Central mechanisms control ventilation. The CNS regulates ventilation through chemoreceptors (central and peripheral) which are sensitive to changes in pO$_2$, pCO$_2$, and blood pH. Chemoreceptors provide feedback to brain respiratory centers which drive respiratory rhythms. Hypoxia or hypercarbia result in cerebral blood vessel dilation and increased cerebral blood flow.

**Acute Hypoxia**
- **Acute Respiratory Failure**
  - Acute respiratory failure is defined by a drop in pO$_2$ below 60 mm Hg or a rise in pCO$_2$ over 50 mm Hg.
  - Neurologic manifestations depend on the onset, duration, and severity of hypoxia. Symptoms range from anxiety, confusion, somnolence, and delirium to impaired consciousness and coma. Tremors or myoclonus may be seen. Prolonged hypoxia as seen in cardiopulmonary arrest may result in a hypoxic ischemic encephalopathy. The cortex, hippocampus, and Purkinje cells are vulnerable to the effects of hypoxia. Severity of neurologic manifestations correlates with acidosis and hypercarbia. Absent pupillary reflexes at initial examination predict a low likelihood of regaining consciousness. Survivors of cardiac arrest often have memory deficits and executive dysfunction.

- **Altitude sickness**
  - High-altitude sickness refers to the abrupt onset, in a non-acclimatized person at 2500 m or higher, of headache plus one of the following: nausea, vomiting, anorexia, insomnia, dizziness, somnolence, or fatigue. Neurologic manifestations can include mental status change, ataxia, cranial nerve palsies, retinal hemorrhage, and papilledema. Development is related to rate of ascent, absolute altitude, and individual physiologic responses. The “tight-fit” hypothesis suggests the young are more predisposed to develop the condition because the lack of cerebral atrophy results in a propensity to develop cerebral edema and raised intracranial pressure. Treatment modalities include descent to a lower altitude, supplemental oxygen, hyperbaric chambers, acetazolamide, and dexamethasone.

**Chronic Hypoxia**
- **Chronic Respiratory Failure**
  - Chronic hypoxia and hypercarbia associated with chronic respiratory failure can cause headache and mental status changes. An acute rise in pCO$_2$ is much more deleterious than a gradual rise. Papilledema and rarely seizures and focal neurologic signs may be present. Giving high concentration of oxygen is harmful because it decreases ventilatory drive by reducing stimulus to the carotid body. This in turn worsens hypercarbia and related symptoms.

**Hypoventilation**
- **Obesity Hypoventilation Syndrome (Pickwickian Syndrome)**
  - The hallmark of this condition is chronic hypercarbia and obesity with dyspnea and cor pulmonale. Blunted respiratory drive and mechanical pressure on the chest wall result in alveolar hypoventilation. Cognitive changes and hypersomnolence may be present.
• **Ondine curse**
  o Though probably initially used in context of bulbar polio, the term is used for various brainstem disorders that affect respiration such as infarcts or tumors. Though it has classically been used to refer to failure of automatic respiration, it is also used in context of central hypventilation syndrome & sleep apnea.  

• **Sleep Disordered Breathing**
  o Sleep disordered breathing or sleep apnea is defined by episodic cessation of breathing for at least 10 seconds (apnea) or a decrease in airflow with a drop in hemoglobin saturation of at least 4% (hypopnea). In general 5 or more apneic or hypopneic episodes per hour are required to make the diagnosis.  
  o Obstructive (OSA), central (CSA), and mixed forms are recognized.  
  o OSA is the most common form. The daytime neurologic manifestations of the sleep fragmentation that accompany sleep apnea include headache, mood and personality change, fatigue, inattention, decreased processing speed, and memory difficulties.  
  o An association between OSA and idiopathic intracranial hypertension has been reported in men. The nocturnal hypercarbia-related cerebral vasodilation is believed to result in increased intracranial pressure.  
  o CSA is diagnosed when there is failure of ventilatory effort in response to apnea. CSA has been linked to medullary lesions, genetic, and paraneoplastic disorders. Congenital central hypventilation is characterized by a blunted response to hypercapnia with decreased ventilation during sleep. Mutations in PHOX2B, a gene responsible for maturation of the neural crest and formation of facial structures, have been identified in this condition. Diffusion tensor imaging in congenital central hypoventilation syndrome has identified myelin injury in the brainstem and cerebellum.  
  o Patients with neuromuscular disorders are prone to both OSA and CSA. Neuromuscular disorders associated with pulmonary complications and sleep disordered breathing include Charcot – Marie Tooth, amyotrophic lateral sclerosis, postpolio syndrome, myotonic dystrophy, myasthenia gravis, acid maltase deficiency, and Duchenne muscular dystrophy. Diaphragmatic weakness, bulbar weakness, respiratory muscle weakness and probably impaired chemosensitivity are all contributing factors.

**Hyperventilation**

• **Acute**
  o Hyperventilation can be seen in a broad spectrum of conditions: pain, sepsis, cardiopulmonary disease, pregnancy, CNS tumors, anxiety, medications, and metabolic derangement. Hyperventilation results in a decreased pCO₂ which in turn causes respiratory alkalosis and decreased plasma calcium. Clinical manifestations of acute hyperventilation include dizziness, perioral and distal paresthesias, carpopedal spasm, and tetany.

• **Chronic**
  o Chronic hyperventilation can be more difficult to diagnose. Clinical manifestations include nonspecific symptoms like fatigue, dizziness, and anxiety. The hyperventilation test can help make a diagnosis (see if symptoms are reproduced by deep breathing for 3 minutes or increasing ventilation to 60 breaths per minute). This test should not be done in cardiopulmonary or cerebrovascular disease, sickle cell anemia, or hyperviscosity states.

**Adult-onset Acid Maltase deficiency**

• The enzyme acid α glucosidase (GAA) degrades lysosomal glycogen. Deficiency of this enzyme results in an autosomal recessive disorder called Pompe’s disease (also called glycogen-storage disease type II or acid maltase deficiency). The classic infantile form is associated with glycogen deposition in the heart, skeletal muscle, and respiratory muscles. The resulting cardiomyopathy, hypotonia, and respiratory failure results in death in infancy. Children and adults have glycogen deposition in the skeletal and respiratory muscles. This results in a limb-girdle myopathy and respiratory failure.  
  o A recent study noted that in a large cohort of unselected adult patients with hyperCKemia and/or limb-girdle muscular weakness the prevalence of late-onset Pompe disease was 2.4%.
In 2006, based on the results of an open-label study of infantile-onset Pompe’s disease, enzyme-replacement therapy with alglucosidase α (a recombinant human GAA) was approved for all patients with Pompe’s disease. More recently a randomized, controlled trial in late-onset Pompe’s disease showed improved walking distance and stabilization of pulmonary function over a 18-month period.

References:


ENDOCRINOLOGY – NEUROLOGY

Thyroid Disease

- **Hypothyroidism**
  - **Types:** Primary hypothyroidism results in decreased production of thyroid hormone and excess thyroid stimulating hormone (TSH). Secondary hypothyroidism is less common and is a central disorder of decreased thyroid stimulation by TSH.
  - **Epidemiology:** Hypothyroidism is more common in women and in the elderly.
  - **Systemic features:** Systemic manifestations of hypothyroidism include a dry/ flaky/thickened/cool skin, cold intolerance, weight gain, puffy hands and feet, facial and periorbital nonpitting edema, constipation, bradycardia, hypertension, hyperlipidemia, and hypotension.
  - **Cretinism:** Congenital hypothyroidism is a treatable cause of mental retardation: neonatal screening is required to not miss these cases. Clinical clues to congenital hypothyroidism include post maturity, macrosomia, open posterior fontanelle, delayed passage of
meconium, prolonged neonatal jaundice, and umbilical hernia. Dysgenesis of the thyroid can be associated with defects in heart septation. **Sporadic cretinism** is caused by defective thyroid gland function in the fetus or infant. It is characterized by retardation of mental and physical development. **Endemic cretinism** is associated with environmental iodine deficiency and endemic goiter. Two clinical presentations of endemic cretinism are recognized: Neurological cretinism (mental deficiency, deaf mutism, autism, strabismus, spastic gait - but no clinical hypothyroidism; goiter is common; the cause is maternal iodine deficiency) and hypothroid or myxedematous cretinism (psychomotor slowing but no deaf mutism or spasticity, incomplete maturation of facial features, thick and dry skin with decreased hair, delayed sexual maturation, less mental retardation, severe hypothyroidism; no goiter; ). Patients may have muscular hypertrophy as seen in the Kocher-Debré-Sémélaigne syndrome. MRI in endemic cretinism may show T1 hyperintensity/ T2 hypointensity involving the globus pallidus and substantia nigra.

**Neuropsychiatric manifestations:** Neuropsychiatric manifestations of hypothyroidism include apathy, psychomotor slowing, inattention, impaired memory, impaired word fluency and abstract thinking, somnolence, and lethargy. Hypothyroidism is a differential diagnosis for depression and for the psychomotor slowing that characterizes extrapyramidal disease. Frank psychosis with hallucinations and agitation is rarely a presenting manifestation of hypothyroidism but has been described in the literature as “myxedema madness”. The role of subclinical hypothyroidism on cognition and mood is controversial. “Myxedematous dementia” is seen with extreme hypothyroidism. The clinical hallmarks are hypersomnolence and bizarre behavior. If untreated it may progress to “myxedematous cachexia” which may progress to seizures (due to hyponatremia and hypoglycemia), myoclonus, and coma.

**Myxedema coma:** Additional features of myxedema coma include seizures, hypothermia, hypotension, bradycardia, hypoventilation, hypercarbia, hypoxemia, and hypotension. The hypothermia may mask an underlying infection. Myxedema coma may be precipitated by cold temperatures, infection, congestive heart failure, stroke, trauma, anesthesia, and drugs like chlorpromazine, sedatives, antidepressants, lithium, narcotics, amiodarone, and hypnotics. It may also result from withdrawal of l-thyroxine. Other reported precipitants of myxedema coma include metabolic disturbances (acidosis, hypoglycemia, hyponatremia, hypercapnia), gastrointestinal bleeding, and ingestion of raw bok choy. Myxedema is more common in elderly women; pregnant women may also be vulnerable. Investigations may reveal hyponatremia, acidosis, anemia, elevated CSF protein and opening pressure. 10% of the hypothyroidism in myxedema coma may be due to a hypothalamic or pituitary cause and the TSH may therefore be low or inappropriately normal. Free T3 and free T4 should therefore be measured. Hyponatremia needs correction. Hydrocortisone is needed due to risk of adrenal insufficiency during replacement therapy. Intravenous T4 (eg 100 to 500 ug followed by 50-100 ug) followed by oral therapy is employed. There are reports of increased mortality with T3.

**Hashimoto encephalopathy:** “Hashimoto encephalopathy” is a syndrome of rapidly progressive dementia with seizures, extrapyramidal manifestations, myoclonus, and focal stroke-like manifestations. The associated anti-thyroid antibodies are not causative. The disorder is perhaps an autoimmune encephalopathy that may respond to steroids or plasma exchange. Postpartum depression may be seen in women with postpartum thyroiditis who are antithyroid antibody positive.

**Myopathy:** Hypothyroidism may be associated with muscle cramping, aching, fatigability with or without frank weakness. Sluggish reflexes (delayed relaxation of ankle jerk: “hung up”) may be present. Myocedema (ridging of the muscle on percussion: electrically silent) may be seen. Muscle hypertrophy may be seen in the Kocher-Debré-Sémélaigne syndrome or Hoffmann syndrome. Hoffmann syndrome refers to an adult-onset myopathic syndrome with muscle (pseudo)hypertrophy and myotonia. A predominantly proximal myopathy may be seen in hypothyroidism. Myopathy may be the presenting and sole manifestation of hypothyroidism. Elevated CPK without a frank myopathy may be seen in hypothyroidism. Rhabdomyolysis and a polymyositis-like
have been reported. Rhabdomyolysis in hypothyroidism may be precipitated by heavy exercise, lipid lowering therapy, and pre-existing renal failure.

- **Neuropathy:** In addition to sensory predominant peripheral neuropathy, hypothyroidism may be associated with entrapment neuropathies, most commonly carpal tunnel syndrome. Thickening of the connective tissue of tendon sheath and nerve entrapment in the retinaculum is believed to underlie carpal tunnel syndrome. Systemic screening for hypothyroidism is of low diagnostic yield in otherwise typical cases of carpal tunnel syndrome. Entrapment neuropathies may also result in hearing impairment, and facial weakness or numbness.

- **Cerebellar ataxia:** A cerebellar syndrome ("myxedema staggers") may occur in hypothyroidism. Also reported is progressive nonfamilial adult onset cerebellar degeneration and increased antithyroid antibodies suggestive of Hashimoto’s/ autoimmune thyroiditis. Mutation is the NKK2-1 gene has been reported to cause an autosomal dominant disorder with hypothyroidism, neonatal respiratory distress, and ataxia.

- **Sleep apnea:** In addition to obstructive sleep apnea, hypothyroidism may be associated with alveolar hypoventilation due to phrenic nerve involvement or a central process.

- **Myasthenia gravis:** Approximately 2% of patients with myasthenia gravis may have hypothyroidism.

- **Others:** Accumulation of myxedematous tissue around the eighth nerve and fluid in the inner ear can cause decreased hearing in hypothyroidism. Untreated hypothyroidism can cause pituitary gland enlargement and compression of the optic chiasm. Night blindness may result from defective synthesis of pigment required for night vision. Myxedematous deposition in the tongue and larynx can cause a thick speech. Distortion of taste and smell may occur. A bilateral nonpulsatile headache may be seen in association with hypothyroidism.

- **Note:** Primary hypothyroidism can be associated with adrenal deficiency (Schmidt syndrome). Alopecia and vitiligo may be clues to polyglandular autoimmune deficiency syndrome. Secondary or tertiary hypothyroidism may be associated with other features of pituitary dysfunction like acromegaly. Coexisting cortisol deficiency must be addressed before thyroxine replacement.

- **Hyperthyroidism**

  - **Systemic features:** Systemic manifestations of hyperthyroidism include those associated with a hypermetabolic state. Hyperthyroidism may be associated with weight loss, palpitations, heat intolerance, dyspnea, hoarseness, hair loss, and dysphagia.

  - **Neuropsychiatric manifestations:** Patients with hyperthyroidism appear restless and are prone to being emotionally labile. Inattention may underlie cognitive impairment. A presentation suggestive of schizophrenia or depression, or acute affective psychosis have been reported. While nervousness and irritability are seen in the young, the elderly may be predisposed to apathy with depression ("apathetic thyrotoxicosis"). These patients may have increased sensitivity to the side effects of tricyclic antidepressants.

  - **Seizures:** Hyperthyroidism may cause seizures or trigger a preexisting seizure disorder. Triphasic waves or epileptic discharges may be seen in a thyrotoxic crisis.

  - **Corticospinal tract disease:** Reversible corticospinal disease (MND mimic) has been reported.

  - **Thyrotoxic crisis:** A thyrotoxic crisis may be seen in hyperthyroid patients who have had thyroid surgery, are in the postpartum period, have had rapid withdrawal of antithyroid medications, have received radiographic contrast, or have an infection. Other precipitating factors include radioactive iodine treatment, thyroid hormone overdose, cytotoxic chemotherapy, aspirin over dosage, and organophosphate toxicity. It can also be seen in infections, pulmonary thromboembolism, myocardial infarction, with brain injury or seizures, and in the setting of metabolic disturbances like diabetic ketoacidosis or hypoglycemia. It has been reported in the setting of surgery, trauma, emotional stress, psychosis, and vigorous palpation of the thyroid. Often no precipitating factor is identified. Clinical features may include fever out of proportion to any infection, tachycardia out of proportion to fever, diaphoresis, hyperreflexia, rhabdomyolysis, renal
failure, gastrointestinal manifestations (nausea, vomiting, diarrhea, jaundice), seizures, stroke, hyperthermia, and mental status changes including agitation, emotional lability, confusion, paranoia, psychosis, and coma. The initial tremulousness and hyperreflexia can progress to a flaccid areflexic quadriparesis with electrodiagnostic evidence of a neuropathy. Death may occur in up to 20% of patients. Thyroid-mediated bone resorption may cause hypercalcemia. There are no set free T4 or T3 criteria for diagnosing thyroid storm. Therapy includes blocking peripheral effects of thyroid hormones (beta-blockers: propranolol, esmolol), inhibiting thyroid hormone release (lithium and sodium iodide/Lugol’s), inhibit new thyroid hormone synthesis (propylthiouracil, methimazole: both higher than standard doses; note PTU may be used in thyroid storm but avoided in treatment of hyperthyroidism due to hepatotoxicity), enhancing clearance of thyroid hormones (cholestyramine, plasmapheresis, dialysis), steroids, and temperature regulation. Stress doses of steroid prevent adrenal insufficiency and decrease peripheral conversion of T4 to T3.

Neuromuscular disease:

- Thyrotoxic myopathy: Fatigue, myalgias, and a sense of generalized weakness are more common in thyrotoxic myopathy than a classic proximal myopathy. Weakness and wasting may be seen; the weakness correlates with the duration of thyrotoxicosis rather than severity. Dysphagia and dysarthria due to bulbar weakness and shortness of breath due to respiratory muscle involvement and have been reported. Bulbar and oropharyngeal involvement may be seen in a thyrotoxic patient experiencing an acute thyroid storm. The creatinine kinase is typically normal. An inflammatory myopathy with elevated CPK levels has been reported in thyrotoxic myopathy.

- Thyrotoxic periodic paralysis: Thyrotoxic periodic paralysis is characterized by recurrent attacks of acute, ascending weakness that can last from a few minutes to a few days. The condition is more common in the Far East than the West. Unlike periodic paralysis, the condition is more common in males, is sporadic, and responds to treatment of the hyperthyroid state. Thyroxine likely increases the activity of the membrane Na/K pump. Patients with thyrotoxic periodic paralysis have 80% greater activity of the pump than those with hyperthyroidism alone. Precipitating factors include a high carbohydrate diet, insulin, exposure to cold, or rest after exercising. Other reported precipitating factors include stress, cold exposure, infection, alcohol intake, pulse steroid therapy, beta-2 adrenergic bronchodilator use, menses. Cranial muscles and sphincters are spared; respiratory involvement is rare. Ocular and bulbar muscles are spared. Smooth muscle is not affected. The serum potassium may decrease (but may not be low). In addition to treating the thyroid disease, therapeutic options include propranolol and potassium replacement. Propranolol blocks beta-adrenergic stimulation of the pump and may cause quicker resolution of the attack. Some consider propranolol as a first line treatment since potassium therapy has the risk of rebound hyperkalemia. Intravenous glucose should be avoided as it may push the potassium inside the cell. In addition to hypokalemia, hypophosphatemia is present. Unlike nonthyrotoxic periodic paralysis, in thyrotoxic periodic paralysis there is a marked decline in urine phosphate excretion—a spot urine calcium/ phosphate ratio of greater than 1.4 mmol/L may help distinguish the two conditions.

- Myasthenia gravis: Approximately 6% of cases of myasthenia gravis have thyrotoxicosis. A higher number may have some form of autoimmune thyroid disease. 1% of patients with Graves disease have myasthenia gravis. The myasthenia gravis and thyroid disease should be treated independently. Coexisting thyrotoxic myopathy may complicate therapy.

Dysthyroid orbitopathy: “Graves’ disease” refers to the combination of hyperthyroidism, exophthalmic ophthalmoplegia or dysthyroid orbitopathy, and goitre. With disease progression optic neuropathy may occur. A pretibial dermopathy may coexist. A Mayo Clinic study noted that 90% of patients with dysthyroid orbitopathy had Graves’ disease, 1% had primary hypothyroidism, 3% had Hashimoto thyroiditis, and 6% were...
euthyroid. Patients with dysthyroid orbitopathy may report blurred vision, photophobia, increased lacrimation, diplopia, or orbital pressure. Examination may reveal exophthalmos, periorbital and eyelid edema, conjunctival chemosis and injection, lid lag and retraction, and exposure keratitis. The presence of exotropia should prompt consideration of myasthenia gravis. Hyperthyroidism in the absence of Graves’ disease may be accompanied by lid lag and retraction. Therapeutic options in aggressive disease include systemic or local steroids, orbital radiotherapy, orbital decompression.

- Neurology: An sensorimotor axonal neuropathy may be seen in patients with hyperthyroidism. Also reported is a demyelinating neuropathy (“Basedow paraplegia”) which should be considered in patients with a thyrotoxic myopathy as an additional cause of weakness. A possibly immune mediated (CIDP-like) recurrent polyradiculoneuropathy has also been described. A thyrotoxicosis related goiter may result in a postganglionic Horner syndrome (due to involvement of ascending sympathetic fibers) or vocal cord paralysis and hoarseness (due to involvement of the recurrent laryngeal nerve). Propothiouracil treatment of hyperthyroidism may cause a peripheral neuropathy. Carpal tunnel syndrome is an additional manifestation of hyperthyroidism. Symptoms remit with control of the endocrinopathy and surgery is generally not necessary.

- Movement disorders: Tremor is the commonest movement disorder associated with thyrotoxicosis. Also reported is chorea. Patients with thyrotoxicosis often are nervous and have a difficulty sitting still.

**Pituitary Disease**

- **Diabetes insipidus**
  - **Introduction:** Vasopressin is the posterior pituitary hormone that is essential for water balance.
  - **Causes:** Causes of neurogenic or central diabetes insipidus include infections (basilar meningitis as seen with tuberculosis, syphilis), trauma or brain surgery, granulomatous disease (sarcoidosis, histiocytosis X), neoplasms, vascular etiologies (aneurysm, stroke), sickle cell disease, pituitary apoplexy, NMO, familial (dominant or recessive) or idiopathic.
  - **Clinical features:** Neurogenic or central diabetes insipidus is characterized by thirst, polyuria, polydipsia, and an inability to maintain water homeostasis in the face of fluid restriction. Fluid restriction does not result in change in urine concentration. Neurologic complications are related to hypernatremia and encephalopathy.
  - **Laboratory features:** The laboratory hallmarks include: urine specific gravity from 1.000 – 1.005, urine osmolality < 300 mmol/kg, urine excretion > 2 ml/kg/h, plasma osmolality > 300 mmol/kg, serum sodium > 143 mmol/l. The test of choice is the water deprivation test which assesses serum and urine osmolality in response to water deprivation and then response of urine osmolality to desmopressin administration.
  - **Treatment:** Acute diabetes insipidus in an alert patient can be treating by free access to water. Exogenous vasopressin and parenteral fluids may be used in patients with an altered mental status. Care should be taken to avoid salt overload. Chronic diabetes insipidus is treated with DDAVP. Care should be taken to avoid water intoxication.

- **Pituitary adenomas**
  - Asymptomatic pituitary adenomas can be seen in up to 10% of MRI scans. Symptomatic pituitary adenomas account for 10 – 25% of all intracranial neoplasms. A tumor < 10 mm is considered a microadenoma. The functional status of a pituitary tumor should be assessed by the following: TSH, free T3, total T4, ACTH, am cortisol, Prl, IGF-1, IGFBP-3 (GH panel), LH/ FSH (not required in women with a normal cycle), testosterone (in men).
  - The differential diagnosis of pituitary and parapituitary lesions includes:
    - **Congenital anomalies** (empty sell syndrome, Rathke’s cleft cyst, encephalocele, suprasellar arachnoid cysts)
    - **Neoplasms** (craniopharangioma, optic chiasm glioma, hypothalamic glioma or hamartoma, sellar and parasellar meningioma, schwannoma and neurofibroma, germ cell tumor, dermoid and epidermoid, metastasis)
Vascular etiologies (aneurysm, pituitary apoplexy)
Sphenoid sinus disease (granulomatous, infectious, malignant, inflammatory)
Infections (tuberculosis)
Others (sarcoidosis, histiocytosis X, lymphocytic hypophysitis)

Prolactin-secreting adenomas
- 60% of all pituitary tumors
- Decreased libido in men
- Amenorrhea and galactorrhea in women
- Microadenomas in men and women who do not wish to conceive can be observed (risk of osteoporosis which in women can be reduced by oral contraceptives)
- Macroadenomas are treated with dopamine agonists (bromocriptine, cabergoline, pergolide, lisuride, quinagolide), surgery, radiation

Growth hormone-secreting adenomas
- Pituitary gigantism (before epiphyseal closure) or acromegaly (after epiphyseal closure)
- Over 75% of patients with acromegaly have macroadenomas at time of presentation
- Diagnosis of acromegaly can be made by measuring serum IGF-1 levels; if elevated measure GH levels after oral glucose load (GH suppression test)
- Surgery
- Radiation
- Somatostatin analogs (octreotide, lanreotide)
- Dopamine agonists (bromocriptine, cabergoline, quinagolide)
- GH-receptor antagonist (pegvisomant)

Corticotropin-secreting adenoma
- Cushing’s disease (excess ACTH)
- 15% of all pituitary tumors
- Over 2/3rd of all cases of Cushing syndrome
- Surgery
- Radiation
- Inhibitors of glucocorticoid synthesis

Thyrotropin-secreting adenomas
- Rare
- Large at time of diagnosis
- Goitre and hyperthyroidism
- Surgery
- Radiation
- Radioactive ablation of thyroid
- Octreotide or lanreotide

Gonadotropin-secreting adenomas
- LH and FSH levels may be normal since only α or β subunits may be secreted which are not detected in assays
- Surgery
- Radiation
- Octreotide

Pituitary apoplexy
- Introduction: Pituitary apoplexy is a heterogeneous clinical syndrome characterized by sudden hemorrhage or infarction of the pituitary gland that is most commonly associated with a pituitary adenoma. Pituitary apoplexy commonly occurs when a pituitary adenoma undergoes acute hemorrhage, infarct, or both. Though often described in patients with a pituitary adenoma, the presence of the same is not required for pituitary apoplexy. Hemorrhagic infarction of the normal pituitary is very rare, may occur in pregnancy (Sheehan’s syndrome), and pathophysologically is different from pituitary apoplexy. Incidental subclinical apoplexy may affect 25% of all pituitary tumors.
- Pathophysiology: Edema and blood accumulation causes an increase in the sella turcica contents. This compresses vessels and surrounding structures. Ischemic necrosis and secondary hemorrhage of the pituitary results.
- Predisposing factors: In most cases pituitary apoplexy is a spontaneous occurrence in an asymptomatic patient. Often there is no preexisting diagnosis of pituitary adenoma and the condition is more commonly seen in nonfunctioning adenomas, often macroadenomas. Macroadenomas are at a higher risk than microadenomas for clinically evident apoplexy. In a study secreting pituitary adenomas and male patients were noted to have a higher probability of developing apoplexy. Identified predisposing factors for apoplexy also include head trauma, hypotension, hypertension, history of pituitary irradiation, surgery (cardiac, others), anticoagulant therapy, certain hormonal treatments (GnRH analogues like androgen deprivation therapy with leuprolide for prostate cancer),
possibly treatment with dopamine agonists, pituitary stimulation tests (dynamic and tolerance testing), angiography, and pregnancy.  

- Clinical manifestations: On one end pituitary apoplexy may result in mild headache, visual disturbance, and/ pituitary deficiency that develops slowly. It can also be a medical emergency that presents with acute blindness, coma, and hemodynamic instability that can result in death. Clinically it may be characterized by sudden-onset severe headache, meningsimus, nausea, vomiting, visual impairment, ophthalmoplegia, altered consciousness and hypopituitarism (particularly acute adrenal insufficiency). A retro-orbital thunderclap headache is often the initial symptom. The headache may be bifrontal or diffuse. Photophobia may be seen. Over hours to days additional features are seen such as visual field defects due to pressure on the optic chiasm and cranial nerve 3, 4, and 6 palsy (cavernous sinus localization). Mental status changes can range from lethargy to coma. Damage to sympathetic fibers may cause a Horner syndrome. Hypothalamic involvement may impair thermal regulation. Leakage of blood or necrotic tissue into the CSF can cause cerebral artery vasospasm and ischemia or fever or meningeal irritation. Decreased caliber of the intracavernous portion of the carotid artery due to vasospasm or its compression can cause cerebral ischemia. Endocrine dysfunction is common and includes corticotropin deficiency seen with secondary adrenal insufficiency which can result in hypotension and hyponatremia. Diabetes insipidus is rare and may be masked by secondary adrenal insufficiency or hypothyroidism. Thyrotropin deficiency may be commonly seen. Bacterial meningitis and subarachnoid bleed are the main differential diagnoses.

- Management: Hydrocortisone 50 mg intravenously every 6 hours is recommended as initial therapy. Emergent transsphenoidal surgical decompression needs consideration. Surgery may be accompanied by prolonged post-operative coma. CSF leak and diabetes insipidus are recognized complications. A conservative treatment may have a role in selected cases: absent or mild or stable signs. Post-operative hormone replacement is often required. A pituitary apoplexy grading system and a pituitary apoplexy score have been suggested.

**Adrenal Insufficiency**

- Causes
  - ACTH stimulates cortisol synthesis and release. It is synthesized and secreted in response to the hypothalamic hormones CRH and vasopressin. Of all the pituitary hormones, only the loss of ACTH is likely to be lethal. Adrenal insufficiency is characterized by a deficiency of adrenocorticosteroid hormones (cortisol, aldosterone, adrenal androgens). It may result from primary adrenal disease or be secondary to pituitary failure. Primary adrenal insufficiency is associated with glucocorticoid and mineralocorticoid deficiency, whereas secondary adrenal insufficiency does not have mineralocorticoid deficiency as the renin-angiotensin-aldosterone system is intact. Primary adrenal insufficiency is more likely to result adrenal crisis than secondary adrenal insufficiency. Glucocorticoid therapy is associated with a risk of suppression of the hypothalamic pituitary axis (HAP). Other primary and secondary causes of adrenal insufficiency are noted below. 10 mg prednisone per day for a month or 20 mg of prednisone for 5 days can potentially cause HPA axis suppression. Acute adrenal insufficiency can be seen in patients with Addison disease who abruptly discontinue steroids or who take insufficient doses of steroids during time of stress like infection/ surgery. Pituitary apoplexy is an additional cause. Increase in corticosteroid tissue levels in acute illness is an important protective response. Many diseases and their treatments interfere with the normal corticosteroid response to illness and induce a state of tissue corticosteroid insufficiency.

- Primary causes/ Addison disease
  - Autoimmune (sporadic, AI polyendocrine syndrome I and II)
  - Infections (TB, fungal, CMV, HIV)
  - Infiltration (amyloidosis, hemochromatosis)
  - Metastasis (lung, breast, kidney, lymphoma)
- Intra-adrenal hemorrhage after meningococcal septicemia
- ALD
- Bilateral adrenalectomy
- Genetic (Congenital adrenal hyperplasia, ACTH resistance syndrome)
- Secondary adrenal insufficiency
  - Exogenous steroids
  - Hypopituitarism, removal of ACTH secreting pituitary adenoma, pituitary tumor/ surgery, granulomatous disease (TB, sarcoid, eosinophilic granulomatosis), infarction – postpartum, pituitary radiation, lymphocytic hypophysitis,
  - Isolated ACTH deficiency
  - TBI and spinal cord injury

**Clinical manifestations**
- Systemic manifestations include fatigue, anorexia, weight loss, nausea, vomiting, abdominal pain, arthralgia, headache, salt craving, memory difficulties, depression, delirium, syncope, hypotension, and even hypovolemic shock. Increased skin pigmentation (seen in primary adrenal insufficiency) may indicate high levels of ACTH, vitiligo may indicate autoimmune Addison disease. Gonadotrophin deficiency in association with hypopituitarism may be associated with oligomenorrhea or amenorrhea and decreased libido. Hypopituitarism associated thyrotropin deficiency may be associated with intolerance to cold or weight gain. Diffuse weakness that can mimic Guillain-Barré syndrome may occur. A myopathy has also been reported. Children may develop hypoglycemia, seizures, and an encephalopathy. Gait difficulty due to flexion contractures of the lower limb may be seen in primary adrenal insufficiency. Many of these are nonspecific features often seen in critically ill patients anyway. Common precipitating events include gastrointestinal illness, surgeries, emotional stress, infections, thyroid replacement therapy, and inadequate exogenous corticosteroid treatment. Flight delays and was bites have also been reported to cause adrenal crisis.

- Features of Addisonian crisis include anorexia, nausea, vomiting, diarrhea, muscle cramps, hypotension, abdominal pain, seizures, delirium, and coma. Many of these are nonspecific features often seen in critically ill patients anyway. Common precipitating events include gastrointestinal illness, surgeries, emotional stress, infections, thyroid replacement therapy, and inadequate exogenous corticosteroid treatment. Flight delays and was bites have also been reported to cause adrenal crisis. Adrenal crisis may be the initial clinical presentation in 50% of cases of primary adrenal insufficiency.

**Investigations**
- Blood should be drawn prior to starting treatment for measurement of cortisol, ACTH, aldosterone, renin, and dihydroepiandrosterone-sulfate. In patients with primary adrenal insufficiency, corticotropin levels are disproportionately elevated relative to plasma cortisol levels. Plasma cortisol levels are measured at 0 and 30 minutes after administration of corticotropin: peak of greater than 19 μg/dl defines a normal response. In critical illness expected cortisol levels vary with the disease type and severity and there are changes in the level of cortisol binding globulin. Hence randomly measured cortisol levels are relied upon. It has been suggested that a threshold of 15 μg/dl identifies persons with clinical features of corticosteroid insufficiency. Adrenal insufficiency is unlikely with random cortisol determination over 34 μg/dl.
- Other tests (rarely) used to assess the HPA include the insulin tolerance test and the glucagon test.
- Biochemical clues for corticosteroid insufficiency include hyponatremia, hyperkalemia (in primary adrenal insufficiency), hypoglycemia, elevated creatinine with prerenal failure, rarely hypercalcemia, and eosinophilia.

**Management**
- The standard perioperative or ‘stress’ dose of glucocorticoid in patients with suspected HPA suppression (or adrenal insufficiency) is 50 to 100 mg hydrocortisone iv every 8 hours. Once stable the glucocorticoid dose can be tapered over 1-3 days to oral maintenance doses, and mineralocorticoid replacement is started once hydrocortisone dose is at 50 mg/ d. Rehydration is necessary to correct hypovolemia and hyponatremia.
Hypoglycemia and Hyperglycemia

- **Hypoglycemia**
  - **Causes:** Hypoglycemia is most commonly seen in the setting of insulin and oral hypoglycemic use. Other causes include insulin-secreting tumors, Adison disease, renal or hepatic failure, and severe sepsis. Hypoglycemia has been defined as a serum glucose <50 mg/dl in the presence of neuroglycopenic symptoms and <40 mg/dl in the absence of symptoms. OR Hypoglycemia is defined as blood glucose below 70 mg/dl.
  - **Clinical manifestations:** Clinical manifestations include fatigue, mental status changes, headache, abnormal behavior, visual or speech disturbance, seizures, myoclonus, and transient focal motor deficits. The adrenergically-mediated warning signs of hypoglycemia (hunger, tachycardia, palpitations, anxiety, nausea, perspiration, tremors) may be masked in the presence of beta blockers or diabetic autonomic neuropathy and delay the diagnosis of hypoglycemia. The medullary phase of hypoglycemia begins at blood glucose levels of 10 mg/dl and manifests as bradycardia, shallow breathing, pupillary dilation, hypotonia, and coma.
  - **Investigations:** EEG changes range from focal slowing to epileptiform activity. A burst suppression pattern may be seen with coma. MRI may show cortical and subcortical abnormalities on DWI sequences: the hippocampi, basal ganglia, and cerebellum may be preferentially involved. The pattern resembles that seen in cerebral hypoxic injury. Cortical laminar necrosis may be seen on DWI MRI.
  - **Prognosis:** Prompt improvement with glucose administration may be seen in comatose individuals. Severe and prolonged hypoglycemia or postictal states may be associated with slower recovery. Permanent deficits including the vegetative state may be seen. (If iv access is not available sc or im glucagon can be given.)

- **Hyperglycemia**
  - **Causes:** Diabetic ketoacidosis (DKA) classically develops in patients with type 1 DM and the hyperglycemic hyperosmolar state (HHS) is more often associated with type 2 DM. DKA is characterized by uncontrolled hyperglycemia, metabolic acidosis, and increased total body ketone concentration. Insulin deficiency is accompanied by an increase in counteregulatory hormones (glucagon, growth hormone, cortisol, catecholamines). The hyperglycemic hyperosmolar state develops more insidiously, has minimal or no ketoacidosis, a greater degree of intravascular volume depletion (osmotic diuresis), and often more profound hyperglycemia and higher mortality. Inciting factors include insulin omission, pancreatitis, stroke, dehydration, and certain medications (corticosteroids, thiazide diuretics, sympathomimetics, amphetamines/ecstasy, antipsychotics).
  - **Clinical manifestations:** Either condition can present with polyuria, polydipsia, weight loss, vomiting, dehydration, weakness, and altered mental status. Altered mental status that may progress to coma is the neurologic hallmark. Coma in diabetic ketoacidosis is due to acidemia and hyperosmolality; in hyperglycemic hyperosmolar states coma results from the hyperosmolality and hyperglycemia rather than ketoacidosis. Coma is more common in HHS than in DKA and correlated with hyperosmolality. Hyperglycemic hyperosmolar states may be associated with focal deficits, seizures (generalized or focal), and involuntary movements like chorea-ballismus. Also reported is epilepsy partialis continua in nonketotic hyperglycemia, and tremors. Seizures are rare in diabetic ketoacidosis due to the anti-epileptic effects of ketosis. Both DKA and HHS have a high incidence of thrombotic events due to elevation of proinflammatory cytokines. Gastrointestinal manifestations like nausea, vomiting, and abdominal pain are more common in DKA than HHS. Despite an underlying infection patients may be normothermic or hypothermic due to peripheral vasodilation.
  - **Investigations:** Either condition may be associated with leukocytosis. Nonspecific amylase and lipase elevation can be seen in DKA. Reversible subcortical white matter changes may be seen on brain MRI in patients with the hyperglycemic hyperosmolar state. Striatal T1 hyperintensity and subthalamic nucleus signal change may be seen with nonketotic hyperglycemia associated hemiballism. Cerebral edema is seen during the treatment phase of diabetic ketoacidosis. The cerebral edema may develop with
rapid treatment of hyperglycemia. An initial clinical and biochemical improvement may be followed by neurologic deterioration if the edema is not detected and treated early.

- **Management:** Fluid replacement followed by insulin therapy, hemodynamic monitoring, and correction of triggering factors are the mainstay of therapy. Overcorrection leading to hypoglycemia or hypokalemia need to be avoided. Cerebral edema is a complication of DKA that can be avoided by rapid reduction in plasma osmolality and blood glucose levels.

- **Update:**
  - Cerebrovascular disease: Diabetics have more than twice the risk of ischemic stroke after correction for other risk factors. Hyperglycemia is common during the acute period of stroke and can occur in patients with or without DM. Raised HbA1C may differentiate previously undiagnosed diabetics from those with stress hyperglycemia. Diabetes and the presence of hyperglycemia are risk factors for poor outcome in stroke. Acute ischemic brain injury may be exacerbated by acute hyperglycemia. The poor prognosis of hyperglycemia in acute ischemic stroke may be more of an issue in nondiabetics than in diabetics. The association between hyperglycemia and poor outcome after stroke is mainly relevant with large vessel infarction. However, that treatment of hyperglycemia is beneficial has not been demonstrated; there is infact danger of worsening due to hypoglycemia in patients with strict glucose control by intensive insulin therapy.
  - Cognition: Diabetes, in particular DM2 is associated with an increased risk of cognitive impairment and dementia, likely due to microvascular disease. The Rotterdam study showed that DM almost doubled the risk of dementia and AD. The increased incidence of AD in DM2 is associated with insulin resistance, hyperinsulinemia, hyperglycemia, and other factors such as hypercholesterolemia, hypertension, and obesity. Insulin deficiency can result in defects in neuronal integrity, connectivity, and neuronal loss in the developing brain. These observations have led to the concept of diabetic encephalopathy and the suggestion that AD may be thought of as type 3 diabetes. Patients with AD have been shown to have abnormalities in insulin and insulin-like growth factor type I and II signalling mechanisms in the brain. AD patients have derangements in brain glucose utilization and responsiveness to insulin and IGF stimulation. These observations have led to studies looking at intranasal insulin as a treatment option in Alzheimer disease. Very high blood glucose concentrations are associated with mood changes and poor memory function, possibly by causing alterations in cerebral blood flow or osmotic changes in neurones, and correction of acute hyperglycaemia appears beneficial.

- **Neuromuscular Complications of DM**
  - **Types:**
    - **Diffuse**
      - Diabetic sensorimotor polyneuropathy (often with autonomic &/ small fiber features)
      - Pandysautonomia
      - Diabetic cachexia
      - Insulin neuritis
    - **Focal**
      - Carpal tunnel syndrome
      - Ulnar nerve compression
      - Mononeuropathy (peroneal, radial)
      - CN (3, 7, 4)
      - Lumbosacral radiculoplexus neuropathy
      - Thoracoabdominal radiculopathy
Note:

- Diabetic cachexia is a rare disorder manifested by severe diffuse pain and paresthesia, SM PN, and weight loss in a diabetic patient that can be precipitated by rapid glycemic control with insulin therapy. Symptomatic recovery is associated with recovery of nerve function, indicating that the pathogenesis is due to hypoxia rather than ischemia.\textsuperscript{136}

- Insulin neuritis (treatment-induced diabetic neuropathy) refers to the development of neuropathic symptoms (often painful peripheral paresthesias) starting soon after initiation of insulin therapy and thought to be related to rapid normalization of nerve glucose levels. Autonomic neuropathy accompanies insulin neuritis with cardiovascular, gastrointestinal, genitourinary, and sudomotor symptoms.\textsuperscript{137} Spontaneous recovery is observed after 18 months of glycemic control. This entity differs from diabetic cachexia in that weight loss is not seen.

- Intensive glycemic control reduces the prevalence of diabetic sensorimotor polyneuropathy in patients with type 1 DM, but variable outcomes are observed in patients with type 2 DM. Strict glycemic control can be associated with negative effects such as increased mortality and no definite change in diabetic sensorimotor neuropathy.\textsuperscript{138} Independent of glycemic status, symptomatic distal symmetric neuropathy is more common in those with additional metabolic syndrome component.\textsuperscript{139}

- Spontaneous recovery is seen in some forms of diabetic neuropathy like lumbosacral radiculoplexus neuropathy, cranial mononeuropathy, thoracoabdominal radiculopathy, and insulin neuritis.

**Hypocalcemia and Hypercalcemia**\textsuperscript{140}

- **Hypercalcemia**\textsuperscript{141, 142}
  
  - **Causes:** Parathyroid adenoma is the commonest cause of primary hyperparathyroidism. Parathyroid carcinoma, parathyroid multiglandular hyperplasia, and tertiary hyperparathyroidism are additional causes. Chronic renal failure results in secondary hyperparathyroidism. Other causes include malignancy (humoral hypercalcemia of malignancy, bony metastasis, multiple myeloma, ectopic vitamin D production by tumors like lymphoma), endocrinopathies (adrenal insufficiency, MEN1, MEN2A, thyrotoxicosis, pheochromocytoma, VIPoma), granulomatous disease (TB, sarcoidosis, histoplasmosis, coccidioidomycosis), leprosy, Crohn, berylliosis), medications (estrogen, lithium, thiazide diuretics, excess vitamin D or A), immobilization, familial hypocalciuric hypercalcemia.
  
  - **Clinical manifestations:** Hypercalcemia can cause altered alertness and confusion which can progress to coma. Other manifestations of hypercalcemia include headache, lethargy, fatigue, and myalgias. Severe hypercalcemia can trigger PRES.\textsuperscript{143} Neuropsychiatric manifestations include irritability, depression, delirium, agitation, and hallucinations. Motor neuron disease-like symptoms have been reported with hypercalcemia but a causal link has not been established. Also reported are bradykinesia (parkinsonism)\textsuperscript{144} and rarely seizures. PRES has been reported due to severe hypercalcemia.\textsuperscript{145} CJD has been reported to present with hyperparathyroidism and seizures.\textsuperscript{146} Neuromuscular manifestations include generalized fatigue, proximal muscle weakness. Other organ systems may be affected: gastrointestinal (anorexia, nausea, vomiting, dyspepsia, abdominal pain); pancreatitis; renal (dehydration, polydipsia, oliguria, nephrocalcinosis); cardiac (vascular calcification, arrhythmias).

  - **Treatment:** Fluid repletion is important since patients in hypercalcemic crisis are hypovolemic. Biphosphonate therapy inhibits osteoclast activity but has a latency until peak effect of 2-5 days. Calcitonin causes acute lowering of calcium. Steroids have a role in granulomatous disease-associated hypervitaminosis D-related hypercalcemia and in lymphoma-related hypercalcemia and in multiple myeloma. Hypomagnesemia and hypophosphatemia may coexist and require treatment.
References:

- **Hypocalcemia**
  - *Causes:* Hypoparathyroidism leads to hypocalcemia. Clinical manifestations of low parathormone levels can result from a parathyroidectomy. Additional causes of parathyroid-related hypocalcemia include autoimmune hypoparathyroidism, postparathyroidectomy hungry bone syndrome, and certain familial syndromes (DiGeorge, Kearns-Sayre, Kenny-Caffey). Serum calcium also falls with reduction in serum protein (volume overload, chronic illness, malnutrition, nephrotic syndrome). Acid-base imbalance and gadolinium-based contrast agents can also cause this pseudohypocalcemia. Hypocalcemia in renal disease, parathyroid resistance, extravascular calcium deposition in acute pancreatitis, vitamin D deficiency or resistance, and with osteoblastic metastasis is associated with high PTH. Vitamin D deficiency and medications that reduce calcium (antiepileptics, chemotherapy drugs, bisphosphonates) cause hypocalcemia. Magnesium deficiency can reduce parathyroid secretion or cause resistance to the action of PTH. The former causes a low PTH and the latter causes a high PTH. Severe hypermagnesemia can also cause hypocalcemia with a low PTH.
  - *Clinical manifestations:* Hypocalcemia can be associated with alterations in cognition and alertness. Hypocalcemia can be associated with chorea or choreoathetosis. Seizures are more common with hypocalcemia than with hypercalcemia. Hypocalcemia can be associated with cramps, fasciculations, carpopedal spasms, finger paresthesias or perioral numbness. Severe hypocalcemia can be associated with laryngeal stridor and opisthotonus. QT prolongation is a well known manifestation of hypocalcemia and long standing cardiomyopathy can result in cardiomyopathy. Pseudotumor cerebri is a rare association of hypocalcemia.
  - *Treatment:* Calcium gluconate is preferred for acute correction as it causes less tissue necrosis than calcium chloride if extravasated. Vitamin D deficiency or hypomagnesemia if present need to be corrected.

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Plasma Cell Dyscrasias

- The most important condition associated with production of abnormal proteins are the plasma cell dyscrasias. Paraproteinemias may also be seen in context of connective tissue disease, vasculitis, malignancies like lymphoma/leukemia/others, or in the absence of known underlying disease.
- Neurologic manifestations related to paraproteinemias may include neuropathy, neurologic symptoms due to hyperviscosity, paraneoplastic disease (e.g., POEMS syndrome: polyneuropathy, organomegaly, endocrinopathy, M-spike, or monoclonal gammopathy, and skin changes), complications related to cryoglobulins (neuropathy, bleeding) and cold agglutinins (bleeding), and infections.
- Paraproteinemias affect 3-4% of the population over age 50 and over 5% of the population over age 70.1
- The paraproteinemias are a heterogeneous group of disorders that include monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma (MM), AL amyloidosis, Waldenström’s macroglobulinemia (WM), and POEMS syndrome. MGUS is the most common of the plasma cell dyscrasias. Peripheral neuropathy is the most common neurologic manifestation and can be seen in any of these plasma cell disorders.
- Monoclonal gammopathies are caused by a proliferation of monoclonal plasma cells or B lymphocytes. They are characterized by proliferation and deposition of M proteins or paraproteins, which are formed by a single heavy chain (M, G, or A) and a light chain (kappa or less commonly lambda).
- The commonest paraprotein in MGUS is IgG. Patients with a MGUS and neuropathy generally have IgM. The immunoglobulin in Waldenström macroglobulinemia is an IgM; in multiple myeloma/amyloidosis/POEMS an IgG or IgA. In AL amyloidosis and in POEMS the causal relationship between the neuropathy and underlying M protein is not suspect. Since neuropathy and an M protein are common, a cause-effect relationship between a PN and MGUS is more difficult to establish.2-10 An M-protein can be detected in 3-5% of patients with a PN.

HEMATOLOGY – NEUROLOGY
### Definition of Multiple Myeloma

- Clonal bone marrow plasma cells ≥10% or biopsy proven bony or extramedullary plasmacytoma* and
- ANY ONE OR MORE OF THE FOLLOWING MYELOMA DEFINING EVENTS (MDE)
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically
    - Hypercalcemia: Serum calcium >0.25 mmol/L (> 1mg/dL) above upper limit of normal or > 2.75 mmol/L (> 11 mg/dL)
    - Renal insufficiency: Creatinine Clearance <40 ml/minute** or Serum creatinine > 177 µmol/L (>2mg/dL)
    - Anemia: Normochromic, normocytic with a hemoglobin value of >2 g/dL below the lower limit of normal or a hemoglobin value <10 g/dL
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT†
  - Any one or more of the following biomarkers of malignancy
    - Clonal bone marrow plasma cell percentage* ≥ 60%
    - Involved/uninvolved serum free light chain ratio‡ ≥100
    - >1 focal lesions on magnetic resonance imaging studies‡‡

### Definition of Smoldering Multiple Myeloma

Both criteria must be met:
- Serum monoclonal protein (IgG or IgA) ≥3gm/dL or urinary monoclonal protein >500 mg per 24 hours and/or clonal bone marrow plasma cells 10%-60%, and
- Absence of myeloma defining events or amyloidosis

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*Clonality should be established by demonstrating kappa/lambda light chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should be preferably estimated on a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.

**Measured or estimated by validated equations.

†M If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.

‡These values are based on the serum Freelite® assay, The Binding Site, Birmingham, United Kingdom. The involved free light chain must be >100 mg/L.

‡‡Each focal lesion must be 5 mm or more in size

CT, computed tomography; PET-CT, (18) F-fluorodeoxyglucose positron emission tomography with computerized tomography.
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Definition</th>
<th>Progression Rate</th>
<th>Primary Progression Events</th>
</tr>
</thead>
</table>
| Non-IgM Monoclonal gammopathy of undetermined significance (non-IgM MGUS) | All 3 criteria must be met:  
- Serum monoclonal protein (non-IgM type) <3gm/dL  
- Clonal bone marrow plasma cells <10%*, and  
- Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) or amyloidosis that can be attributed to the plasma cell proliferative disorder | 1% per year | Multiple Myeloma, Solitary plasmacytoma, Immunoglobulin related amyloidosis (AL, AHL, AH) |
| IgM Monoclonal gammopathy of undetermined significance (IgM MGUS) | All 3 criteria must be met:  
- Serum IgM monoclonal protein <3gm/dL  
- Bone marrow lymphoplasmacytic infiltration <10%, and  
- No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, hepatosplenomegaly or other end-organ damage that can be attributed to the underlying lymphoproliferative disorder. | 1.5% per year | Waldenstrom Macroglobulinemia, Immunoglobulin related amyloidosis (AL, AHL, AH) |
| Light Chain MGUS | All criteria must be met:  
- Abnormal FLC ratio (<0.26 or >1.65)  
- Increased level of the appropriate involved light chain (increased kappa FLC in patients with ratio > 1.65 and increased lambda FLC in patients with ratio < 0.26)  
- No immunoglobulin heavy chain expression on immunofixation  
- Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) or amyloidosis that can be attributed to the plasma cell proliferative disorder | | Light Chain Multiple Myeloma, Immunoglobulin light chain amyloidosis |
| Solitary Plasmacytoma | All 4 criteria must be met  
- Biopsy proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells  
- Normal bone marrow with no evidence of clonal plasma cells  
- Normal skeletal survey and MRI of spine and pelvis (except for the primary solitary lesion)  
- Absence of end-organ damage | | Multiple Myeloma |
such as hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) that can be attributed to a lympho-plasma cell proliferative disorder

<table>
<thead>
<tr>
<th>Solitary Plasmacytoma with minimal marrow involvement**</th>
<th>All 4 criteria must be met</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Biopsy proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells</td>
<td></td>
</tr>
<tr>
<td>- Clonal bone marrow plasma cells &lt;10%</td>
<td></td>
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<tr>
<td>- Normal skeletal survey and MRI of spine and pelvis (except for the primary solitary lesion)</td>
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<tr>
<td>- Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) that can be attributed to a lympho-plasma cell proliferative disorder</td>
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</tr>
</tbody>
</table>

**Multiple Myeloma**

<table>
<thead>
<tr>
<th>POEMS Syndrome</th>
<th>All 4 criteria must be met</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Polyneuropathy</td>
<td></td>
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<tr>
<td>- Monoclonal plasma cell proliferative disorder (almost always lambda)</td>
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</tr>
<tr>
<td>- Any one of the following 3 other Major criteria:</td>
<td></td>
</tr>
<tr>
<td>1. Sclerotic bone lesions</td>
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<tr>
<td>2. Castleman’s disease</td>
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<tr>
<td>3. Elevated levels of vascular endothelial growth factor (VEGF)*</td>
<td></td>
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<tr>
<td>- Any one of the following 6 Minor Criteria</td>
<td></td>
</tr>
<tr>
<td>1. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)</td>
<td></td>
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<tr>
<td>2. Extravascular volume overload (edema, pleural effusion, or ascites)</td>
<td></td>
</tr>
<tr>
<td>3. Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)**</td>
<td></td>
</tr>
<tr>
<td>4. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails)</td>
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<tr>
<td>5. Papilledema</td>
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<tr>
<td>6. Thrombocytosis/polycythemia</td>
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</table>

**Note:** Not every patient meeting the above criteria will have POEMS syndrome; the features should have a temporal relationship to each other and no other attributable cause. Anemia and/or thrombocytopenia are distinctively unusual in this syndrome unless Castleman disease is present.
*The source data do not define an optimal cut off value for considering elevated VEGF level as a major criterion. We suggest that VEGF measured in the serum or plasma should be at least 3-4 fold higher than the normal reference range for the laboratory that is doing the testing to be considered a major criteria

** In order to consider endocrinopathy as a minor criterion, an endocrine disorder other than diabetes or hypothyroidism is required since these two disorders are common in the general population

<table>
<thead>
<tr>
<th>Systemic AL Amyloidosis</th>
<th>All 4 criteria must be met:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Presence of an amyloid-related systemic syndrome (such as renal, liver, heart, gastrointestinal tract, or peripheral nerve involvement)</td>
</tr>
<tr>
<td></td>
<td>• Positive amyloid staining by Congo red in any tissue (e.g., fat aspirate, bone marrow, or organ biopsy)</td>
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<tr>
<td></td>
<td>• Evidence that amyloid is light-chain related established by direct examination of the amyloid using Mass Spectrometry (MS)-based proteomic analysis, or immuno-electron microscopy, and</td>
</tr>
<tr>
<td></td>
<td>• Evidence of a monoclonal plasma cell proliferative disorder (serum or urine M protein, abnormal free light chain ratio, or clonal plasma cells in the bone marrow).</td>
</tr>
<tr>
<td><strong>Note:</strong> Approximately 2-3 percent of patients with AL amyloidosis will not meet the requirement for evidence of a monoclonal plasma cell disorder listed above; the diagnosis of AL amyloidosis must be made with caution in these patients.</td>
<td></td>
</tr>
</tbody>
</table>

Occasional patients may develop Multiple Myeloma

* A bone marrow can be deferred in patients with low risk MGUS (IgG type, M protein <15 gm/L, normal free light chain ratio) in whom there are no clinical features concerning for myeloma

** Solitary plasmacytoma with 10% or more clonal plasma cells is considered as multiple myeloma

¹ Patients with AL amyloidosis who also meet criteria for multiple myeloma are considered to have both diseases.

MGUS, monoclonal gammopathy of undetermined significance; AL, immunoglobulin light chain amyloidosis; AHL, immunoglobulin heavy and light chain amyloidosis; AH, immunoglobulin heavy chain amyloidosis; FLC, free light chain.

**MGUS**
- **Definition**
  - Monoclonal gammopathy of undetermined significance is a premalignant disorder characterized by limited monoclonal plasma cell proliferation in the bone marrow and
absence of end organ damage. By definition these are non-malignant gammopathies: monoclonal protein < 3 g/dl; < 10% plasma cells in marrow; no evidence of anemia, hypercalcemia, hepatosplenomegaly, renal failure, or bony plasmacytomas. Urinary Bence-Jones protein (urine monoclonal light chains) is usually absent.

- **Epidemiology**
  - MGUS (IgM or non-IgM [IgG/A]) occurs in 3% of individuals over 50 years. An additional 1% may have light chain-MGUS. The prevalence of monoclonal gammopathy increases with age (over 5% in those over 70 years). Prevalence rates are higher in men than women. The age-adjusted prevalence of MGUS is 3-fold higher in African Americans compared with whites.

- **Natural history**
  - The rate of progression of MGUS to multiple myeloma or related malignancies is 1% per year. The true lifetime probability of progression is lower when competing causes of death are taken into account: 11% at 25 years. The risk of progression does not decrease with time. IgM MGUS carries a risk of progression to Waldenström macroglobulinemia, while non-IgM MGUS carries a risk of progression to multiple myeloma.
  - The progression to (light-chain) multiple myeloma in patients with light-chain MGUS is 0.3% per 100 person-years. All forms of MGUS can progress to AL amyloidosis.
  - Additonally immunogenic properties of the M protein can cause organ damage (PN, MPGN, and necrobiotic xanthogranuloma).

- **Type of protein**
  - MGUS is classified as IgM and non-IgM types (IgG and IgA)
  - Although IgG is the most common paraprotein associated with MGUS, neuropathies are more common with IgM paraprotein. Kappa light chains are more common than lambda. The majority of patients with an IgM paraprotein have MGUS, the remainder may have Waldenström’s macroglobulinemia or another lymphoproliferative disorder.

- **Investigations**
  - A third of patients with a monoclonal gammopathy have a PN with a majority being IgM. For screening in patients with a peripheral neuropathy serum immunofixation and serum free light chain assay should generally suffice. Additional testing in patients with a M protein should include cell count, serum calcium, serum creatinine, urinalysis (protein excretion), 24 hr urine protein electrophoresis with immunofixation. A skeletal survey and bone marrow are considered in MGUS patients unless they are in the low risk category (<1.5 g/dl M spike, IgG, normal free light chain ratio). Serum free light chain ratio and 24 hour urine protein electrophoresis and immunofixation have utility particularly if amyloidosis is suspect (small fiber neuropathy/autonomic manifestations).
  - A bone marrow aspirate and biopsy are indicated when the M protein level is greater than or equal to 1.5 g/dl and when abnormalities are noted in the cell count, serum calcium, serum creatinine, or skeletal survey. It should also be considered in patients with non-IgG MGUS and patients with an abnormal serum free light chain ratio.
  - A plasma VEGF level may be obtained if POEMS is suspect.

- **Follow up**
  - If there is no evidence of abnormalities on these tests and MGUS is likely, periodic follow up is required. The nature and frequency depends on the nature of the MGUS (IgG, IgA, IgM), the amount of M protein spike, and the free light chain ratio. IgG, M-protein < 1.5 mg/dl, and normal free light chain ration defines the low risk group. Greatest risk of progression is seen with a non-IgG MGUS (IgM more than IgA), abnormal free light chain ratio, and a M-protein level > 1.5 g/dl. The percentage of clonal bone marrow plasma cells is the strongest predictor of progression. Patients with low-risk MGUS can be assessed in 6 months and then once every 2 years or possibly only at time of symptom progression. Others need reassessment at 6 months and yearly thereafter.

- **Neuropathy and MGUS**
  - IgM-associated neuropathies: 50% of MGUS are associated with an IgM gammopathy and upto 50% of patients with IgM MGUS have a symptomatic neuropathy. Overall a third of
patients with MGUS have a neuropathy and IgM is seen in about half of patients with MGUS neuropathy.

- **Anti-MAG (anti–myelin associated glycoprotein)**
  - 50% of IgM-associated MGUS neuropathies have antibodies against myelin-associated glycoprotein (anti-MAG). The presence of anti-MAG antibodies in a patient with MGUS has been suggested by some to predict the future development of a neuropathy.\(^2\) These patients are often older men who present with a slowly progressive, painless, large fiber, sensorimotor, demyelinating neuropathy that may be associated with hand tremors and prominent sensory ataxia.\(^10,23,24\) The characteristic clinical picture goes by the acronym DADS (distal acquired demyelinating sensory neuropathy).\(^25\) Immunofluorescent techniques on nerve biopsy show IgM deposition on the myelin sheath. A characteristic finding on electron microscopy is separation of outer layers of compacted myelin. Specific treatment with IVIG, PLEX, steroids, rituximab or cytotoxic therapy should likely be reserved for patients with moderate or severe impairment and a progressive course.\(^10,26-29\)

- **Non-MAG IgM MGUS**
  - This group resembles anti-MAG neuropathy but tests of anti-nerve antibodies are negative or reveal antibodies of indeterminate significance (sulfatides, myelin basic protein, gangliosides, sulfate-3-glucuronyl-paragloboside). Nerve biopsy does not show myelin deposition of antibodies or myelin lamellar splitting as seen in anti-MAG neuropathy. In some cases there are axonal changes rather than evidence of demyelination. Amyloidosis should be excluded in these cases. Treatment is symptomatic.

- **Higher age at onset and demyelination increase the risk, whereas anti-MAG antibodies decrease the risk, of developing Rankin Scale score \(> or \equiv 3\) in polyneuropathy associated with immunoglobulin M monoclonal gammopathy (IgM MGUSP).\(^30\)

- **Ig-G and IgA MGUS neuropathies:** Neuropathies associated with IgG and IgA are more heterogeneous and less common than the IgM neuropathies. These are most often axonal and don’t benefit from immunomodulatory therapy. Unless an IgG monoclonal gammopathy is associated with myeloma, amyloid, or POEMS; it is possible that its detection may be an incidental finding. Treatments similar to those used in CIDP may have a possible role in the demyelinating subgroup: these treatments are more likely to be helpful than in those with IgM-MGUS.\(^10\)

- **MPGN and MGUS**
  - Monoclonal gammopathy has also been recognized as an important cause of membranoproliferative glomerulonephritis.\(^37,32\)

- **Vasculitides and MGUS**
  - Of the vasculitides associated with MGUS, those that are monoclonal IgA may result in a cutaneous vasculitis (eg, leukocytoclastic, erythema elevatum diutinum)

**Multiple Myeloma**\(^33\)

- Multiple myeloma (MM) is the second most common hematologic malignancy (after non-Hodgkin lymphoma). The median age of onset is 70 years. MM is almost always preceded by a MGUS. At times an intervening stage called smoldering myeloma may be identified.

- Multiple myeloma is associated with high serum and urinary concentrations of monoclonal proteins, infiltration of bone marrow by malignant plasma cells, and multiple bony plasmacytomas.

- Using fluorescent in situ hybridization, cytogenetics, and plasma cell labeling index two groups of MM are recognized: those in which MM cells are hyperdiploid, usually trisomies, (better outcome) and the nonhyperdiploid group (typically having translocations involving chromosome 14 Ig heavy-chain locus with other chromosomes that lead to activation of their oncogenes).\(^34\)

- Several variants of MM exist. **Plasma cell leukemia** is an aggressive disease with a poor prognosis. **Solitary extramedullary plasmacytoma** develops within the head and neck and typically has a good
prognosis but some later develop typical MM. **Solitary plasmacytomas** typically develop in the axial skeleton and most eventually develop into systemic disease. A small percentage of MM cases are **nonsecretory myelomas**. Approximately 15% of MM patients have only monoclonal free light chain and no monoclonal intact immunoglobulin secreted by the malignant clone.

- **Direct effects of myeloma**
  - Spinal involvement with root or cauda or cord compression may require steroids, pain control, radiation, chemotherapy, and in some cases surgery. This may result from an extramedullary plasmacytoma or a bony fragment due to vertebral body fracture. The thoracic region is most commonly affected.
  - Mononeuropathies, plexopathies, myelomatous infiltration of the dura, leptomeningeal myelomatosis, parenchymal involvement by plasma cells, and dural or parenchymal plasmacytomas are very rare. Brain involvement in MM is more commonly due to hematologic spread rather than direct extension and generally occurs with relapsed or refractory disease.
  - Hyperviscosity occurs with immunoglobulin concentration over 4000 mg/dl. It may be associated with epistaxis, gingival bleeding, visual changes, headache, dizziness, vertigo, nystagmus, decreased hearing, ataxia, paresthesia, coma, and hemorrhage. A fundus exam may show retinal vein engorgement, flame-shaped hemorrhages, or rarely papilledema. **PLEX** may be required in addition to systemic therapy. \(^\text{35}\)
  - 10-20% of patients with multiple myeloma develop a neuropathy. \(^\text{3,36}\) 30% of cases are due to perineural deposition of IgG and IgM, with or without amyloidosis. Neuropathies associated with typical lytic multiple myeloma include a distal sensorimotor neuropathy, a CIDP-like syndrome, and a sensory neuropathy resembling carcinomatous ataxic sensory neuropathy. These patients may also develop amyloid neuropathy. A painful small-fiber neuropathy with autonomic features should suggest amyloidosis. Carpal tunnel syndrome may be present.

- **Indirect effects of myeloma**
  - Renal failure, dehydration, and hypercalcemia in a patient with myeloma can result in an encephalopathy. Hyperammonemia due to possibly excess ammonia production by myeloma cells may also be responsible for encephalopathy. Light chain deposition can cause a rapidly progressive nephropathy. Additional causes of nephropathy include amyloidosis, hypercalcemia, pyelonephritis, and hyperuricemia. Complications can result from anemia, infections, and immunosuppression. Thalidomide and bortezomib used in treatment of MM are associated with neuropathy, often painful.

- **Treatment**
  - Treatment of neuropathies associated with myeloma is directed at the underlying disease. \(^\text{37,38}\) Therapeutic options include melphalan, prednisone, thalidomide, lenalidomide (an analogue of thalidomide with lesser toxicity), bortezomib, and stem cell transplant. Prolonged use of thalidomide can result in a predominantly sensory neuropathy. \(^\text{39}\) Bortezomib, a protease inhibitor, affects the dorsal root ganglion and causes a dose dependent small fiber painful neuropathy in up to 30% of patients. \(^\text{36,39-42}\) Weekly administration of bortezomib reduces the incidence of neuropathy and the neuropathy tends to improve with dose reduction or discontinuation. CyBorD (cyclophosphamide, bortezomib, dexamethasone) has been used for myeloma and light chain amyloidosis.

**Free Light Chains**

- Monoclonal light chain diseases (light chain multiple myeloma, AL, light chain deposition disease) and nonsecretory multiple myeloma often don’t have serum monoclonal proteins in high enough concentration to be detected and quantitated by SPEP. In such cases FLC assay can provide a positive identification of a monoclonal serum light chain when the serum IF is negative. It can also be useful to monitor disease activity in patients with NSMM and AL.

- Changes of $>25\%$ or trending of multiple specimens is required to conclude biological significance. Lipemia interferes with testing. FLC increase may be seen with renal insufficiency or polyclonal hypergammaglobulinemia.

**Solitary Plasmacytoma**
- Solitary plasmacytoma may be confined to bone or occur in extramedullary sites (upper respiratory tract, gastrointestinal tract, CNS etc).
- To make the diagnosis the bone marrow should be normal and there should be no evidence of end-organ damage that can be attributed to a plasma cell proliferative disorder. Evidence of clonal plasma cells is seen on biopsy of the solitary lesion. In addition to a skeletal survey an MRI of the spine and pelvis should be performed since occult lesions can otherwise be missed.
- Patients with a solitary plasmacytoma are at risk of progression to multiple myeloma. Patients with a serum M protein greater than 1 g/dl have a high risk of persistence of an M protein after radiation. M protein persistence a year after radiation in associated with an increased chance of progression to multiple myeloma. While progression to myeloma generally occurs in the first 3 years, life-long follow up is required.

**Systemic AL (Immunoglobulin Light Chain) Amyloidosis**

- AL amyloidosis (previously called primary amyloidosis) refers to the type of amyloidosis generally derived from the variable portion of a monoclonal light chain and occurs as a result of a clonal plasma cell proliferative disorder. The hallmark is deposition of fibrillary monoclonal light chains in various tissues. AL amyloidosis may be localized (a benign disorder) or systemic. Systemic AL amyloidosis is also referred to as primary systemic amyloidosis (PSA) or primary amyloidosis. Systemic AL amyloidosis and multiple myeloma or Waldenström’s macroglobulinemia or NHL can coexist in the same patient. Most cases of systemic AL amyloidosis occur in the absence of a malignant plasma cell dyscrasia.

**Clinical manifestations:**
- PSA is suspected when a disease like neuropathy (peripheral neuropathy, autonomic neuropathy), restrictive cardiomyopathy, nephrotic syndrome is accompanied by a plasma cell proliferative disorder (as suggested by the presence of a serum or urine monoclonal protein). Other stigmata may include macroglossia and purpura (periorbital or facial). Liver or gastrointestinal or pulmonary involvement may be seen. Systemic manifestations include fatigue and weight loss. Clinical manifestations result from tissue deposition of fragments of the variable portion of a monoclonal light chain, most often lambda. A similar illness occurs in an inherited form (transthyretin-related). Amyloidosis secondary to chronic inflammatory disease is not associated with neuropathy.
- At diagnosis 17% of patients with PSA have a peripheral neuropathy. The neuropathy is caused by deposition of amyloid fibrils within the wall of nerve vessels. The neuropathy is most commonly a distal, symmetric, sensorimotor neuropathy with autonomic involvement; its presence is a patient with PSA is considered a poor prognostic marker. Rarely patients can present with focal nerve involvement due to an amyloidoma. A third of patients have muscle weakness in some cases be accompanied by dysphagia, myalgias, macroglossia, jaw claudication, and hoarseness. A third of patients have muscle pain. A coexisting neuropathy may be evident on electrodiagnostic studies. CPK is often normal. Elevation of cardiac troponin T levels in the absence of cardiac disease is a clue to diagnosis. A recent study noted that median time from symptom onset to diagnosis is almost 2 years. The same study noted median overall survival of 32 months. Factors associated with inferior survival include involvement of more than two organs, cardiac involvement, and absence of stem cell transplant.

**Diagnosis:**
- Biopsy of the iliac crest bone marrow combined with abdominal subcutaneous fat aspiration will identify amyloid deposits in 85% of patients. Diagnosis requires documentation of positive amyloid staining on tissue biopsy (fat aspirate, marrow, other organ) and supporting evidence that the amyloid is derived from immunoglobulin light chains (direct amyloid examination by immunoperoxidase staining, direct sequencing etc). Evidence of a monoclonal clonal plasma cell proliferative disorder is provided by serum or urine M protein (λ light chain), abnormal FLC ratio, or clonal plasma cells in the marrow. Immunofixation reveals an M protein in the serum or urine in most patients (> 95%). Those lacking an M protein may have inherited disease. The FLC ratio is abnormal in most. Regardless of the number of
plasma cells in the marrow, the syndrome is called PSA as long as amyloid fibrils are composed of immunoglobulin light chain (usually \(\lambda\) isotype).

- **Treatment:**
  - Unsatisfactory results with melphalan and prednisone have resulted in stem cell transplantation as the possible preferred therapy.\(^{11,55,56}\) Treatment-related mortality is higher than in myeloma. Patients ineligible for stem cell transplantation may benefit from melphalan and dexamethasone.\(^{57}\) Improvement in free light chain assay correlates with improvement in neuropathy. Additional options include thalidomide and dexamethasone or lenalidomide\(^{58,59}\) CyBoRD (cyclophosphamide, bortezomib, dexamethasone) has been used for myeloma and light chain amyloidosis.

- **Note:**
  - The prognosis and presentation for AL amyloidosis is similar to AH amyloidosis.
  - AA amyloidosis was previously called secondary amyloidosis. The precursor protein is serum amyloid A protein.
  - The precursor protein for ALECT2 is leukocyte chemotactic factor. (Renal presentation, acquired)
  - A\(\beta\)2M has \(\beta\)2 microglobulin as precursor protein. Implicated in CTS/arthropathy.
  - The precursor protein for AGel is gelsolin. Clinically presents as cranial neuropathy.

**Familial Amyloid Polyneuropathy**
- FAP is a rare, hereditary, autosomal dominant form of amyloidosis caused by transthyretin (TTR) gene mutations. Val30Met is the most common gene mutation in FAP. hMIsfolding and aggregation of the TTR protein results in formation of insoluble amyloid fibril.\(^{60}\) Tissue deposition of mutant and wild-type TTR fibrils results in peripheral neuropathy, autonomic neuropathy, &/cardiomyopathy. Survival after diagnosis is typically 5 to 15 years.\(^{61,62}\) Diflunisal, a NSAID, stabilizes transthyretin tetramers and prevents amyloid fibril formation in vitro. A recent randomized, double-blind, placebo controlled study noted reduced rate of progression of neurological impairment over two years in patients with FAP.\(^{63}\) Another drug – tafamidis – showed slower progression in FAP patients who received the drug but the difference was not statistically significant.
- ATTR can be from mutated TTR (FAP) or wild type TTR (age related/ senile). Latter can be associated with restrictive CMP/CTS.

**POEMS (Osteosclerotic Myeloma)**\(^{64,65}\)
- POEMS syndrome is a rare paraneoplastic syndrome due to an underlying plasma cell disorder. Unlike typical MM, POEMS is associated with sclerotic rather than lytic bone lesions. Additionally bone pain and progressive anemia are uncommon and renal failure when present is not related to light chain disease. Polyneuropathy is rare in typical lytic multiple myeloma but occurs very commonly in osteosclerotic myeloma (POEMS). Further, patients with osteosclerotic myeloma are not systemically ill, have an indolent course, and a prolonged survival.
- The acronym refers to many but not all features of the syndrome: polyradiculoneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes. Not all features of the acronym are required to make the diagnosis.
- Other important features not included in the acronym but included in the diagnostic criteria are indicated below:

*Diagnostic Criteria for POEMS*\(^a\) (also see table at start of this section)

<table>
<thead>
<tr>
<th>Mandatory major criteria</th>
<th>Other major criteria (one required)</th>
<th>Minor criteria (one required)</th>
<th>Other symptoms and signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyneuropathy (typically demyelinating)</td>
<td>Castleman disease(^b)</td>
<td>Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)</td>
<td>Clubbing</td>
</tr>
<tr>
<td>Monoclonal plasma cell-proliferative disorder (almost always (\lambda))</td>
<td>Sclerotic bone disease</td>
<td>Extravascular volume overload (edema, pleural effusion, or ascites)</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Vascular endothelial growth factor elevation</td>
<td>Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)</td>
<td>Hyperhidrosis</td>
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<td>--------------------------------------------</td>
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</tr>
<tr>
<td>Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangioma, plethora, acrocynosis, flushing, white nails)</td>
<td>Pulmonary hypertension/ restrictive lung disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papilledema</td>
<td>Thrombotic diathesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytosis/ polycythemia</td>
<td>Diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low vitamin B&lt;sub&gt;12&lt;/sub&gt; values</td>
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</tbody>
</table>

**Note:**

a. Polyneuropathy, Organomegaly, Endocrinopathy, M protein, Skin changes - POEMS. Other names: Osteosclerotic myeloma, Takatsuki syndrome, Crow-Fukase syndrome

b. The syndrome should be distinguished from the Castleman disease variant of POEMS syndrome, which has no clonal plasma cell disorder and typically little or no peripheral neuropathy but has several of the minor diagnostic criteria for POEMS syndrome.

c. The diagnosis of thyroid disease or diabetes is not sufficient to meet this criteria.

- **Clinical Features:**
  
  - Patients are typically in their late 40s and often have a severe sensorimotor neuropathy. The syndrome is commonly mistaken for CIDP. Elevated VEGF levels and thrombocytosis in a patient with possible CIDP should prompt consideration of POEMS. Patients with POEMS are more likely to be older and have a painful component to their neuropathy with significant weakness and wasting; cranial nerve involvement is less likely. The distal involvement is more severe without sural sparing and the slowing is more uniform along the nerve. The neuropathy severity does not correlate with VEGF levels. Other clinical features are as in the diagnostic criteria noted above.
  
  - Patients with POEMS have a more painful component to their neuropathy with significant weakness and wasting; cranial nerve involvement is less likely. The distal involvement is more severe without sural sparing and the slowing is more uniform along the nerve. The neuropathy severity does not correlate with VEGF levels. Other clinical features are as in the diagnostic criteria noted above.

- **Investigations:**
  
  - Electrophysiology shows a demyelinating neuropathy with superimposed axonal loss, nerve biopsy shows endoneurial deposits and uncompacted myelin lamellae.
  
  - Compared with CIDP, neuropathy in POEMS is associated with greater axonal loss, greater slowing of the intermediate nerve segments, less common temporal dispersion and conduction block, and absent sural sparing. These findings imply that the pathology of POEMS syndrome is diffusely distributed (uniform demyelination) along the nerve where the pathology of CIDP is probably predominantly proximal and distal.

- **Treatment:**
  
  - Patients with an iliac crest bone marrow biopsy that does not reveal a plasma cell clone are candidates for local radiation therapy. Patients with diffuse sclerotic lesions or disseminated bone marrow involvement or disease progression 3 to 6 months after completing radiation need systemic therapy. Those with 2 or fewer lesions may get curative doses of radiation to the affected sites. Corticosteroids have a temporizing role. Definitive treatment includes alkylators (low dose conventional therapy or high dose with stem cell transplantation). Autologous stem cell transplantation has been associated with improvement or stabilization of neuropathy. Lenalidomide shows promise. Lenalidomide possesses immunomodulatory and antiangiogenic properties. Its exact mechanism of action is unknown but it has been
shown in vitro to affect inflammatory cytokines and inhibit cell proliferation of various cell lines. The benefit of thalidomide and bortezomib is countered by the risk of exacerbating the neuropathy. The data on anti-VEGF antibodies is conflicting.

**Castleman disease**
- Castleman’s disease (CD, angiofollicular lymph node hyperplasia) is a heterogenous group of lymphoproliferative disorders associated in a subset of cases with the human immunodeficiency virus (HIV) and human herpesvirus 8 (HHV-8).
- CD comprises at least two distinct diseases (unicentric and multicentric). It is the multicentric form that is associated with prominent systemic symptoms, immunosuppression, and HHV-8.
- CD may also be associated with other malignancies, including Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, and POEMS syndrome.

**Waldenström’s macroglobulinemia (includes what was previously called lymphoplasmacytic lymphoma)**
- WM is a clonal IgM monoclonal protein secreting lymphoid and plasma cell disorder. The size of the M protein is immaterial (earlier patients with an IgM M protein level less than 3 g/dl who met the criteria for WM had been classified as having “lymphoplasmacytic lymphoma with an IgM M protein”). There is > 10% bone marrow lymphoplasmacytic infiltration by small lymphocytes that show a plasmacytoid or plasma cell differentiation and a typical immunophenotype that excludes other lymphoproliferative disorders. Smoldering Waldenström’s macroglobulinemia is defined as serum IgM monoclonal protein > 3 g/dl and/ or bone marrow lymphoplasmacytic infiltration > 10% and no evidence of end-organ damage.

**Clinical manifestations:**
- **Non-neurologic:** Clinical manifestations include those related to anemia, constitutional symptoms (fatigue, weight loss, night sweats), hepatosplenomegaly, lymphadenopathy, hyperviscosity, cryoglobulinemia, and neuropathy.
- **Neuropathy:** Symptomatic neuropathies occur in 5-10% of WM. They resemble the neuropathy seen in IgM MGUS. A more severe phenotype resembling a polyradiculoneuropathy may be seen. WM has been reported with anterior horn cell disease but whether the gammopathy plays any role in the anterior horn cell involvement is unclear.
- **CNS:** CNS involvement is a rare complication on WM and is called the Bing-Neel syndrome. Perivascular infiltration with small lymphocytes, lymphoplasmacytoid cells, and plasma cells is seen. The infiltrates surround Virchow Robin spaces, perivascular spaces, and leptomeninges and can coalesce to be more solid and tumor-like. Leptomeningeal involvement is more common than parenchymal involvement. Symptoms may result from a stroke, subarachnoid hemorrhage, or encephalopathy. Seizures, headaches, cognitive decline, paresthesias, weakness, hearing impairment, dizziness, ataxia and sixth cranial nerve palsy are some of the reported clinical features. Though rare, a myelopathy from WM has also been reported. Bing-Neel syndrome can be the presenting manifestation of WM though some patients may have a prior diagnosis of MGUS. Its appearance in a patient with WM may not be accompanied by evidence of systemic progression.

**Pathophysiology:**
- The underlying mechanism for the neurologic manifestations is infiltration or hyperviscosity.

**Investigations:**
- Enhancing lesions on brain MRI (subcortical-periventricular, brainstem, dural, leptomeningeal) and lymphocytosis on CSF may be seen. Meningeal involvement has been reported. The CSF protein is elevated and IgM κ or λ light chain restriction is seen. A biopsy is often required for a definitive diagnosis. Therapeutic options include radiation,
rituximab, and chemotherapeutic agents like methotrexate, carmustine, 2-chlorodeoxyadenosine, and cyclophosphamide (with steroids).\textsuperscript{80}

- **Treatment:**
  - Treatment options include rituximab, fludarabine or cladarabine, chlorambucil, thalidomide, bortezomib, RCHOP, interferon alpha, methotrexate, carmustine, 2-chlorodeoxyadenosine, cyclophosphamide (with steroids), radiation, and stem cell transplantation.\textsuperscript{80, 88} PLEX is indicated for treatment of hyperviscosity syndrome.\textsuperscript{89} Rituximab may be used to treat neuropathy in the absence of a symptomatic lymphoma.\textsuperscript{78}

### Cryoglobulinemia

- A minority of patients with MM, WM, and MGUS have cryoglobulins. These are immunoglobulins that reversibly precipitate at temperatures below 37 degrees C. A mononeuropathy multiplex or a symmetric sensorimotor neuropathy may be seen.\textsuperscript{90} Nerve biopsy may show epineural vasculitis. (see section on Rheumatology)
- I: with B-cell lymphoproliferative disorders
- II: with hepatitis C
- III: with connective tissue diseases

### Light chain deposition disease

- Light chain deposition disease has a similar pathogenesis and shares some clinical manifestations with AL amyloidosis: the primary difference is that deposited light chain fragments generally do not form fibrils. Peripheral nerves are spared also so in secondary amyloidosis). Solid organ failure may be present.

### Hemoglobinopathies: Sickle cell disease

- Hemoglobinopathies result from genetic variations that result in the production of abnormally shaped or reduced amounts of hemoglobin.\textsuperscript{91} Sickle cell anemia is a group of conditions in which HbS is the predominant hemoglobin. Hemoglobin SS (sickle cell disease) is the most common hemoglobinopathy in North America. The disease is particularly common in African Americans. The sickle cell trait (HbS/HbA) is seen in approximately 8% of African Americans but is generally not symptomatic.\textsuperscript{91}
- **Genetics:** The underlying molecular lesion is a point mutation (GAG to GTG) in exon 1 of the β-globin gene. This results in substitution of valine for glutamine at position 6 of the β-globin peptide chain which causes abnormal polymerization and sickling. In the initial stages sickling is reversible with reoxygenation.
- **Clinical features:**
  - **Hemolytic anemia:** The misshapen red cells are eventually destroyed resulting in hemolytic anemia.
  - **Vaso-occlusive episodes:** Vaso-occlusive episodes result in infarction in many organs. These vaso-occlusive events are likely not entirely due to sludging of sickled cells but may result from endothelial activation, inflammation, abnormal adhesion, and hypercoagulability.\textsuperscript{91, 92}
  - **Vasculopathy:** Vasculopathy involving small and large vessels is an additional cause of organ ischemia.\textsuperscript{91, 92} Most clinically relevant strokes are due to large vessel vasculopathy. The presence of moyamoya collaterals increases the risk of recurrent cerebrovascular events in patients with sickle cell disease despite chronic transfusions.\textsuperscript{94} Other neurologic complications in sickle cell anemia include silent infarcts, cerebral atrophy, neurocognitive and behavioral manifestations.

### Neurologic complications of hemoglobinopathies\textsuperscript{91}

<table>
<thead>
<tr>
<th>Cerebral infarction (silent &amp; overt)</th>
<th>• Common, particularly in children and elderly\textsuperscript{93} • Risk factors: h/o TIA, elevated systolic pressure, low steady state hemoglobin concentration, recent vasoocclusive crisis of pulmonary vasculature\textsuperscript{93} • Children with asymptomatic lesions may be at higher stroke risk\textsuperscript{95}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral hemorrhage (subarachnoid-aneurysm,</td>
<td>• Rare in childhood, peak in third decade • Progressive course due to a large vessel vasculopathy may result from</td>
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intraparenchymal) development of a moyamoya syndrome.

Meningitis
- Functional asplenia and predisposition to *Streptococcus pneumoniae*, *Hemophilus influenzae*
- Use of prophylactic and empiric antibiotics and *S pneumoniae* polysaccharide vaccine

Cognitive impairment, seizures, headache
- Often related to infarction (less commonly infection or venous thrombosis)
- Hemolysis may cause folate deficiency which may be exacerbated to anti-epileptic drugs
- An additional cause of headache may be orofacial and dental pain related to focal sickling crisis

- **Stroke Prevention in Sickle Cell Anemia**
  - *Transcranial Doppler*: Transcranial Doppler is used to identify high risk individuals for stroke. (Stroke Prevention Trial in Sickle Cell Anemia). Sick cell disease patients at high risk of stroke (and transfusion consideration) include those with two mean velocity readings greater than 200 cm/s. Periodic blood transfusion therapy that lowers HbS to <30% in children from 2 to 16 years with abnormal TCD studies resulted in a 92% reduction in stroke. Stroke risk is low before 2 years of age because of the protective effects of fetal hemoglobin on sickling. Screening should be initiated at 2 years of age and a normal result confirmed yearly until 11 years of age. Those with abnormal velocities are monitored more frequently.
  - *Transfusion*: Periodic transfusions in children (aged 2 to 16) afflicted by sickle cell disease and abnormal TCD velocities are recommended. Transfusions are targeted to reduce the HbS to less than 30% of the total hemoglobin. Iron overload is a major concern. The duration of chronic transfusion is controversial. The SIT trial (Silent cerebral infarct transfusion trial) showed that children with silent infarcts on MRI may benefit from periodic transfusions regardless of transcranial Doppler.
  - *Other options*: In children at high risk for stroke who are unable or unwilling to be treated with regular red blood cell transfusion, it might be reasonable to consider hydroxyurea or bone marrow transplantation. Long term transfusions is also associated with the risks of alloimmunization and iron overload. A randomized controlled trial supporting use of hydroxyurea in primary stroke prevention has not been performed.

- **Stroke Treatment in Sickle Cell Disease**
  - Tissue plasminogen activator is not recommended for treatment of strokes in children with sickle cell disease (it can possibly be used in adults with the usual tPA caveats). Correction of hypotension, hypoxemia, and addressing hydration status are all important as is exchange transfusions directed at reducing sickle hemoglobin to less than 30% of total hemoglobin. Stroke recurrence rate is approximately 66% and is greatest during 2-3 years after the initial stroke. Scheduled transfusions to keep percentage of HbS to less than 30% decrease the recurrent stroke risk to less than 10%. While switch to hydroxyurea and phlebotomy for secondary stroke prevention seems like an attractive alternative to transfusions and chelation, the SWITCH trial (Stroke with Transfusions Changing to Hydroxyurea) trial showed superiority of the latter approach.

- **Thalassemias**
  - The thalassemias are a group of congenital anemias that have in common a deficient synthesis of one or more of the globin subunits of the normal human hemoglobin. The thalassemias represent the most common monogenetic disorder worldwide. Thalassemia major warrants regular blood transfusion starting at an early age. Thalassemia heterozygosity confers some immunity against malaria.
  - Neurological complications of thalassemia result from chronic hypoxia, bone marrow expansion, iron overload, folic acid/ vitamin B12 deficiency and iron chelator – related neurotoxicity. Not infrequently neurological complications are subclinical.
  - **Extramedullary hematopoiesis**: Extramedullary hematopoiesis is a physiological compensatory phenomenon that occurs because insufficient bone marrow function is unable to meet demands. It may affect the spinal canal or peripheral/ cranial nerves. Spinal epidural hematopoietic tissue may extrude through the trabecular bone of the vertebral body or extend through thin trabeculae at the proximal end
of ribs. The thoracic region is most commonly involved. Paraspinal tumors with or without cord compression may be seen. Majority of patients with this are asymptomatic. Management options include blood transfusion, radiotherapy, surgical decompression, hydroxyurea, or a combination of these modalities.

- **Desferrioxamine toxicity**: Clinically used iron chelators include desferrioxamine, deferiprone, and deferasirox. Desferrioxamine can cause dizziness, peripheral neuropathy, paresthesias, seizures, hearing loss, tinnitus, and visual disturbance (decreased acuity, blurred vision, dyschromatopsia, night blindness, field defects, scotoma, pigmented retinopathy, optic neuritis, cataracts). 104

- **Other complications**: Neurocognitive issues are likely related to the challenges associated with chronic disease. 104 Thalassemia may be associated with masked vitamin B12 or folic acid deficiency. Chronic hemolysis results in a hypercoagulable state and may cause cerebral infarcts, often silent. This may be due to hypercoagulability-related thromboembolism or due to cardioembolism. 103

**Thrombotic Thrombocytopenic Purpura**

- TTP is a fulminant multisystem consumptive coagulopathy classically defined by the pentad of fever, renal dysfunction, microangiopathic hemolytic anemia, thrombocytopenia, and CNS involvement.
- ADAMTS13 is a plasma metalloproteinase that cleaves von Willebrand Factor multimers. TTP results from a primary deficiency of ADAMTS13 or due to acquired inhibition of the enzyme. 106
- Neurologic involvement at presentation is reported in half of patients with TTP. 107 Ultimately 90% of patients have CNS involvement. 108
- PRES is the most common brain imaging abnormality in severe manifestations of TTP. Large infarctions and hemorrhage are infrequent. Abnormal brain imaging does not seem to impact patient outcome and full neurologic recovery is possible even in comatose patients with extensive brain abnormalities on MRI. 109
- Neurologic abnormalities can precede the onset of striking hematologic abnormalities in TTP. Atypical TTP may be the underlying stroke etiology in young and middle-aged women without cardiovascular risk factors and subtle or no hematologic abnormalities. 110

**Leukemias and Lymphomas**

- Leukemias are neoplasms of myeloid and lymphoid precursors. 33 The term traditionally refers to malignant changes in hematopoietic stem cells from which mature myeloid and lymphoid blood cells develop; they are associated with widespread involvement of the marrow and peripheral blood. They can be acute or chronic and are classified further depending on whether the abnormal excessive blast cells are myeloid or lymphoid.
- Lymphomas are solid lymphoid tissue tumors. The term traditionally refers to proliferation of lymphoid cells that arise as discrete tissue masses. Most lymphomas are of B-cell origin (less commonly of T-cell origin). Lymphomas include Hodgkin lymphoma (HL) and the larger, less specific category of non-Hodgkin lymphoma (NHL). NHL cells circulate within the vascular system and are often widespread at the time of diagnosis. HL cells spread contiguously from their site of origin.
- A tissue characterization is always required.
- Neurologic involvement is seen in a third of patients with lymphoma and is more common in NHL than in HL. Leptomeningeal involvement is the most common complication. Epidural or intraparenchymal metastases can be seen as well.
- The incidence of neurologic complications in NHL is the highest in Burkitt and lymphoblastic lymphoma. 111 CNS prophylaxis is routinely used in these two situations.
- Unique manifestations include neurolymphomatosis and lymphomatosis cerebri for NHL and primary CNS angitis and paraneoplastic disease for HL.
- Neurologic manifestations in patients with leukemia and lymphoma may additionally result from
  - Infections: viral: EBV/VZV/CMV, fungal, parasitic, bacteria: eg Nocardia; Note: aspergillosis or mucormycosis with neutropenia; T cell dysfunction may necessitate inclusion of sulfadiazine or trimethoprim/ sulfamethoxazole to cover Nocardia
  - Treatment Chemotherapy: myelopathy with intrathecal methotrexate, ara-C, cisplatin/ neuropathy with vinca alkaloids, platinum compounds, taxanes, thalidomide, bortezomib, Revlimid/ cerebrovascular disease with bevacizumab, imatinib/ seizure with cisplatin, oxaliplatin, ara-C, cyclophosphamide/ aseptic meningitis with methotrexate/ encephalopathy
with ifosfamide, methotrexate, sorafenib/ cerebellar syndrome with ara-C, 5FU/ venous sinus thrombosis due to l-asparaginase therapy in ALL

- **Treatment Radiation**: a mineralizing microangiopathy with dystrophic grey matter calcification after radiation has been described.\(^\text{112}\)
- **Transplantation**: related complications.
- **Cerebrovascular disease**: Intracerebral hemorrhage related to coagulopathy (disseminated intravascular coagulation, thrombocytopenia, hyperviscosity) may be seen. Hyperviscosity in leukemia may be associated with increased intracranial pressure. Patients with leukemia (specially AML) may develop complications related to leukostasis (headache, dizziness, blurred vision, ataxia, confusion, stupor, coma)
- **Paraneoplastic disease**: cerebellar degeneration, sensory neuropathy, acute sensorimotor neuropathy, autonomic neuropathy, dermatomyositis-polymyositis, neuromyotonia; anti-Yo and anti-Tr associated with HL
- **Hematologic malignancy-related vasculitis**: have been described. The NHLs are more commonly associated with disorders like leukocytoclastic vasculitis, lymphocytic cutaneous granulomas, polyarteritis nodosa, and Henoch Schöönlein purpura than are HLs.\(^\text{33}\) Cryoglobulins are commonly seen in patients with NHL and vasculitis.

- **Lymphoma**
  - Lymphoma cells enter the CNS via a hematogenous route, contiguously from adjacent bones, or along neurovascular structures.\(^\text{113}\) CNS dissemination is generally in context of systemic recurrence and is seen with aggressive lymphomas like diffuse large B-cell, or T-cell lymphoma, or some cases of Burkitt lymphoma, or mantle cell lymphoma. An additional reason of CNS lymphoma is that poor CNS penetration of antineoplastic therapy results in the CNS becoming a protected site. The brain, cord (epidural or rarely intramedullary), leptomeninges, or eyes can be involved.\(^\text{114}\)\(^\text{115}\)\(^\text{116}\) Features associated with increased risk of CNS disease include age over 60, high International Prognostic Index, multiple sites of extranodal involvement, elevated LDH, and advanced stage.\(^\text{114}\) The presence of high risk features may prompt use of iv methotrexate. There is no evidence supporting use of prophylactic intrathecal chemotherapy. The median time to CNS involvement is less than a year and most present during treatment or shortly after completion.
  - **Intravascular lymphoma** is a rare subtype of extranodal large B-cell lymphoma that primarily affects the elderly. It can present with ischemic spinal cord or brain lesions.\(^\text{115}\) There may be cranial nerve, nerve root, peripheral nerve, or muscle involvement.\(^\text{116}\) Skin involvement is common. Liver, spleen, or marrow involvement may be present. There may be a role for skin or muscle biopsy; brain or leptomeningeal biopsy is often required.\(^\text{116}\)\(^\text{117}\) This is an aggressive disease that spares lymph nodes. Systemic symptoms, elevation of LDH and inflammatory markers may be a clue. MRI may show infarcts and widespread enhancement.\(^\text{118}\) FDG-PET is usually negative. Angiotropic large cell lymphoma has a predilection for tumor cells to aggregate inside vascular lumen.\(^\text{112}\) An Asian variant is associated with hemophagocytic lymphohistiocytosis syndrome. RCHOP is a commonly employed chemotherapy protocol but prognosis is poor. An Asian variant of intravascular lymphoma has been associated with hemophagocytic lymphohistiocytosis syndrome.\(^\text{119}\)
  - **Primary CNS lymphoma (PCNSL) – including lymphomatosis cerebri**\(^\text{120}\): PCNSL is a NHL, typically a diffuse large B-cell lymphoma. PCNSL comprises 0.8% of all lymphomas and 2.0% of all primary brain tumors. HIV testing is recommended in all cases.\(^\text{121}\) In HIV-related PCNSL a ring enhancing lesion may be seen. Toxoplasmosis therefore enters the differential diagnosis (factors that favor toxoplasmosis include non sub-ependymal location, multifocality, ring or nodular enhancement, decreased SPECT uptake, decreased rCBV, reduced choline peak on MRS). Immunocompetent individuals often have a uniformly enhancing lesion that may involve the cerebral hemisphere, thalamus or basal ganglia, corpus callosum, periventricular region, or cerebellum. Bulky infiltration of the corpus callosum is a characteristic sign.\(^\text{122}\) Meningeal dissemination can occur in PCNSL.\(^\text{121}\) Cauda equina involvement in PCNSL can resemble an inflammatory polyradiculoneuropathy.\(^\text{123}\) A rare manifestation of PCNSL is a diffuse infiltrating form without a mass lesion: *lymphomatosis cerebri*. These patients present with a rapidly progressive dementia and gait disorder with patchy T2 brain hyperintensities which are nonenhancing and suggest a diffuse
leukoencephalopathy. Treatment include high-dose methotrexate based chemotherapy; intrathecal administration may be required with a positive CSF cytology, radiation may be required with suboptimal response or relapse. Refractory cases may need autologous stem cell transplantation. Conditioning regimens may include BCNU, etoposide, cytarabine, and melphalan after high-dose methotrexate based induction. Other agents used include lomustine (CCNU), procarbazine, intrathecal or intraventricular rituximab, intraarterial carboplatin, topotecan, temozolomide etc.

- **Parenchymal intracranial metastasis:** These can develop prior to or with development of systemic disease or as the site of relapse without evidence of systemic disease. They are more common with NHL than with HL. Risk factors for intracranial metastases in HL include history of immunosuppression or prior EBV infection. Systemic chemotherapy and radiation are the treatment options.

- **Cord metastasis:** In NHL cord mets may be the presenting manifestation or site of relapse, in HL it is seen in the setting of advanced disease; in either situation it is rare. External beam radiation, high dose iv methotrexate, or other systemic chemotherapy are treatment options.

- **Dural and epidural lymphoma:** Primary dural lymphoma is rare and generally is an extranodal manifestation of a marginal zone lymphoma that arises from the dura. The primary differential diagnosis is meningioma. The tumor is radiosensitive, surgical resection is difficult, recurrence risk necessitates long-term monitoring. Leptomeningeal involvement (either primary or as part of systemic disease) can also be seen. Epidural metastases in NHL and less commonly HL develops from a paravertebral mass directly invading the epidural space through the intervertebral foramina. It may present with radicular or myelopathic manifestations. Treatment options include high dose steroids and radiation. Acute vertebral collapse with cord compression may require surgical decompression.

- **Leptomeningeal lymphoma:** The leptomeninges can be involved in patients with systemic non–Hodgkin lymphoma, secondary to dissemination in PCNSL, or in context of primary leptomeningeal lymphoma (PLML). Leptomeningeal involvement is the most common neurologic complication of NHL. Primary leptomeningeal lymphoma without synchronous parenchymal brain/spine or systemic disease is rare: approximately 7% of all PCNSL Patients usually present with multifocal symptoms. Investigations may show leptomeningeal enhancement and abnormal CSF studies (CSF cytology, flow cytometry and receptor gene rearrangement studies may show evidence of a monoclonal population). Eosinophilic pleocytosis or the Reed-Sternberg cell may be seen in HL. Rarely a leptomeningeal biopsy may be required. Treatment options include fractionated radiotherapy, systemic chemotherapy (often with intravenous methotrexate), intra–CSF chemotherapy (in the absence of CSF flow obstruction), or combinations of these. A recent report by the International Primary CNS Lymphoma Collaborative Group suggests that patients have a better prognosis than previously reported and a subset may be cured.

- **Cranial vault lymphoma:** Cranial vault lymphoma is generally a large B-cell lymphoma that presents in older individuals as a focal skull deformity or scalp swelling.

- **Neurolymphomatosis:** Neurolymphomatosis is characterized by infiltration of lymphomatous cells into the perineurium and endoneurium of peripheral nerves, plexus, dorsal root ganglia, or spinal roots. It can be a primary process or in the setting of systemic disease. The peripheral nerve involvement may be accompanied by leptomeningeal involvement. It may precede the detection of systemic lymphoma in half the patients or occur in patients in hematologic remission. It can present as a painful polynuropathy or polyradiculopathy, cranial neuropathy, painless polynuropathy, or a peripheral mononeuropathy. The cauda equine or sciatic nerve are commonly involved. Neurolymphomatosis is usually seen in context of a large B-cell lymphoma (less commonly T-cell NHL) but may also result from a PCNSL. Contrast-enhanced plexus or limb MRI or fused FDG PET/CT and directed biopsy (CD20 reactivity) are useful diagnostic aids. Nerve ultrasound may show nerve enlargement and increased blood flow and may be a useful diagnostic aid. Peripheral neuropathy is a common occurrence in NHLs associated with paraproteinemias. Recognition of systemic disease and staging are important. High dose iv methotrexate-based chemotherapy may be combines with intrathecal chemotherapy or external beam radiation. A median survival of 10 moths from diagnosis has been reported.
- **Paraneoplastic diseases**: Most paraneoplastic neurologic syndromes are not associated with an antibody. They are more common with HL and generally seen with disease that is not limited at time of diagnosis. Limbic encephalitis is seen in HL and may be associated with antibodies to metabotropic glutamate receptor 5 (mGluR5). Tumor treatment may result in full neurologic recovery. Paraneoplastic cerebellar degeneration also occurs almost exclusively in HL and may precede the diagnosis in a majority of patients. It may be associated with anti-Tr antibodies. This is often irreversible but likely has a better prognosis when seen in the setting of HL as compared to solid tumors. Primary angiitis of the CNS is an antibody negative paraneoplastic association of HL shows clinical manifestations due to small infarcts. Cyclophosphamide and steroids are the mainstay of treatment. It is important to exclude zoster. Cancer associated myositis occurs in NHL in patients over 50–generally dermatomyositis and often before NHL diagnosis.

- **EBV**: Lymphomatoid granulomatosis is a rare, systemic, EBV virus-positive lymphoproliferative disorder characterized by B-cell proliferation and T-cell infiltration. Pathology shows angiocentric and angiodestructive infiltrates with large B cells. Lung involvement is common. MRI shows multifocal lesions with punctate or linear enhancement. Steroids, IF-alpha, and chemotherapy are the mainstays of therapy.

- **HTLV-1**: Acute T-cell leukemia/lymphoma develops in a small minority of patients infected with HTLV-1. Clinical presentations can range from indolent or asymptomatic disease to aggressive CNS involvement.

- **Neuropathy**: Neuropathy in association with lymphoma may also be due to infection or nutritional deficiency or compression or treatment related issues or hyperviscosity or amyloidosis.

**Leukemia**

- Neurologic manifestations may result from leptomeningeal disease, central nervous system mass lesions, CNS hemorrhage, venous sinus thrombosis, extramedullary myeloid tumors, and peripheral nervous system involvement.

- Meningeal involvement is common in ALL and acute myelomonocytic leukemia. Risk factors for leptomeningeal involvement in ALL include young age, mature B-cell ALL, T-cell lineage, high LDH, high WBC count, high proliferative index, elevated beta2-microglobulin and extramedullary disease. Due to the high incidence of CNS involvement at relapse, CNS prophylaxis is recommended in all. A combination of intravenous and intrathecal therapy with or without craniospinal irradiation is used. Leptomeningeal involvement is less common in AML. Risk factors include monoblastic differentiation and WBC count over 100,000/mm3 at presentation. There is no role for CNS prophylaxis. Treatment includes intrathecal therapy with cytarabine and/or methotrexate. CNS involvement in CLL is rare and can be due to parenchymal or meningeal involvement by CLL or with CNS disease associated with transformation to a more aggressive form of large cell lymphoma (Richter syndrome).

- Chororomas (extramedullary myeloid tumors, granulocytic sarcoma) are seen in AML and CML. The spine is most commonly involved. With a spinal localization, the thoracic and lumbar canal are commonly involved. They are also seen adjacent to the skull or facial bones (with a dural attachment). An intracranial choroma may mimic a subdural hematoma or meningioma. Parenchymal involvement by choromas is rare. Rarely nerve roots, plexus, and peripheral nerves may be involved. Neurologic extramedullary myeloid tumors may be the presenting manifestation and may precede the leukemia diagnosis by years. Treatment options include radiation or chemotherapy. Prognosis is poor.

- CNS hemorrhage, most commonly intraparenchymal, is common in acute leukemias, particularly acute promyelocytic leukemia. Hemorrhage may be seen with a blast crisis and extreme leukocytosis. Extreme leukocytosis can cause blood hyperviscosity and sludging of blast cells; a complication that can be prevented by oral hydroxyurea/leukapheresis/whole brain radiation. Other causes of intracranial hemorrhage in acute leukemia include DIC, disseminated aspergillosis or mucormycosis, thrombocytopenia, and L-asparaginase therapy (L-asparaginase induces hyperfibrinogenemia and results in venous or sinus thrombosis with infarction and hemorrhage).

- A peripheral neuropathy is most commonly seen in CLL (often demyelinating and with a monoclonal protein).
o AML can occur de novo or in association with a preexisting myeloproliferative disorder. The standard treatment includes 7 days of cytarabine and 3 days of daunorubicin (followed by 5 days of cytarabine and 2 days of daunorubicin if disease persists based on a day 14 bone marrow biopsy). Postremission therapy includes consolidation chemotherapy with cytarabine in patients younger than 60 years and autologous or allogenic stem cell transplantation. ALL therapy includes weekly vincristine with 14-21 days of prednisone or dexamethasone. The CNS is a major sanctuary site in ALL (particularly with meningeal leukemia). CNS prophylaxis with intrathecal methotrexate and/or cytarabine is routinely given. CNS directed therapy has been a key factor in improving survival in ALL. Neurocognitive deficits following radiation has been responsible for modification of treatment regimens to include intensified systemic and intrathecal chemotherapy. Whole brain radiation may be given in some patients with established CNS disease. Patients with CLL often need no treatment. CML is really a myeloproliferative disorder associated with a chromosomal translocation on the Philadelphia chromosome.

**Neuro_Sweet Disease:**

Sweet syndrome (acute febrile neutrophilic dermatosis) is an acute multisystem disorder characterized by fever, painful red skin lesions, and neutrophils in the upper dermis. It is often associated with a malignancy or drug exposure. Neurologic manifestations (Neuro-Sweet disease: NSD) include meningoencephalitis or parenchymal lesions (which can cause hemiparesis, psychiatric disturbance, or movement disorders). The parenchymal lesions have a predilection for the thalamus and basal ganglia and may enhance. CSF may show lymphocytic pleocytosis. Diagnostic criteria require steroid responsive neurologic symptoms, painful red plaques or nodules on the face or upper body with neutrophilic infiltration on histopathology, and absence of uveitis or cutaneous vasculitis (which are characteristic of Behçet diseases).

**References:**


GASTROENTEROLOGY – NEUROLOGY

- The current consensus-based nomenclature and classification system of gluten related disorders is as follows:¹

**Gluten Related Disorders**

**Autoimmune (adaptive immunity)**
- Dermatitis herpetiformis (no neurologic dysfunction)
- Celiac disease
- Gluten ataxia

**Allergic**
- Wheat allergy (IgE based, wheat triggers histamine release, skin testing & specific IgE antibodies, no neurologic dysfunction, eg: baker’s asthma)²

**Non-Immune Non-Allergic (?innate immunity)**
- Gluten sensitivity

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**Spectrum of gluten related disorders**

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**Gluten sensitivity (non-celiac gluten sensitivity)** ¹, ³, ⁴
Nonceliac gluten sensitivity is the term used to describe gastrointestinal and/or extraintestinal symptoms associated with gluten ingestion¹, ³, ⁴

- Neuropsychiatric manifestations may be more common than those seen in celiac disease.¹ Its clinical features overlap with those of celiac disease and wheat allergy.⁴ The pathophysiology is thought to be an innate immune mechanism, whereas CD and wheat allergy are autoimmune and allergen-mediated respectively.¹, ³, ⁴ These individuals show improvement with dietary exclusion of gluten. Gluten sensitivity is not accompanied by anti-tTG autoantibodies and small bowel pathology is absent.

- The concept of gluten sensitivity and related neurological disorders is controversial.⁶ It is unclear if the neurologic complications seen are caused by celiac disease or are simply an epiphenomenon. Also unclear is whether the proposed complications respond to a gluten free diet. Contradictory data exist. A causality has not been conclusively demonstrated. Ataxia is the best characterized neurological manifestation of gluten sensitivity.²-¹¹ Patients with gluten ataxia often don't have gastrointestinal symptoms.⁹ MRI evidence of cerebellar atrophy is commonly seen. Antigliadin antibody positivity is commonly seen in patients with apparently idiopathic sporadic and hereditary ataxia.¹² The ataxia is possibly a result of immunological damage to the cerebellum, posterior columns of the spinal cord, and peripheral nerves. Antigliadin antibodies cross-react with epitopes on Purkinje cells and patients with
Celiac Disease

- Celiac disease is an immune-mediated enteropathy triggered by the ingestion of gluten-containing grains (wheat, rye, barley) in genetically susceptible individuals. It is characterized by mucosal inflammation and resultant malabsorption. Celiac disease can present with intestinal or extraintestinal symptoms (like the skin rash of dermatitis herpetiformis) or may even be detected in asymptomatic individuals. The diagnostic guidelines for celiac disease have required the presence of characteristic lesions on small bowel biopsy and demonstration of clinical improvement following elimination of gluten from the diet. Recent population-based studies suggest that subclinical celiac disease may be much commoner than what has previously been recognized. The prevalence of celiac disease is America may be 0.71% or even higher. The prevalence of dermatitis herpetiformis is lower than that of celiac disease, and unlike celiac disease, the incidence seems to have decreased according to a recent population study. With awareness of a high disease prevalence has come recognition of a broad spectrum of clinical presentations.

- Neurologic manifestations

  - Neurological complications may occur in 6-13% of patients with celiac disease though some reports suggest that 22.5% patients with celiac disease may have neurologic manifestations. In earlier reports, neurologic manifestations associated with celiac disease were attributed to specific nutrient deficiencies (iron, folate, calcium and vitamin D, vitamin A, vitamin E, copper, pyridoxine, vitamin K, and vitamin B12). More recently the focus has been on immunologic mechanisms. Severe malabsorption is generally rare in patients with a neurologic presentation. Documentation of patients with neurologic manifestations and elevated gluten-directed antibodies (primarily antigliadin and deamidated gliadin peptide antibodies), often without gastrointestinal manifestations, has led to the suggestion that gluten sensitivity (as opposed to celiac disease) can cause neurologic manifestations without gastrointestinal symptoms or small bowel biopsy changes. In some of these cases neurologic manifestations may be followed by intestinal manifestations.

  - Ataxia and peripheral neuropathy are the best characterized neurologic manifestations of celiac disease. In one study neuropathy accounted for 17% of the neurologic abnormalities seen in celiac disease, in another study it accounted for 30% of the neurologic manifestations of celiac disease, and in yet another neuropathy was seen in 23% of patients with celiac disease and abnormalities of neuropsychological testing in 31%. As compared to controls, patients with celiac disease have a 2.5 fold increase in development of neuropathy. The types of neuropathy described include pure sensory, pure motor, or mixed; axonal or mixed axonal and demyelinating; multifocal or symmetrical; small fiber or large fiber or mixed. In patients with small fiber neuropathy, frequent facial involvement and a non-length-dependent pattern on skin biopsy findings, may suggest a sensory ganglionopathy or an immune-mediated neuropathy. Evidence of classic celiac disease on duodenal biopsy is seen in a small percentage of patients with gluten ataxia. (see section on gluten sensitivity for additional discussion on gluten ataxia.)

  - Cognitive impairment, including rapidly progressive dementia, may also be seen in association with celiac disease. Other reported accompaniments include a wide spectrum of psychiatric disorders, myoclonic ataxia, inflammatory myopathy, inflammatory neuropathy, isolated ocular myopathy, inclusion body myositis, neuromyotonia, chorea, paroxysmal nonkinesogenic dystonia, restless legs, headaches including some with transient deficits and MRI evidence of white matter abnormalities, brainstem encephalitis, multifocal leukoencephalopathy, myelopathy, neuromyelitis optica, multiple sclerosis, internuclear ophthalmoplegia, autonomic dysfunction, pseudotumor cerebri, epilepsy with or without
occpital calcification, and others. The significance of many of these associations is indeterminate. A recent pediatric study failed to show an association between celiac disease and epilepsy.\textsuperscript{36} Headaches and celiac disease may be a bona fide association.\textsuperscript{37, 38}

- Causes alternative to gluten exposure for neurologic dysfunction should be looked for among most gliadin-antibody positive patients without CD.\textsuperscript{39} Additionally, nutritional deficiency and coexisting autoimmunity may cause neurologic dysfunction in CD.

### Investigations

- Circulating IgG and IgA antibodies to gliadin have been used in the past while working up patients with CD. These antibodies have low sensitivity and specificity and 10-20% of the general population may have these antibodies. They have been replaced by deamidated gliadin antibodies (IgA/IgG) which may also be helpful for assessing compliance to a gluten-free diet. Serologic tests may resolve and histologic findings may improve with removal of gluten from the diet. IgA antiendomysial antibody (EMA) and IgA/IgG tissue transglutaminase antibody (tTGA) are however more specific for the disease.\textsuperscript{40} The reported specificity of these antibodies approaches 100% and over 95% respectively. IgA tTG has a better sensitivity than EMA. The positive predictive value of these two antibodies together (IgA tTG followed by EMA) is over 90%. IgA EMA is a qualitative test involving subjective interpretation of the IF staining. IgA EMA can be negative with lesser degrees of villous atrophy. tTG IgA antibody has a slightly better sensitivity and fairly comparable specificity to EMA but is a quantitative test (ELISA) which is quicker to perform and is cheaper.\textsuperscript{41} False positive tissue transglutaminase antibody results may occur in chronic liver disease, myeloma, monoclonal gammopathy, and type 1 diabetes.\textsuperscript{41} IgA deficiency is common in the general population (1 in 500) and is more commonly associated with celiac disease. Hence serologic testing for the IgA antibodies associated with celiac disease will be falsely negative in patients with selective IgA deficiency and celiac disease. In cases of selective IgA deficiency IgG tTGA may be obtained but the IgG-based tests are less sensitive and specific than the IgA-based tests in those with normal levels of IgA. Therefore the first step in the serologic cascade for celiac disease testing is IgA levels (see algorithm). Antiganglioside antibodies have been described in patients with celiac disease and neurologic manifestations.\textsuperscript{28} The significance of this is unclear as these antibodies may be present in patients with celiac disease without neurologic symptoms.

- Approximately 95% of patients with celiac disease have HLA DQ2 and most of the remainder have HLA DQ8.\textsuperscript{42} If celiac disease is suspected despite negative serological tests, the presence of these disease-associated alleles can be looked for and small intestinal mucosal biopsy considered. Multiple biopsies should be taken from the second part of the duodenum or beyond. The pathologic abnormality in the small intestine is characteristic but not specific and includes partial villous atrophy, crypt lengthening, increase in lamina propria, and intraepithelial lymphocytes.\textsuperscript{22}

- CD may be the underlying cause of unexplained elevations of liver enzyme levels.\textsuperscript{43} Other hepatobiliary associations of CD include nonspecific hepatitis, nonalcoholic fatty liver disease, and autoimmune and cholestatic liver disease.\textsuperscript{43}

### Management

- Reports in the literature on the effect of a gluten-free diet on neurological manifestations are conflicting. Further, strict adherence to a gluten free diet is difficult to achieve and is also complicated by a lack of clear food-labeling policy. There is also a group of patients with celiac disease who are resistant to a gluten-free diet (“refractory sprue”). While there are reports of neurological improvement on a gluten-free diet, there are also reports of persistence or progression of neurological symptoms despite a gluten free diet. Generally response of the neurological manifestations is less robust to a gluten-free diet than that of gastrointestinal manifestations. In light of these uncertainties, the best approach seems to be to offer a gluten-free diet to patients with a recognized neurological presentation and celiac disease. In some patients with neurological manifestations immunosuppressive therapy has been empirically tried.\textsuperscript{30} Coexisting vitamin or mineral deficiencies in association with celiac disease should be looked for and appropriately treated.
- Celiac Disease Testing: Algorithm (Mayo Medical laboratories)

Celliac Disease Diagnostic Testing Algorithm

- Normal IgA
  - TTGA/82587 Tissue Transglutaminase (TG) Antibody, IgA, Serum
    - <4.0 U/mL
      - Celliac disease very unlikely. Exception:
        - ~10% of patients with celliac disease are seronegative
          - If celliac disease is highly suspected, consider CELU/88906 Celliac-Associated HLA-DQ Alpha 1 and DQ Beta 1 Medium-High Resolution DNA Typing, Blood
          - Negative (EMA negative and d-gliadin < 20.0 Units)
            - Possible false-positive TG result
            - Celliac disease possible but unlikely
              - If strong suspicion of celliac disease remains, perform HLA typing.
              - CELU/88906 Celliac-Associated HLA-DQ Alpha 1 and DQ Beta 1 Medium-High Resolution DNA Typing, Blood
                - Negative
                  - Not celliac disease
                - Positive for DQ2 or DQ8
                  - Possible celliac disease
          - Positive (EMA positive and/or d-gliadin ≥ 20.0 Units)
            - Proceed to biopsy
              - Biopsy results inconsistent with serology
                - Negative
                  - Celliac disease
                - Positive
                  - Follow-up patient for future development of celliac disease
            - Selective IgA deficiency
              - TTG/83671 Tissue Transglutaminase (TG) Antibodies, IgA and IgG Profile, Serum
                - >10.0 U/mL
                  - All results normal
                  - Celliac disease very unlikely. Exception:
                    - ~10% of patients with celliac disease are seronegative
                      - If celliac disease is highly suspected, consider CELU/88906 Celliac-Associated HLA-DQ Alpha 1 and DQ Beta 1 Medium-High Resolution DNA Typing, Blood
              - DGICO/89031 Gliadin (Deamidated) Antibodies Evaluation, IgG and IgA, Serum
                - IgA ≥ 1 mg/dL and below age-matched reference values
                  - Normal IgA
                    - TTG/83660 Tissue Transglutaminase (TG) Antibody, IgG, Serum
                      - >10.0 U/mL
                        - All results normal
                        - Celliac disease very unlikely. Exception:
                          - ~10% of patients with celliac disease are seronegative
                            - If celliac disease is highly suspected, consider CELU/88906 Celliac-Associated HLA-DQ Alpha 1 and DQ Beta 1 Medium-High Resolution DNA Typing, Blood
                      - DGICO/89030 Gliadin (Deamidated) Antibody, IgG, Serum
                        - IgA < 1 mg/dL
                          - Selective IgA deficiency
"
Whipple Disease

- Whipple disease (WD) is a rare, chronic, relapsing, multisystem disease due to infection with *Tropheryma whipplei* (an Actinobacteria) that has a predilection for middle aged men and affects the gastrointestinal, musculoskeletal, neurological, cardiopulmonary, dermatologic, ocular, and lymphatic systems. A prodromal stage characterized by arthralgias and fever is followed by a steady-state stage with weight loss, diarrhea, and malabsorption. Skin hyperpigmentation may be seen in up to a third of patients. Diarrhea, weight loss, and abdominal pain are the classic gastrointestinal symptoms. *Tropheryma whipplei* may produce a self-limited gastroenteritis. Other manifestations include migratory polyarthralgias, lymphadenopathy, anemia, fever, cough, malaise, heart failure, hypotension, pericardial friction rub, splenomegaly, glomerulonephritis, and uveitis or retinitis. Based on the presence of *T whipplei* DNA in the saliva of healthy individuals it has been suggested that this organism could be a commensal organism that is ubiquitous and generally not pathogenic. Prevalence of *T whipplei* in duodenal-biopsy specimens, saliva, stool, and blood from healthy persons is however controversial. The organism is a soil-dwelling organism and this may explain the increased incidence of the infection in farmers. Asymptomatic stool carrier rates are particularly high in children, sewage workers, and the homeless. Exposure to the organism is in of itself not sufficient to produce the infection: host factors are important.

- Neurologic manifestations

Celiac disease (CD) diagnostic testing algorithm. DGP, deamidated gliadin peptide; HLA, human leukocyte antigen; Ig, immunoglobulin; TTGA, tissue transglutaminase antibody.
Approximately a third of patients with WD experience neurologic symptoms. CNS symptoms may be seen in approximately 15% of patients with WD and in some can be the initial or only manifestation in some. Post-mortem examination reveals CNS involvement in a much higher percentage (over 90%). Asymptomatic neurologic involvement has been shown by demonstration of DNA from *T. whipplei* in CSF by PCR assay. The CNS is also a site of symptomatic relapse following apparently successful therapy, often with antibiotics like tetracycline that have poor penetration into the CNS.

A wide spectrum of neurologic manifestations may be seen. Psychiatric symptoms such as depression or personality change and cognitive impairment including dementia are commonly seen. Oculomotoric myorhythmia (OMM) and oculo-facial-skeletal myorhythmia (OFSM) are considered pathognomonic for CNS WD and are often accompanied by a supranuclear vertical gaze palsy. OMM refers to pendular vergence oscillations which occur with slow rhythmic mouth and palatal movements. These are invariably accompanied by a supranuclear vertical gaze palsy. OFSM refers to slow pendular vergence oscillations which occur synchronously with rhythmic movements of the mouth, face, and extremities and persist during sleep. Myoclonus is seen in a quarter of patients with neurologic involvement and may be the presenting manifestation. Spinal segmental myoclonus may be seen. Symptoms suggestive of hypothalamic involvement such as polydipsia, hyperphagia, changes in the sleep-wake cycle, and a change in libido may be present. Both severe insomnia and hypersomnia have been described. Cerebellar ataxia may be more common than was earlier recognized. Ependymal bacterial accumulation has been reported to cause obstructive hydrocephalus. Other neurological manifestations that have been reported to occur in CNS WD include pyramidal and extrapyramidal manifestations, headache, progressive deafness, a stroke-like syndrome, and a proximal myopathy. Ocular manifestations may include uveitis with vitreous opacities, and papilledema. Isolated cervical myelitis is rare. Spinal cord involvement in Whipple’s disease may prominently affect the posterior column. Peripheral neuropathy may occur but may be due to nutritional factors rather than direct involvement.

### Investigations
- Diagnosis and treatment of definite CNS Whipple's disease should be based on the presence of pathognomonic signs (OMM or OFSM) or positive biopsy or polymerase chain reaction results. Due to the protean manifestations and variability in organ involvement a high index of suspicion is required and the diagnosis usually depends on additional diagnostic studies. Possible CNS Whipple's disease should be considered in the setting of unexplained systemic symptoms and neurological signs (supranuclear vertical gaze palsy, rhythmic myoclonus, dementia with psychiatric symptoms, or hypothalamic manifestations).
- Blood studies in Whipple’s disease may show anemia, leukocytosis, eosinophilia, elevation of acute-phase reactants, and laboratory evidence of malabsorption.
- Radiographic assessment undertaken because of gastrointestinal symptoms may show abdominal lymphadenopathy, thickening of mucosal folds, hepatosplenomegaly, or ascites.
- Mild elevations of CSF protein and mild pleocytosis are common, but the CSF may be normal. Increased CSF immunoglobulin production or oligoclonal bands may be seen. The CSF cytologic hallmark in WD is the presence of histiocytes with PAS-positive, granular, sometimes sickle-shaped particles in the cytoplasm.
- Brain MRI may show a high signal intensity on T2 weighted images involving one or more of the following structures: the midbrain, hypothalamus, thalamus, optic chiasm, mamillary body, medial temporal lobes, uncus, and cerebellar or cerebral peduncles. Diffusion is not restricted; slight enhancement may be present. Symmetric T2 hyperintensity without mass effect involving the corticospinal tract may be present. Also reported are nodular parenchymal lesions, leptomeningeal enhancement, and stroke-like presentations of focal tumor like lesions.
- Due to the patchy involvement, brain biopsy is often a low yield procedure. Those with possible CNS Whipple's disease should undergo small-bowel biopsy. Up to a third of patients with CNS WD may have a negative small bowel biopsy. Endoscopy may show pale yellow mucosa alternating with erythematous mucosa in the postbulbar region of the duodenum and jejunum. Biopsy samples should be taken from the proximal and distal...
duodenum or the jejunum. Bowel wall infiltration is associated with widening and flattening of the villi with dilated lacteals containing yellow lipid deposits. On light microscopy examination, PAS stained small-biopsy specimen shows magenta-stained inclusions within macrophages of the lamina propria. The PAS-positive intracellular inclusions are nonspecific. The bacteria can be differentiated from the intracellular inclusions of *Mycobacterium avium* complex which, unlike the Whipple bacterium, is acid-fast positive. Electron microscopy may detect the distinctive, rod shaped, trilaminar cell wall of *T. whipplei*. Noncaseating, epithelioid-cell, sarcoïd-like granulomas may be present in lymphatic tissue, gastrointestinal tract, bone marrow, and other tissues. These are often PAS-negative. Immunohistochemical staining or autoimmunochemical staining for antibodies against *T. whipplei* is more sensitive and specific than PAS staining but is not widely available. Recent developments using molecular analysis have allowed PCR amplification of the 16s ribosomal RNA sequences that are specific for Whipple’s organism and permits identification of the infection from a variety of tissues or body fluids including peripheral blood. When amplified product is detected, the presence of *T. whipplei* should be confirmed by sequencing or by using fluorescence-labeled oligonucleotide hybridization probes in a real-time PCR assay. While the sensitivity of PCR for WD in the CSF and serum is high, the predictive value is not known. *T. whipplei* can be found within the CSF in patients years after a prolonged course of antibiotics, but it is not known if this is due to incomplete eradication or re-infection. Asymptomatic CNS involvement may be seen in up to 50% of cases with WD; hence CSF PCR assessment has been recommended in all diagnosed individuals.

**Treatment**

- Particularly in the initial stages of the disease a high proportion of patients may have asymptomatic CNS infection. Only a small proportion of these develop clinical or radiologic evidence of CNS involvement during the course of their illness. Diagnostic evaluation of the CSF should therefore be included in the work up of patients with WD even in the absence of CNS symptoms. The prognosis for patients with manifest CNS involvement or CNS relapse is poor. A quarter of such patients die with 4 years and a quarter have major sequelae. The recommended treatment is oral administration of 160 mg of trimethoprim and 800 mg of sulfamethoxazole twice per day for 1 to 2 years, usually preceded by parenteral administration of streptomycin (1 g per day) together with penicillin G (1.2 million U per day) or ceftriaxone (2 g daily) for 2 weeks. Approximately 60% of patients with CNS WD experience some improvement in symptoms with antibiotic therapy. There are also reports of patients in whom IVIG has been used with a favorable outcome.

**Guidelines for Diagnostic Screening, Biopsy, and Treatment of CNS Whipple’s Disease**

**Definite CNS WD**
Must have any 1 of the following 3 criteria:
1. Oculomasticatory myorhythmia or oculo-facial-skeletal myorhythmia
2. Positive tissue biopsy
3. Positive PCR analysis
If histological or PCR analysis was not performed on CNS tissue, then the patient must also demonstrate neurological signs. If histological or PCR analysis was performed on CNS tissue, then the patient need not demonstrate neurological signs (i.e., asymptomatic CNS infection).

**Possible CNS WD**
Must have 1 of 4 systemic symptoms, not due to another known etiology:
1. Fever of unknown origin
2. Gastrointestinal symptoms (steatorrhea, chronic diarrhea, abdominal distention, or pain)
3. Chronic migratory arthralgias, or polyarthritis
4. Unexplained lymphadenopathy, night sweats, or malaise
Also must have 1 of 4 neurological signs, not due to another known etiology:
1. Supranuclear vertical gaze palsy
2. Rhythmic myoclonus
3. Dementia with psychiatric symptoms
4. Hypothalamic manifestations
Inflammatory Bowel Disease

- Extraintestinal manifestations and complications of inflammatory bowel disease (ulcerative colitis or Crohn’s disease) may precede or follow the gastrointestinal manifestations and may occur independent of exacerbation of bowel symptoms. Neurological manifestations seen in association with inflammatory bowel disease may be related to the basic disease, be coincidental, or be a consequence of disease complications or treatment. They may be divided into immune mediated and nonimmune mediated complications.

**Neurologic Manifestations**
- IBD can involve the CNS or PNS.  
- Peripheral neuropathy is the most common neurologic complication of IBD. In a retrospective review of 638 patients with inflammatory bowel disease, neurological involvement was noted in 10 Crohn’s disease and 9 ulcerative colitis patients. In nearly three-quarters of these patients neurological involvement started within 6 years following the diagnosis of inflammatory bowel disease. Over a half of these patients had other extraintestinal manifestations. Peripheral nervous system disorders were most commonly seen and included acute inflammatory demyelinating polyneuropathy (3), mononeuritis multiplex (1), bifacial plexopathy (1), myasthenia gravis (1), and myopathy (3). One patient had the Melkerson-Rosenthal syndrome and 5 had a myelopathy. Patients with inflammatory bowel disease may also have chronic inflammatory demyelinating peripheral neuropathy, multifocal motor neuropathy, small or large-fiber sensory axonal sensory peripheral neuropathy, and large fiber axonal sensorimotor peripheral neuropathy. Both demyelinating and axonal neuropathies may show response to immunotherapy. Autonomic neuropathy may be seen in IBD and may contribute to gastrointestinal symptoms. Subclinical autonomic dysfunction may occur early in the course of Crohn disease. Despite reports of patients who have both Crohn’s disease and Melkerson-Rosenthal syndrome, search for the former in patients with the latter is not justified in the absence of gastrointestinal symptoms.

- Myopathic processes reported include polymyositis, dermatomyositis, rimmed vacuole myopathy, granulomatous myositis, orbital myositis, and gastrocnemius myalgia syndrome. Muscle involvement seems to appear during periods of gastrointestinal activity.

- A recent study on 84 patients with IBD noted neurologic complications in 13 patients with ulcerative colitis and 12 patients with Crohn disease. Demyelinating disease was the most frequent complication and noted in 8 patients. Nonenhancing, hyperintense focal white-matter lesions have been reported in the brain of patient’s with inflammatory bowel disease and are may represent an extra-intestinal manifestation. They are more common in older patients and in those with longer disease duration, and are unrelated to the presence of cardiovascular risk factors. An increased concurrence of inflammatory bowel disease and multiple sclerosis has been shown in Olmsted County using the database of the Rochester Epidemiology Project. Similar findings were noted in the department of Defense Military Health System Database.

- Immune-mediated sensorineural hearing loss has also been reported in IBD (ulcerative > Crohn’s). This includes acute impairment or chronic subclinical deficits.

- Cerebrovascular manifestations included sinus venous thrombosis (2), recurrent transient ischemic attacks (1), and recurrent strokes (1). The incidence of arterial or venous thromboses is increased in patients with inflammatory bowel disease and often occurs with disease exacerbation, possibly secondary to a hypercoagulable state or associated vasculitis. An increased concurrence of inflammatory bowel disease and multiple sclerosis has also been reported in association with IBD. In one study cerebrovascular disease was responsible for 10% of the vascular complications seen in IBD. Posterior reversible encephalopathy syndrome has been reported with acute exacerbation of ulcerative colitis and following sepsis in Crohn’s disease: it may be due to immunosuppression rather than the disease process.

- Penetrating Crohn disease can rarely result in a spinal epidural abscess.

- Restless legs has been reported with Crohn’s and while not associated with current iron deficiency it seemed to be more common with a history or iron deficiency.
Migraine seems to be present in both Crohn’s and inflammatory bowel disease but has not been well studied.\textsuperscript{107}

Peripheral neuropathy in IBD occurs more frequently in patients receiving metronidazole in high doses for a long duration.\textsuperscript{79, 108} Cyclosporine can be used to induce remission in acute severe ulcerative colitis and may be associated with neurologic complications like tremors, seizures, ataxia, paresthesias, motor deficits, visual hallucinations. Some of these manifestations may relate to a progressive reversible encephalopathy syndrome. Anti-TNFα therapy in IBD may be associated with central and peripheral demyelination.\textsuperscript{83, 109-112} Use of natalizumab (a humanized monoclonal antibody against the cellular adhesion molecule α4-integrin) in Crohn disease may be associated with the risk of PML.\textsuperscript{113}

\section*{Neurological involvement in Inflammatory Bowel Disease}

\subsection*{Immunologic mechanisms}

1. Probable immune-mediated extra-intestinal manifestation of IBD
2. Demyelination induced by anti-TNFα agents

\subsection*{Non-immunologic mechanisms}

1. Micronutrient deficiency due to malabsorption, surgical resection, short bowel syndrome
2. Hypercoagulability (acquired prothrombotic state and inherited thrombophilias)
3. Side effects of medications (metronidazole, cyclosporine)
4. Local disease extension into the spinal cord (penetrating CD)
5. Systemic or central nervous system infections with immunosuppressants, including natalizumab-induced progressive multifocal leukoencephalopathy (JC virus reactivation)

\textbf{Note:}

- Anti-saccharomyces cerevisiae mannan antibodies and pANCA are associated with Crohn’s disease and ulcerative colitis respectively.\textsuperscript{114}

\section*{Tropical sprue}

- Tropical sprue is a chronic diarrheal illness of presumed infectious etiology that occurs in individuals who reside in or have been to the tropics. Neurological manifestations of tropical sprue include subacute combined degeneration, peripheral neuropathy, myopathy, tetany, night blindness, and mental changes and are likely a consequence of nutrient deficiencies secondary to chronic malabsorption.\textsuperscript{115}

\section*{Campylobacter jejuni infection}

- Campylobacter jejuni is the most common cause of bacterial gastroenteritis in developed countries. Nonspecific prodromal symptoms are followed by a diarrheal illness and after a brief incubation period Guillain–Barré syndrome may result. Up to 26% of patients with Guillain–Barré or Miller Fisher syndrome may have evidence of \textit{C. jejuni} infection.\textsuperscript{116} The resulting Guillain–Barré syndrome is associated with axonal degeneration, slow recovery, and residual disability.\textsuperscript{116} A seasonal form of acute motor axonal neuropathy in rural areas of China is also frequently associated with IgG and IgM antibodies against \textit{C. jejuni}.

\section*{Gastrointestinal Dysfunction in Neurologic Disease}

- The enteric nervous system provides the gut with a neural apparatus capable of modulating intestinal function.\textsuperscript{117, 118} Its activity is modulated by input from the CNS provided by autonomic nerves (sympathetic and parasympathetic). Shared morphological characteristics between the enteric nervous system and the central nervous system make both vulnerable to similar afflictions. It is therefore common for patients with neurological disease to have gastrointestinal dysfunction.

- A neurogenic cause for dysphagia may be suggested by the presence of drooling, nasal regurgitation, and episodes of choking or coughing during swallowing. Neurogenic dysphagia may result from involvement of the cortical areas concerned with swallowing, their efferent pathways, brainstem nuclei, lower cranial nerves, neuromuscular junction, or the striated muscle. In most patients the
neurologic cause for dysphagia is quite evident. Rarely dysphagia may be the presenting manifestation of the underlying neurological disorder. A videofluoroscopy can clarify the etiology, quantify the severity, demonstrate aspiration, and provide suggestions for compensatory maneuvers. Motor dysfunction resulting in delayed gastric emptying is commonly seen in autonomic neuropathies such as that associated with diabetes mellitus. Symptoms may be limited to vague postprandial abdominal discomfort or include recurrent postprandial emesis with malnutrition. In such cases gastric outlet obstruction needs to be excluded. Scintigraphic gastric emptying studies may help confirm the diagnosis. Chronic intestinal pseudo-obstruction refers to symptoms suggestive of intestinal obstruction in the absence of a mechanical cause. This syndrome may result from degeneration of the gut smooth muscle, dysfunction of the myenteric plexus, or neurologic diseases extrinsic to the gut. Motility studies may differentiate myopathic and neuropathic processes and exclude mechanical obstruction. Neurological disorders that impair mobility are often associated with constipation. Lack of rectal sensation with impaired urge to defecate may also contribute to constipation in certain neurological disorders. These patients may be evaluated with colon transit studies or radioscintigraphy. Neurologic damage to the pelvic nerves with denervation of pelvic floor musculature and denervation of the external anal sphincter is associated with fecal incontinence. The combination of incontinence and impaired rectal sensation suggests a pudendal neuropathy. Sympathetic denervation causes weakness of the internal anal sphincter and manifests as nocturnal incontinence. Stress incontinence suggests loss of external anal sphincter control and results from pudendal nerve or S2-4 lesions. Anorectal manometry, defecating proctography, and external anal sphincter EMG may be required in selected cases. Gastrointestinal manifestations of neurological disorders are discussed below according to site of neurologic involvement.

- **Disorders affecting the Cortex and brain stem**
  - Dysphagia, often transient, may be seen in up to 50% of patients after a stroke. It is more commonly seen in strokes involving the brainstem but may also be seen with bilateral or even unilateral cerebral hemispheric infarctions. A lateralization of swallowing function in the cortex may account for the latter.
  - Episodes of nausea, vomiting, abdominal pain, or hunger may occur as a seizure or seizure aura.
  - Migraine is often associated with nausea, vomiting, and at times abdominal pain. Tumors involving the anteromedial frontal lobe may be associated with disturbances of micturition and less often defecation. Tumors involving the medullary vomiting center or the chemoreceptor trigger zone in the area postrema may be associated with vomiting. Impaired gastrointestinal motility may also be seen with brainstem tumors.
  - Traumatic brain injury can be associated with dysphagia, delayed gastric emptying, and stress ulcers with gastrointestinal hemorrhage.
  - Progressive bulbar palsy is associated with dysphagia.
  - In Chiari I malformation, tonsillar herniation may result in lower cranial nerve traction and dysphagia.

- **Disorders affecting the Basal Ganglia**
  - Patients with Parkinson disease (PD) may have drooling, defects in tongue movements, delayed swallowing reflex, aspiration, reduced pharyngeal peristalsis, gastroesophageal reflux, and gastrointestinal hypomotility with delayed gastric emptying and constipation. A paradoxical contraction of the striated sphincter muscles during defecation called anismus may occur and is considered a focal dystonia. Involvement of the dorsal motor nucleus of the vagus in PD might produce gastrointestinal dysfunction. The presence of Lewy bodies in the myenteric plexus of both the esophagus and colon suggests that the PD process may also affect the enteric nervous system and contribute to gastrointestinal dysfunction through a peripheral mechanism. Lewy bodies have also been found in the dorsal group of the nucleus intermediolateralis of the third sacral segment of the spinal cord. Levodopa administration may help by improving swallowing. Intraparotid injections of botulinum toxin may alleviate parkinsonian drooling.
  - In addition to the gastrointestinal abnormalities seen in PD, patients with multiple system atrophy are also prone to develop postprandial hypotension. This is due to vasodilatation in the splanchnic circulation that is not counterbalanced by compensatory cardiovascular changes because of sympathetic dysfunction. Anal sphincter EMG studies have delineated a
characteristic pattern of denervation and reinnervation but the reliability of this abnormality has been questioned.

- **Dysphagia** is almost invariably present in advanced progressive supranuclear palsy and may be accompanied by drooling and aspiration. Eating difficulties may be compounded by difficulty with inferior gaze and by neck extension.
- **Dysphagia** is also seen in Huntington and Wilson disease.
- **Dysphagia** in spasmatic torticollis is largely due to head and neck posture.

### Disorders affecting the Spinal Cord

- Parasympathetic innervation of the descending colon, rectum, and anus is from the sacral parasympathetic centers in the spinal cord and is therefore affected in cord lesions at all levels. Sympathetic supply to the gastrointestinal tract is from T5-L3 and is therefore affected in cervical and upper thoracic lesions. During the stage of spinal shock following spinal cord injury there is slowing of colonic motility with ileus. Patients with neurological sequelae secondary to spinal cord injury may develop esophageal dysmotility and reflux, delayed gastric emptying, decreased bowel movement frequency with a vague abdominal bloating and postprandial distention. Lesions of the cauda equina or conus are associated with fecal incontinence. With higher cord lesions the external anal sphincter becomes spastic and loss of conscious sphincter control with anorectal dyssynergia results. Impaired sensations secondary to the spinal cord injury may cause delayed recognition of acute abdominal emergencies like intestinal obstruction and peritonitis. Autonomic dysreflexia may be the manifestation of acute abdominal pathology and is characterized by hypertension, pallor, sweating, and piloerection. It is seen with cervical and upper thoracic cord injuries, reflects loss of cerebral inhibitory input on thoracolumbar outflow, and is due to massive sympathetic over-activity triggered by noxious stimuli below the level of a lesion.

### Central Nervous System Disorders associated with multiple sites of involvement

- **Dysphagia** and esophageal dysmotility in multiple sclerosis patients may be due to disease in the brainstem. Gastroparesis, constipation, and delayed colon transit time may be seen. During attempted defecation patients may experience paradoxical contraction or failure of relaxation of the puborectalis muscle. Dysmotility of the gut is due to impaired supraspinal and spinal control of sacral parasympathetic supply to the colon. In amyotrophic lateral sclerosis, damage to corticobulbar pathways and cranial nerve motor nuclei in the brainstem cause impairment of lingual, pharyngeal, and esophageal function.

### Disorders involving the Peripheral Nerves, Muscles and Neuromuscular junction

- **Prominent bulbar involvement** may be seen in Guillain-Barré syndrome.
- **Weakness of masticatory and pharyngeal muscles with chewing and swallowing difficulties** are commonly seen in myasthenia gravis. Seronegative myasthenics with positive anti-MuSK antibodies have prominent faciobulbar weakness.
- **Dysphagia** may be seen in some congenital myopathies and may be the presenting manifestation of oculopharyngeal muscular dystrophy. Dysphagia is also seen in inflammatory muscle disease, thyrotoxic myopathy, and rarely in inclusion body myositis. In these disorders facial and masticatory muscles are spared. In addition to striated muscle involvement, disorders like myotonic dystrophy, Duchenne muscular dystrophy, and mitochondrial myopathy, can be associated with smooth muscle involvement. An associated neurogenic component with impaired innervation and motility of striated and smooth muscle can be seen in myotonic dystrophy and certain mitochondrial myopathies. Myotonic dystrophy may be associated with dysphagia, delayed gastric emptying, diarrhea, abdominal cramps, or radiological evidence of megacolon. Dystrophin is abundant in striated and smooth muscle and gastrointestinal complaints like masticatory disturbance, dysphagia, esophageal dysmotility, delayed gastric emptying, and gastric dilation are common in Duchenne muscular dystrophy. Patients with Kearns Sayre syndrome may have progressive involvement of pharyngeal and esophageal muscle with resulting dysphagia. The mitochondrial myopathy with obligatory gastrointestinal involvement is MNGIE (mitochondrial neurogastrointestinal encephalopathy).

### Disorders affecting the Enteric Plexus

- **Achalasia** is characterized by failure of relaxation of the lower esophageal sphincter with absence of peristalsis in the esophageal body. There is loss of ganglion cells and destruction
of the myenteric plexus including loss of inhibitory nerves containing vasoactive intestinal peptide, somatostatin, and nitric oxide.

- The distal bowel aganglionosis in Hirschprung’s disease results from incomplete migration of neuroneural ganglion cells from the neural crest to the most distal part of the gut. Hirschprung’s disease presents soon after birth and is associated with constipation and gaseous distention. There is a narrowed distal bowel segment in which there is loss of parasympathetic ganglion cells from the intramural plexus.

**Disorders affecting the Autonomic Nervous System**

- Motility disturbance is the commonest gastrointestinal manifestation of autonomic nervous system disorders affecting the gastrointestinal tract. Gastrointestinal manifestations may be the presenting or only manifestation of autonomic neuropathies. Gastrointestinal manifestations of autonomic neuropathies can include abdominal pain, paralytic ileus, intestinal pseudoobstruction, gastroparesis with early satiety and bloating, nausea, vomiting, constipation, or diarrhea. Accompanying evidence of sympathetic dysfunction (orthostatic hypotension, anhidrosis) or parasympathetic failure (dry eyes and mouth, constipation, blurred vision, urinary retention) may be present. A small fiber neuropathy with distal impairment of pain and temperature may be seen. Patients with idiopathic orthostatic hypotension and idiopathic autonomic neuropathy may have gastrointestinal dysmotility.

- Many acute and subacute onset autonomic neuropathies are immune-mediated. A limited form of autonomic neuropathy involving the gastrointestinal tract may occur (autoimmune gastrointestinal dysmotility). These autonomic neuropathies may occur as a paraneoplastic manifestation with detection of antibodies like ANNA-1 or anti-Hu and CRMP-5. Autoantibodies to ganglionic acetylcholine receptors have been identified in patients with autoimmune autonomic neuropathies (also called autoimmune autonomic ganglionopathies). In some patients these antibodies may be associated with gastrointestinal dysmotility. Substantial autonomic involvement is seen in Guillain-Barré syndrome. Selective cholinergic dysfunction is seen in acute cholinergic neuropathy. Gastrointestinal dysfunction may also be seen in other conditions included in the differential diagnosis of acute autonomic neuropathies such as botulism, porphyria, and autonomic neuropathies due to drugs like vincristine and vacor.

- Diabetic autonomic neuropathy may be associated with gastroparesis, constipation, fecal incontinence, or diarrhea.

- Autonomic dysfunction may be the cause of diarrhea in patients with human immunodeficiency virus infection. Chagas’ disease is caused by *Trypanosoma cruzi*. Chronic Chagas’ disease develops years after primary infection and commonly affects the heart and gastrointestinal system. Patients may complain of dysphagia and constipation and have a chronic cholinergic megaeosophagus, megaduodenum, and megacolon.

- In sporadic systemic amyloid neuropathy or familial amyloidotic polyneuropathy infiltration of the myenteric and submucosal plexus may cause diarrhea or constipation. Amyloid infiltration of the lower esophagus may cause dysphagia. Autonomic impairment is less common in amyloidosis associated with multiple myeloma.

- Gastrointestinal symptoms are also seen in familial dysautonomia (Riley-Day syndrome, HSAN type III).

**Common neurological causes of chronic intestinal pseudo-obstruction**

**Neuropathic:**
- Parkinson’s disease
- Brainstem tumor
- Multiple sclerosis
- Spinal cord transection
- Chagas’ disease
- Diabetes mellitus
- Porphyria
- Lead poisoning
- Drugs: tricyclic antidepressants, narcotics

**Myopathic:** Myotonic and other dystrophies

**Neuropathic or Myopathic:** Infiltrative disorders: Progressive systemic sclerosis


Amlyodiosis

References:


HEPATOLOGY – NEUROLOGY

Hepatic Encephalopathy

• Hepatic encephalopathy (HE) refers to the neuropsychiatric manifestations of liver failure and is associated with shunting of portal venous blood into the systemic circulation.1-5 Manifestations range from subclinical dysfunction to coma. Intrinsic hepatic disease may or may not be present.
  - Type A: acute liver failure
  - Type B: porto-systemic shunting in the absence of intrinsic liver disease
  - Type C: chronic disease from cirrhosis and portal hypertension

• Nomenclature and grading6

<table>
<thead>
<tr>
<th>Type</th>
<th>Nomenclature</th>
<th>Subcategory</th>
<th>Subdivision</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>Acute liver failure induced HE</td>
<td></td>
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<tr>
<td>B</td>
<td>Portosystemic bypass induced HE without intrinsic hepatocellular disease</td>
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<tr>
<td>C</td>
<td>Cirrhosis induced HE with associated portal hypertension or portosystemic shunts</td>
<td>Episodic HE</td>
<td>Precipitated/ spontaneous/ recurrent</td>
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<tr>
<td></td>
<td>Persistent HE</td>
<td></td>
<td>Mild/ severe/ treatment dependent</td>
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<tr>
<td></td>
<td>Minimal HE</td>
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Note: The term “subclinical hepatic encephalopathy” has been replaced by minimal HE. Minimal HE is the mildest form of HE. Abnormalities in this preclinical stage may be evident on neuropsychological tests and include inattention-related cognitive difficulties. This may result in impaired performance of complex tasks.

• West Haven Criteria for semiquantitative grading of mental state in HE5,8

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Trivial lack of awareness, euphoria or anxiety or depression, shortened attention span, impaired performance of addition, psychomotor slowing, sleep disturbance</th>
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<tbody>
<tr>
<td>Grade 2</td>
<td>Lethargy or apathy, minimal disorientation for time or space, subtle personality change, inappropriate behavior, impaired performance of subtractions, motor manifestations (asterixis, bradykinesia, rigidity, cerebellar dysarthria, ataxia)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Somnolence to semi-stupor (but responsive to verbal stimuli), confusion, gross disorientation,</td>
</tr>
</tbody>
</table>
extrapyramidal manifestations, hyperreflexia and extensor plantar reflexes, dysphasia, paranoia and hallucinations

**Grade 4** Coma (unresponsive to verbal or noxious stimuli)

- **International Society for Hepatic Encephalopathy and Nitrogen Metabolism**
  - This divides the West Haven scale to Normal, Covert (minimal or grade I), and Overt (grade II, II, IV)
  - Identification of patients with minimal or covert hepatic encephalopathy is a major challenge for neurologists.

- **Pathogenesis**
  - **Potential etiologies**: Potential factors that have been implicated in the development of HE include ammonia, manganese, proinflammatory cytokines (TNF-alpha, IL-1\(\beta\), IL-6), mercaptans, phenols, octanoic acid, hyponatremia, and benzodiazepines.
  - **Oxidative and nitrosative stress**: Low-grade cerebral edema seen in HE is associated with an increased production of reactive oxygen and nitrogen oxide species. This leads to changes in protein expression and RNA modifications, which disrupts brain function.
  - **GABAergic tone**: Altered blood brain barrier permeability and increased \(\gamma\)GABA transmission involving endogenous benzodiazepines also contribute to HE. Mechanisms related to increased GABAergic tone include increased brain GABA, increased number of GABA-A receptors, increased concentration of brain endogenous benzodiazepine-like compounds that would increase activation of GABA-A receptors, increased concentration of brain neurosteroids that would increase activation of GABA-A receptors, and enhanced activation of GABA receptors by ammonia.
  - **Osmotic Glutamine Hypothesis**: The glutaminase in enterocytes converts glutamine into glutamate and ammonia. Normally liver converts ammonia into urea. Additionally in other organs ammonia is consumed when glutamate is converted into glutamine via glutamine synthetase. In hepatic failure liver’s ability to detoxify ammonia is impaired and portosystemic shunting results in hyperammonemia. Astrocytes convert glutamate and ammonia into glutamine which accumulates and causes cell swelling (and Alzheimer type II astrocytosis).
  - **Manganese**: Liver failure is associated with impaired elimination of manganese via the hepatobiliary system. Hypoalbuminemia associated with liver failure may result in increased blood brain barrier transport of manganese.

- **Clinical features**
  - **General**
    - Patients with hepatic encephalopathy present with altered level of alertness and consciousness. Personality changes and mood disturbance may be seen early. In the initial stages sleep disturbance is common: delay in bedtime and awakening time. Minimal HE can be present for a long time without progression to higher grades. Patients with HE may develop asterixis and “fetor hepaticus”. Clinical manifestations of various stages of HE are noted in accompanying table.
    - 15% of patients with hepatic encephalopathy have EEG evidence of epileptiform discharges: this is a poor prognostic feature. Seizures may be focal or generalized; patients may have status epilepticus.
  - **Cirrhosis**
    - With underlying cirrhosis, extrapyramidal manifestations can be detected in early stages of HE. (The other encephalopathy associated with extrapyramidal manifestations is that due to hypoxia-ischemia: the extrapyramidal manifestations there are delayed in onset). HE in cirrhosis progresses very slowly. HE can progress to clinically obvious encephalopathy with deteriorating liver function and other precipitating factors (see below under management). Particularly with precipitating factors, a striking degree of reversibility and fluctuations may be seen.
    - Some patients show progressive neurologic deterioration despite therapeutic interventions. A rapidly progressive spastic paraparesis (hepatic myelopathy) may be seen. This may be preceded by episodes of HE. The underlying pathology is corticospinal tract demyelination.
A more slowly progressive parkinsonian syndrome called hepatolenticular degeneration is well described. Disturbance in cognition and consciousness is less prominent.

The chronic progressive disease can’t be treated by the treatments employed for HE. Reversibility is generally not seen. Some reports of improvement after transplantation do exist.21, 22

- Acute liver failure3, 23, 24
  - Fulminant hepatic failure involves23, 25: severe liver injury, potentially reversible, no preexisting liver disease, hepatic encephalopathy within 8 weeks of first symptoms
  - Causes of acute liver failure:
    - Drugs: acetaminophen, phenytoin, rifampicin, INH, sulfonamides, tetracycline, amiodarone, propylthiouracil, valproate
    - Viruses: HSV, EBV, CMV, adeno, parvovirus B19, hepatitis A, B, C, D and E
    - Toxins: CCl4, Amanita phalloides mushrooms
    - Ischemic hepatitis
    - Budd-Chiari
    - Autoimmune
    - Wilson
    - Reye syndrome
    - HELLP syndrome: hemolysis, elevated liver enzymes, low platelets
  - Encephalopathy in acute liver failure progresses rapidly. Irritability, insomnia, concentration deficits, disorientation, and agitation are frequently seen.26, 27 Rapid progression to drowsiness, stupor, and coma may occur within a few hours. Brain edema and seizures are common. The cerebral edema may develop so rapidly that no papilledema is seen. In the presence of increased intracranial pressure chances of survival without liver transplantation are poor.24 Lowering cerebral ammonia metabolism helps prevent increased ICP. Hypertonic saline or mannitol or controlled hyperventilation may delay onset of increased intracranial pressure. Hemorrhage related to ICP monitoring may increase mortality.28 Ischemia, hyperammonemia, and hypoglycemia are additional causes of seizures in patients with acute liver failure.29
  - N-acetylcysteine is used in the setting of acetaminophen toxicity. Hypothermia (moderate: 35-36 degree C) is recommended in acute liver failure though there is no evidence that it affects outcome.30 Rifaxamin and neomycin are ineffective in acute liver failure. Lactulose may cause dehydration and electrolyte abnormalities and worsen the underlying condition.23

- Investigations
  - Commonly employed laboratory investigations in HE include liver function tests, serum ammonia levels, ascitic fluid analysis for cell count over 250/mm3, ascitic fluid culture, and a coagulation panel. Overlapping ammonia levels in different grades of hepatic encephalopathy limits utility of the test. False elevations may occur with failure to keep sample on ice or delay in getting sample to lab or with tourniquet use. There is controversy over use of arterial vs venous ammonia.
  - Neuropsychological evaluation may be useful in early stages.
  - EEG abnormalities include nonspecific diffuse slowing or bilateral synchronous delta waves and triphasic waves. EEG abnormalities may not correlate with the stage of HE. EEG has limited utility with minimal disease, it may be useful for following progress in an individual patient; EEG pattern alterations may be indicative of increased risk of overt encephalopathy and death.30
  - CT head may show edema in acute stages and cerebral atrophy in late stages. MRI may show edema, atrophy, pallidal and midbrain (substantia nigra) T1-hyperintensity, and white matter signal change in or around the corticospinal tract.31-33 The T1-hyperintensity may involve the subthalamic nucleus, tectal plate, and hypothalamus. Gadolinium enhancement of the pallidal hyperintensity has been reported.34 It has been suggested that the pallidal T1-hyperintensity
may be related to hyperammonemia or hypermanganesemia. Some studies suggest that the pallidal T1-hyperintensity may not correlate with the stage of HE. MRS may show an elevated glutamine/glutamate peak coupled with decreased myo-inositol and choline signals on proton MR spectroscopy, representing disturbances in cell-volume homeostasis secondary to brain hyperammonemia.

- Abnormalities of auditory evoked potentials and P300 have been noted.

**Management**

- Identification and treatment of a precipitating cause

  - Common precipitating causes of HE in patients with liver disease include gastrointestinal hemorrhage, infection (including spontaneous bacterial peritonitis), constipation, protein-rich meals, benzodiazepine or opiate use, hypokalemia or hyponatremia, hypovolemia and prerenal azotemia. Other potential precipitating factors include anorexia, hypoglycemia, uremia, electrolyte imbalance, blood transfusions, systemic alkalosis or acidosis, psychoactive drugs including sedative-hypnotics, anemia, and hypoxemia. Medications that can precipitate hepatic encephalopathy also include diuretics, anesthetics like halothane, and high dose aspirin. *H pylori* infection has been associated with high serum ammonia levels and HE worsening. HE may result from progressive liver damage, development of hepatocellular cancer, viral or drug-induced liver disease (acetaminophen, valproate), alcohol abuse, portal vein thrombosis or portal vein shunting (spontaneous, surgical, TIPS: transjugular intrahepatic portosystemic shunts). Decreasing the diameter of the TIPS or embolization (transhepatic or transvenous) or surgical ligation may be beneficial in refractory cases.

<table>
<thead>
<tr>
<th>Increased Nitrogen Load</th>
<th>Gastrointestinal hemorrhage, protein-rich meals, constipation, renal failure, blood transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>Spontaneous bacterial peritonitis, <em>H pylori</em>, skin/respiratory/urinary tract</td>
</tr>
<tr>
<td>Fluid-Electrolyte</td>
<td>Hyponatremia, hypokalemia, hypovolemia, acidosis, alkalosis,</td>
</tr>
<tr>
<td>disturbance</td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td>Benzodiazepine, opiates, aspirin, acetaminophen, valproate, halothane, diuretics</td>
</tr>
<tr>
<td>Hepatic Injury</td>
<td>Progressive liver damage, hepatocellular carcinoma, viral hepatitis, alcohol abuse</td>
</tr>
<tr>
<td>Others</td>
<td>Anorexia, anemia, hypoxia, portal vein thrombosis/shunting</td>
</tr>
</tbody>
</table>

- Reducing the production and absorption of ammonia

  - Protein restriction had been an important component of HE therapy. Patients with cirrhosis are catabolic and need 1.5 g/kg protein per day. Protein restriction has not shown to be beneficial in the management of HE. Vegetable and probably dairy proteins are better tolerated than animal proteins. Administration of branched chain amino acids has not been conclusively beneficial in clinical studies.

  - Non-absorbable disaccharides such as lactulose (dose titrated to cause 2-4 soft, acidic stools per day: 500 ml in 500 ml saline or water rectally every 4-6 hrs followed by maintenance dose of 30-60 g/d given orally) or lactitol (more palatable, 0.3-0.5 g/kg/d) or oral lactose (in lactase deficient patients) remove dietary and endogenous ammoniagenic substrates from the intestinal lumen. They have a cathartic effect, acidify the intestinal content and result in reduction of ammonia absorption and movement of ammonia from the blood into the bowel, promote growth of nonurease producing bacteria, and interfere with the uptake of glutamine and its metabolism to ammonia in the gut wall. Despite its common use in HE, it has been suggested by some that there is insufficient evidence to support or refute its use in HE.

  - Probiotics modify the gut microflora and have been advocated as a possible treatment in patients with minimal HE. The formation of yogurt is associated with fermentation of lactic acid in milk. Yogurt has natural bacteria including *Lactobacillus bulgaricus*. Yogurt ingestion results in decrease of urease-producing bacteria (*Escherichia coli, Fusobacterium, Staphylococci*).
• Antibiotics such as neomycin, paromomycin, metronidazole, and rifaximin (550 mg bid) are poorly absorbed antibiotics that reduce nitrogenous-producing organism in the gastrointestinal tract. Neomycin (4-6 g/d) has some systemic absorption and may cause nephrotoxicity and ototoxicity. Neomycin administration for longer than 3-4 consecutive weeks is not recommended. Metronidazole may cause peripheral neuropathy. Rifaximin is commonly used and has a fairly safe tolerability profile.\textsuperscript{44, 45}

• A decrease in plasma ammonia levels can be achieved by increasing glutamine synthesis in muscle with L-ornithine-L-aspartate (LOLA).\textsuperscript{39, 46} Ornithine and aspartate are substrates for the conversion of ammonia to glutamine and urea.

• Note:
  o Others
    • IV N-acetylcysteine improves cognition in grade 1 and 2 encephalopathy in acute liver failure and improves survival without need for transplant (use per acetaminophen overdose protocol).\textsuperscript{47}
    • Zinc is a cofactor of urea cycle enzymes and may be recommended in patients with low zinc levels.
    • The benzodiazepine antagonist flumazenil has also been tried in some patients with HE.
    • Experimental therapies (largely animal studies) include use of acetylcholinesterase inhibitors, neurosteroid inhibitors, and indomethacin.\textsuperscript{2}
    • Tolvaptan is a selective, competitive vasopressin receptor 2 antagonist used to treat hyponatremia associated with congestive heart failure, cirrhosis, and the syndrome of inappropriate antidiuretic hormone (SIADH).

  o ICP
    • Arterial ammonia levels over 300 ug/dl are a reasonable predictor of raised ICP and brain herniation in acute liver failure.\textsuperscript{48} Mild hypothermia reduces ICP in acute liver failure likely by reducing ammonia production and uptake in brain.\textsuperscript{49}

  o Liver transplantation
    • In patients with acute liver failure hepatic transplantation is the definitive treatment.\textsuperscript{18} The ensuing HE needs to be managed until transplantation is possible. Patients with chronic liver failure and cirrhosis may also benefit from liver transplantation.
    • Extracorporeal systems (“artificial liver devices”) include single-pass albumin dialysis, the molecular adsorbent recycling system (MARS) and Prometheus. Their use is controversial and none are approved for treatment of HE is the US.
    • The Child-Pugh score has been replaced by the MELD score. MELD score predicts survival for patients with advanced liver disease. It uses the patient's values for serum bilirubin, serum creatinine, and the international normalized ratio for prothrombin time (INR) to predict survival. It is calculated according to the following formula: \textit{MELD} = 3.78 x \ln(\text{serum bilirubin (mg/dL)}) + 11.2 x \ln(\text{INR}) + 9.57 x \ln(\text{serum creatinine (mg/dL)}) + 6.43\textsuperscript{50}
    • An updated version also incorporates serum sodium level since it too is an important predictor of survival among candidates for liver transplantation. Patients with a diagnosis of liver cancer will be assigned a MELD score based on how advanced the cancer is.
    • United Network for Organ Sharing has made the following modifications to the score: If the patient has been dialyzed twice within the last 7 days, then the value for serum creatinine used should be 4.0; Any value less than one is given a value of 1 (i.e. if bilirubin is 0.8, a value of 1.0 is used) to prevent the occurrence of scores below 0 (the natural logarithm of 1 is 0, and any value below 1 would yield a negative result).
**Hepatitis C and other hepatitis virus infection-associated neurologic dysfunction**

- Hepatitis C is a global problem with an estimate worldwide prevalence of 2.8%. Though neurological and psychiatric problems have been commonly reported with hepatic C, the association is at times weak with causation not having been conclusively demonstrated. In part a confounder is neuropsychiatric side effects of HCV therapy in the interferon era. Fatigue and cognitive difficulties are known to accompany liver disease (cirrhosis or acute liver failure). Hepatitis C virus infection may cause cognitive difficulties, fatigue, and musculoskeletal pain that is unrelated to the severity of the underlying liver disease. The fatigue emerges episodically over the day. Some patients may have a dementia-like presentation. Manifestations include inattention, anxiety, depression, and difficulty with memory. Motor function is typically not affected. The underlying pathophysiology is unknown. Direct viral infection of the brain or a further autoimmune reaction are suspect. An alteration in serotoninergic neurotransmission has been implicated based on a response of the fatigue to ondansetron. A recent study noted that in HIV-infected patients, HCV coinfection does not contribute to neurocognitive impairment, at least in the absence of substantial HCV-associated liver damage. Hepatitis C has been associated with an increased risk of Parkinson disease in a recent study. It is unclear if interferon exposure as part of treatment for hepatitis C could have been a potential confounder.

- Interferon and antiretroviral treatment can be associated with depression, memory decline, delirium, irritability, and rarely psychosis.

- Rarely transverse myelitis and ADEM have been reported.

- Mixed cryoglobulinemia is commonly seen with hepatitis C infection. Less commonly the cryoglobulinemic syndrome associated with hepatitis C can result in neuropathy or stroke or an encephalopathy. Besides peripheral neuropathy, patients may have mononeuropathy, mononeuropathy ulitplex, or cranial neuropathy (V motor, VI, VIII). In addition to antiviral therapies, coexisting cryoglobulinemic vasculitis may prompt use of steroids, rituximab, or cyclophosphamide.

- Hep A, B, and E have also been associated with myelitis. There are reports of hepatitis A being associated with GBS, meningoencephalitis, ADEM, and acute myelitis. Similar manifestations have less commonly been reported with hepatitis B. Neurological manifestations can rarely be seen with hepatitis E infection and include GBS, brachial plexopathy, encephalitis, ataxic neuropathy, and myopathy.

**Chronic acquired (non – Wilsonian) hepatocerebral degeneration**

- CAHD may be associated with extrapyramidal (Parkinsonism, action – postural/ head tremor, chorea, dystonia, myoclonus, asterixis, oral-buccal dyskinesia), cerebellar (ataxia, dysarthria), cognitive (acute: irritability, agitation, delirium, chronic: apathy, slowness, impaired attention), or myelopathic (spastic gait) manifestations. Sleep disturbance may include somnolence or insomnia. The parkinsonian syndrome is typically a symmetrical akinetic rigid syndrome that may mimic progressive supranuclear palsy or multiple system atrophy. Patients with atypical parkinsonism should be investigated for underlying liver disease. The parkinsonian syndrome associated with liver disease may initially respond to levodopad. Liver transplantation may result in marked improvement.

- Cortical laminar necrosis and polymicrocavitation in the cortex and basal ganglia are combined with cerebral and cerebellar atrophy. Microscopically, Alzheimer type II astrocytes and cytoplasmic glycogen granules are characteristic.

- MRI may show a hyperintense T1 signal in the pallidum, putamen, and, rarely, mesencephalon. The pallidal T1-hyperintensity may relate to severity of liver disease and resolve in some cases with normalization of deranged liver function after transplantation.

- Using clues from a similar MR appearance in patients receiving total parenteral nutrition as well as animals given parenteral manganese, and the knowledge that manganese is cleared by the hepatobiliary system, deposition of manganese in the brain is postulated in patients with CAHD.

- A manganese storage disorder due to mutations in the manganese transporter gene SLC30A10 manifests with childhood-onset dystonia or as an asymmetrical parkinsonian presentation in adulthood. These patients can have hepatic cirrhosis. This condition should be considered in the differential diagnosis of Wilson disease. Laboratory investigations include polycythemia, increased manganese levels, and basal ganglia T1 hyperintensity of MRI. Chelation with CaNa2EDTA can result in increased manganese excretion and clinical improvement.
Peripheral neuropathy and chronic liver disease
- Peripheral neuropathy (generally axonal) may occur in chronic liver disease, particularly so in patients with cirrhosis.\textsuperscript{82-85} Demyelinating features may be seen with underlying autoimmune hepatitis. Neuropathy in the setting of hepatitis C-related cirrhosis may be due to cryoglobulinemia and neuropathy in autoimmune hepatitis may be due to vasculitis.\textsuperscript{84} Neuropathy accompanying chronic liver disease may improve following transplantation.\textsuperscript{83, 86, 87}

Myelopathy in chronic liver disease
- The myelopathy seen in chronic liver disease is typically a progressive spastic paraparesis typically without sensory manifestations.\textsuperscript{88-92} Dorsal column dysfunction has been reported. The upper extremities are spared. It is typically seen in the setting of portosystemic shunts. One reported patient had polycythemia and laboratory and imaging manifestations of hypermanganeseemia.\textsuperscript{93} It may coexist with extrapyramidal features. Liver transplantation may result in improvement of the myelopathy.\textsuperscript{94-96}

Muscle involvement in chronic liver disease
- Cramps are commonly seen in patients with cirrhosis.\textsuperscript{97, 98} Polymyositis and granulomatous myositis have been reported in primary biliary cirrhosis.\textsuperscript{99, 100} Inclusion body myositis (and a cryoglobulinemic small fiber neuropathy) has been reported with hepatitis C infection.\textsuperscript{101}

Neurological Complications of TIPS (transjugular intrahepatic portosystemic shunt)
- TIPS may be complicated by encephalopathy in up to 30% of cases.\textsuperscript{102}

Neurological complications of liver transplantation\textsuperscript{103-111}
- Neurological complications are commonly seen after orthotopic liver transplantation. They are more common after a cadaveric graft as compared to living donor liver transplantation.

Immunosuppressive therapy
- Neurotoxicity is commonly seen with the most commonly used immunosuppressants in liver transplantation: the calcineurin inhibitors cyclosporin and tacrolimus (FK506). Other immunosuppressants used include mycophenolate mofetil, sirolimus, everolimus, steroids, OKT3, and antithymocyte globulin.
- Neurotoxicity related to the calcineurin inhibitors often occurs in the early postoperative period and is not always related to drug levels.
- Minor manifestations of calcineurin inhibitors – related neurotoxicity include tremor, headache, insomnia, paresthesias, and major manifestations include encephalopathy, akinetic mutism, seizures, speech disorders, and according to some neuropathy/myopathy. Predisposing factors include hypocholesterolemia, hypomagnesemia, hypertension, and hepatic encephalopathy. MRI may show PRES-like or CPM-like changes.
- Management may include switching from cyclosporine to tacrolimus or vice versa and use of non-calcineurin inhibitor.

Seizures
- Seizures following liver transplant may occur as a complication of immunosuppressive therapy or rejection.\textsuperscript{112, 113} Seizures often occur early after surgery. Additional etiologies include metabolic derangements, hypoxic-ischemic injury, cerebral lesions, narcotic withdrawal, or changes in or discontinuation of antiepileptic medications.
- Levetiracetam is a preferred antiepileptic given the fact that is has no protein binding, no dependence on liver cytochrome P450, no active metabolites, and no significant drug interactions. It is renally excreted. In most cases antiepileptic therapy can be discontinued after 3 months. The enzyme inducing anti-epileptics (carbamazepine, oxcarbazepine, phenobarbital, and phenytoin) may reduce cyclosporin, tacrolimus, and corticosteroid levels with a delayed effect of up to 10 days.

Central pontine myelinolysis
- Cirrhotic patients not uncommonly have hyponatremia. Fluid replacement during surgery can result in a rapid correction of sodium and can result in CPM.
• **Neuromuscular disorders**
  - Neuromuscular complications reported following liver transplantation include mononeuropathies, polyneuropathy (including AIDP, CIDP, critical illness), and necrotizing myopathy.

• **Cerebrovascular disease**
  - A diffuse encephalopathy may obscure focal deficits related to a stroke. In addition to standard cerebrovascular disease-related risk factors, cerebrovascular injury may result from coagulation disturbance, paradoxical air emboli, perioperative cerebral hypoperfusion, and *Aspergillus* angiopathy.

• **Infections**
  - Infections seen within 1 month are due to a pathogenic agent that was present before transplantation or acquired through the transplanted organ or a complication of surgery or acquired in the ICU. Organisms implicated in this setting include staphylococci, gram-negative bacteria, enterococci, or *Candida*.
  - Opportunistic pathogens are implicated in infections seen from 1 to 6 months after transplantation: fungi, parasites, viruses (HSV1, HSV2, HHV6, CMV, VZV). Beyond 6 months opportunistic infections may be seen in those with chronic rejection needing more aggressive immunosuppression. Additional considerations include EBV-associated lymphoproliferative disorder and infection with hepatitis B or C.

**Wilson Disease**

• Wilson disease (WD) is a rare autosomal recessive disorder of copper metabolism that results in copper accumulation and multi-organ damage. The brain and liver are preferentially affected. Prompt institution of treatment is essential for a favorable outcome. Untreated disease is likely fatal. Several recent review articles provide detailed bibliographies for the interested reader.\(^81, 114-126\)

• The worldwide prevalence of WD ranges from 1 in 5000 to 1 in 30,000, the carrier frequency is 1 in 90, and the incidence ranges from 15 to 30 per million.\(^127\) WD is more prevalent in those populations in which consanguineous marriage is common. A particularly high prevalence and incidence has been noted in East Asia, Sardinia, Greece, and Italy.

• **Genetics**
  - WD is caused by mutations in the gene coding for a metal-transporting P-type ATPase (*ATP7B*).\(^128-131\) The gene is located on chromosome 13. The WD protein is a late endosome-associated membrane protein that binds copper in its large N-terminal domain and then translocates it to the endosomal lumen, ultimately delivering excess copper to biliary canaliculi for excretion. The WD protein is also responsible for incorporation of copper into apoceruloplasmin. Approximately 500 plus mutations have been identified in the WD gene and many more are likely to exist.\(^81, 132-133\) A majority of affected individuals are compound heterozygotes. In most ethnic groups a small number of mutations are prevalent in addition to other more rare mutations. Two commonly observed mutations among Europeans and North Americans are *His1069Gln* and *Gly1267Arg*. Deletions, insertions, splice site mutations, missense and nonsense mutations have all been identified; missense mutations are most frequent. Nonsense mutations and frameshift deletions cause a truncation of the translated protein and may result in a more severe form of the disease.\(^134\) The same mutation may be associated with different phenotypes. This suggests the presence of additional modifying factors. The phenotype can be modulated by modifier genes such as *ATOX1* and *COMMD1* (originally called *MURR1*). Patients with apoE epsilon 3/3 genotype have a delayed onset of symptoms compared to all other apoE genotypes.\(^135\)

• **Pathophysiology**
  - Copper absorbed by the intestinal cells is stored in the enterocytes (bound to metallothionein) in a non-toxic form (*Figure 2*). It is delivered into the circulation by the copper transporting protein ATP7A. Copper complexed to albumin reaches the liver. *Figure 3* is a schematic representation of copper metabolism in the hepatocyte. Impaired function of ATP7B (the WD protein) leads to decreased hepatocellular excretion of copper into bile with subsequent hepatocellular copper accumulation and injury. Additionally the defective ATP7B protein likely fails to incorporate copper into apoceruloplasmin. This results in secretion of
apoceruloplasmin instead of holoceruloplasmin. Apoceruloplasmin has a shorter half-life than holoceruloplasmin and is rapidly metabolized. A reduced serum ceruloplasmin level results. In WD urinary copper excretion increases but this increase is unable to compensate for the defect in biliary copper excretion. When hepatic storage capacity is exceeded copper is released in the blood and is deposited in other organs like brain, cornea, kidney, and bones. There is an increase in the circulating free copper which is toxic. Copper elevation causes a reduction in the protein X-linked inhibitor of apoptosis (XIAP) which causes caspase 3-initiated apoptosis and cell death. The primary cerebral pathology is in the basal ganglia. Copper deposition causes a brownish discoloration of the lenticular nuclei. Additional sites of involvement are the thalamus, brainstem, cerebellum, and cerebral cortex. With disease progression there is necrosis and gliosis. Cystic changes in the basal ganglia (Figure 1B) is a characteristic finding.

- **Clinical Findings**
  - The initial presentation of WD is neurologic, hepatic, and psychiatric in approximately 40%, 40%, and 20% cases respectively. WD presents with liver disease more often in children and young adults than in older individuals. Any patient younger than 50 years with unexplained liver disease should be screened for WD. Patients who present with neurologic disease generally do so in the second and third decades. Most patients with neurologic involvement have liver disease at the time of presentation but they are not symptomatic from their liver disease. The possibility of WD should be considered in any young patient with a movement disorder. Presentation with neurologic disease as late as the eighth decade has also been reported. Clinical manifestations of copper excess are relatively rare in the preschool age, probably because copper accumulation takes time to develop. Many atypical presentations are recognized (Table 2).
  - The most common mode of hepatic presentation in WD is progressive cirrhosis. In some cases incidental detection of hepatomegaly, splenomegaly due to portal hypertension, or elevated serum aminotransferases may be the only abnormality. Hepatic presentations also include acute hepatitis, recurrent hepatitis, chronic active hepatitis, fulminant hepatitis, or liver failure. Viral hepatitis or autoimmune hepatitis are frequently entertained differential diagnoses. 5% of all cases of acute liver failure are due to WD. This mode of presentation has a high mortality. Hemolysis induced by copper released from necrotic hepatocytes may complicate acute liver disease. Associated renal failure may be present.
  - Three main neurologic phenotypes are recognized: (1) a parkinsonian syndrome, (2) generalized dystonia, (3) postural and intention tremor with ataxia and dysarthria (“pseudosclerosis”). The onset is generally subacute or chronic. Rarely acute onset generalized severe dystonia (status dystonicus) or chorea or tremor may be seen. The most frequent presenting neurologic manifestation of WD is tremors. The tremor may be resting, postural, or kinetic. A proximal, slow, high amplitude upper extremity tremor is the classic finding. It may take on a coarse, “wing-beating” appearance. Tremor in WD may also be distal and small in amplitude. Head titubation may be present. Dystonia is seen in nearly 40% of cases with a neurologic presentation and may involve the tongue, face, jaw, pharynx, neck, trunk, and limbs. Dystonia of the face and jaw may result in a stiff face with gaping mouth (“vacuous smile”, “risus sardonicus”), drooling, and dysarthria. The dysarthria seen in WD may have extrapyramidal or cerebellar or infrequently pyramidal features. Rarely patients can become anarthric and mute. A “whispering dysphonia” has been described in WD. Also described is an unusual laugh in which most of the sound is generated during inspiration. An unusual cough due to respiratory dyskinesia has been reported as a presenting symptom. Chorea, tics, athetosis, and myoclonus are unusual. Generalized myoclonus associated with extensive white matter lesions has been described. Early pseudobulbar features are common. Cerebellar dysfunction develops in approximately 25% of patients with neurologic WD. It is unusual for WD to present as a gait disorder. A painless variant of painful legs and moving toes has been reported in WD. Isolated tongue protrusion movements may occur. Abnormalities in extraocular movements such as slow horizontal saccades, upgaze restriction, impaired convergence, and rarely eyelid apraxia or ophthalmoplegia may be seen. Seizures are relatively infrequent. Status epilepticus is rare. Seizures may be the presenting manifestation, or occur during de-coppering therapy. Rarely it is the terminal event. Majority
of patients become seizure free after decoppering therapy. Autonomic dysfunction has been reported in nearly a third of cases with neurologic WD. A peripheral neuropathy may also be seen and is rarely the presenting manifestation. Olfactory dysfunction may be present in patients with neurologic WD; the same may parallel the severity of neurologic disease. Vision and sensation are not affected. Paralysis does not occur. Pyramidal tract involvement is rare. Other reported manifestations include altered rapid eye movement sleep, hypersomnia, cramps, writer’s cramp, and priapism. Cognitive difficulties include frontal-executive dysfunction, difficulty with visuospatial processing, impaired memory, and pseudobulbar emotional affect. Cognitive impairment is often more apparent than real. Many individuals with neurologic or psychiatric disease have cirrhosis but are not symptomatic from their liver disease. In the presence of advanced liver disease the neurologic manifestations may be mistaken for hepatic encephalopathy.

- Psychiatric symptoms may predominate or antedate the neurologic symptoms.

Psychiatric manifestations appear at some point in the course of the disease in most patients with neurologic WD. WD should be considered with unexplained psychiatric symptoms in young individuals, particularly if accompanied by neurologic or hepatic dysfunction. The most common psychiatric manifestations of WD include personality or behavior changes and mood disturbances, most commonly depression. Psychosis is rare, Antisocial or criminal behavior, and sexual preoccupation and disinhibition have been reported. Other psychiatric manifestations include anxiety, phobias, attention deficit hyperactivity disorder, impulsivity, delusions, obsessive compulsive behavior, schizophrenia, and manic-depressive psychosis. In the pediatric age group the manifestations are often subtle and may include coordination difficulty and deterioration in schoolwork.

- Copper accumulation in the Descemet’s membrane in the limbic area of the cornea (Kayser-Fleischer or K-F ring) is frequently seen patients of WD, particularly so in those who have neurologic manifestations (Figure 4). Excess copper is uniformly distributed throughout the inner surface of the cornea. Sulfur-copper complexes are found only in the Descemet’s membrane and account for the visible ring. The color of the ring can be gold, brown, or green. It can be difficult to see in individuals with brown irises and is best visualized by slit lamp. Ring formation is first evident in the superior aspect of the cornea, the inferior aspect, followed by the medial and lateral aspects. The pigment first appears in the periphery of the cornea at the limbus and then spreads centrally. The ring is frequently not seen in asymptomatic siblings and in those with only hepatic involvement (particularly children). Rarely patients with neurologic WD may not have the K-F rings. K-F rings are generally bilateral; unilateral formation has been reported. The ring is not pathognomic of WD and may be rarely seen in other cases of cholestatic liver disease. The K-F ring can disappear with therapy. Copper deposits in the lens are rare and may also be seen on slit-lamp examination. They assume a sunburst or sunflower appearance (sun-flower cataract) with a central disc and radiating petal-like spokes. It too may disappear with effective therapy.

### Clinical manifestations of Wilson disease

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Not affected: vision, sensation

**Hepatic**
- Progressive cirrhosis (compensated or decompensated), incidental detection of hepatomegaly/ splenomegaly/ serum aminotransferases, fulminant hepatic failure (with or without hemolysis/ renal failure), hepatitis (acute, recurrent, chronic active, fulminant)
- Rare: Hepatoma or hepatocellular carcinoma

**Psychiatric**
- Depression, Anxiety, phobias, personality or behavior change: inattention, hyperactivity, impulsivity, obsessions, compulsions
- Coordination difficulty and deterioration in school work
- Rare: psychosis, schizophrenia, antisocial or criminal behaviors, sexual preoccupation, disinhibition

**Hematology**
- Hemolytic anemia, thrombocytopenia
- Rare: WD in a patient with the antiphospholipid antibody syndrome

**Ophthalmic**
- K-F rings, sunflower cataracts
- Rare: night blindness, optic neuritis, optic disc pallor, exotropic strabismus

**Renal (Rare)**
- Renal tubular dysfunction (hypercalcuiaria, hyperphosphaturia, aminocadiuria), nephrocalcinosis, hypokalemia with muscle weakness with or without respiratory paralysis (possibly due to renal tubular dysfunction)

**Cardiac (Rare)**
- Cardiomyopathy, congestive heart failure, arrhythmias

**Endocrine (Rare)**
- Hypoparathyroidism, glucose intolerance, hypoglycemia

**Musculoskeletal (Rare)**
- Osteoporosis, osteomalacia, rickets, osteochondritis, osteoarthritis, osteochondritis dissecans, chondrocalcinosis, spontaneous fractures, vertebral column abnormalities, subchondral cyst formation, azure lunulae of fingernails

**Gynaecology (Rare)**
- Infertility, menstrual irregularity, delayed puberty, gynecomastia, repeated miscarriages

**Dermatology (Rare)**
- Leg hyperpigmentation (misinterpreted as Addison disease)

**Investigations**
- **Overview**: Patients with WD may show laboratory evidence of hepatic, hematologic, or renal derangement. These tests, in particular pattern of derangement in liver enzymes in patients presenting with hepatic failure, are suggestive but lack diagnostic specificity. Liver histology findings are also nonspecific. Absence of the “second peak” in the radio-copper test had been used for the diagnosis of WD. Significant overlap between affected patients and heterozygotes, and technical challenges has resulted in abandonment of the test. A combination of clinical findings and biochemical testing is necessary to establish a diagnosis of WD. The laboratory hallmarks of WD include a low serum ceruloplasmin and an elevated urine 24-hour copper excretion. Hepatic copper is frequently elevated. These tests, along with genetic testing and MRI are the primary diagnostic modalities. There is no single ideal test (Table 3).
- **Serum ceruloplasmin**: Serum ceruloplasmin is frequently reduced in WD; a commonly cited value is less than 20 mg/dl. However, the cut off level and normal ceruloplasmin range is dependent on the assay used (enzymatic or immunologic) and varies considerably among different laboratories. Immunological assays are easier to perform and standardize but overestimate ceruloplasmin concentrations since they don’t discriminate between apoceruloplasmin and holoceruloplasmin. Serum ceruloplasmin may be normal in 15% - 25% of patients with WD, particularly so with a hepatic presentation. A normal ceruloplasmin level cannot exclude the diagnosis of WD. Ceruloplasmin levels tend to be lower in patients with K-F rings or neurologic disease, and higher in patients with a hepatic presentation of WD. Approximately 10 - 20% of heterozygotes have decreased level of serum ceruloplasmin. A low ceruloplasmin can also be seen in chronic or fulminant liver disease, various causes of copper deficiency, and with renal or enteric protein loss. Ceruloplasmin is absent in aceruloplasminemia (a disorder of iron metabolism). Ceruloplasminemia is low in carriers of aceruloplasminemia. A low level of ceruloplasmin is therefore not sufficient to make the diagnosis of WD. A subnormal ceruloplasmin in fact has a very low positive
predictive value for WD. Serum ceruloplasmin concentration is age-dependent. It can be low in normal neonates, it rises to adult levels in the first year, then further increases to its maximum at 2 to 3 years of age, then falls until 12 years of age when it reaches adult levels. Ceruloplasmin is also an acute-phase reactant and its levels increases with inflammation, infection, trauma, hepatitis, estrogen supplementation, steroid use, and pregnancy.

- **Serum copper**: Most of the copper in serum is bound to ceruloplasmin; less than 5% circulates as free copper. Normal serum copper ranges from 75 to 145 µg/dl. Serum copper in WD is frequently less than 100 µg/dl. This simply reflects reduced ceruloplasmin. Hemolysis associated with liver disease may result in substantially elevated serum copper levels. In acute fulminant hepatic failure due to WD, serum copper levels may be markedly elevated due to sudden copper release from tissue stores. Normal or elevated serum copper in association with decreased ceruloplasmin indicates increase in nonceruloplasmin-bound copper. Normal values of nonceruloplasmin (free) copper range from 8 – 12 µg/dl. This nonceruloplasmin-bound copper is over 25 µg/dl in most untreated patients with WD. It is also elevated in acute liver failure of any cause, chronic cholestasis, and copper poisoning. Direct measurements of free copper concentration is not routinely available. The free serum copper can be calculated by subtracting three times the ceruloplasmin level (mg/dl) from the total serum copper (µg/dl). The nonceruloplasmin-bound copper concentration is useful in monitoring therapy and values < 5 µg/dl in combination with low 24-hour urinary copper excretion may indicate systemic copper depletion that may rarely occur with prolonged therapy. This measurement is also valuable in cases in which falsely high levels of serum ceruloplasmin are suspected, and when a measurement of urinary copper is difficult to obtain.

- **Urinary copper**: Urinary copper excretion reflects the amount of nonceruloplasmin-bound copper in the circulation. 24-hour urinary copper excretion is frequently increased in patients with WD (generally over 100 µg). 24-hour urinary copper excretion may be less than 100 µg at presentation in approximately 10%-20% of patients diagnosed with WD. Despite this limitation it is perhaps the best available screening test. It may be elevated in other cholestatic disorders also. Intermediate levels of urinary copper excretion may be seen in heterozygote and presymptomatic individuals. Incorrect collection and copper contamination are common sources of error. Copper-free jugs should be used for collection. Samples from children may show reduced urinary copper excretion because of difficulties with sample collection. Urinary copper excretion may not be elevated in neonates with low body copper load. Even after penicillamine administration 24-hour urinary copper is not consistently elevated in WD.

Further, this provocation test has only been standardized in a pediatric population.

- **Liver copper**: Normal liver copper concentrations rarely exceed 50µg/g dry weight of liver. In about 80% of cases with WD the value is over 250 µg/g of dry tissue. Hepatic copper elevations are also seen in asymptomatic individuals with WD. Hepatic copper concentration in heterozygotes is frequently elevated above normal but does not exceed 250 µg/g dry weight. Other causes of elevated liver copper levels include patients with chronic cholestasis, neonates and young children, subjects with exogenous copper overload, and in idiopathic copper toxicosis syndromes like Indian childhood cirrhosis. Hepatic copper may be < 50 µg/g in 3.5% of WD cases. Low hepatic copper values may be seen in WD with advanced cirrhosis. The cirrhotic liver may have significant regional differences in hepatic copper distribution and sampling error may be responsible for normal or borderline values of hepatic copper content. Contamination, particularly in block specimens, may result in falsely elevated hepatic copper values. Despite this limitation it is perhaps the best available biochemical test. It is invasive and is not required in all cases. Its use should be reserved for those cases where simpler approaches have not provided a definitive diagnosis. Further, it is generally not required in patients with neurologic disease as other tests can provide the diagnosis. Its utility is primarily in patients who present with hepatic dysfunction as in these cases the copper has not been discharged to other tissues.

- **CT and MRI**: Brain CT is relatively insensitive for the diagnosis of WD. It may reveal hypodensities and atrophy involving the basal ganglia, brainstem, cerebellum, and cerebral cortex. Brain MRI abnormalities are seen in nearly all patients with neurological WD. T2-weighted sequences show increased T2 signal in the caudate, putamen, thalamus, midbrain
Laboratory diagnosis of Wilson disease

**Abbreviations:** WD: Wilson disease, <: less than, >: greater than

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Causes of increase</th>
<th>Causes of decrease</th>
<th>Additional comments</th>
</tr>
</thead>
</table>

- **Laboratory diagnosis of Wilson disease**: when routine testing is equivocal. The presence of two mutations (one per allele) can confirm the diagnosis. While there are several mutations that occur at an appreciable frequency in specific ethnic groups, the vast majority of patients are compound heterozygous for one common mutation and one rare mutation. Given this, the preferred approach is direct DNA sequencing. In this method, the entire coding region of the gene is sequenced without prior selection of candidate exons. Furthermore, once mutations are identified in the index case, asymptomatic relatives can be screened for carrier status by direct mutation analysis of the known familial mutations. Haplotype analysis of markers around the ATP7B gene may have a role in sibling screening when it has not been possible to detect both mutations in the index case by mutation analysis or direct DNA sequencing.

- **Screening**: All first-degree relatives of known patients should be screened for WD. Laboratory abnormalities or clinical signs may indicate need for prophylactic treatment. In some cases a liver biopsy or molecular genetic testing may be required.

- **MRS and PET**: Magnetic resonance spectroscopy (MRS) in WD may show evidence of neuronal loss (reduction in the N-acetylaspartate:creatine and choline:creatine ratios). Creatine is relatively stable as it is present in glial cells which are less affected in WD. MRS may also show decreased levels of myo-inositol in patients with porto-systemic shunting. MRS may have some utility in monitoring treatment efficacy in WD. Single photon emission computed tomography (SPECT) imaging has shown evidence of presynaptic dopaminergic damage. SPECT scans have shown a decrease in dopamine transporter function and in D2 receptors in the striatum. Positron emission tomography (PET) using 18F-fluorodopa shows reduced uptake in the striatum indicating loss of the dopaminergic nigrostriatal pathway. Transcranial sonography may show lenticular hyperechogenicity. The same may also be seen in asymptomatic individuals with WD. It has been suggested that this correlates with disease severity and may be useful for disease monitoring.

- **Genetic**: ATP7B is a relatively large gene (approximately 80kb in size) and comprises 21 exons. The large number of mutations reported (http://www.wilsondisease.med.ualberta.ca/database.asp) in the WD gene analysis and the presence of regulatory mutations in noncoding regions, had made commercial genetic testing impractical. The advent of high throughput methodologies has changed the mutation identification paradigm. Molecular testing can be a valuable tool in the work up of a suspected patient, particularly so when routine testing is equivocal. The presence of two mutations (one per allele) can confirm the diagnosis. While there are several mutations that occur at an appreciable frequency in specific ethnic groups, the vast majority of patients are compound heterozygous for one common mutation and one rare mutation. Given this, the preferred approach is direct DNA sequencing. In this method, the entire coding region of the gene is sequenced without prior selection of candidate exons. Furthermore, once mutations are identified in the index case, asymptomatic relatives can be screened for carrier status by direct mutation analysis of the known familial mutations. Haplotype analysis of markers around the ATP7B gene may have a role in sibling screening when it has not been possible to detect both mutations in the index case by mutation analysis or direct DNA sequencing.

**Normal parameter for Wilson disease**

- **Parameter**: normal value for Wilson disease

**Causes of decrease**

- **Causes of increase**

**Additional comments**

- **Notes**: WD: Wilson disease, <: less than, >: greater than

- **Notes**: WD: Wilson disease
## Treatment
- The treatment of WD is directed at restoring and maintaining copper balance. A lifelong commitment to treatment is required. Limitation of dietary copper intake is desirable but is generally ineffective. Pharmacological management is necessary (Table 4). Pharmacologic treatment is based on the use of chelators to promote copper excretion or zinc to reduce copper absorption or both. The initial treatment of symptomatic patients is with chelating agents like penicillamine or trientine. Some reports suggest that primary treatment with zinc alone may be adequate in some patients. In the maintenance phase (typically 2 to 6 months after initiation of therapy), the dose of these chelating agents is reduced. Alternatively the chelators are replaced by zinc or zinc is added to prevent further copper absorption. The potential role of combination therapy of zinc in conjunction with, but temporally separated from a chelator like trientine or penicillamine or tetrathiomybdate has theoretical appeal but

### Table 4: Laboratory Findings in WD

<table>
<thead>
<tr>
<th>Test</th>
<th>Range</th>
<th>Conditions</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ceruloplasmin</td>
<td>20 – 40 mg/dl</td>
<td>Reduced in WD, often &lt; 20 mg/dl (varies among different laboratories, depends on method employed)</td>
<td>Infection, Inflammation, Trauma, Hepatitis, Estrogen supplementation, Steroid use, Pregnancy</td>
</tr>
<tr>
<td>Serum copper</td>
<td>75 – 145 µg/dl</td>
<td>Reduced in WD, often &lt; 100 µg/dl</td>
<td>WD, Copper deficiency, Cirrhosis</td>
</tr>
<tr>
<td>Urinary 24-hour copper excretion</td>
<td>15 – 60 µg</td>
<td>Elevated in WD, often &gt; 100 µg</td>
<td>Copper deficiency &lt; 100 µg/24-hour in 10 – 20% of WD, False negative in presymptomatic cases</td>
</tr>
<tr>
<td>Liver copper</td>
<td>&lt; 50 µg/g dry weight</td>
<td>Elevated in WD, often &gt; 250 µg/g dry weight</td>
<td>WD, Fulminant liver disease, Cirrhosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal in approximately 20% of WD patients, particularly with hepatic presentation. Ceruloplasmin is an acute phase reactant.</td>
</tr>
</tbody>
</table>
few studies. Asymptomatic patients are treated with maintenance doses of chelators or zinc from the outset. The definitive treatment is liver transplant. It is considered in patients refractory to medical treatment and is often required in patients who present with fulminant hepatic failure. Its potential role in patients with neurologic disease is encouraging but awaits further studies. The severity of the disease at the time of initiation of treatment determines the level of disability. With timely intervention complete recovery can be expected. Residual dysarthria and mild dystonia are common neurologic sequelae.

- **Penicillamine:** Penicillamine has a free sulfhydryl group which functions as the copper chelating moiety. It reduces copper bound to protein which in turn decreases affinity of the protein to copper and permits binding of copper to penicillamine. It may also act by inducing metallothionein in individuals with WD. By promoting metallothionein synthesis it detoxifies tissue copper. Copper chelation with penicillamine is an effective therapy for WD. It is started in a dose of 250 to 500 mg/day and increased by 250 mg every 4 to 7 days to a target dose of 1 to 2 g/day in 2 to 4 divided doses. Initial neurologic deterioration may occur. There is no data to confirm that a gradual titration decreases the risk of initial neurologic deterioration. Penicillamine should be given 1 hour before or 2 hours after meals. Penicillamine is a pyridoxine antagonist. Vitamin B₆ supplementation in a dose of 25-50 mg/week is often recommended. Currently however penicillamine is synthesized and the racemic mixtures that interfered with pyridoxine action are no longer used. There is no consensus on the continued need for pyridoxine supplementation. The copper mobilized by penicillamine is then excreted in the urine. It takes weeks (often 2-6 months) before clinical improvement is evident and improvement may continue over 1-2 years. Psychiatric manifestations improve less consistently that neurologic disease. Initially there is significant cupruresis. Subsequently copper excretion decreases to around 0.5 mg/day. Serum ceruloplasmin tends to decrease after initiation of treatment. It may increase with recovery of synthetic liver function. With established clinical and biochemical benefit the dose of penicillamine can be reduced to 500 to 1000 mg/day in 2 divided doses. Zinc can be added and is given on an empty stomach, temporally separated from penicillamine. With maintenance therapy 24-hour urinary copper excretion should be in the range of 200 to 500 μg/day and nonceruloplasmin bound copper should normalize; a suggested target is between 5 and 15 μg/dl. An increase in receding or stable 24-hour urinary copper excretion may indicate suboptimal compliance. A serum non-ceruloplasmin bound copper level below 5 μg/dl may suggest overtreatment. During penicillamine administration clinical, hematologic, biochemical (transaminases, serum ceruloplasmin and copper), and urinary (protein and 24-hour copper) parameters are monitored periodically (weekly for the first month, monthly for the next 6 months, and 6 monthly thereafter). Significant toxicity including acute neurologic deterioration following initiation of therapy has raised some skepticism about penicillamine being the first line agent. The neurologic deterioration can be severe; in one patient it resulted in severe dystonia (status dystonicus) and death. Worsening of neurologic symptoms during the initial treatment phase is generally seen after 6 weeks but may be seen from 2 weeks to 12 months. Following initial deterioration patients may not return to their baseline level of functioning. When neurologic deterioration is present the drug can be withdrawn and reintroduced in a smaller dose with a slower titration with or without steroid cover. If neurologic deterioration recurs, the medication should be withdrawn and replaced by other chelators or zinc alone. Severe side effects requiring drug discontinuation occur in 10 to 30% of patients. Immune mediated side effects generally occur within the first 3 weeks and if present prompt cessation of therapy is required. These include leukopenia, eosinophilia, thrombocytopenia, fever and cutaneous eruptions, lymphadenopathy, and proteinuria. Late reactions include nephrotoxicity (nephrotic syndrome), lupus-like syndrome, polyarthritis, Goodpasture’s syndrome, myasthenia gravis-like syndrome, polymyositis, bone marrow suppression, loss of taste, immunoglobulin A depression, serous retinitis (retinal hemorrhages), hepatotoxicity, and a spectrum of dermatologic toxicities (aphthous stomatitis, elastosis perforans serpiginosa, progeriatric changes). Penicillamine dermatopathy refers to a brownish skin discoloration and is due to recurrent subcutaneous bleeding during incidental trauma. There is damage of collagen and elastin which causes weakness of subcutaneous tissue so that slight trauma causes bleeding leaving brown papules with wrinkling and
thinning of the skin. Also reported is hypothyroidism in children and in infants born to a mother on penicillamine treatment for WD.\textsuperscript{188}

- **Trientine:** Trientine (triethylene tetramine) has a similar mechanism of action as penicillamine. It is less potent and the initial deterioration is of lesser concern.\textsuperscript{181, 185} It is considered by many as the initial therapy of choice, even with decompensated liver disease. It is often used in patients intolerant to penicillamine. The usual dose is 750 mg to 2000 mg/day in 2 or 3 divided doses on an empty stomach. Lower doses (750 or 1000 mg /day) are used for maintenance therapy. The targeted 24-hour urinary copper excretion should be in the range of 200 to 500 µg/day and nonceruloplasmin bound copper should normalize. Sideroblastic anemia is a major adverse effect. Pancytopenia and lupus nephritis have been rarely reported. Copper deficiency induced by trientine may result in iron overload in livers of patients with WD, similar to that observed for penicillamine.\textsuperscript{189}

- **Zinc:** Zinc induces metallothionein formation in the intestinal enterocyte. The increased metallothionein binds copper preferentially and traps it within the intestinal mucosal cells. These cells are eventually sloughed off and excreted in the feces. Since copper also enters the gastrointestinal tract from saliva and gastric secretions, zinc can remove stored copper and generate a negative copper balance.\textsuperscript{190} Zinc may also act by inducing levels of hepatocellular metallothionein.\textsuperscript{191} Zinc has assumed an increasingly important role in the management of WD.\textsuperscript{192, 193} It has a role in chronic maintenance therapy following initial therapy with more potent decoppering agents and for management of WD in pregnancy and in children. More recently zinc monotherapy has been proposed as initial therapy, particularly so for mild cases. Due to the slow response it is not the preferred agent for initial therapy in severe cases. It has a role in the life-long management of preclinical WD, It is administered as acetate, sulfate, or gluconate. Acetate may cause the least gastrointestinal distress and gluconate may be more tolerable than sulfate. Zinc sulfate (25 to 50 mg three times a day at least 1 hour apart from meals) may help maintain a neutral or even negative copper balance. Neurologic deterioration is uncommon. Urinary copper excretion should be less than 75 µg per 24 hours on stable treatment. A 24-hour urinary zinc excretion of less than 2 mg indicates inadequate compliance. In a patient on zinc maintenance therapy, a 24-hour urinary copper level below 35 µg may indicate copper deficiency due to overtreatment. Additionally nonceruloplasmin bound copper should normalize with effective treatment. Rarely over treatment of WD with zinc may cause hematologic manifestations of copper deficiency or a copper deficiency-related axonal sensorimotor peripheral neuropathy.\textsuperscript{194}

- **Ammonium tetrathiomolybdate:** Ammonium tetrathiomolybdate has a unique dual mechanism of action. It limits gastrointestinal absorption of copper by forming a nonabsorbable tripartite complex with copper and albumin within the gut lumen. Formation of the same complex in the bloodstream prevents cellular uptake of free copper. This dual mechanism of action necessitates a complicated dosing regimen: it binds copper in the gut when given with food and is best absorbed into the blood stream when given on an empty stomach. It has been used in a dose of 60-180 mg/day. A typical regimen in 20 mg given six times a day: three times a day with meals and three times a day in between meals. With time tissue stores become depleted. Initial worsening of neurologic symptoms is rare and may relate to rapid dose escalation.\textsuperscript{182, 195} A rapid reduction in circulating nonceruloplasmin-bound copper occurs during the first 8 weeks of therapy.\textsuperscript{182, 195, 196} Rarely copper depletion and cytopenias, reversible bone marrow suppression, or aminotransferase elevation may complicate ammonium tetrathiomolybdate therapy. It is not intended for long term treatment. The initial 8 weeks of therapy is followed by long-term maintenance therapy with zinc. Neurologic recovery is often delayed and may occur over the first few years. Ammonium tetrathiomolybdate has not been approved by the federal drug administration and has limited availability.

- **Liver transplantation:** The mortality rate with medical treatment in patients with WD who develop fulminant hepatic failure is close to 100%. Hepatic transplantation is curative in such individuals.\textsuperscript{197} Treatments such as plasmapheresis and hemofiltration may help bridge the patients to transplantation. Orthotopic liver transplantation only partially corrects the underlying metabolic defect and converts the copper kinetics from that characteristic of an individual affected with a homozygous disease to that of an individual who is an obligate
heterozygote, thereby resulting in a phenotypic cure. Living donor liver transplantation has also been successfully employed in WD. Copper metabolism may be suboptimal if the donor was a WD carrier. The role of liver transplantation in the management of patients with neurologic WD in the absence of hepatic insufficiency is encouraging but still uncertain. Patients with neuropsychiatric and hepatic dysfunction have a lower survival than those with hepatic dysfunction alone. Many of these patients can be managed with chelation therapy. There are reports of patient who have shown no neurologic improvement or neurologic worsening, as well as reports of patients with neurologic improvement with or without coexisting hepatic disease.

- **Pregnancy:** Although penicillamine and trientine are potentially teratogenic, the available information is not sufficient to warrant discontinuation of treatment with these agents during pregnancy. Their use through pregnancy has been associated with a satisfactory outcome but dose reduction of 25% to 50% is required. The dosage of zinc salts is maintained without change in pregnancy. Abrupt cessation of the drug can be fatal. With adequate decoppering, maintenance with zinc alone can suffice. Therapy with British anti-Lewisite (BAL) is rarely employed but may has been life saving in some cases. BAL is not suitable for chronic therapy. Symptomatic treatment with anti-dystonia drugs such as levodopa, dopamine agonists, tizanidine, baclofen, benzodiazepines, and anticholinergics may be beneficial. Botulinum toxin injection can be used in focal limb dystonia. Often more than one antiepileptic drug is required for seizure control. Atypical neuroleptics are used to manage psychiatric disturbance. Hepatic encephalopathy is managed with protein restriction and lactulose.

**Treatment of Wilson disease**

For all treatment modalities the target nonceruloplasmin bound copper is 5-15 μg/day

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Dose</th>
<th>Side effects</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Penicillamine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>250 mg capsule</td>
<td>Chelation of copper</td>
<td>Initial: 1000-2000 mg/d</td>
<td>Early: leukopenia, eosinophilia, thrombocytopenia, fever, cutaneous, lymphadenopathy, proteinuria</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Late: nephrotoxicity, lupus-like, polyarthritis, Goodpasture’s syndrome, myasthenia gravis-like, polymyositis, bone marrow suppression, loss of taste, IgA depression, serous retinitis, hepatotoxicity, dermatologic toxicities</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Initial neurologic deterioration Monitoring: cell blood count, liver enzymes, serum copper and ceruloplasmin, 24-hour urine copper</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Target 24-hour urinary copper: 200-500 μg</td>
</tr>
<tr>
<td>250 mg tablet</td>
<td></td>
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</tr>
<tr>
<td><strong>Trientine</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>250 mg capsule</td>
<td>Chelation of copper</td>
<td>Initial: 750-2000 mg/d</td>
<td>Sideroblastic anemia, pancytopenia, Lupus nephritis, Copper deficiency (rare)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>On empty stomach, 2-3 divided doses Target 24-hour urinary copper: 200-500 μg</td>
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<tr>
<td><strong>Zinc</strong></td>
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<tr>
<td>Zinc-220 capsule</td>
<td>Decrease copper absorption</td>
<td>Initial: 150 mg elemental zinc/d</td>
<td>Gastrointestinal distress</td>
</tr>
<tr>
<td>(220 mg of zinc sulfate)</td>
<td></td>
<td></td>
<td>Copper deficiency</td>
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</tbody>
</table>

<p>| | | | |
|      |      |              |                     |
|      |      |              |                     |</p>
<table>
<thead>
<tr>
<th><strong>Tetrathiomolydate</strong></th>
<th><strong>Investigational drug</strong></th>
<th><strong>Decrease copper absorption and chelation</strong></th>
<th><strong>Initial:</strong> 20 mg three times a day with meals and 20 mg three times a day between meals (Not intended for long term use)</th>
<th><strong>Bone marrow suppression</strong></th>
<th><strong>Aminotransferase elevation</strong></th>
<th><strong>Copper deficiency (rare)</strong></th>
<th><strong>With and in between meals, 6 divided doses</strong></th>
<th><strong>Initial neurologic deterioration is rare and may relate to rapid dose escalation</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Molecular diagnosis and use of genetic testing in screening of first degree relatives will likely find wider use. Continued compilation of results of mutation analysis will permit separation of function altering mutations from incidental polymorphisms. Population screening using techniques like immunosassay for urinary ceruloplasmin or ceruloplasmin detection in protein eluted from stored blood spots may find a role in newborn screening. Tetrathiomolydate may be an additional therapeutic option in patients with a neurological presentation. Living donor liver transplantation holds promise. Liver transplantation for a primary neurologic indication needs further studies. Experimental models for hepatocyte transplant and gene therapy are additional areas of active research. These future directions are discussed in a recent review.</strong></td>
<td></td>
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</tbody>
</table>

### Summary

- Advances in genetic testing technology has permitted easier identification of affected alleles.
- Molecular diagnosis and use of genetic testing in screening of first degree relatives will likely find wider use. Continued compilation of results of mutation analysis will permit separation of function altering mutations from incidental polymorphisms. Population screening using techniques like immunosassay for urinary ceruloplasmin or ceruloplasmin detection in protein eluted from stored blood spots may find a role in newborn screening. Tetrathiomolydate may be an additional therapeutic option in patients with a neurological presentation. Living donor liver transplantation holds promise. Liver transplantation for a primary neurologic indication needs further studies. Experimental models for hepatocyte transplant and gene therapy are additional areas of active research. These future directions are discussed in a recent review.

### References:

25. Ferro JM, Oliveira S. Neurologic manifestations of gastrointestinal and liver diseases. Curr Neurol Neurosci Rep 2014;14:487-
<table>
<thead>
<tr>
<th>Page</th>
<th>Reference</th>
</tr>
</thead>
</table>
RHEUMATOLOGY – NEUROLOGY

Vasculitis

- Nomenclature and classification of vasculitides

Jennette et al.

<table>
<thead>
<tr>
<th>Large vessel vasculitis (Granulomatous vasculitis)</th>
<th>Primary vasculitides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giant cell (temporal) arteritis (&gt;50 yrs)</td>
<td>Affecting large, medium, and small vessels</td>
</tr>
<tr>
<td>Takayasu arteritis (&lt; 40 yrs)</td>
<td>- Giant cell (temporal) arteritis</td>
</tr>
</tbody>
</table>

Medium-sized vessel vasculitis

- Takayasu arteritis

- Giant cell (temporal) arteritis
- Polyarteritis nodosa
- Kawasaki disease

**Small vessel vasculitis**
- ANCA-associated vasculitis
  - Microscopic polyangiitis
  - Granulomatosis with polyangiitis (Wegener)
  - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
- Immune complex small vessel vasculitis
  - Anti-GBM disease
  - Essential cryoglobulinemic vasculitis
  - IgA vasculitis (Henoch-Schönlein purpura)
  - Hypocomplementemtic urticarial vasculitis (anti-C1q vasculitis)

**Variable vessel vasculitis**
- Behcet’s disease
- Cogan syndrome

**Single-organ vasculitis**
- Cutaneous leukocytoclastic angiitis
- Cutaneous arteritis
- PCNS vasculitis
- Isolated aortitis
- Others

**Vasculitis associated with systemic disease**
- Lupus vasculitis
- Rheumatoid vasculitis
- Sarcoid vasculitis
- Others

**Vasculitis associated with probable etiology**
- Hepatitis C virus-associated cryoglobulinemic vasculitis
- Hepatitis B virus-associated vasculitis
- Syphilis-associated aortitis
- Drug-associated immune complex vasculitis
- Cancer-associated vasculitis
- Others

**Isolated angiitis of the central nervous system**

**Affecting predominantly medium and small vessels**
- Polyarteritis nodosa
- Churg-Strauss syndrome
- Granulomatosis with polyangiitis

**Affecting predominantly small vessels**
- Microscopic polyangiitis
- Henoch-Schönlein purpura
- Cutaneous leukocytoclastic vasculitis

**Miscellaneous conditions**
- Buerger’s disease
- Cogan syndrome
- Kawasaki disease

**Secondary vasculitides**
- Infection-related (mycobacterium tuberculosis, hepatitis, varicella-zoster, HIV 1, spirochetes: Treponema pallidum, Borrelia burgdorferi, fungi, Step pneumo)
- Secondary to connective tissue disease (SLE, scleroderma, rheumatoid arthritis, Sjögren syndrome, mixed connective tissue disease, Behçet’s disease)
- Drug hypersensitivity (amphetamine, cocaine, heroin, ephedrine, pseudoephedrine, phenylpropanolamine, penicillins)
- Secondary to mixed essential cryoglobulinemia
- Malignancy-related
- Hypocomplementemtic urticarial
- Post-organ transplant
- Pseudovasculitis

---

**Temporal Arteritis Criteria** (1990 American College of Rheumatology)

3 of the following 5 items must be present (sensitivity 93.5%, specificity 91.2%):

1. Age of onset greater than 50 years
2. New-onset headache or localized head pain
3. Temporal artery tenderness to palpation or reduced pulsation
4. ESR greater than 50 mm/h
5. Abnormal arterial biopsy (necrotizing vasculitis with granulomatous proliferation and infiltration)

**Additional points:**

Not all have temporal artery involvement
Limbs ischemia, aortic aneurysm, mesenteric ischemia may be present
PMR coexists
HA in 90%, ophthalmoparesis, HA and large vessel stroke-think GCA
Cranial arteries involvement suggested by vision loss, jaw claudication, ear pain, scalp tenderness

---

79
MRI\(^7\) of superficial cranial arteries and FDG PET\(^8\) may assist with confirming diagnosis in temporal artery biopsy negative patients.

Role of zoster\(^9, 10\)

- **Takayasu Arteritis Criteria** \((1990\text{ American College of Rheumatology})\)\(^11\)

  Classification as Takayasu arteritis if at least 3 of the following 6 criteria are present (sensitivity of 90.5% and specificity of 97.8%):
  1. Age at disease onset less than 40 years
  2. Claudication of extremities (especially upper extremities)
  3. Decreased brachial artery pulse
  4. Systolic blood pressure difference greater than 10 mm Hg between arms
  5. Bruit on auscultation over one or both subclavian arteries or abdominal aorta
  6. Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia, or similar causes; with changes usually focal or segmental.

  **Additional points:**
  - Pulseless disease
  - HT (RAS), limb claudication, arterial tenderness and bruits, systemic inflammatory symptoms
  - Coronary, mesenteric, pulmonary
  - Neuro: 50%, dizziness/ visual obscurations/ headache, stroke,\(^12\) PRES\(^13\)

- **Polyarteritis Nodosa Criteria** \((1990\text{ American College of Rheumatology})\)\(^14\)

  A patient with vasculitis is diagnosed with PAN if at least 3 of the following criteria are present:
  1. Weight loss over 4 kg
  2. Livedo reticularis
  3. Testicular pain or tenderness
  4. Myalgias (excluding shoulder and hip girdle), weakness of muscles or tenderness of leg muscles, or polyneuropathy
  5. Mononeuropathy, multiple mononeuropathy, or polyneuropathy
  6. Diastolic blood pressure over 90 mm Hg
  7. Elevated blood urea nitrogen or creatinine
  8. Hepatitis B virus antigen or antibody in serum
  9. Arteriogram showing aneurysm or occlusion of the visceral arteries not due to arteriosclerosis, fibromuscular dysplasia, or other noninflammatory causes
  10. Biopsy of small- or medium-sized artery containing polymorphonuclear cells

- **Cogan syndrome**

  CS is a rare variable vessel vasculitis of young adults. It causes interstitial keratitis with vestibulocochlear dysfunction leading to hearing and vision loss and vertigo; in “atypical” disease the ocular inflammation is present but not interstitial keratitis or the eye and vestibular disease occur >2 years apart. Systemic symptoms may be present as in PAN, most commonly headache, arthralgia, and fever. Neurologic manifestation include ischemic stroke, venous sinus thrombosis, encephalopathy, meningoencephalitis, cranial neuropathy, polyneuropathy, mononeuritis multiplex, autonomic neuropathy, and myopathy.\(^15\)

- **Behçets disease**

  A rare, systemic, relapsing variable vessel vasculitis with oral and genital ulcers, uveitis, skin lesions, arthritis, gastrointestinal involvement, large vessel vasculopathy, and neurological manifestations.

  **International Criteria for Behçet’s Disease.** \(^16\)

<table>
<thead>
<tr>
<th>Sign/symptom</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular lesions</td>
<td>2</td>
</tr>
<tr>
<td>Genital aphthosis</td>
<td>2</td>
</tr>
<tr>
<td>Oral aphthosis</td>
<td>2</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>1</td>
</tr>
<tr>
<td>Neurological manifestations</td>
<td>1</td>
</tr>
<tr>
<td>Vascular manifestations</td>
<td>1</td>
</tr>
<tr>
<td>Positive pathergy test (optional)</td>
<td>1</td>
</tr>
</tbody>
</table>

  Score \(> or = 4\) indicates a Behçet’s Disease diagnosis.
**International Consensus Recommendation Criteria for Neuro-Behcet Disease Diagnosis**

**Definite NBD meeting all of the following three criteria:**
1. Satisfy the (current accepted) International Study Group criteria for BD
2. Neurological syndrome (with objective neurological signs) recognized to be caused by BD and supported by relevant and characteristic abnormalities seen on either or both:
   a. Neuroimaging
   b. CSF
3. No better explanation for the neurological findings

**Probable NBD meeting one of the following two criteria in the absence of a better explanation for the neurological findings:**
1. Neurological syndrome as in definite NBD, with systemic BD features but not satisfying the ISG criteria
2. A non-characteristic neurological syndrome occurring in the context of ISG criteria-supported BD

**Recognized neurological syndromes**
Parenchymal syndrome (one or more of the following presentations at first/subsequent attack(s) or progression):
- Brainstem: symptoms and signs of brainstem involvement including ophthalmoparesis, cranial neuropathy, cerebellar or pyramidal dysfunction.
- Multifocal (diffuse): variable combination of brainstem signs and symptoms, cerebral or spinal cord involvement
- Myelopathy
- Cerebral: symptoms and signs suggestive of cerebral hemispheric involvement including encephalopathy, hemiparesis, hemisensory loss, seizures and dysphasia, and mental changes including cognitive dysfunction and psychosis
- optic neuropathy

Non-parenchymal syndromes:
- Cerebral venous thrombosis
- Intracranial hypertension syndrome (pseudotumour cerebri)
- Acute meningeal syndrome

**Characteristic MRI findings in NBD**
Parenchymal NBD:
Nature of the lesions:
- Acute/subacute lesions are hypo-intense to iso-intense on T1-weighted (T1W) images, commonly enhanced with contrast on Gad-T1W images, are hyper-intense on T2W and FLAIR images, hyper-intense on diffusion-weighted images, and show a restricted apparent diffusion coefficient (ADC) on ADC map
- In chronic phase, smaller lesions might be seen, usually non-enhancing, but might resolve completely.
There might be evidence of atrophy especially in the brainstem. Nonspecific white matter lesions can be seen.
Location: depends on the clinical presentation:
- The brainstem is the typical predilection site, lesions usually involving the pons, might extend upwards to involve midbrain, basal ganglia, and the diencephalon
- With cerebral presentation, multiple small, white matter lesions without a clear predisposition for periventricular regions can be seen. Isolated cerebral hemisphere lesions can be seen, which need differentiation from tumour, abscess, and congenital cysts, etc.
- Single or multiple inflammatory lesions of variable length involving the cervical or thoracic cord can be seen, mostly in the presence of brainstem, basal ganglia, or cerebral lesions. Isolated spinal cord lesions are rare.
Non-parenchymal NBD
- MR venography or CT venography show evidence of cerebral sinus or vein thrombosis
- Normal appearances are seen in intracranial hypertension syndrome
- Meningeal enhancement is seen in acute meningeal syndrome, especially on Gad-T1W images

**Characteristic CSF finding**
Inflammatory changes involving one or more of:
- Increased cells
- Increased protein
- High IL-6
Specific conditions to be excluded:
• CNS infections
• CNS neoplasms
• Neurological complications of therapies for BD

Additional points:
  Headache is the most common presentation in NBD
  PNS involvement (PN, MM, inflammatory myopathy) is rare

• **Kawasaki disease** is an acute, generalized, pediatric medium-vessel vasculitis. Irritability is seen within 10 days prior to diagnosis.¹⁸ Neurologic involvement is rare and includes aseptic meningitis, meningoencephalitis, altered mental status, seizure, ADEM, mononeuritis multiplex, cranial neuropathy, and stroke.¹⁹ ²⁰

• **Henoch-Schönlein Purpura (1990 American college of Rheumatology)** ²¹
  Classification as HSP if at least 2 of the following 4 criteria are present (sensitivity of 87.1% and specificity of 87.7%)
  1. Probable purpura (unrelated to thrombocytopenia)
  2. Age at symptom onset < 20 years
  3. Bowel angina: diffuse abdominal pain, worse after meals, or the diagnosis of bowel ischemia, usually including bloody diarrhea
  4. Histologic changes showing granulocytes in walls of arterioles or venules

• **Salient Clinical Features and Neurologic Manifestations Associated with Other vasculitides** ²²
  (Polyarteritis nodosa, Wegner granulomatosis, Churg-Strauss syndrome, Microscopic Polyangiitis, Henoch-Schönlein purpura, Mixed Cryoglobulinemia)


### Polyarteritis Nodosa (PAN)

- 40 to 60 years
- Has become rare due to decrease in HBV & due to exclusion of microscopic polyangiitis (MPA)
- Idiopathic/Infection-related (HBV: poor prognosis, HCV, HIV, CMV, Parvo B19, HTLV-1) / related to other disorders (cryoglobulinemia, leukemia, arthritis, Sjögren syndrome)
- Skin, kidney (not GN), peripheral nerve, gastrointestinal, coronary, eye, rarely respiratory, mesenteric vessel, testicular, joint involvement
- Constitutional symptoms (fever, chills, weight loss, fatigue, myalgia, arthralgia)
- ANCA –ve, CPK, BUN, microaneurysms in hepatic/renal/mesenteric vasculature, skin & nerve & muscle biopsy, PMNs is small/medium vessels (pan-mural vascular inflammation with fibrinoid necrosis)
- **Prognosis:** Untreated mortality is 90%, with steroids it decreases to 50%, HBV-associated disease has a worse prognosis
- **Treatment:** prednisone, cyclophosphamide, azathioprine, PLEX, IVIG, mycophenolate mofetil, rituximab

**Additional points:**

- PN with predilection for legs (mononeuropathy: single/multiple, SM, S, GBS-like)
- Muscle (vasculitis, myalgia, muscle infarction)
- **CNS**
  - Stroke (rarely intracranial hemorrhage)
  - Encephalopathy
  - CN II, III, IV, VI, VII, VIII, IX, XII
- Seizures
- Spinal cord
Granulomatosis with polyangiitis (Wegner granulomatosis - old name)

- Average age 40 years, men more than women
- Upper & lower respiratory tracts, kidneys, ocular involvement (pseudotumor, scleritis, uveitis) with systemic vasculitis and neurologic disease, skin, arthralgias, fever, anorexia, gastrointestinal, cardiac, oral ulcers, hearing
- Limited forms or severe multisystem
- c-ANCA, Pr-3: serine protease 3, (p-ANCA, MPO), vasculitis & necrotizing granulomatous inflammation (lung biopsy)
- Additional points: Severe CNS manifestations could represent a clinical hallmark of patients with generalized GPA/ WG who are consistently negative for ANCA (Reinhold-Keller E, de Groot K, Holl-Ulrich K, et al. Severe CNS manifestations as the clinical hallmark in generalized Wegener’s granulomatosis consistently negative for antineutrophil cytoplasmic antibodies (ANCA). A report of 3 cases and a review of the literature. Clin Exp Rheumatol 2001;19:541-549.)
- Treatment: Prednisone and cyclophosphamide

Churg-Strauss syndrome (Eosinophilic granulomatosis with polyangiitis: EGPA)

- Prodromal phase (allergic rhinitis, nasal polyposis, sinusitis), second phase (asthma, peripheral blood & tissue eosinophilia: gastrointestinal and lung), finally systemic necrotizing vasculitis (PNS)
- Cardiac, skin, gastrointestinal, renal
- ACR requires 4/6 to make a probable diagnosis:
  - asthma
  - peripheral eosinophilia (>10%)
  - paranasal sinusitis
  - pulmonary infiltrates
  - histological proof of vasculitis with extravascular eosinophils
  - neuropathy (MM or PolyN)
- p-ANCA, MPO, eosinophilic necrotizing vasculitis/ eosinophilic infiltration, extravascular granulomas

Microscopic polyangiitis (MPA)

- Separated from PAN at first Chappel Hill Consensus Conference
- Average onset age 50 years, men more than women
- Predominant small vessel vasculitis goes against a diagnosis of PAN and suggests MPA even if medium sized arteries are affected
- Rapidly progressive focal segmental necrotizing

<table>
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<tr>
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<td>- PN (MM, SM, S)</td>
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<td>CNS</td>
</tr>
<tr>
<td>- Rapidly progressive focal segmental necrotizing</td>
<td>- Reported but poorly characterized</td>
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glomerulonephritis and pulmonary involvement distinguish MPA from PAN, skin nodules and purpura, ocular, weight loss, fever, arthralgias
- Indolent course followed by explosive phase
- p-ANCA, MPO, nongranulomatous inflammation of small arteries, rarely c-ANCA/Pr-3
- **Treatment:** steroids and cyclophosphamide

### Henoch-Schönlein Purpura

- **Children**
- Association with malignancy, infection, drugs
- Nonthrombocytopenic purpura, arthralgia, abdominal pain, systemic: fever, malaise, renal: nephritis, edema
- Elevated IgA, IgA in vessel wall, leukocytoclastic vasculitis on skin biopsy
- **Differential:** endocarditis, DIC, SLE, meningococcemia, Waldenström’s, hyperglobulinemic purpura
- **Treatment:** supportive, steroids

### Mixed Cryoglobulinemia

- Cryoglobulins: cold-precipitable monoclonal or polyclonal immunoglobulins that precipitate in vitro at < 37 C
- IgG or IgM or both
- **Type I:** monoclonal, myelo- and lymphoproliferative disorders (myeloma, leukemia, lymphoma), asymptomatic
- **Type II:** mixed (mono, poly), hepatitis C or lymphoproliferative disorder
- **Type III:** mixed (poly), essential/secondary (infection like HCV, inflammatory disorders, hematologic malignancy), most commonly associated with rheumatologic disease (vasculitis, connective tissue disease)
- Weakness, arthralgias, purpura, liver, renal, sicca, Raynaud’s, bleeding diathesis may be associated with brain purpura
- Leukocytoclastic vasculitis on skin biopsy
- Consider mixed cryoglobulinemia in a patient with hypocomplementemia, cutaneous vasculitis, and elevated liver enzymes
- Essential – primary vs Secondary – infection, inflammatory disorder, hematologic malignancy

Note: CNS involvement by vasculitis can be associated with headache, encephalopathy, seizures, stroke, visual symptoms, cranial nerve palsies, myelopathies, hemorrhage, and coma.

**Laboratory Evaluation in Suspected Vasculitis**

- **Blood**
  - CBC, ESR
  - Electrolytes, creatinine, urea, liver enzymes
  - CPK
  - Immunofixation electrophoresis
  - T and B cell panels, quantitative immunoglobulins
• ANA, RF, complement levels, cryoglobulins, anti-SS-A (Ro) and SS-B (La), antibodies to Sm, Scl-70, c-ANCA, p-ANCA, MPO, proteinase 3
• Antibodies to hepatitis B and C, HIV, Lyme (ELISA, western blot)

○ Imaging
  • CXR
  • CT chest, abdomen, pelvis
  • MRI brain with contrast
  • MRA and MRV
  • SPECT, PET
  • Systemic and cerebral angiography

○ Others
  • EEG
  • EMG and NCS
  • CSF (pleocytosis, elevated proteins, evidence of intrathecal synthesis of immunoglobulins and oligoclonal bands)

○ Pathology
  • Nerve biopsy
  • Muscle biopsy
  • Temporal artery biopsy
  • Meningeal and cortex biopsy
  • Skin biopsy
  • Systemic organs
  • Lymph nodes

Note: A favorable response to immunosuppressive/immunomodulating therapy should not be taken to support the diagnosis of a vasculitis. As far as possible a tissue diagnosis should be obtained.

• Primary Angiitis of the CNS (PACNS)\textsuperscript{35}
  • Symptoms, often nonspecific, appear gradually over months. Common manifestations include headache, encephalopathy, focal neurologic signs or symptoms due to ischemia or hemorrhage, seizures, meningitis, or myelopathy. The course may be relapsing-remitting. Systemic symptoms should be absent: if present consider a secondary CNS vasculitis.
  • Brain MRI may be normal. Abnormalities when present include confluent white matter lesions, cortical and subcortical T2 lesions, multiple areas of restricted diffusion, microhemorrhages or large hematomas, multiple or single small or large enhancing lesions, enhancing vessels, leptomeningeal enhancement.\textsuperscript{35} "Beads on a string" appearance on vascular imaging has a limited specificity. Normal vascular studies does not rule out the diagnosis.\textsuperscript{35, 36} Brain biopsy (directed at an abnormal imaging area, include cortex and leptomeninges) is the confirmatory test.
  • Reversible cerebral vasoconstriction is an important differential: a normal parenchymal brain MRI favors this condition over PACNS.\textsuperscript{37}
  • Treatment is initiated with high dose steroids & cyclophosphamide (oral 2 mg/kg or iv 1 g/mth). This may need to be continued for 6-12 months. Azathioprine or methotrexate or mycophenolate are added. Rituximab is an alternative to cyclophosphamide.

• Nonsystemic Vasculitic Neuropathy (NSVN)\textsuperscript{38-42}
  • NSVN is an organ-specific vasculitis (like isolated CNS vasculitis). It is the most common vasculitic neuropathy.\textsuperscript{41} It refers to vasculitis confined to the PNS. NSVN is the commonest vasculitic neuropathy.\textsuperscript{41} There may be local involvement of skin or muscle contiguous to the affected nerve. Systemic signs like weight loss and fever may be seen in a minority.
  • The erythrocyte sedimentation rate is commonly elevated. PNS manifestations in NSVN include mononeuropathy multiplex, distal asymmetric polyneuropathy, distal symmetric polyneuropathy, and rarely pure sensory neuropathy. Also reported are cranial neuropathy, radiculopathy, and lumbosacral plexopathy. Pain is commonly present. The neuropathy is axonal. Nerve and muscle biopsy are useful in making the diagnosis of NSVN. Nerve biopsy has a limited sensitivity (about 50%).\textsuperscript{41}
As compared to systemic vasculitic neuropathy, the disease course in NSVN is more favorable with slower progression. The course may be monophasic, relapsing/remitting, or rapidly progressive either from onset or after a period of stabilization. The course may be prolonged. Favorable response to steroids or in some cases cytotoxic or immunosuppressive therapy is seen. Possible for cyclophosphamide, rituximab, IVIG, PLEX. Maintenance therapy for 18-24 months may be required.

Criteria for the diagnosis of nonsystemic vasculitic neuropathy:

1. Patient meets criteria for pathologically definite or clinically probable vasculitic neuropathy as defined by the PNS Guideline
2. Constitutional symptoms may occur and do not exclude NSVN (fever, weight loss, malaise, fatigue, myalgias, arthralgias)
3. None of the following exclusions which suggest an underlying “systemic” vasculitis:
   - Signs, symptoms, or laboratory evidence of involvement of other organ(s) other than peripheral nerve likely due to vasculitis (e.g., CNS, gastrointestinal, heart, kidney, liver, lung, skin)

   Positive visceral angiogram (if done)

   Laboratory markers of systemic inflammation or connective tissue disease
   - Anti-Pr3 or MPO
   - Mixed cryoglobulins
   - ESR ≥ 100 mm/hr
   - SSA, SSB, Smith, RNP, Scl-70, centromere, dsDNA, CCP antibodies if patient satisfies diagnostic criteria for the associated connective tissue disease

   Biopsy evidence of vasculitis in tissues other than peripheral nerve (muscle excepted)

   Serological, PCR, or culture evidence for vasculitis-associated infection
   - HBV, HCV, HIV, CMV, leprosy, Lyme, HTLV-1

   Predisposing conditions of factors
   - Connective tissue disease
   - Sarcoidosis
   - Inflammatory bowel disease
   - Active malignancy
   - Hypocomplementemic urticarial vasculitis
   - Cutaneous polyarteritis nodosa
   - Drugs thought to cause vasculitis

Connective Tissue Diseases

Neuropsychiatric syndromes observed in systemic lupus erythematosus

Neuropsychiatric lupus (NPSLE) manifestations can occur in the absence of either serologic or other systemic disease manifestations. Infection should always be suspect in a SLE patient with CNS manifestations. NPSLE can antedate other manifestations of SLE or be present any time during the disease course or be present when in remission. A recent metaanalysis estimated NPSLE prevalence to be 56.3%.

Not infrequently NPSLE is accompanied by lupus-related autoantibodies (ANA, dsDNA, anti-ribosomal P, antiphospholipid).

Neurologic manifestations may be primary or secondary to renal involvement, therapy, or infections. CNS manifestations are more common than PNS manifestations and commonly include headache, mood disorders, cognitive dysfunction, seizures, and cerebrovascular disease. Peripheral neuropathy (distal sensory or sensorimotor), and less commonly cranial neuropathy or mononeuropathies (median, ulnar) are the common PNS manifestations. An inflammatory myopathy may be seen in 5% of patients with SLE but is not noted in either the ACR or the SLICC criteria.

MRI head findings are often nonspecific but may suggest vascular disease. Vascular disease may have an inflammatory basis. White matter hyperintensities may correlate with cognitive dysfunction, low CH50, and a lupus anticoagulant; lupus anticoagulant may be associated with microbleeds and lacunes and large vessel disease. SLE may be associated with premature atherosclerosis in the absence of traditional risk factors for vascular disease. Additionally there may be evidence of endocarditis, valvular involvement, or supraventricular arrhythmias.

The risk for cerebrovascular disease may increase in the presence of autoantibodies and aggressive stroke risk factors monitoring becomes important in SLE.
The following is a listing of the central and peripheral nervous system manifestations associated with SLE as listed by the American College of Rheumatology. Note ACR does not include the term lupus cerebritis.

- **Central nervous system (12)**
  - Aseptic meningitis
  - Cerebrovascular disease (stroke, TIA, cerebral venous sinus thrombosis)
  - Demyelinating syndrome, including transverse myelitis
  - Headache (migraine, benign intracranial hypertension)
  - Movement disorder (chorea)
  - Myelopathy
  - Seizure
  - Acute confusional state
  - Anxiety disorder
  - Cognitive dysfunction
  - Mood disorder
  - Psychosis

- **Peripheral nervous system (7)**
  - AIDP (GBS)
  - Autonomic neuropathy
  - Mononeuropathy (single/multiplex)
  - Myasthenia gravis
  - Cranial neuropathy
  - Plexopathy
  - Polyneuropathy

**Hypereosinophilic Syndrome**

- **Terminology**
  - Hypereosinophilia: Blood eosinophils > 1.5 X 10^9/L on two examinations separated in time by at least one month and/or tissue hypereosinophilia.
  - Tissue hypereosinophilia: on marrow a % of eosinophils that exceeds 20% of all nucleated cells &/ extensive tissue infiltration &/ marked deposition of eosinophil granule protein in tissue in the absence of major tissue infiltration by eosinophils.
  - Hypereosinophilic syndrome: Hypereosinophilia as defined above associated with eosinophil-mediated organ damage and/or dysfunction, provided other potential causes for damage have been excluded.
    - Variants of HES
      - Myeloproliferative variants including myeloproliferative neoplasms and T cell lymphocytic variants
      - Familial HES
      - Idiopathic HES
      - Overlap HES: blood eosinophilia with single organ involvement
      - Associated HES: blood eosinophilia with a distinct second diagnosis (but eosinophilia is not the predominant abnormality driving end-organ manifestations)
      - Gleich syndrome: episodic angioedema with eosinophilia
      - Hypereosinophilia of undetermined significance
  - Note: It is debated whether Churg-Strauss syndrome should be placed in the overlap or associated categories

- **Clinical Features**
  - Cardiac: eosinophilic myocarditis
  - Thrombotic complications
  - Skin disease: eczema, erythroderma, lichenification, dermatographism, urticaria, angioedema
  - Pulmonary disease
  - Gastrointestinal disorders
Neurologic disease: cerebral thromboemboli, encephalopathy, venous sinus thrombosis, PN (including radiculopathy or mononeuropathy multiplex).

**Dego Disease**
Dego disease or malignant atrophic papulosis is a thrombo–obliterative disorder associated with cutaneous, gastrointestinal and neurologic manifestations. MR findings include infarction and hemorrhage, often associated with subdural fluid collections.

**IgG4-Related Disease**
IgG4-related disease is a systemic disorder characterized by infiltration of IgG4-bearing plasma cells and a distinctive histopathology (storiform fibrosis, obliterative phlebitis, lymphoplasmacytic infiltrate, and mild to moderate tissue eosinophilia). It was initially described in context of sclerosing pancreatitis (now called type I or IgG4-related autoimmune pancreatitis). It has subsequently described in nearly every organ. The key neurologic manifestations include hypertrophic pachymeningitis. Also reported are cranial involvement by tumor like masses, bony destruction (orbit, mastoid, temporal, maxillary), pituitary involvement. Laboratory evidence of eosinophilia, hypergammaglobulinemia, hypocomplementemia, and elevated IgE levels may be clues. Elevated serum IgG4 levels are of limited utility. Blood plasmablast concentrations may be superior to serum IgG4 and may permit longitudinal evaluation of disease activity. Plasmablasts can be identified through flow cytometry analysis of peripheral blood, gating on cells that are CD19-CD38+CD20-CD27+.

Diagnosis rests on the pathologic findings noted above and immunohistochemical demonstration of tissue infiltration by IgG4-bearing plasma cells. Steroids, methotrexate, and rituximab form the mainstay of therapy.

- **Historical**
  Autoimmune pancreatitis was linked to elevated serum IgG4 concentrations in 2001. In 2003, extrapancreatic manifestations were identified in patients with autoimmune pancreatitis. This lead to its recognition as a systemic condition.

- **Epidemiology**
  Unlike other autoimmune diseases, IgG4-related disease has a male predominance. This is particularly true to IgG4-related pancreatitis. IgG4-related sialadenitis has a more equal sex distribution. Most reported cases are older than 50 years. Many reports that address the issue of epidemiology are from Japan and from the autoimmune pancreatitis literature. A Mayo Clinic series noted that of 245 patients who underwent pancreatic resection for benign indications, 11% had autoimmune pancreatitis.

- **Synopsis**
  - IgG4-related disease is a fibroinflammatory condition characterized by tumefactive lesions, a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, "storiform" fibrosis, and elevated serum IgG4 concentrations (these are neither required nor sufficient for the diagnosis: that said, they are often present).
  - Elevated serum and tissue IgG4 levels can also be seen in multicentric Castleman’s disease, allergic disorders, Churg-Strauss syndrome, sarcoidosis, etc.

- **Subtypes**
  - **Type 1:** IgG4-related disease
  - **Type 2:** Substantial clinical overlap with type 1 but distinctive pathologic features

- **Path**
  - The defining pathologic feature of the disease is the presence of a dense lymphoplasmacytic infiltrate that is organized in a storiform (matted and irregularly whorled) pattern, obliterative phlebitis, and mild to moderate eosinophil infiltrate. The “storiform” pattern refers to a cartwheel appearance of the arranged fibroblasts and inflammatory cells (“the nuclear streaming artifact”).
  - In glandular organs the infiltrate is around ductal structures, the inflammatory lesion forms a tumefactive mass that may destroy the organ, neutrophils are rare, granulomas are distinctly unusual.
  - While the presence of IgG-bearing plasma cells is required for the diagnosis, their presence is nonspecific, and their detection, even in substantial numbers, is not diagnostic. In late stages the presence of fibrosis may pose a diagnostic challenge. The pattern of fibrosis and ratio of IgG4 to total IgG may help. Lymphomas are histopathologic mimickers of the disease and clonality studies
may be required to make the distinction. The lymphoid infiltrate in IgG4 disease is predominantly T cells (diffusely distributed). B cells are typically organized in germinal centers.

- A diffuse plasma-cell infiltrate with more than 30 IgG4-positive cells per HPF and a ratio of IgG4 to IgG that is higher than 50% provides compelling evidence of IgG4-related disease particularly in conjunction with the characteristic histopathological appearance.54
- Despite the traditional view of IgG4 as an antiinflammatory immunoglobulin, this molecule is assumed to play a central role in certain immune mediated conditions.

- **Organs involved** 54

The commonest or perhaps best recognized manifestations are type 1 autoimmune pancreatitis and salivary gland disease

- Non neuro: biliary tree, pancreas, salivary glands, kidneys, lungs, lymph nodes, hematologic manifestation (eosinophilia), aorta, breast, prostate, thyroid, pericardium, bone, skin
- Neuro: orbital tissues,68, 71 meninges (including leptomeninges),72 cranial nerves,67, 71, 81-83 craniofacial skeleton,41 pituitary,67 skull base lesions,65 cavernous sinus lesions,67 and isolated reports of radicular involvement61 or neuropathy.66 Also reported is reversible rapidly progressive dementia.87

Note: The following conditions are now believed to fall within the spectrum of IgG4 related diseases: Mikulicz’s syndrome (salivary, lacrimal), Kuttners tumor (submandibular glands), Riedel’s thyroiditis, eosinophilic angiocentric fibrosis (orbits & upper resp tract), multifocal fibrosclerosis, inflammatory pseudotumor (orbits, lungs, kidneys etc), mediastinal fibrosis, retroperitoneal fibrosis (Ormond’s diseases), periaortitis & periarteritis, inflammatory aortic aneurysm, idiopathic hypo complementemetic tubulointerstitial nephritis with extensive tubulointerstitial deposits

### Complications (neurologic) related to treatment of rheumatologic disease

| **steroids** | Myopathy with type 2 fiber atrophy |
| **chloroquine** | Vacuolar myopathy which may be accompanied by cardiomyopathy and PN |
| **cyclosporine** | Myopathy |
| **penicillamine** | Myositis |
| **TNFa inhibitors** | Central and peripheral demyelination,88 axonal PN89 Also reported: neurosarcoidosis,90 small fiber neuropathy,91, 92 APS with CNS lupus,91 encephalitis91 |
| **leflunomide** | PN97 |
Salient Clinical features, Criteria, Neurologic manifestations Associated with Common Connective Tissue Diseases

Clinical Criteria
1. Acute cutaneous lupus
   including lupus malar rash (do not count if malar discoid)
   bullous lupus
   toxic epidermal necrolysis variant of SLE
   maculopapular lupus rash
   photosensitive lupus rash
   
   \textit{in the absence of dermatomyositis}

   or subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)

2. Chronic cutaneous lupus
   including classical discoid rash: localized (above the neck) or generalized (above and below the neck)
   hypertrophic (verrucous) lupus
   lupus panniculitis (profundus)
   mucosal lupus
   lupus erythematosus tumidus
   chillblains lupus
   discoid lupus/lichen planus overlap

3. Oral ulcers: palate/ buccal/ tongue or nasal ulcers \textit{in the absence of other causes, such as vasculitis, Behçets, infection (herpes), inflammatory bowel disease, reactive arthritis, and acidic foods}

4. Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs \textit{in the absence of other causes - alopecia areata, drugs, iron deficiency and androgenic alopecia}

5. Synovitis involving two or more joints, characterized by swelling or effusion OR tenderness in 2 or more joints and thirty minutes or more of morning stiffness.

6. Serositis
   typical pleurisy for more than 1 day or or pleural effusion or pleural rub
   typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day or pericardial effusion or pericardial rub or pericarditis by EKG \textit{in the absence of other causes, such as infection, uremia, and Dressler's pericarditis}

7. Renal
Urine protein/creatinine (or 24 hr urine protein) representing 500 mg of protein/24 hr
or
Red blood cell casts
8. Neurologic
  seizures
  psychosis
  mononeuritis multiplex in the absence of other known causes such as primary vasculitis
  myelitis
  peripheral or cranial neuropathy in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus
  acute confusional state in the absence of other causes, including toxic-metabolic, uremia, drugs
9. Hemolytic anemia
10. Leukopenia (< 4000/mm3 at least once) in the absence of other known causes such as Felty's, drugs, and portal hypertension
or
  Lymphopenia (< 1000/mm3 at least once) in the absence of other known causes such as corticosteroids, drugs and infection
11. Thrombocytopenia (<100,000/mm3) at least once in the absence of other known causes such as drugs, portal hypertension, and TTP

Immunological Criteria
1. ANA above laboratory reference range
2. Anti-dsDNA above laboratory reference range, except ELISA: twice above laboratory reference range
3. Anti-Sm
4. Antiphospholipid antibody: any of the following
   lupus anticoagulant
   false-positive RPR
   medium or high titer anticardiolipin (IgA, IgG or IgM)
   anti-β2 glycoprotein I (IgA, IgG or IgM)
5. Low complement
   low C3
   low C4
   low CH50
6. Direct Coombs test in the absence of hemolytic anemia
   (Criteria are cumulative and need not be present concurrently.)

Classification Rule:
Classify a patient as having SLE if:
The patient satisfies four of the criteria listed including at least one clinical and one immunologic criterion.
or
The patient has biopsy-proven nephritis compatible with SLE and with ANA or anti-dsDNA antibodies.
<table>
<thead>
<tr>
<th>Criteria etc</th>
<th>Neurologic manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SLE</strong></td>
<td>CNS</td>
</tr>
<tr>
<td><em>ACR Criteria - Diagnosis requires the presence of 4 or more of the following 11 criteria, serially or simultaneously:</em>&lt;sup&gt;95,96&lt;/sup&gt;</td>
<td>• See above</td>
</tr>
<tr>
<td>1. Malar rash</td>
<td>• Cerebrovascular disease: nonbacterial thrombotic endocarditis, vasculitis, hypercoagulability, microangiopathy, hypertension</td>
</tr>
<tr>
<td>2. Discoid rash</td>
<td>• Inflammatory meningoencephalitis</td>
</tr>
<tr>
<td>Fixed erythema over the malar eminences</td>
<td>• Nonbacterial thrombotic endocarditis with cerebral embolization &amp; DIC, hypercoagulability</td>
</tr>
<tr>
<td>3. Photosensitivity</td>
<td><strong>PNS</strong></td>
</tr>
<tr>
<td>Skin rash as a result of unusual reaction to sunlight</td>
<td>• PN (mononeuropathy: single/ multiple, S, SM, M, small fiber, autonomic)</td>
</tr>
<tr>
<td>4. Oral ulcers</td>
<td>• AIDP, CIDP</td>
</tr>
<tr>
<td>Oral or nasopharyngeal ulceration</td>
<td>• MG, LEMS</td>
</tr>
<tr>
<td>5. Arthritis</td>
<td>• Plexopathy</td>
</tr>
<tr>
<td>Nonerosive arthritis of 2 or more peripheral joints</td>
<td>• Myopathy (DM, PM, IBM, treatment related, nonspecific, vasculitis)</td>
</tr>
<tr>
<td>6. Serositis</td>
<td><em>Note:</em> anti-RNP in SLE with inflammatory myopathy, patients with inflammatory myopathy &amp; SLE are younger, &gt; alopecia/ erosive joint/ oral ulcers/ pulmonary/ Sjögren symptoms, &lt; renal)</td>
</tr>
<tr>
<td>Pleuritis or pericarditis</td>
<td>• Cranial nerve (VIII commonest)</td>
</tr>
<tr>
<td>7. Renal disorder</td>
<td><strong>Note:</strong></td>
</tr>
<tr>
<td>Persistent proteinuria &gt;0.5gm/day or &gt; 3+ or cellular casts</td>
<td>• Anti-DNA antibody or anti-Sm antibody or antiphospholipid antibody positivity</td>
</tr>
<tr>
<td>8. Neurologic disorder</td>
<td><strong>Additional points:</strong></td>
</tr>
<tr>
<td>Seizures or psychosis</td>
<td>• Affects women 9 times more than men</td>
</tr>
<tr>
<td>9. Hematologic disorder</td>
<td>• African Americans, Hispanics, Asians affected more than non-Hispanic whites</td>
</tr>
<tr>
<td>Hemolytic anemia or leucopenia or thrombocytopenia</td>
<td>• Drug-induced lupus (minocycline, phenytoin, hydralazine) affects skin, joint, or serosal surfaces but rarely kidneys or nervous system</td>
</tr>
<tr>
<td>10. Immunologic disorder</td>
<td>• Other common sites of involvement are pulmonary, gastrointestinal, ocular</td>
</tr>
<tr>
<td>Anti-DNA antibody or anti-Sm antibody or antiphospholipid antibody positivity</td>
<td>• Acute onset associated with greater disease activity</td>
</tr>
<tr>
<td>11. Antinuclear antibody positivity</td>
<td>• Additional tests: hypocomplementemia, joint x-rays</td>
</tr>
</tbody>
</table>

**Additional points:**
- Affects women 9 times more than men
- African Americans, Hispanics, Asians affected more than non-Hispanic whites
- Drug-induced lupus (minocycline, phenytoin, hydralazine) affects skin, joint, or serosal surfaces but rarely kidneys or nervous system
- Other common sites of involvement are pulmonary, gastrointestinal, ocular
- Acute onset associated with greater disease activity
- Additional tests: hypocomplementemia, joint x-rays
- Antiribosomal P protein antibodies: investigational but specific for SLE
- Treatment: hydroxychloroquine, steroids, cyclophosphamide, mycophenolate mofetil
- There exists a SLE disease activity index 2000

**Rheumatoid Arthritis (RA)**

*Definite clinical swelling in ≥ 1 joint, no better explanation, and a score of ≥ 6 among following domain(s) necessary for a definite RA diagnosis:

- Joint involvement: 1 large: 0, 2-10 large: 1, 1-3 small (with or without large): 2, 4-10 small (with or without large): 3, >10 (at least 1 small): 5
- Serology: -ve RF & anti-CCP: 0, Low +ve RF or anti-CCP: 2, High positive RF or anti-CCP (>3X)
- Acute phase reactants: N CRP and ESR: 0, Abnormal CRP or ESR: 1
- Disease duration: <6 wks: 0, ≥6 wks: 1

*PNS*
- Entrapment neuropathy (most common PNS manifestation, most commonly median nerve)
- PN (S, SM, mononeuropathy multiplex, digital, autonomic, subclinical)
- Muscle (Inflammatory myopathy - including nodular myositis, vasculitic myositis, PM, DM, disuse, nonspecific, an unrelated IBM, treatment related myopathy: steroids)
- Treatment related: gold (PN, AIDP, Miller Fisher, CN), leflunomide (PN: axonal > demyelinating), TNF-α inhibitors (AIDP, CIDP, aseptic meningitis), D-penicillamine related (MG), hydroxychloroquine (tinnitus, neuromyopathy)
- Radiculopathy (arthropathy or rheumatoid nodules)
- PNS vasculitis (in the setting of vasculitis concomitant cutaneous vasculitis, low C4, and severe neuropathy affecting more than 2 limbs are predictors of morality)
- CNS (less common than PNS, seen with seropositivity and longer disease duration)
  - Atlantoaxial subluxation/ atlantoaxial impaction (basilar invagination)/ subaxial subluxations/ vertical subluxation (cranial settling or superior migration of the odontoid), cervical myelopathy, acquired cervical syringomyelia, synovial cysts, odontoid erosion is very specific for RA (RA can involve any small or large joint in the upper or lower extremity but spares the vertebral column except the cervical spine, severity of RA as suggested by seropositivity, high CRP at disease onset, and polyarthritis is predictive of extent of progression of cervical spine involvement)
  - Rheumatoid meningitis/ meningoencephalitis/ nodules (dural, extradural, leptomeningeal)—may be presenting manifestation, pachymeningeal or leptomeningeal, nodule may mimic neoplasm, CNS vasculitis (rare), VBI due to rheumatic degeneration
  - PML and hyperviscosity syndrome have been reported
  - Cognitive dysfunction, depression, anxiety
  - Headache
  - Epilepsy

**CNS**
- Atlantoaxial subluxation/ atlantoaxial impaction (basilar invagination)/ subaxial subluxations/ vertical subluxation (cranial settling or superior migration of the odontoid), cervical myelopathy, acquired cervical syringomyelia, synovial cysts, odontoid erosion is very specific for RA (RA can involve any small or large joint in the upper or lower extremity but spares the vertebral column except the cervical spine, severity of RA as suggested by seropositivity, high CRP at disease onset, and polyarthritis is predictive of extent of progression of cervical spine involvement)
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- PML and hyperviscosity syndrome have been reported
- Cognitive dysfunction, depression, anxiety
- Headache
- Epilepsy
4. Symmetric arthritis
   Simultaneous involvement if the same joint area as in 2 bilaterally
   (absolute symmetry is not required for PIPs, MCPs, MTPs)
5. Rheumatoid nodules
   Over bony prominences, extensor surfaces, or in juxtaarticular
   regions
6. Serum rheumatoid factor positivity
7. Radiographic changes
   Erosions or bony decalcification in or adjacent to involved joints
   (osteoarthritis changes alone do not qualify)

Additional points:
- Involvement of skin, eyes, lung, heart
- Systemic inflammation is linked to high rates of cardiovascular disease and
decreased life expectancy
- Neurologic complications in RA appear late

• Stroke risk increased
Sjögren Syndrome (SjS)\(^{101, 110}\)

**Diagnosis of primary Sjögren’s syndrome requires the presence or 4 of the following 6 criteria, as long as item IV or VI is present OR 3 of 4 (III-VI).** Diagnosis of secondary Sjögren’s syndrome in patients with a potentially associated disease (SLE/RA/Scl) requires the presence of item I or II and any 2 of items III-V.

I. Ocular symptoms (at least 1 of 3: dry eyes for over 3 months, recurrent sand or gravel sensation in eyes, tear substitutes used more than three times a day)

II. Oral symptoms (at least 1 of 3: dry mouth for over 3 months, recurrent or persistently swollen salivary glands, frequently drinking liquids to aid swallowing)

III. Ocular signs (Schirmer’s test or ocular dye score like Rose Bengal)

IV. Histopathology in minor salivary glands

V. Salivary gland involvement shown by reduced salivary flow, abnormal sialography or scintigraphy

VI. SSA or SSB antibody present, or both.

**Exclusion criteria:**

- Past head/neck radiation
- Hepatitis C infection
- AIDS
- Lymphoma
- Sarcoidosis
- Graft versus host disease
- Use of anticholinergic drugs

**Additional points:**

- Primary or Secondary (SLE, RA, Scl)
- Primary SjS is rarely associated with early vascular disease
- Others: articular, cutaneous, respiratory, renal, hepatic, vascular, constitutional
- Patients with Sjögren may have small vessel vasculitis and have increased risk of lymphoma
- Role of conjunctival biopsy
- Anti-SSA/SSB are not very sensitive
- Positive ANA/RF, hypergammaglobulinemia, anemia with lymphopenia

**PNS\(^{111-113}\)**

- PN: frequently overlaps (S: painful sensory/ sensory ataxic neuronopathy, SM, small-fiber, M, MM-vasculitis, autonomic, CIDP, AMAN, sensory ganglionopathy-lymphocytic infiltration of the dorsal root ganglion,\(^{48}\) asymmetric, asymptomatic)
- Polyradiculopathy (including thoracic), radiculoneuropathy
- Entrapment (carpal tunnel)
- Cranial (V – often bilateral, others: III-XII, multiple)
- MG
- Muscle (PM, DM, IBM, vasculitis, myalgia)

**CNS**

- Inflammatory meningoencephalitis, aseptic meningitis
- Neuropsychiatric manifestations
- MS-like brain and cord lesions
- Focal > diffuse (seizure, aphasia, movement disorders, incoordination)
- Coexistence with NMO\(^{112}\)
- Sensory ataxic neuronopathy

**Additional points:**

- Fever may be more common with neurologic involvement\(^{112}\)
- Sjögren specific antibodies may be less common in those without neurologic involvement\(^{48}\)
- Neurological finding may antedate typical xerostomia and xerophthalmia
**Behçet’s Disease**[^12]

**Criteria for the diagnosis of Behçet’s disease.**[^13]

**Diagnosis of Behçet’s disease requires the presence of:**

1. Recurrent oral ulceration (aphthous or herpetiform, at least 3 recurrences over 12 months)

**Plus 2 of the following:**

2. Recurrent genital ulceration (aphthous)
3. Eye lesions (anterior or posterior uveitis, vitreal cells, or retinal vasculitis)
4. Skin lesions (erythema nodosum, pseudofolliculitis, papulopustular lesions, or acneiform nodules if post-adolescent and not on steroids)
5. Positive pathergy test

**Additional points:**

- Mediterranean/ Middle eastern descent
- HLA-B51 is associated with susceptibility to BD especially in endemic areas & with more severe forms of the disease. The +ve predictive value is 76% in endemic areas & 7% in nonendemic areas. So in a patient of western European background, HLA-B51 presence is not diagnostic, but its absence rules out BD 95% of the time.[^16]
- Neurologic: venous thrombosis and raised ICP or parenchymal disease, Almost all patients with Neuro Behçet have a history of oral ulcers by the time neurological symptoms develop (recurrent oral ulcers are required for the diagnosis)
- Others: ocular, joint, GI, vascular (retinal and cutaneous vasculitis)
- Treatment: prednisone, azathioprine, cyclophosphamide, ?PLEX

**Mixed Connective Tissue Disease**[^17]

1. Serological
   - Anti-RNP titer ≥ to 1:1600
2. Clinical
   - Hand edema
   - Synovitis
   - Myositis
   - Raynaud’s phenomenon
   - Acrosclerosis

**Diagnosis requires serological criteria and at least 3 clinical criteria to be fulfilled.** If clinical criteria consist of hand edema, Raynaud’s, and acrosclerosis then at least one

**CNS**
- Inflammatory meningoencephalitis with brainstem involvement, encephalopathy, dementia, seizures
- Stroke
- Headache
- Cranial nerves, cochlear & vestibular dysfunction

**PNS**
- Muscle (focal myositis, vasculitis, diffuse inflammatory)
- PN (SM, S, recurrent tibial, mononeuropathy: single/ multiple)
- Polyradiculopathy

[^12]: Behçet’s Disease
[^13]: Criteria for the diagnosis of Behçet’s disease
[^14]: Diagnosis of Behçet’s disease requires the presence of:
[^15]: 1. Recurrent oral ulceration (aphthous or herpetiform, at least 3 recurrences over 12 months)
[^16]: Plus 2 of the following:
[^17]: Mediterranean/ Middle eastern descent
[^18]: Additional points:
[^19]: HLA-B51 is associated with susceptibility to BD especially in endemic areas & with more severe forms of the disease. The +ve predictive value in 76% in endemic areas & 7% in nonendemic areas. So in a patient of western European background, HLA-B51 presence is not diagnostic, but its absence rules out BD 95% of the time.
[^20]: Neurologic: venous thrombosis and raised ICP or parenchymal disease, Almost all patients with Neuro Behçet have a history of oral ulcers by the time neurological symptoms develop (recurrent oral ulcers are required for the diagnosis)
[^21]: Others: ocular, joint, GI, vascular (retinal and cutaneous vasculitis)
[^22]: Treatment: prednisone, azathioprine, cyclophosphamide, ?PLEX
[^23]: Mixed Connective Tissue disease
[^24]: 1. Serological
[^25]: 2. Clinical
[^26]: Hand edema
[^27]: Synovitis
[^28]: Myositis
[^29]: Raynaud’s phenomenon
[^30]: Acrosclerosis
[^31]: Diagnosis requires serological criteria and at least 3 clinical criteria to be fulfilled. If clinical criteria consist of hand edema, Raynaud’s, and acrosclerosis then at least one
of the other clinical criteria must be fulfilled.

Additional points:
SLE + Scl + DM+PM, anti-U1-RNP 9without anti-Ssm and anti ds-DNA)

**Scleroderma/ systemic Sclerosis (SSc)**

*Systemic:* diffuse cutaneous scleroderma or dcSSc (proximal, truncal), CREST (calcinosis, Raynaud’s, esophageal disease, sclerodactyly, cutaneous telangiectasia), limited cutaneous (distal to elbows & knees) or lcSSc, scleroderma without skin involvement or SSc

*Localized* (skin, subcutaneous tissue, subjacent muscle): localized scleroderma (morphea, linear scleroderma, coup de sabre), generalized morphea

Additional points:

**Non neurologic**
- Lungs: PAH, pulmonary fibrosis
- GI tract: dysmotility, specially esophagus
- Kidney: ischemia, renal crisis
- Heart: pericardial effusion, myocarditis, constrictive pericarditis, contr band necrosis
- Thyroid: fibrosis
- Salivary or lacrimal gland: fibrosis
- Peis: ED independent of dysautonomia

**Serology**
- anti Scl-70: ILD, anti-pul HT, diffuse cutaneous Scl
- anti-centromere: anti-ILD, limited cutaneous Scl
- anti RNA polymerase III: pul HT
- anti U3RNP: pul HT, malignancy
- anti PM-Scl: inflammatory myopathy

**PNS**
- Muscle (myalgias, nonspecific myopathy, steroid myopathy, fibrotic myopathy, inflammatory myopathy, PM, DM, scleroderma vasculopathy, necrotizing vasculitis, IBM-may be steroid responsive, dropped head, bent spine…Note: anti-PM-Scl is a marker for Scl-associated inflammatory myopathy)
- MG (association rather than cause-effect)
- Entrapment neuropathy (median)
- PN (SM, MM, vasculitic - CREST)
- Autonomic
- Lumbosacral plexopathy (CREST-vasculitis)
- CN (V)

**CNS**
- Epilepsy in coup de sabre (common)
- Depression & anxiety in SSc
- Headaches & seizures in SSc
ACR/EULAR Criteria for the Classification of Systemic Sclerosis.\textsuperscript{121, 122} 

1. These criteria are applicable to any patient considered for inclusion in a SSc study. 
2. These criteria are not applicable to:
   a) Patients having a SSc-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabetorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic cheiropathy. 
   b) Patients with "Skin thickening sparing the fingers". 

<table>
<thead>
<tr>
<th>Items</th>
<th>Sub-items</th>
<th>Weight / Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints</td>
<td>(sufficient criterion)</td>
<td>9</td>
</tr>
<tr>
<td>Skin thickening of the fingers</td>
<td>Puffy fingers</td>
<td>2</td>
</tr>
<tr>
<td>(only count the highest score)</td>
<td>Sclerodactyly of the fingers (distal to MCP but proximal to the PIPs)</td>
<td>4</td>
</tr>
<tr>
<td>Fingertip lesions</td>
<td>Digital Tip Ulcers</td>
<td>2</td>
</tr>
<tr>
<td>(only count the highest score)</td>
<td>Finger Tip Pitting Scars</td>
<td>3</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Abnormal nailfold capillaries</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary Arterial Hypertension and/or Interstitial Lung Disease</td>
<td>PAH</td>
<td>2</td>
</tr>
<tr>
<td>(Maximum score is 2)</td>
<td>ILD</td>
<td></td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Scleroderma related antibodies</td>
<td>Anti-centromere,</td>
<td></td>
</tr>
<tr>
<td>Anti-topoisomerase I (anti-Scl 70),</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-RNA polymerase III</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>(Maximum score is 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional points;</td>
<td>Risk of renal crisis with steroid use in diffuse cutaneous Scl</td>
<td></td>
</tr>
</tbody>
</table>
Antiphospholipid Antibody Syndrome

- **Primary and Secondary:** Antiphospholipid (aPL) antibody syndrome (APS) is frequently seen in patients with SLE, but can be seen in patients without SLE. Secondary APS refers to the association with SLE or some other connective tissue disease and primary APS is the term used when the syndrome occurs in the absence of an underlying connective tissue disease. aPL antibodies can be seen in mixed connective tissue disease, vasculitides, HIV, Lyme, myasthenia gravis, syphilis, and various viral infections.

- **Definition:** APS is defined as an episode of arterial or venous thrombosis leading to tissue ischemia or recurrent fetal loss in the presence of antiphospholipid antibodies (aPLs) of moderate to high titer or a lupus anticoagulant (LA) that is present on at least two occasions at least 12 weeks apart.

**Note:** It has been suggested that recurrent thrombotic events and some other nonstroke neurologic manifestations may be more commonly seen in SLE patients with APS.

- **Classification Criteria:**
  - According to the revised Sapporo criteria, definite APS is considered if at least one clinical and at least one laboratory criteria is satisfied.
  - **Clinical Criteria**
    - Vascular thrombosis: One or more episodes of arterial, venous, or small vessel thrombosis in any tissue or organ. Thrombosis must be confirmed via imaging (Doppler studies) or histopathology (with the exception of superficial venous thrombosis). For histopath confirmation thrombosis should be present without significant vessel wall inflammation.
    - Pregnancy morbidity: one or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation with normal fetal morphology documented by ultrasound or examination or one or more premature births of a morphologically normal neonate at or before the 34th week of gestation because of preeclampsia or severe placental insufficiency or three or more unexplained consecutive spontaneous abortions before the 10th week of gestation with maternal anatomic or hormonal abnormalities and exclusion of maternal and paternal chromosomal causes.
  - **Laboratory Criteria**
    - Anticardiolipin antibody of IgG and/or IgM isotype and measured by a standard ELISA or anti-beta2-glycoprotein 1 of IgG and/or IgM isotype in blood, present in medium or high titer (>40 GPL or MPL/ > 99th percentile), on two or more occasions 12 weeks or more apart.
    - Lupus anticoagulant present in plasma on two or more occasions 12 weeks or more apart and detected according to the guidelines of the International Society of Thrombosis and Hemostasis, in the following steps:
      - Documentation of a prolonged phospholipid-dependent coagulation screening test, eg activated partial thromboplastin time, kaolin clotting time, dilute Russell’s viper venom time, dilute Prothrombin time, Texatarin time
      - Failure to correct the prolonged screening test by mixing with normal platelet-poor plasma
      - Shortening or correction of the prolonged screening test by the addition of excess phospholipid
      - Exclusion of other coagulopathies as appropriate, eg, factor VIII inhibitor, heparin
  - Clinical manifestations
    - Venous thromboembolism is the most common initial presentation of APS. Since aPL antibodies are prothrombotic they have been causally associated with DVT, PE, intracardiac thrombus, and stroke (arterial and venous).
    - aPLs are a risk factor in a first ischemic stroke but their role in recurrent stroke is less clear. Their role as a possible stroke mechanism is probably more important in younger individuals. Left-sided valvular lesions characterized by valve thickening have been shown in patients with aPLs, suggesting a cardioembolic basis. It has also been suggested that the presence of LA may be more important in determining stroke risk than aCL antibodies alone. Thrombotic events
(stroke, myocardial infarction, pulmonary embolism) in patients with aPLs and SLE have been identified to be a poor prognostic factor.\(^{100}\)

- Persistently positive aPLs have been associated with cognitive dysfunction in SLE.\(^ {131}\) High aPLs levels are often seen in the elderly without SLE or other connective tissue diseases. Some studies have noted a relationship between cognitive dysfunction and high aPLs levels in a nonelderly population but this needs further study.\(^{132}\)
- There is an association between aPLs and transverse myelopathy, particularly so in patients with SLE.\(^ {133}\)
- aPLs have been linked to epilepsy in patients with and without lupus.\(^ {134}\)
- The relationship between aPLs and other diseases like migraine, multiple-sclerosis like illness is less clear.\(^ {98}\) The same is true for psychiatric disorders and other neurological manifestations that have been associated with aPLs like chorea, Guillain Barré syndrome, neuropathy, hearing loss (sensorineural), transient global amnesia, orthostatic hypotension.\(^ {98, 135}\)
- aPL-associated cardiac valve disease, livedo reticularis, nephropathy, thrombocytopenia have all been defined.\(^ {124}\)

**Investigations**

- aPLs (aCL, LA, anti-beta2-GP1) testing should be considered in a stroke patient with any of the following features:
  - less than 45 years of age
  - concomitant diagnosis of SLE
  - other features of APS
  - thrombocytopenia
  - a prolonged activated partial thromboplastin time
  - positive VDRL.
- A weakly positive aPLs test may not be significant.
- aPL antibodies can cause false positive VDRL and RPR serologic tests for syphilis (but not FTA ABS)
- Other stroke etiologies should be pursued even in the presence of a positive result.
- There is no indication for evaluating aPLs in other neurologic diseases.
- MRI abnormalities suggestive of vascular disease may be seen: these may be more common in those with LA positivity.\(^ {136}\)

**Treatment**

- Treatment in APS can be directed at thrombo-occlusive events using anti-thrombotic medications or at modulating the immune system using immunotherapy.\(^ {98}\) On empiric grounds aspirin has been suggested for patients with a persistently positive LA or moderate to high titer aPL antibody. Warfarin has been recommended in patients with an incident cerebrovascular manifestation of APS. The antiphospholipid antibodies and stroke study (APASS) suggests patients with first ischemic stroke and a positive aPL may be treated with aspirin (325 mg/d) or warfarin.\(^ {137}\) The AHA recommendations indicate that antiplatelet therapy is reasonable in cases of cryptogenic ischemic stroke or TIA and positive aPL antibodies.\(^ {138}\) For patients with ischemic stroke or TIA who meet the criteria for APS with venous and arterial occlusive disease in multiple organs, miscarriages, and livedo reticularis, oral anticoagulation with a target INR of 2 to 3 is reasonable.\(^ {138}\) Indefinite anticoagulation is indicated in patients of APS who have venous thromboembolism.
103
Uremic encephalopathy may accompany acute or chronic renal failure. The development of uremia may not correlate with absolute value of BUN or creatinine. Chronic renal failure is defined as a GFR of less than 60 ml/min that persists for at least 3 months.

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O Uremic encephalopathy may accompany acute or chronic renal failure. The development of uremia may not correlate with absolute value of BUN or creatinine. Chronic renal failure is defined as a GFR of less than 60 ml/min that persists for at least 3 months.

Uremia can be associated with a spectrum of manifestations that include fatigue, apathy, irritability, inattention, emotional instability, forgetfulness, perceptual errors, impaired cognition, personality changes, and in later stages fluctuating sensorium, disorientation, delusions, hallucinations, seizures, agitation, delirium, and coma.2,4 Sleep disturbance is common. Involuntary movements associated with uremic encephalopathy include tremor, asterixis, chorea, and myoclonus.

O Causes of encephalopathy in renal disease are diverse and include: hypoglycemia, uremia, electrolyte disturbance (hypo/hypernatremia, hypo/hypercalcemia, hypermagnesemia, hypophosphatemia, hypo/hyperosmolality), hypertensive encephalopathy, reversible posterior leukoencephalopathy syndrome, drug toxicity, Wernicke encephalopathy, dialysis dementia, dialysis disequilibrium, and rejection encephalopathy.

Seizures
• Movement disorders
  o Asterixis and myoclonus are the best characterized movement disorders in uremia.3,4 Muscle twitches, fasciculations, and tremors may be present. A syndrome of intense asterixis, myoclonus, fasciculations, twitches, and seizures has been referred to as a "twitch-convulsive" syndrome.13 Parkinsonism with basal ganglia lesions due to vasogenic edema has been reported in uremia.14,15 Also reported are chorea with basal ganglia lesions16 and generalized dyskinesia/gait difficulty and basal ganglia lesions.17 This syndrome of basal ganglia lesions and extrapyramidal disease is rare but when present generally seen in diabetics. A recent report noted control of myoclonus and tremor (twitch-convulsive syndrome) with dexmedetomidine infusion.18

• Stroke
  o Chronic kidney disease is associated with an increased risk of ischemic and hemorrhagic stroke. Chronic kidney disease has been reported to be associated with silent brain infarcts, cerebral white matter lesions, and cerebral microbleeds, independently of vascular risk factors.19,20 Atherosclerosis and chronic renal failure share similar risk factors and hyperhomocysteinemia can be seen in both conditions.21 Risk factors specific to renal failure include accumulation of guanidine compounds, hyperhomocysteinemia, oxidative and carbonyl stress, and disturbance of calcium-phosphate metabolism. Anemia is often seen in chronic renal failure and is an independent risk factor for stroke and cardiovascular events.22
  o Among dialysis patients, the relative risk of hospitalization for ischemic stroke or hemorrhagic stroke is between 4 to 10 times higher than that of patients without chronic kidney disease.23 Intradialytic hypotension may be operative.
  o End stage renal disease is associated with a 10 – 20 fold increased rate of cardiovascular mortality and advanced carotid atherosclerosis compared to the general population.24,25 Serum creatinine levels over 1.3 mg/dl increase the risk of cerebrovascular events,26 decrease in GFR is associated with lacunar infarcts,27 and albuminuria is an independent risk factor for stroke.28
  o Venous sinus thrombosis may be seen in nephrotic syndrome.29 This presents with venous infarctions with hemorrhagic conversion.
  o Platelet dysfunction and altered platelet-vessel wall interaction are some of the causes of intracranial hemorrhage in renal failure.7 Other causes of hemorrhagic stroke include hypertension, polycystic kidney disease, and use of anticoagulants and platelet anti-aggregants. The manifestations of subdural hematoma can mimic uremic encephalopathy; hence clinicians should have a low threshold for cranial imaging in patients on dialysis. The presence of intracranial hemorrhage may prompt consideration of alternative means of dialysis like peritoneal dialysis or heparin-free dialysis.

• Sleep disturbance
  o Sleep disorders are common in patients of hemodialysis and include insomnia, obstructive sleep apnea, restless leg syndrome, and excessive daytime sleepiness.30-32 Other sleep disorders include periodic limb movements, nightmares, sleepwalking, REM behavior disorder, and narcolepsy. Factors that may contribute to restless leg syndrome include iron deficiency, ”uremic toxins”, a central dopaminergic disturbance, or an associated polyneuropathy. Kidney transplantation may result in significant improvement of restless leg syndrome.33

• Cognitive impairment
  o Chronic kidney disease is an independent risk factor for cognitive impairment.34,35 Dementia in patients with renal disease is independent of cerebral small vessel ischemic disease.35 Retinal artery disease also has an independent relationship with chronic kidney disease and cognitive impairment.19
The biologic basis may relate to coexisting cerebrovascular disease (or cerebral small vessel disease), anemia, erythropoietin deficiency, and metabolic abnormalities (like hyperparathyroidism). Improvement in cognitive function following renal transplantation has been described. An additional cause of cognitive impairment in patients on chronic dialysis is Wernicke encephalopathy.

PNS Manifestations of Uremia

- **Polyneuropathy**
  - Chronic renal failure is commonly associated with a length-dependent, axonal, distal, sensorimotor, large-fiber neuropathy. Autonomic involvement may be seen. Cranial nerve dysfunction (II, V, VII, and most commonly VIII) has been reported. Also reported are cases of pure sensory and pure motor neuropathy. Mononeuropathies (ulnar, median, femoral) may be due to increased susceptibility to compression and ischemia (see below). CSF protein may be significantly increased. Neuropathy can be seen due to diseases that involve the kidneys and PNS like DM, vasculitis, connective tissue disease, and plasma cell dyscrasias.
  - Uremic neuropathy can improve or stabilize during dialysis; rapid resolution of paresthesias has been noted after initiation of hemodialysis.

- **Mononeuropathy**
  - The peripheral nerves are susceptible to compression and ischemia in patients with renal disease. The ulnar, median, and femoral nerves are most often involved. Carpal tunnel syndrome and ulnar neuropathy at the wrist can both be seen in renal failure. Nerve compression or ischemia may result in a femoral neuropathy during renal transplantation.

- **Myopathy**
  - GFR less than 25 ml/min may be associated with a myopathy; cardiomyopathy may be a rare accompaniment. Electrolyte disturbances seen in uremia like hypermagnesemia, hypocalcemia, hypercalcemia, hypokalemia, hyperkalemia may cause manifestations that mimic a myopathy. Myopathy in renal failure can also result from steroid use or ischemia. Other factors implicated in uremic myopathy include “uremic toxins”, disordered vitamin D metabolism, insulin resistance, carnitine deficiency, and malnutrition.

Inherited Renal Diseases Associated with Neurologic Syndromes

- **Glomerular disease**
  - Alport syndrome: autosomal recessive autosomal recessive or X-linked dominant disorder associated with injury to the glomerular/tubular basal membranes (causing a hemorrhagic nephritis), eyes (ocular changes typically don’t affect vision), and cochlea due to changes in collagen type IV chains. It often presents with progressive symmetric sensorineural hearing impairment. The genes involved are COL4A3 (AR, AD) or COL4A4 (AR, AD) or COL4A5 (X-D).
  - Fabry disease: Fabry disease is an X-linked inborn error of glycosphingolipid metabolism. It results from deficient activity of the enzyme α-galactosidase (α-Gal A) and resulting lysosomal deposition of globotriaosylceramide (GL-3) in cells throughout the body (blood vessels, nerves, kidney, cardiac cells). It is the second most common lysosomal storage disorder after Gaucher disease. The classic form occurs in males with less than 1% α-Gal A enzyme activity. It has its onset in childhood or adolescence with periodic crises of severe pain in the extremities (acroparesthesias), the appearance of vascular cutaneous lesions (angiokeratomas), hypohidrosis, characteristic corneal and lenticular opacities, and proteinuria. Paresthesias are precipitated by illness, fever, stress, exercise, and heat. Urinary sediment may show casts, red cells, and lipid inclusions with birefringent Maltese cross configurations. Gradual deterioration of renal function to end-stage renal disease usually occurs in men in the third to fifth decade. Renal manifestations include proteinuria, Fanconi syndrome, renal cysts and hypertension. In middle age, most males successfully treated for ESRD develop cardiovascular and/or cerebrovascular disease (TIA, infarction, dolichoectasia). Additional neurologic manifestations include hearing impairment, vascular dementia, aseptic meningitis, a small fiber neuropathy, and cramp-fasciculation syndrome without peripheral neuropathy. Heterozygous females typically have milder symptoms at a later age of onset than males. 70% of carrier females may be asymptomatic. Males with greater than 1% α-Gal A activity may have either a cardiac variant phenotype that usually presents in the sixth to eighth decade with left ventricular hypertrophy, mitral insufficiency and/or cardiomyopathy, and proteinuria, but without ESRD; or a renal variant phenotype, associated with ESRD but without the skin lesions or pain. In males, the most efficient and reliable method of
diagnosing Fabry disease is the demonstration of deficient enzyme activity in plasma, isolated leukocytes, and/or cultured cells. In females, measurement of α-Gal A enzyme activity is unreliable. GLA is the only gene known to be associated with Fabry disease. Nearly 100% of affected males have an identifiable GLA mutation. Molecular genetic testing is the most reliable method for the diagnosis of carrier females. MRI may show T1 hyperintensity and low N-acetylaspartate/creatine ratio in the pulvinar nuclei. Enzyme replacement therapy with agalsidase beta is available. Enzyme replacement therapy (ERT) with intravenous infusions of recombinant human alpha-galactosidase A consistently decreases Gb3 levels in plasma and clears lysosomal inclusions from vascular endothelial cells. The effects of ERT on other tissues are not as obvious, suggesting that treatment must be initiated early in the course of the disease to be optimally effective or that some complications of the disease are not responsive to enzymes delivered intravenously.

- **Proximal tubular disease**
  - Proximal type II renal tubular acidosis may be due to SLC4A4 mutations (AR). It is associated with a hyperchloremic, hypokalemic metabolic acidosis. It is also seen in Fanconi syndrome, Wilson disease, Lowe syndrome and other conditions. The neurologic manifestations in the condition are related to hypokalemia. SLC4A4 mutations are associated with impaired psychomotor and cognitive function, BG opacification.
  - Lowe syndrome (oculocerebralrenal syndrome): Lowe syndrome (X-linked recessive) results from mutations in the OCRL1 gene at Xq26.1 that codes for the enzyme phosphatidylinositol (4,5) biphosphate 5 phosphate in the trans-Golgi network. Neurologic manifestations include neonatal hypotonia, psychomotor delay, stereotypic behaviors, aggressiveness, obsessive-compulsive behaviors, seizures, and peripheral neuropathy. Nystagmus may result from aphakia and retinal degeneration. Other ocular manifestations include cataracts, glaucoma, corneal/conjunctival cheloids. It is also a cause of renal tubular acidosis and Fanconi syndrome. Brain MRI may show ventriculomegaly, periventricular cysts, and diffuse foci of increased T2 signal that spares the commissural fibers, pyramidal tracts, and cerebellum.
  - Hartnup disease: Hartnup disease is an autosomal recessive disorder linked to mutations in SLC6A19 and SLC6A18 genes that are responsible for transport of neutral amino acids. The primary renal manifestation is aminoaciduria. Enhanced tryptophan loss results in niacin deficiency and related manifestations. Neurologic manifestations of Hartnup disease include cerebellar ataxia and psychiatric disturbance.

- **Loop of Henle disease**
  - Bartter syndrome is an AR disorder of potassium, calcium, magnesium reabsorption. The site of defect is the ascending limb of the loop of Henle. The term “Bartter-like syndromes” encompasses a variety of disorders of renal electrolyte transport. Neonatal Bartter syndrome is observed in newborn infants and is characterized by polydramnios, premature delivery, life-threatening episodes of fever and dehydration, growth retardation, mental retardation, hypercalciuria, and early-onset nephrocalcinosis. Two molecular defects have been identified: either at the gene encoding the renal bumetanide-sensitive Na-K-2Cl cotransporter (NKCC2) or the gene encoding an ATP-sensitive inwardly rectifying K channel (ROMK). "Classic" Bartter syndrome is mostly observed during infancy and childhood and is characterized clinically by polyuria and growth retardation. Nephrocalcinosis is not present. Deletions or mutations at the gene encoding a renal chloride channel (ClC-Kb) have been identified.

- **Distal tubular disorders**
  - Gitelman syndrome (AR) is a distal convoluted tubule disorder. It is observed in older children and adults and presents with fatigue, and intermittent episodes of muscle weakness and tetany, as well as limb cramps. Hypokalemia, hyperreninemia, hyperaldosteronism, hypocalciuria, metabolic alkalosis, and hypomagnesemia may be present. Mutations at the gene encoding the thiazide-sensitive Na-Cl cotransporter (SLC12A3) have been identified in the majority of patients studied.
Distal (type 1) renal tubular acidosis (AD—SLC4A1/AR-ATP6V0A4 & ATP6V1B1) is a distal nephron acidification defect that can cause periodic hypokalemic paralysis. Nephrocalcinosis and nephrolithiasis may be seen in either form. The AR may be associated with hearing impairment and hyperchloremic metabolic acidosis. Distal RTA may be linked to certain autoimmune diseases like Sjogren syndrome.

- **Parenchymal disease**
  - Autosomal polycystic kidney disease (related to PKD1 and PKD2 mutations) are associated with saccular cerebral aneurysms that rupture at smaller sizes and in younger individuals. Polycystic kidney disease is also associated with dolichoectasia and cervicocephalic artery dissection. Rare associations include subdural hemorrhage and CSF hypotension. Subdural hematomas may result from arachnoid membrane cysts. Meningeal diverticula may result in craniospinal hypovolemia. Indications for screening for aneurysms include a family history of intracranial aneurysm or subarachnoid hemorrhage, prior intracranial aneurysm rupture, high-risk profession, or high patient anxiety. Coil embolization is safe and effective; there is however concern regarding contrast induced nephropathy. Renal function is often maintained despite cyst rupture until the fourth to sixth decade of life. Hypertension is present in about half the patients with normal renal function and in all with ESRD. Pain of renal origin is common.
  - Von Hippel-Lindau disease is an autosomal dominant disorder due to mutations in VHL tumor suppressor gene. Renal cysts and renal cell carcinoma may be seen. Additional associations include pheochromocytoma, pancreatic neuroendocrine tumors, and endolymphatic sac tumors. Neurologic manifestations include retinal and CNS hemangioblastomas, ataxia, syringobulbia and syringomyelia. Management of CNS hemangioblastomas include surgical resection of symptomatic tumors.
  - Joubert syndrome is an autosomal recessive disorder characterized by vermian hypoplasia and renal cysts. Neurologic manifestations include ataxia, psychomotor delay, hypotonia, nystagmus. Chronic renal failure may be present. Prominent superior cerebellar peduncles referred to as “molar tooth sign” of the midbrain-hindbrain junction is a pathognomonic MRI finding.

**Acquired Disease With Concomitant Renal and Neurologic Impairment**

- **Poststreptococcal glomerulonephritis**
  - Acute disseminated encephalomyelitis has been associated with poststreptococcal glomerulonephritis (occurring after pharyngitis or impetigo).

- **Renal cell cancer**
  - Paraneoplastic disease associated with renal cell cancer includes opsoclonus-myoclonus, a lower motor neuron syndrome with weakness and fasciculations, neuromyotonia, limbic encephalitis, cerebellar ataxia, chorea, neuropathy, and myopathy. Renal cell cancer may be associated with cerebral, cerebellar, or pituitary metastasis. Also reported are metastasis to the spine or cauda or endoneurial metastasis of the sciatic nerve. Renal infiltration by non-Hodgkin lymphoma has been reported to cause hypokalemia with associated neurologic disease.

- **Vasculitis and connective tissue disorders**
  - Primary vasculitides associated with neurologic and renal involvement include polyarteritis nodosa, Churg-Strauss syndrome, Granulomatosis with polyangiitis (Wegner granulomatosis), and cryoglobulinemia. Connective tissue diseases associated with vasculitis-related renal involvement and neurologic disease include rheumatoid arthritis, lupus erythematosus, and Sjogren syndrome.

- **Plasma cell dyscrasias**
  - Nephrotic syndrome and renal failure can be seen in multiple myeloma and Waldenstrom macroglobulinemia. The POEM syndrome is associated with glomeruloid hemangiomas. Monoclonal gammopathy has also been recognized as an important cause of membranoproliferative glomerulonephritis. MGUS can be accompanied by proteinuria. The neurologic manifestations of these conditions are discussed in a separate section.

- **Thrombotic microangiopathy**
  - Renal and neurologic involvement is seen in hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). TTP can present in healthy individuals as a severe microangiopathic hemolytic anemia or in patients with other disorders like SLE. The classic features include thrombocytopenia, fever, acute renal failure, and neurologic manifestations (confusion, headache,
transient focal deficits, seizures, stroke, coma). HUS is a syndrome of microangiopathic hemolytic anemia, thrombocytopenia, and renal failure caused by a diarrheal infection due to Shiga toxin-producing bacteria, complement deficiency, or pneumococcal infection. Neurologic manifestations include seizures, coma, stroke, pyramidal or extrapyramidal syndromes, dysphasia, diplopia, and cortical blindness. Both TTP and HUS have been associated with PRES.

- **Infections**
  - Renal and neurologic manifestations can be seen in a variety of infections:
    - Bacterial/mycobacterial/rickettsial: tuberculosis, leprosy, streptococci, leptospirosis, scrub typhus
    - Protozoa: malaria
    - Virus: HIV, dengue, hantavirus, CMV, VZV

**Neurologic Disease Related to therapy of renal disease**

- **Hemodialysis**

  - **Dialysis disequilibrium** is seen at initiation of hemodialysis or with highly effective hemodialysis in severe azotemia. It may be seen with peritoneal dialysis as well. Patients at extremes of age are vulnerable. Clinically it presents with headache, irritability, emesis, blurred vision, nausea, cramps and twitching that occur towards the end of dialysis and subside over several hours. Severe forms may have delirium, myoclonus, and seizures that last for days. Focal deficits have been reported. The underlying pathophysiology is development of brain edema due to increased osmotic gradient related to more rapid clearing of urea from the blood than brain (“reverse urea hypothesis”). The “idiogenic osmole hypothesis” suggests that newly formed brain osmoles produce an osmotic gradient between brain and plasma during rapid dialysis. It has also been proposed that cerebral edema may result from increased production of organic acids leading to intracellular acidosis in the cerebral cortex. Dialysis disequilibrium syndrome is preventable by slower rates of dialysis, increased frequency of dialysis, shorter duration of dialysis, use of smaller dialysate volume, and addition of osmotically active solutes in the dialysate. Increased awareness and preventive measures have decreased the incidence: intracranial bleeding or infection may be primary considerations with obtundation during dialysis.

  - **Dialysis encephalopathy/dialysis dementia/hemodialysis encephalopathy/progressive myoclonic dialysis encephalopathy** is a subacute onset, progressive condition associated with a broad range of neurologic manifestations: dysarthria, dysphasia with dysgraphia, ataxia, apathy, paranoid delusions, depression, myoclonus, seizures, dementia, and eventually immobilization and mutism. Reduction in the aluminum concentration in the dialysate (was used to bind phosphate) and use of aluminum-free phosphate binders has reduced the incidence of dialysis dementia. The syndrome progressed to death in 6 months. Chelation with deferoxamine may help. Sporadic cases still occur due to use of aluminum hydroxide.

  - **Patients on hemodialysis can develop Wernicke encephalopathy.** Subdural hematomas may be seen in patients undergoing hemodialysis. Rapid ultrafiltration and use of hypertonic dialysate can cause subdural hematoma. Uremia related coagulation disturbances and use of anticoagulants for dialysis are additional contributing factors. Subdural hematomas are often related to trauma.

  - **Ischemic optic neuropathy** related to dehydration, hypotension, and anemia may be seen in patients of hemodialysis. Both anterior and posterior ischemic optic neuropathy have been reported.

  - **Mononeuropathies, particularly carpal tunnel syndrome** may be seen in patients on hemodialysis. The pathogenesis involves β2-microglobulin associated amyloid deposition. A wrist arteriovenous fistula is a potential risk factor for the same.

  - **Ischemic monomelic neuropathy** manifests as motor and sensory dysfunction in the distribution of multiple peripheral nerves within hours of fistula construction. It is a result of shunting of blood away from the distal regions of the arm leading to peripheral nerve ischemia. This condition has been reported almost exclusively in patients with diabetes or severe peripheral vascular disease. Also reported is a subacute vascular steal phenomenon occurring over weeks to months following fistula creation: treatment of this condition requires fistula ligation or banding.

  - **Hemodialysis-related headache** may result from a large amount of water and electrolyte shifts. According to the IHS criteria:
a. At least 3 attacks of acute headache fulfilling criteria C and D
b. Patient is on haemodialysis
c. Headache develops during at least half of haemodialysis sessions
d. Headache resolves within 72 hours after each haemodialysis session and/or ceases altogether after successful transplantation

- **Peritoneal dialysis**
  - Dialysis disequilibrium
  - The high glucose content in peritoneal dialysis may cause hyperosmolar coma in diabetics. Osmotic icodextrin used in peritoneal dialysis may mask hypoglycemia and predispose to hypoglycemic coma. Acute sensorimotor peripheral neuropathy has been reported in diabetics treated with peritoneal dialysis.

- **Renal transplantation**
  - Compression by retractors or nerve ischemia may result in femoral neuropathy or involvement of the lateral femoral cutaneous nerve of the thigh.
  - The distal part of the spinal cord receives its blood supply from branches of the internal iliac artery in some patients. When this artery is used to supply the allograft, spinal cord ischemia may result.
  - Rejection encephalopathy occurs within 3 months of transplant. Cases following 2 years from transplantation have been reported. It manifests as headache, confusion, and seizures in a patient with systemic features of renal allograft rejection. Cytokines produced by the rejection process are likely responsible. Rapid and complete recovery after treatment of the rejection episode is seen.
  - Tacrolimus and sirolimus bind to the cytosolic protein FK binding protein 2. The complex that this protein forms with tacrolimus inhibits calcineurin which inhibits secretion of IL-2, sirolimus is not a calcineurin inhibitor but a mTOR (mammalian target of rapamycin: rapamycin being the old name for sirolimus) and inhibits response to IL-2 thus blocking activation of T and B cells Immunosuppressants like tacrolimus, sirolimus, cyclosporine may result in PRES. These agents can also cause tremors, headache, an encephalopathy, and disabling pain syndromes. OKT3 can result in aseptic meningitis, headache, seizures, and encephalopathy. Mycophenolate mofetil can be associated with dizziness, headache, insomnia, tremors, paresthesias, and PML. Cyclosporine and tacrolimus are calcineurin inhibitors and should not be given concurrently. They can cause nephrotoxicity, hepatotoxicity, and gastrointestinal side effects: the latter being more common with tacrolimus. Cyclosporine is more commonly associated with hypertension and hyperlipidemia. Tacrolimus is more commonly associated with glucose intolerance. Tacrolimus is more commonly associated with neurotoxicity: tremors, headache, insomnia, paresthesias. Sirolimus can cause hyperlipidemia, hypertension, hematologic side effects, interstitial pneumonitis, and nephrotoxicity. Neurologic side effects are less than with tacrolimus.
  - Seizures in the post-transplant setting may also result from antibiotics like penicillin, cephalosporin, carbapenem, and quinolones.
  - Patients have an increased risk of opportunistic infection. Recognition of opportunistic infections in the post-transplant setting is a challenge. The usual signs of infection are blunted. The organisms involved are uncommon/ atypical.

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<thead>
<tr>
<th>Bacterial/ mycobacterial</th>
<th>Nocardia asteroides, Listeria monocytogenes, M tb</th>
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<tbody>
<tr>
<td>Virus</td>
<td>HSV, CMV, EBV, JC</td>
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<tr>
<td>Fungi</td>
<td>Cryptococcus neoformans, Aspergillus fumigatus, Candida, Pneumocystis carinii, Histoplasma, Mucor, Paracoccidioides</td>
</tr>
<tr>
<td>Protozoa</td>
<td>Toxoplasma gondii, Trypanosoma cruzi</td>
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- Post-transplant lymphoproliferative disorder describes the range of abnormal proliferations of B lymphocytes that occurs in renal transplant recipients. The majority of PTLDs are of B cell origin and EBV has been implicated. Reduction of immunosuppressive therapy if the primary treatment. PCNSL is common in renal transplant recipients and can occur as early as 3 months post-transplant.
Neoplasms such as malignant menigioma and brain metastasis occur more frequently after renal transplant. Glioblastoma may occur at a higher incidence in patients who undergo renal transplant.90

**Nephrogenic Systemic Fibrosis**

- NSF occurs after exposure to gadolinium-based contrast agents in the presence of renal failure. Symptoms typically begin within 2 months of exposure to gadolinium based contrast agents and include tightness and burning of skin with redness and swelling. Ultimately joint contractures and limitation in mobility results.93

**References:**