Visceral pain

Anu Kansal
John Hughes

Abstract

Pain is one of the most common symptoms that patient presents with. Visceral organs were thought to be insensitive to pain in the past, but we now know this is not true. It is more common than somatic pain and originates from the internal organs in the thorax, abdomen or pelvis. These organs are innervated by the parasympathetic (vagus and sacral parasympathetic fibres) and sympathetic (thoracolumbar sympathetic chain: T1–L2) nervous systems. The afferent and efferent fibres to the organs accompany the sympathetic nervous system. The sensory system to the gut is specialized and divided into an enteric and extrinsic nervous system. The physiology of visceral pain is poorly understood compared to somatic pain, but it is well established that peripheral and central sensitization along with dysregulation of the descending pathways plays a significant role. Pain originating from visceral organs is usually diffuse, dull aching, poorly localized and can be associated with phenomenon such as referred somatic pain, referred hyperalgesia, visceral hyperalgesia and viscero-visceral hyperalgesia. Treatment of visceral pain involves identifying and treating the cause, if identified, and the management of pain. Patient education and information plays an important part in management along with pharmacological and non-pharmacological treatments.

Keywords Neuroanatomy; visceral hyperalgesia; visceral pain; viscero-somatic convergence; viscero-visceral hyperalgesia

Royal College of Anaesthetists CPD Matrix: 1A01, 1A02, 2EO3, 3E00

Learning objectives

After reading this article you, should be able to:

- explain the neuroanatomy of visceral pain
- describe the pathophysiology of visceral pain
- identify the clinical presentation of visceral pain
- formulate a management plan

Introduction

Vertebrates have been considered 'dual entities', composed of 'somatic' and 'visceral' components responding to different environments: an external environment in which the organism is situated, and an internal environment in which the tissue elements live.[1]

Pain is one of the most common presentations to seek medical help. Visceral pain is pain that results from the activation of nociceptors of the thoracic, pelvic or abdominal visceral organs. In the past, visceral organs were considered insensitive to pain but now it is clear that the social burden of visceral pain is much greater than somatic pain. Pain in the viscera usually comes from distension, inflammation or ischaemia.

Anu Kansal *MBBS MD Anaesthesia FRCA FFPMRCA is a Consultant in the Department of Pain Medicine at James Cook University Hospital, Middlesbrough, UK. Conflict of interest: None declared.*

John Hughes *MBBS FRCA FFPMRCA is a Consultant in Pain Medicine at James Cook University Hospital, Middlesbrough, UK. Conflict of interest: None declared.*

Neuroanatomy of visceral pain

Visceral efferents

Most of the thoracic and abdominal visceral organs, except the pancreas, are innervated by both the parasympathetic (craniosacral) and sympathetic (thoracolumbar) nervous system. The vagus is the main parasympathetic nerve for thoracic and upper abdominal viscera, while the sympathetic fibres come from thoracolumbar sympathetic trunk (T1 to L2 and may extend to L3). The lower abdomen and pelvis are mainly supplied by thoracolumbar sympathetic fibres and sacral parasympathetic fibres.

The sympathetic preganglionic fibres originate from the respective ventral root and pass to the sympathetic trunk via the grey rami communicans. Most sympathetic fibres synapse in the sympathetic trunk. Post-ganglionic myelinated fibres pass via the splanchnic nerves to the ganglions (e.g. coeliac ganglia, superior mesenteric ganglia and inferior mesenteric ganglia) and onward to the end organs. The fibres that do not synapse at the sympathetic chain, synapse in the ganglion near the organs. The parasympathetic fibres travel via either the vagus nerve or the pelvic parasympathetic fibres and synapse in the ganglion near the organs. Some parasympathetic fibres pass with the sympathetic fibres.

Visceral afferents

The general visceral afferent (GVA) fibres conduct sensory impulses from the viscera, glands and blood vessels to the central nervous system (CNS). They are considered to be part of the visceral nervous system, not the autonomic nervous system. In the abdomen the afferent fibres accompany the sympathetic efferent fibres.

The primary sensory afferents are pseudo-unipolar cells having central and peripheral axonal processes. The peripheral process innervating the visceral organ may have specialized end-organ-like Pacinian corpuscles or free nerve endings. The afferent fibres (abdomen and most of the pelvis) usually accompany sympathetic fibres and pass from the receptors in the end organ to the respective ganglion. From here, they go via the splanchnic nerves to the sympathetic trunk without synapsing in the ganglia or sympathetic trunk, pass into the dorsal root via the grey rami communicans. These fibres follow the dorsal root into the dorsal root ganglion, where the cell-bodies of the visceral afferents are located. They converge with the somatic afferent nerve fibres in the dorsal horn of spinal cord (lamina V) (Figure 1).

The path of the efferent fibres diverges from the afferent fibres as efferent come via the ventral root of the spinal column before entering the grey rami communicans to the sympathetic ganglia.

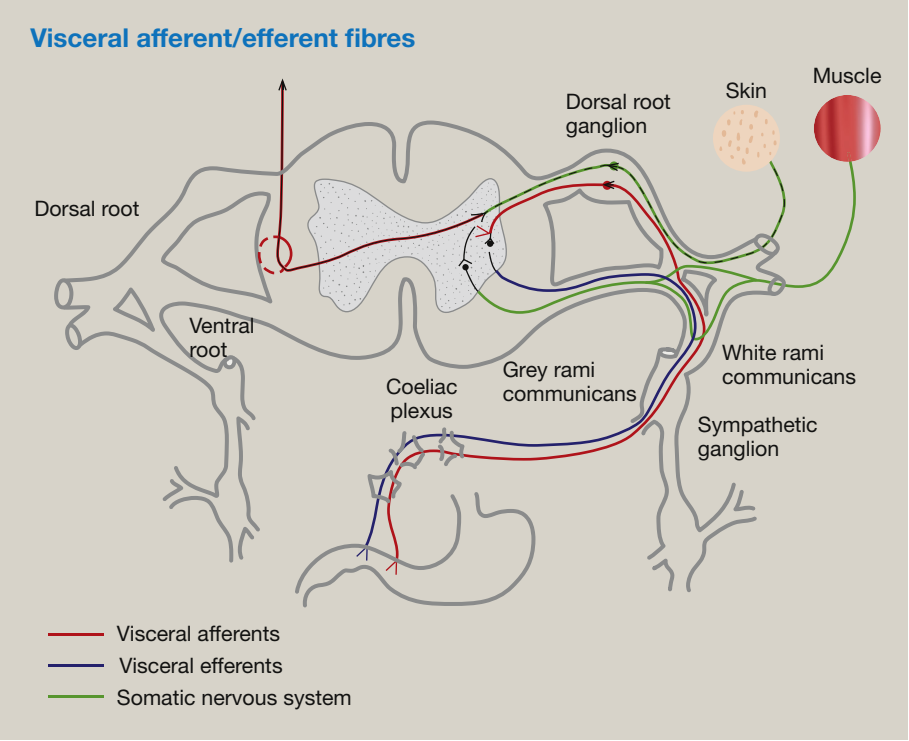

Figure 1

This convergence of the somatic and visceral fibres at the level of the dorsal root explains the 'referred pain' seen with visceral pathology. There is also convergence of the afferent fibres from different internal organs allowing for viscero-visceral referral patterns.

Some of the afferents from the lower pelvis follow the parasympathetic efferent system.

Enteric nervous system

The sensory system of the gastrointestinal tract consists of intrinsic (enteric) sensory system and extrinsic (vagus, spinal, and pelvic) afferents. The intrinsic system functions independently of the CNS. Neurons are directly exposed to the mechanical forces and the chemical environment which is unlike somatic afferents neurons. Enterochromaffin and enteroendocrine cells within the mucosa release serotonin, cholecystokinin, orexin and leptin that modulate and regulate motor activity. The submucosal enteric plexus and myenteric plexus have a high degree of synaptic interactions that can be either inhibitory or stimulatory for the purpose of regulating gastrointestinal motility and peristalsis. Both plexuses received input from parasympathetic and sympathetic efferents. There is a crosstalk between intrinsic and extrinsic systems.

Neurophysiology of visceral pain

The physiology of visceral pain remains less well understood compared with that of somatic pain.[2] This may be in part due to the diverse nature of the visceral organs and their function. In spite of this, it is well established that visceral pain can occur due to:

- sensitization of primary sensory afferents innervating the viscera
- hyper-excitability of spinal ascending neurons (central sensitization) receiving synaptic input from the viscera
- dysregulation of descending pathways that modulate spinal nociceptive transmission.

As with somatic pain, peripheral and central mechanisms both play a significant role in the pathophysiology of visceral pain. Inflammation or excessive stimulation of the visceral organ (e.g. over distension) will cause the lowering of the threshold of the 'high threshold' receptors and stimulation of the 'silent receptors' which are found in abundance in all visceral organs. This results in peripheral sensitization and an increased barrage of impulses into the CNS.[2]

Increased input to the spinal cord leads to neuroplastic changes in the CNS such as increased sensitivity and excitability leading to central sensitization. N-methyl-D-aspartate (NMDA) receptor plays a significant role in mediating increase in central excitability.

The peripheral and central sensitization plays a significant role in visceral and viscero-visceral hyperalgesia. This involves sensitization of the central neurons receiving convergent input from multiple visceral organs.

In addition to increased signals from the periphery, changes in the descending modulatory system can further influence visceral hyperalgesia.

Clinical presentation of visceral pain

There are several phenomena associated with visceral pain and it can present in a variety of forms.[3]

True visceral pain

Visceral pain is usually diffuse, poorly localized, dull and aching in character. This is due to the low density of the sensory innervation of viscera and the extensive divergence of visceral input within the CNS. It usually has a temporal evolution and can be difficult to identify in the initial stages. Sometimes it presents with only a vague sense of discomfort, malaise or oppression. It can be associated with marked autonomic phenomena, such as pallor, profuse sweating, nausea, vomiting, changes in blood pressure and heart rate, gastrointestinal disturbances (e.g. diarrhoea) and changes in body temperature. There may also be associated emotional reactions such as anxiety and sometimes a sense of impending doom. A typical example is painless myocardial infarction, which may produce a sense of gastric fullness, heaviness, pressure, squeezing or choking. There is no direct correlation between the intensity of the pain and the extent of the injury. The co-occurrence of visceral pain and negative emotion may enhance the formation of pain-related memories.

Referred pain and hyperalgesia (viscero-somatic convergence)

The visceral pain can present as a pain at a somatic sites and this phenomenon is known as 'referred pain'. It is due to convergence of innervation from the visceral organ and somatic areas at the same spinal sensory neurons. This pain typically presents as deep somatic pain, sharper, better localized and not accompanied with any sympathetic or emotional reactions. It may be associated with hyperalgesia (i.e. increased sensitivity to painful stimuli) that is usually confined to the muscles but may extend superficially to subcutaneous tissue and skin. The referred hyperalgesia from internal organs is likely to result from a process of central sensitization, involving viscero-somatic convergent neurons ('convergence facilitation'). It can persist even after the primary stimuli have ceased. Referred hyperalgesia is often accompanied by trophic changes, typically a thickening of the subcutaneous tissue and some degree of local muscle atrophy. Both of these events are presumed to result from viscero-somatic reflexes activation by the afferent visceral barrage.

Visceral hyperalgesia

This is defined as an increased sensitivity of an internal organ such that even non-pathological, normal stimuli may produce pain from that organ. This is commonly associated with visceral pain and is thought to be due to peripheral and central sensitization. Examples include pain upon ingestion of food or liquids in the oesophagus or stomach when the mucosa is inflamed, or pain from a normal degree of bladder distension during inflammatory processes of the lower urinary tract.

Viscero-visceral hyperalgesia

This is augmentation of pain due the sensory interaction between two different internal organs that share at least part of their afferent circuitry. It consists of an enhancement of both direct and referred symptoms from all the involved viscera, producing a complex clinical picture.[4] For example, patients with coronary heart disease plus gallbladder calculosis may experience more frequent attacks of angina and biliary colic than patients with a single condition; this happens due to partial overlapping (T5) afferent pathways from the heart and gallbladder. Viscero-visceral hyperalgesia is probably produced by sensitization processes involving viscero-visceral convergent neurons in the CNS.

Management of visceral pain

Management of the visceral pain involves:

1. Identifying and treating the pathology, if identifiable.
2. Management of pain.

Identifying and treating the pathology

The pathology may involve a number of organs and may require specialist input (e.g. cardiologist for chest pain or gastroenterologist for pancreatic pain). A thorough history, examination and investigations as appropriate help make the diagnosis. Treatment should be aimed at the underlying cause with symptomatic pain treatment offered as required.

There are many cases where there is no identifiable cause found or it has been optimally treated and the pain persists. Pain management will be the main goal of management in these cases.

It is not possible to cover the management and treatment of all visceral pathologies. The next section will concentrate on the pain management.

Management of pain

Pain management as a symptomatic treatment involves taking a detailed history (including pain history, bladder and bowel problems, menstrual history, dietary history, etc.), physical examination and investigations as required.

Management involves:

1. **Patient education and information**: Patient education plays a very important role in the management of any pain syndrome. The patient should be informed about all the results of the investigations and the probable diagnosis as it will help in decreasing anxiety which may have a significant effect on pain. Pain-based education and self-management tools also benefit patients. Providing information to patients empowers them with the knowledge and helps them when making choices for management along with developing realistic expectations.
2. **Pharmacotherapy**: Symptomatic treatment of visceral pain mainly relies upon pharmacotherapy.[5]

   Classical pain killers: Simple pain killers such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) have a limited role in visceral pain. Paracetamol is a weak cyclo-oxygenase-2 inhibitor and a selective cyclo-oxygenase 3 inhibitor. It is commonly used for pain, but little is known about visceral pain responses since most studies have not focused on visceral pain. Several studies involving animal models of visceral pain have confirmed benefits of NSAIDs plus paracetamol combinations.

   NSAIDs are effective in reducing cancer pain in a dose-dependent fashion. Multiple studies have found NSAIDs are as effective as opioids for biliary colic with fewer side effects. One of the mechanisms by which NSAIDs work in renal or biliary colic may involve acetylcholine blockade. Diclofenac also blocks acetylcholine-induced smooth muscle contraction.

   Anti-spasmolytic agents: As the visceral pain may be associated with smooth muscle spasm, anti-spasmolytic agents

can play a role in the management of visceral pain. For example, pain associated with renal colic or dysmenorrhoea.
Opioids: have a limited role in visceral pain due to their low efficacy.[6] They are associated with dysmotility of the gut and constipation, which causes aggravation of visceral pain. Their use is associated with visceral hyperalgesia. Features of hyperalgesia are increased pain intensity, spread of pain area or radiation of pain with reduced responsiveness to opioid analgesia. Opioid-induced hyperalgesia mimics pain associated with progression of the underlying pathological condition. Physicians unaware of this phenomenon increase the opioid dose only to further exacerbate visceral pain. Combinations of analgesics which include opioids have been reported in the management of visceral pain in animal models.
Anti-neuropathic medications: Treatment for neuropathic pain may have utility for visceral pain as the pathophysiology shares many features with neuropathic pain, including contributions from peripheral and central sensitization, altered descending inhibition and similar molecular targets. The treatment can be started according to NICE guidelines[7] for neuropathic pain with tricyclic anti-depressants or gabapentinoids.

Lee et al. showed efficacy of gabapentin in 43 patients with diarrhoea-predominant irritable bowel syndrome in a randomized, double-blind, placebo controlled study. Pregabalin was found to have a non-significant improvement in self-assessed pain scores in the patients with IBS and rectal hypersensitivity.
NMDA receptor blockers: Central sensitization plays a key role in visceral pain. The barrage of pain signals from the periphery leads to several changes in the spinal cord. The glial cells are activated and release pro-inflammatory cytokines, which in turn increases the neuronal excitability. NMDA receptors are activated and result in central sensitization and 'wind up'. NMDA receptor blockers (e.g. ketamine) can reduce central sensitization and help in visceral pain but their use is associated with significant side effects such as nausea, vomiting, dreams, hallucinations and headache.
Other agents: There are several other pharmacological agents that have been used for visceral pain. For example, nitrates can be used for the pain associated with cardiac ischemia, Anti-histamines have a role in gastric pain. Octreotide reduces visceral hyperalgesia which is a logical choice to use with morphine in malignant-related bowel obstruction. Hormonal agents are recommended in the recent NICE guidance for endometriosis.[8]

3. **Invasive interventions**: Interventions have a limited role in the management of visceral pain. They may be associated with significant side effects and are most commonly used in patients who have pain related to cancer. The common interventions for visceral pain includes:
Sympathetic nervous system block: Coeliac plexus, lumbar, hypogastric, splanchnic and Ganglion-Impar block (diagnostic or destructive)
Selective lesioning of visceral pain pathways (e.g. DRES, cordotomy).
4. **Non-pharmacological interventions**: Non-pharmacological methods play an important role in the management of visceral pain (e.g. TENS, acupuncture, heat or cold).
5. **Physiotherapy:** As the underlying pathophysiology of visceral pain is common with many other pain syndromes, it has been suggested that management should follow the same general approach as that used for other pain syndromes. Therefore physiotherapy approaches can be utilized with visceral pain. Pain management physiotherapy is provided within a cognitive behavioural therapy (CBT) framework. Exercise and movement are an important component of long-term pain management, but there is no evidence supporting specific exercises over general exercises.[9] There may be muscle and subcutaneous changes subsequent to visceral pathology where physiotherapy has a specific role (i.e. pelvic floor hyperalgesia secondary to bladder pain syndrome).
6. **Psychological interventions**: The biopsychosocial model of pain describes a complex interaction between pain, behaviour, cognition, emotion and social context. Psychological interventions have an important role in assessment and management of visceral pain as it has an emotional and cognitive impact in addition to functional limitations. The effect of visceral pain extends to relationships with family, friends, social life, work and study. It should be provided by the multi-disciplinary team including a psychologist.

Cognitive and behavioural techniques are aimed to reverse the impact of pain, but the experience of the pain also usually improves. A biopsychosocial assessment followed by CBT as a group or individual programme is provided along with physical therapy and medical management.
7. **Neuromodulation**: There is evidence to suggest a role of dorsal column pathways in maintaining visceral pain. Implantation of spinal cord stimulation (SCS) has been recommended by NICE for neuropathic pain (failed back surgery syndrome, angina pectoris, peripheral nerve injury pain and complex regional pain syndrome) and has shown good outcomes in pain of ischemic origin.[10] It also suppresses the visceral response to colon distension in an animal model. There are several case reports that have shown good response of SCS in visceral pain. ◆

REFERENCES

1 Romer AS. The vertebrate as dual animal - somatic and visceral. *Evol Biol* 1972; **6:** 121–56.
2 Sengupta J. Visceral pain: the neurophysiological mechanism. *Handb Exp Pharmacol* 2009; **194:** 31–74.
3 Carr, et al. Visceral pain. IASP: pain clinical update, December 2005.
4 Giamberardino MA, Costantini R, Affaitati G, et al. Viscero-visceral hyperalgesia: characterization in different clinical models. *Pain* November 2010; **151:** 307–22.
5 Davis MP. Drug management of visceral pain: concepts from basic research. *Pain Res Treat* 2012; **2012:** 265605.
6 https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware-Opioids Aware: A resource for patients and healthcare professionals to support prescribing of opioid medicines for pain. (2015).
7 Nice Guidelines: https://www.nice.org.uk/Guidance/CG173: Neuropathic pain in adults: pharmacological management in non-specialist settings (accessed November 2013).

8 Nice guidelines: https://www.nice.org.uk/guidance/ng73: Endometriosis: diagnosis and management (accessed September 2017).
9 Messelink B, Baranowski A, Hughes J: Abdominal and pelvic pain: from definition to best practice: chapter-21/Physiotherapy in assessment and management of pain
10 Nice guidelines: https://www.nice.org.uk/Guidance/TA159: Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: October 2008.