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Congenital Insensitivity to Pain

orphanaesthesia

a project of the German Society
of Anaesthesiology and Intensive Care Medicine

SUPPLEMENT NR. 8 | 2025

OrphanAnesthesia –
ein krankheitsübergreifendes Projekt des Wissenschaftlichen Arbeitskreises Kinderanästhesie der Deutschen Gesellschaft für Anästhesiologie und Intensivmedizin e.V.

Ziel des Projektes ist die Veröffentlichung von Handlungsempfehlungen zur anästhesiologischen Betreuung von Patientinnen und Patienten mit seltenen Erkrankungen. Damit will OrphanAnesthesia einen wichtigen Beitrag zur Erhöhung der Patientensicherheit leisten.

Patientinnen und Patienten mit seltenen Erkrankungen benötigen für verschiedene diagnostische oder therapeutische Prozeduren eine anästhesiologische Betreuung, die mit einem erhöhten Risiko für anästhesieassoziierte Komplikationen einhergehen. Weil diese Erkrankungen selten auftreten, können Anästhesistinnen und Anästhesisten damit keine Erfahrungen gesammelt haben, sodass für die Planung der Narkose die Einholung weiterer Information unerlässlich ist. Durch vorhandene spezifische Informationen kann die Inzidenz von mit der Narkose assoziierten Komplikationen gesenkt werden. Zur Verfügung stehendes Wissen schafft Sicherheit im Prozess der Patientenversorgung.

Die Handlungsempfehlungen von OrphanAnesthesia sind standardisiert und durchlaufen nach ihrer Erstellung einen Peer-Review-Prozess, an dem eine Anästhesistin bzw. ein Anästhesist sowie eine weitere Krankheitsexpertin bzw. ein weiterer Krankheitsexperte (z. B. Pädiaterin bzw. Pädiater oder Neurologin bzw. Neurologe) beteiligt sind. Das Projekt ist international ausgerichtet, sodass die Handlungsempfehlungen grundsätzlich in englischer Sprache veröffentlicht werden.

Ab Heft 5/2014 werden im monatlichen Rhythmus je zwei Handlungsempfehlungen als Supplement der A&I unter www.ai-online.info veröffentlicht. Als Bestandteil der A&I sind die Handlungsempfehlungen damit auch zitierfähig. Sonderdrucke können gegen Entgelt bestellt werden.

Bisher in A&I publizierte Handlungsempfehlungen finden Sie unter:

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OrphanAnesthesia –
a project of the Scientific Working Group of Paediatric Anaesthesia of the German Society of Anaesthesiology and Intensive Care Medicine

The target of OrphanAnesthesia is the publication of anaesthesia recommendations for patients suffering from rare diseases in order to improve patients' safety. When it comes to the management of patients with rare diseases, there are only sparse evidence-based facts and even far less knowledge in the anaesthetic outcome. OrphanAnesthesia would like to merge this knowledge based on scientific publications and proven experience of specialists making it available for physicians worldwide free of charge.

All OrphanAnesthesia recommendations are standardized and need to pass a peer review process. They are being reviewed by at least one anaesthesiologist and another disease expert (e.g. paediatrician or neurologist) involved in the treatment of this group of patients.

The project OrphanAnesthesia is internationally oriented. Thus all recommendations will be published in English.

Starting with issue 5/2014, we'll publish the OrphanAnesthesia recommenations as a monthly supplement of A&I (Anästhesiologie & Intensivmedizin). Thus they can be accessed and downloaded via www.ai-online.info. As being part of the journal, the recommendations will be quotable. Reprints can be ordered for payment.

Find a survey of the recommendations published until now on:

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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 variations. 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 the SCN9A and PRDM12 variants generally possess normal intellectual capacities. 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 characterised 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 traumatised and inflamed tissues, and activation of tyrosine kinase receptor type A in nociceptive neurons potentiates pain through several mechanisms.[3,4]

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.

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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 anaesthesia (GA). In selected cases, regional anaesthesia 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 exist.
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 stated 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, they will be very difficult to interpret due to the extreme rarity. A negative sympathetic skin response may also be helpful in the diagnosis when based on the lack of sudomotor nerves in a skin biopsy. A histopathologic evaluation may reveal 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 a 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 temperature should therefore be evaluated throughout the entire perioperative period. A 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, the surface of which should be padded to rule out 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 anaesthetic 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 haemodynamic instability, bradycardia and an inability to regulate their body temperature. Thus bronchial aspiration prophylaxis should be performed and anaesthetic cardiodepressant medications should be carefully titrated.

There are no assessment studies onpain scores in this population , presumably because patients rarely experience pre- or postoperative pain.

Anaesthetic procedure

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

A careful pre-anaesthetic evaluation is mandatory to decrease the anxiety and emotional stress of respective patients. Although pain stimuli are absent, anxiety associated with surgical procedures may cause stress and consequent haemodynamic instability. It may be necessary to minimise preoperative apprehension and anxiety with sedation.[10]
Patients with CIPA lack pain sensation, but may have tactile hyperaesthesia or dysaesthesia, during surgical manipulation.[12,13] Patients may still show 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 haemodynamics. In addition, while remifentanil may typically lead to acute tolerance and hyperalgesia, a patient with CIP can avoid this complication.[18]

Although CIP patients might display 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. No association between CIP and malignant hyperthermia has not yet 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 anaesthesia 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.

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Patients have varying thermal sensitivity, so temperature should be evaluated throughout theperioperative period. The patient's temperature 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 may be higher intra- and postoperatively . The exact mechanism of the bradycardia and hypotension in this population is still 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 traumas. They should be closely supervised throughout the hospitalisation period, as they may need sedation and monitored as the ability to perceive 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

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

Ambulatory anaesthesia

Not reported.

Obstetrical anaesthesia

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

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