orphanaesthesia

Anaesthesia recommendations for

Congenital Insensitivity to Pain

Disease name: Congenital Insensitivity to Pain

ICD 10: G60.8

Synonyms: Congenital Insensitivity to Pain; Hereditary Sensory and Autonomic Neuropathy type IV (HSAN IV)

Disease summary: Congenital insensitivity to pain (CIP) presents a spectrum of phenotypic variation. The genes related to the disease are CLTCL1 (rare), NGF (rare), NTRK1 (common), PRDM12 (intermediate), SCN9A (common), SCN11A (rare), ZFHX2 (rare, one family reported). Development and intellect may be normal or delayed/impaired. Individuals with disease caused by SCN9A and PRDM12 variants generally have normal intellect. Individuals with CIP with anhydrosis caused by biallelic pathogenic variants in NTRK1 have variable degrees of intellectual disability, hyperactivity, impulsivity, and attention deficit.[1]

Congenital insensitivity to pain and anhidrosis (CIPA), is a rare autosomal recessive neuropathy characterized by insensitivity to painful stimuli, changes in temperature control, and varying degrees of cognitive impairment.[2] Mutations in the NTRK1 gene inhibit the development of NGF-dependent sensory and autonomic neurons during the embryonic period.[3] 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.[3]

Insensitivity to pain and cognitive impairment predisposes patients with CIP 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.[5,6] 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.[6]

The diagnosis of CIP is based on the clinical presentation (particularly self-mutilation in early life) and genomic sequencing. When the known genes are sequenced and no disease-causing variant is identified, it is exceptional to have absence of pain sensation as opposed to a raised pain threshold. Many people have a high pain threshold, particularly those with an autistic spectrum disorder. Pharmacological testing (intradermic reaction to 1:10,000 histamine), and neuropathological exam can be considered in patients with a remarkable genomic sequencing after expert review.

Specific treatment is not available.

Medicine is in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

Emergency information

A	**AIRWAY / ANAESTHETIC TECHNIQUE**	The vast majority of reports describe procedures performed under general anesthesia (GA). In selected cases, regional anesthesia with light sedation is well tolerated. GA is the technique of choice in patients with severe cognitive impairment.
B	**BLOOD PRODUCTS (COAGULATION)**	No specific recommendations.
C	**CIRCULATION**	Reduction of central and peripheral activities of norepinephrine and anhidrosis may lead to the development of perioperative hypotension, bradycardia and hyperthermia.
D	**DRUGS**	No specific recommendations.
E	**EQUIPMENT**	No specific recommendations.

Typical surgery

Typical procedures are orthopaedic, dental and ophthalmic surgeries, along with incisional drainage and debridement.[7]

In younger children, self-mutilation such as tongue or finger biting is very common and may require dental extractions.

In older children, osteomyelitis and bone/joint deformities require frequent surgical procedures, including rarely amputations.

Type of anaesthesia

The majority of reports describe procedures performed under general anaesthesia. In selected cases, regional anaesthesia with light sedation is well tolerated.[8,9]

Necessary additional pre-operative testing (beside standard care)

CIP is an ultra rare disorder. True absence of nociception is much less common than cases of raised pain threshold (the latter requiring standard and full anaesthesia/pain control). As above, when genomic sequencing is unremarkable, patients require expert review, to differentiate between raised threshold and absent nociception. Neurophysiological tests may provide additional information, but like all laboratory testing for CIP, will be very difficult to interpret due to the extreme rarity. A negative sympathetic skin response may also be helpful in the diagnosis due to the lack of sudomotor nerves in skin biopsy. Histopathologic evaluation may show a hyperplastic epidermis with acanthosis and hyperkeratosis and a decreased amount of sweat and sebaceous glands.[10]

Particular preparation for airway management

Although some patients may have predictors[11], there is no documented relationship between the disease and difficult airway.

Particular preparation for transfusion or administration of blood products

Not reported.

Particular preparation for anticoagulation

Not reported.

Particular precautions for positioning, transportation and mobilisation

Uncooperative patients should be monitored permanently. Care must be taken not to risk damage caused by insensitivity to pain and cognitive impairment.

Patients have varying thermal sensitivity so temperature should be evaluated throughout the perioperative period. Reduction of central / peripheral activities of norepinephrine and anhidrosis may lead to the development of perioperative hypotension and hyperthermia.[6]

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 emergence. The development of corneal damage is favored by the insensitivity.

Interactions of chronic disease and anaesthesia medications

The major anesthetic concern in patients with CIPA is autonomic nervous system dysfunction, which may predispose patients to an increased risk of gastric content regurgitation and subsequent aspiration. Patients may be prone to hemodynamic instability, bradycardia and inability to regulate body temperature. Thus bronchial aspiration prophylaxis should be performed and anesthetic cardiodepressant medications should be carefully titrated.

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

Anaesthetic procedure

Progression of the disease can be associated with multiple surgical interventions, mainly orthopaedic due to late presentation of injuries.

A careful pre-anesthetic evaluation is mandatory to decrease the anxiety and emotional stress of those patients. Although pain stimuli are absent, anxiety associated with surgical procedures may generate stress and consequent hemodynamic instability. It may be necessary to minimize preoperative apprehension and anxiety with sedation.[10]
Patients with CIPA lack pain sensation, but may have tactile hyperesthesia or dysesthesia, during surgical manipulation.[12,13] Patients may still have an intact sympathetic response to laryngoscopy and surgical manipulation due to touch, pressure, and vibratory sensation.[14]

There are reports of surgical procedures with minimal or no analgesic agents in patients with CIP.[8,11,14 -17] Despite the lack of pain sensitivity, a small dose of remifentanil may be sufficient to maintain stable hemodynamics. In addition, while remifentanil may typically lead to acute tolerance and hyperalgesia, a patient with CIP can avoid this complication.[18]

Although CIP patients can have very low plasma levels of norepinephrine and epinephrine, cardiovascular reflexes are preserved. Temperature regulation may be impaired due to anhidrosis. As a result, CIP patients can suffer from recurrent episodes of unexplained fever. Prevention of hyperthermia requires careful monitoring of temperature, adjustment of room temperature and the use of cool blankets if necessary. The association between CIP and malignant hyperthermia has not been reported.

Patients with CIP may have autonomic nervous system abnormalities, which can lead to postoperative nausea and vomiting or aspiration. It has previously been suggested that all CIP patients should be considered having a “full stomach,” regardless of their nil per os status, because of their risk of aspiration. Therefore, rapid sequence induction with an endotracheal tube may be the most appropriate management in these patients.[19]

Cognitive impairment can range from none to severe. There is no absolute contraindication to anesthesia techniques, but general anaesthesia is the technique of choice in patients with severe cognitive impairment.[8,11,20-26]

Particular or additional monitoring

Monitoring should be oriented towards the patient’s pre-existing, organ-specific diseases.

Patients have varying thermal sensitivity, so temperature should be evaluated throughout the perioperative period. The temperature of the patient should always be monitored and remain stable during the procedure. The room temperature should be kept between 22 and 24 °C.[11]

Possible complications

Autonomic nervous system abnormalities in patients with CIP may predispose to gastroparesis and delayed gastric emptying, as well as an increased risk of regurgitation and aspiration.[19]

If hyperpyrexia is not well controlled, CIPA can be fatal in the first few years of life. Regurgitation, hyperthermia, hyperpyrexia, and aspiration are uncommon, but the incidence of hypotension and bradycardia intra and postoperatively may be higher. The exact mechanism of the bradycardia and hypotension in this population remains unknown.[7]

Post-operative care

Primarily, postoperative care is based upon intervention and the patient's pre-existing conditions.

CIP is associated with self-mutilation, corneal lacerations, new fractures and other non-painful trauma. They should be closely supervised throughout the hospitalization period, they may need sedation and monitored since perception of tactile stimuli and pressure may produce unpleasant sensations.[12,13] A stay in intensive care is not mandatory.

Disease-related acute problems and effect on anaesthesia and recovery

In CIPA reduction of central and peripheral activities of norepinephrine and anhidrosis may lead to the development of perioperative hypotension, bradycardia and hyperthermia.[6] Although there is insensitivity to pain, some patients present tactile hyperesthesia.[12,13] Despite reports in the literature of patients undergoing neuraxial blocks, and even procedures without anesthesia, intravenous anaesthesia provides adequate conditions for a surgical procedure.

Ambulatory anaesthesia

Not reported.

Obstetrical anaesthesia

There are few data around management of pregnant patients with CIP.[9] Analgesic requirements may be minimal to nil. Neuraxial anaesthesia and general anesthesia have both been performed successfully in this population. Patients may be unaware that they are in labor. Meticulous positioning is advised given patients' insensitivity to pain.

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