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Dorsal root ganglion stimulation provides functional improvement from debilitating abdominal pain in Crohn's disease: A 12-month follow-up

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ABSTRACT

Background: Crohn's disease (CD) is a chronic relapsing-remitting, immunological, inflammatory bowel disease involving any part of the gastrointestinal tract, most commonly, the terminal ileum. Abdominal pain is a prominent debilitating symptom of CD due to continuous intestinal inflammation, associated with disease severity and complications. However, abdominal pain has shown to occur even with disease remission.
Case presentation: A female college student with a history of Crohn's Disease was referred for severe, chronic abdominal pain, with frequent flare-ups and hospitalizations. Due to her refractory debilitating pain, DRG stimulation was initiated with leads placed at right T11 and T12. Twelve months post-implantation, the patient reports 50–60 % reduction in pain, tolerance of an oral diet without postprandial pain, no occurrence of flares since implant, and an overall improvement in function and quality of life.
Conclusion: This report showcases the therapeutic potential of DRG stimulation in managing intractable chronic abdominal pain in inflammatory bowel diseases such as Crohn's disease.

1. Introduction

Crohn's disease (CD) is a chronic inflammatory disorder characterized by a relapsing and remitting course. It can affect any part of the gastrointestinal tract, however most commonly, the terminal ileum and perianal region [1]. The pathophysiology is complex, involving a combination of environmental factors, genetic susceptibility, altered immune response, and microbiome changes, ultimately resulting in tissue inflammation [2]. Abdominal pain in inflammatory bowel disease (IBD) remains to be a common and debilitating symptom [3]. Over 70 % of IBD patients report abdominal pain at some point during the course of their disease [4]. Ongoing intestinal inflammation can be one of the primary causes of pain, but other IBD related manifestations can also be the culprit. Abdominal pain generally improves with decreased disease activity or treatment of the related structural issues. However, it has been shown to occur even in the absence of active disease. Approximately 20%–50 % of patients in CD remission, both clinically and endoscopically, have been shown to have significant abdominal pain [4,5]. This could be explained by coexisting functional disorders like irritable bowel syndrome or the development of chronic pain through central desensitization [3]. Chronic abdominal pain continues to have significant impact on quality of life and often is the leading factor behind patients seeking medical care [4]. Chronic abdominal pain has also shown to be related to poor oral intake, negative dietary outcomes and weight loss [6].

Sensory neural transmission from the gastrointestinal tract to the central nervous system begins with spinal afferents. These travel via the splanchnic or pelvic nerves, whose cell bodies reside in the dorsal root ganglia (DRG), receiving nociceptive sensations from the gut [7]. Chronic gastrointestinal inflammation can lead to hyperexcitability of these neurons, potentially resulting in central sensitization. Dorsal root ganglion stimulation (DRGS), approved in 2016 [8], is an innovative therapy that targets the afferent neurons by placing the electrical field near the cell nuclei within the DRG [9]. The colon is innervated primarily by the thoracolumbar and lumbosacral neurones. DRG located at these levels hence are a target for neuromodulation for IBD. Since DRGs at each spinal level receive sensory information from a specific dermatomal region, pain relief can be selectively targeted, having both diagnostic and therapeutic potential [10]. The purpose of DRGS is to target incoming afferent pain signals prior to transformation within the spinal

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cord, hence modulating pain perception. This case presents a one-year follow up of permanent DRGS implant in a patient with chronic refractory abdominal pain from CD.

2. Case report

A 21-year-old female with a past medical history of Juvenile Idiopathic Arthritis and CD was evaluated for debilitating, chronic abdominal pain, secondary to Crohn's disease. She reported persistent dull, aching pain in her right lower abdomen. This pain particularly worsened with the ingestion of fatty and high fiber foods. The pain was rated as 8/10 on the Numerical Rating Scale (NRS), with episodes of 10/10 in intensity, post-prandially. Due to poor tolerance of oral intake, the patient was eventually initiated on total parenteral nutrition (TPN). The patient would have frequent CD flare-ups, often requiring hospitalization. With chronic right-sided abdominal pain refractory to her medication regimen, the plan to trial DRGS was made. The patient's desired outcome was to achieve pain relief, with hope to return to eating solid foods, exercise, and attend school. Trial leads were percutaneously placed unilaterally along the right T10 and T12 DRG (Fig. 1). Ten days later, upon follow up after trial placement, the patient's pain score decreased from 8/10 to a 4–6/10. She reported a significant improvement in quality of life, being able to tolerate some food orally, improved sleep due to reduced nighttime awakenings due to pain and had started engaging in moderate activity. However, the patient reported inadequate benefit from the T10 lead as it provided stimulation in the upper abdomen away from the site of her pain and preferred a T12 lead. Four months later, DRGS leads were implanted at the T11 and T12 levels for a total of two leads (Fig. 2). The patient had gastrojejunostomy tube placed and was started on tube feeds. The patient had sustained improvement at two and four week follow ups post implant. The patient was weaned off TPN one month after this follow up, and increasingly tolerated oral intake and tube feeds with minimal post-prandial pain.

The patient resided out of state and continued follow up with her gastroenterologist and primary care physician. The patient had no

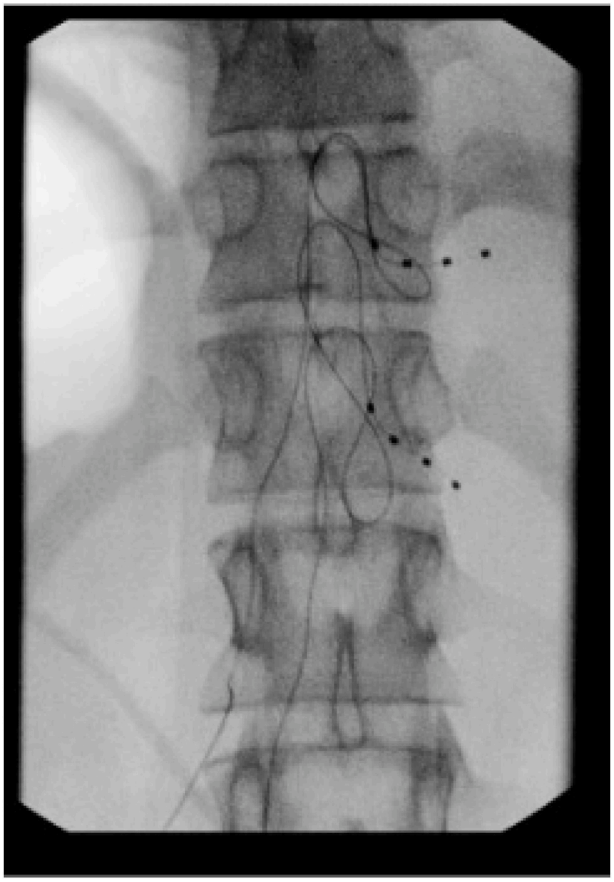

Fig. 2. Fluoroscopic image demonstrating right T10 and T12 DRGS permanent lead placement.

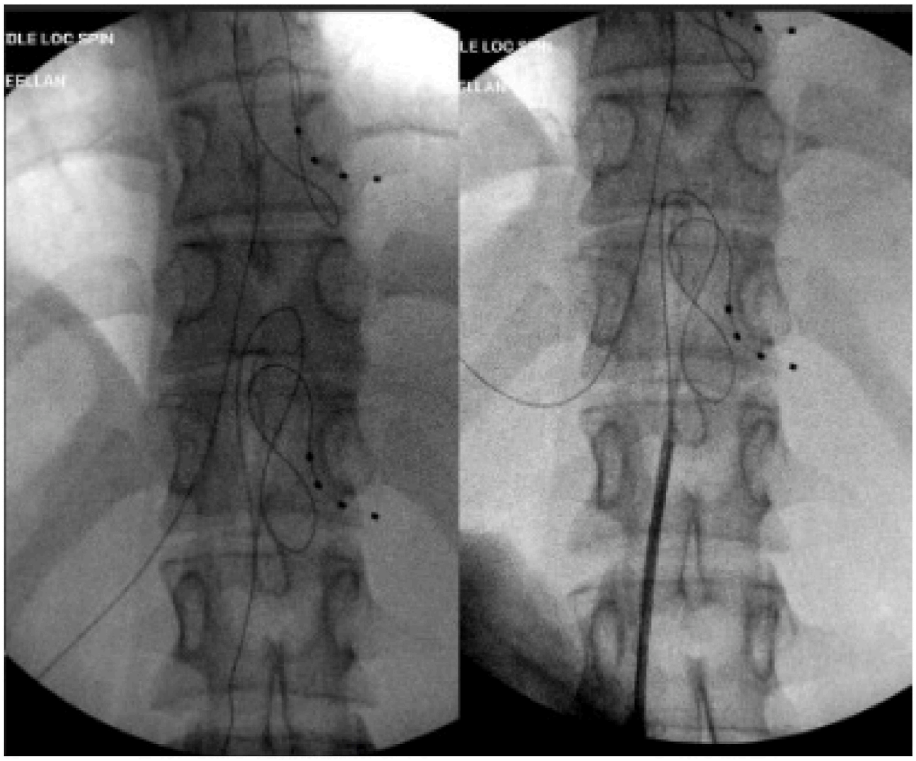

Fig. 1. Fluoroscopic images demonstrating right T10 and T12 DRGS trial leads placement.

complications and stayed in touch with her clinical specialist for the device. Twelve months later, the patient followed up with the pain clinic virtually. She reported continued significant improvement in her abdominal pain since the permanent implant. Her pain was, on average, 4 out of 10 from the initially severe 8–9/10 (50–60 % reduction). She noted no increase in her pain levels postprandially, with continued tolerance of oral diet. She remains off parenteral nutrition with significant weight gain returning to baseline. During the post-implant period, the patient went from having frequent flares (sometimes lasting up to six months) to no flares. She has also had no recent hospitalizations for Crohn's related issues or required any other interventions to date. The patient has maintained close follow up with gastroenterology for the management of her Crohn's with no changes to her medication regimen. The patient also reported an overall improvement in quality of life and has returned to attending classes full-time from her previous bed-ridden state. With being able to tolerate oral intake, eating a mixed variety of foods and improved sleep, the patient has been able to return to her daily life activities. (Table 1 and Fig. 3).

3. Discussion

Crohn's Disease is driven by an excessive immune response against the gut microbiome. Genetic variations lead to decreased intestinal mucus production, combined with a complex interaction between immune cells, integrins, adhesion molecules and increased levels of cytokines like TNF-α, IL-12 and IL-23, lead to mucosal inflammation [2]. The management of Crohn's is multifold, with therapies targeted to address the underlying pathways in the development of CD, such as methotrexate, thiopurines, and biologics, targeting specific proteins involved in the inflammation cascade [11]. Abdominal pain associated with active Crohn's flare or disease progression involves the escalation of primary regimen. Additionally, antispasmodics, opioids, anticonvulsants and antidepressants can be utilized [12].

Table 1
Comparison of different factors pre-implant and post-implant at one month and one year.

	Pre-Implant	Post-Implant (1 month)	Post-Implant (1 year)
Pain Intensity	8/10	5/10	4/10
Post-Prandial Pain Intensity	10/10	5-6/10	4/10
Oral Intake	Poor tolerance, reliant on Total Parenteral Nutrition (TPN)	Tolerating soft diet, Enteral nutrition via GJ tube	Tolerating a mixed foods diet TPN and enteral nutrition discontinued
Flare-ups/ Hospitalizations	Frequent flares Multiple hospitalizations	No flares No hospitalizations	No flares No hospitalizations
Medication Regimen	Ustekinumab infusion q5weeks Gabapentin 900mg TID Nortriptyline 10mg daily Duloxetine 60mg daily Acetaminophen prn	No changes	No changes
Sleep	Interrupted sleep Nighttime awakenings	Improved sleep No nighttime awakenings	Continues to have improved sleep No nighttime awakenings
Activity	Decreased ambulation during flares Increased time in bed	Improved activity	Continued increase in activity Walking
Quality of Life	Poor	Improved, engaging in daily activities	Significant improvement, regular exercise, attending classes

Ongoing inflammation in IBD triggers mast cell activation releasing histamine and tryptase which can sensitize nerve receptors [5,7]. Pro-inflammatory cytokines can lower sensory neuron activation thresholds, contributing to visceral hypersensitivity, through long term changes in the DRG. Chronic GI inflammation can alter sodium channels increasing neuronal excitability and can lead to changes centrally, leading to hyperalgesia and hypersensitivity even in the absence of inflammatory mediators [5,7].

Vagal afferent and efferent nerve fibres primarily relay and control physiologic responses involved in hormone secretion, gastric motility and digestion [13]. Thoracolumbar nerves carry both afferent and efferent axons from the GI tract that respond to nociceptive stimuli [13]. Spinal afferents relay nociception from the GI tract from sensory receptors located within the walls of gastrointestinal organs. These are carried through Aδ and C fibers, traveling along sympathetic nerves such as splanchnic nerves which originate from the thoracolumbar region (T5-L2) of the spinal cord and ascend through the sympathetic chain and enter the spinal cord through the DRG [14].

The Gate Control Theory is a key concept in understanding pain mechanisms [15]. Pain perception is modulated through a gate mechanism, in the dorsal horn, which either amplifies or inhibits pain transmission from small-diameter Aδ and C fibers [15]. Activation of large-diameter Aβ, originating in the DRG, carrying non-painful stimuli, can block pain signals, reducing overall pain perception [10,16]. DRGS can preferentially activate large-diameter fibers, inhibiting the transmission of pain signals from the Aδ and C fibers, thus "closing" the gate. DRG is an enlargement of the dorsal root containing a cluster of sensory neuron cell bodies located at the intervertebral foramen of vertebral levels bilaterally [10]. These pseudo-unipolar neurons have afferent axons that bifurcate at the T-junction [9,17]. Following injury or inflammation, afferent cell bodies can become hyperexcitable, generating spontaneous ectopic action potentials, that disrupt normal pain processing [9]. The T-junction can obstruct, facilitate, or filter electrical impulses from the peripheral nociceptors [17]. DRGS enhances low-pass filtering of C-neurons by inducing action potentials that cause calcium influx and potassium efflux, leading to hyperpolarization of the neuron, preventing pain signals from propagating past the T-junction and entering the spinal cord [18]. This mechanism is thought to contribute to DRGS's analgesic effect. Other mechanisms studied in DRG stimulation include modulation of inflammation by regulating satellite glial cell activity, facilitation of antidromic action potential propagation involved in neurogenic inflammation, regulation of neurotransmitter release and neural excitability via modulation of sodium, calcium channels and excitatory glutamatergic receptors, as well as supraspinal effects involved in central pain processing [17].

Our initial paper reported improvement of this patient's abdominal pain at one month [19]. This report presents a one-year update on this patient, who had significant relief of abdominal pain with overall reductions in her Crohn's disease symptoms, with no flares or hospitalizations, twelve months after DRGS implantation. Another case report reported use of DRGS to manage chronic abdominal pain in CD, reported near-total pain relief with improved stool consistency after DRGS implantation [20]. The benefit of DRGS in abdominal wall pain has been shown in multiple studies. A case report of a patient with chronic pain after bypass surgery who underwent bilateral T11 DRGS trials revealed >90 % pain relief at six months [21]. Additionally, a prospective case series, involving 34 patients with chronic groin pain, after previous inguinal hernia repair, reported greater than 50 % improvement after DRGS trial at L1 and L2 in 30 patients [22]. Abdominal pain remains to be one of the most debilitating symptoms in IBD patients, leading to reduced health-related quality of life [23]. Addressing this pain can therefore improve quality of life and decrease anxiety associated with this chronic disease.

Despite improvement in abdominal pain presented in this patient,

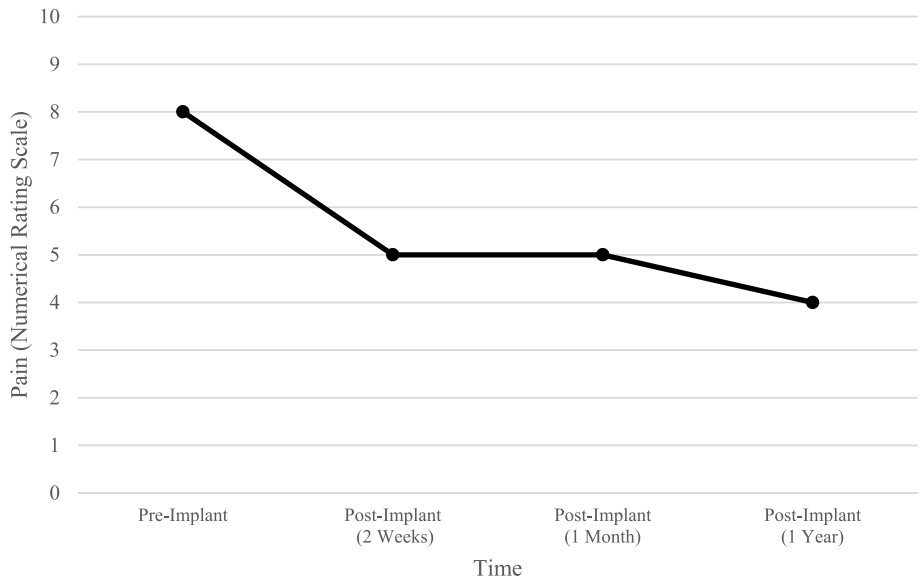

Fig. 3. Patient reported pain rating pre-implantation and post-implantation at two weeks, one month and one year intervals*.
* The spacing between the data points on this graph does not correspond to the actual time intervals between them as the graph is not scaled proportionally.

given the relapsing-remitting course of Crohn's disease, it is difficult to attribute improvement in flares and oral intake to the DRGS implantation. Long term follow up is needed to continue monitoring symptoms and response. Further, limitations exist for the use of this technique. DRGS is currently not FDA approved for the use of chronic visceral abdominal pain. Given the targeted nature of DRGS, its use in CD may be complex, due to the underlying unpredictable course and the ability to affect multiple non-contiguous segments of the GI tract. Managing chronic pain in IBD, such as Crohn's, first requires ensuring control of the primary disease through guideline-directed management, to maintain overall disease stability, ensure disease remission and prevent disease migration. Accurately diagnosing the pain generator is crucial for treatment efficacy and optimizing therapeutic potential.

4. Conclusion

Chronic inflammation of the GI tract can sensitize visceral afferent nerve fibers, dysregulating ion channels in the DRG, leading to hyperexcitability and persistent abdominal pain. DRGS is an innovative and emerging technique shown to modulate sensory neuron activity, targeting stimulation at specific spinal levels. Sustained abdominal pain relief in our patient with significant functional improvement, highlights the therapeutic potential of DRGS in managing intractable chronic abdominal pain in IBD. Large-scale studies to further explore the application of DRGS in IBD and associated chronic visceral pain syndromes are necessary. Additional research is needed to solidify specific mechanisms involved in visceral hypersensitivity and DRG neuromodulation.

Consent

Informed consent was obtained from the patient prior to the production of this manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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