

THE PAIN THAT TRAVELS: A COMPREHENSIVE REVIEW OF REFERRED PAIN

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Abstract: Referred pain is a fascinating and clinically significant phenomenon in which pain is perceived at a location distant from its actual source of origin. This neurophysiological phenomenon poses a substantial diagnostic challenge for clinicians, as the site of discomfort often does not correspond to the underlying pathological process. Common examples include cardiac ischemia presenting as left shoulder or jaw pain (angina pectoris), diaphragmatic irritation causing shoulder tip pain, and lumbar disc herniation producing sciatic pain radiating down the lower extremity. This article provides a systematic review of the historical understanding, neuroanatomical basis, and leading theories of referred pain, including the convergence-projection theory, the facilitation theory, and the axonal branching theory. The clinical relevance of referred pain is explored across multiple medical specialties, including cardiology, gastroenterology, pulmonology, orthopedics, and neurology. The article also discusses diagnostic approaches, including the use of local anesthetic blocks and imaging, and outlines management strategies. The review concludes with a discussion of the clinical red flags (e.g., sinister causes of referred pain such as aortic dissection or pancreatic cancer) and future research directions, including central sensitization and neuroimaging studies.

Keywords: Referred pain, convergence-projection theory, somatic referred pain, visceral referred pain, angina pectoris, diaphragmatic irritation, sclerotomal pain, neuroanatomy, central sensitization, differential diagnosis.

Аннотация: Иррадиационная боль — это увлекательное и клинически значимое явление, при котором боль ощущается в месте, удаленном от ее фактического источника. Это нейрофизиологическое явление представляет собой серьезную диагностическую проблему для врачей, поскольку место дискомфорта часто не соответствует лежащему в основе патологическому процессу. К распространенным примерам относятся ишемия сердца, проявляющаяся болью в левом плече или челюсти (стенокардия), раздражение диафрагмы, вызывающее боль в кончике плеча, и грыжа межпозвоночного диска поясничного отдела позвоночника, вызывающая ишиас, иррадиирующий в

нижнюю конечность. В данной статье представлен систематический обзор исторического понимания, нейроанатомической основы и ведущих теорий иррадиационной боли, включая теорию конвергенции-проекции, теорию облегчения и теорию ветвления аксонов. Клиническая значимость иррадиационной боли рассматривается в различных медицинских специальностях, включая кардиологию, гастроэнтерологию, пульмонологию, ортопедию и неврологию. В статье также обсуждаются диагностические подходы, включая использование местной анестезии и методов визуализации, и излагаются стратегии лечения. Обзор завершается обсуждением клинических тревожных признаков (например, серьезных причин иррадиационной боли, таких как расслоение аорты или рак поджелудочной железы) и будущих направлений исследований, включая центральную сенсibilизацию и нейровизуализационные исследования.

Ключевые слова: иррадиационная боль, теория конвергенции-проекции, соматическая иррадиационная боль, висцеральная иррадиационная боль, стенокардия, раздражение диафрагмы, склеротомальная боль, нейроанатомия, центральная сенсibilизация, дифференциальная диагностика.

Annotatsiya: Yo'naltirilgan og'riq - bu og'riq uning asl kelib chiqish manbasidan uzoqda joylashgan joyda seziladigan qiziqarli va klinik jihatdan ahamiyatli hodisa. Ushbu neyrofiziologik hodisa klinisyenlar uchun jiddiy diagnostika muammosini tug'diradi, chunki noqulaylik joyi ko'pincha asosiy patologik jarayonga mos kelmaydi. Keng tarqalgan misollar orasida chap yelka yoki jag' og'rig'i (stenokardiya) sifatida namoyon bo'ladigan yurak ishemiyasi, yelka uchida og'riqni keltirib chiqaradigan diafragma tirnash xususiyati va pastki ekstremitadan pastga tarqaladigan siyatik og'riqni keltirib chiqaradigan bel disk churrasi mavjud. Ushbu maqolada yo'naltirilgan og'riqning tarixiy tushunchasi, neyroanatomik asoslari va yetakchi nazariyalari, jumladan, konvergensiya-proyeksiya nazariyasi, fasilitatsiya nazariyasi va aksonal tarmoqlanish nazariyasi tizimli ravishda ko'rib chiqiladi. Yo'naltirilgan og'riqning klinik ahamiyati kardiologiya, gastroenterologiya, pulmonologiya, ortopediya va nevrologiya kabi ko'plab tibbiy mutaxassisliklarda o'rganiladi. Maqolada shuningdek, mahalliy anestetik blokklar va tasvirlashdan foydalanishni o'z ichiga olgan diagnostika yondashuvlari muhokama qilinadi va davolash strategiyalari bayon qilinadi. Sharh klinik xavfli belgilar (masalan, aorta disseksiyasi yoki oshqozon osti bezi saratoni kabi og'riqning xavfli sabablari) va markaziy sensibilizatsiya va neyrovizual tadqiqotlarni o'z ichiga olgan kelajakdagi tadqiqot yo'nalishlarini muhokama qilish bilan yakunlanadi.

Kalit so'zlar: Yo'naltirilgan og'riq, konvergensiya-proyeksiya nazariyasi, somatik yo'naltirilgan og'riq, visseral yo'naltirilgan og'riq, angina pektorisi, diafragma

tirnish xususiyati, sklerotomal og'riq, neyroanatomyiya, markaziy sensibilizatsiya, differentsial tashxis.

Introduction

Pain is the most common reason patients seek medical attention. However, the location of pain does not always accurately indicate the site of the underlying pathology. Referred pain—pain perceived at a site remote from the originating organ or tissue—represents one of the most intriguing and clinically important phenomena in medicine. A patient with a myocardial infarction may complain of left arm or jaw pain rather than chest pain. A patient with acute cholecystitis may present with right shoulder pain. A patient with pancreatitis may feel pain in the mid-back. These clinical presentations are not anatomical curiosities; they are everyday diagnostic challenges that, if misunderstood, can lead to delayed or incorrect treatment.

The concept of referred pain is ancient. Hippocrates and Galen described pain in the shoulder associated with splenic and hepatic disorders. However, it was not until the late 19th and early 20th centuries that systematic physiological investigations began. The British physician James Mackenzie (1853–1925) mapped referred pain patterns from various viscera and coined the term "referred pain". Subsequently, Sir Henry Head (1861–1940) described dermatomal zones of referred tenderness, known as Head's zones, which remain clinically useful today.

This article aims to provide a comprehensive, evidence-based review of referred pain. Section 2 defines referred pain and distinguishes it from related phenomena (radiating pain, radiating pain, and secondary hyperalgesia). Section 3 presents the major neurophysiological theories. Section 4 describes common clinical patterns by organ system. Section 5 addresses diagnostic approaches and red flags. Section 6 covers management strategies. Section 7 discusses future directions, and Section 8 concludes.

Definition and Distinctions

Definition

Referred pain is defined as pain perceived in a region of the body that is innervated by nerves different from those supplying the actual source of nociceptive input. In other words, the pain "travels" or is "referred" from its true origin to a distant site. The referred area typically is not the site of tissue damage, and the patient often has no awareness of the true source.

Distinction from Radiating Pain

Referred pain must be distinguished from radiating pain (also called radicular pain). Radiating pain follows the anatomical course of a nerve root or peripheral nerve, such as sciatic pain radiating from the lower back down the posterior thigh and leg in L5 or S1 radiculopathy. In radiating pain, the pain travels along the nerve's dermatomal

or peripheral distribution because the nerve itself is compressed, inflamed, or irritated. In referred pain, by contrast, the perceived location does not follow a specific nerve's anatomical pathway; for example, cardiac pain referred to the jaw does not follow the trigeminal nerve distribution.

Distinction from Secondary Hyperalgesia

Secondary hyperalgesia refers to increased pain sensitivity in uninjured tissue surrounding an injury site, mediated by central sensitization. While secondary hyperalgesia shares mechanisms with referred pain, referred pain typically involves a more distant, non-contiguous site. Table 1 summarizes these distinctions.

Feature	Referred Pain	Radiating (Radicular) Pain	Secondary Hyperalgesia
Anatomical pathway	Unknown; convergence	Along nerve root or nerve	Surrounding tissue
Distance from source	Often distant	Contiguous	Contiguous
Mechanism	Central convergence	Ectopic nerve firing	Central sensitization
Example	Shoulder tip pain in cholecystitis	Sciatica from disc herniation	Sunburn tenderness.

Neurophysiological Theories of Referred Pain

Multiple theories have been proposed to explain referred pain. The most widely accepted is the convergence-projection theory, though the facilitation theory and axonal branching theory also contribute.

Convergence-Projection Theory

The convergence-projection theory, first proposed by Ruch in 1946 and refined by later researchers, is the dominant explanation. The theory rests on three principles:

1. **Convergence:** Afferent (sensory) neurons from both visceral organs (e.g., heart, gallbladder) and somatic structures (e.g., skin, muscles) converge onto the same second-order neurons in the dorsal horn of the spinal cord.

2. **Projection:** The brain cannot distinguish the true origin of the signal. Because the brain is accustomed to receiving pain signals from somatic structures (skin, muscles, joints), it "projects" the sensation to the somatic region rather than the less familiar visceral source.

3. **Somatotopic organization:** The convergence follows a segmental pattern. For example, afferents from the heart (T1–T4 spinal segments) converge with somatic afferents from the chest, left arm, and jaw (also T1–T4), explaining why cardiac ischemia refers to these areas.

Neuroanatomical evidence supports this theory. Retrograde tracing studies have shown that visceral and somatic afferents from corresponding spinal segments indeed terminate on overlapping populations of dorsal horn neurons.

Facilitation (Convergence-Facilitation) Theory

The convergence-projection theory explains the location but not the intensity or the tenderness often observed in referred pain zones. The facilitation theory proposes that visceral nociceptive input creates a "sensitized" or "facilitated" state in the dorsal horn neurons. Subthreshold somatic input that would normally not produce pain now reaches threshold, resulting in referred pain and secondary hyperalgesia in the referred zone.

This explains why referred areas are often tender to palpation even though the tissue itself is normal.

Axonal Branching (Peripheral) Theory

A minority of visceral afferent neurons have peripheral branches that innervate both visceral and somatic structures. When the visceral branch is activated by pathology, the signal travels antidromically down the somatic branch, releasing inflammatory mediators (substance P, calcitonin gene-related peptide) and producing local pain and neurogenic inflammation. This theory explains some cases of referred pain but cannot account for most patterns, as the anatomical distribution is too limited.

Central Sensitization

Central sensitization—increased excitability of spinal dorsal horn neurons following persistent nociceptive input—underlies both referred pain and the spread of pain over time. In chronic visceral pain conditions (e.g., irritable bowel syndrome, interstitial cystitis, chronic pancreatitis), patients often develop widespread referred pain and hyperalgesia beyond the initial segmental zones, reflecting spinal and supraspinal reorganization.

Clinical Patterns of Referred Pain

Referred pain patterns are clinically predictable based on the embryologic origin and spinal segmental innervation of the affected organ. Table 2 summarizes common visceral referred pain patterns.

Cardiovascular System

Myocardial ischemia (angina pectoris) is the classic and most life-threatening example of referred pain. Cardiac afferents enter the spinal cord at T1–T4. Pain is typically perceived in the substernal chest but may refer to the left shoulder, left arm (medial aspect, ulnar distribution), neck, jaw, or epigastrium. Aortic dissection may refer pain to the interscapular region (between the shoulder blades) as the dissection propagates along the thoracic aorta.

Respiratory and Diaphragmatic System

The diaphragm is innervated by the phrenic nerve (C3–C5). Irritation of the diaphragmatic pleura or peritoneum (e.g., from subdiaphragmatic abscess, splenic rupture, cholecystitis, or ectopic pregnancy) produces referred pain to the shoulder tip (C4 dermatome). This is known as Kehr's sign when associated with splenic rupture.

Central diaphragmatic irritation (e.g., from pericarditis or mediastinal pathology) may refer to the neck or trapezius ridge.

Gastrointestinal System

Organ Spinal Segments Referred Pain Locations

Esophagus T1–T4 Substernal, upper back, lower neck

Stomach, duodenum T5–T10 Epigastrium, mid-back (T7–T9)

Liver, gallbladder T5–T9 (right) Right upper quadrant, right shoulder (phrenic), right scapula

Pancreas T5–T10 Epigastrium, left upper quadrant, mid-back (band-like)

Small intestine T9–T11 Periumbilical

Appendix T10–T12 Periumbilical (early), right lower quadrant (late)

Colon T11–L1 Lower abdomen, back (T11–L1)

Kidney, ureter T10–L1 (renal), T11–L2 (ureter) Flank, lower back, groin, testis/labium

Important clinical pearls:

- Acute cholecystitis refers pain to the right shoulder and right scapular tip.
- Pancreatitis causes band-like mid-back pain (T7–T9).
- Appendicitis: Early pain is periumbilical (T10); after inflammation reaches the parietal peritoneum, pain localizes to the right lower quadrant.
- Ureteric colic (kidney stone) refers from the flank to the groin and ipsilateral testis or labium as the stone migrates down the ureter.

Musculoskeletal System

Somatic referred pain (also called sclerotomal pain) originates from deep somatic structures (muscles, ligaments, intervertebral discs, facet joints) and refers to distant somatic sites. This is distinct from radicular pain (nerve root compression). For example:

- Lumbar disc herniation without nerve root compression may produce referred pain in the gluteal region or posterior thigh, but not below the knee (unlike radicular sciatica).
- Sacroiliac joint dysfunction refers pain to the buttock, groin, and posterior thigh.
- Temporomandibular joint (TMJ) disorders refer pain to the teeth, ear, temple, and neck.
- Myofascial trigger points in the upper trapezius refer pain to the temple and jaw; in the infraspinatus, to the anterior shoulder and arm.

Pelvic and Reproductive Organs

- Uterus and cervix (T10–L1, S2–S4): Menstrual pain (dysmenorrhea) refers to the lower abdomen, back, and inner thighs.

· Prostate (T10–L1, S2–S4): Prostatitis refers to the perineum, sacrum, and lower back.

· Ovaries (T10–T11): Ovarian cyst pain refers to the lower quadrant and groin.

Diagnostic Approach and Red Flags

Clinical History

The history is the most important diagnostic tool. Key questions include:

- Where exactly is the pain? (Ask the patient to point with one finger.)
- Does the pain move or radiate?
- What relieves or aggravates the pain? (Visceral referred pain often worsens with specific physiological states—eating for cholecystitis, exercise for angina—and improves with rest or position changes.)
- Are there associated symptoms? (Nausea, sweating, dyspnea, fever, jaundice.)

Physical Examination

- Palpation of referred zones may reveal tenderness (allodynia) or hyperalgesia in the absence of local pathology.
- Injection of a local anesthetic into the referred zone (e.g., tender trigger point) may temporarily relieve referred pain but does not eliminate the source.
- Examination of the putative source organ (e.g., cardiac auscultation, abdominal examination, rectal examination) is essential.

Diagnostic Tests

Diagnostic tests target the suspected source organ rather than the referred site:

- Cardiac: ECG, troponin, stress testing, coronary angiography.
- Abdominal: Ultrasound (gallbladder, kidneys, appendix), CT, amylase/lipase (pancreatitis), liver function tests.
- Musculoskeletal: MRI of spine or joints, diagnostic nerve blocks, electromyography.

Red Flags (Sinister Causes)

Referred pain can be a manifestation of life-threatening conditions. The clinician must maintain a high index of suspicion for:

Red Flag Possible Diagnosis

Shoulder tip pain + hypotension + abdominal trauma Ruptured spleen (Kehr's sign)

Interscapular pain + tearing sensation + pulse deficit Aortic dissection

Jaw/arm pain + dyspnea + diaphoresis Myocardial infarction

Back pain + fever + neurological deficits Epidural abscess

Periumbilical pain + weight loss + palpable abdominal mass Pancreatic cancer

Management of Referred Pain

Management targets the underlying cause rather than the referred site.

Treat the Source

- Myocardial ischemia: Reperfusion (angioplasty, thrombolysis), anti-ischemic medications.
- Cholecystitis: Cholecystectomy, antibiotics.
- Ureteric colic: Analgesia, hydration, stone removal (lithotripsy or ureteroscopy).
- Musculoskeletal referred pain: Treat the primary structure (e.g., disc, joint, trigger point) with physical therapy, manual therapy, injections, or surgery.

Symptomatic Management

While treating the source is paramount, symptomatic relief may be necessary:

- Analgesics: NSAIDs, acetaminophen, opioids (for acute severe pain).
- Neuromodulators: Gabapentinoids (gabapentin, pregabalin) or tricyclic antidepressants (amitriptyline) for chronic referred pain syndromes.
- Local anesthetic blocks: Injection of the referred zone (e.g., trigger point injection) can provide temporary relief but does not replace source treatment.

Prevention of Chronicity

Unresolved referred pain can lead to central sensitization, transforming acute referred pain into chronic widespread pain. Early diagnosis and effective treatment of the source are essential to prevent this maladaptive plasticity.

Future Directions

Emerging research is refining our understanding of referred pain through:

- Functional neuroimaging (fMRI, PET): Revealing cortical and subcortical processing of visceral and referred pain, demonstrating that the same brain regions (insular cortex, anterior cingulate cortex, thalamus) are activated regardless of the perceived location.
- Quantitative sensory testing (QST): Characterizing referred pain zones (e.g., pressure pain thresholds, thermal detection thresholds) to differentiate central from peripheral mechanisms.
- Animal models of viscerosomatic convergence: Enabling mechanistic studies of central sensitization and the development of novel therapeutics targeting spinal dorsal horn hyperexcitability.

Conclusion

Referred pain is a common, diagnostically challenging, and clinically critical phenomenon. It arises primarily from the convergence of visceral and somatic afferents onto common spinal neurons, leading the brain to misinterpret the origin of nociceptive signals. The convergence-projection theory provides the most robust explanation, though facilitation and central sensitization contribute to the tenderness and spread of referred pain.

Clinically, referred pain follows predictable segmental patterns: cardiac pain refers to the left arm and jaw; diaphragmatic irritation refers to the shoulder tip;

gallbladder pain refers to the right shoulder and scapula; pancreatic pain refers to the mid-back; and ureteric colic refers to the groin. Recognizing these patterns allows clinicians to identify the true source of pain quickly, potentially saving lives in conditions such as myocardial infarction, aortic dissection, or ruptured spleen.

Management focuses on treating the underlying cause, not the referred site. However, symptomatic relief and prevention of central sensitization are important adjuncts. As neuroimaging and basic science research advance, our understanding of the central mechanisms of referred pain will continue to deepen, leading to better diagnostic and therapeutic strategies for this fascinating and clinically vital phenomenon.

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