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## Underlying Causes of Paresthesia

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### 1. Introduction

Sensations from various parts of the body are taken by the peripheral sensory nerves to the spinal cord. From spinal cord, the signals reach the brain with the help of the trigeminal nerve and brain stem. Hence, any problem in this pathway may result in paresthesia. Paresthesia is an abnormal condition which causes an individual to feel a sensation of burning, numbness, tingling, itching or prickling. It frequently happens in the extremities, but it can occur in other parts of the body as well.

The purpose of this chapter is to review the causes of paresthesia from studies indexed in PubMed. We describe the underlying conditions that may cause paresthesia based on two subdivisions: Transient and Chronic Paresthesias.

### 2. Causes of transient paresthesia

This paresthesia subtype involves temporary numbness or tingling that disappears quickly as can occur from sitting with your legs crossed for a long time or sleeping on your arm in a bent position. This is a very common type of paresthesia.

- **Obdormition:** Obdormition is a numbness caused by prolonged pressure on a nerve, such as when a leg falls asleep if the legs are crossed for a prolonged period. It disappears gradually as the pressure is relieved (1).
- **Whiplash:** Paresthesias in the upper extremity may occur after whiplash injury (2), a type of cervical soft tissue injury (3). Pujol et al showed that 13% of patients with whiplash had associated paresthesias (4). Recovery usually arises within 6 months after injury (5).
- **Hyperventilation syndrome:** Paresthesia constitutes 35% of presenting complaints in patients with hyperventilation syndrome (6) and may begin after as little as three-minute of hyperventilation (7). After increasing the depth or frequency of respiration,

the alkaline shift produced selectively increases  $\text{Na}^+$  conductance and ectopic discharges in normal cutaneous afferent nerves can be induced (8). Other electrolytes, i.e. magnesium, potassium, chloride, phosphate and bicarbonate, also demonstrated significant changes in concentration (7).

- Panic attack: Paresthesiae of the mouth, hands and feet are common, transient symptoms of the related conditions of hyperventilation syndrome and panic attacks. Ietsugu et al demonstrated that paresthesia can be used as a reliable indicator of severe panic attacks (9).
- Transient ischemic attack (TIA): TIA may be manifested by paresthesias. Several reasons may cause TIA such as thrombosis, embolus, intravascular debris and blood vessels disruption. Perez et al. reported the initial manifestation of cardiac myxoma can be paresthesias caused by TIA (10). Post-ischemic paresthesia occurs when hyperpolarization by the  $\text{Na}^+/\text{K}^+$  pump is transiently halted by elevated extracellular  $\text{K}^+$ . The electrochemical gradient for  $\text{K}^+$  is reversed and inward transport of  $\text{K}^+$  triggers regenerative depolarization (8).
- Seizures: Paresthesia may happen during and after a partial seizure (11). Treatment of seizures with vagus nerve stimulation can also trigger paresthesias and is considered an adverse event associated with this treatment modality (12).
- Dehydration: At around 5% to 6% cumulative water loss, paresthesia may occur.
- Insufficient blood supply: Circulatory disorders could lead to transient or chronic paresthesia.

Acute arterial occlusion by an embolism or in situ thrombosis is a dramatic event which produces severe ischemia of distal tissue. The warning signs are the 5 Ps: pallor, pain, pulselessness, paralysis and paresthesia. In such cases, emergent restoration of blood flow by surgery may be vital to prevent limb loss (13). Aneurysms and dilated forms of atherosclerosis can be both the cause of in situ thrombosis as well as the source of an embolism (14).

In Buerger's disease (thromboangiitis obliterans), an occlusive intraluminal thrombus with a predominantly acute inflammatory infiltrate causes ischemic ulcers, claudication, paresthesia and pain at rest (15, 16).

Raynaud's syndrome describes a condition characterized by the sensation of coldness, burning pain or numbness in the fingers or toes. This syndrome occurs when the blood vessels in the fingers or toes spasm, restricting the flow of blood. Some causative factors can activate Raynaud's syndrome including contact to cold and emotional stress (17, 18).

- Apheresis: Because of improvements in technique and instrumentation used for apheresis, symptoms of mild ionized hypocalcemia, such as paresthesias or lightheadedness, are increasingly easily manageable and quickly reversible with flow-rate adjustments. Puig et al. reported a 2.27 percent incidence of paresthesia in therapeutic apheresis (19).
- Beta-alanine ingestion: Beta-alanine supplementation is used as a nutritional strategy to improve high-intensity anaerobic performance (20). Paresthesia may be observed if a single dose higher than 800 mg is ingested but is transient and abates as plasma concentration declines. This side effect can be prevented by using controlled release capsules and smaller dosing strategies (21).

### 3. Causes of chronic paresthesia

Chronic paresthesia or intermittent paresthesia over a long period of time is generally a sign of neurological disease or traumatic nerve damage. Paresthesia usually arises from nerve damage due to infection, inflammation, trauma, or other abnormal process. Paresthesia is rarely due to life-threatening disorders, but it can occur as a result of stroke and tumors. Whereas paresthesia is a loss of sensation, paralysis usually involves both a loss of movement and sensation.

- Nervous System Disorders

Paresthesias are common manifestations of central and peripheral pathological processes and are due to ectopic impulse activity in cutaneous afferents or their central projections (8).

- Central nervous system etiologies

In the central nervous system, the most common etiologies of paresthesia include ischemia, compressive phenomena, infection, inflammation, and degenerative conditions (22).

- Stroke: Paresthesia and sensory deficits are considered as signs of stroke (23). In unusual cases, mandibular or ear paresthesia may be the only presenting symptom of a cerebrovascular accident (24). A persistent unpleasant numbness after a cerebrovascular accident can result from central poststroke paresthesia (25).
- Paresthesia may be caused by selective lacunar infarcts in the diencephalic and mesencephalic regions or in the diaschisis in the parietal cortex. Chang and Huang reported a patient who presented with unilateral paresthesia after acute isolated infarct of the splenium (26). Kim reported that paresthesia or pain occurred between 0 to 24 months after lenticulocapsular hemorrhage, more prominently in the leg than other body parts (27). In another case report, a thalamic lacunar infarct led to sudden isolated left-sided paresthesia involving the face, upper and lower limbs (28). Cheiro-oral syndrome is characterized by paresthesia and sensory impairment confined to the perioral region and ipsilateral fingers or hand, and arises from small stroke-related lesions to various sites between the medulla and cortex (29).
- Intra-cerebral hemorrhage: Paresthesia is a symptom of acute intra-cerebral hematoma (30). Epidural or subdural hematoma or subarachnoid hemorrhage should be considered as part of the differential diagnosis for acute paresthesia and extremity weakness (31-33). Kishida et al. reported that a small hematoma localized in the ventroposterior lateral nucleus caused paresthesia limited to the forearm and the palm (34).
- Brain tumor: A sudden numbness especially when accompanied by headache, nausea or vomiting, double vision, or weakness could suggest a possible brain tumor or metastasis (35). Cavernous angioma which typically presents with neurological deficits, low back pain and sciatica or as a subarachnoid hemorrhage could be a cause of paresthesia (36). A small round tumor of the somatosensory cortex may present with radicular hand pain and paresthesia (37). Trigeminal sensory neuropathy presents with anesthesia and paresthesia of the orofacial region may herald underlying malignancy (38). Syringomyelia, which is generally related to congenital malformations and tumors, may lead to paresthesia (39).

- Head trauma: Brain injury patients report high rates of complaints generally recognized as being associated with neuropsychological impairment such as paresthesia (40). Trigeminal trophic syndrome is an unusual complication after peripheral or central damage to the trigeminal nerve, characterized by anesthesia, paresthesias, and ala nasi ulceration. It can be preceded by head trauma, iatrogenic injury or other causes (41, 42).
- Encephalitis and meningitis: Brain inflammations may lead to paresthesia (43). Eosinophilic meningitis is typically induced by the nematode *Angiostrongylus cantonensis* and presents with headache, vomiting and fever, and may also induce paresthesia and neck stiffness (44).
- Abscess: A primary brain abscess may begin with neurologic deficit such as paresthesia (45, 46).
- Lumbar spinal stenosis: 70% of patients experience paresthesia which is exacerbated by extension, and improves with spinal flexion (47, 48).
- Systemic lupus erythematosus: Systemic vasculitis may present with multiple neurologic and psychiatric symptoms due to involvement of the central and peripheral nervous systems. Painful paresthesias and weakness of the limbs have been reported in cases of systemic lupus erythematosus (49, 50).
- Multiple sclerosis: One of the most common presenting symptoms in Multiple Sclerosis is paresthesia (51, 52). About 40% of the patients reported that such symptoms had an important adverse influence on daily activities. Painful paresthesia leads to avoidance of any triggering activities (53).
- Transverse myelitis: Sensory impairment and paresthesia in the extremities are two common presentations of acute transverse myelitis (54-57). That is a relatively uncommon neurological disease in which affected patients exhibit acute debilitating symptoms associated with the loss of spinal cord segment function.
- Spinal puncture: Paresthesia rarely occurs during spinal puncture or injection of local anesthetic for spinal anesthesia (58). A paresthesia may result from needle-to-nerve contact with a spinal nerve in the epidural space, or, with far lateral needle placement, such as during placement of a spinal needle into the intervertebral foramen (59). It seems that lateral decubitus position results in a higher incidence of paresthesiae than the sitting position (60).
- Vitamin B<sub>12</sub> deficiency: Neurological symptoms such as paresthesia are frequent in vitamin B<sub>12</sub> deficiency (61, 62). However therapeutic response to vitamin B<sub>12</sub> with resolution of associated symptoms is dramatic (63).
- Peripheral nervous system etiologies (with or without pain)
 

The most common source of paresthesia is peripheral neuropathy. Cutaneous afferents nerves are more volatile than motor axons, due to differences in their biophysical properties. These differences maybe include more persistent Na<sup>+</sup> conductance and inward rectification on cutaneous afferents, properties which probably give greater protection from impulse-dependent conduction failure but produce a greater tendency for ectopic activity (8).

  - Entrapment neuropathies

Numbness and paresthesia are two more common complaints in patients with peripheral neuropathies (64).

- Carpal tunnel syndrome: Carpal tunnel syndrome is the most common entrapment neuropathy caused by compression of the median nerve within the carpal tunnel. It is characterized by pain and paresthesia, with a usual night exacerbation and aggravation by activity along the distribution of the median nerve (65-67).
- Lateral femoral cutaneous syndrome: Meralgia paresthetica is a rarely encountered sensory mononeuropathy characterized by paresthesia, pain or sensory impairment along the distribution of the lateral femoral cutaneous nerve (LFCN) caused by entrapment or compression of the nerve as it crosses the anterior superior iliac spine and runs beneath the inguinal ligament. Ultrasound-guided blockade of the LFCN is a safe and success technique to treat this condition (68, 69).
- Isolated femoral neuropathy: This neuropathy occurs due to direct compression of the femoral nerve, indirect compression by the psoas muscle during pelvic surgery, direct ischemia of the nerve by clamping of the iliac artery during the vascular anastomosis or vessel dissection, or by postoperative hematoma in the retroperitoneum or psoas muscle. Isolated femoral neuropathy causes numbness and paresthesia located in the anteromedial part of the thigh (70).
- Tarsal tunnel syndrome: Paresthesia in the foot is the most frequent symptom of tarsal tunnel syndrome and may have an arterial etiology (71). Kim and Childers suggested ultrasound-guided injection of 0.5% lidocaine to temporarily resolve the paresthesia as a diagnostic modality (72).
- Sciatica: Sciatica is commonly due to a prolapsed intervertebral disc, although spinal canal stenosis, spondylolisthesis, piriformis syndrome, spinal tumours and other causes must be considered. Leg pain, paresthesia and weakness are the most bothersome symptoms in sciatica (73-75).
- Disc herniation: Radicular compression by a disc herniation may lead to the radiating paresthesia into the extremities (76, 77)
- Cervical spondylosis: Hand paresthesia is a frequent and early symptom found in patients either with cervical spondylosis or carpal tunnel syndrome (78). In cervical spondylosis, paresthesia is not commonly nocturnal, aggravated by hand activity, or associated with hand pain, in contrast to carpal tunnel syndrome (67).
- Pressure palsy: Paresthesia may be a presenting complaint in pressure palsy (79). Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal-dominant inherited disease clinically characterized by painless and episodic or recurrent neurological symptoms such as peripheral palsy or paresthesia, often preceded by minor trauma or toxic damage (80, 81). However, the presence of mild symptoms and the marked phenotypic variability of the disease result in underdiagnosis of HNPP (82).
- Charcot-Marie-Tooth disease: Charcot-Marie-Tooth hereditary neuropathy refers to a group of disorders characterized by a chronic motor and sensory polyneuropathy (83). The affected individual typically has distal muscle weakness and atrophy often associated with mild to moderate sensory loss, depressed tendon reflexes, high-arched feet, severe cramps and painful paresthesia (83, 84)

- Amyloid neuropathy: In 1975, Kyle and Bayrd investigated 236 cases of amyloidosis and reported that paresthesia was one of the most common presenting symptoms besides fatigue, light-headedness and weight loss (85). Paresthesia may have a glove and stocking or even thoraco-abdominal distribution (86).
- Repetitive motion or prolonged vibration: Nerve compression in repetitive motion disorders is being recognized with increasing frequency. The pathophysiology of chronic nerve compression spans a broad spectrum beginning with subperineurial edema and progressing to axonal degeneration. The changes seen depend on the amount and duration of the compressive forces and lead to pain, tingling, numbness and paresthesia (87).
- Neuralgia: Neuralgia is a painful sensation in one or multiple nerve distribution which can be mild or severe, and acute or chronic. Many patients with neuropathic pain exhibit persistent or paroxysmal pain and paresthesias that are independent of any stimulus (88).
- Removal of impacted mandibular third molars (M3s): Extraction of impacted M3s may cause temporary or permanent neurosensorial disturbances of the inferior alveolar and lingual nerves (89, 90).
- Circulatory disorders (As mentioned before, insufficient blood supply could lead to transient or chronic paresthesia).
- Thoracic outlet syndrome (TOS)
  - Arterial TOS. The symptoms of Arterial TOS include digital ischemia, claudication, pallor, coldness, paresthesia and pain in the hand but seldom in the shoulder or neck. These symptoms are the result of arterial emboli arising either from mural thrombus in a subclavian artery aneurysm or from a thrombus forming just distal to a focus of subclavian artery stenosis.
  - Venous TOS. Paresthesia in the fingers and hands is common in venous TOS and may be secondary to swelling in the hand rather than to nerve compression in the thoracic outlet area.
  - Neurogenic TOS. Pain, paresthesia, and weakness in the hand, arm, and shoulder, plus neck pain and occipital headaches are the classical symptoms of Neurogenic TOS. Raynaud's phenomenon, hand coldness and color changes is also frequently seen in NTOS. It is the latter symptoms that can lead to an erroneous diagnosis of Arterial TOS (91).
- Metabolic disorders
  - Diabetes: The most common causes of paresthesia in the United States are diabetes and alcoholism (22). Sensory nerve dysfunction is a progressive form of diabetic neuropathy, and is often accompanied by other microvascular complications. This complication is more common in middle aged and elderly men with type 2 diabetes mellitus (92).
  - Alcoholism: The most common complication of chronic alcohol intake is a toxic polyneuropathy. Nutritional deficiency as well as the direct neurotoxic effects of ethanol or its metabolites can cause alcoholic neuropathy (93). This neuropathy is manifested by distal sensory disturbances with pain and paresthesia in a glove and stocking pattern (94).
  - Hypoglycemia: Specific symptoms and signs may vary by age, the severity of the hypoglycemia and the speed of the decline in blood sugar. Paresthesia may be a

neuroglycopenic or adrenergic manifestations of hypoglycemia. Recurrent hypoglycemia which is commonly seen in patients with an insulinoma causes periodic weakness, vertigo and perioral paresthesia (95).

- Hypothyroidism: Paresthesia is a more frequent clinical manifestation observed in hypothyroidism (96, 97). About 40% of hypothyroid patients have predominantly sensory signs of a sensorimotor axonal neuropathy early in the course of thyroid disease. It appears that the axonal myelin sheath begins to degenerate without sufficient thyroid hormone, and regeneration of damaged nerves also slows (98).
- Hypoparathyroidism: Hypoparathyroidism is the most common cause of hypocalcemia. Acute hypocalcemia causes increased neuromuscular irritability which in milder forms lead to paresthesia and numbness of acral and perioral areas (99, 100).
- Hyperaldosteronism: Most clinical effects of hyperaldosteronism result from hypokalemia, which increases neuromuscular irritability and produces weakness, paralysis, and paresthesia (101).
- Menopause: One of the most common reported somatic symptoms is paresthesia in the extremities (102). Decreasing estrogen production causes decreased structural effectiveness of collagen and thinning of the skin. This leads to reduced blood flow to the superficial nerves and symptoms of numbness and tingling (103).
- Abnormal blood levels of calcium, potassium or sodium (*See Hyperventilation syndrome in Causes of transient paresthesia*)
- Uremia: Polyneuropathy is one of the most frequent manifestations in chronic uremia. Hemodialyzed uremic patients have been found to have vitamin B<sub>6</sub> deficiency which may lead to paresthesia (104). Uremia can also cause restless legs syndrome which is clinically defined as an urge to move the legs with or without associated paresthesia (105).
- Porphyria: The most common symptoms of porphyria are abdominal pain, peripheral polyneuropathy, flaccid paresis, with or without autonomic involvement (106). Nerve biopsy shows segmental demyelination and axonal degeneration and also many small vacuolations are seen in the cell body of affected nerves (107).
- Amyloidosis (*See Amyloid neuropathy in Peripheral nervous system etiologies*)
- Infections and post-infection syndromes
  - Herpes simplex virus: Herpetic infection causes paresthesia. Immunohistochemical studies suggest that sensory ganglion infection occurs via centripetal axonal migration of the virus (108). Topical caffeine can inhibit this paresthesia through direct action on sensory neurons (109).
  - Herpes zoster virus: Primary infection by varicella-zoster virus (VZV) may be associated with several neurologic complications such as paresthesia (110, 111). VZV remains dormant in dorsal root and cranial nerve ganglia and can be reactivated as a consequence of declining VZV-specific cellular immunity leading to herpes zoster (shingles) (112). Following reactivation, centrifugal migration of herpes zoster virus occurs along sensory nerves to produce a characteristic painful cutaneous or mucocutaneous vesicular eruption that is generally limited to the affected dermatome (113). The commonest prodromes are pain, itching and paresthesia (114-116)



- Canker sores: Canker sores or aphthous ulcers are painful and round white sores with a red border that occur inside the mouth. There is a tingling or burning sensation prior to the appearance of the sores. They are associated with various nutritional and immunological deficiencies. However, they are more common in individuals with acute HIV infection (117, 118).
- Lyme disease: Lyme disease, caused by the tick-borne spirochete *Borrelia burgdorferi*, is associated with a wide variety of neurologic manifestations. Neuropathic symptoms such as symmetric, distal and nonpainful paresthesia, and asymmetric radicular pain begin 8 months after erythema migrans occurs and are present for up to 12 months (119, 120)
- Human Immunodeficiency Virus type-1 (HIV-1): Peripheral neuropathies commonly complicate all stages of the HIV-1 disease. Whereas symptomatic neuropathies occur in approximately 10% to 15% of HIV-1-infected patients overall, pathologic evidence of peripheral nerve involvement is present in virtually all end-stage AIDS patients. The dominant clinical features in distal sensory polyneuropathy which is the most common among the HIV-1-associated neuropathies include distal pain, paresthesia and numbness in a typical length-dependent fashion with a proximal to distal gradient (121, 122).
- Leprosy: Leprosy is a slowly progressive, chronic infectious disease caused by the bacillus *Mycobacterium leprae*. The skin and peripheral nerves are the most commonly affected organs (123). Predominant presenting symptoms are paresthesia, pain and sensory/motor deficit (124).
- Syphilis: Neurosyphilis may cause paresthesia (125, 126). Paresthesia can be due to spinal myelitis caused by neurosyphilis (127).
- Guillain-Barré syndrome (GBS): GBS is an acute, symmetrical polyneuropathy with distinctive features. The early clinical course involves painful paresthesia that is usually followed by proximal motor weakness (128). Some infectious pathogens may play a role in the pathogenesis of GBS (129).
- Rabies: Rabies, which is an acute, progressive, fatal zoonotic infectious disease, is almost always caused by the bite of rabid animals (130, 131). The rabies virus travels to the brain by following the peripheral nerves. Once the rabies virus reaches the central nervous system and symptoms begin to show, the infection is effectively untreatable and usually fatal within days. Early-stage symptoms of rabies are malaise, headache and fever, progressing to acute pain, paresthesia, violent movements and hydrophobia (132).
- Autoimmune diseases
  - Rheumatoid arthritis: Dry mouth, pruritus and paresthesia are frequent complaints in patients with rheumatoid arthritis (133). Rheumatoid cervical myelopathy causes paresthesia in the arms and neck pain (134).
  - Systemic lupus erythematosus (*See Systemic lupus erythematosus in Central nervous system etiologies*)
  - Sjogren's syndrome: Peripheral neuropathy occurs in Sjogren's syndrome. The history often reveals complaints of burning, tingling paresthesias in a symmetrical stocking or glove distribution or in the face (Trigeminal Nerve) area (135-137).
  - Pernicious anemia (*See Vitamin B<sub>12</sub> deficiency in Central nervous system etiologies*)
  - Diabetes (*See Diabetes in Methabolic disorders*)

- Arthritis: The involvement of the cervical spine is the most serious skeletal manifestation of rheumatoid arthritis. In patients with basilar impression and/or rheumatoid cervical myelopathy, paresthesia in the upper limbs was significantly more common (134, 138). Paresthesia can occur in psoriatic arthritis (139).
- Fibromyalgia: Fibromyalgia is a frequent disorder of the middle aged, particularly in women characterized by chronic, diffuse musculoskeletal pain and by a low pain threshold at specific anatomical points (tender points) (140). Cacace et al. found that paresthesia had the highest frequency among associated clinical distress in fibromyalgia (141).
- Nutrient deficiency
  - Vitamin B<sub>1</sub>: Thiamine (vitamin B<sub>1</sub>) deficiency leads to Beri-Beri which takes two forms. Dry beri-beri has symptoms of peripheral neuropathy with ataxia, weakness, paresthesia, and patchy sensory loss with areflexia (142).
  - Vitamin B<sub>5</sub>: It seems that pantothenic acid (vitamin B<sub>5</sub>) can cause sensory polyneuropathy (143).
  - Vitamin B<sub>6</sub>: The symptoms related to pyridoxine (vitamin B<sub>6</sub>) deficiency are peripheral neuropathies, such as paresthesia and burning dysesthesias (104).
  - Vitamin B<sub>12</sub> (See Vitamin B<sub>12</sub> deficiency in Central nervous system etiologies)
    - Malignancies: Local paresthesia can be caused by a malignancy which puts pressure on adjacent nerves. For example a reported osteosarcoma in the left segment of the maxilla led to swelling and paresthesia in the left cheek (144), and periorbital paresthesia is usually a sign of malignancy (145). Multiple myeloma with extraosseous lesions may result in paresthesia of soft tissue (146). On the other hand the association between polyneuropathy and multiple myeloma as the result of various clinical variants should be considered (147). POEMS syndrome which is identified as Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy and Skin changes, presents with abdominal distension, progressive paresthesia and motor weakness of both lower extremities (148).
    - Skin disorders
      - Burns: Studies of patients recovering from significant burns show that abnormal sensations such as paresthesia are frequently reported as long as several years after the injury (149, 150). Furthermore long-term paresthesia is a complication reported after electrical burns (151, 152).
      - Frostbite: Frostbite injuries occur mainly in the toes, fingers, ears, nose and cheek. Typically an initial vasoconstriction in the skin will protect against drop in core temperature. Ice crystal development occurs when tissue temperature drops to -2° C, leading to increased osmolality of the extracellular fluid and intracellular dehydration. White-cyanotic discoloration, pain and paresthesia followed by hypoesthesia are the symptoms of frostbite injury (153).
      - Ito syndrome: Hypomelanosis of Ito is a rare neurocutaneous disorder. It is characterized by depigmented skin areas often associated with ocular, musculoskeletal and neurological abnormalities (154).
      - Pink disease: Acrodynia (pink disease) occurs in children exposed to mercury for prolonged periods (155). Affected patients are initially listless, anorexic, and

irritable. Their blood pressure and heart rate increase. Significant pain occurs in the hands and feet preventing sleep. Finally the hands and feet will swell and become paresthetic, becoming a dusky pink color along with a similar process which occurs in the nose (156).

- Acroparesthesia: Postmenopausal women may experience acroparesthesia. Hormone therapy can increase forearm/hand blood flow, and help ameliorate these symptoms (157).
  - Migraine: The somatosensory aura of a migraine may consist of digitolingual or cheiro-oral paresthesias. The paresthesia may migrate up the arm and then extend to involve the face, lips and tongue (158).
  - Psychological disorders: Anxiety, panic attack and psychiatric diseases may cause hyperventilation which can lead to paresthesia (6). Paresthesia also can be a manifestation of depression (159).
  - Medications: Paresthesia can be a side effect of some medications such as anti-convulsant drugs, topiramate, amiodarone, digoxin, dimercaprol, colistimethate, mefloquine, metronidazole, HIV medications, riluzole, tetrodotoxin, thallium, vincristine, diphenoxylate, overdose of lidocain or vitamin B<sub>6</sub> (1). Sertraline can induce facial paresthesia (160). SSRI withdrawal may cause paresthesia. The neurotoxicity of immuno-suppressive agents (e.g. calcineurin-inhibitors) may cause mild symptoms, such as tremors and paresthesia (161). Motexafin lutetium which is used in the treatment of coronary atherosclerosis or vulnerable plaque can cause the paresthesia (23).
  - Toxins
    - Alcohol (See Alcoholism in Metabolic disorders)
    - Tobacco: Smoking is a strong risk factor for arteriosclerosis and Buerger's disease which can cause sensitive axonal polyneuropathy (15, 162).
    - Drug abuse: Intravenous administrating of strong pharmaceutical drugs acting on the central nervous system, mainly opioids especially in non-medical use (drug abuse) can lead to neurological manifestations such as paresthesia (1).
    - Heavy metals
      - Mercury: toxicity from organic mercurials includes neurologic decompensation with mental deterioration, ataxia, spasms, paresthesia, deafness, and eventually coma (156).
      - Arsenic: Neurological and neurophysiological studies indicate that the functions of the central and peripheral nervous system may be impaired under conditions of exposure to arsenic (163).
      - Lead: The prominent findings among the lead-exposed workers are fatigue, abdominal discomfort, backache, myalgia and paresthesia (164).
  - Nitrous oxide: Exposure to nitrous oxide may damage the nervous system which can lead to ascending paresthesia of the limbs, severe ataxia of gait, tactile sensory loss on the limbs and trunk, and absent tendon reflexes (165, 166).
  - Carbon monoxide: Paresthesia, emesis, diarrhea, unilateral headache, palpitation or death are non-specific but common symptoms of carbon monoxide poisoning (167).
  - Snake bites: Some venom contains toxins which attack the nervous system, causing neurotoxicity. The victim may present with strange disturbances to their vision, paresthesia, difficulty speaking and respiratory paralysis (168).

- Ciguatera: Ciguatera is the most frequently observed form of tropical fish poisoning. It blocks the sodium channel leading to slowed nerve conduction and causes the peripheral and central nervous system symptoms such as facial paresthesia, myalgia, cramps and weakness. Ciguatera poisoning leads to the gastrointestinal and cardiovascular disturbances too (169, 170).
  - Radiation exposure: Chronic progressive radiation myelopathy develops with a latency of several months to years after spinal cord irradiation. The symptoms are paresthesia, paresis or paralysis, leading to severe physical disability (171).
  - Chemotherapy: Intrathecal injections of cytarabine and methotrexate can lead to paresthesias and weakness causing patient to be wheelchair bound (172).
  - Hereditary diseases
- Fabry disease: Fabry syndrome is a genetic disease related to changes on the X chromosome. It is caused by deficient activity of alpha-galactosidase A and is characterized by intralysosomal storage of glycosphingolipids. The main clinical features are paresthesia, hypohidrosis, angiokeratoma, renal insufficiency, and cardiovascular or cerebral complications (173, 174).
- Refsum syndrome: Refsum's disease is an autosomal recessive disorder with clinical features that include retinitis pigmentosa, blindness, anosmia, deafness, sensory neuropathy, ataxia and accumulation of phytanic acid in plasma- and lipid-containing tissues (175).
- Charcot-Marie-Tooth disease (*See Charcot-Marie-Tooth disease in Peripheral nervous system etiologies*)
- Porphyria (*See Porphyria in Metabolic disorders*)
- Ataxia-teleangiectasia: Ataxia-telangiectasia is a progressive neurodegenerative disorder, with onset in early childhood. It is an autosomal recessive disorder that includes progressive cerebellar ataxia, dysarthric speech, oculomotor apraxia, choreoathetosis and, later, oculocutaneous telangiectasia (176, 177).
  - Immune deficiency: The immune response dysfunction induced by the human immunodeficiency virus infection sometimes causes inflammatory lesions of the central and peripheral nervous system leading to neurological symptoms such as paresthesia (178).

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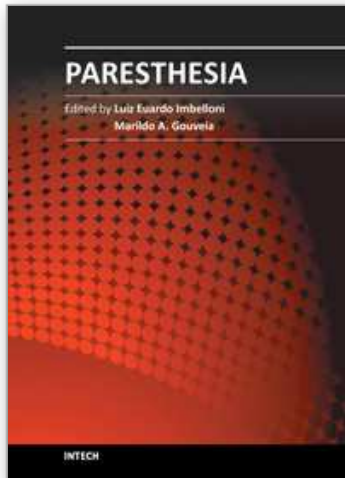
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## **Paresthesia**

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Paresthesias are spontaneous or evoked abnormal sensations of tingling, burning, pricking, or numbness of a person's skin with no apparent long-term physical effect. Patients generally describe a lancinating or burning pain, often associated with allodynia and hyperalgesia. The manifestation of paresthesia can be transient or chronic. Transient paresthesia can be a symptom of hyperventilation syndrome or a panic attack, and chronic paresthesia can be a result of poor circulation, nerve irritation, neuropathy, or many other conditions and causes. This book is written by authors that are respected in their countries as well as worldwide. Each chapter is written so that everyone can understand, treat and improve the lives of each patient.

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