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Case Reports

Misdiagnosed Chronic Pelvic Pain: Pudendal Neuralgia Responding to a Novel Use of Palmitoylethanolamide

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Abstract

Background. Pudendal neuralgia is a cause of chronic, disabling, and often intractable perineal pain presenting as burning, tearing, sharp shooting, foreign body sensation, and it is often associated with multiple, perplexing functional symptoms.

Case Report. We report a case of a 40-year-old man presenting with chronic pelvic pain due to pudendal nerve entrapment and successfully treated with palmitoylethanolamide (PEA).

Conclusion. PEA may induce relief of neuropathic pain through an action upon receptors located on the nociceptive pathway as well as a more direct action on mast cells via an ALIA (autocoid local injury antagonism) mechanism.

As recently demonstrated in animal models, the present case suggests that PEA could be a valuable pharmacological alternative to the most common drugs (anti-epileptics and antidepressants) used in the treatment of neuropathic pain.

Key Words. PEA; Pudendal Neuralgia; Chronic Pain

Introduction

Pudendal neuralgia (PN) is a cause of chronic, disabling, and often intractable perineal pain and it is mostly due to pudendal nerve entrapment.

Neuropathic pain is referred as burning, tearing, sharp shooting, and foreign body sensation in the distribution of the pudendal nerve and it is often associated with multiple, perplexing functional symptoms (i.e., urinary frequency, erectile dysfunction, and pain after sexual intercourse).

Patients typically present with pain in the labia or penis, perineum, anorectal region, and scrotum, which is aggravated by sitting, relieved by standing, and absent when recumbent or when sitting on a lavatory seat. In the absence of pathognomonic imaging, laboratory, and electrophysiology criteria, the diagnosis of PN remains primarily clinical [1], and it is often delayed. Furthermore, this condition is frequently misdiagnosed and sometimes results in unnecessary surgery. Here in we describe a 40-year-old man presenting with chronic pelvic pain due to pudendal nerve entrapment, misdiagnosed as chronic prostatitis.

After different uneffective pharmacological therapies, the patient was treated with palmitoylethanolamide (PEA), an endogenous lipid with antinociceptive and anti-inflammatory properties [2,3] with significant improvement of his neuralgia.

Case Report

A 40-year-old healthy man developed since 5 years a progressive predominantly left-sided perineal pain described as burning sensation. Initially, the patient experienced the pain only in the sitting position, but pain gradually became continuous and extended to penis. Moreover, it was often referred as deeper in the anorectal region (as a feeling of "foreign body") and sometimes in distal urethra. Pain was exacerbated while sitting, relieved while standing, and nearly absent when recumbent or sitting in a toilet seat. Furthermore, in some circumstances, pain was associated to painful ejaculation, erectile dysfunction, urge incontinence, and dysuria. The patient also referred intolerance to tight clothes and underwear. Over this long period, he saw many different health care professionals (family practitioners, urologists, neurologists, and psychiatrists), and he was given different diagnoses (abacterial chronic prostatitis, prostatodynia, idiopathic proctalgia, coccygodynia, and psychogenic pain).

Urinalysis with culture, semen analysis, sexual hormones blood level, pelvic, and transrectal prostatic ultrasounds were normal. As chronic pelvic pain syndrome was supposed, he was treated with several drugs such as antibiotics (ciprofloxacin, levofloxacine, gentamicin, azitromycine, and trimethoprim/sulfamethoxazole), antimicotics (fluconazole), and anti-inflammatories (nimesulid, corticosteroids) with only transient mild relief.

At our evaluation, the patient's physical and neurological examinations were unremarkable with the exception of a mild hyperesthesia in the perineal area during the pinprick sensory test. Interestingly, digital rectal exploration evidenced unilateral perineal and rectal pain after pressure on the left ischial spine. The personal history (the patient was an amateur bicycler and regularly attended a fitness/body-building center) and the neuropathic pain features, also reproduced during rectal exam, led us to the diagnosis of PN probably secondary to nerve compression. Pain was rated by the patient at 8 on the 0–10 visual analog scale (VAS). Magnetic resonance imaging of the pelvic area failed to point out organic lesions of the nerve trunk. Pudendal somatosensory evoked potentials and bulbocavernosus reflex with the electromyography of the pelvic floor musculature showed denervation activity of the anal sphincter. Thus, the patient was treated with pregabalin, up to 150 mg/day, prematurely withdrawn because of significant side effects. As the patient refused any other specific pharmacological pain treatment (i.e., antidepressants and anti-epileptics), PEA, up to 900 mg/day, was introduced with a significant improvement of his neuralgia and associated symptoms.

Discussion

The pudendal nerve is a mixed nerve (motory, sensory, and autonomic) composed of three branches: dorsal nerve of penis/clitoris, perineal nerve, and inferior anal nerve, all derived from sacral S2-S4 roots. It supplies the anal and urethral sphincters and pelvic floor muscles and provides anal, perineal, and genital sensitivity. Pudendal nerve entrapment at different levels (ischial spine, sacrospinous, and sacrotuberous ligament, Alcock's canal) is a cause of disabling, chronic, and intractable pelvic pain that is eminently variable and complex as it is often associated with multiple, perplexing functional symptoms.

In our patient, the delay of diagnosis was probably due to the complexity of urogenital symptomatology that led to a misdiagnosis of chronic pelvic pain syndrome, as perineal pain was associated to erectile dysfunction, painful ejaculation, and dysuria.

In the absence of pathognomonic imaging, laboratory, and electrophysiology criteria, the diagnosis of PN is primarily clinical and empirical. Indeed, in the presence of the essential clinical diagnostic criteria validated by a multidisciplinary working party in Nantes (France) and shown in Table 1, PN secondary to nerve entrapment should be suspected. The penile thermal threshold test could moreover be useful to evaluate the somatosensory and autonomic system functions through the sensitive small fibers stimulation [4].

Diagnostic techniques, including computed tomography-guided nerve block and electroneuromyographic (ENMG) studies can confirm the diagnosis.

Perineal ENMG may provide various clues in favor of the diagnosis. Nevertheless, it has a limited sensitivity and specificity as it remains particularly useful for assessing motor innervations in the pudendal nerve territory before surgical decompression, but not for localizing the site of compression [5]. In our patient, ENMG of the anal sphincter was abnormal confirming the diagnosis of pudendal nerve compression.

Indications for surgery includes a diagnosis of pudendal entrapment failed conservative treatment (i.e., behavioral modifications such as avoiding offending factors that cause pain, physical therapy with specific stretches and exercises, and pharmacologic treatment such as anti-epileptics and tricyclic antidepressants) and no long-lasting improvement after steroid pudendal block [6].

In the described case, the patient was administered pregabalin for a short time, withdrawn because of significant

Table 1 Nantes criteria, September 23–24, 2006

Diagnostic Criteria for Pudendal Neuralgia by Pudendal Nerve Entrapment

A. Essential criteria
   - Pain in the territory of the pudendal nerve: from the anus to the penis or clitoris
   - Pain is predominantly experienced while sitting
   - The pain dose not wake the patient at night
   - Pain with no objective sensory impairment
   - Pain relieved by diagnostic pudendal nerve block

B. Complementary diagnostic criteria
   - Burning, shooting, stabbing pain, numbness
   - Allodynia or hyperpathia
   - Rectal or vaginal foreign body sensation (sympathalgia)
   - Worsening of pain during the day
   - Predominantly unilateral pain
   - Pain triggered by defecation
   - Presence of exquisite tenderness on palpation of the ischial spine
   - Clinical neurophysiology findings in men or nulliparous women

C. Exclusion criteria
   - Exclusively coccygeal, gluteal, pubic, or hypogastric pain
   - Pruritus
   - Exclusively paroxysmal pain
   - Imaging abnormalities able to account for the pain

D. Associated signs not excluding the diagnosis
   - Buttock pain on sitting
   - Referred sciatic pain
   - Pain referred to the medial aspect of the thigh
   - Suprapubic pain
   - Urinary frequency and/or pain on a full bladder
   - Pain occurring after ejaculation
   - Dyspareunia and/or pain after sexual intercourse
   - Erectile dysfunction
   - Normal clinical neurophysiology

side effects. As he refused any other specific drug, he was treated with PEA (up to 900 mg/day in the acute phase) with an important improvement of symptoms. Moreover, patient was advised to avoid or reduce all those behaviors possibly causing or exacerbating PN. At 1 year follow-up, he occasionally presented mild pain (VAS score from 2 to 4) in the perineal area and only after heavy physical activity.

PEA, an endogenous fatty acid, is a congener of endocannabinoid anandamide (AEA) that belongs to a class of lipid mediators, the superfamily of N-acylethanoamines. It can be considered a particular nutrition supplement as in Italy it is classified among the ADDFS ("Alimenti Dietetici Destinati ai Fini medici Speciali," i.e., nutrition supplements for specific medical use). Indeed, it is approved and commonly used for the treatment of chronic pelvic pain and as an effective adjuvant treatment for all neuropathies due to endoneural edema. PEA may exert a local antagonism on inflammation by preventing mast cell degranulation through the already-described autacoid local injury antagonism (ALIA) [7]. In addition to this known anti-inflammatory activity, PEA may elicit analgesia in acute [8] and inflammatory pain [9]. It has recently been reported that pain hypersensitivity after sciatic nerve constriction in rats is associated with a significant decrease in the level of endogenous PEA in spinal cord and mesolimbic areas [10]. Moreover, PEA administration may evoke a relief of both thermal hyperalgesia and mechanical allodynia in neuropathic mice [11]. Darmani and coworkers [12], reported that high blood PEA concentrations in neuroinflammatory and neuropathic conditions in both animals and humans may exert a local anti-inflammatory and analgesic action.

Despite its potential clinical significance, the molecular mechanism responsible for the antinociceptive action of PEA is still poorly understood. PEA has a weak affinity for cannabinoid CB1 and CB2 receptors, thus uncharacterized CB2-like receptors have been supposed [13]. A recent "entourage hypothesis" proposes that PEA may act as an enhancer of the anti-inflammatory and antinociceptive activity exerted by AEA via the inhibition of is metabolic degradation due to the ability of PEA to compete with AEA for fatty acid amide hydrolase catalytic activity [14]. Therefore, PEA may induce relief of neuropathic pain through its action on receptors located on the nociceptive pathway, i.e., cannabinoid receptor CB1, transient receptor potential channel of the vanilloid type 1, and peroxisome proliferator-activated receptor γ via an "entourage effect," as well as a more direct action on an exclusive target, namely the mast cells via an ALIA mechanism.

Our report suggests the hypothesis that PEA, an endogenous mediator potentially affording protection against neuropathic pain, could be a valuable alternative to the most commonly used treatments. Further studies should be carried out in humans to investigate the potential use of PEA as therapeutic drug.

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