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Autoimmune Neurology of the Central Nervous System

W. Oliver Tobin, MBBCh, BAO, PhD; Sean J. Pittock, MD. Continuum (Minneap Minn). June 2017;23(3 Neurology of Systemic Disease):627–653.

Abstract

Purpose of Review:

This article reviews the rapidly evolving spectrum ofautoimmune neurologic disorders with a focus on those that involve the central nervous system, providing an understanding of how to approach the diagnostic workup of patients presenting with central nervous system symptoms or signs that could be immune mediated, either paraneoplastic or idiopathic, to guide therapeutic decision making.

Recent Findings:

The past decade has seen a dramatic increase in the discovery of novel neural antibodies and their targets. Many commercial laboratories can now test or these antibodies, which serve as diagnostic markers of diverse neurologic disorders that occur on an autoimmune basis. Some are highly specific for certain cancer types, and the neural antibody profiles may help direct the physician's cancer search.

Summary:

The diagnosis of an autoimmune neurologic disorder is aided by the detection of an objective neurologic deficit (usually subacute in onset with a luctuating course), the presence of a neural autoantibody, and improvement in the neurologic status after a course of immunotherapy. Neural autoantibodies should raise concern for a paraneoplastic etiology and may inform a targeted oncologic valuation (eg, *N*-methyl-D-aspartate [NMDA] receptor antibodies are associated with teratoma, antineuronal nuclear antibody type 1 [ANNA-1, or anti-Hu] are associated with small cell lung cancer). MRI, EEG, functional imaging, videotaped evaluations, and neuropsychological evaluations provide objective evidence of neurologic dysfunction by which the success of immunotherapy may be measured. Most treatment information emanates from retrospective case series and expert opinion. Nonetheless, early intervention may allow reversal of deficits in many patients and revention of future disability.

Key Points

- Unless a high degree of suspicion exists for a single antigenic target in patients presenting with neurologic disorders, such as in neuromyelitis optica, the authors advocate a global screen for a number of potential causative antibodies.

- Indirect tissue immunofluorescence and immunohistochemistry serve as excellent screening tools for the presence of neural antibodies.
- Western blot is best suited for detecting antibodies that bind to cytosolic or nuclear antigens.
- A high rate of false-positive results for neuromyelitis optica IgG exists with use of enzyme-linked immunosorbent assays.
- Ideally, paired samples of serum and CSF should be tested in patients with suspected autoimmune neurologic disease.
- Paraneoplastic antibodies are more strongly predictive of tumor type than of a particular clinical syndrome.
- Some antibody clusters, when present, should alert the clinician to a high probability of systemic malignancy.
- The presence of risk factors for malignancy, such as smoking or a family history, or the presence of a neural antibody with an oncologic association should prompt an evaluation for malignancy.
- Cytologic and molecular classification systems have been proposed to describe antibody-associated diseases.
- The most recent iteration of the diagnostic criteria for neuromyelitis optica spectrum disorder emphasizes the importance of detecting neuromyelitis optica IgG with a sensitive and specific assay in the correct clinical context (optic neuritis, brainstem or area postrema syndrome, myelitis, symptomatic narcolepsy, or diencephalic syndrome with neuromyelitis optica spectrum disorder– typical brain MRI).
- The entity of seronegative neuromyelitis optica spectrum disorder requires a more stringent set of criteria to be filled in the absence of neuromyelitis optica IgG detection.
- Myelin oligodendrocyte glycoprotein–specific antibodies are associated with a distinct phenotype of central nervous system demyelinating disease, including conus-predominant myelitis and bilateral optic neuritis, often occurring simultaneously, associated with ''cotton wool'' brain lesions with poorly defined margins.
- Antibodies to the glial fibrillary acidic protein-α isoform have recently been described as a biomarker of a steroid-responsive autoimmune meningoencephalomyelitis.
- Antibodies directed against targets at or near the *N*-methyl-D-aspartate receptor account for the second most common form of autoimmune encephalitis after acute disseminated encephalomyelitis.
- Viral herpes simplex type 1 encephalitis can be followed by *N*-methyl-D-aspartate receptor encephalitis.
- Rapid-onset cognitive impairment, in particular if associated with a personal or family history of autoimmunity or abnormal CSF findings, should prompt consideration of an autoimmune cause.
- Any treatment of cognitive impairment with immunotherapy should be accompanied by careful objective documentation of cognitive deficits before embarking on an immunotherapy trial to allow an objective demonstration of any treatment response.
- Features that should prompt the clinician to consider an autoimmune cause for seizures include a new-onset seizure disorder with frequent events; new-onset refractory status epilepticus; multiple event types in one individual; antiepileptic drug treatment resistance; CSF abnormalities; and a history of malignancy, smoking, or autoimmune disease.
- CSF abnormalities are not invariable in autoimmune conditions, so the presence of a normal CSF should not dissuade the clinician from considering autoimmune causes.
- Features that should prompt the clinician to consider an autoimmune cause for a movement disorder include a subacute onset and a widespread distribution of symptoms and signs, including involvement of the trunk and head as well as extremities.

- A family history of autoimmune disease, such as autoimmune thyroid disease, lupus, or rheumatoid arthritis, may suggest a predisposition toward neuromyelitis optica spectrum disorder or other antibody-mediated myelopathies.
- The clinical course of a myelopathy can yield clues to the differential diagnosis, with typical transverse myelitis being of subacute onset over days to weeks and conditions such as neurosarcoidosis and paraneoplastic myelopathies having a progressive course from onset.
- The goal of initial treatment of neuromyelitis optica is to determine the maximum response that can be obtained with immunotherapy.
- In patients with a suspected autoimmune neurologic syndrome with no therapeutic response to immunotherapy, the diagnosis should be reevaluated.
- Objective measures of disability and treatment response should be obtained before and after treatment of suspected autoimmune neurologic conditions.
- In patients treated with IVIg, false-positive antibody results can be seen due to the transfused immunoglobulin.
- Patients who have a clinical response when treated with azathioprine tend to have a
- 5-femtoliter or more elevation in mean corpuscular volume in response to treatment.
- Therapeutic drug monitoring is not routinely recommended in patients treated with mycophenolate mofetil; however, in patients with loss of disease control, mycophenolic acid serum levels are useful to guide treatment toward dose escalation or drug switching.

Neurologic Complications of Cardiac and Aortic Disease

James P. Klaas, MD. Continuum (Minneap Minn). June 2017;23(3 Neurology of Systemic Disease):654–668.

Abstract

Purpose of Review:

This article discusses neurologic complications that can arise from cardiac and aortic disease and dysfunction.

Recent Findings:

Advances in the care of patients with cardiac or aortic disease include the use of prolonged cardiac monitoring in cryptogenic stroke and the pproval of the use of left atrial appendage closure devices for stroke prevention in patients with atrial fibrillation who are not candidates for anticoagulation. Continuing controversy surrounds patent foramen ovale closure, and new evidence indicates that cognitive impairment following coronary artery bypass grafting surgery may be less common than previously thought.

Summary:

Dysfunction of the cardiovascular system can cause serious neurologic injury. In some cases, both the initial presenting symptom and the most serious damage done by cardiac or aortic dysfunction may be neurologic. Prompt recognition of the symptoms, combined with recent

advances in both cardiology and neurology, may permit more accurate diagnoses, more effective treatment, and less injury to patients.

Key Points

- Prolonged cardiac monitoring should be considered for patients with cryptogenic stroke.
- Left atrial appendage closure is an emerging stroke prevention treatment option for patients with atrial fibrillation for whom anticoagulation is problematic.
- Randomized controlled trials have not shown a benefit of patent foramen ovale closure over medical therapy for prevention of recurrent stroke or transient ischemic attack.
- Infective endocarditis frequently causes neurologic complications. Stroke is the most common.
- The risk of neurologic complications from infective endocarditis declines rapidly with the initiation of antibiotics.
- Atrial myxomas and papillary fibroelastomas are the most common cardiac tumor types and the types most frequently associated with neurologic complications.
- Atrial fibrillation and heart failure may be independent risk factors for dementia.
- Cognitive impairment as a consequence of coronary artery bypass grafting surgery may be less common than previously thought.
- Aortic aneurysms can cause direct neurologic dysfunction by compressing neuronal structures, such as the left recurrent laryngeal nerve.
- Aortic dissections can be painless, and the initial presenting symptom of a dissection may be neurologic.
- Stroke is the most common neurologic complication of a type A aortic dissection.
- Development of a syndrome resembling progressive supranuclear palsy can rarely develop after surgical repair of ascending aortic dissection or aneurysm.
- Aortic plaques are an underrecognized cause of ischemic stroke.
- Consider screening for cerebral aneurysms in patients with coarctation of the aorta.

Neurologic Complications of Lymphoma, Leukemia, and Paraproteinemias

Michelle L. Mauermann, MD, FAAN. Continuum (Minneap Minn). June 2017;23(3 Neurology of Systemic Disease):669–690.

Abstract

Purpose of Review:

This article reviews the spectrum of neurologic complications associated with lymphoma, leukemia, and paraproteinemic disorders. While leptomeningeal metastasis is the most common complication of lymphoma and leukemia and peripheral neuropathy is the most common complication of paraproteinemic disorders, clinicians need to be familiar with the diverse neurologic complications of these disorders.

Recent Findings:

Lymphomatous nervous system involvement can be difficult to diagnose, especially when it is the presenting symptom. CSF cytology and flow cytometry, as well as the imaging pattern, assist in diagnosis. Neurologic complications are less common in Hodgkin lymphoma; however, some unique paraneoplastic syndromes are associated with Hodgkin lymphoma, including primary central nervous system angiitis, limbic encephalitis, and cerebellar degeneration. Recent reports suggest that anti–metabotropic glutamate receptor 5 (mGluR5) antibodies are associated with limbic encephalitis and that anti-Tr antibodies are associated with cerebellar degeneration in Hodgkin lymphoma. Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome is often misdiagnosed as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). A lambda protein, thrombocytosis, and elevated vascular endothelial growth factor (VEGF) can all be helpful clues in diagnosis. Early recognition is important, as the neuropathy responds to radiation therapy or chemotherapy.

Summary:

Neurologic involvement can occur throughout the disease course in lymphoma and leukemia, including at presentation, with systemic progression, and at relapse. In paraproteinemias, the peripheral neuropathy phenotype, monoclonal protein type, and associated autonomic and systemic features aid in identification of an underlying plasma cell disorder.

Key Points

- The majority of patients with non-Hodgkin lymphoma present with nervous system involvement during treatment or shortly following completion.
- Lymphomatous infiltration of the leptomeninges is the most common neurologic complication of non-Hodgkin lymphoma.
- The identification of Reed-Sternberg cells in the CSF is the definitive test for leptomeningeal metastases from Hodgkin lymphoma.
- Epidural metastases occur in 2% to 5% of patients with non-Hodgkin lymphoma and develop from a paravertebral mass invading the epidural space through the intervertebral foramina.
- The MRI in lymphomatosis cerebri demonstrates diffuse white matter disease with little or no contrast enhancement.
- Neurolymphomatosis most frequently involves the cauda equina or sciatic nerve and is
- very painful.
- Treatment of neurolymphomatosis consists of systemic chemotherapy with high-dose IV methotrexate.
- Limbic encephalitis and paraneoplastic cerebellar degeneration are paraneoplastic syndromes seen in Hodgkin lymphoma.
- Limbic encephalitis in Hodgkin lymphoma is associated with antibodies to metabotropic glutamate receptor 5, and paraneoplastic cerebellar degeneration in Hodgkin lymphoma is associated with anti-Tr antibodies.
- Primary angiitis of the central nervous system presents with headache, encephalopathy, and stroke.
- Intravascular lymphoma has a multifocal presentation with systemic symptoms and is due to occlusion of small vessels by lymphoma cells.
- Leptomeningeal metastasis in leukemia is most common in acute lymphoblastic leukemia, and patients are routinely given central nervous system prophylaxis.

- Extramedullary myeloid tumors may be the initial presentation of acute myelogenous leukemia or chronic myelogenous leukemia and frequently affect the thoracic spine, causing spinal cord compression.
- Intracranial hemorrhage is the second most common complication in adult patients with hematologic malignancies, and the risk is highest in acute leukemia.
- Paraproteinemias affect 3% to 4% of the population older than the age of 50 and more than 5% of the population older than the age of 70.
- Peripheral neuropathy is a common complication of paraproteinemias.
- Epidural spinal cord compression occurs in 6% of patients with multiple myeloma and typically presents with back pain with radicular features or lower limb weakness.
- Hyperviscosity can occur in multiple myeloma and Waldenström macroglobulinemia and is treated with plasma exchange in addition to systemic therapy.
- Bing-Neel syndrome is due to perivascular infiltration of lymphocytes and plasma cells surrounding Virchow-Robin spaces (perivascular spaces) and leptomeninges.
- Stroke occurs in 10% of patients with polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome and is associated with thrombocytosis and bone marrow plasmacytosis.
- POEMS syndrome should be considered in patients with treatment-refractory chronic inflammatory demyelinating polyradiculoneuropathy with a lambda monoclonal protein.
- AL amyloid neuropathy causes a length-dependent neuropathy with prominent early involvement of somatic and autonomic fibers.
- AL amyloid myopathy often has a normal creatine kinase.
- IgM neuropathy (distal acquired demyelinating symmetric neuropathy) often presents in older men with sensory ataxia.

Rheumatology and Neurology

Elliot L. Dimberg, MD, FAAN. Continuum (Minneap Minn). June 2017;23(3 Neurology of Systemic Disease):691–721.

Abstract

Purpose of Review:

This article reviews the various rheumatologic disorders that have neurologic complications and manifestations.

Recent Findings:

Recent advances have improved the understanding of the true epidemiology of many rheumatologic diseases and their complications. Many years of observation have clarified findings even in rarer disorders. Classification and diagnostic criteria have been updated and validated. As newer pharmacologic agents have become available, new information regarding efficacy and toxicity has emerged.

Summary:

Rheumatologic disorders are common, as can be their neurologic complications. In many instances, these complications are treatable, but clinicians' understanding of the underlying disorder, its neurologic risks, and the risk of therapy is required.

Key Points

- Rheumatologic disorders are common and can present with central or peripheral nervous system manifestations; they can also develop at any time during the disease course.
- Central nervous system manifestations of neuropsychiatric lupus are more common than peripheral nervous system presentations. Headache, mood disorders, cognitive dysfunction, seizures, and cerebrovascular disease are most common.
- Chronic inflammation is implicated in accelerated atherosclerosis; in systemic lupus erythematosus, this manifests as increased risk for cardiovascular and cerebrovascular disease independent of other vascular risk factors.
- Rheumatoid arthritis is the most common inflammatory arthritis and affects 1% to 2% of the population. Central nervous system complications are rare but more common with seropositivity, including anti–cyclic citrullinated peptide antibodies, rheumatoid factor, antinuclear antibody, and C-reactive protein, and with longer disease duration.
- Cervical spine subluxation is a common complication of rheumatoid arthritis, with atlantoaxial subluxation being most common, leading to progressive myelopathy; surgical stabilization may be necessary to prevent progression.
- Patients with rheumatoid arthritis may develop vasculitis, which can cause a vasculitic neuropathy, including mononeuritis multiplex or a distal symmetric sensory or sensorimotor peripheral neuropathy; this is an independent predictor of mortality.
- Sensory neuronopathy (ganglionopathy) is a classic presentation of sjögren syndrome, manifesting with non–length-dependent sensory loss, pseudoathetosis, and ataxia due to lymphocytic inflammation of the dorsal root ganglion.
- Longitudinally extensive demyelinating lesions of the spinal cord in patients with Sjögren syndrome are considered to be reflective of primary neuromyelitis optica rather than a central nervous system complication of Sjögren syndrome itself.
- Inflammatory myopathy in the setting of systemic sclerosis is more frequent with anti-PM/Scl antibody positivity; if seen in diffuse cutaneous systemic sclerosis, corticosteroids should be avoided as their use can lead to renal crisis.
- Numerous systemic vasculitides exist, but primary angiitis of the central nervous system and nonsystemic vasculitic neuropathy represent two forms of vasculitis isolated to the central nervous system and peripheral nervous system, respectively.
- Biopsy is the diagnostic procedure of choice for primary angiitis of the central nervous system and nonsystemic vasculitic neuropathy, but its sensitivity is not 100% in either case, requiring high clinical suspicion.
- The vasculitides are categorized according to the size of vessels involved, although neurologic involvement is not specific to the vessel size involved.
- The presence of mixed cryoglobulinemia in the setting of peripheral neuropathy should prompt a search for hepatitis C infection, although a minority of patients with hepatitis C will develop neuropathy.
- Antiphospholipid antibodies are prothrombotic and can cause false-positive Venereal Disease Research Laboratory and rapid plasma reagin tests; they also occur in systemic lupus erythematosus and are associated with other, nonstroke-related neurologic manifestations.
- Pachymeningitis is a classic presentation of IgG4-related disease but requires biopsy confirmation with specific pathologic criteria met for the diagnosis.
- Tumor necrosis factor α inhibitor administration may be complicated by demyelination of the central nervous system, peripheral nervous system, or both.

Renal Disease and Neurology

Sara E. Hocker, MD. Continuum (Minneap Minn). June 2017;23(3 Neurology of Systemic Disease):722–743.

Abstract

Purpose of Review:

Neurologic dysfunction is prevalent in patients with acute and chronic renal disease and may affect the central nervous system, peripheral nervous system, or both. Neurologic manifestations may result directly from the uremic state or as a consequence of renal replacement therapy. Early recognition of neurologic dysfunction may provide opportunities for intervention and reduced morbidity.

Recent Findings:

Advances in the understanding of neurologic complications of renal disease and its treatments have led to more widespread recognition and earlier identification of encephalopathy syndromes such as cefepime neurotoxicity and posterior reversible encephalopathy syndrome (PRES), dramatic reductions in the incidence of dialysis disequilibrium syndrome and dialysis dementia, and improved survival in disorders such as von Hippel-Lindau disease and thrombotic thrombocytopenic purpura.

Summary:

This article summarizes the conditions that affect both the renal and the nervous systems, the effects of renal failure on the nervous system, and the neurologic complications of dialysis.

Key Points

- Neurologicmanifestations of autosomal dominant polycystic kidney disease include saccular cerebral aneurysms, cervicocephalic artery dissections, and dolichoectasia.
- Screening for intracranial aneurysms in autosomal dominant polycystic kidney disease is recommended in patients with a family history of intracranial aneurysm or subarachnoid hemorrhage, previous intracranial aneurysm rupture, high-risk professions (eg, airline pilots), or patient anxiety despite adequate information.
- Neurologicmanifestations of von Hippel-Lindau disease include retinal and central nervous system hemangioblastomas, ataxia, syringobulbia, and syringomyelia.
- Early detection of tumors through presymptomatic screening of at-risk individuals may enhance overall outcome in patients with von Hippel-Lindau disease.
- By middle age, most patients with Fabry disease develop cardiovascular or cerebrovascular disease, which may manifest as transient ischemic attacks, cerebral infarctions, or dolichoectasia.
- In the presence of delayed recognition of thrombotic thrombocytopenic purpura, the pentad of thrombocytopenia, fever, acute renal failure, microangiopathic hemolytic anemia, and neurologic findings will develop and lead to death; however, since the use of therapeutic plasma exchange has become routine, the presence of the full pentad has become rare.
- Hemolytic uremic syndrome is a syndrome of microangiopathic hemolytic anemia, thrombocytopenia, and renal failure in which seizures, coma, stroke, pyramidal or extrapyramidal syndromes, dysphasia, and cortical blindness may occur.

- Acidosis and alkalosis both can present with neurologic signs, predominantly altered consciousness.
- Neurologicmanifestations of the uremic state include both central nervous system complications (eg, lethargy, encephalopathy, seizures, acute movement disorders, and coma) and peripheral nervous system complications (eg, neuropathy and myopathy).
- Symptoms of uremia are usually alleviated by dialysis or renal transplantation.
- The use of cefepime in the setting of renal failure may result in neurotoxicity, which commonly presents with reduced consciousness, encephalopathy, and myoclonus and less commonly with nonconvulsive status epilepticus.
- A diagnosis of posterior reversible encephalopathy syndrome should be considered when acute neurologic symptoms develop in patients with renal failure, blood pressure fluctuations, autoimmune disorders, use of cytotoxic drugs, or eclampsia.
- Polyneuropathy may result from uremia alone, or it may develop in diseases that involve the kidney, such as diabetes mellitus, vasculitis, connective tissue diseases, and plasma cell dyscrasias.
- Uremic neuropathy is classically a length-dependent, distal, axonal, sensorimotor, large fiber neuropathy.
- Uremic myopathy presents with proximal limb weakness and muscle wasting with bone pain and tenderness, and the progression mirrors the decline of renal function.
- The relative risk of hospitalization for ischemic or hemorrhagic stroke among patients on dialysis is estimated to be fourfold to tenfold higher than that of patients without chronic kidney disease.
- Dialysis disequilibrium syndrome presents with a variable constellation of symptoms, including headache, irritability, blurred vision, nausea, muscle cramps, encephalopathy, and seizures. It may be prevented or alleviated by adding osmotically active solutes to the dialysate and slowing the rate, increasing the frequency, and shortening the duration of dialysis.
- Poor-quality sleep, which has been associated with restless legs syndrome and snoring, has been documented in the majority of patients with end-stage renal disease.
- End-stage renal disease is a risk factor for Wernicke encephalopathy due to a combination of reduced oral intake and increased loss of the water-soluble vitamin thiamine during dialysis.
- Patients who are dependent on dialysis are at higher risk for the development of subdural hematoma than the general population due to trauma, uremia-related coagulation disturbances, use of anticoagulants for dialysis, and use of rapid ultrafiltration and hypertonic dialysate.
- Mononeuropathies, particularly median neuropathy at the wrist, may be seen in association with dialysis.

Gastroenterology and Neurology

Ronald F. Pfeiffer, MD, FAAN. Continuum (Minneap Minn). June 2017;23(3 Neurology of Systemic Disease):744–761.

Abstract

Purpose of Review:

Just as gastrointestinal dysfunction may develop in the setting of neurologic disease, neurologic dysfunction may become evident in the setting of gastrointestinal disease. This article describes the range of neurologic features that have been described in three primary gastrointestinal diseases: celiac disease and gluten-related disorders, inflammatory bowel disease, and Whipple

disease. Particular emphasis is placed on the controversial and evolving clinical picture of neurologic dysfunction in disorders of gluten sensitivity.

Recent Findings:

Gluten-related disorders, including both the traditional autoimmunebased celiac disease and the more recently recognized nonautoimmune, nonallergic gluten sensitivity, have been the source of much attention in both medical and lay publications. The possible association between Crohn disease and neurologic disorders also is receiving attention. The recognition that, although Whipple disease is an exceedingly rare disorder, a surprising percentage of the population may be asymptomatic stool carriers of the causative organism makes it important to always be cognizant of the disorder.

Summary:

The range of neurologic dysfunction in gastrointestinal diseases is broad and spans the spectrum from peripheral to central processes. Peripheral neuropathy, myopathy, myelopathy, cerebrovascular events, epilepsy, encephalopathy, and cerebellar dysfunction have all been described. Neurologists should be aware of the possibility that an underlying gastrointestinal disease process may be present in and responsible for the neurologic dysfunction that has prompted referral of an individual for evaluation.

Key Points

- The enteric nervous system contains approximately 100 million neurons, about the same number as the spinal cord.
- Wheat allergy and other allergic gluten-related disorders are characterized by the presence of IgE antibodies.
- Celiac disease is an autoimmune enteropathy involving the adaptive immune system.
- The classic clinical features of celiac disease are diarrhea, malabsorption, weight loss, and gassy distension.
- Gluten sensitivity disorders are not accompanied by anti–tissue transglutaminase antibodies and typically do not display small intestinal pathology.
- The innate immune system may be involved in gluten sensitivity disorders.
- Allergic gluten-related disorders do not display neurologic manifestations.
- Neurologic dysfunction may appear in up to 22.5% of persons with celiac disease.
- Individuals with celiac disease have a 2.5-fold increased risk of developing peripheral neuropathy.
- Purkinje cell loss and lymphocytic infiltration in the cerebellum has been described in gluten ataxia.
- Anti–tissue transglutaminase 6 antibodies have been described in gluten ataxia.
- Patients with gluten ataxia may respond to a gluten-free diet.
- Various neuropsychiatric symptoms may be present in individuals with gluten sensitivity.
- The pathology of ulcerative colitis is confined to the colon; Crohn disease may involve the entire gastrointestinal tract.
- The reported presence of neurologic dysfunction in inflammatory bowel disease ranges from 0.25% to 37.5%.
- Peripheral neuropathy is the most frequent manifestation of neurologic involvement in inflammatory bowel disease.
- Cerebrovascular events, both arterial and venous, are uncommon but potentially devastating neurologic manifestations of inflammatory bowel disease.

- Whipple disease is a multisystem disorder and not simply a gastrointestinal disease.
- Whipple disease is caused by *Tropheryma whippleii*, an Actinobacteria that may dwell in the soil.
- Postmortem examination demonstrates central nervous system involvement in over 90% of patients with Whipple disease, many of whom have no neurologic symptoms.
- Oculomasticatory myorhythmia develops in 20% of patients with Whipple disease and is pathognomonic for the disorder.
- Prolonged 1-year antibiotic treatment of Whipple disease is necessary to prevent relapse.

Liver Disease and Neurology

Robert N. Schwendimann, MD, FAAN; Alireza Minagar, MD, FAAN. Continuum (Minneap Minn). June 2017;23(3 Neurology of Systemic Disease):762–777.

Abstract

Purpose of Review:

Neurologists often encounter patients with acute and chronic liver disease and must be aware of how these diseases can affect the nervous system. This is particularly true when evaluating patients with alterations in cognition and level of consciousness. Wilson disease, while uncommon, is a treatable condition with many neurologic and psychiatric symptoms. Neurologic disorders associated with liver disease may affect not only the brain, but also the spinal cord and peripheral nervous system. This article reviews the association of liver disease and the nervous system and provides new information regarding diagnostic and therapeutic approaches to evaluating patients with liver diseases.

Recent Findings:

Early recognition of hepatic encephalopathy may be possible using a combination of clinical suspicion and various neuropsychological studies. Management of severe hepatic encephalopathy from acute liver failure is important to neurologists involved in neurocritical care. Next-generation genetic testing may aid in the diagnosis of patients suspected of having Wilson disease. The relationship of numerous neurologic findings from hepatocerebral degeneration and from viral hepatitis is more widely recognized.

Summary:

It is important for neurologists to recognize the neurologic symptoms that may occur in patients with acute and chronic liver failure, Wilson disease, and viral hepatitis to inform prompt diagnostic and management decisions.

Key Points

- Hepatic encephalopathy has a wide spectrum of neurologic and psychiatric symptoms ranging from subclinical alterations to coma.
- Hepatic encephalopathy can be caused by acute liver failure, portosystemic shunting with intrinsic liver disease, or chronic liver disease related to cirrhosis and portal hypertension.

- The West Haven criteria for staging of clinical symptoms are a useful way to determine the severity of hepatic encephalopathy. Simpler scales divide hepatic encephalopathy into covert and overt forms.
- Laboratory studies that typically are helpful in patients with more advanced stages of encephalopathy may be of little help in the patient who is cognitively normal or who manifests only minimal hepatic encephalopathy.
- The presence of triphasic waves on EEG recording may be seen in numerous types of metabolic encephalopathies.
- Brain imaging is generally of little use in the diagnosis of hepatic encephalopathy, although patients with chronic liver disease may show T1-weighted hyperintensities in the basal ganglia thought to represent accumulations of manganese.
- Manganese toxicity is believed to be a major factor in the development of symptoms of acquired hepatocerebral degeneration that may mimic many of the symptoms of Wilson disease.
- Hepatic myelopathy must be differentiated from numerous other causes of myelopathy. Liver transplantation may result in some improvement of symptoms.
- Viral hepatitis is a common cause of acute liver failure in developing countries, while in the United States the toxic effect of acetaminophen is the most common cause.
- Aggressive efforts to prevent the development of cerebral edema leading to increased intracranial pressure are necessary to increase the chances of survival in acute liver failure.
- Wilson disease is caused by mutation of the gene ATP7B on chromosome 13q14 coding for the protein ATP7B. Next-generation sequencing of this gene may be less time consuming and more cost effective than older techniques in assessing the presence of this genetic abnormality.
- Kayser-Fleischer rings may be absent in patients with Wilson disease who do not have evidence of neurologic involvement.
- Routine serum copper level is not particularly helpful in screening for Wilson disease since it measures total serum copper, which is bound to ceruloplasmin.
- Perhaps the best single screening test for Wilson disease is the 24-hour urinary copper measurement.
- With early diagnosis and treatment, symptoms of Wilson disease can be controlled. Treatment typically is with drugs such as penicillamine, trientine, and other chelating agents. Oral zinc can also be used to inhibit absorption of copper in the gastrointestinal tract.
- Fifty percent of patients with hepatitis C have mixed cryoglobulinemia.
- Hepatitis C is a worldwide problem that can cause numerous neurologic problems, including cerebrovascular symptoms, problems with cognitive function, inflammatory processes affecting the spinal cord, and peripheral nerve pathology.
- Hepatitis E is an emerging viral infection that may cause neurologic symptoms in up to 5% of cases.

Endocrine Emergencies With Neurologic Manifestations

Makoto Ishii, MD, PhD. Continuum (Minneap Minn). June 2017;23(3 Neurology of Systemic Disease):778–801.

Abstract

Purpose of Review:

This article provides an overview of endocrine emergencies with potentially devastating neurologic manifestations that may be fatal if left untreated. Pituitary apoplexy, adrenal crisis, myxedema coma, thyroid storm, acute hypercalcemia and hypocalcemia, hyperglycemic emergencies (diabetic ketoacidosis and hyperglycemic hyperosmolar state), and acute hypoglycemia are discussed, with an emphasis on identifying the signs and symptoms as well as diagnosing and managing these clinical entities.

Recent Findings:

To identify the optimal management of endocrine emergencies, using formal clinical diagnostic criteria and grading scales such as those recently proposed for pituitary apoplexy will be beneficial in future prospective studies. A 2015 prospective study in patients with adrenal insufficiency found a significant number of adrenal crisis–related deaths despite all study patients receiving standard care and being educated on crisis prevention strategies, highlighting that current prevention strategies and medical management remain suboptimal.

Summary:

Early diagnosis and prompt treatment of endocrine emergencies are essential but remain challenging because of a lack of objective diagnostic tools. The optimal management is also unclear as prospective and randomized studies are lacking. Additional research is needed for these clinical syndromes that can be fatal despite intensive medical intervention.

Key Points

- As endocrine emergencies can be successfully managed if accurately and promptly diagnosed, clinical neurologists should be aware of the neurologic manifestations of endocrine emergencies.
- Pituitary apoplexy is a heterogeneous clinical syndrome characterized by sudden hemorrhage or infarction of the pituitary gland and is most commonly associated with a pituitary adenoma.
- Depending on the extent of hemorrhage, necrosis, and edema, the course of pituitary apoplexy can include very mild symptoms of headache, visual disturbances, or pituitary deficiencies developing slowly over weeks to a true medical emergency presenting with acute onset of blindness, coma, and hemodynamic instability that can result in death if untreated.
- Lumbar puncture has limited utility in differentiating pituitary apoplexy from subarachnoid hemorrhage; however, if bacterial meningitis is suspected, CSF cultures should be obtained.
- Empiric corticosteroid replacement should be initiated for patients with acute pituitary apoplexy with hemodynamic instability, altered consciousness, reduced visual acuity, severe visual field deficits, or signs of hypoadrenalism.
- Adrenal insufficiency can be classified as a primary disorder (eg, autoimmune destruction of the adrenal gland) or a secondary disorder (eg, hypopituitarism caused by pituitary apoplexy) or may result from drug-induced adrenal insufficiency (eg, glucocorticoid withdrawal after chronic exogenous glucocorticoid therapy).

- Adrenal crisis occurs when, during an acutely stressful event, a patient with adrenal insufficiency fails to mount a normal physiologic response of increased endogenous cortisol production and is not adequately compensated with exogenous glucocorticoids.
- Fluid resuscitation and steroid replacement are the main therapies of an adrenal crisis.
- Myxedema coma is typically triggered by a systemic illness, such as a pulmonary or urinary infection; congestive heart failure; stroke; trauma; or certain medications in a patient with previously undiagnosed or untreated hypothyroidism.
- The cardinal hallmarks of myxedema coma are hypothermia and depressed mental status or coma.
- The main goal of treatment of myxedema coma should involve airway protection, thyroid hormone therapy, fluid repletion, empiric hydrocortisone because of the relative risk of adrenal insufficiency, correction of any hyponatremia, and treatment (including empiric antibiotics) of any inciting factors.
- Patients with thyroid storm have variable clinical manifestations, with exaggerated signs and symptoms of thyrotoxicosis accompanied by multiorgan decompensation.
- No set serum thyroxine (T4) or triiodothyronine (T3) criteria exist for diagnosing a thyroid storm, but a full laboratory evaluation including thyroid-stimulating hormone, free T3, and free T4 (even with a normal thyroid-stimulating hormone level) should be conducted in all suspected cases.
- The goals of treatment of thyroid storm are to inhibit new thyroid hormone synthesis, inhibit thyroid hormone release, block the peripheral effect of thyroid hormones, and enhance the clearance of thyroid hormones.
- The most common cause of hypercalcemia is an underlying primary hyperparathyroidism caused by a single benign parathyroid adenoma, but hypercalcemia can result from malignancies, endocrinopathies, granulomatous diseases, immobilization, and medications such as thiazide diuretics and lithium.
- Hypercalcemic crisis usually results from an underlying mild to moderate hypercalcemia that evolves into an acute exacerbation of severe hypercalcemia, often with a known precipitating factor such as an illness or use of thiazide diuretics.
- The overall goals of therapy of a hypercalcemic crisis are to lower calcium levels, rehydrate, increase renal calcium excretion, and decrease osteoclast-mediated bone resorption, followed by definitive curative therapy of the hypercalcemia.
- Disorders of parathyroid hormone and vitamin D are the major causes of hypocalcemia, with acquired hypoparathyroidism as a complication of thyroid and neck surgeries being the most common cause of hypocalcemia in adults.
- Typical central nervous system manifestations of hypocalcemia are encephalopathy and seizures, both of which can be the initial manifestation of the hypocalcemia.
- On examination, tetany or neuromuscular irritability caused by hypocalcemia can be demonstrated by eliciting the Chvostek sign (ipsilateral facial contraction after facial nerve percussion) or Trousseau sign (painful carpopedal spasm after inflating a sphygmomanometer placed on the upper arm above the systolic blood pressure for 3 minutes).
- Treatment for patients with acutely symptomatic hypocalcemia consists of IV calcium given as a bolus, followed by a slow continuous infusion, with the goal of maintaining serum calcium levels in the low-normal range.
- As the brain relies almost entirely on glucose for its energy source, insufficient glucose in the brain can have a wide range of potentially devastating neurologic consequences, from altered mental status to focal neurologic deficits that are often, but not always, reversible.

- Diabetic ketoacidosis is characterized by the triad of uncontrolled hyperglycemia, metabolic acidosis, and increased total body ketone concentration.
- Hyperglycemic hyperosmolar state is characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence of significant ketoacidosis.
- The most common precipitant of diabetic ketoacidosis and hyperglycemic hyperosmolar state is infection, but other causes include omission of or inadequate insulin dosing, pancreatitis, myocardial infarction, stroke, and certain drugs (eg, corticosteroids, thiazide diuretics, sympathomimetics, and antipsychotics).
- Both diabetic ketoacidosis and hyperglycemic hyperosmolar state classically present with polyuria, polydipsia, weight loss, vomiting, dehydration, weakness, and altered mental status.
- Both diabetic ketoacidosis and hyperglycemic hyperosmolar state can be associated with altered mental status, including lethargy and coma. These are more common in hyperglycemic hyperosmolar state and correlate with hyperosmolality.
- The goals of therapy in hyperglycemic crises are to correct the dehydration, hyperglycemia, and electrolyte abnormalities and to identify and treat the underlying inciting factor.
- The most common cause of hypoglycemia is the inadvertent or deliberate overdose of hypoglycemic agents, but, less commonly, insulin-secreting tumors, Addison disease, renal or hepatic failure, or severe sepsis can cause symptomatic hypoglycemia.

Neurologic Complications of Transplantation

Amy A. Pruitt, MD. Continuum (Minneap Minn). June 2017;23(3 Neurology of Systemic Disease): 802–821.

Abstract

Purpose of Review:

This article describes the diagnosis and management of neurologic problems during hematopoietic cell and solid organ transplantation using time elapsed since transplantation as a guide to expected complications, including drug toxicities, infections, strokes, autoimmune phenomena, disease recurrence, and secondary neoplasms.

Recent Findings:

Growing clinical experience in the neurology of transplantation has led to appreciation of the diverse clinical and radiographic spectrum of calcineurin inhibitor–related posterior reversible encephalopathy syndrome (PRES) and progressive multifocal leukoencephalopathy. Novel autoimmune phenomena illustrate the delicate balance between adequate immunosuppression and necessary host inflammatory defenses that can lead to organ rejection. The spectrum of infectious complications has changed with the evolution of new conditioning regimens.

Summary:

Neurologic problems remain an important source of morbidity and mortality, both in the immediate transplantation period and for years after the procedure. As perioperative management has reduced the incidence of acute infections, graft versus host disease, and organ rejection,

problems of long-term survivors require neurologic input into multidisciplinary management of chronic neurologic conditions impacting quality of life.

Key Points

- Tacrolimus and cyclosporine have multiple adverse effects and must be included in the differential diagnostic possibilities among the wide variety of central and peripheral nervous system complications that may occur following hematopoietic cell transplantation or solid organ transplantation.
- Posterior reversible encephalopathy syndrome, often caused by tacrolimus or cyclosporine, can occur at any point in the patient's course after hematopoietic cell transplantation or solid organ transplantation, is not necessarily related to drug level, and can present variably with altered sensorium, cortical blindness, seizures, spinal cord involvement, or hydrocephalus.
- Posttransplant acute limbic encephalitis is usually caused by human herpesvirus 6 and is associated with seizures, anterograde amnesia, MRI abnormalities in the hippocampi, and severe graft versus host disease, with early posttransplantation mortality.
- Neutropenia for more than 10 days is the biggest risk factor for invasive aspergillosis, which can present as a sentinel headache or sinus infection or as hemorrhage from aneurysms. CSF or serial serum galactomannan testing is useful. CSF may be neutrophilic or acellular.
- Varicella-zoster infections begin to emerge in the second month posttransplant and are common in both hematopoietic cell transplantation and solid organ transplantation recipients, with manifestations ranging from dermatomal rash to cranial neuritis, myelitis, multifocal stroke, acute retinal necrosis, spinal cord infarction, and a temporal arteritis–mimicking syndrome.
- If the symptoms of varicella-zoster virus have been present for less than 1 week, polymerase chain reaction is the best diagnostic test. However, CSF varicella-zoster virus testing should include anti-varicella IgM and IgG in addition to CSF polymerase chain reaction if symptoms have been present longer than 1 week.
- Chronic graft versus host disease affects multiple organs. The two most distinctive peripheral nervous system manifestations of chronic graft versus host disease are dermatomyositis and polymyositis, although myasthenia gravis, acute inflammatory demyelinating polyradiculoneuropathy, and chronic inflammatory demyelinating polyradiculoneuropathy are also associated with the syndrome.
- A relationship between calcineurin inhibitors and white matter abnormalities on MRI must always be suspected. This consideration will dictate a workup to exclude progressive multifocal leukoencephalopathy and will avoid unnecessary medicines such as multiple sclerosis drugs. Changing the immunosuppressive regimen may improve the clinical and radiographic signs and symptoms.
- The clinical and radiographic picture of progressive multifocal encephalopathy can be quite varied. Variable degrees of enhancement can occur, and immune reconstitution after reduction of immunosuppression can lead to neurologic symptom exacerbation as well as intensified graft versus host disease, threatening the viability of transplanted organs.
- Management of long-term survivors of transplantation becomes surveillance of a chronic condition, the treatment of which predisposes patients to multiple complications, including metabolic syndrome, cataracts, secondary neoplasm, osteoporosis, the need for revaccination, and ongoing risk of rejection or recurrence of original disease.
- Donor organ–associated infections include West Nile virus, lymphocytic choriomeningitis virus, rabies, *Balamuthia mandrillaris*, and *Cytomegalovirus*.

- Cryptococcosis can be difficult to diagnose in solid organ transplantation recipients as many patients have little inflammation and nondiagnostic initial CSF. Immune reconstitution inflammatory syndrome can occur when immunosuppression is reduced, with ensuing raised intracranial pressure and meningeal inflammation.
- Posttransplant lymphoproliferative disorder, the most common brain neoplasm in transplant recipients, is a spectrum of B-cell proliferations ranging from polyclonal hyperplasia to fulminant multifocal parenchymal disease. The fulminant disorder can occur shortly after transplantation, while more indolent neoplasia can develop several years posttransplantation.
- Important neurologic conditions relevant to liver transplantation include both preoperative neurologic problems and those due to the transplantation procedure, including hyperammonemic encephalopathy, raised intracranial pressure, seizures, stroke, osmotic demyelination, and hepatic myelopathy.
- Cardiac transplant recipients have the highest risk of posttransplantation stroke and the highest risk for toxoplasmosis.

Nutrients and Neurology

Neeraj Kumar, MD. Continuum (Minneap Minn). June 2017;23(3 Neurology of Systemic Disease):822–861.

Abstract

Purpose of Review:

This article provides an update on the clinical presentation and management of neurologic disease related to key nutrient deficiencies.

Recent Findings:

Major advances have been made in understanding the pathway related to vitamin B12 absorption and distribution. It is now known that deficiencies of vitamin B12 and copper have similar neurologic manifestations. Bariatric surgery is a risk factor for both. Alcoholism is just one of the many causes of thiamine deficiency. Early neurologic complications following bariatric surgery are often due to thiamine deficiency. Encephalopathy in the setting of alcoholism that persists despite thiamine replacement should prompt consideration of niacin deficiency. Pyridoxine deficiency and toxicity both have neurologic sequelae. Vitamin D deficiency and the risk for multiple sclerosis has been an area of ongoing research.

Summary:

Optimal functioning of the nervous system is dependent on a constant supply of certain vitamins and nutrients. This article discusses neurologic manifestations related to deficiency of these key nutrients.

Key Points

- Early neurologic complications following bariatric surgery may be related to thiamine deficiency, while delayed complications are often due to copper or vitamin B_{12} deficiency.

- Marasmus is due to caloric insufficiency and results in growth failure and emaciation in early infancy.
- Kwashiorkor presents between 2 and 3 years of age. Its underlying cause is protein deficiency.
- Food-bound cobalamin malabsorption refers to reduced liberation of cobalamin from food proteins and results from achlorhydria, gastritis, gastrectomy, and the use of proton pump inhibitors or antacids. It is the most common cause of vitamin B_{12} deficiency and may affect up to 20% of older adults.
- Many patients with clinically expressed or disabling cobalamin deficiency have intrinsic factor–related malabsorption such as that seen in pernicious anemia.
- Vitamin B_{12} deficiency is not universal in vegetarians but does develop more rapidly with malabsorption in vegetarians.
- Clues to possible vitamin B_{12} deficiency in a patient with polyneuropathy include a relatively sudden onset of symmetric symptoms, findings suggestive of an associated myelopathy, the onset of symptoms in the hands, concomitant involvement of upper and lower limbs, and the presence of a risk factor for vitamin B_{12} deficiency or laboratory markers of vitamin B_{12} deficiency.
- The bulk of evidence suggests that vitamin B_{12} supplementation does not result in improved cognition or slowed cognitive decline despite normalization of vitamin B_{12} levels.
- Although a widely used screening test, serum vitamin B_{12} measurement has technical and interpretive problems and lacks specificity and sensitivity for the diagnosis of vitamin B_{12} deficiency.
- Vitamin B_{12} bound to transcobalamin (holotranscobalamin) is the fraction of total vitamin B_{12} available for tissue uptake. Holotranscobalamin concentration and transcobalamin saturation (holotranscobalamin to total transcobalamin) has been proposed by some as potentially useful alternative indicators of vitamin B_{12} status.
- A common approach in the diagnosis of pernicious anemia as a cause of vitamin B_{12} deficiency is to combine the specific but insensitive intrinsic factor antibody test with the sensitive but nonspecific serum gastrin or pepsinogen I level.
- Patients with pernicious anemia have a higher frequency of thyroid disease, diabetes mellitus, carcinoid, and iron deficiency and should be screened for these conditions.
- Acquired folate deficiency rarely exists in the pure state.
- Small intestinal bacterial overgrowth may be associated with increased folate levels due to bacterial synthesis.
- Serum folate falls within 3 weeks after decrease in folate intake or absorption, red blood cell folate declines weeks later, and clinically significant depletion of folate stores may be seen within months.
- For unclear reasons, neurologic manifestations involving the spinal cord or peripheral nerves, such as those seen in vitamin B_{12} deficiency, are relatively rare in folate deficiency.
- Plasma homocysteine levels are commonly elevated in patients with clinically significant folate deficiency.
- Serum folate fluctuates daily and does not correlate with tissue stores. Red blood cell folate is more reliable than plasma folate because its levels are less affected by short-term fluctuations in intake.
- Alcoholism is just one of many causes of thiamine deficiency, and thiamine deficiency is increasingly being recognized in individuals who are not alcoholics.
- Wernicke encephalopathy often results from severe short-term thiamine deficiency, while peripheral neuropathy is more often a consequence of prolonged mild to moderate thiamine deficiency.

- Patients with Wernicke encephalopathy may have none of the manifestations related to the classic triad, although one or more components of the triad do generally appear later in the course.
- h It is important to recognize that a patient who does not recover fully and spontaneously from intoxication may have Wernicke encephalopathy.
- Korsakoff syndrome is an amnestic-confabulatory syndrome characterized by severe anterograde and retrograde amnesia that follows Wernicke encephalopathy; Korsakoff syndrome emerges as ocular manifestations and encephalopathy subside. Rarely, Korsakoff syndrome may be present without Wernicke encephalopathy.
- Alcoholic neuropathy is a slowly progressive, painful, predominantly sensory neuropathy, with preferential involvement of small fiber function. In contrast, thiamine deficiency–related neuropathy is often a more rapidly progressive sensorimotor neuropathy, with large fiber–predominant sensory loss.
- Wernicke encephalopathy is largely a clinical diagnosis.
- A normal serum thiamine level does not exclude Wernicke encephalopathy.
- IV glucose infusion in patients with thiamine deficiency may consume the available thiamine and precipitate acute Wernicke encephalopathy. Patients who are at risk should therefore receive parenteral thiamine before administration of glucose or parenteral nutrition.
- A commonly used thiamine replacement regimen is 200 mg IV every 8 hours. Higher doses of thiamine may be required in Wernicke encephalopathy, particularly when it occurs in the setting of alcoholism.
- Unexplained progressive encephalopathy in alcoholics that is not responsive to thiamine or escalating doses of benzodiazepines should raise the possibility of pellagra.
- The two most prevalent forms of pyridoxine-dependent epilepsy include the autosomal recessive disorders associated with antiquitin deficiency and pyridoxal 5"-phosphate oxidase deficiency.
- Excess consumption of vitamin B_6 has been associated with a predominantly sensory ganglionopathy. It is characterized by sensory ataxia, areflexia, impaired cutaneous and deep sensations, and a positive Romberg sign.
- Vitamin D status is assessed by 25-hydroxyvitamin D levels.
- Mutations in *TTPA*, the gene that encodes α-tocopherol transfer protein, results in ataxia with vitamin E deficiency. Additional disorders associated with vitamin E deficiency include hypobetalipoproteinemia, abetalipoproteinemia, and chylomicron retention disease.
- The neurologic manifestations of vitamin E deficiency include a spinocerebellar syndrome with variable dorsal column and peripheral nerve involvement. The phenotype is similar to that of Friedreich ataxia.
- Hyperlipidemia increases the plasma carriers for vitamin E. Hyperlipidemia can, therefore, independently increase serum vitamin E without reflecting similar alterations in tissue levels of the vitamin.
- The most common cause of acquired copper deficiency is a prior history of gastric surgery for peptic ulcer disease or bariatric surgery.
- Excessive zinc ingestion is a well-recognized cause of copper deficiency.
- Other nutrient deficiencies, notably vitamin B_{12} deficiency, can coexist with copper deficiency.
- The most common manifestation of acquired copper deficiency is that of a myelopathy that resembles the subacute combined degeneration seen with vitamin B_{12} deficiency.
- A rise in ceruloplasmin is accompanied by an increase in serum copper in conditions such as pregnancy, oral contraceptive use, liver disease, malignancy, hematologic disease, myocardial infarctions, uremia, and various inflammatory and infectious diseases.

Environmental Neurologic Injuries

Rodolfo Savica, MD, PhD. Continuum (Minneap Minn). June 2017;23(3 Neurology of Systemic Disease):862–871.

Abstract

Purpose of Review:

This article discusses neurologic complications resulting from environmental injuries and the treatment modalities for these conditions.

Recent Findings:

Recent advances include improved management of altitude sickness. Relatively uncommon conditions, such as keraunoparalysis (lightning-induced paralysis) and high-pressure neurologic syndrome, are areas of ongoing study.

Summary:

Environmental injuries may be associated with serious neurologic sequelae. This article reviews thermal and electrical injuries as well as injuries related to aviation, altitude, and diving. Recognition of signs and symptoms of such complex injuries and exposures will permit accurate diagnoses and improved outcomes.

Key Points

- Approximately 20% of cases of high-temperature syndromes may have long-term consequences.
- Heat exhaustion occurs at temperatures between 37 °C (98.6°F) and 40°C (104°F). The syndrome is milder than heatstroke and can be treated by replenishing fluids and electrolytes; avoid rapid correction of temperature.
- A direct lightning strike is rare; most injuries are secondary to falling trees or blast injuries. Neurologic manifestations can be preceded by cutaneous damage and metabolic complications.
- Keraunoparalysis is an immediate but rare consequence of lightning strike; transient paralysis of the lower limbs improves in hours without treatment.
- Lightning strike does not leave entry marks, but alternating current electrical injury does.
- Reports of itchiness and joint pain after scuba diving require a neurologic evaluation because type I decompression sickness can evolve to the more severe type II decompression sickness. Information regarding the rate of descent/ascent is crucial for an accurate evaluation.
- Decompression sickness must be treated with 100% oxygen immediately at the onset of symptoms, followed by use of a decompression chamber. About 70% of patients have a good prognosis and no consequences.
- Neurologic symptoms of high-altitude exposure are more common between 2500 m (8202 ft) and 3500 m (11,483 ft). Return to a lower level or to sea level will restore the baseline physiologic status.

- In acute mountain sickness, acetazolamide is commonly used to cause metabolic acidosis; dexamethasone can be used in conjunction with acetazolamide. Portable hyperbaric chambers are needed in climbing expeditions to make treatment readily accessible.
- Decompression sickness can be caused by decreased pressure at flight altitude, but the symptoms appear less severe than in immersion-related decompression sickness. Administering 100% oxygen and descending to a lower altitude produce immediate improvement.