

Many leukoencephalopathies have a genetic basis, and genetic testing is crucial for diagnosing hereditary forms of the condition. Examples include leukodystrophies, which are a group of rare genetic disorders characterized by abnormalities in the myelin, the protective covering of nerve fibers. Genetic Counseling:

Genetic counseling is recommended before and after genetic testing. It involves discussions about the purpose of testing, potential results, and the implications for the individual and their family. Counselors help individuals understand the genetic basis of the condition, discuss inheritance patterns, and provide support in decision-making. Interpretation of Results:

Genetic testing results are interpreted by geneticists and genetic counselors in the context of the individual's clinical presentation and family history. Results may include the identification of pathogenic mutations, variants of uncertain significance (VUS), or no identified mutations. Implications for Treatment and Management:

Genetic testing results can influence treatment decisions, inform prognosis, and guide management strategies. In some cases, there may be specific interventions or therapies targeting the underlying genetic cause.

CSF analysis

Can be a valuable tool in the evaluation of various neurological disorders, including leukoencephalopathy. Here are some aspects of CSF analysis as it relates to leukoencephalopathy:

1. Purpose of CSF Analysis:

CSF analysis helps assess the composition of the cerebrospinal fluid, which can provide insights into the presence of infection, inflammation, bleeding, or other abnormalities affecting the central nervous system. 2. Indications for CSF Analysis in Leukoencephalopathy:

CSF analysis may be recommended when there is suspicion of an infectious or inflammatory component contributing to leukoencephalopathy. It is particularly useful in cases where neuroimaging

findings are inconclusive, and additional information is needed to guide diagnosis and treatment. 3. Procedure:

A lumbar puncture (spinal tap) is the most common method for obtaining a CSF sample. During this procedure, a thin needle is inserted into the spinal canal in the lower back to collect a small amount of CSF. 4. CSF Parameters:

Cell Count: Elevated white blood cell count in the CSF may indicate inflammation or infection. Protein Levels: Increased protein levels may be associated with various neurological conditions, including inflammatory processes. Glucose Levels: Abnormal glucose levels may suggest infectious or inflammatory processes. 5. Infectious Causes:

CSF analysis can help identify the presence of infectious agents such as bacteria, viruses, or fungi. Specific tests for these agents can be performed on the CSF sample. 6. Oligoclonal Bands:

Oligoclonal bands may be present in the CSF of individuals with certain inflammatory or demyelinating disorders, providing additional information in the context of leukoencephalopathy. 7. Differential Diagnosis:

CSF analysis helps differentiate between infectious, inflammatory, and other potential causes of neurological symptoms. It's important to note that CSF analysis is just one component of the diagnostic process for leukoencephalopathy. It is typically used in conjunction with clinical evaluation, neuroimaging (such as MRI), and, in some cases, genetic testing.

If a lumbar puncture is being considered, the decision should be made by a neurologist or another healthcare professional based on the specific clinical presentation and suspected underlying causes. Interpretation of CSF results requires expertise, and collaboration between neurologists and clinical laboratory professionals is essential for accurate diagnosis and appropriate management.

Differential diagnosis

anoxia/ischemia

demyelinating disease

b) ADEM (intoxication: cyanide, organic solvents, carbon monoxide

vitamin deficiencies: B12 with subacute combined degeneration

infectious, especially viral: a) progressivemultifocalleukoencephalopathy(PML)

b) herpesvaricella-zosterleukoencephalitis

c) HIV infection (AIDS): perivascular pattern of demyelination

d) cytomegalovirusinfection

e) Creutzfeldt-Jakobdisease:smallandperivasculardemyelination

metabolic derangements: hyponatremia, excessively rapid correction of hyponatremia (causing osmotic myelinolysis)

hereditary: metachromatic leukodystrophy, adult-onset Schilder’s disease

leuko-araiosis

multiple myeloma

lowgrade(WHOgradeIIinfiltrating)glioma

The term Leukoencephalopathy is a broad term for leukodystrophy-like diseases.

It is applied to all brain white matter diseases, whether their molecular cause is known or not. It can refer specifically to any of these diseases:

Progressive multifocal leukoencephalopathy

Toxic leukoencephalopathy

Leukoencephalopathy with vanishing white matter

Leukoencephalopathy with neuroaxonal spheroids

Reversible posterior leukoencephalopathy syndrome

Megalencephalic leukoencephalopathy with subcortical cysts.

It can also refer to gene MLC1 or Megalencephalic leukoencephalopathy with subcortical cysts 1, a human gene related to the former disease.

Hypertensive leukoencephalopathy

The classification of leukoencephalopathies is a matter of debate. Some authors divide leukoencephalopathies into hereditary disorders and acquired disorders. The hereditary demyelinating disorders are then classified according to the localization of the underlying metabolic defect, and they include the Leukodystrophies when myelin growth is the underlying problem.

The acquired demyelinating disorders are classified according to their underlying causes into five groups: noninfectious–inflammatory, infectious–inflammatory, toxic–metabolic, hypoxic–ischemic (vascular problems like Binswanger's disease), and traumatic.

This classification is diffuse sometimes. For example CADASIL is at the same time hereditary and hypoxic.

Case reports

A 56-year-old right-handed woman was successfully treated by coil embolisation for a large unruptured paraclinoid aneurysm of the left internal carotid artery. Though she was discharged on day 3 after the intervention with uneventful clinical course, she was rehospitalised for continuous headache and right upper limb weakness 2 weeks after the treatment. Subsequent progression of cognitive dysfunction and right hemiparesis were observed. Repeated MRI revealed diffuse leucoencephalopathy within the ipsilateral brain hemisphere. Clinical course, serological examination,

and radiological findings were consistent with localised hypocomplemental vasculitis caused by delayed hypersensitivity reaction. Immunosuppressive treatments using prednisolone successfully improved her symptoms. After a washout period for immunosuppressant, skin reaction test was performed and revealed polyglycolic-polylactic acid, coating material of the coil, positive for delayed allergic reaction. Given the increased frequency of endovascular treatment for unruptured aneurysms, even such a rare complication should be recognised and treated properly to avoid neurological sequelae [2)].

Treatment

The treatment of leukoencephalopathy depends on the underlying cause and the specific type of leukoencephalopathy. Leukoencephalopathy encompasses a diverse group of disorders with various etiologies, including genetic, metabolic, autoimmune, infectious, and vascular factors. Therefore, the management approach is often tailored to address the specific factors contributing to the condition.

Genetic Leukoencephalopathies:

Symptomatic Treatment: In many cases, treatment focuses on managing symptoms and providing supportive care. Physical therapy, occupational therapy, and speech therapy may be beneficial to address motor and cognitive symptoms. Genetic Counseling: For hereditary leukoencephalopathies, genetic counseling is essential to discuss the genetic basis of the condition, potential inheritance patterns, and family planning. Metabolic Leukoencephalopathies:

Dietary Modifications: In cases where leukoencephalopathy is associated with metabolic disorders, dietary modifications or specific nutritional interventions may be recommended. Enzyme Replacement Therapy: Some metabolic disorders may benefit from enzyme replacement therapy. Autoimmune Leukoencephalopathies:

Immunosuppressive Therapy: For autoimmune forms of leukoencephalopathy, immunosuppressive medications may be prescribed to modulate the immune response and reduce inflammation. Plasma Exchange (Plasmapheresis): In certain cases, plasma exchange may be considered to remove harmful antibodies from the bloodstream. Infectious Leukoencephalopathies:

Antiviral or Antibiotic Therapy: If leukoencephalopathy is caused by an infectious agent, antiviral or antibiotic medications may be used to target the specific pathogen. Supportive Care: Supportive care may be necessary to manage complications and optimize overall health. Vascular Leukoencephalopathies:

Vascular Risk Factor Management: Addressing and managing vascular risk factors such as hypertension, diabetes, and hyperlipidemia is crucial in vascular leukoencephalopathy. Antiplatelet or Anticoagulant Therapy: In some cases, antiplatelet or anticoagulant medications may be considered to prevent further vascular events. Symptomatic Treatment:

Medications: Symptomatic treatment may involve medications to manage specific symptoms, such as pain, spasticity, or cognitive impairment. Rehabilitation Therapies: Physical therapy, occupational therapy, and speech therapy can be valuable in improving functional abilities and enhancing quality of life. It's important to emphasize that the management of leukoencephalopathy is often multidisciplinary, involving collaboration between neurologists, geneticists, metabolic specialists, infectious disease specialists, and other healthcare professionals. Treatment plans are individualized based on the underlying cause, the progression of the condition, and the specific needs of the patient.

Patients and their families should work closely with their healthcare team to understand the nature of the condition, explore available treatment options, and address supportive care needs. Regular follow-up and ongoing communication with healthcare providers are crucial for monitoring disease progression and adjusting the treatment plan as needed.

1)
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2)
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