

## EDITORIAL VIEW

## PAIN MANAGEMENT

# A life without pain

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## Abstract

In majority of cases, anesthesia is a routine procedure, following well-established protocols, but in some patients with rare diseases there are additional challenges for the clinical anesthesiologist. Pain is a defense mechanism that expresses damage or deterioration of the body. The body protects itself from noxious stimuli resulting from this sensation. This mechanism is broken in Congenital Insensitivity to Pain and Anhidrosis (CIPA), which is a rare autosomal recessive disorder characterized mainly by the lack of reaction to these stimuli.

**Key words:** Anesthesiology; Anesthesia, General; Congenital Insensitivity to Pain; Anhidrosis; Hereditary Sensory and Autonomic Neuropathies type IV

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A few years ago I had the opportunity to anesthetize twice, in the interval of 5 years, a patient with CIPA. This rare genetic disease was initially described by Swanson in two brothers with changes in temperature control and insensitivity to pain, it is a rare autosomal recessive neuropathy of the group of hereditary sensory and autonomic neuropathies, characterized by insensitivity to painful stimuli, changes in temperature control, and varying degrees of mental impairment.<sup>1</sup>

CIPA is secondary to a mutation in the neurotrophic tyrosine kinase receptor type 1 (NTRK1) gene, located in chromosome 1q21-q22. It encodes the tyrosine kinase receptor type A that is autophosphorylated in response to nerve growth factor (NGF) activating several intracellular signalling pathways. Mutations in the NTRK1 gene inhibit the development of NGF-dependent sensory and autonomic neurons during the embryonic period.<sup>2</sup> In adults, NGF is not necessary for cellular survival; however, it plays a crucial role in pain generation and hyperalgesia in acute and chronic pain. The expression of NGF is increased in traumatized and inflamed tissues, and activation of tyrosine kinase receptor type A in nociceptive neurons potentiates pain through several mechanisms.<sup>3</sup>

Insensitivity to pain and mental retardation causes those patients to self-mutilation (especially fingers, lips, and tongue), corneal lacerations, non-painful fractures, Charcot arthropathies, and joint deformities leading to chronic osteomyelitis and septic arthritis.<sup>4</sup> Thermal sensitivity varies, but most patients have some degree of cold and heat sensitivity. The reduction in the central and peripheral activities of noradrenaline and anhidrosis can lead to the development of perioperative hypotension, bradycardia and hyperthermia.<sup>5</sup> The diagnosis of CIPA is based on the clinical presentation, pharmacological test, and neuropathological exam: absence of unmyelinated fibres (C fibres), reduction in the number of small myelinated fibres (A $\delta$  fibres), and normal distribution of large myelinated fibres (A $\alpha$  and A $\beta$  fibres). The structure of the sweat glands is normal but they are not innervated. Genetic analysis looking for mutations in the NTRK1 gene represents the last diagnostic step. Specific treatment is not available and due to the high morbidity associated with this disorder patients usually do not live past the second decade of life. There are very few reports of anesthesia in patients

with this disease, which is very rare but it is related to some ethnic groups and consanguinity.<sup>6</sup>

In the first procedure, the patient was 19 years old, weighing 65 kg, 153 cm height. She was scheduled for bilateral arthrodesis of the ankle with blade plate fixation. CIPA was not diagnosed until she was 8 years old. Family members reported that the parents were cousins and the patient had two siblings, one younger with the same characteristics and one brother who died as a child. Preoperative laboratory exams were within normal limits. Standard anesthesia monitors were applied, including noninvasive arterial blood pressure, electrocardiogram, and pulse oximeter. The patient was sedated with IV midazolam. Spinal anesthesia was performed with the patient in the sitting position, using bupivacaine. A sensorial block could not be evaluated. The patient was placed in the supine position immediately after injection and 15 min later was positioned prone. Supplemental oxygen was provided via nasal prongs at the rate of 3 L.min<sup>-1</sup>. Transient intraoperative hypotension was treated with an incremental bolus of 5 mg ephedrine, totalling 15 mg. The surgery lasted 4 hours. Analgesics were not needed.<sup>7</sup>

In the second intervention, she was 24 years and weighing 82 kg, and was admitted for the surgical treatment of Charcot arthropathy in the left ankle. She expressed a desire to receive general anesthesia, so we opted for TCI (target-controlled Infusion) of propofol. After venipuncture, the patient was sedated with IV midazolam and anesthetic induction was initiated with oxygen under a face mask, target-controlled infusion of propofol at 4.0 µg/L for four minutes, followed by the administration of cisatracurium (a bolus of 0.2 mg/kg when the bispectral index reached 45). A 7.5 mm ET tube was used for tracheal intubation. Monitoring of end-expiratory pressure of carbon dioxide and the oesophageal temperature was added. Although laryngoscopy and intubation were not difficult, a discrete elevation in blood pressure and heart rate was also observed. Controlled ventilation with an inspired oxygen fraction of 0.5 was instituted, and anesthesia was maintained with TCI of propofol that ranged from 2.0 to 3.0 µg.mL<sup>-1</sup> until 10 minutes before the end of the surgery when the infusion of propofol was discontinued. An infusion of remifentanyl was ready, but it was not used, and additional doses of the neuromuscular blocker were not required. The patient was extubated after the 120-

minute long procedure and she was transferred to the post-anesthetic care unit without complaints.<sup>8</sup>

The patient did not require the intra- and postoperative use of analgesics, and the anesthetic plane was maintained with a hypnotic agent in doses similar to those used in the general population with minimal cardiovascular manifestations during laryngoscopy, intubation, and surgical incision. The increase in blood pressure and heart rate during manipulation of the airways may occur secondary to the integrity of the airway reflexes; however, in our case, extubation was not associated with the same changes. A thermal mattress was placed before the surgery, but its use was not necessary during the procedure. The patient was discharged from the hospital after two days.<sup>8</sup>

Patients with CIPA have autonomic and nociceptive dysfunction; therefore, the anesthetic conduct represents a challenge for the anesthesiologist. In a review of the literature, some important aspects of those patients are emphasized, especially concerning the type of anesthesia and perioperative temperature control.<sup>9</sup>

Although those patients have insensitivity to pain, some of them have tactile hyperesthesia, which can cause an uncomfortable perception during surgical manipulation.<sup>10,11</sup> There are reports of surgical procedures without anesthesia in patients with CIPA, such as the case of a patient who underwent amputation of both feet under sedation, but without analgesia.<sup>12</sup>

There are no assessment studies of pain scores in this population performed, likely because they rarely experience pre- or postoperative pain.

Although patients with CIPA have low plasma concentrations of adrenaline and noradrenaline, cardiovascular reflexes are preserved. However, several patients have hemodynamic instability due to sepsis secondary to severe infectious disorders, such as osteomyelitis and septic arthritis.<sup>4,9</sup>

Bispectral encephalography represented an important intraoperative monitoring tool, remaining stable and showing adequate levels of hypnosis during the entire procedure.

Due to the variable phenotypic expression, mental retardation can vary from mild to severe, but some patients are described as apparently normal.<sup>13</sup> In the first intervention, neuraxial block with mild sedation

can be used, but general anesthesia is the technique of choice in patients with severe mental impairment.<sup>14</sup>

The patient should be carefully placed on the surgical table, whose surface should be padded to prevent pressure injury and reduce the risk of new traumas secondary to involuntary movements during awakening. Involuntary injuries and self-inflicted injuries are common. The development of corneal lesions is favoured by imprudence and indifference to pain, especially in children and patients with mental impairment.<sup>15</sup>

Progression of the disease is associated with several limitations of activities of daily living since childhood, requiring parents to be extremely attentive and careful. The psychosocial impact on the patient and family members is as important as the anesthetic-surgical aspect of the disease, since those patients may require frequent surgeries.

In a world where many desire fantastic fictional powers, we might think that insensitivity to pain would be a blessing, a life without pain. But as we see, not having the repressive pain stimulus can also be a scourge. All the senses of man, since prehistory, have been valuable in their survival, and these cases reaffirm the feeling that even pain, conquered by anesthesia, has its role in evolution.

## Conflict of Interest

None to declare

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