

Differential Diagnosis of Pain of Non-Odontogenic Origin
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Michael J. Apicella, DDS, MS

Pain Physiology

What is Pain? International Association for the Study of Pain

“An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.”

The 5th Vital Sign

- Temperature
- Pulse
- Respiration
- Blood pressure
- Pain

Physiology of Pain Perception – Six steps to pain

- Transduction
- Transmission
- Modulation
- Perception
- Interpretation
- Behavior

What is Pain?

- Sensory/discriminative
- Emotional/ motivational
- Cognitive

Acute Pain - Nociceptive

- Short duration
- Identifiable cause – Noxious stimulus
- Focal to the site of injury
- Generally self-limited
- Responds to a straight forward treatment plan

Chronic Pain - Neuropathic

- Unrelenting
- No identifiable cause
- Spread beyond the original site of injury
- Serves no biological function
- Psychological disturbances
- Treatment more complex
- Poorer prognosis

Sensitization Process

- Hyperalgesia – increase in pain response from a painful stimulus
- Allodynia – painful response from a non-painful stimulus

Peripheral Nervous System – pseudounipolar nerve cells

A-beta fibers – Cutaneous touch and pressure sensation.

A-delta fibers – Nociception: Mechanoreceptors, thermoreceptors.

C fibers – Nociception: Chemoreceptors, mechanoreceptors, thermoreceptors.

Chronic Orofacial Pain

<p>Axis I</p> <ul style="list-style-type: none">• Somatic Tissues<ul style="list-style-type: none">○ Superficial<ul style="list-style-type: none">▪ Skin, mucosa, gingiva○ Deep<ul style="list-style-type: none">▪ Musculoskeletal▪ Visceral• Neurogenic Tissues<ul style="list-style-type: none">○ Peripheral Nervous system○ Central Nervous System○ Autonomic Nervous System	<p>Axis II</p> <ul style="list-style-type: none">• Anxiety disorders• Mood disorders• Somatoform disorders• Psychological factors
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Pain Transduction

- Mechanical
- Thermal
- Chemical
 - Exogenous
 - Endogenous – Bradykinin, Serotonin, Histamine, Prostaglandins

Voltage Gated Sodium Channels

- Essential for nerve conduction
 - VGSCs – 9 isoforms
- Nociceptors - $Na_v1.7$, $Na_v1.8$, $Na_v1.9$
- TTX – Sensitive $Na_v1.7$
 - Erythromelalgia
 - Congenital insensitivity to pain
- TTX – Resistant $Na_v1.8$, $Na_v1.9$
 - Upregulated by inflammation
 - May play a role in neuropathic pain

Potassium channels

- Essential role in the membrane resting potentials
- Have anti-nociceptive effects

Calcium channels

- Regulates intra-cellular events
- Critical in controlling neurotransmitter release
- Pivotal role in mechanisms that control pain and anti-nociception

Heat/Cold Sensors

- Transient Receptor Potential – TRP
 - TRPV1 – ion channel
 - Capsaicin
 - $> 43^\circ\text{C}$
 - Low pH
 - TRPV2 – ion channel $> 52^\circ\text{C}$
 - TRPM8 – Menthol, $< 25^\circ\text{C}$

Central Nervous System – Transmission

2nd Order Neurons – Dorsal Horn, Nucleus Caudalis (spinothalamic tract, trigeminothalamic tract)

- NS - Nociceptive specific
- WDR - Wide Dynamic Range
- LTM - Low Threshold Mechanoreceptors

3rd Order Neurons –Thalamus

- Somatosensory Cortex – thalamocortical tract
- Limbic System
- Prefrontal Cortex

Modulation: Central Nervous System - Neurotransmitters

- Nociceptive – Pain transmission
 - Neurotransmitters - Glutamate
 - Neuropeptides - SP, CGRP
- Interneurons – Pain modulation, inhibitory
 - GABA, endorphins, 5-HT, norepinephrine
- Glia – receptors and neurotransmitters involved in pain

Central Nervous System – Transmitters/Receptors

- Glutamate – AMPA, Kainate, NMDA
- SP – NK1
- CGRP – CGRP₁, CGRP₂
- GABA – GABA_A, GABA_B
- Fast – Ionotropic receptors
- Slow - Metabotropic
- Excitatory vs inhibitory

Pain Processing – Spinal Dorsal Horn, Nucleus Caudalis

- Central Terminals of afferent neurons
- Interneurons
- Projection neurons
- Descending neurons
- Glia

Modulation of Pain

- Endorphins
- Opiates
- Brainstem
 - Periaqueductal gray (PAG)
 - Raphe nuclei – 5-HT
 - Locus Coeruleus – NE

Somatosensory Cortex

- Input from thalamus
- Sensory discriminative aspects of pain
- CNS – analysis, integration, and formulation of response

PAIN Experience – Detection → Processing → Perception

- Transduction
- Transmission
- Modulation
- Perception
- Interpretation

- Behavior

What is Pain?

- Highly subjective
 - Physiological process
 - Psychological
 - Emotional
 - Context

Trigeminal Nerve – A complex neural system

- CN V Nuclei
- Mesencephalic
- Main sensory
- Spinal tract
 - Oralis
 - Interpolaris
 - Caudalis – Medullary dorsal horn
- V, VII, IX, X – all converge in the medullary dorsal horn

Peripheral Sensitization -1st Order Neurons

- Inflammation
- Nerve Sprouting
- Neuroma formation
- Pain
 - Increased pain intensity
 - Lower thresholds
 - Spontaneous firing

Central Sensitization – 2nd Order Neurons or higher

- Wind-up
- Decreased receptor threshold
- Increase receptor field size
- Phenotypic changes
- Nerve Sprouting
- Decreased Inhibition
- Glial Cells

Pain Mechanisms – Clifford J Woolf 2004

Nociceptive – activation of nociceptors

Pain linked to high intensity stimulus
 Thermal, Mechanical, Chemical
 Serves as a warning signal to prevent tissue damage

Inflammatory – localized by pain hypersensitivity

Short Term – peripheral and central sensitization
 Modulation – increased neuronal response
 Tissue damage – trauma, infection, surgical procedures

Neuropathic – localized pain hypersensitivity

Modulation – central sensitivity
 Modulation – increase membrane excitability, pain outlasting duration of stimulus, or spontaneous
 Peripheral nerve damage – surgery, post-herpetic neuralgia, diabetic neuropathies
 Central Damage – stroke, multiple sclerosis, spinal cord injuries

Functional – Central amplification

Poorly understood

Hypervigilance – abnormal processing of peripheral stimuli in the central nervous system

Fibromyalgia, chronic neck and shoulder pain, tension type headaches, TMD

The Non-Odontogenic Toothache

Source of Odontogenic Pain – Pulp, Periodontal Tissue

Pulpal Pain – Visceral Pain

- All or none response
- Lack of proprioception
- Difficult to localize pain that is purely pulpal
- Sessle et al 1986
 - Nerves show high levels of convergence
 - 74% of neurons tested in the nucleus caudalis showed convergence from multiple tooth pulp

Periodontal Pain – Musculoskeletal Pain

- Graded response
- Mechanoreceptors present
- Easier to localize location pain

Classification of Orofacial Pain – Okeson, Bell's Orofacial Pain 6th Edition, see chart on page 178

Sources of Non-Odontogenic Pain

- Musculoskeletal
 - Myofascial Pain
 - TMD
- Primary Headache
 - Migraine Headache
 - Autonomic Cephalgias
- Neuropathic Pain
 - Episodic
 - Continuous
- Idiopathic
 - Persistent Pain
 - Burning mouth syndrome
- Vascular
 - Giant Cell Arteritis
- Other Diseases
 - Local Pathology
 - Distant Pathology
 - Systemic Diseases

Non-Odontogenic Toothache – General Characteristics

- Toothache without adequate local cause
- Usual provocation - equivocal results
- LA to tooth – no decrease in pain
- Failure of reasonable therapy

Musculoskeletal Pain

- Masticatory Muscle Pain
 - Local myalgia
 - Myofascial pain

- Centrally mediated pain
- Myospasm
- Myositis
- Myofibrotic contracture
- Neoplasia
- Temporomandibular Pain
- Pain sensations – Diffuse, Constant, Dull, Aching, Throbbing

Travell and Simmons' – Myofascial Pain and Dysfunction, The Trigger Point Manual Volume 1. Upper Half of Body, 2nd Edition 1999

- Temporalis
- Masseter
- Lateral Pterygoid
- Medial Pterygoid
- Sternocleidomastoid
- Anterior Trapezius
- Anterior & Posterior Digastric

Primary Headaches

- Neurovascular
 - Migraine
- Autonomic Cephalgias
 - Cluster Headache
 - Chronic paroxysmal hemicrania
 - Hemicrania continua
 - SUNCT

Case Series of Four Different Headache Types Presenting as Tooth Pain

- Case Reports – Migraine, Cluster, Paroxysmal Hemicrania, Hemicrania continua
- Aurelio Alonso and Donald Nixdorf, Journal of Endodontics November 2006;32:1110-1113

Headaches and Orofacial Pain –what is the relationship between headaches & orofacial pain symptoms

Think of headaches and orofacial pain disorders as different variations of trigeminal nerve events. Both are trigeminal phenomena – anterior 2/3 of brain = V₁ innervation

Migraine Pathophysiology – Goadsby PJ et al N Engl J Med 2002;346:257-270

The Neurovascular Theory

- Trigger - neural activation
- Peripheral neuropeptide release
- Neurogenic inflammation
 - sP, CGRP, NKA
- Vasodilation
- Plasma extravasation
 - 5HT, histamine, BK, PGs
- Nociceptor activation
- Parasympathetic Activation – SSN
 - VIP
- Cortical spreading depression - Aura

Migraine Symptoms

- Episodic brain disorder with impaired central sensory processing
 - Throbbing

- Sensitivity to light, sound, smell, and head movement
- Abnormal central processing of normal signals
 - V1 – headache
 - V2 – facial pain

Migraine Headaches

- Common Migraine – no aura
- Classic Migraine – preceded by an aura, 15%
 - Visual – spots, flashing lights, or zigzag lines
 - Sensory - paresthesia
 - Motor
- Location – frontal, orbital, temporal, and occipital region
- More common in women
- Family history

Migraine without Aura (Cephalalgia 2004;24 Supple 1:1-160; Cephalalgia 2005;25:460-165.)

- At least five attacks fulfilling criteria B-D
- Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
- Headache has at least two of the following characteristics:
 - Unilateral location
 - Pulsating quality
 - Moderate or severe pain intensity
 - Aggravation by or causing avoidance of routine physical activity
- During headache at least one of the following:
 - Nausea and/or vomiting
 - Photophobia and phonophobia
- Not attributed to another disorder

Sinus Headache

- Mehle M, Kremer PS Headache 2008;48:67-71
 - Patients frequently report headaches thought to be of sinus origin
 - Approximately 70-75% fulfill the criteria for migraine
 - Few have sinus disease on CT
- Cady RK, Schreiber CP. Neurology 2002;58(Suppl 6)S10-S14
 - 98% (46/47) of patient with self-described sinus headaches has symptoms fulfilling IHS criteria for migraine (70%) or migrainous headache (28%)

TAC – trigeminal autonomic cephalgias

- Cluster
- Paroxysmal hemicrania
- SUNCT
- Autonomic signs –
 - Parasympathetic system – tearing, conjunctival injection, rhinorrhea, nasal congestion, facial flushing, forehead perspiration
 - Sympathetic system – ptosis, miosis

Pathophysiology

- Trigeminal distribution
 - Trigeminal vascular activation
- Hypothalamic activation
 - Circadian rhythm
- Parasympathetic hyperactivity – Autonomic symptoms
- Sympathetic impairment – Miosis and ptosis

Trigeminal autonomic cephalalgias – A review and implications for dentistry
Balasubramaniam, Klasser, Delcanho – JADA December 2008;139:1617-1623

- Review of Cluster Headache, paroxysmal hemicrania, and SUNCT
- “it is important for dentist to recognize these disorders and refer patients to a neurologist”
- “Thus avoiding well-intentioned but inappropriate dental therapy”

Cluster Headache (Cephalalgia 2004;24 Supple 1:1-160; Cephalalgia 2005;25:460-165.)

- A. At least five attacks fulfilling criteria B-D
- B. Severe or very severe unilateral orbital, supraorbital, and or temporal pain lasting 15 – 180 minutes if untreated
- C. Headache is accompanied by at least one of the following:
 1. Ipsilateral conjunctival injection and/or lacrimation
 2. Ipsilateral nasal congestion and/or lacrimation
 3. Ipsilateral eyelid edema
 4. Ipsilateral forehead and facial sweating
 5. Ipsilateral miosis and/or ptosis
 6. Sense of restlessness or agitation
- D. Attacks have a frequency from 1 to 8 per day
- E. Not attributed to another disorder

Cluster Headache

- Occurs predominately in men, mid-thirties
 - Smoking, drinking, nitroglycerin, histamine
- Quality: throbbing, neuralgic
 - ‘hot poker’ ‘stabbing’ feeling in the eye, cheekbone
- Periods of pain and remission
- Cluster can last weeks to months
- Remission can last for months or years
- “Suicide” headache
- Patient’s will appear restless

Cluster Headache Management

Prophylactic Medications

- Verapamil
- Lithium
- Prednisone
- Methysergide
- Valproic acid
- Topiramate
- Gabapentin

Abortive

- Oxygen
 - 100% at 7 - 10 Liters/min
 - 20 minutes
- Subcutaneous Sumatriptan
- Sumatriptan nasal spray
- Dihydroergotamine
- Intranasal lidocaine 4 -10%

Paroxysmal Hemicrania - CPH

- Unilateral pain
 - Temporal, frontal, ocular, maxilla
- Female predominance

- Throbbing, boring, stabbing
- Moderate to severe intensity
- Short attacks 2 -30 minutes
- Up to 40 episodes per day
- Autonomic symptoms
- Relieved with indomethacin 75 to 225 mg daily

SUNCT – Short lasting, unilateral neuralgiform headache attacks with conjunctival injection and tearing

- Pain may have trigger by light stimuli or spontaneous
- Unlike TN – there is no refractory period to trigger
- Male dominance
- 5-250 seconds
- 1/ day to 30 per hour
- Stabbing type pain
- Orbital, temporal region
- Autonomic features

SUNCT Therapy

- Resistant to both anti-neuralgic and anti-vascular drug therapy
- Lamotrigine – treatment of choice
- Gabapentin
- Topiramate
- Microvascular decompression

Neuropathic Pain – Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system

Inappropriate activation of pain sensitive pathways

- Stimulus – independent
- Stimulus - dependent

Neuropathic Pain – Hansson PT – Pain 2008

- Peripheral Pain
 - Traumatic nerve injury
 - Nerve compression/entrapment
 - Phantom pain
 - Post-herpetic neuralgia
 - Trigeminal neuralgia
 - Cancer related pain
 - Scar pain
- Central Pain
 - Stroke
 - Multiple sclerosis
 - Spinal cord injury
 - Neuropathic Pain

Intermittent Neuropathic Pain

- Bright
- Stimulating
- Electric
- Sharp
- Burning
- Trigger zones

Continuous

- Due to nerve damage
- Continuous pain
- Burning numbness

Intermittent Neuropathic Pain

- Trigeminal neuralgia
- Glossopharyngeal neuralgia
- Nervous Intermedius

Trigeminal Neuralgia (V)

- Severe, unilateral lancinating/electrical pain short duration, refractory period
- V2 and V3 branch mostly commonly affected
- Triggered by touch, chewing, talking, brushing teeth
- No or low level discomfort between attacks
- Classic – no identifiable pathology present
- Symptomatic: intracranial pathology, and multiple sclerosis

Diagnostic Criteria For Classic Trigeminal Neuralgia

White, Sweet. Pain and the neurosurgeon. Springfield (Ill): Charles C. Thomas; 1969.

- The pain is paroxysmal
- The pain may be provoked by light touch to the face (trigger zones)
- The pain is confined to the trigeminal distribution
- The pain is unilateral
- The clinical sensory examination is normal

Pathophysiology – Neuralgia

- Vascular compression
- Focal demyelination
- Damaged neuron
- Ephaptic transmission
- “short circuit” leads to electric jolt of pain

Neuralgia Treatment

- Medical Management
 - Carbamazepine
 - Gabapentin
 - Baclofen
 - Clonazepam
 - Lamotrigine
 - Oxcarbazepine
 - Topiramate
- Surgical Management
 - Radiofrequency thermal rhizotomy
 - Microvascular decompression
 - “Gamma Knife” radiation

Glossopharyngeal Neuralgia (IX)

- Similar to TN, except involves the pharynx, posterior tongue, ear and infra-auricular retromandibular area
- Triggered by chewing, talking, yawning and swallowing
- Dx: topical applied to pharyngeal mucosa

- Rule out intra-cranial pathology
- Tx: Similar to TN

Nervous Intermedius (VII)

- Pain in ear, soft palate, or anterior tongue
- Pain not as intense as TN
- May have facial paralysis
- Ramsey Hunt syndrome
 - Herpes zoster
 - Vesicles in the ear
- Tx: similar to TN

Pretrigeminal Neuralgia

- Dull, continuous pain in maxilla or mandible
- May mimic pulpal or sinus like pain
- May be triggered by jaw functions or hot/cold liquids
- Eventually progresses to Trigeminal neuralgia
- Treated like TN

Continuous Neuropathic Pain

- Nerve injury
- Post-surgical or post traumatic neuralgia – root canal therapy, tooth extractions
- Viral infection – Herpes zoster
- Systemic disease – Diabetic neuropathy
- CRPS – complex regional pain syndrome

Peripheral Neuritis

- Inflammation of a peripheral nerve trunk
 - Traumatic, bacterial, viral
- Symptoms are different from typical odontogenic tooth aches
 - i.e. paresthesia or anesthesia
 - Can have motor and autonomic symptoms
- NS RCT or extraction results in no relief of pain
- Anesthesia central to the pain source required to alleviate pain
- Tx: management involves controlling the source of inflammation
 - Antibiotics, antivirals, or steroids

Persistent Idiopathic Facial Pain

- Phantom tooth pain
- Atypical facial pain
- Atypical odontalgia
- Deafferentation pain
- NVOP –neurovascular orofacial pain

Diagnosis

- No cardinal findings on clinical and/or neurologic examination
- May see:
 - Muscular pain due to co-contraction
 - Allodynia
- No definitive Dx tests
- Diagnosis by exclusion

Persistent Idiopathic Facial Pain Characteristics

- Diffuse poorly localized pain

- Usually constant duration and intensity
- Dull aching, burning, tingling, itching, throbbing, stabbing
- May or may not be associated with sensory changes
 - paresthesia, allodynia
- Associated with surgical or invasive procedures
- Patient's many times have significant psychological disturbance or history of depression
- Generally no aggravating or alleviation factors
- May be increased by stress/sympathetic activation

Persistent Idiopathic Facial Pain

- Marbach et al OOO 1982 – Phantom Tooth Pain
 - 3% - 3/256 patients, one-month follow-up
- Campbell et al 1990
 - 5% - S RCT, 6/118 patients
- Polycarpou N et al IEJ 2005 – Persistent Post-endodontic pain
 - 12% 21/175 patients, 12 month follow-up
- Oskima et al J Endod 2009 – 5.9%
 - 10/16 after NS RCT retreatment
 - 5/16 primary NS RCT
- Nixdorf DR et al J Endod 2010, Systematic review
 - 3.4% - 48/1,125 teeth with non-odontogenic pain
- Factors significantly associated with neuropathic pain
 - Long duration of preoperative pain
 - Severe symptoms/pain
 - Painful treatment in the orofacial region
 - Female gender
 - May represent half of all cases of persistent tooth pain

Pain Management

- Prevention
 - Pre-emptive Analgesia
 - Decreasing peripheral input
- Medical Management
 - Topical Medications
 - Centrally Acting Medications
 - Tri-cyclic antidepressants
 - Anti-convulsants

Burning Mouth Syndrome (Klasser, Fischer, Epstein. OMFS Clinic N America 2008;20:255-271)

- Pain in the mouth or oral mucosa tissues
- Daily persistent
- Oral mucosa normal has normal appearance
- May be due to local and/or systemic diseases
 - Candidiasis, lichen planus, geographic tongue, allergies, xerostomia, dental treatment, spicy foods, or burns from hot foods.
 - Medications such as ACE inhibitors.
 - Systemic – diabetes and nutritional disorders
- Etiology – unknown
 - Neuropathic pain
 - Local/systemic/medications
- Female gender, post-menopausal
- Tx: Clonazepam, amitriptyline, Alpha-lipoic acid

Temporal Arteritis /Giant Cell Arteritis (Allen DT et al JADA 2000;131(12):1738-1741)

- Female predilection over 50 years of age
- Mild to Severe headache in the temporal region
 - New onset headache
 - Abrupt onset of visual disturbances
- May have complain of unexplained jaw or tooth pain
- Throbbing or stabbing pain
- Temporal artery may feel tender to palpation
- Jaw claudication – pain on chewing

Etiology – Temporal Arteritis

- Chronic vasculitis of large and medium sized blood vessels
- Similar to polymyalgia rheumatica
- Elevated erythrocyte sedimentation rate (ESR) and/ or C-reactive proteins (CRP)
- Unexplained fever or anemia
- Biopsy of temporal artery
- Loss of Vision - Involvement of posterior ciliary arteries can lead to anterior ischemic optic neuropathy and blindness

Management – Temporal Arteritis

- Medical emergency
- Refer to a physician
- Obtain ESR (erythrocyte sedimentation rate)
- Biopsy to confirm diagnosis
- Prednisone 60 – 80 mg
- Therapy continued until symptoms subside and ESR returns to normal – months to years

Inflammatory Pain

- Acute Maxillary Rhinosinusitis
- Pain referred to the maxillary teeth
 - Dull
 - Aching
 - Throbbing
- Pressure below the eyes
- Pain increases when bending the head, applying pressure over the sinuses, coughing or sneezing
- Nasal discharge not pain is indicative of a sinus infection
- A history of URI or sinus congestion

Migraine and sinus headaches

- Migraines are a major cause of headaches and facial pain
- Over 50% remain undiagnosed
- 58-88% of sinus headaches with no infection were diagnosed as migraine headaches
- Migraine type headaches can cause facial pain, nasal congestion, and rhinorrhea
- Time course
 - Migraine headaches 4 – 72 hours
 - Acute rhinosinusitis 5 – 7 days

Systemic Diseases that can refer pain

- Cardiac Pain
- Rheumatoid arthritis
- Psoriatic arthritis
- Salivary glands

- Systemic lupus erythematosus
- Fibromyalgia
- Lyme Disease
- Intra-cranial pathology

Psychogenic Pain

- Rare
- Diagnosis of exclusion
- Pain does not usually fit normal anatomic distribution or physiologic pattern
- May not respond as expected to therapy
- Clinical psychologist referral

Case Report on Chronic Orofacial Pain Patients

- 120 Patients seen at New York Tertiary Pain Clinic from January 1999 – April 2001
- Female-to-male ratio 3:1, mean age 49 years, average pain duration 81 months
- 6 - average number of previous specialists
- 32% - Patients with Prior Tx
- Israel et al. J Oral Maxillofac Surg 61:662-667, 2003

Diagnosis is the Key

- Accurate history
- Careful physical examination
- You cannot diagnose what you don't know
- You cannot find what you don't look for

Solving the Puzzle

- Location
- Onset
- Pain Intensity
- Quality
- Frequency
- Duration
- Initiating Factors
- Aggravating Factors
- Alleviating Factors
- Associated Factors

Summary

- No adequate cause
- Local anesthesia doesn't eliminate pain
- Spontaneous multiple toothaches
- Stimulating, burning, non-pulsatile pain
- Constant, unremitting pain, non-variable toothache
- Persistent, recurrent toothache
- Failure of toothache to respond to reasonable therapy

Recommended Reading

*Cohen's Pathways of the Pulp, Tenth Edition, Chapter 3, Diagnosis of Nonodontogenic Toothache

Orofacial Pain – Guidelines for Assessment, Diagnosis, and Management, 4th Edition, The American Academy of Orofacial Pain, Edited by Dr. Leeuw.

Bell's Orofacial Pains – The Clinical Management of Orofacial Pain, 6th Edition, Dr. Okeson

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