Gastroenterology 2016;150:1408–1419

Centrally Mediated Disorders of Gastrointestinal Pain

Laurie Keefer,[1] Douglas A. Drossman,[2] Elspeth Guthrie,[3] Magnus Simrén,[4] Kirsten Tillisch,[5] Kevin Olden,[6] and Peter J. Whorwell[7]

[1]Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, New York; [2]Center for Functional GI and Motility Disorders, University of North Carolina and Center for Education and Practice of Biopsychosocial Care LLC, Drossman Gastroenterology PLLC, Chapel Hill, North Carolina; [3]Mental Health and Social Care Trust, Manchester Royal Infirmary, Manchester, UK; [4]Department of Internal Medicine and Clinical Nutrition, Institute of Medicine Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [5]Oppenheimer Family Center for Neurobiology of Stress Division of Digestive Diseases, David Geffen School of Medicine at UCLA, Los Angeles, California; [6]SJHMC Internal Medicine Department, Phoenix, Arizona; and [7]Education and Research Centre Wythenshawe Hospital, Manchester, UK

Centrally mediated abdominal pain syndrome, formerly known as functional abdominal pain syndrome, can be distinguished from other functional gastrointestinal disorders by its strong central component and relative independence from motility disturbances. Centrally mediated abdominal pain syndrome is a result of central sensitization with disinhibition of pain signals rather than increased peripheral afferent excitability. A newly described condition, narcotic bowel syndrome/opioid-induced gastrointestinal hyperalgesia, is characterized by the paradoxical development of, or increases in, abdominal pain associated with continuous or increasing dosages of opioids. Patients only have relief when opioids are withdrawn. We define both conditions in the context of epidemiology, pathophysiology, clinical evaluation, and treatment, emphasizing the importance of a physician—patient relationship in all aspects of care.

Keywords: Chronic Abdominal Pain; Narcotic Bowel; Functional Abdominal Pain; Centrally Mediated Pain; Rome IV.

This paper describes our approach and recommendations related to 2 gastrointestinal (GI) disorders whose primary symptoms are believed to have a central determinant—centrally mediated abdominal pain syndrome (CAPS), formerly known as functional abdominal pain syndrome, and a new condition, narcotic bowel syndrome (NBS)/opioid-induced GI hyperalgesia.

D1. Centrally Mediated Abdominal Pain Syndrome

Definition

CAPS is characterized by continuous, nearly continuous, or frequently recurrent abdominal pain that is often severe and only rarely related to gut function. CAPS is associated with loss of function across several life domains, including work, intimacy, social/leisure, family life, and caregiving for self or others, and must be present for at least 6 months before diagnosis.

Like other functional gastrointestinal disorders (FGID), CAPS cannot be explained by a structural or metabolic disorder using currently available diagnostic methods. Abdominal pain can be produced by or attributed to non-digestive organs, such as those in the urinary or gynecologic systems, and disorders in these locations that explain such pain should be excluded before the diagnosis of CAPS can be established. A substantial proportion of CAPS patients suffer significant negative contributions from multiple, probably unnecessary, surgical interventions performed in an attempt to address their pain complaints,[1] and attribute their pain to "adhesions." Adhesions can cause symptoms of acute or subacute obstruction, which in turn cause pain, but there is no good evidence that adhesions themselves are a cause for chronic unrelenting pain, such as that seen in CAPS.[2]

The predominance of pain as the central complaint, almost to the exclusion of other symptoms, distinguishes CAPS from other painful FGID, such as irritable bowel syndrome (IBS) and functional dyspepsia (FD), primarily by the poor relationship of pain with food intake or defecation. CAPS may represent the far end of the spectrum of IBS severity, where psychosocial factors and more generalized central hypersensitivity predominate. It is distinguished from chronic pelvic pain by its abdominal location and from "abdominal migraine" in that the pain from CAPS is constant rather than cyclical.

Pain associated with CAPS may be colicky in nature, as in IBS, although it tends to be more prolonged and widespread. Another description that is quite common, especially after a previous surgery, is that pain is burning in character; this form is particularly challenging to treat.[3] CAPS can be associated with other unpleasant somatic symptoms and syndromes, such as fibromyalgia and chronic fatigue syndrome. While not part of the diagnostic criteria, psychological comorbidities are common when pain is persistent

Abbreviations used in this paper: **CAPS, centrally mediated abdominal pain syndrome; FD, functional dyspepsia; FGID, functional gastrointestinal disorder; GI, gastrointestinal; IBS, irritable bowel syndrome; NBS, narcotic bowel syndrome; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TLR, Toll-like receptor.**

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0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2016.02.034

over a long period of time, are further associated with chronic pain behaviors, and dominate the patient's life. [3]

Epidemiology

CAPS is considered less common than other FGIDs, such as functional heartburn, FD, or IBS, with prevalence data ranging from 0.5% to 2.1%.[4] CAPS seems to be between 1.5 and 2 times more common in women,[4,5] and its prevalence reaches a peak in the fourth decade of life (35−44 years in the US householder survey) and then decreases with age.[6]

Approximately 80% of CAPS patients have consulted a physician, and half had seen a physician between 1 and 3 times per year specifically for abdominal pain,[4,7] 4 times more frequently than people without abdominal complaints. CAPS patients in the United Kingdom required 5.7 consultant visits, completed 6.4 endoscopic or imaging investigations, and underwent 2.7 surgical interventions (primarily hysterectomy and exploratory laparotomy) during a follow-up period of 7 years.[8] In the United States, CAPS patients missed work a mean of 11.8 days in the previous year, 3 times more than subjects without abdominal symptoms, and "felt too sick to go to work" at the moment of the survey in 11.2% of cases, about 3 times more frequently than respondents without FGIDs.[4]

D1. Diagnostic Criteria[a] for Centrally Mediated Abdominal Pain Syndrome[b]

Must include all of the following:

- Continuous or nearly continuous abdominal pain
- No or only occasional relationship of pain with physiological events (eg, eating, defecation, or menses)[c]
- Pain limits some aspect of daily functioning[d]
- The pain is not feigned
- Pain is not explained by another structural or functional gastrointestinal disorder or other medical condition

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

[b]CAPS is typically associated with psychiatric comorbidity, but there is no specific profile that can be used for diagnosis.

[c]Some degree of gastrointestinal dysfunction may be present.

[d]Daily function could include impairments in work, intimacy, social/leisure, family life, and caregiving for self or others.

Pathophysiology

The biology of CAPS is likely similar to other chronic visceral pain disorders, such as IBS, FD, and interstitial cystitis. While these disorders are all defined by discrete symptom criteria, they have in common comorbidity with other pain syndromes, predisposing life events, and treatment responses. As with many chronic somatic pain disorders, CAPS does not fit easily into the traditional categories of neuropathic or inflammatory pain. Rather, alterations in modulatory and motivational pain dimensions play a major role in both the generation and perpetuation of CAPS.

Altered central sensory processing in gastrointestinal pain syndromes: lessons learned from irritable bowel syndrome and functional dyspepsia. The brain receives interoceptive input from the abdominal viscera, which is then combined with cognitive, emotional, and other sensory information for conscious interpretation in the anterior insula. Neuroimaging studies in IBS are consistent with an abnormality in central processing of pain signals, with functional and structural abnormalities noted in sensory (mid-cingulate, insular, and somatosensory cortices, and thalamus), emotional arousal (anterior cingulate cortex, amygdala), and prefrontal cortical modulatory regions. Modulation of descending pain regulatory pathways in the brainstem by these cortical regions can lead to exaggerated sensitivity to both noxious and innocuous stimuli. Evidence that patterns of brain activation during anticipation of experimental pain are abnormal in IBS further supports this pathophysiologic model. Patients with FD show similar abnormalities compared with healthy control subjects.[9]

One way in which CAPS differs from IBS and FD is that the pain symptoms are, by definition, reported as more constant and unrelated to peripheral events, such as food intake or defecation. This suggests that, unlike IBS and FD, the phasic, physiologic visceral afferent input from the gut plays a lesser role in symptom generation. These observations, along with the common responsiveness of CAPS symptoms to low-dose tricyclic antidepressants (TCA), raises the question of whether some CAPS patients have a peripheral or gut-based neuropathic pathophysiologic process. Unfortunately, neither the characteristically enlarged pain referral areas nor the response to TCAs (which work on both peripheral and central neuropathic pain conditions) make it possible to differentiate between these possibilities. However, even in the setting of a peripheral insult, once central sensitization is established, symptoms can persist in the absence of ongoing abnormal peripheral stimulation or worsen with minimal stimulation.[10] Because no consistent initiating triggers are noted in CAPS, and the risk factors seem to be primarily psychosocial, it is presumed that central processes, such as altered descending pain modulation, are responsible for the chronicity of CAPS.[11]

Altered brain structure in chronic pain. Altered brain structure has also been described in multiple visceral and somatic pain disorders. In women with IBS, increased cortical thickness in the somatosensory cortex and decreased cortical thickness in regions of pain processing, including the insula and anterior cingulate cortex, is observed.[12] IBS symptom severity was negatively correlated with the cingulate thickness, suggesting a role for loss of neural density in symptom generation. Using another metric