Case Report

Spinal cord stimulation for relief of abdominal pain in two patients with familial Mediterranean fever

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Familial Mediterranean fever is a hereditary disease characterized by recurrent attacks of fever and serosal inflammation that commonly presents as severe abdominal pain. Though colchicine remains the mainstay of treatment, a significant proportion of patients are partially responsive, unresponsive or intolerant to it. We present two such cases where spinal cord stimulation (SCS) was used to manage the paroxysmal abdominal pain associated with this disease. Abdominal visceral pain pathways and the application of SCS techniques in its management are discussed.

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Familial Mediterranean fever (FMF, recurrent polyserositis, periodic disease) is an ancient disease, dating back at least 2500 yr. Its incidence in eastern Mediterranean populations ranges from 1 in 250 to 1 in 1000, making it the most common auto-inflammatory syndrome.1 Our successful use of spinal cord stimulation (SCS) to manage abdominal pain in two patients with FMF offers another avenue of pain management in refractory cases.

Case report 1

A 49-yr-old female who suffered from FMF was seen in our pain clinic. She experienced frequent attacks of abdominal pain accompanied by fever, nausea and vomiting. The pain was mainly localized to the lower abdomen (T10–T12 dermatomes) and was described as intense, burning, and occasionally stabbing. The FMF crises, each lasting for 24–48 h, occurred approximately 2–3 times a month. Though colchicine prophylaxis had reduced the frequency and severity of attacks, she still needed fentanyl lozenges, codeine phosphate and paracetamol during attacks. Despite these, pain control remained unsatisfactory; on several occasions, the pain had been severe enough to necessitate emergency hospital admission.

We decided to undertake a trial of SCS to manage her pain. Under local anaesthesia, the epidural space was accessed at L2–L3 levels and a single octopolar SCS lead (Advanced Neuromodulation systems Inc., Plano, TX, USA) was advanced under fluoroscopic guidance to the T8–T9 level in the dorsal epidural space. This was connected to an external pulse generator; intraoperative stimulation tests confirmed good truncal paraesthesia in the T9–T12 dermatomes. The patient experienced a FMF crisis on day 6 of the trial. SCS activation achieved a reduction in visual analogue scale (VAS) pain scores from 9/10 to 2/10. Therefore, we proceeded to permanent SCS implantation under general anaesthesia. This procedure involves replacing the temporary external pulse generator with a permanent one that is implanted in a s.c. pocket (usually over the anterior abdominal wall); the original SCS lead in situ is then connected to it via a subcutaneous tunnel. She was discharged home a week later with full instructions on using the SCS system; she was also asked to keep a diary of VAS pain scores, analgesia intake and activity levels during FMF crises.

The initial benefit was maintained at follow-up a month later. By 3 months, she was weaned off all systemic opioids and returned to her full-time job by 6 months. However, at 12 months, the efficacy of SCS was found to have decreased (VAS 5/10). X-ray did not show any lead migration. Reprogramming of stimulation parameters was enough to re-achieve the initial benefit. This analgesia was maintained at her second and third year follow-ups.

Case report 2

A 38-yr-old male was referred to our pain unit for management of FMF-related severe episodic abdominal
pain accompanied by fever, nausea and vomiting. FMF crises occurred every 1–2 weeks and lasted for 24–72 h on each occasion; the abdominal pain was usually diffuse (T8–T11 dermatomes) and poorly localized. He reported poor compliance with colchicine therapy because of frequent diarrhoea and used fentanyl lollipops, oral morphine, codeine phosphate and paracetamol during attacks. He had even tried smoking cannabis with little benefit. The pain and disability had led to the loss of his job and divorce; he expressed feelings of frustration, anger and low mood.

Based on our previous experience, a trial of SCS was planned. Under local anaesthesia, the epidural space was accessed at L3–L4 levels and a single octopolar SCS lead (Precision SCS System®, Advanced Bionics Corp, Sylmar, CA, USA) was advanced under fluoroscopic guidance to the T6–T7 level in the dorsal epidural space. Intraoperative stimulation tests confirmed good truncal paraesthesia in the T7–T12 dermatomes. On day 3 of the trial, however, he experienced paraesthesia in his legs. An X-ray of the thoracic spine demonstrated migration of the SCS lead down to T9 level (Fig. 1). However, reprogramming was enough to achieve target area stimulation and minimize leg paraesthesiae. On day 5 of the trial, our patient experienced a FMF crisis, for which he had near-complete symptom abolition on activating the SCS. Therefore, we proceeded to permanent SCS implantation under general anaesthesia. At the same time, a second octopolar lead was also implanted parallel to the first one to improve lead stability and provide greater programming options (Fig. 2).

Follow-up at months 1 and 3 after implantation of SCS demonstrated a reduction in VAS pain scores from 10/10 to 1/10 after SCS activation during a FMF crisis, without the need for any opioids.

Discussion
This is the first reported use of SCS for the management of abdominal pain in FMF. FMF is a hereditary auto-inflammatory disease characterized by self-limited recurrent attacks of fever and serositis. The recurrent attacks of fever are accompanied by severe abdominal pain along with a marked increase in acute-phase reactants. In addition to peritonitis, the fever may be accompanied variously by arthritis, pleuritis, pericarditis, myalgia or erysipelas-like skin erythema. The fever and serositis may last from 1 to 4 days and the frequency of attacks may vary from weekly to once every 3 yr; FMF patients are symptom-free between attacks. Historically, this autosomal recessive disease affected mainly Jews, Turks, Arabs and Armenians. With the migrations of the past century, however, FMF is no longer confined to eastern Mediterranean countries and milder mutations are now found in other European populations. The disease is caused by mutations in the MEFV (for MEditerranean FeVer) gene located on chromosome 16, coding for the protein ‘pyrin’. Pyrin is expressed in granulocytes and is probably involved in the down-regulation of mediators of inflammation. FMF attacks are characterized by a massive influx of polymorphonuclear leucocytes into the inflamed regions, suggesting the disruption of pyrin in these cells may lead to their uncontrolled activation and migration to serosal tissues. There is also postulated to be a link between FMF and catecholamine metabolism, since metaraminol infusion may provoke a FMF attack. During attacks, acute-phase reactants such as C-reactive protein, fibrinogen and serum amyloid A are increased, along with a raised erythrocyte-sedimentation rate and white blood cell count. Colchicine is the drug of choice for prophylaxis against FMF attacks and FMF-associated amyloidosis. A total of 65% of patients respond to colchicine with complete remission, and 20–30% experience a reduction in the number and severity of attacks, with 5–10% being either non-responders or non-compliant. Reduced patient compliance can be attributed to the
gastrointestinal side-effects (nausea, vomiting, abdominal pain and profuse diarrhoea) that often complicate colchicine therapy.\(^4\) In clinical practice there is no alternative drug for colchicine-resistant FMF.\(^5\) Though our patients were on a combination of opiates and simple analgesics, analgesia was far from satisfactory. Implantation of an intrathecal or epidural opiate delivery system was deemed impractical because of the unpredictable and intermittent nature of the FMF attacks. In comparison, SCS is a more practical alternative owing to its easy titratability by the patient, rapid onset of analgesia and relative lack of systemic side-effects.

In SCS, an array of electrodes (ranging from 4 to 8) is placed in the dorsal epidural space under fluoroscopic guidance. These electrodes, connected to a pulse generator, are then programmed in combinations of anodes and cathodes to generate an electric field, which stimulates the axons of dorsal root and dorsal column fibres in the spinal cord. Stimulation of these fibres results in inhibition of pain transmission in the lateral spinothalamic tracts, as well as increased activity in descending antinociceptive pathways. Clinically, SCS creates paraesthesia, which has been described by patients as a ‘tingling’ sensation in their skin. In the application of SCS, a successful clinical outcome relies upon the overlap of the painful areas with paraesthesia.\(^6\) Slight migration of the lead may result in a shift of the activating field and loss of the desired paraesthesia. Percutaneous leads with multiple contacts have been shown to provide statistically improved long-term outcomes, primarily because of their ability to allow for postoperative reprogramming to capture stimulation targets following micro- or macro-migration.\(^6\)

SCS has widely been applied for the treatment of neuropathic pain with excellent outcomes; however, its use in nociceptive visceral pain syndromes has been hampered by the belief that nociceptive pain cannot be modulated by stimulation of the spinal cord.\(^7\) Visceral pain has been thought of as a vague generalized pain that does not seem to have any correlation between the visceral innervations (or the levels of their afferents in the spinal cord) and the location of the pain experienced. In reality, however, visceral innervation, in a manner analogous to cutaneous dermatomes, follows the embryological origin and location of the viscera and is arranged in viscerotomes. Painful visceral afferents can be traced back into the spinal cord at the corresponding viscerotome and also project their painful sensations in the concordant dermatome.\(^7\)\(^8\) Visceral innervation occurs via sympathetic and parasympathetic pathways; parasympathetic afferents enter the vagal trunks while sympathetic afferents carrying nociceptive information enter the lower 6 thoracic and upper 3 lumbar spinal segments. Thus SCS targeted at these spinal segments can be expected to block visceral pain transmission.\(^7\) Recently, Khan and colleagues published case studies exemplifying the application of SCS for treatment of abdominal pain in chronic non-alcoholic pancreatitis and following abdominal surgery.\(^7\) Our report demonstrates that the same logic extends to the successful application of SCS techniques for treatment of abdominal pain in FMF.

References