Secondary Orofacial Pain and Headache: Systemic Diseases, Tumors, and Trauma

This chapter presents an overview of systemic diseases that may induce orofacial pain or headache. As clinicians, it is important to identify pain that may be secondary to systemic and remote disease processes and therefore amenable to therapy of the primary condition. These conditions include not only common entities such as hypertension but also rare causes such as dialysis-induced headaches. The mechanisms involved in the pathogenesis of systemically induced pain are highly variable but may include inflammatory (see chapter 15) and neuropathic processes (see chapters 2 and 12). Neuronal injury may be caused by ischemia, demyelination, dysmyelination, or metabolic processes.

Orofacial Pain in Metabolic and Endocrine Disorders

Clinicians must be aware of the possibility that certain systemic metabolic disorders may cause facial pain, and this pain may even be the initial presentation of the disorder. Because the metabolic condition is systemic, the effects usually appear in multiple sites. The more common pain-inducing metabolic disorders that clinicians should note are diabetes, alcoholism, and nutritional neuropathies. The common hallmark of these disorders is involvement of peripheral nerves by alteration of the structure or function of myelin and axons due to metabolic pathway dysregulation. However, the exact mechanism by which a systemic condition can induce pain is still controversial (see also chapter 12). In most of these conditions, the pain associated with these metabolic polyneuropathies is customarily found in the extremities and not in the orofacial structures. However, even though pain in the facial region is rare, clinicians must appreciate the possibility that such neuropathies exist.
in order to direct therapy to the actual source of the condition.

**Diabetic neuropathy**

Demyelination of peripheral nerves associated with diabetes may lead to neuropathic changes in the motor, autonomic, and sensory nervous systems. Up to 48% of persons with diabetes suffer from neuropathy. The incidence of crani-al nerve involvement ranges from 3% to 14%, and most of these are motor neuropathies.

Diabetic polyneuropathy is multifactorial in etiology. Results from the Diabetes Control and Complications Trial demonstrated that hyperglycemia and insulin deficiency contribute to the development of diabetic neuropathy and that glycemic control lowers the risk of neuropathy by 60% over 5 years. Researchers hypothesize that decreased bioavailability of systemic insulin in diabetes may contribute to more severe axonal atrophy or loss. Additionally, hyperglycemia may cause microvasculitis, which may lead to an ischemic injury and result in demyelination and axonal dystrophy. Elevated endoneurial glucose, fructose, and sorbitol levels in diabetes are associated with neuronal degeneration and the severity of neuropathy.

Involvement of the third, fourth, sixth, and seventh cranial nerves in diabetic neuropathies have been well documented. The trigeminal (fifth cranial) nerve rarely appears to be involved in diabetes, although there are case reports. In a case-control study involving 29 patients with type 2 diabetes, orofacial pain was reported by 55.2%, and 17.2% of patients had burning mouth syndrome. The authors observed a somatosensory impairment of the right maxillary branch of the trigeminal nerve, which suggests an asymmetric pattern, such as in distal body areas typical of this disease. Sensory loss at the trigeminal area was also observed based on poor control of glycemia and glycated hemoglobin. Patients with diabetic neuropathy often complain of a sharp, shooting pain in the mandible and tongue with occasional involvement of the mucosa. Additionally, it has been found that peripheral polyneuropathies often cause subclinical damage to the trigeminal nerve (thus leading to an underreporting of such events). The mandibular branch is often affected, and patients complain of unilateral fa-cial paresthesia or hypoesthesia in the mental nerve distribution, mandibular pain, and abnormal motor responses in facial or masticatory muscles. The cramped anatomical route of nerves in the mandibular canal or below the internal pterygoid muscle and fascia may expose them to an increased risk of damage. Primary treatment should be directed at the underlying metabolic condition. Symptoms of polyneuropathy may be treated with an approach similar to that of other neuropathic pain (see chapters 12 and 16).

**Alcohol and nutritional neuropathy**

Alcoholism, or addiction to alcohol, is a worldwide problem with enormous medical, social, and economic costs to the affected person and to society. People who engage in chronic alcohol consumption are at risk for a number of serious medical complications, including neurologic disorders. Alcoholic polyneuropathy can be purely motor or purely sensory in its effects, although the most common clinical presentation is mixed. Persons with alcoholism frequently suffer from entrapment or pressure neuropathies, especially in the ulnar and peroneal nerves. Paresthesias, pain, and weakness are common, mainly in the extremities. Several reports appear in the literature that describe patients with alcoholism who have hearing loss, balance disturbances, and facial weakness related to degeneration of the eighth cranial nerve. Distal muscle weakness and atrophy are also common findings in the extremities but have not been reported from the orofacial region.

The pathogenesis of alcoholic polyneuropathy is not fully understood. Some believe that most associated medical disorders may be due to ethanol neurotoxicity. Other reports suggest that malnutrition is the cause of most alcohol-related neurologic disorders; patients with alcoholism often obtain as much as 50% of their calories from ethanol, which allows serious nutritional deficiencies to develop, particularly for protein, thiamine, folate, and niacin. Another possibility may be that alcohol consumption has direct negative effects on the gastrointestinal mucosa and pancreas that result in malabsorption of essential nutrients. Neuropathy is characterized by axonal degen-
eration and demyelination, and evidence suggest that ethanol has a direct neurotoxic effect on the peripheral nerves.17

**Hypothyroidism**

Hypofunction of the thyroid gland is one of the most common endocrine disorders in older women and may be associated with headaches. Of 102 adult patients with hypothyroidism, 30% reported headaches 1 to 2 months after initial symptoms of hypothyroidism.18 Headaches are usually bilateral, mild, nonpulsatile, and continuous, and there is a female preponderance and an association with a history of migraine in childhood. The headache is not associated with nausea or vomiting.19 The condition has a good response to abortive salicylates, and administration of thyroid hormone usually leads to headache resolution. The pathophysiology of hypothyroidism-related headache may be due to an underlying metabolic or vascular process.18

**Orofacial Pain in Joint Disorders**

Polyarthritides are a group of disorders in which the articular surfaces become inflamed and that sometimes involve the temporomandibular joint (TMJ). The signs and symptoms in polyarthritides may be similar to those found in degenerative joint disease (osteoarthritis); however, the causative factors are different (see chapter 9). The polyarthritides include rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, infectious arthritis, hyperuricemia, traumatic arthritis, Reiter syndrome, and neck-tongue syndrome. Differentiating among these various conditions is important as treatment modalities differ. As a general rule, systemic polyarthritides rarely involve the TMJ.

**Rheumatoid arthritis**

Rheumatoid arthritis is a systemic, chronic, inflammatory disease of unknown etiology. Factors associated with rheumatoid arthritis include the possibility of infectious triggers, genetic predisposition, and autoimmune response in that CD4+ T cells stimulate the immune cascade, which leads to cytokine production such as tumor necrosis factor-α and interleukin-1.20,21 The disease affects the articular surfaces, including the synovial tissues, capsule, tendons, and ligaments. The inflammatory process leads to the secondary destruction of the articular cartilage and subchondral bone.22 Rheumatoid arthritis has an insidious onset with periods of exacerbation and remission.

The prevalence in Western populations is 0.5% to 1%, and the female-male ratio is approximately 3:1.23 The disease can occur at any age, though onset is usually between the ages of 25 and 50 years, and the incidence peaks in the fourth and fifth decades of life. Characteristically, rheumatoid arthritis affects small peripheral joints, such as those in the hands, wrists, and feet. Joint involvement in rheumatoid arthritis tends to be symmetric and more generalized in its clinical presentation compared with degenerative joint disease.24 The prevalence of TMJ involvement in patients with rheumatic disease varies greatly, depending on the diagnostic criteria, the population studied, and the measures of assessment. Clinical involvement of the TMJ is present in approximately 50% of patients with rheumatoid arthritis and seems to correlate with disease duration and severity.25 The most common clinical signs and symptoms in the orofacial region are bilateral, deep, dull, aching pain (exacerbated during function); tenderness and swelling in the preauricular regions; limitation of mandibular range of movement; stiffness in the TMJ upon awakening; intracapsular joint sounds (crepitus/clicking); and tenderness of the masticatory muscles.22,24,26 As the disease progresses, limitation in opening may be worsened because of fibrous or bony ankylosis.27,28 If greater destruction of the condyles occurs, the patient may develop a progressive Class II malocclusion with heavy posterior occlusal contacts and an anterior open bite caused by loss of ramus height.24,29

Approximately 50% to 80% of patients with rheumatoid arthritis have radiographic evidence of TMJ abnormalities.30 The radiographic findings of the TMJ, although not evident in the early stages of the disease process, become more apparent with disease progression. Use of magnetic resonance imaging (MRI) and computed tomography reveal joint effusions, disc
displacements, and condylar abnormalities, including erosions, flattening, sclerosis, subchondral cysts, and osteophytes.\textsuperscript{31,32}

Symptomatic TMJs in patients with rheumatoid arthritis demonstrate a high frequency of synovial inflammation and connective tissue degeneration, similar to what is seen in patients with osteoarthritis but different from matched control subjects. Additionally, pronounced inflammatory and degenerative changes develop faster in rheumatoid arthritis than osteoarthritis.\textsuperscript{33}

A pediatric form termed \textit{juvenile rheumatoid arthritis} (the term commonly used in the United States), \textit{juvenile idiopathic arthritis} (the term used mainly in pediatric rheumatology), or \textit{juvenile chronic arthritis} occurs in patients under the age of 16 years. Prevalence estimates in the United States range from 0.2 to 0.5 cases per 1,000 children, and there is a predominance in females (female-male ratio of 2–3:1).\textsuperscript{34}

Juvenile rheumatoid arthritis is characterized by two peaks of onset, one between the ages of 1 and 3 years and the other between the ages of 8 and 12 years.\textsuperscript{35} The prevalence of TMJ involvement in patients with juvenile rheumatoid arthritis is variable because different methods are used in assessment,\textsuperscript{36} and when present, it may lead to adverse effects on occlusion and facial growth.\textsuperscript{37} Juvenile rheumatoid arthritis is subclassified into three categories: polyarticular (ie, multiple joints affected), pauciarticular or oligoarticular (ie, fewer than our joints affected), and systemic, which features high fever, rash, and multiple organ involvement.\textsuperscript{35} The International League of Associations for Rheumatology has a more extensive classification system (seven subtypes with specific exclusion and inclusion criteria) for juvenile idiopathic arthritis.\textsuperscript{38} Although the TMJ may be involved in any of these categories, it is most often affected by the polyarticular form.\textsuperscript{39} The clinical and radiographic features are similar to those observed in the adult form of the disease. A characteristic feature of advanced juvenile rheumatoid arthritis is a significant reduction in the dimensions of the lower third of the face caused by a combination of micrognathia and a Class II skeletal distortion termed \textit{birdface deformity}. This is the result of destruction of the condylar growth site by the disease process.\textsuperscript{40,41}

### Psoriatic arthritis

Psoriatic arthritis is an inflammatory condition associated with psoriasis, which is a chronic, often pruritic dermatologic disease with a genetic component that affects 1% to 2% of the population. Associated arthritis affects approximately 6% of this population, making this a relatively uncommon condition.\textsuperscript{42} Indeed, fewer than 40 cases of psoriatic arthritis affecting the TMJ have been reported.\textsuperscript{43,44} However, clinical and radiographic findings associated with temporomandibular disorders (TMDs) in patients with generalized psoriatic arthritis seem to be more common than these case reports suggest.\textsuperscript{45}

Psoriatic arthritis of the TMJ is often unilateral, of sudden onset, and episodic. Patients commonly complain of tenderness and pain in the preauricular region and the muscles of mastication, morning stiffness, fatigue, and tiredness in the jaws. Signs include joint crepitation, painful mandibular function, and a progressive decrease in interincisal opening.\textsuperscript{44,46} Ankylosis of the joint has been reported in severe cases.\textsuperscript{37,48} Spontaneous remission has also been reported.

Radiographic changes of the TMJs associated with psoriatic arthritis are quite common and include the following nonspecific findings: erosion, flattening, osteoporosis, limited range of motion, joint space narrowing, subchondral cysts, and ankylosis.\textsuperscript{32}

### Ankylosing spondylitis

Ankylosing spondylitis (Bechterew’s disease), a chronic inflammatory disease of unknown etiology, is usually progressive and most often affects the sacroiliac joints and vertebral column. The main locus of pathology is the site where the ligaments and capsule insert into the bone and not the synovium.\textsuperscript{49} This condition affects 1% to 2% of the white population and has a male-female prevalence ratio ranging from 6:1\textsuperscript{50} to 2:1.\textsuperscript{52} The affected male population demonstrates more involved joints and increased disease severity than the female population. Onset of the disease is usually between the ages of 16 and 40 years.\textsuperscript{50} The prevalence of TMJ involvement is quite rare and ranges from 4% to 35%, depending
on the diagnostic criteria used, the population studied, and the methods used to assess TMJ involvement. The clinical findings are similar to those of other arthritic conditions and include tenderness and/or pain in the masticatory muscles and TMJ, morning stiffness, fatigue in the jaws, limitation in mouth opening, and joint sounds. Common radiographic signs consist of condylar erosions, flattening and sclerosis, flattening of the temporal bone, and joint space narrowing.

### Infectious arthritis

Infectious (septic) arthritis of the TMJ is a rare disease and is not frequently documented in the literature. The condition is an inflammatory reaction of the articular surfaces that results from bacterial invasion caused by a penetrating external injury and that spreads infection from adjacent structures (dental, parotid gland, or otic origins) or from bacteremia associated with systemic infection, such as tuberculosis, syphilis, and gonorrhea. The most common bacteria involved with infectious arthritis are *Staphylococcus aureus*, *Neisseria gonorrhoeae*, and *Haemophilus influenzae*. Risk factors include diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis, other immunosuppressive diseases, or previous joint disease. Patients often complain of limited and painful mouth opening with a warm, erythematous preauricular swelling. Mandibular deviation at rest to the contralateral side is due to joint effusion and is often associated with a malocclusion. Radiographically, the TMJ may appear clinically normal; however, with disease progression, there may be signs of erosion of the articular surfaces and bone destruction. Bone scanning using technetium-99 phosphate has been used to detect physiologic bone changes earlier than radiographic anatomical changes; specificity is low but sensitivity is high, so a negative result strongly argues against an infectious arthritis. If uncertain, white blood cell counts may provide helpful data on the presence or absence of infection. TMJ fibrosis and ankylosis resulting in impaired joint mobility and function are potential complications that usually occur in the later stages of the disease process.

### Hyperuricemia

Hyperuricemia (gout) comprises a heterogeneous group of arthritic disorders characterized by the deposition or concentration of monosodium urate monohydrate crystals in joints and tendons (crystal arthritis). The metatarsophalangeal joint (big toe) is involved in 90% of patients. Gout progresses through four clinical phases: asymptomatic hyperuricemia, acute gouty arthritis, intercritical gout (intervals between acute attacks), and chronic tophaceous gout characterized by radiographically evident chalky deposits of sodium urate. Pseudogout, another form of crystal arthritis, is due to the deposition of calcium pyrophosphate dihydrate crystals. Cases of pseudogout have been reported to affect the TMJ. Gout is rare and affects at least 1% of the population in Western countries; peak incidence occurs in men 30 to 50 years old.

Uric acid is the end product of purine metabolism and has no physiologic role. Humans genetically lack the enzyme uricase, which allows for the degradation of uric acid to the water-soluble and easily excreted product known as allantoin, thereby preventing uric acid accumulation. Elevated serum levels are a result of an overproduction and/or an underexcretion of uric acid. These mechanisms predispose a person to develop microcrystals that may precipitate in the synovium. Additionally, it may be caused by hematologic disorders or by the use of certain medications.

Although the prevalence of gout has been increasing during the past two decades, involvement of the TMJ is very rare, and there are only 10 reports in the English-language literature. If the TMJ is involved, the disease is usually confined to the joint space, which leads to pain and limitation of mouth opening. However, a case where the disease process extended beyond the joint capsule into the pterygoid muscle with concomitant destruction of the head of the condyle, the temporal bone, and the greater wing of the sphenoid bone has been described.

### Reiter syndrome

Reiter syndrome, also known as reactive arthritis, was described in 1916 by Hans Reiter...
as a triad of arthritis, nongonococcal urethritis, and conjunctivitis, occurring concurrently or sequentially. More recently, Reiter syndrome has also been defined as a peripheral arthritis lasting longer than 1 month that is associated with urethritis, cervicitis, or diarrhea; additional features include mucocutaneous lesions, cardiac involvement, and central or peripheral nerve involvement. Reactive arthritis refers to an acute nonpurulent (aseptic) arthritis initiated by a remote infection. Reiter syndrome is triggered by enteric or urogenital (venereal) infections. The bacteria implicated in the enteric form include Shigella, Salmonella, and Yersinia spp, whereas Chlamydia, Mycoplasma, and Yersinia spp are associated with the urogenital type. Reiter syndrome is associated with human leukocyte antigen (HLA)-B27, although HLA-B27 is not always present in an affected person, particularly in the presence of HIV. The arthritis involved with this syndrome is usually in multiple joints, though the lower extremities are affected most often. The syndrome occurs mostly in men between the ages of 20 and 30 years.

Signs and symptoms of muscle and joint dysfunction in 52 men with Reiter syndrome were more frequent and severe than those in 52 matched control subjects with no general joint disease. One-quarter of the Reiter syndrome group reported TMJ signs or symptoms, and the most characteristic were pain on function, tenderness to palpation, and pain when opening wide (15% of subjects). Tenderness to palpation of the masticatory muscles (19%) and stiffness/tiredness of the jaws in the morning were also reported.

Patients with Reiter syndrome more frequently display radiographic findings in the condyle (33%), and the most common finding is unilateral erosion (12%).

Neck-tongue syndrome

Neck-tongue syndrome consists of the appearance of occipital or upper neck pain associated with an abnormal sensation on the ipsilateral side of the tongue. Pain is initiated by head rotation, usually to one side, and lasts some minutes. Pain is usually sharp and radiates to the occipital, cervical, and lingual regions. In the tongue, paresthesia, dysesthesia, or anesthesia may be reported, lasting from a few seconds to about 2 minutes. This may or may not be preceded by tongue pain. Patients may describe radicular symptoms and display restricted neck movements. Although considered extremely rare, about 59 cases have been reported in the literature and a prevalence of 0.22% has been estimated.

Excessive range of movement of the atlantoaxial joint with impaction and stretching of the second cervical root (C2) is thought to underlie neck-tongue syndrome. This in turn compresses proprioceptive fibers from the tongue that pass from the ansahypoglossi to the C2 ventral ramus. Surgical findings confirm C2 nerve compression by the atlantoaxial joint.

Spinal immobilization (soft collar), atlantoaxial fusion, or resection of the C2 spinal nerve may be needed; in uncomplicated cases, spinal manipulation may help.

Orofacial Pain in Bone Disorders

Osteoporosis is the most common bone disease in humans and affects both men and women. Osteoporosis may be diagnosed after a low-impact or fragility fracture. Low bone mineral density is best assessed by central dual-energy x-ray absorptiometry. Both nonpharmacologic therapy (calcium and vitamin D supplementation, weight-bearing exercise, and fall prevention) and pharmacologic treatments (antiresorptive and anabolic agents) may be helpful in the prevention and treatment of osteoporosis.

The literature suggests that osteoporosis is linked to TMDs and atypical facial pain, and female hormones are implicated as a common risk factor. This is based on the strong female prevalence in atypical facial pain and the physiologic and therapeutic modification of estrogen levels in patients with these pain conditions as well as in patients with osteoporosis. The connection remains speculative (see also chapter 12).

Paget’s disease of bone is characterized by bone resorption in focal areas followed by ex-
cessive new bone formation, with eventual replacement of the normal bone marrow by vascular and fibrous tissue. The etiology of Paget’s disease is not well understood; however, one gene linked to Paget’s disease and several other susceptibility loci have been identified, and paramyxoviral gene products have been detected in Pagetic osteoclasts. Because of the excessive bone formation in the craniofacial complex, neurologic deficits are common and include sensory changes in hearing, sight, and smell. Comparison of oral status between patients with Paget’s disease and healthy control subjects demonstrated that those with Paget’s disease were more likely to report pain when opening the mouth.

Orofacial Pain in Immunologically Mediated Diseases

Immunologically mediated diseases are those with a prominent involvement of immunocytes and/or their products. In this section the presentation of orofacial pain in autoimmune diseases, allergy, and granulomatous and immune complex diseases is reviewed.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease involving multiple organ systems. Characteristically, there is a state of immune hyperactivity and antibodies directed against cell nuclei. Autoantibodies, circulating immune complexes, and T lymphocytes all contribute to the expression of disease. Multi-system involvement appears as dermatologic, renal, central and peripheral nervous system, hematologic, musculoskeletal, cardiovascular, pulmonary, vascular endothelium, and gastrointestinal manifestations. Ninety percent of those suffering from SLE are women, and most (80%) are in their childbearing years. This led to the hypothesis that women who are exposed to estrogen-containing oral contraceptives or hormone replacement therapy have an increased risk of developing or exacerbating SLE; however, other studies do not support this finding. TMJ involvement has been reported in SLE; one-third of patients had current complaints, and two-thirds had a history of severe symptoms from the TMJ. Objective findings included locking or dislocation, tenderness to palpation, and pain on movement of the mandible in 22% of patients. Additionally, radiographic changes of the condyles, including flattening, erosions, osteophytes, and sclerosis were observed in 30% of patients. These findings were confirmed in a study that reported that 50.0% patients with SLE experienced TMJ pain, 36.4% experienced TMJ sounds, and more than a quarter had difficulty opening their mouth. Trigeminal sensory neuropathy has been associated with SLE, most commonly facial numbness, paresthesia, dysesthesia, and pain; however, other cranial nerves may be involved. Trigeminal neuropathy may be the initial feature of SLE or may follow disease onset, but it usually develops slowly. Oral ulcerations have also been associated with SLE and may induce acute pain.

Intractable headaches, so-called lupus headaches, have long been thought of as a common and characteristic manifestation of SLE. However, a controlled study showed that headache is not specifically related to SLE expression or severity. Accepting the presence of headaches, even severe, as a neurologic manifestation of SLE in the absence of seizures or overt psychosis may result in overestimation of the disease status. This approach was further supported by a recent meta-analysis. Chronic pain in patients with SLE correlates with sleep disturbance, and 55% to 85% of these patients suffer from sleep disturbances or overt psychosis may result in overestimation of the disease status. This approach was further supported by a recent meta-analysis. Researchers suggest that mood disorder, which results in part from chronic pain, is a main contributing factor to sleep disorders in SLE.

Sjögren’s syndrome

Sjögren’s syndrome is a chronic, systemic autoimmune disorder of unknown etiology that affects the exocrine glands and is histologically characterized by a lymphocytic infiltrate of the affected glands. The hallmark manifestations of Sjögren’s syndrome are dryness of the mouth and eyes due to involvement of the salivary and lacrimal glands. In addition,
Sjögren’s syndrome may cause skin, nose, and vaginal dryness and may affect other organs of the body, including the kidneys, blood vessels, lungs, liver, pancreas, and brain. Sjögren’s syndrome affects 1 to 4 million people in the United States, and patients are usually over the age of 40 years at diagnosis. Women are nine times more likely to have the condition than men. Primary Sjögren’s syndrome occurs in people with no other rheumatologic disease. Secondary Sjögren’s syndrome occurs in people who have another rheumatologic disease, most often SLE or rheumatoid arthritis and progressive systemic sclerosis (scleroderma).

The presence of dry mouth increases the risk for mucosal sensitivity and, because of impaired lubrication, often leads to secondary infection, mostly candidiasis.105 Dry mouth also contributes to an increased risk of mucosal trauma, periodontal disease, and dental caries, which may lead to pain.106,107 When interdental salivary flow rate is reduced, the cleansing effect of saliva is minimized, and retrograde infection with acute sialoadenitis may be associated with pain.

Distal, symmetric sensory neuropathy is present in 10% to 20% of patients with primary Sjögren’s syndrome,108 but there are reports of asymmetric neuropathies.109 Isolated cranial nerve sensory neuropathy has been reported in a number of patients with Sjögren’s syndrome,110,111 including in the trigeminal nerve.112 Trigeminal sensory neuropathy in Sjögren’s syndrome is characterized by a slowly progressing, unilateral, or bilateral facial numbness or paresthesia, occasionally associated with pain.8 Independent of these reports of neuropathies in these patients, it does not seem that neuropathies are more common in patients with primary Sjögren’s syndrome compared with healthy controls.113 This also seems to be true of headaches, except for tension-type headaches, which may be more common in primary Sjögren’s syndrome.114 Headaches possibly relate more to the signs and symptoms of Sjögren’s syndrome, such as dry eyes, than to the diagnosis.115 The emotional aspects of pain in patients with the syndrome may significantly and negatively contribute to pain perception and reporting.116 This is due in part to the fear of illness that is potentially associated with the reported pain. This may explain why patients with Sjögren’s syndrome are more likely to report fatigue and pain than patients with SLE, whereas fibromyalgia is more often diagnosed in patients with SLE than with Sjögren’s syndrome.117

**Systemic sclerosis (scleroderma)**

Systemic sclerosis is a multisystem connective tissue disorder of unknown etiology characterized by inflammation as well as vascular and fibrotic alterations in the skin, which becomes indurated and fixed to the underlying connective tissue.118 The condition also involves various other internal organs, such as the gastrointestinal tract, heart, lungs, and kidneys, and causes fibrosis by the deposition of too much collagen. Scleroderma is a rather generic term that is used to describe a systemic as well as a localized cutaneous variant. The systemic form of scleroderma is classified as CREST syndrome, which is an acronym for the clinical manifestations: calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia. This can be further subdivided into morphea scleroderma (a localized form of the disease) and linear scleroderma (a specific type of localized scleroderma). Diffuse systemic sclerosis, also known as progressive systemic sclerosis, is rare and carries a poor prognosis.119 Women are affected more often than men, with a ratio of 3:1, and this tends to increase to 4:1 during the childbearing years; the highest onset of symptoms is between the ages of 30 and 50 years.118

The most characteristic orofacial manifestations are microstomia, resulting in limited mouth opening; mucogingival problems; fibrosis of the hard and soft palate; telangiectasis and chro-matosis of the face and oral mucosa; xerostomia; dry eyes; widening of the periodontal ligament space; TMJ dysfunction; and trigeminal neuropathy.120,121 These manifestations are either a direct result of the substitutions of normal tissues with collagen or the deposition of collagen around nerves or endothelial tissues.122 TMJ noises and pain are extremely prevalent in scleroderma and may be experienced by more than 85% of patients.97 Voice changes are also often reported in scleroderma, and patients report a significant decrease in quality of life.123 TMJ dysfunction is most often related to gross changes to the mandible, which include...
osteolytic activity and result in bone resorption of the coronoid process, condyles, angle of the mandible, and ramus.\textsuperscript{119,120} These changes result in articular pain and swelling due to tenonitis and synovitis, with the accompanying radiographic changes described earlier.\textsuperscript{124}

Trigeminal sensory neuropathy may involve all three branches and appears to be the most frequent orofacial phenomenon to precede this disorder.\textsuperscript{98} Of 22 patients with scleroderma, 9 reported trigeminal neuropathy as the first symptom of the disorder.\textsuperscript{125} The symptomatology consists of paresthesia, burning, and/or an intense sharp/stabbing pain that may be provoked by jaw use or movement, thus mimicking the presentation of trigeminal neuralgia.\textsuperscript{118,126}

### Mixed connective tissue disorder

The clinical findings in mixed connective tissue disorder often include Raynaud phenomenon, polyarthralgia or arthritis, lymphadenitis, cutaneous and mucosal lesions, and serositis in the form of pulmonary involvement. These features are commonly found in a number of different connective tissue diseases, including SLE, scleroderma, rheumatoid arthritis, and polymyositis. Thus, mixed connective tissue disorder is characterized by overlapping, nonspecific clinical features that may occur simultaneously or sequentially.\textsuperscript{127}

The orofacial manifestations of these connective tissue disorders, although uncommon, include trigeminal sensory neuropathy and arthritis of the TMJ. The presence of trigeminal neuropathy has also been reported to include both pain and numbness, and it appears that neurovascular headaches of mild to moderate severity are relatively common in this disorder.\textsuperscript{98,127}

Patients with mixed connective tissue disorder demonstrate signs and symptoms of dysfunction of the masticatory system.\textsuperscript{128} Masticatory muscle and TMJ tenderness, with associated clicking or crepitation, are common.\textsuperscript{22} Radiographic changes of the TMJs were observed in 7 of 10 patients examined.\textsuperscript{128} Moreover, in five of six patients with normal-appearing mucosa, histologic examination revealed chronic inflammation. Three of the 10 patients had clinically atrophic and erythematous oral mucosa; histologic examination again revealed chronic inflammation.

Mixed connective tissue disorder is often associated with secondary Sjögren’s syndrome,\textsuperscript{129} although this association does not influence the clinical course of mixed connective tissue disorder.\textsuperscript{130} Suspicious cases of Sjögren’s syndrome–like symptoms that are undiagnosed should be referred for medical assessment.

### Antiphospholipid syndrome

The antiphospholipid syndrome (Hughes syndrome), first described in 1983, is a prothrombotic disease in which neurologic events feature prominently. Cerebrovascular accidents (CVAs), transient ischemic attacks, and headaches are important complications. Other neurologic symptoms, including diplopia, memory loss, ataxia, and multiple sclerosis–like features, are common.\textsuperscript{131} Antiphospholipid syndrome is characterized by serum autoantibodies to phospholipids, which are deposited in small vessels and lead to intimal hyperplasia and acute thromboses, especially in cerebral, renal, pulmonary, cutaneous, and cardiac arteries. Antiphospholipid syndrome may be seen in isolation or associated with SLE or other connective tissue diseases, including Sjögren’s syndrome.

Headache in antiphospholipid syndrome can vary from typical episodic migraine to an almost continuous incapacitating headache. Patient histories are often remarkably similar: teenagers with headaches that are frequently migrainous in character and temporally associated with premenstrual days. These headaches may subsequently disappear for 10 to 20 years only to return when the patient reaches the age of 30 to 40 years. Significantly, there is a strong family history of headaches or migraine in many of these patients, which suggests common genetic influences. Moreover, as in migraine with aura, some patients report headaches that are accompanied by visual or speech disturbance or by transient ischemic attacks.\textsuperscript{131}

The association of migraine and antiphospholipid antibodies is controversial, and results vary widely. Some have reported association with lupus anticoagulant or anticardiolipin,\textsuperscript{132,133} but others report no associations.\textsuperscript{134} The difficulty in demonstrating a true association between anticardiolipin positivity and migraine stems in part from the high prevalence of mi-
graine in the healthy population and the relatively low prevalence of anticardiolipin positivity in otherwise healthy people (see chapter 10). One of the major problems is that headaches, often nonmigrainous, have been loosely termed migraine, and these headaches may precede or accompany transient ischemic attacks or CVAs. Antiphospholipid antibodies have also been detected in patients with transient neurologic symptoms, including migraine aura. Therefore, the controversy may be due in part to the inherent difficulty in distinguishing the transient focal neurologic events of migraine from transient ischemic attacks. The available data suggest an association between the migraine-like phenomena and antiphospholipid antibodies but not between migraine headache and antiphospholipid antibodies.

Anecdotal reports show that anticoagulation treatment is sometimes effective in reducing the number and the intensity of headache attacks in selected patients with antiphospholipid syndrome. Similarly, memory loss often improves dramatically with appropriate warfarin dosage.

Wegener’s granulomatosis

Wegener’s granulomatosis is an autoimmune disease that has a clinical predilection for the upper airways, lungs, and kidneys. Wegener’s granulomatosis is a necrotizing granulomatous vasculitis characterized by the presence of antineutrophil cytoplasmic antibody. Neurologic involvement in this autoimmune disease is rare at onset. However, a case where headache was the initial, dominant presentation was reported. The headache was migratory, throbbing, and accentuated by head movement; the symptoms disappeared when the treatment was directed at the underlying Wegener’s granulomatosis. Two further cases have been published where the headache in Wegener’s granulomatosis was described as a severe, lancinating, left-sided facial pain with green nasal discharge, postnasal drip, nasal obstruction, and photophobia, with the eventual development of hyperalgesia and allodynia. The described pain was localized to the frontoethmoid area, extended retro-orbitally, and kept the patient awake at night. In the second case, hearing loss was also present. Unusual presentations of Wegener’s granulomatosis include severe and bilateral facial palsy associated with ear pain or meningitis.
**Neurosarcoidosis**

Neurosarcoidosis is a multisystem granulomatous disease of unknown cause, most commonly affecting young adults. Sarcoid lesions are noncaseating epithelioid granulomas. Involvement of the central nervous system (CNS) is clinically evident in 5% and silent in 10% of patients with systemic sarcoidosis. It may occur at presentation in 10% to 30% of patients and more rarely is strictly confined to the CNS. Intracranial lesions are detectable by MRI.\(^{153}\)

Headache and/or primary headaches are frequently reported in patients with neurosarcoidosis (30%) but rarely present as an initial symptom of the disease. However, occasional rare cases of headaches have been reported as a presenting symptom of sarcoidosis.\(^{154,155}\) Headache character varies in relation to neuropathologic involvement; focal lesions, meningitis, cranial nerve palsies, and no typical characteristics of headache are known. Intractable headaches located occipitally and radiating frontally, with associated nausea and visual disturbances, have been reported in patients with isolated supratentorial tumor-like lesions.\(^{156}\) Diffuse or bifrontal pain is a more typical symptom of leptomeningeal involvement, which may be associated with papilledema.\(^{157}\) Other forms of cranial pain may be related to trigeminal or optic nerve involvement, and migraine has also been reported.\(^{158}\)

**Melkersson-Rosenthal syndrome**

Melkersson-Rosenthal syndrome is an uncommon condition of uncertain pathogenesis and course. The classic triad of signs includes recurrent orofacial edema, recurrent facial nerve palsy, and lingua plicata (fissured tongue). Seventy-five percent of all patients had labial swelling, 50% had facial edema, and 33% had Bell’s palsy.\(^{159}\) The condition produces nontender, persistent swelling of one or both lips and affects primarily young adults. Histologically, non-necrotizing granulomatous inflammation is seen.\(^{160}\) Therefore, facial neuropathy involving facial palsy or symptomatic lip swelling should include Melkersson-Rosenthal syndrome as a differential diagnosis. Some authors suggest that Melkersson-Rosenthal syndrome is a variant of Crohn’s disease.\(^{161}\) Others have suggest- ed a link between Hashimoto’s thyroiditis and Melkersson-Rosenthal syndrome because of the common presence of antithyroid peroxidase antibodies in both conditions.\(^{162}\)

**Giant cell arteritis**

Giant cell arteritis (GCA), also referred to as temporal arteritis, is a chronic vasculitis of large and medium-sized arteries. GCA is usually accompanied by head, face, or neck pain. The condition predominantly affects patients over the age of 50 years, typically in the seventh and eighth decades, and women are affected about twice as often as men.\(^{163,164}\) The incidence is age related and rises from 2.3/100,000/year in 60-year-olds to 44.7/100,000/year in 90-year-olds.\(^{165-169}\) GCA mainly affects whites, particularly people of Scandinavian or northern European descent, irrespective of their residence.\(^{165,167-169}\) Additionally, genetic studies suggest an inherited component, and most point to an association with the HLA antigen system.\(^{170}\)

The diagnosis of GCA relies on the presence of a swollen and tender scalp artery (usually the temporal artery) accompanied by an elevated erythrocyte sedimentation rate (ESR) and a rapid response (< 48 hours) to steroid therapy.\(^{73}\) However, all of these factors may not always occur in a particular case, and definitive diagnosis is dependent on an artery biopsy demonstrating typical histopathology.

In relevant cases, an ESR is considered indicative of GCA, but ESRs < 40 mm/hour occur in up to 22.5% of patients, and clinically normal levels do not exclude diagnosis.\(^{170,171}\) Constitutional symptoms are more common in patients with ESR > 100 mm/hour, and in patients with elevated ESR, disease activity correlates with ESR changes.\(^{170,172}\) ESR is affected by sex, a number of autoimmune and hematologic disorders, malignancy, liver dysfunction, and use of anti-inflammatory drugs. Moreover, there is some disagreement as to the normal range of ESR. C-reactive protein has several advantages over ESR: It is unaffected by sex, age, plasma composition, and red cell morphology, and it has an accurately defined and accepted normal range. C-reactive protein is commonly used in conjunction with ESR for the diagnosis of GCA and significantly improves specificity.\(^{173}\)
The diagnosis of GCA is dependent on temporal artery biopsy and should be performed in all patients, though up to 15% may have a negative biopsy. The threat of blindness mandates that corticosteroid therapy not be delayed and that temporal artery biopsy be performed as soon as possible. Because of the presence of skip lesions (discussed later), biopsy should include a length of at least 2.0 to 2.5 cm of artery, which should be serially sectioned every 1 mm. Sections should be stained with hematoxylin and eosin and with an elastin-specific stain. A negative biopsy in a clinically suspect patient may be an indication for a further, contralateral biopsy. Contralateral biopsy may be positive in up to 15% of patients after an initially negative ipsilateral result.

Elevated platelet counts are commonly observed in GCA and promptly return to normal after steroid therapy. A number of other tests are more rarely used for the diagnosis and or monitoring of GCA, including plasma viscosity, interleukin-6, fibrinogen, and liver function tests. Imaging techniques that may be useful include duplex ultrasonography, angiography, positron emission tomography, MRI, and computed tomography. However, though most of these techniques are suitable for the assessment of large vessels, they are of limited value in the small cranial vessels. In expert hands with state-of-the-art equipment, ultrasonography is reliable (sensitivity, 88%; specificity, 99.5%) for the diagnosis of GCA, even in small vessels. MRI has been shown to accurately detect areas of mural inflammation, even in the relatively small temporal artery. MRI may therefore be a future possibility for diagnosis or to guide biopsy site selection.

GCA is well known for its variable clinical manifestations. The clinical signs are the result of damage to the arterial supply, which leads to tissue ischemia and injury. The most common presenting complaints include headache, scalp tenderness, jaw claudication, and arthralgia. Jaw claudication may be expressed as tiredness and inefficient chewing, which lead to clinical similarities with TMDs. Uncommonly, areas with severe ischemia may necrose, including intraorally.

Patients with GCA may visit an orofacial pain clinic complaining primarily of pain, most commonly over the muscles of mastication, the TMJ, and the eye. Headache is present in 90% of patients and often localizes to the temple (ipsilateral or bilateral) and forehead, but location is highly variable.

Pain quality may be throbbing, burning, boring, or lancinating and may vary from mild to severe. Head tenderness and allodynia, particularly over the temporal regions, may be marked. The temporal artery may be prominent, tender, or beaded, but these findings are inconsistent, and in more advanced cases the artery may not be easily located. Ophthalmoscopy may reveal anterior ischemic optic neuropathy with a pale and swollen optic disc.

Ocular involvement may occur in 14% to 70% of patients with GCA. Transient visual disturbances, such as diplopia or ocular pain, are reported by 2% to 30% of patients. Bilateral blindness has been reported in a third of patients and is usually the result of ischemic damage to the optic nerve, retina, or choroid.

Constitutional symptoms may include fever, weight loss, anorexia, and malaise. Additionally, alterations in mental status, including depression, dementia, confusion, and delusional thinking, have been reported. Many of these symptoms are common in the elderly secondary to infectious, malignant, or age-related disease and may therefore be missed as a presenting sign of GCA. Typical clinical manifestations may be totally absent in up to 38% of patients who present solely with visual symptoms, termed silent or occult GCA.

Concurrent symptoms commonly include proximal muscle ache, morning stiffness, and polymyalgia rheumatica, which is very common and affects 1 in every 130 persons over the age of 50 years and may be the presenting manifestation of GCA in up to 50% of patients. Clinically, polymyalgia rheumatica is characterized by bilateral severe aching pain and morning stiffness of the neck, shoulder, and pelvic girdles. Women are more often affected, incidence increases with age, and there are signs of systemic inflammation, suggesting similarities with GCA. Therefore, some consider polymyalgia rheumatica and GCA to be different phases of the same disease. However, polymyalgia rheumatica lacks the inflammatory infiltrate and vaso-occlusive ischemic manifestations of GCA. Polymyalgia rheumatica is often an isolated condition and does not
demonstrate the strong HLA association seen in GCA.166,189–192 Debate continues as to the precise nature of the comorbidity of polymyalgia rheumatica and GCA.170

The initial event that triggers the cascade of immune and inflammatory reactions underlying GCA has been suggested to be infective but remains unclear.170 Current theory points to the activation of immature dendritic cells residing in the arterial wall. Activated dendritic cells then produce inflammatory cytokines and chemokines, which ultimately attract T cells and macrophages.193,194 Many patients with GCA demonstrate signs of systemic inflammation. Interleukin-1 and interleukin-6 are considered to play a key role in the pathophysiology of GCA and induce the production of acute-phase proteins by the liver, fever, and myalgia.170

The aorta and its extracranial branches are specifically but not solely affected. In particular, the superficial temporal, ophthalmic, posterior ciliary, and vertebral arteries are commonly involved.170 The central retinal and other branches of the external carotid artery are less commonly affected, whereas the intracranial arteries are spared.

In active disease, nodular inflammatory granulomatous reactions affect arteries with an elastic lamina; the distribution of disease correlates with the distribution of elastin.185 Often, disease activity is variable within the same artery, which leads to skip lesions, that is, segments of inflamed regions adjacent to unaffected areas.196–198 This is the rationale indicating that long sections of artery should be obtained as biopsy specimens.

Histopathology of affected arteries shows inflammation of the adventitia, media, and intima. Also seen is predominant aggregation of CD4+ (T-helper/inducer) cells and a select group of T cells within the adventitial layer; these produce interferon gamma, which is thought to be the key regulating cytokine in GCA.199 Macrophages are present in distinct functional groups throughout the arterial wall and induce a proinflammatory response in the adventitia and destruction of the media. Ischemic symptoms are probably secondary to narrowing of the lumen, but thrombosis is often present. Intimal thickening observed in GCA correlates with circulating levels of interferon gamma and is probably a healing response.194,200,201

GCA may run a self-limiting course lasting 2 to 4 years, but many patients require long-term therapy.178,202–204 Because of the potentially severe effects, rapid and efficient treatment with corticosteroids is indicated.170,178 Patients with suspected GCA should be rapidly assessed and referred for ophthalmologic examination and biopsy; however, steroid therapy should not be withheld.176,178 Onset of visual loss after initial symptoms may be rapid and varies from weeks to months. The loss of vision in one eye usually indicates loss of vision in the second eye within 1 or 2 months.170

Recent recommendations suggest beginning with 60 to 80 mg of prednisone daily.170,178 Patients with ocular involvement at presentation commonly receive very high initial doses (1,000 mg/day for 3 days). Resolution of systemic symptoms occurs within 24 to 72 hours, and the dose should be increased if necessary to attain symptomatic relief. The ESR normalizes only after several weeks. The effective dose should be maintained for 4 to 6 weeks and then tapered while closely monitoring clinical signs, ESR, and C-reactive protein. The dose is reduced by 10 mg per month, then 5 mg per month, and then 1 mg per month once a daily dose of 10 to 15 mg is attained.170 Total treatment may span 1 or 2 years, and all dose adjustments should be accompanied by clinical and laboratory testing. Relapses are common, particularly in the first 18 months, and may be accurately predicted by changes in C-reactive protein levels.170,205

Patients on corticosteroids require expert medical management of side effects, including osteoporosis, depression, and gastrointestinal problems.178 The incidence of serious effects associated with corticosteroid therapy is more than 50%.205 For this reason, steroid-sparing drugs have been developed, but there is no consensus concerning their use for this condition. Patients taking aspirin before or at diagnosis demonstrate lower risk for visual loss.206 However, aspirin may further increase gastrointestinal morbidity, so a proton pump inhibitor should therefore be prescribed.

**Behçet’s disease**

Behçet’s disease is a clinical triad of oral and genital ulceration and uveitis that affects young
adult men, particularly in Turkey and Japan, and has an association to HLA-B5 and HLA-B51. Clinical features, such as arthralgia and vasculitis, suggest an immune complex–mediated basis, which is supported by findings of circulating immune complexes, but the antigen responsible has not been identified. Immunologic changes occur in Behçet’s disease, including T-lymphocyte abnormalities, changes in serum complement, and increased polymorphonuclear motility. Mononuclear cells and natural killer cells may also be involved.207,208

Recurrent headache has been reported in more than 80% of patients with Behçet’s disease.209,210 Most fulfill the IHS criteria for migraine (see chapter 10) and have a higher than normal prevalence of visual sensory aura (52% of patients). In addition, 62% of patients showed moderate or severe disability according to the Migraine Disability Assessment Score.208 Because the nervous system is involved in 5% of patients with Behçet’s disease, headache appears to occur independently.211 A much lower incidence of headache has been reported in patients with Behçet’s disease (58%); however, migrainous headache was commonly associated with exacerbations of some of the systemic symptoms of the syndrome. Therefore, this form of headache is not specific for Behçet’s disease but may be explained by a vascular headache triggered by the immunomedi­ated disease activity in susceptible individuals.

Finally, a report indicated that patients with Behçet’s disease may be more likely to be diagnosed with fibromyalgia, especially women.212 The diagnosis of fibromyalgia in patients with Behçet’s disease did not seem to affect the presence of oral ulcers but contributed to musculoskeletal pain, as would be expected.

Orofacial Pain in Neurologic Disorders

Headache associated with neurologic disorders is mainly observed in CVAs, multiple sclerosis, and changes in intracranial pressure (see also chapters 12 and 13).

CVA is a syndrome of rapidly developing clinical signs and symptoms of focal and, at times, global disturbances of cerebral function lasting more than 24 hours or resulting in death within that time. When blood flow to the brain is interrupted for more than a few seconds, brain cells can die, causing infarction. The most common cause of CVA or stroke is cerebral atherosclerosis, which may lead to the main types of CVA: hemorrhagic (intracerebral or subarachnoid), thrombotic, or embolic. Rarely, strokes are secondary to other pathologies, such as carotid dissection, carotid stenosis, cocaine use, and syphilis.

In a prospective study involving 240 patients experiencing acute CVA, it was found that headache occurred in 38%. Headache patients were younger, and a history of tension-type headache was more significant in the headache group than in the nonheadache group. In patients with ischemic stroke, the incidence of headache was lower, and pain was shorter, more localized, and less intense compared with that in patients with hemorrhagic CVA.213 The IHS has well-described criteria for headaches associated with cranial vascular disorders.19 The association between migraine and stroke remains controversial.214,215 Epidemiologic studies suggest that migraine may be an independent risk factor for ischemic stroke in women younger than 45 years, and additional risk factors are cigarette smoking and oral contraceptive use.216 The pathogenesis is not well understood but is thought to be related to common biochemical mechanisms between migraine and stroke. A classification of migraine-related stroke has been proposed that includes three major entities: coexisting stroke and migraine, stroke with clinical features of migraine, and migraine-induced stroke.214 Coexisting stroke and migraine was proposed as an explanation for the relationship between stroke and migraine in patients affected by cardiovascular disease. In such a condition, a possible cause of ischemic stroke may be an increased propensity toward paradoxical cerebral emboli during migraine attacks when there is a condition of platelet hyperaggregation.

Stroke with clinical features of migraine stems from the hypothesis that in some arteriovenous malformations or neurologic diseases, circulation in the CNS may be affected by multiple minor infarcts, and the patient may present with migraine as a symptom of a minor infarct.
Orofacial Pain in Cardiovascular Diseases

The concept of migraine-induced stroke is well represented by migrainous infarction, which is described as having one or more migraine aura symptoms associated with an ischemic brain lesion in the appropriate territory demonstrated by neuroimaging. Interestingly, the condition mainly occurs in younger women in the posterior circulation, and most studies have shown a lack of association between migraine without aura and ischemic stroke.

An association between multiple sclerosis and headache has been suggested. In 137 patients with multiple sclerosis, 88 reported headache, 21 of whom developed headache after initiation of interferon treatment. The prevalence of all headaches not due to interferon was 57.7%. Migraine was found in 25.0% of patients, tension-type headache in 31.9%, and cluster headache in only one patient. A significant correlation between migraine and relapsing-remitting multiple sclerosis was also found. Some authors suggest that the mechanism for this is a serotoninergic link between multiple sclerosis and migraine headache.

Headache may be caused by raised intracranial pressure and intracranial hypotension. Extremely high intracranial pressure commonly causes headache. Benign intracranial hypertension is a rare syndrome of increased intracranial pressure manifesting as headache, transient visual obscuration, and palsy of the sixth cranial nerve. In most patients, benign intracranial hypertension is idiopathic, but possible causes include tetracycline use, endocrine disorders such as obesity, hypoparathyroidism, hypervitaminosis A, and thyroid replacement. Cerebral edema, high cerebrospinal fluid outflow resistance, high cerebral venous pressure, or a combination of the three is thought to underlie benign intracranial hypertension. The management of benign intracranial hypertension includes symptomatic headache relief, removal of offending risk factors, and medical or surgical reduction of intracranial pressure. Spontaneous intracranial hypertension, characterized by postural headache, is rarer than benign intracranial hypertension. Diminished cerebrospinal fluid production, hyperabsorption, and cerebrospinal fluid leak are postulated mechanisms of spontaneous intracranial hypertension; cerebrospinal fluid pressure is typically less than 60 mm H₂O. Empiric treatment includes bed rest; administration of caffeine, corticosteroids, or mineralocorticoids; epidural blood patch; and epidural saline infusion.

The IHS describes secondary headaches that may occur in patients affected by inflammatory diseases of the CNS, which are classified as headaches attributed to nonvascular intracranial disorders. Headaches are frequently reported in patients with neurosarcoidosis (30%), Behçet’s disease (55%), and acute disseminated encephalomyelitis (45% to 58%).

Orofacial Pain in Cardiovascular Diseases

Orofacial pain in hypertension

Headache is generally regarded as a symptom of high blood pressure, in spite of conflicting opinions on their precise association. Most studies have shown that mild, chronic hypertension and headache are not associated. Whether moderate hypertension predisposes a person to headache remains controversial, but there is little evidence. However, headaches caused by significant disturbances in arterial pressure are included in the IHS classification. The headaches that are associated with severe disturbance in arterial pressure were attributed to pheochromocytoma, malignant hypertension, preeclampsia and eclampsia, and acute pressor response to an exogenous agent.

The potential impact of hypertension on facial pain has been evaluated, and conflicting results have been reported. Patients with periapical dental disease had blood pressure and pain recorded before and after nonsurgical endodontics. A significant correlation was observed between preoperative systolic blood pressure and posttreatment pain (P < .05), which suggests an interaction between the cardiovascular and trigeminal regulatory systems. In a retrospective review of 84 patients with trigeminal neuralgia, hypertension was present in 37% compared with 32% of control subjects (not significant), which suggests that as both conditions are common in older adults, they likely represent coexisting conditions.
The most common symptom of pheochromocytoma is a rapid-onset headache, which has been reported by up to 92% of patients with this condition. The headache, which lasts less than an hour in most patients, is bilateral, severe, and throbbing, and it may be associated with nausea in 50% of patients. Paroxysms can begin spontaneously or be triggered by physical exertion, certain medications, emotional stress, changes in posture, and increases in intra-abdominal pressure.

In malignant hypertension, the rate and extent of the increase in blood pressure are the most important factors in the development of acute cerebral syndrome. The presenting symptoms can be headache, nausea, and vomiting. Additional signs and symptoms include blurred vision, scintillating scotoma or visual loss, anxiety, and then decreased levels of consciousness until seizures begin.

Preeclampsia occurs in up to 7% of pregnancies, and eclampsia is found in up to 0.3%. Some have suggested that headache in women with preeclampsia is strongly associated with the presence of abnormal cerebral perfusion pressure. A strong association between migraine history and preeclampsia development, specifically the severe form of preeclampsia, has been shown.

A sudden severe headache due to a rapid increase in blood pressure may occur in persons taking monoamine oxidase inhibitors concomitantly with drinking red wine, eating foods with high tyramine content (eg, cheese, chicken livers, or pickled herring), or taking sympathomimetic medications such as pseudoephedrine. However, monoamine oxidase inhibitors are rarely used today in medical management.

Orofacial pain of cardiac origin

Ischemic heart disease may lead to the onset of painful symptoms usually located retrosternally or precordially with radiation to the left arm, left shoulder, and neck. This symptom is termed angina pectoris and may be more rarely accompanied by referred pain to the back, right arm, epigastrium, head, and orofacial region.

Stable angina pectoris is precipitated by effort, relieved by rest, and associated with coronary artery disease, whereas unstable angina pectoris is characterized by increasing pain frequency and/or duration and novel onset at rest or with minimal effort. Atypical forms of angina pectoris may occur during sleep or at rest (eg, Prinzmetal’s angina) or may not be associated with detectable coronary artery disease (eg, microvascular angina). Acute coronary syndrome describes the continuum from unstable angina pectoris at one end of the spectrum to myocardial infarction at the other end.

Ischemic cardiac pain is usually described as variations of pressure-like descriptors (heavy, pressing, tight, squeezing) but may also be aching, sharp, burning/searing, or a burst-open feeling. Accompanying manifestations will vary depending on whether the symptoms reflect stable/unstable angina pectoris or myocardial infarction. Patients commonly report accompanying sweating, weakness, nausea, dyspnea, and vomiting but may not report any manifestation other than pain.

Pain referral to the orofacial region in angina pectoris or myocardial infarction has been variably reported from 4% to 18% of patients. Headache associated with ischemic chest pain (cardiac cephalalgia) is defined by the IHS and requires the presence of head pain aggravated by exercise and accompanied by nausea. Evidence must exist for concomitant acute myocardial ischemia, and symptoms should resolve with effective cardiac therapy. Cardiac cephalalgia has been reported in 5.2% of one series of patients with myocardial infarction and usually accompanies chest symptoms. In rarer instances, myocardial infarction pain may be primarily felt as headache (3.4% of patients), jaw pain (3.6%), or neck pain (8.4%). Orofacial pain (8.3%) is more common in inferior myocardial infarction, and cardiac cephalalgia is more frequently reported (7.3%) in anterior myocardial infarction, which suggests that anatomical factors influence the prevalence of pain referral. However, other studies have shown that women report a higher frequency of jaw pain associated with angina pectoris than do men, even after controlling for myocardial infarction severity and location.

Reports of patients with headache and orofacial pain as the cardinal manifestation of ischemic heart disease have appeared in the literature. Diagnosis is often dependent on the temporal profile, which may be suggestive of cardiac cephalalgia/orofacial pain. Typical-
ly, onset is in close proximity to exercise and subsides with rest or antianginal therapy. Rarely, as in unstable angina pectoris, pain may be felt at rest. Pain may be moderate to severe and located in the neck, mandible (it may involve teeth and gums), unilaterally in the head, or even referring to the vertex. At-risk groups are patients older than 50 years with new-onset headache and risk factors for heart disease.

The mechanisms of referred pain in ischemic heart disease are unclear and may be multiple. Convergence of sympathetic or vagal fibers that transduce cardiac pain with trigeminocervical pathways has been shown, and indeed, sympathectomy relieves angina pectoris in a subset of patients. Compromised cardiac function with impaired venous return may lead to increased intracranial pressure and subsequent pain. Cardiac ischemia may induce the release of a number of mediators that can cause distant pain.

Headache is common in hypertension and was present in 75% of patients with severe hypertension followed by the presence of chest pain and shortness of breath (62%) and dizziness (50%). Mild or moderate hypertension may not be associated with headache, whereas severe hypertension and rapid change in blood pressure may be associated with headache.

Intracranial hypertension is associated with headache, which improves after diagnosis and effective treatment. Diagnosis is critical, as treatment can avoid serious visual and CNS complications. Clinicians should be aware that migraine sufferers have an elevated incidence of vascular disease that may be critical to recognize. Patients with classic migraine with aura may have an increased risk of ischemic stroke and an association with cardiac disease that needs further evaluation. Once alerted, management of potential risk factors such as hypertension, tobacco use, and use of oral contraceptives may reduce cardiac risk. A high prevalence of headache, particularly migraine, is seen in patients with atrial septal defects, which suggests benefits from atrial septal defect repair. Furthermore, cardiac abnormalities are associated with a prolonged duration of migraine (> 10 years). Associations have been shown between migraine headache and heart disease, and headache patients have increased cardiovascular disease risk factors.

Vascular risk is known in women with migraine, particularly in the presence of smoking, hypertension, diabetes, thrombophilia, age over 35 years, and use of oral contraception. Though obtaining a history of prior cardiovascular disease and cardiovascular disease risk factors is appropriate in headache patients, testing for cardiovascular disease is not supported in the literature.

Cervical artery dissection

Extracranial dissections of the internal carotid artery and vertebral artery are quite common, with an annual combined incidence of 5/100,000 persons; co-occurrences are termed cervical artery dissections. The mean patient age is in the early 40s, and approximately 70% of patients are younger than 50 years. Women, on average, are 5 years younger than men at the time of dissection and are more likely to have dissections in multiple vessels. Spontaneous dissections occur with no history of trauma, whereas some patients report blunt trauma, particularly extension-flexion (whiplash) or rotation injuries to the neck. Cervical artery dissections arise from a tear in the intima (inside-out theory) that allows blood to enter the artery wall under high pressure. The resulting intramural hematoma may compromise the lumen and lead to stenosis or may expand outward as an aneurismal dilation. New evidence suggests that the pathologic process may begin with degenerative changes at the medial-adventitial border associated with neoangiogenesis of capillary vessels branching from the vasa vasorum in the adventitia (outside-in theory).

The clinical presentation is varied and may consist of a single symptom or a combination of symptoms, such as pain, Horner syndrome, and neck tenderness. The most common presentation of cervical artery dissections is head, face, or neck pain with or without other signs, with up to 95% of patients reporting such pain in internal carotid artery and 70% in vertebral artery dissection.
a steady or throbbing quality.\textsuperscript{263,273} Frequently, pain occurs in the orbital, periorbital, and frontal regions and may commonly involve the cheek, angle of the mandible, jaw, and ear. Anterolateral neck pain occurs in 25\% of patients. Other accompanying signs include diplopia, pulsatile tinnitus, tongue paresis, and dysgeusia.\textsuperscript{266,274} In vertebral artery dissections, the headache is unilateral in two-thirds of patients and ipsilateral to the dissection. Pain is located in the posterior or head and is rarely associated with facial pain. Posterior neck pain is noted in almost 50\% of patients with vertebral artery dissections. Horn er syndrome may be the presenting sign of internal carotid artery dissection in about half of patients with or without pain.\textsuperscript{263,269,270,275}

Diagnosis is by angiography, Doppler, MRI, or magnetic resonance angiography, but false-negatives are possible. Treatment may include anticoagulation therapy, antiplatelet therapy, surgery, or placement of stents, and mortality from cervical artery dissection is low (5\%); the prognosis for cervical artery dissections is considered to be very good in the vast majority of patients.\textsuperscript{263,276,277} Pain resolves within 1 week but may last up to 5 weeks.\textsuperscript{266} Recurrence is not uncommon, however, and is most frequent within the first 2 months after the initial event; 6\% to 17\% of patients will suffer a dissection in another vessel within 10 years.\textsuperscript{263,278} Early recurrences of dissection in the weeks after the initial event could be a manifestation of a unique transient disorder, whereas late recurrences occurring several months or years later could indicate an underlying connective tissue weakness.\textsuperscript{279,280}

Orofacial Pain in Blood Disorders

Disorders of the red blood cells may cause orofacial pain and headaches. Anemia, defined as a reduction in the oxygen-carrying capacity of the blood, is usually related to a decrease in the number of circulating red blood cells or to an abnormality in the red blood cell hemoglobin content. In some forms of hemoglobinopathies—thalassemia and sickle cell anemia—facial pain or headache may be present as part of the clinical presentation.

Thalassemias are autosomally dominant inherited disorders in which either alpha- or beta-globin chains are synthesized at a low rate, thereby lessening the production of hemoglobin A. The unaffected chains are produced in excess and precipitate within the erythrocytes to cause excessive erythrocyte fragility and hemolysis. Thalassemias are characterized by a hypochromic microcytic anemia and may be severe (major, homozygous) or mild (minor, heterozygous) and may affect beta-chains (beta thalassemia) or alpha-chains (alpha thalassemia).

In beta thalassemia, neurologic complications have been attributed to various factors, such as chronic hypoxia, bone marrow expansion, iron overload, and desferrioxamine neurotoxicity.\textsuperscript{281} Cranial nerve palsies have been described in thalassemia due to the extramedullary hematopoiesis resulting in pressure on the nerves.\textsuperscript{282,283} Thromboembolic events have been frequently reported in patients with beta thalassemia in association with such risk factors as diabetes, complex cardiopulmonary abnormalities, hypothyroidism, liver function anomalies, and post splenectomy thrombocytosis. A multicenter Italian study identified 32 patients with thromboembolic episodes in a total of 735 subjects with thalassemia. The researchers found great variation in localization of the thromboemboli, mainly in the CNS (16/32), with a clinical picture of headache, seizures, and hemiparesis.\textsuperscript{284} Thalassemia major may present with multiple orofacial abnormalities. A study of 54 patients with thalassemia major identified dental/jaw pain in 40.0\% and headache in 29.6\%.\textsuperscript{285} Anecdotally, patients with thalassemia may experience painful swelling of the parotid glands, with xerostomia caused by iron deposition, and a sore or burning tongue related to folate deficiency.\textsuperscript{286}

In sickle cell anemia, amino acid substitution in the globin chain results in hemoglobin with a propensity to polymerize or precipitate, causing gross distortions in the shape of erythrocytes and membrane damage. The erythrocytes lose flexibility and sickle, which may cause microvascular occlusions. Painful crises that are usually due to infarction as a result of sickling are brought on by infection, dehydration, hypoxia, acidosis, or cold; cause severe pain and pyrexia; and may occur in the jaw. Orofacial pain
during sickle-cell crises may occur, and dental care should be deferred until the crisis is managed and specific diagnosis of dental disease is made. Headaches, mental nerve paresthesia, and jaw pain have been reported in sickle-cell crises, probably because of the intensive extramedullary hematopoiesis or necrosis in the jaws. Painful infarcts in the jaws may be mistaken for toothache or osteomyelitis. Pulpal symptoms are common in the absence of any obvious dental disease, and pulpal necrosis has sometimes resulted. Skull infarction should be considered as a cause of new-onset headache located at the vertex in patients with sickle cell disease, especially if scalp edema is present.

A study on the characteristics of headaches in children with sickle cell disease showed an incidence of 31.2% of frequent headaches (greater than once a week) with moderate average pain severity (5.8 on a scale of 0 to 10). Duration of headaches ranged from 30 minutes to several days (mean, 5 hours). Based on IHS criteria, 50.0% of children had headache symptoms consistent with tension-type headaches, 43.8% with migraines, and 6.2% with migraine with aura. Children with symptoms of migraine had significantly greater functional disability compared with children with symptoms of tension-type headaches.

The use of cytokines and growth factors, some with known toxicities, has become common in the treatment of hematologic disorders. Granulocyte macrophage colony-stimulating factor (GM-CSF) is administered to prevent myelotoxicity or accelerate hematopoietic recovery after chemotherapy and has been reported to cause headache. A common adverse event due to the ability of GM-CSF to increase hematopoiesis in bone marrow is bone pain with the potential involvement of the jaw. GM-CSF is increasingly used to mobilize hematopoietic stem cells to the peripheral blood in the healthy donor population, thereby exposing this group to potential adverse events presenting in the orofacial complex.

Orofacial Pain in Dialysis and Renal Disorders

Dialysis may induce severe headache as a result of overhydration and electrolyte shifts. About 70% of patients on hemodialysis complain of headache, and about 57% of patients experience headache during hemodialysis sessions. The most prevalent features of dialysis headache include bilateralism; frontotemporal, occipital, or diffuse location; moderate to severe intensity; throbbing quality; and duration less than 4 hours. The IHS criteria for headache related to hemodialysis specify that the headaches must begin during hemodialysis and spontaneously terminate within 72 hours after the end of the hemodialysis session. This headache commonly occurs in association with hypotension and dialysis disequilibrium syndrome. However, variations of headache related to hemodialysis may not follow these specific criteria. The literature suggests that the dialysis protocol may also affect headache frequency. Sporadic reports describe a complication of nephrotic syndrome that causes headache, specifically cerebral venous thrombosis.

Alport syndrome is an unusual genetic disease that ultimately results in renal failure and has an associated high incidence of sensorineural hearing loss that may present as one of the first symptoms. A case of a patient with Alport syndrome and TMJ involvement is described in the literature. The patient had complaints of facial and joint pain that resembled TMD with headache, tinnitus, joint pain, and temporal swelling.

Orofacial Pain in Pulmonary Diseases

Chronic obstructive pulmonary disease is a chronic, slowly progressive irreversible disease characterized by breathlessness, wheezing, cough, and sputum production. About 30% of patients with moderate or severe, stable chronic obstructive pulmonary disease complain of headache, and 45.5% re-
port sleep disorders. Significant risk factors include a family history of chronic obstructive pulmonary disease, presence of other systemic or sleep disorders (eg, snoring, bruxism), and laboratory data indicating chronic hypoxemia and airway obstruction. This suggests a relationship between chronic hypoxemia and headache.

Asthma is a state of bronchial hyperreactivity that causes paroxysmal expiratory wheezing, dyspnea, and cough. Generalized reversible bronchial narrowing is caused by excessive bronchial smooth muscle tone, mucosal edema and congestion, and mucus hypersecretion with diminished ciliary clearance. Evidence for an association between migraine and asthma is based on a matched case-control study including a patient population of more than 5 million subjects. However, the mechanism shared by migraine and asthma is unclear. Orofacial pain may be referred from the chest due to heart or lung disease via the vagus nerve and present as facial pain, and in some patients it may be an early manifestation of an occult cardiovascular or malignant disease.

Orofacial Pain in Patients with Cancer

Patients with oropharyngeal and head and neck cancer often experience pain and suffering that reduce quality of life. Of patients with advanced cancer, 75% to 90% experience significant pain, and up to 85% of patients with head and neck cancer report pain at the time of diagnosis. More than three-fourths suffer from pain secondary to bone destruction and nerve injury involving inflammatory and neuropathic mechanisms. After treatment of head and neck cancer, 78% of patients reported pain in the head, face, or mouth; 54% in the cervical region or shoulder; and some at distant sites, including the chest (7%), lower back (7%), and limbs (5%).

Cancer pain reduces quality of life and increases anxiety and depression. An estimated 45% to 60% of all patients with cancer do not have adequate pain control possibly because of patient reluctance to report pain, practices of health care providers, pre-conceived fears of addiction, and the strict regulations regarding opioids.

The pathogenesis of oral cancer pain is not fully understood (Table 14-1). Many mediators have been implicated, including endothelin-1, proteases, and nerve growth factor. The evidence is weaker for the role of other mediators, such as protons, transient receptor potential vanilloid, substance P, calcitonin gene–related peptide, adenosine triphosphate, and bradykinin.

Orofacial pain in patients with cancer can be classified according to the underlying pathophysiology (eg, nociceptive, inflammatory, infectious, neuropathic), the location of the tumor (local versus distant), the primary initiating agent (cancer or cancer therapy), or the relation between the onset of pain and the time of cancer treatment (before, during, or after cancer therapy). The following sections cover orofacial pain due to cancer, orofacial pain due to cancer therapy, and orofacial pain of noncancerous etiology in patients with cancer.

Orofacial pain due to cancer

Orofacial pain may occur in primary oropharyngeal and head and neck cancers, by way of local involvement of systemic cancers, and from metastases to the head and neck from distant tumors. The orofacial pain may also be referred from cancers at distant sites.

Pain in regional malignancy

Local regional cancers commonly causing pain in the head and neck include oral, oropharyngeal, sinus, nasopharyngeal, salivary gland, intracranial, and extracranial primary and metastatic tumors. Some reports state that pain is the initial complaint of oral cancer in 30% to 50% of patients, and the reported incidence of pain is up to 85% in these patients when referred for cancer treatment.

In patients with oral cancer pain, symptoms were nonspecific and included descriptions such as sore throat, pain on function (swallowing, chewing), and pain in the region of the tongue, mouth, teeth, and ear. Symptoms varied from mild discomfort to severe pain. Pain was found to be associated with advanced disease and lesions located on the tongue.
Primary tumors to the jaw and infratemporal fossa may cause neurologic symptoms presenting as pain and numbness. Interestingly, excruciating pain after the first few bites (i.e., first-bite syndrome) may be the presentation of a mass in the parotid region.323 Patients with nasopharyngeal cancer often report pain in the TMJ region and may be misdiagnosed as having a TMD.324–326 In such cases, pain is described as dull and aching and resulting in a headache, earache, or jaw, midface, or neck discomfort.324

Systemic cancers such as leukemia may affect the head and neck area, causing pain and loss of function.308,327 Infiltration of the leukemic cells into enclosed oral spaces creates pressure that causes pain. In addition, hematologic cancers cause oral pain indirectly by increasing the risk of secondary infections (fungal, bacterial, and viral) because of damaged mucosal barriers and possible myelosuppression.328–330

Lymphoma is a common neoplasm occurring in the oral region and accounting for 3.5% of oral malignancies.331,332 Lymphoma may present as a firm rubbery mass associated with discomfort in approximately half of patients.333

Pressure from the mass on local structures can cause pain or neuropathy. Secondary inflammation may also contribute to the pain.

Multiple myeloma frequently presents as asymptomatic lytic bony lesions.333 The less frequent extramedullary presentation varies greatly, ranging from a mass to an ulcer associated with pain, and may pose a diagnostic challenge.333,334

Metastasis to the jaw may present similarly. Bone pain results from structural damage, periosteal irritation, and nerve entrapment. Metastatic tumors to the jaw commonly arise from the breast, colon, prostate, thyroid, lung, and kidney.335-338 Metastases to the jaw rarely involve the soft tissues and usually occur in the posterior mandible, angle of the jaw, and ramus.339 In up to 30% of patients, oral metastases are the first indication of a distant tumor.339

Other orofacial malignancies, such as malignant melanoma and intraoral sarcomas, are rare but can present as a mass accompanied with discomfort.340,341

Orofacial pain or headache is reported in up to 6% of patients with intracranial tumors342-347 (see also chapters 12 and 13). The presentation

<table>
<thead>
<tr>
<th>Table 14-1</th>
<th>Mechanisms of pain in malignant disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immediate affectors</strong></td>
<td><strong>Macroscopic and microscopic mechanism</strong></td>
</tr>
<tr>
<td><strong>Pain due to cancer</strong></td>
<td></td>
</tr>
<tr>
<td>Mass pressure/ altered function</td>
<td>Mechanical nerve pain, nerve entrapment, hypoxia, movement dysfunction/TMD</td>
</tr>
<tr>
<td>Tumor invasion</td>
<td>Connective tissue, neurogenic pain, nerve invasion/dysfunction, vascular penetration</td>
</tr>
<tr>
<td>Barrier damage</td>
<td>Erythema/atrophy/erosion/ulceration</td>
</tr>
<tr>
<td>Inflammation/ neurogenic sensitization</td>
<td>Reactive oxygen species, cytokine release (e.g., tumor necrosis factor), low pH, algesic compounds (prostaglandins, cyclo-oxygenase-2, bradykinin, norepinephrine, serotonin, substance P, calcitonin gene–related peptide), upregulation of peripheral opioid receptors</td>
</tr>
</tbody>
</table>

| **Pain due to treatment of malignant disease** | | |
| Surgery | Acute: surgical Chronic: fibrosis and change in function, nerve pain, inflammation |
| Radiation therapy | Barrier damage: reactive oxygen species, cytokine release (e.g., tumor necrosis factor), low pH, algesic compounds (prostaglandins, cyclo-oxygenase-2, bradykinin, norepinephrine, serotonin, substance P, calcitonin gene–related peptide), upregulation of peripheral opioid receptors, response to secondary microbial irritation |
| Chemotherapy | Same as radiation therapy; in addition, mucosal toxicity and neuropathy |
| Tumor lysis | Same as radiation therapy |
may be similar to that of trigeminal neuralgia, persistent facial pain, and TMDs. About 60% of these patients have sensory or motor function loss at presentation.348

Pain as an isolated symptom is an unreliable predictor of orofacial malignancy because pain quality and intensity are highly variable. However, the combination of numbness, pain, and swelling is highly predictive of malignancy, particularly in the presence of systemic signs (eg, weight loss, fatigue, anemia).

Pain secondary to malignancy at a distant site

Orofacial pain may arise from a distant, nonmetastasized cancer, most commonly from the lungs,349–351 due to activation of nociceptive pathways in mediastinal or head and neck structures.351 Pain may occur due to invasion or compression of the vagus nerve,352 and referred facial pain may be mediated by termination of vagal afferents in the spinal trigeminal nucleus.353,354 In addition, the phrenic nerve may refer pain from the pleura and subdiaphragmatic areas to the head and neck.355 Paraneoplastic processes resulting in peripheral neuropathies and cytokine production are common, particularly in lung cancer.356–358 Typical presentations include unilateral dull aching pain (ipsilateral to the lung tumor), often located around the ear, jaw, and temporal regions; weight loss; hemoptysis; persistent cough; and chest wall pain.351 Similar mechanisms may be associated with gastrointestinal and pancreatic cancers that present with orofacial pain.359,360

Peripheral neuropathy was found in 48% of patients with lung cancer before chemotherapy.361 Neuromuscular dysfunction occurs in 30% of patients with diverse tumors, most commonly in ovarian, testicular, or bronchogenic cancers.362 Often, these neuropathies are accompanied by detectable autoantibodies that aid in diagnosis.

Orofacial pain due to cancer therapy

Treatment-related orofacial pain is almost universal in patients with head and neck cancer. Pain may be acute during active therapy or delayed due to late complications of therapy. In this chapter, orofacial pain due to cancer therapy is presented according to etiology.

Pain due to conventional chemotherapy and radiotherapy

The most common acute oral side effect of cancer chemotherapy or radiotherapy is mucositis (Table 14-2). Oral mucositis pain results from tissue injury that causes the release of reactive oxygen species, proinflammatory cytokines, and neurotransmitters that activate nociceptive receptors. The severity of the pain is related to the degree of tissue damage and is modified by the emotional and sociocultural background of the patient.363–365 Other factors that may influence the severity of mucositis are age, mucosal infection, and oral hygiene.363,366,367

In chemotherapy-induced mucositis, the sites most commonly involved are nonkeratinized (buccal and labial mucosa, ventral and lateral aspects of the tongue, soft palate, and floor of the mouth). Signs of mucositis appear approximately 6 to 10 days after treatment, although the biologic changes begin immediate-
Orofacial Pain in Patients with Cancer

Pain associated with mucositis is the most distressing symptom in patients undergoing aggressive neutropenia-inducing chemotherapy regimens. Mucositis is also well documented in patients undergoing hematopoietic stem cell transplantation and is the most frequent serious side effect of therapy in the first 100 days. Patients treated with high-dose cancer chemotherapy for solid malignancies, particularly of epithelial origin (eg, gastrointestinal and breast), suffer painful oral mucositis due to mucosal toxicity of chemotherapy, and prevalence and severity increase throughout successive courses of chemotherapy.

Mucositis from radiation therapy typically affects nonkeratinized mucosa in the radiation field beginning at week 3 of therapy, peaking at weeks 5 to 6, and then remitting 4 to 8 weeks after therapy. The incidence, severity, and duration of mucositis increase with use of combined chemoradiotherapy of head and neck cancer. Mucosal symptoms continue for 6 to 12 months in up to a third of patients, even after clinical resolution of the mucosal lesion, which suggests epithelial atrophy and/or neuropathy. Patients with mucosal pain before cancer therapy may experience more severe mucositis-associated pain during treatment, which suggests the establishment of sensitization. Newer radiotherapy technologies allow reduction of the high-dose volume while increasing the area of low-dose exposure in the region treated.

Pain due to oral mucositis has a dramatic impact on quality of life and frequently requires opioid analgesics, tube feeding, extended hospitalization, and unanticipated rehospitalization, and it may lead to the modification or interruption of cancer therapy. Mucositis pain can be severe, preventing oral intake of food and medications and limiting verbal communication, which causes psychosocial distress. Oral mucosal pain can be exacerbated by comorbidities such as dry mouth and secondary mucosal infection (eg, candidiasis). The breakdown of the epithelial barrier in mucositis produces a portal for opportunistic systemic infection. Dry mouth may be secondary to dehydration or due to the effects of radiation therapy on salivary glands.

Acute mucosal injury may progress into chronic mucosal change, and symptoms range from mild sensitivity to severe, debilitating pain. Associated signs may be mucosal atrophy, vascular change (telangiectasia), depapillation of the tongue, and dry mouth.

Some neurotoxic cytotoxic agents (eg, vincristine, vinblastine, platinum derivatives, taxanes, cyclophosphamide, and thalidomide) may cause jaw pain and neuropathy.

Soft tissue necrosis and osteonecrosis after radiation therapy are known complications that may be associated with pain. The onset of symptoms is variable and may appear decades after radiation therapy.

**Acute Pain**

Surgical procedures result in acute orofacial pain and may ultimately lead to chronic pain involving inflammatory and neuropathic mechanisms. Adjuvant therapies may affect the severity and frequency of pain, and neck dissection may increase musculoskeletal dysfunction and cause neuropathic pain. Radiation therapy may increase postsurgical fibrosis and dysfunction and result in posttraumatic neuropathy.

Orofacial pain after head and neck cancer therapy can develop due to secondary musculoskeletal syndromes (TMDs) or neuropathic syndromes. The impact may be severe if there is discontinuity of the jaw or if fibrosis of muscles and soft tissue occurs. Resection of the mandible to excise a tumor inevitably leads to sensory impairment; 50% of patients experience regional hyperalgesia or allodynia. Two to 5 years after maxillectomy, approximately 90% of patients reported persistent pain. Functional consequences are often secondary to pain and postsurgical fibrosis.

Pain scores after head and neck cancer surgery were highest for oral cavity cancers followed by cancers of the larynx, oropharynx, and nasopharynx. More than 50% of these patients experienced postoperative functional problems. For example, persistent impairment from moderate to severe pain was found in 34.3% of patients more than 6 months after surgery. The most frequent sites of pain were the shoulder (31.0% to 38.5% of patients), neck (4.9% to 34.9%), TMJ (4.9% to 20.1%), oral cavity (4.2% to 18.7%), and other sites of the
Orofacial pain of noncancerous etiology in patients with cancer

Orofacial pain of noncancerous causes occurs frequently during cancer treatment. Immunosuppression, surgery, and emotional stress contribute to increased risk for orofacial infections. Pain may be due to oral bacterial or fungal infection or due to reactivation of viral infections in the oral tissues. Postherpetic neuralgia may result in chronic pain in approximately 10% of patients, and pain may persist for years (see chapter 12). Pain may also be due to local dental disease (see chapter 6), and if it is due to infection, the pain may be more significant in patients who are myelosuppressed.

Osteonecrosis of the jaws due to antiresorptive compounds occurs in approximately 7% (range, 0% to 27.5%) of patients treated with bisphosphonates, denosumab, sunitinib, and bevacizumab for oncology indications, and it is associated with pain in most identified cases of necrosis. Pain in patients with osteonecrosis of the jaws may be explained by secondary infection, local ischemia, or bone fracture. Neuropathy may develop when the lesion involved in osteonecrosis of the jaws is adjacent to the mandibular nerve.

As the use of targeted therapies increases, more oral complications are reported, including pain. Stomatitis associated with the mammalian target of rapamycin inhibitor may affect more than 50% of patients and has a different presentation from conventional cytotoxic mucositis. The pain from the oral ulcers was found to be severe enough to prompt a dosage reduction in 24% of patients. As data accumulate, the pathophysiologies of pain-preventive approaches and pain-management techniques are expected to improve. Disruption of the oral mucosa barrier likely causes inflammation, and the areas become infected secondarily. Stomatitis and oral pain were also reported in patients treated with epidermal growth factor receptor inhibitors, such as cetuximab and erlotinib, and in those receiving imatinib, the tyrosine kinase inhibitor for platelet-derived growth factor receptor.

Oral graft-versus-host disease (GVHD) is a manifestation of systemic GVHD, secondary to allogeneic hematopoietic stem cell transplantation. Little information is known about acute oral GVHD. Chronic oral GVHD mimics a number of autoimmune disorders, including lichen planus, SLE, and systemic sclerosis and has a clinical presentation that includes mucosal erythema, atrophy, pseudomembranous ulceration, hyperkeratotic striae, plaques, and papules.

Treatment of orofacial pain in patients with cancer

Effective management of orofacial pain in patients with cancer requires comprehensive assessment of the multifactorial etiologies and treatment directed at these causative factors. Treatment of cancer-related pain is accomplished by effective treatment of the malignant disease. Treatment of head and neck cancer is beyond the scope of this book. For the management of oral complications in patients with cancer, the reader is referred to several systematic reviews. Numerous studies regarding oral mucositis are described later, and principles of palliative care are relevant to all oral mucosal injuries.

Prevention of mucosal damage

Treating malignancies with minimal damage to healthy tissues is a goal of cancer therapy. However, because of poor cure rates in head and face (4.2% to 15.6%), which reflects morbidity secondary to tumor and regional lymph node resection. Despite the fact that more than 60% of patients reported pain, most of which was rated as severe, 75% of these patients were not taking analgesics. In any event, analgesics and physiotherapy were found to be largely ineffective in the treatment of chronic pain in these patients. At 54 to 60 months after surgery, a smaller proportion of reviewed patients (14.9%) had persistent pain, which suggests gradual remission over time. In patients after cancer surgery, pain is characterized as acute and chronic. The acute pain lasts 1 or 2 months and gradually improves. The chronic pain in survivors of head and neck cancer is often unrecognized and therefore untreated, though it may remain more than 3 years and is associated with functional problems.
and neck cancer, particularly in advanced disease, more intense radiation protocols with hyperfractionation, combined chemoradiotherapy, and radiation for recurrences increase the intensity, severity, and duration of mucositis. Patients receiving these intensive regimens are at a greater risk of mucositis, which then limits therapy.375 Considerable effort is made to minimize mucositis, including radiation treatment planning (intensive modulated radiotherapy); changes in chemotherapy drugs, doses, or schedule of delivery; and effective prophylaxis and early treatment of emerging mucositis. According to the clinical practice guidelines for the management of oral mucositis developed by the Multinational Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO), several modalities are recommended for the prevention of oral mucositis. The guidelines are specific to the population of cancer patients. Prevention of oral mucositis indirectly reduces pain423 (Table 14-3).

Basic oral care
The goal of basic oral care is to maintain oral health, reduce tissue irritation, and control dental plaque levels. Evidence suggests that good oral hygiene, which decreases the microbial load, may reduce the frequency and severity of oral mucositis and, therefore, of associated pain.432 The MASCC/ISOO clinical practice guidelines suggest that an oral care protocol be implemented to prevent oral mucositis in all age groups and across all cancer treatment modalities.424

Topical approaches for mucosal pain relief
The oral mucosa is accessible for topical interventions, although the unpleasant taste, associated nausea, and diluting effects of saliva may limit compliance and effectiveness (see chapter 16). Topical anesthetics are used to treat pain from mucosal injury. Topical anesthetics have a limited duration of effect (15 to 30 minutes), may sting upon application to damaged mucosa, and suppress taste and the gag reflex. After lidocaine rinse, systemic absorption across ulcerated mucosal surfaces is increased compared with that for healthy persons; however, the difference is relatively minimal.433 Topical anesthetics are often mixed with coating and antimicrobial agents, such as milk of magnesia, diphenhydramine, or nystatin (often called “magic mouthwash” or “oncology mouthwash”).

The MASCC/ISOO guidelines for the management of oral mucositis include a few topical treatment modalities and present evidence that doxepin and morphine reduce pain423 (see Table 14-3). Doxepin (a tricyclic antidepressant) 0.5% mouthrinse in patients with cancer results in analgesia and is maintained for at least 4 hours after a single application.434 Topical morphine in a 2% mouthwash has been shown to be effective for relieving pain,435 but there is concern about dispensing large volumes of the medication.

Coating agents have been promoted for managing pain from mucosal injury. Sucralfate was suggested for pain management, although it has not been shown to reduce oral mucositis.436 Other coating agents, such as antacids and milk of magnesia, have not been shown to significantly reduce pain.

Nonpharmacologic local approaches for pain relief in patients with cancer include light therapy and cryotherapy.423 Other agents mentioned in the MASCC/ISOO systematic review and additional guidelines may develop as data accumulate.420–422,424–431,437

Systemic medications
The World Health Organization (WHO) Pain Management Ladder has been recommended for managing pain in patients with cancer318 (Box 14-1). Pain is reduced by following the WHO ladder to one-third of pretreatment intensity in 70% to 90% of patients 438,439; therefore, 10% to 30% of patients with cancer do not achieve adequate pain control.440 The WHO analgesic ladder assumes that pain progresses gradually, which may not be accurate. Furthermore, a meta-analysis has challenged the effectiveness of weak opioids (step II medications); no difference in effectiveness was seen between nonsteroidal anti-inflammatory medications (NSAIDs; step I) and weak opioids (step II) regarding pain management, but there were increased side effects from the weak opioids.441,442 The strong opioids (step III), however, provide better pain control.443 Therefore, a
### Table 14-3: MASC/ISOO evidence-based clinical practice guidelines for mucositis secondary to cancer therapy

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendations in favor</strong></td>
<td></td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>30 minutes of oral cryotherapy should be used to prevent oral mucositis in patients receiving bolus 5-fluorouracil chemotherapy.</td>
</tr>
<tr>
<td>Recombinant human keratinocyte growth factor-1/palifermin</td>
<td>Recombinant human keratinocyte growth factor-1/palifermin should be used to prevent oral mucositis (at a dose of 60 μg/kg per day for 3 days before conditioning treatment and for 3 days after transplant) in patients receiving high-dose chemotherapy and total body irradiation, followed by autogenous stem-cell transplantation for a hematologic malignancy.</td>
</tr>
<tr>
<td>Low-level laser therapy</td>
<td>Low-level laser therapy (wavelength at 650 nm, power of 40 mW, and each square centimeter treated with the required time to a tissue energy dose of 2 J/cm²) should be used to prevent oral mucositis in patients receiving hematopoietic stem-cell transplantation conditioned with high-dose chemotherapy, with or without total body irradiation.</td>
</tr>
<tr>
<td>Patient-controlled analgesia</td>
<td>Patient-controlled analgesia with morphine should be used to treat pain due to oral mucositis in patients undergoing hematopoietic stem-cell transplantation.</td>
</tr>
<tr>
<td>Benzydamine</td>
<td>Benzydamine mouthwash should be used to prevent oral mucositis in patients with head and neck cancer receiving moderate-dose radiation therapy (up to 50 Gy) without concomitant chemotherapy.</td>
</tr>
<tr>
<td><strong>Suggestions in favor</strong></td>
<td></td>
</tr>
<tr>
<td>Oral care protocols</td>
<td>Oral care protocols should be used to prevent oral mucositis in all age groups and across all cancer treatment modalities.</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>Cryotherapy should be used to prevent oral mucositis in patients receiving high-dose melphalan, with or without total body irradiation, as conditioning for hematopoietic stem-cell transplantation.</td>
</tr>
<tr>
<td>Low-level laser therapy</td>
<td>Low-level laser therapy (wavelength around 632.8 nm) should be used to prevent oral mucositis in patients undergoing radiotherapy, without concomitant chemotherapy, for head and neck cancer.</td>
</tr>
<tr>
<td>Transdermal fentanyl</td>
<td>Transdermal fentanyl may be effective to treat pain due to oral mucositis in patients receiving conventional or high-dose chemotherapy, with or without total body irradiation.</td>
</tr>
<tr>
<td>Morphine mouthwash</td>
<td>2% morphine mouthwash may be effective to treat pain due to oral mucositis in patients receiving chemoradiation for head and neck cancer.</td>
</tr>
<tr>
<td>Doxepin mouthwash</td>
<td>0.5% doxepin mouthwash may be effective to treat pain due to oral mucositis.</td>
</tr>
<tr>
<td>Zinc</td>
<td>Systemic zinc supplements administered orally may be of benefit to prevent oral mucositis in patients with oral cancer who are receiving radiation therapy or chemoradiation.</td>
</tr>
<tr>
<td><strong>Recommendations against</strong></td>
<td></td>
</tr>
<tr>
<td>PTA and BCoG antimicrobial lozenges and PTA paste</td>
<td>PTA and BCoG antimicrobial lozenges and PTA paste should not be used to prevent oral mucositis in patients receiving radiation therapy for head and cancer.</td>
</tr>
<tr>
<td>Iseganan antimicrobial mouthwash</td>
<td>Iseganan antimicrobial mouthwash should not be used to prevent oral mucositis in patients receiving high-dose chemotherapy, with or without total body irradiation, for hematopoietic stem-cell transplantation (level of evidence II), or in patients receiving radiation therapy or concomitant chemoradiation for head and neck cancer.</td>
</tr>
<tr>
<td>Sucralfate mouthwash</td>
<td>Sucralfate mouthwash should not be used to prevent or treat oral mucositis in patients receiving chemotherapy for cancer or in patients receiving radiation therapy or concomitant chemoradiation for head and neck cancer.</td>
</tr>
<tr>
<td>Intravenous glutamine</td>
<td>Intravenous glutamine should not be used to prevent oral mucositis in patients receiving high-dose chemotherapy, with or without total body irradiation, for hematopoietic stem-cell transplantation.</td>
</tr>
</tbody>
</table>
change in the WHO ladder has been discussed, where step I medications are used for mild pain, and the lowest effective doses of strong opioids are individually titrated (dose and administration route) to control more severe pain\(^{444}\) (see Table 14-3). Transdermal fentanyl has become widely used in the management of oropharyngeal pain in patients with cancer.\(^{445,447}\) Evidence supports the use of transdermal fentanyl for the management of oral mucositis pain.\(^{423}\) Ideally, patients should be as close to pain free as possible with regular analgesics, and additional analgesics should be administered for breakthrough pain.\(^{448,450}\) Daily assessment of pain levels and modification of pain medications according to the WHO ladder have been shown to improve pain control in patients with head and neck cancer who are receiving radiotherapy.\(^{451}\)

Addiction to opioids is not a concern for patients with cancer. The focus should be on escalating to stronger opioids as needed and using adjuvant approaches to provide adequate pain relief. Tolerance and physical side effects, such as constipation, nausea, vomiting, and mental clouding, may occur with opioid use and should be anticipated and managed prophylactically, if possible.

Improved pain control may be achieved with opioid substitution and rotation.\(^{448,449,452}\) Parenteral opioids have been shown to provide improved analgesia for patients suffering from cancer pain who have not responded to

**Table 14-3** (cont)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorhexidine mouthwash</td>
<td>Chlorhexidine mouthwash should not be used to prevent oral mucositis in patients receiving radiation therapy for head and neck cancer.</td>
</tr>
<tr>
<td>Granulocyte macrophage colony-stimulating factor mouthwash</td>
<td>Granulocyte macrophage colony-stimulating factor mouthwash should not be used to prevent oral mucositis in patients receiving high-dose chemotherapy for autologous or allogeneic stem-cell transplantation.</td>
</tr>
<tr>
<td>Misoprostol mouthwash</td>
<td>Misoprostol mouthwash should not be used to prevent oral mucositis in patients receiving radiation therapy for head and neck cancer.</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>Systemic pentoxifylline, administered orally, should not be used to prevent oral mucositis in patients undergoing bone marrow transplantation.</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>Systemic pilocarpine, administered orally, should not be used to prevent oral mucositis in patients receiving radiation therapy for head and neck cancer (level of evidence III) or in patients receiving high-dose chemotherapy, with or without total body irradiation, for hematopoietic stem-cell transplantation.</td>
</tr>
</tbody>
</table>

PTA, polymyxin, tobramycin, amphotericin B; BCoG, bacitracin, clotrimazole, gentamicin.

**Box 14-1** Steps in the management of orofacial pain in patients with cancer (based on the modified WHO pain ladder)

1. Diagnose/treat cause
2. Topical therapy for mucosal pain
3. Nonopioid analgesics
4. Strong opioids
   - Adjunctive medications: centrally acting analgesics*
   - Adjunctive/complementary management†
5. Repeated assessment of effect and side effects

*For example, tricyclic antidepressants, gabapentin, antiseizure medications, antianxiety agents, muscle relaxants, and sleep-promoting medications.
†Physical therapy, acupuncture, and psychologic management.
oral opioids, which suggests that a change in route of administration can be effective. Administration of more than one opioid may also offer increased pain relief; for example, oxycodone used in addition to morphine and methadone may improve pain relief.438

NSAIDs for patients with cancer reduce the need for opioids, although they may lead to gastrointestinal discomfort.453 Topical agents should be continued after systemic medications have been started.

Adjuvant medications, such as centrally acting pain medications (eg, tricyclic antidepressants, gabapentin) have been suggested.438,454 Amitriptyline has been studied in a placebo-controlled trial in addition to morphine in neuropathic cancer pain. A limited additional analgesic effect was reported, but sleep improved. However, increased side effects including drowsiness, confusion, and dry mouth were observed.448,449 Improved pain control from combining gabapentin with morphine was noted during wound dressing changes in patients with cancer454 and may affect the neuropathic component of pain.438

### Box 14-2 Additional and complementary pain management techniques in oncology

- Palliative radiation therapy
- Cold/moist heat applications
- Hypnosis
- Acupuncture
- Psychologic
  - Distraction techniques
  - Relaxation/imagery techniques
- Music therapy or drama therapy

- Counseling
- Cognitive-behavioral therapy
- Topical anesthetics/analgesics
- Adjunctive medications
  - Anxiolytics
  - Coanalgesics/centrally acting agents
  - Anticonvulsants
  - Antidepressants

Complementary pain management strategies

Complementary pain-management techniques are presented in Box 14-2 (see also chapter 17). Hypnosis has been studied in randomized trials as a complementary method of pain control in patients with cancer. A variety of hypnotic techniques have been discussed, including vocal techniques, listening, and instrumental techniques, but there are no controlled studies of their impact on cancer pain.438,450 Additional psychologic techniques, including counseling, distraction, relaxation, and other cognitive and behavioral training programs have been discussed. Physical management of orofacial pain may include ice chips for oral cooling and cold compresses.

Complementary and alternative medicine, including acupuncture, transcutaneous nerve stimulation, group therapy, self-hypnosis, relaxation, imagery, cognitive-behavioral training, and massage therapy have been assessed for pain management in patients with advanced cancer and may reduce pain.429,456 A controlled trial showed that relaxation and imagery improve pain in oral mucositis.457

### Orofacial Pain in Patients with HIV

#### HIV-related headache

Headache is a common symptom in patients with HIV infection. Primary or secondary headache may be seen in 42% to 50% of patients,458–460 although there is great variability in the reported incidence of primary headache in patients with HIV infection. Primary headache was found to occur in 2.8% of patients with HIV infection admitted to an HIV service over a 1-year period. This incidence was much higher than the incidence of headache among HIV-negative patients admitted to the neurology service (0.8%).461 Others have reported the incidence of primary headache in HIV-positive patients to be as high as 38%.460,462 The most prevalent types of primary headaches are ten-
Orofacial Pain in Patients with HIV

Cluster headache is much less common (10%). Identifiable, serious causes of headache are found in up to 82% of patients with HIV infection who presented with headache.

TMDs may be associated with headache and cause facial pain and dysfunction. Patients with HIV infection often report chronic pain and pathologies targeting body joints during retroviral therapy, including TMDs.

Because HIV is a neurotropic virus, it can be anticipated that neurologic complications in AIDS are common. HIV crosses the blood-brain barrier, infects macrophages and microglia in the CNS, and is a common cause of neurocognitive impairment. The release of inflammatory mediators by HIV-infected microglia and macrophages and the concurrent neuronal damage play central roles in the HIV-related neuropathology.

Secondary headaches in HIV patients have numerous causes, such as acute HIV meningitis and malignant disease. Head and neck and CNS cancer due to local primary cancer, systemic cancer, and metastatic disease may cause pain in HIV-positive persons.

A chronic form of headache in HIV is associated with cerebrospinal pleocytosis. Headaches may be caused by neoplasms and opportunistic infections, resulting in meningitis (cryptococcal, tuberculous, or syphilitic), focal brain lesions (lymphoma, toxoplasmosis), or diffuse brain disease (cytomegalovirus, herpes simplex, progressive multifocal leukoencephalopathy). Cryptococcal meningitis (39%) and CNS toxoplasmosis (16%) were the leading infectious etiologies for HIV headache.

Facial pain may be caused by sinusitis, ocular pathology, and systemic infection and may be associated with diagnostic testing (eg, intracranial hypotension from diagnostic lumbar puncture).

Sinusitis due to deep mycotic infection may present chronic pain until diagnosed and successfully treated. Affected patients usually have advanced HIV infection. A correlation between the presence of headache and the degree of immunosuppression has been observed. Nevertheless, HIV-related headaches can occur at any time during infection—at seroconversion, during the incubation period, in patients with symptomatic HIV infection, or after an AIDS-defining illness. Investigators have suggested that progression of immunologic deficiency is related to a decrease in the frequency of migraine and an increase in the frequency of tension-type headache.

The stage of disease also has a practical implication, as the value of computed tomography scan was shown to be highest for patients with CD4 counts less than 200 cells/μL. The highest prevalence of positive scans was found in patients with advanced disease. This is in accordance with the fact that CD4 counts predict the relative risk of developing opportunistic infections and neoplasms, including those in the CNS. Thus, in the absence of significant immunosuppression, computed tomography or MRI is not suggested unless focal findings are present on neurologic examination. However, the headache frequency and characteristics may bear no relation to CD4 counts, cerebrospinal fluid parameters, cranial MRI abnormalities, the presence of sinusitis, or the use of zidovudine.

Treatment of head or facial pain is directed at the etiology when this is possible. Unfortunately, headaches in patients with HIV frequently do not respond to conventional management and carry a poor prognosis.

HIV-related oral painful mucosal lesions

The oral cavity is a common site of painful lesions in patients who are seropositive for HIV and is one of the most common sites of pain in the whole body. A report of 157 HIV-positive people, 99 on highly active antiretroviral therapy (HAART) and 58 not on HAART, found greater risk of orofacial pain, oral lesions, and periodontal pockets for those on HAART and for those on long-term HAART than those on short-term treatment (P < .05).

Oral candidiasis, the most common oral lesion identified, may cause an oral burning sensation. Other oral infections—fungal, viral, and bacterial—are well recognized and often result in local pain with possible systemic febrile episodes.

Patients with HIV may suffer from the major form of oral recurrent aphthous ulcers, which can result in considerable pain that affects oral function. Although recurrent aphthous ulcers are not etiologically related to a specific patho-
gen, secondary infection can occur at the lesion’s site.477
Necrotizing gingivitis and necrotizing periodontitis can progress rapidly and can be extremely painful.478 A more extensive form, necrotizing stomatitis, is also reported.478,479 Recurrent herpetic simplex infections and herpes zoster can be of extended duration, involve keratinized and nonkeratinized mucosa, and result in persisting pain.

**HIV-related neuropathy**

Neurologic manifestations of HIV have been reported in the head and neck480 but are rare.481 Some cases of facial nerve dysfunction482,483 and cases of recalcitrant headaches have been reported.484 Peripheral neurologic symptoms have been recognized early in primary HIV infection485,486 and later in the disease progression, mainly as a potential side effect of HIV antiviral medications.487–489 Although often difficult to manage, peripheral neuropathy due to medications such as thalidomide may be improved if the suspected medication is discontinued.490

Strong associations between neuropathies and opportunistic viral infections or thalidomide have been documented.491–493 Clinical management of neuropathic pain should be aggressive with a multidisciplinary, comprehensive approach similar to that for cancer-related pain.484,493,494 Clinicians should address the etiology of the pain, whenever possible, especially in cases of the viral-related pain that still is commonly observed in HIV disease.495

Lyme disease has been reported in HIV-positive patients and is estimated to be more common in infected persons than in healthy persons, with more severe symptoms in increasingly immunosuppressed patients and associated with CNS and neuropathologic symptoms.496

**Amyloidosis**

Amyloid is an eosinophilic hyaline protein that pathologically accumulates within tissues in a number of diseases and is thus nonspecific. Amyloid has a characteristic fibrillar structure, seen on electron microscopy, that varies in different forms of amyloidosis but is in all cases associated with a nonfibrillar component termed amyloid P. The widespread lesions in amyloid disease and the possible involvement of virtually any system make this disorder protean in its manifestations. Systemically, amyloid is deposited mainly in the heart, skeletal muscle, and gastrointestinal tract, so that normal function of these organs is severely compromised. Orofacial manifestations may occur by

**Aggregation Disease**

**Fabry disease**

Fabry disease is a rare (reported annual incidence of 1 in 100,000, but this may be an underestimation) X-linked lysosomal storage disorder caused by a deficiency of the enzyme alpha-galactosidase A, which causes glycolipids, such as globotriaosylceramide, to accumulate in the vascular endothelium of several organs, including the skin, kidneys, nervous system, and heart, thereby triggering inflammation and fibrosis. These processes generally result in organ dysfunction, which is usually the first clinical evidence of Fabry disease. Evolving knowledge about the natural course of disease suggests that it is more appropriate to describe Fabry disease as a disease with a wide spectrum of heterogenously progressive clinical phenotypes. Most female heterozygotes develop symptoms due to as-yet undetermined mechanisms, and a high percentage of females develop vital organ involvement, including the kidneys, heart, and/or brain about a decade later than males.497,498 One of the predominant signs of Fabry disease found in a cohort of young patients was acroparesthesia (paresthesia of the limbs and tips of other extremities due to nerve compression or polyneuritis).499 Cranial nerve dysfunction resulting in facial paresthesia, odontogenic-like pain, trigeminal neuralgia, taste and smell impairment, or glossomotor dysfunction has been described.500 Neurologic and psychologic changes, such as headache, recurrent vertigo, tinnitus, diminished level of activity, fatigue, and depression, have also been reported in patients with Fabry disease.499 In patients with Fabry disease, it is noteworthy that there is an increased prevalence of cutaneous and mucosal angio-keratomas and telangiectasia as well as cysts or pseudocysts of the maxillary sinuses.501,502

**[AU: Edits ok?]**
Craniofacial Pain Related to Miscellaneous Medical Conditions

Medication-overuse headache

Medication-overuse headache (MOH) is a refractory chronic headache associated with medication management for pain. The development of MOH is associated with frequency of use of medication and behavioral predispositions, including potential psychopathology and drug dependence. MOH affects quality of life and causes symptoms that may include daily and incapacitating headaches, insomnia, poor sleep, distress, and reduced functioning. Acetaminophen, combination analgesics (caffeine combinations), opioids, barbiturates, NSAIDs, and triptans are common classes of drugs implicated in MOH. Migraine seems to be the most common diagnosis leading to MOH.

MOH is associated with biochemical, structural, and functional brain changes. Relapse after detoxification is a challenge but can be addressed by scheduling expert and regular follow-up on an ongoing basis, using prophylactic pharmacotherapy, using abortive medication with minimal risk of MOH, withholding previously overused medication, and providing psychologic support.

MOH appears to be due to increased excitability of neurons in the cerebral cortex and trigeminal system after medication overuse. Prior chronic exposure to analgesics may increase susceptibility to evoked cortical-spreading depression. Cortical hyperexcitability may facilitate cortical spreading, and increased excitability of trigeminal neurons may facilitate peripheral and central sensitization. These changes may lead to altered central serotonin (5-hydroxytryptamine) and perhaps cannabinoid modulation, leading to a decrease in inhibitory control that may then lead to central sensitization. Low 5-hydroxytryptamine levels may also increase release of calcitonin gene–related peptide from the trigeminal ganglion and sensitize trigeminal nociceptors. This central modulation of the trigeminal system associated with chronic medication use may increase sensitivity to facial pain and headache.

A systematic literature review of MOH included 27 studies. The commonly used case definition for MOH was headache for at least 15 days per month with concurrent medication overuse of at least 3 months. A wide range of prevalence—0.5% to 7.2%—was observed due to variable definitions and criteria for drug overuse and persisting headache symptoms that may overlap symptoms.

NSAIDs may be associated with MOH and rebound headache. Inhibition of cyclooxygenase-1 and cyclooxygenase-2 may result in inhibition of synthesis of prostaglandins and may also increase risk of vascular complications, including stroke.

The medical treatment of patients with chronic primary headache syndromes (chronic migraine, chronic tension-type headache, chronic cluster headache, hemicrania continua) is challenging. When a definitive lack of responsiveness to conservative treatments is observed, consideration should be given to the potential for MOH. Approaches to management include discontinuing probable etiologic agent(s), potential trial of neurologically active agents such as valproic acid, and neuromodulation. A total of 694 patients with MOH were treated by detoxification and prophylactic treatment. Management resulted in a 58.4% reduction in headache days (P < .001) and a 57.1% reduction in disability score from baseline (P < .001). The number of patients with depression was reduced by 50.7%, and the number with anxiety was reduced by 27.1% (both P < .001) (see also chapter 10). The impact of treatment emphasizes the need for awareness of potential overuse of headache medications.

Tolosa-Hunt syndrome

Tolosa-Hunt syndrome is defined as unilateral orbital pain associated with paresis of one or
more of the third, fourth, and/or sixth cranial nerves caused by a granulomatous inflammation in the cavernous sinus, superior orbital fissure, or orbit, according to the International Classification of Headache Disorders (ICHD). Considering that the trigeminal nerve; internal carotid artery; the third, fourth, and sixth cranial nerves; and the autonomic nerves of the eye are intimately related in the cavernous sinus, lesions in this area can cause facial pain associated with a number of ocular signs depending on which nerves are affected.

Two reports laid the groundwork for the definition of this syndrome. In large series, Tolosa-Hunt syndrome was reported to develop in the fifth decade on average; however, it affects people of all ages. The diagnostic criteria for the syndrome were revised in 2013 (Box 14-3). Accordingly, Tolosa-Hunt syndrome is characterized by episodes of unilateral orbital pain persisting for weeks. Coinciding with the onset of pain, or closely following it, is paresis of one or more of the third, fourth, and sixth cranial nerves. Previously, the response to corticosteroids was considered a diagnostic criterion, but this was removed in the most recent ICHD classification. Debate continues in the literature regarding diagnostic criteria.

Diagnosis is based on the clinical presentation, biopsy, and MRI demonstrating a granulomatous lesion. The typical clinical presentation is pain in the orbital or retro-orbital area of severe and fluctuating intensity. The pain is described as pressure, boring, or knifelike pain in the eye. The third nerve is involved in most patients (90%) and the fourth nerve in 40%. The incidence of identifiable lesions in the cavernous sinus increases with the number of nerves involved. Often, there may be a reduced pupillary light reflex and ptosis suggestive of autonomic dysfunction. Periorbital hypoesthesia and a reduced corneal reflex are secondary to sensory dysfunction of the frontal branch of the ophthalmic nerve. Optic nerve involvement (reduced acuity) and involvement of the maxillary nerve suggest lesion enlargement.

The typical MRI findings include T1 iso-intense and T2 hypointense focal-enhancing masses expanding the ipsilateral cavernous sinus. Occasionally, lateral bulging of the anterior cavernous sinus contour and internal carotid artery narrowing are seen on the MRI. Obtaining evidence of the granulomatous nature of the lesion is challenging, and occasionally no evidence of inflammation is observed on the imaging; therefore, the subclassifications benign Tolosa-Hunt syndrome and granulomatous lesion–related Tolosa-Hunt syndrome have been suggested.

Clinical variations include involvement of other cranial nerves or bilateral involvement. Involvement of the fifth nerve (commonly the first division) or optic, seventh, or eighth nerve was reported, as well as sympathetic innervation of the pupil. This presentation suggests that Tolosa-Hunt syndrome may be a presentation of a more widespread disorder.

The differential diagnosis of the syndrome includes other vascular disorders, such as cavernous sinus thrombosis and giant cell arteritis of the temporal artery, diabetic neuropathy, and

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**Box 14-3** ICHD-3 diagnostic criteria for Tolosa-Hunt syndrome

A. Unilateral headache fulfilling criterion C
B. Both of the following:
   1. Granulomatous inflammation of the cavernous sinus, superior orbital fissure, or orbit, demonstrated by MRI or biopsy
   2. Paresis of one or more of the ipsilateral third, fourth, and/or sixth cranial nerves
C. Evidence of causation demonstrated by both of the following:
   1. Headache has preceded paresis of the third, fourth, and/or sixth nerves by at least 2 weeks or developed with it
   2. Headache is localized around the ipsilateral brow and eye
D. Not better accounted for by another ICHD-3 diagnosis

[AU: What does the asterisk denote?]
Craniofacial Pain Related to Miscellaneous Medical Conditions

ophthalmoplegic migraine. Neoplastic and infectious processes in the region and infiltrative disorders such as SLE, lymphoma, sarcoidosis, and syphilis have also been associated with orbital pain.531,532

Treatment is with high-dose steroids (80 to 100 mg of prednisone daily) tapered over 7 to 14 days. Longer treatment is often needed to completely resolve the symptoms. Surgical excision may be necessary. Recurrence and resistant cases have been described, and there has been some success using experimental treatments.533,534

Cervicogenic headache

Musculoskeletal spine disease may be associated with cervicogenic headache. The clinical features of cervicogenic headache are nonspecific and often mimic migraines or tension-type headaches. Headaches may be unilateral or bilateral. Quality is nonthrobbing, is of moderate intensity, and may be continuous or intermittent. The headache is usually aggravated by neck movements, pressure on the neck, or awkward neck postures. Reduced cervical range of motion and pain referral to the ipsilateral shoulder and arm may also be observed. Autonomic signs such as nausea, vomiting, phonophobia, photophobia, and edema or flushing around the eye may be present, but much less than in migraine and tension-type headache. Provocation of the cervicogenic headache by digital pressure on neck muscles is suggestive of the diagnosis but not considered conclusive.19 The ICHD diagnostic criteria help differentiate cervicogenic headache from other headaches (Box 14-4). Cervicogenic headache may or may not be accompanied by neck pain; however, it is clearly triggered by cervical structures,535 and cervical lesions have been detected by neuroimaging techniques in some patients.

Although the neck is the origin of this headache, it has been suggested that the neck is not an independent headache generator.535 Accordingly, the pathophysiology of cervicogenic headache includes local neck changes and a central predisposition that activates the trigeminovascular system and generates pain. Another hypothesis is that musculoskeletal problems in the neck cause headache by the mechanism of referred pain. The greater and lesser occipital branches of the sensory second cervical (C) root may refer pain to the back of the head. The sensory first cervical root may refer pain to the vertex or frontal region, but some consider this unlikely. Connections between C2 branches from the posterior fossa to branches of the ophthalmic nerve would refer pain to the front of the head.

Clearly, when an underlying organic disease is identified as the cause of the cervicogenic headache, treatment should be aimed at the source of the problem. Various treatment approaches have been examined: steroids,536 manual therapy and physical therapy,537–539 electric therapy,540 botulinum toxin injections,541 cervical anesthetic blocks targeting distinct nerves or roots, and surgery. [AU: Ok?] Physical therapy may decrease pain outcomes in

<table>
<thead>
<tr>
<th>Box 14-4</th>
<th>ICHD-3 diagnostic criteria for cervicogenic headache</th>
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<tbody>
<tr>
<td>A. Any headache fulfilling criterion C</td>
<td></td>
</tr>
<tr>
<td>B. Clinical, laboratory, and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck, known to be able to cause headache</td>
<td></td>
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<tr>
<td>C. Evidence of causation demonstrated by at least two of the following:</td>
<td></td>
</tr>
<tr>
<td>1. Headache has developed in temporal relation to the onset of the cervical disorder or appearance of the lesion</td>
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<tr>
<td>2. Headache has significantly improved or resolved in parallel with improvement in or resolution of the cervical disorder or lesion</td>
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<tr>
<td>3. Cervical range of motion is reduced and headache is made significantly worse by provocative maneuvers</td>
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<tr>
<td>4. Headache is abolished after diagnostic blockade of a cervical structure or its nerve supply</td>
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<tr>
<td>D. Not better accounted for by another ICHD-3 diagnosis</td>
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patients with cervicogenic headache. More studies are needed to determine the effectiveness of these treatments.

Craniofacial pain attributed to trauma or injury to the head and/or neck

Traumatic injury to the head is defined as structural or functional damage from the action of external forces on the head. These include striking the head, or using the head to strike an object, penetration of the head by a foreign body, forces generated from blasts or explosions, and other forces yet to be defined.

Headache or facial pain that occurs de novo in close temporal relation to trauma or an existing pain disorder that becomes significantly worse may be classified as having headache attributed to trauma or injury (HATI). In the previous ICHD-2 classification, the equivalent term was posttraumatic headache.

According to the ICHD-3, HATI may be acute or persistent and may be subclassified according to the severity of the injury as mild or moderate to severe (Table 14-4). Acute HATI occurs within 7 days and resolves within 3 months of injury; persistent HATI is diagnosed if pain persists beyond 3 months.

No criteria comparable with those of the IHS have been established for posttraumatic facial pain. Extrapolating from the ICHD criteria would allow the description “HATI” to be added to patients where the facial pain began in close temporal proximity to a traumatic event (< 7 days) and persists beyond 3 months.

The long-term persistence of CFPATI is unrelated to physical variables associated with the trauma, such as severity or loss of consciousness. The factors that significantly increased the persistence of CFPATI 22 years after trauma were female sex, high intensity of the acute CFPATI, and psychiatric comorbidity.

CFPATI epidemiology and risk factors

Acute headache that occurs after trauma to the head or face region is relatively common and occurs in 30% to 90% of patients. The number of patients that continue to suffer pain and develop chronic CFPATI is variable. About a third of patients with head injury report persistent headache at 3 months, a quarter or more may still report pain 4 or 5 years after injury, and 11% suffer frequent headaches after 22 years of follow-up. Most chronic CFPATI cases were caused by motor vehicle accidents, some by falls or assaults, and a minority by sports injuries.

The clinical features commonly resemble tension-type headache or migraine, and more than one disorder may occur concomitantly. Migraine-type headaches seem to be more common after acceleration/deceleration injuries to the neck, that is, whiplash injuries to the cervical complex. Musculoskeletal-type pain has also been reported. In rare cases, acute CFPATI could be clinically similar to cluster headaches, hemicrania continua, chronic paroxysmal hemicrania, and SUNCT syndrome (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing).
### Table 14-4: ICHD-3 diagnostic criteria for headache attributed to traumatic injury to the head and/or neck

<table>
<thead>
<tr>
<th>Acute 5.1</th>
<th>Persistent 5.2</th>
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<tbody>
<tr>
<td><strong>Diagnostic criteria</strong></td>
<td><strong>Diagnostic criteria</strong></td>
</tr>
<tr>
<td>A. Any headache fulfilling criteria C and D</td>
<td>A. Any headache fulfilling criteria C and D</td>
</tr>
<tr>
<td>B. Traumatic injury to the head has occurred</td>
<td>B. Traumatic injury to the head has occurred</td>
</tr>
<tr>
<td>C. Headache is reported to have developed within 7 days after one of the following:</td>
<td>D. Either of the following:</td>
</tr>
<tr>
<td>1. Injury to the head</td>
<td>1. Headache has resolved within 3 months after the injury to the head</td>
</tr>
<tr>
<td>2. Regaining consciousness after injury to the head</td>
<td>2. Headache has not yet resolved but 3 months have not yet passed since the injury to the head</td>
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<tr>
<td>3. Discontinuation of medication(s) that impair ability to sense or report headache after injury to the head</td>
<td>3. Discontinuation of medication(s) that impair ability to sense or report headache after injury to the head</td>
</tr>
<tr>
<td></td>
<td>D. Headache persists for &gt; 3 months after injury to the head</td>
</tr>
<tr>
<td>E. Not better accounted for by another ICHD-3 diagnosis</td>
<td>E. Not better accounted for by another ICHD-3 diagnosis</td>
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**Subtypes**

**Attributed to moderate or severe traumatic injury to the head**

A. Headache fulfilling criteria for 5.1 acute headache attributed to traumatic injury to the head

B. Injury to the head associated with at least one of the following:
   1. Loss of consciousness for > 30 minutes
   2. Glasgow Coma Scale score < 13
   3. Posttraumatic amnesia lasting > 24 hours
   4. Alteration in level of awareness for > 24 hours
   5. Imaging evidence of a traumatic head injury, such as intracranial hemorrhage and/or brain contusion

**Attributed to mild traumatic injury to the head**

A. Headache fulfilling criteria for 5.1 acute headache attributed to traumatic injury to the head

B. Head injury fulfilling both of the following:
   1. Associated with none of the following:
      a. Loss of consciousness for > 30 minutes
      b. Glasgow Coma Scale score < 13
      c. Posttraumatic amnesia lasting > 24 hours
      d. Altered level of awareness for > 24 hours
      e. Imaging evidence of a traumatic head injury, such as intracranial hemorrhage and/or brain contusion
   2. Associated, immediately after head injury, with one or more of the following symptoms and/or signs:
      a. Transient confusion, disorientation, or impaired consciousness
      b. Loss of memory for events immediately before or after the head injury
      c. Two or more other symptoms suggestive of mild traumatic brain injury: nausea, vomiting, visual disturbances, dizziness and/or vertigo, impaired memory and/or concentration

A. Headache fulfilling criteria 5.2 persistent headache attributed to traumatic injury to the head

B. Head injury fulfilling both of the following:
   1. Associated with none of the following:
      a. Loss of consciousness for > 30 minutes
      b. Glasgow Coma Scale score < 13
      c. Posttraumatic amnesia lasting > 24 hours
      d. Altered level of awareness for > 24 hours
      e. Imaging evidence of a traumatic head injury, such as intracranial hemorrhage and/or brain contusion
   2. Associated, immediately after head injury, with one or more of the following symptoms and/or signs:
      a. Transient confusion, disorientation, or impaired consciousness
      b. Loss of memory for events immediately before or after the head injury
      c. Two or more other symptoms suggestive of mild traumatic brain injury: nausea, vomiting, visual disturbances, dizziness and/or vertigo, impaired memory and/or concentration

A. Headache fulfilling criteria 5.2 persistent headache attributed to traumatic injury to the head

B. Head injury fulfilling both of the following:
   1. Associated with none of the following:
      a. Loss of consciousness for > 30 minutes
      b. Glasgow Coma Scale score < 13
      c. Posttraumatic amnesia lasting > 24 hours
      d. Altered level of awareness for > 24 hours
      e. Imaging evidence of a traumatic head injury, such as intracranial hemorrhage and/or brain contusion
   2. Associated, immediately after head injury, with one or more of the following symptoms and/or signs:
      a. Transient confusion, disorientation, or impaired consciousness
      b. Loss of memory for events immediately before or after the head injury
      c. Two or more other symptoms suggestive of mild traumatic brain injury: nausea, vomiting, visual disturbances, dizziness and/or vertigo, impaired memory and/or concentration
When headache occurs in conjunction with symptoms of dizziness, fatigue, reduced ability to concentrate, anxiety, personality changes, and irritability, post-concussion syndrome is considered.\textsuperscript{19,561}

Chronic CFPATI may form part of a symptom complex termed \textit{posttraumatic stress disorder} (PTSD), which includes psychologic, social, and cognitive impairments.\textsuperscript{554,559,560,562-565} After orofacial injury, acute PTSD is particularly prominent and may persist with associated disabilities.\textsuperscript{566,567} If PTSD becomes established, a multidisciplinary approach involving pain specialists, psychologist/psychiatrists, physiotherapists, social workers, family physicians, as well as cooperation from family members and coworkers, is required. Additionally, patients may be involved in litigation, and although there is no evidence to suggest that CFPATI is related to ongoing litigation,\textsuperscript{543,568} a careful workup to exclude malingering should be performed\textsuperscript{569}.

Posttraumatic sleep disturbances, mood disturbances, and psychosocial stressors may aggravate CFPATI. The overuse of abortive pain medications may contribute to the persistence of CFPATI (see the section on medication-overuse headache).

\textbf{CFPATI pathophysiology}

The pathophysiology of CFPATI is unclear and probably involves a number of mechanisms that interplay with the psychosocial capabilities and genotype of the patient to dictate who will or will not suffer chronic pain.\textsuperscript{568} The role of trauma in some craniofacial pain syndromes, such as TMDs, is well established (see chapters 8 and 9). Direct injury to musculoskeletal structures may initiate changes that result in persistent pain in susceptible persons. The degree of brain injury is not consistently associated with the incidence or severity of pain. Thus, frank injury to brain tissue plays some part, but other factors are involved. Shear forces applied to the brain result in a phenomenon termed \textit{diffuse axonal injury} (see chapter 12), which may be involved in the initiation of some CFPATI symptoms.

\textbf{CFPATI treatment}

Symptomatic treatment includes the use of drugs relevant to the primary pain disorders (see chapters 8 through 12, 15, and 16) and usually requires additional modalities, such as physical therapy, trigger point injections, and occlusal splints (see chapters 8 and 9). Cognitive-behavioral therapy may be indicated (see chapter 4) and is successful in patients with persistent CFPATI.\textsuperscript{570}

\textbf{Other type of craniofacial pain attributed to trauma}

Whiplash injury results from sudden and inadequately restrained acceleration/deceleration movements of the head with flexion/extension of the neck.\textsuperscript{19} Whiplash most commonly occurs in the context of motor vehicle accidents. Headaches attributed to whiplash are subclassified into acute and persistent based on the duration of the pain (> 3 months is considered persistent).

Whether whiplash induces TMDs is unclear and is discussed in chapter 8. Acute pain occurring locally in the neck after whiplash injuries is relatively common.\textsuperscript{549} Acute headache occurs after many whiplash injuries.\textsuperscript{571} Additionally, whiplash may lead to chronic cervical pain with disability and may induce headache, as described later.\textsuperscript{572} Whiplash-associated disorders have been defined and categorized\textsuperscript{573}; subtype I includes cervical pain and tenderness, and type II has additional features of reduced range of motion and point tenderness. Whiplash-associated disorders I and II are referred to in this section as \textit{chronic whiplash pain}. Types III and IV are associated with fractures and distinct neurologic signs and are beyond the scope of this book. Depending on culture and geographic distribution, up to 82% of patients continue to suffer from chronic pain after whiplash injury.\textsuperscript{549,574,575} The persistence of pain is not consistently related to the degree of trauma or cervical pathology. Similarly, many patients with structural cervical lesions suffer no pain.\textsuperscript{549}

A recent study identified a list of risk factors for persistent problems after acute whiplash injury: The significant variables included high baseline pain intensity (> 5.5/10), report of headache at inception, less than postsecondary education, no seatbelt used during the accident, report of lower back pain at inception, high Neck Disability Index score (> 14.5/50), preinjury neck pain, report of neck pain at in-
ception (regardless of intensity), high catastrophizing, female sex, whiplash-associated disorders I or III, and whiplash-associated disorder III alone.576

Diffuse axonal injury, as described earlier (see also chapter 12), may be involved in the initiation of chronic pain after whiplash injury. The role of litigation in persistence of chronic whiplash pain is unclear. However, one study has shown that when compensation for pain and suffering is eliminated, there is a decreased incidence and improved prognosis of whiplash injury.577

Structural lesions of the cervical spine should be assessed by an orthopedic surgeon or neurologist. Similarly, conservative treatment of chronic whiplash pain should be performed in cooperation with an orthopedic surgeon or neurologist and should involve the use of multimodal therapy/medication, physical therapy, soft collars, trigger point injections, and cognitive-behavioral therapy.

Other types of trauma-related headaches include headache attributed to craniotomy, which is defined as headache of less than 3 months’ duration caused by surgical craniotomy. Headache attributed to radiosurgery of the brain is defined by its temporal relationship to radiosurgery. Similar to HATI, it is subclassified as acute if resolved within 3 months after radiosurgery and persistent if it lasts longer.

**Box 14-5**

**ICHD-3 diagnostic criteria for paratrigeminal oculosympathetic (Raeder) syndrome**

A. Constant, unilateral headache fulfilling criterion C
B. Imaging evidence of underlying disease of either the middle cranial fossa or the ipsilateral carotid artery
C. Evidence of causation demonstrated by both of the following:
   1. Headache has developed in temporal relation to the onset of the underlying disorder
   2. Headache has either or both of the following features:
      a. Localized to the distribution of the ophthalmic division of the trigeminal nerve, with or without spread to the maxillary division
      b. Aggravated by eye movement
D. Ipsilateral Horner syndrome
E. Not better accounted for by another ICHD-3 diagnosis

**Paratrigeminal oculosympathetic syndrome**

Paratrigeminal oculosympathetic syndrome (POSS), formerly known as *Raeder syndrome*, was originally described as trigeminal nerve dysfunction or pain accompanied by ocular sympathetic dysfunction19 (Box 14-5). This was proposed to be the result of a lesion in the middle cranial fossa in the paratrigeminal area. The sympathetic nerve supply to the eye (oculosympathetic outflow) arises from the internal carotid plexus in the middle cranial fossa, medial to the trigeminal ganglion. A lesion in this area would induce trigeminal symptoms (paresthesia, pain) and sympathetic dysfunction of the eye—miosis or ptosis (Horner syndrome). POSS should appear with no alteration in forehead sweating; sympathetic innervation to the sweat glands is mediated by fibers that exit the carotid plexus before the middle cranial fossa and relatively laterally to the oculosympathetic outflow.578 In some instances, however, the parasympathetic system reinnervates the sweat glands so that intact sweating does not signify a functional sympathetic innervation.578 Although the original case had a paratrigeminal neoplasm, later cases were described with no organic pathology.271 Thus, various subgroups were described that presented with a similar phenotype, that
is, Horner syndrome with ipsilateral trigeminal pain/dysfunction.\textsuperscript{271} Patients with oculosympathetic loss, miosis or ptosis, or both, with normal forehead sweating and evidence of trigeminal involvement (either sensory change or neuralgic pain), are highly likely to have a lesion in the middle cranial fossa that is medial to the trigeminal ganglion (paratrigeminal). These patients should be classified as having POSS and should be thoroughly examined, including an MRI at baseline and further studies as needed.\textsuperscript{578} In addition to paratrigeminal middle cranial fossa neoplasms, the most common differential diagnosis is pathology of the carotid artery, which would affect the sympathetic plexus. In particular, carotid artery dissection may occur with unilateral facial pain and Horner syndrome.\textsuperscript{263} In support of a crucial role of the carotid artery in the etiology of POSS, a case report demonstrated that POSS-like symptoms could develop in a patient immediately after surgical manipulation of the carotid artery during an endovascular trapping of a carotid artery aneurysm.\textsuperscript{579}

\section*{Conclusion}

Orofacial pain in a medically complex patient represents a potentially challenging diagnosis and management. Underlying conditions and diseases may be the cause of pain or may represent comorbidities. If the etiology of the pain can be addressed, or if comorbid conditions can also be managed, better pain management can often be achieved. Pain practitioners must have broad knowledge and use high-level diagnostic skills. Often, a multimodal interdisciplinary team approach is required for comprehensive patient care.

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