

Aslan, D. and F. Sarikayalar (1997). "Congenital insensitivity to pain with anhidrosis." Cutis **60**(4): 188-190.

Congenital insensitivity to pain with anhidrosis is one of a group of rare diseases termed hereditary sensory-motor neuropathies, Primary clinical features of this entity include congenital analgesia, inability to sweat, and mental retardation, Besides the rarity of these clinical entities, difficulty in evaluating the sensory disturbances, especially in small children, makes the diagnosis a clinical problem, In this article a 3-year-old boy, with consanguineous parents and no family history of the disorder, who was evaluated for two years because of ulcerating lesions on his knees, is presented, Physical examination revealed deep ulceration on his knees and scars from burns on his neck and scalp, Moderate mental retardation and analgesia were noted, There Ras symmetrical loss of pain and touch sensation on his hands and feet. Electromyographic examination showed absence of action potentials of the ulnar and sural nerves, decrease in the sensory and motor nerve conduction velocities, and amplitude of action potentials, The result of the application of pilocarpine showed anhidrosis, His skin and nerve biopsy specimens were also examined.

Axelsson, H. E., J. K. Minde, et al. (2009). "Transient Receptor Potential Vanilloid 1, Vanilloid 2 and Melastatin 8 Immunoreactive Nerve Fibers in Human Skin from Individuals with and without Norrbottnian Congenital Insensitivity to Pain." Neuroscience **162**(4): 1322-1332.

Transient receptor potential vanilloid 1 (TRPV1), vanilloid 2 (TRPV2) and melastatin 8 (TRPM8) are thermosensitive cation channels expressed on primary sensory neurons. In contrast to TRPV1, which is present on nociceptive primary afferents and keratinocytes in human skin, less is known about the distribution of TRPV2 and TRPM8 in this tissue. Immunohistochemistry of human forearm skin identified TRPV2 and TRPM8 immunoreactive nerve fibers in epidermis-papillary dermis and around blood vessels and hair follicles in dermis, although these nerve fibers were less abundant than TRPV1 immunoreactive nerve fibers throughout the skin. The TRPV2 and TRPM8 immunoreactive nerve fibers also showed immunoreactivity for calcitonin gene-related peptide (CGRP) and to a lesser extent substance P (SP). Neither of the TRP ion channels co-localized with neurofilament 200 kDa (NF200), vasoactive intestinal peptide (VIP) or tyrosine hydroxylase (TH). Nerve fibers immunoreactive for TRPV1, TRPV2, TRPM8, CGRP and SP were absent or substantially reduced in number in individuals with Norrbottnian congenital insensitivity to pain, an autosomal disease selectively affecting the development of C-fiber and A delta-fiber primary afferents. Quantitative real time PCR detected mRNA transcripts encoding TRPV1 and TRPV2, but not TRPM8, in skin from healthy volunteers, suggesting that these ion channels are also expressed extraneuronally. In conclusion, nerve fibers in human skin express TRPV1, TRPV2 and TRPM8 that co-localize with the sensory neuropeptides CGRP and SP, but not with NF200, VIP or TH. A dramatic loss of such nerve fibers was seen in skin from individuals with

Norrbotnian congenital insensitivity to pain, further suggesting that these ion channels are expressed primarily on nociceptive primary sensory neurons in human skin. (C) 2009 IBRO. Published by Elsevier Ltd. All rights reserved.

Bachiocco, V., B. Rosalba, et al. (2007). "Sensory phenotype assessment in a young girl affected by congenital insensitivity to pain (CIPA)." *Pediatric Anesthesia* **17**(12): 1237-1237.

Bachiocco, V., B. Rosalba, et al. (2007). "Sensory phenotype assessment in a young girl affected by congenital insensitivity to pain (CIPA)." *Pediatric Anesthesia* **17**(11): 1105-1110.

Sensory phenotype was assessed in a young girl affected by congenital insensitivity to pain (CIPA) scheduled for an open surgical drainage. The sensory profile showed that only the A beta fibers were functioning normally, whereas A delta and C fibers did not respond to nociceptive stimuli. On the basis of these findings and the results of cardiovascular reflexes, she was submitted to abscess incision and debridement under midazolam sedation alone. She did not report pain or other discomfort during surgery. The sensory (and sympathetic) assessment may have a high potential value in planning anesthesia and analgesia in children with CIPA. This psychophysical procedure could be introduced as standard component of clinical evaluation before surgery.

Baker, R. H. J., M. Smith, et al. (2006). "The insensate burn: Pain insensitivity syndrome." *Burns* **32**(2): 255-257.

Bar-On, E., D. Weigl, et al. (2002). "Congenital insensitivity to pain - Orthopaedic manifestations." *Journal of Bone and Joint Surgery-British Volume* **84B**(2): 252-257.

We reviewed 13 patients with congenital insensitivity to pain. A quantitative sweat test was carried out in five and an intradermal histamine test in ten. DNA examination showed specific mutations in four patients. There were three clinical presentations: type A, in which multiple infections occurred (five patients); type B, with fractures, growth disturbances and avascular necrosis (three patients), and type C, with Charcot arthropathies and joint dislocations, as well as fractures and infections (five patients, four with mental retardation).

Patient education, footwear and periods of non-weight-bearing are important in the prevention and early treatment of decubitus ulcers. The differentiation between fractures and infections should be based on aspiration and cultures to prevent unnecessary surgery. Established infections should be treated by wide surgical debridement. Deformities can be managed by corrective osteotomies, and shortening by shoe raises or epiphysiodesis. Joint dislocations are best treated conservatively.

Barone, R., L. Lempereur, et al. (2005). "Congenital insensitivity to pain with anhidrosis (NTRK1 mutation) and early onset renal disease: Clinical report on three sibs with a 25-

year follow-up in one of them." Neuropediatrics **36**(4): 270-273.

Congenital insensitivity to pain with anhidrosis (CIPA) is an autosomal recessive disorder caused by mutations in the neurotrophic tyrosine receptor kinase 1 (NTRK1) gene which encodes the receptor for nerve growth factor (NGF). We report the clinical course in three sibs with CIPA and proven NTRK1 gene mutations with a follow-up over a 25-year period in one of them. They had the characteristic clinical features of an abnormally high pain threshold, and mental retardation; in addition their clinical course was marked by the occurrence of early onset renal disease with recurrent microhematuria and proteinuria and frequent observations of increased serum creatinine and blood urea levels. Light microscopy study of a renal biopsy performed in one of them at age of 20 months showed focal glomerulosclerosis, interstitial fibrosis and tubular atrophy. This patient and his younger brother died because of renal failure at the age of 25 years and 14 years, respectively. The sister still alive showed renal impairment and deep venous thrombosis associated with lupus anticoagulant activity, decrease of circulating autoreactive CD5(+) B lymphocytes and increased urinary levels of IgG and kappa and lambda light chains, suggesting a possible defect in regulation of B-lymphocyte function. In the light of the NGF-related molecular defect, the extra-neurological tissue involvement in CIPA might in part reflect dysregulation of immune mechanisms which possibly brings about a chronic inflammatory response. This, in turn, could result in renal disease which should be mentioned among the life-threatening complications associated with this disorder.

Beigelman, A., J. Levy, et al. (2009). "Abnormal neutrophil chemotactic activity in children with congenital insensitivity to pain with anhidrosis (CIPA): The role of nerve growth factor." Clinical Immunology **130**(3): 365-372.

A 1926-ins-T mutation in the TrkA gene encoding the tyrosine kinase receptor for nerve growth factor (NGF) was previously documented in patients with congenital insensitivity to pain with anhidrosis (CIPA). These patients suffer from skin lacerations which often evolve into deep tissue infections. Abnormality in neutrophil functions may explain this high rate of severe infections. In this study we show that chemotaxis was significantly ($P < 0.001$) suppressed in patients' neutrophils, compared to healthy controls. Although NCF alone did not exert a chemotactic effect, its presence enhanced both migration toward fMLP and phosphorylation of MAP kinases (ERK and JNK) in neutrophils from healthy controls, but not in neutrophils from CIPA patients. The significantly impaired chemotactic activity of neutrophils from a CIPA patient, which has been attributed to the molecular defect in the TrkA receptor, may contribute to the high rate of infection. (C) 2008 Elsevier Inc. All rights reserved.

Beigelman, A., J. Levy, et al. (2005). "Abnormal neutrophil's chemotactic activity in children with congenital insensitivity to pain with anhidrosis (CIPA): The role of nerve growth factor in chemotactic activity." Clinical Immunology **115**: S237-S238.

Benhalima, H., S. Kerrary, et al. (2012). "Congenital insensitivity to pain: Difficulty of management." Revue De Stomatologie Et De Chirurgie Maxillo-Faciale **113**(1): 46-49.

Introduction. Congenital insensitivity to pain with anhidrosis (CIPA) is a very rare disorder, most often of genetic origin.

Case report. The authors present the case of two siblings, 10 and 13 years old, both followed-up since the age of 2 for CIPA diagnosed after discovering insensitivity to pain during iterative falls, burns, and of severe oro-digital self-mutilating behavior. Sural nerve biopsy and an electromyogram confirmed the diagnosis.

Discussion. CIPA with anhidrosis is a very rare disease. It is characterized by unexplained fever episodes, anhidrosis, pain insensitivity, self-mutilating behavior, and sometimes mental retardation. Complications of this insensitivity (non-treated fractures, burns, and oro-digital mutilation) may be lethal. Treatment remains preventive. The patient must observe a very strict hygiene. Prevention for maxillofacial involvement consists in breaking the cycle of oral self-mutilation. (c) 2011 Elsevier Masson SAS. All rights reserved.

Berkovitch, M., L. Copeliovitch, et al. (1998). "Hereditary insensitivity to pain with anhidrosis." Pediatric Neurology **19**(3): 227-229.

Hereditary sensory neuropathy type IV is an autosomal-recessive disorder characterized by congenital insensitivity to pain and anhidrosis and resulting in recurrent hyperpyrexia, self-mutilation, recurrent infections, chronic osteomyelitis, bone and joint deformities, and limb amputations. Described is a child with signs as well as skin and nerve biopsy results compatible with this disease, emphasizing the importance of early diagnosis and appropriate medical and educational care to prevent complications. (C) 1998 by Elsevier Science Inc. All rights reserved.

Biedner, B., M. Dagan, et al. (1990). "Congenital Insensitivity to Pain with Neuroparalytic Keratitis." Annals of Ophthalmology **22**(8): 312-313.

Biersdorff, K. K. (1991). "Pain Insensitivity and Indifference - Alternative Explanations for Some Medical Catastrophes." Mental Retardation **29**(6): 359-362.

Bolgul, B. S., N. Hamamci, et al. (2010). "Congenital Insensitivity to Pain: A Case Report with Dental Implications." Hong Kong Journal of Paediatrics **15**(3): 234-237.

Congenital insensitivity to pain is a rare disorder seen in early childhood. Five different types of hereditary sensory and autonomic neuropathy have been identified, to date, with different patterns of sensory and autonomic dysfunction, peripheral neuropathy, clinical features, and genetic abnormalities. Absence of pain and self-mutilation are characteristic findings of this syndrome. Teeth in the oral cavity can cause damage to the oral tissues and tongue. When diagnosed, there should be cooperation between the dentist and neurologist. Using an oral shield prevents biting, and thus tissue trauma can be prevented. Here, we

present the case of a 6-month-old boy with congenital insensitivity to pain (hereditary sensory and autonomic neuropathies; HSAN type V) with self-mutilation injuries to his tongue and fingers caused by biting, along with a discussion of treatment strategies. The results of this report suggest that early diagnosis and specific dental management for patients with congenital insensitivity to pain are important for prevention of the characteristic oral and dental problems accompanying this disorder.

Bonkowsky, J. L., J. Johnson, et al. (2003). "An infant with primary tooth loss and palmar hyperkeratosis: A novel mutation in the NTRK1 gene causing congenital insensitivity to pain with anhidrosis." *Pediatrics* **112**(3): E237-E241.

Patients with congenital insensitivity to pain and anhidrosis (CIPA), caused by mutations in the NTRK1 gene, can be difficult to diagnose because of their variable presentation, the lack of simple diagnostic tests, and the paucity of cases reported in North America. We describe a 1-year-old infant who had tooth loss and palmar hyperkeratosis as the primary manifestations of CIPA. He was initially evaluated by a pediatric dentist and epidermal dysplasia syndromes were considered, but insensitivity to pain was suspected after a skeletal survey revealed an unrecognized skull fracture. Nerve conduction studies were normal, as was his response to subdermal histamine injection. Sequence analysis of his NTRK1 gene revealed 2 mutations: 1 mutation is novel, while the other has been described previously in a patient of northern European descent. An antibody directed against NTRK1 revealed persistent expression in keratinocytes, consistent with the mutations in this patient. Skin biopsy specimens revealed a lack of epidermal and sweat gland innervation. Immunohistochemistry of skin biopsy specimens, together with routine nerve conduction studies, can provide quick and reliable confirmation if CIPA is clinically suspected.

Brandes, I. F. and E. A. E. Stuth (2006). "Use of BIS monitor in a child with congenital insensitivity to pain with anhidrosis." *Pediatric Anesthesia* **16**(4): 466-470.

We describe a case of a 14-year-old boy with congenital insensitivity to pain and anhidrosis (CIPA) who underwent tarsal tunnel release for tarsal tunnel syndrome. Because of abnormal pain perception, the patient's response to normally painful surgical stimuli is severely impaired and not adequately reflected in a corresponding rise in blood pressure or heart rate. This lack of autonomic feedback to pain stimuli may make it more difficult to assess whether anesthetic depth is adequate to prevent intraoperative awareness and thus to safely conduct anesthesia, especially if muscle paralysis is required for surgical indications. We describe for the first time the use of processed EEG monitoring with a BIS A-2000 monitor to gauge anesthetic depth in a patient with CIPA. Initial forehead bispectral index (BIS) values prior to induction were normal (98) and then ranged between 23 and 79 during the whole surgical procedure. Propofol and lidocaine were used for induction and deep extubation; isoflurane was used as the sole anesthetic for maintenance with concentrations ranging

from 0.21% to 0.92% to maintain a target BIS of 40-60. Volatile anesthetic requirements remained low throughout the procedure and no narcotics were necessary during surgery. The BIS monitor served as an adequate tool to help avoid excessive use of volatile anesthetic while assuring a processed EEG consistent with unconsciousness and amnesia. After the patient had recovered and was oriented to place and time in the recovery room, he was asked whether he remembered anything about the surgery and the presence of a breathing tube in his mouth. He denied any recall of such events.

Butler, J., P. Fleming, et al. (2006). "Congenital insensitivity to pain - review and report of a case with dental implications." Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontics **101**(1): 58-62.

Pain is a protective mechanism for the body. Absence of pain is a symptom in several disorders, both congenital and acquired. The congenital types are present at birth and affect the number and distribution of types of nerve fibers. At present, 5 types of hereditary sensory and autonomic neuropathies have been identified. The various disorders within this group are classified according to the different patterns of sensory and autonomic dysfunction and peripheral neuropathy and the presence of additional clinical features such as learning disability. However, the field is currently moving away from classification based on clinical presentation toward classification based on underlying genetic abnormality. In the absence of pain, patients are at risk of late presentation with illnesses or injuries, and have an increased incidence of traumatic injury. Self-mutilation is an almost invariable feature of these disorders. We report the case of a patient with congenital insensitivity to pain that presented with self-mutilation injuries to his hands and oral tissues caused by biting. The severe nature of these injuries necessitated serial extraction of his primary teeth soon after eruption, which led to a cessation of the problem. The mutilation has not returned following the eruption of the first of his permanent teeth, suggesting that he has learned not to bite himself, even though to do so causes him no discomfort.

Calvino, B. (1997). "Congenital insensitivity to pain with anhidrosis in patients with mutated TrkA, the receptor of NGF." M S-Medecine Sciences **13**(3): 390-390.

Canbay, O., E. A. Kose, et al. (2007). "Anesthesia for congenital insensitivity to pain with anhidrosis." Pediatric Anesthesia **17**(2): 190-192.

Cassidy, R. C. and W. O. Shaffer (2008). "Charcot arthropathy because of congenital insensitivity to pain in an adult." Spine Journal **8**(4): 691-695.

BACKGROUND: Congenital insensitivity to pain is a rare disorder that call lead to neuropathic arthropathy of any joint including the spine. Most of the case reports in the literature are in the pediatric Population.

PURPOSE: This case report emphasizes the importance of anterior and posterior fusion in patients with congenital insensitivity to pain. The patient was initially treated as

if the deformity was postinfectious.

STUDY DESIGN/SETTING: The patient was treated in a university-based tertiary care center.

METHODS: The patient underwent an anterior decompression and fusion with instrumentation that failed with ambulation. An anterior and posterior revision with instrumentation was then performed to stabilize the Charcot spine.

RESULTS: The patient had an excellent final outcome. At 2 years postoperatively, he is solidly fused and back to his normal occupation.

CONCLUSION: Anterior and posterior fusion is essential in neuropathic spinal arthropathy. Congenital insensitivity to pain can manifest problems into adulthood. (C) 2008 Elsevier Inc. All rights reserved.

Cox, J. J., J. Sheynin, et al. (2010). "Congenital Insensitivity to Pain: Novel SCN9A Missense and In-frame Deletion Mutations." *Human Mutation* **31**(9): E1670-E1686. SCN9A encodes the voltage-gated sodium channel Na(v)1.7, a protein highly expressed in pain-sensing neurons. Mutations in SCN9A cause three human pain disorders: bi-allelic loss of function mutations result in Channelopathy-associated Insensitivity to Pain (CIP), whereas activating mutations cause severe episodic pain in Paroxysmal Extreme Pain Disorder (PEPD) and Primary Erythralgia (PE). To date, all mutations in SCN9A that cause a complete inability to experience pain are protein truncating and presumably lead to no protein being produced. Here, we describe the identification and functional characterization of two novel non-truncating mutations in families with CIP: a homozygously-inherited missense mutation found in a consanguineous Israeli Bedouin family (Na(v)1.7-R896Q) and a five amino acid in-frame deletion found in a sporadic compound heterozygote (Na(v)1.7- Δ R1370-L1374). Both of these mutations map to the pore region of the Na(v)1.7 sodium channel. Using transient transfection of PC12 cells we found a significant reduction in membrane localization of the mutant protein compared to the wild type. Furthermore, voltage clamp experiments of mutant-transfected HEK293 cells show a complete loss of function of the sodium channel, consistent with the absence of pain phenotype. In summary, this study has identified critical amino acids needed for the normal subcellular localization and function of Na(v)1.7. (c) 2010 Wiley-Liss, Inc.

Danziger, N., I. Faillenot, et al. (2009). "Can We Share a Pain We Never Felt? Neural Correlates of Empathy in Patients with Congenital Insensitivity to Pain." *Neuron* **61**(2): 203-212.

Theories of empathy differ regarding the relative contributions of automatic resonance and perspective taking in understanding others' emotions. Patients with the rare syndrome of congenital insensitivity to pain cannot rely on "mirror matching" (i.e., resonance) mechanisms to understand the pain of others. Nevertheless, they showed normal fMRI responses to observed pain in anterior mid-cingulate cortex and anterior insula, two key regions of the so-called "shared circuits" for self and other pain. In these patients (but not in healthy controls),

empathy trait predicted ventromedial prefrontal responses to somatosensory representations of others' pain and posterior cingulate responses to emotional representations of others' pain. These findings underline the major role of midline structures in emotional perspective taking and understanding someone else's feeling despite the lack of any previous personal experience of it—an empathic challenge frequently raised during human social interactions.

Danziger, N., K. M. Prkachin, et al. (2006). "Is pain the price of empathy? The perception of others' pain in patients with congenital insensitivity to pain." *Brain* **129**: 2494-2507.

Empathy is a complex form of psychological inference that enables us to understand the personal experience of another person through cognitive/evaluative and affective processes. Recent findings suggest that empathy for pain may involve a 'mirror-matching' simulation of the affective and sensory features of others' pain. Despite such evidence for a shared representation of self and other pain at the neural level, the possible influence of the observer's own sensitivity to pain upon his perception of others' pain has not been investigated yet. The aim of this study was to explore how patients with congenital insensitivity to pain (CIP), who are largely deprived of common stimulus-induced pain experiences, perceive the pain of others. Ratings of verbally presented imaginary painful situations showed that CIP patients' semantic knowledge regarding the pain of others did not differ from control subjects. Moreover, the propensity to infer pain from facial expressions was very similar between CIP patients and control subjects. On the other hand, when asked to rate pain-inducing events seen in video clips in the absence of visible or audible pain-related behaviour, CIP patients showed more variable and significantly lower pain ratings, as well as a reduction in aversive emotional responses, compared with control subjects. Interestingly, pain judgements, inferred either from facial pain expressions or from pain-inducing events, were strongly related to inter-individual differences in emotional empathy among CIP patients, while such correlation between pain judgement and empathy was not found in control subjects. The results suggest that a normal personal experience of pain is not necessarily required for perceiving and feeling empathy for others' pain. In the absence of functional somatic resonance mechanisms shaped by previous pain experiences, others' pain might be greatly underestimated, however, especially when emotional cues are lacking, unless the observer is endowed with sufficient empathic abilities to fully acknowledge the suffering experience of others in spite of his own insensitivity.

Danziger, N. and J. C. Willer (2005). "Tension-type headache as the unique pain experience of a patient with congenital insensitivity to pain." *Pain* **117**(3): 478-483.

Congenital insensitivity to pain (CIP) is a rare clinical syndrome characterized by dramatic impairment of pain perception since birth and is generally caused by a hereditary sensory and autonomic neuropathy (HSAN) with loss of the small-

calibre, nociceptive nerve fibres. We report the case of a 32-year-old woman with CIP and a presumptive diagnosis of HSAN type V, who experienced physical pain for the first and unique time in her life shortly after the sudden loss of her brother. This patient had sustained innumerable painless injuries during childhood, including bone fractures and severe burns. The only pain she ever felt consisted in an intense headache, which took place in a context of strong emotional overload and anxiety, 3 weeks after her younger brother died suddenly in a car accident. The description of this inaugural episode of headache fulfilled the diagnostic criteria of episodic tension-type headache. This case strongly suggests that the transcription of the grief of bereavement into physical pain may sometimes occur independently of the peripheral mechanisms of nociception and despite the lack of previous pain experience. In the light of recent experimental data showing that the same neural mechanisms that regulate physical pain may also control the expression of separation distress and the feeling of social exclusion, this unique case helps to better understand why some patients may feel physically hurt after the loss of someone they love. (c) 2005 International Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.

Danziger, N. and J. C. Willer (2009). "Congenital insensitivity to pain." Revue Neurologique **165**(2): 129-136.

Congenital insensitivity to pain (CIP) is a rare syndrome with various clinical expressions, characterized by a dramatic impairment of pain perception since birth. In the 1980s, progress in nerve histopathology allowed to demonstrate that CIP was almost always a manifestation of hereditary sensory and autonomic neuropathies (HSAN) involving the small-calibre (A-delta and C) nerve fibres which normally transmit nociceptive inputs along sensory nerves. Identification of the genetic basis of several clinical subtypes has led to a better understanding of the mechanisms involved, emphasizing in particular the crucial role of nerve growth factor (NGF) in the development and survival of nociceptors. Recently, mutations of the gene coding for the sodium channel Nav1.7 - a voltage-dependent sodium channel expressed preferentially on peripheral nociceptors and sympathetic ganglia - have been found to be the cause of CIP in patients showing a normal nerve biopsy. This radical impairment of nociception mirrors the hereditary pain syndromes associated with "gain of function" mutations of the same ion channel, such as familial erythromelalgia and paroxysmal extreme pain disorder. Future research with CIP patients may identify other proteins specifically involved in nociception, which might represent potential targets for chronic pain treatment. Moreover, this rare clinical syndrome offers the opportunity to address interesting neuropsychological issues, such as the role of pain experience in the construction of body image and in the empathic representation of others' pain. (C) 2008 Elsevier Masson SAS. Tous droits reserves.

Derwin, K. A., R. A. Glover, et al. (1994). "Nociceptive Role of Substance-P in the Knee-

Joint of a Patient with Congenital Insensitivity to Pain." Journal of Pediatric Orthopaedics **14**(2): 258-262.

This case report describes the immunocytochemical examination of tissue from a 9-year-old black child diagnosed with congenital insensitivity to pain at age 5. A recent fall and resulting patella fracture required surgical treatment. Biopsies of the distal pole and surrounding soft tissue, as well as a sample of his patellofemoral joint fluid, were taken at the time of partial patellectomy and analyzed for substance-P (SP). Morphologic staining of the patella showed a grossly degenerated patellofemoral articular surface. Examination of tissue sections stained either immunocytochemically with diaminobenzidine DAB or by a rhodamine fluorescent labeling technique showed no evidence of SP-positive nerve fibers. Furthermore, only a trace amount of SP (7.29 pg/ml) was detected in a sample of the patient's knee joint synovial fluid. This patient's absence of pain sensation in conjunction with the absence of SP nerve fibers in stained patella sections and identification of only trace levels of SP in his synovial fluid, further implicates this neuropeptide in nociceptive innervation of diarthrodial joints.

Dworkin, R. H. (1994). "Pain Insensitivity in Schizophrenia - a Neglected Phenomenon and Some Implications." Schizophrenia Bulletin **20**(2): 235-248.

The literature on insensitivity to pain in schizophrenia is reviewed. Numerous reports indicate that, relative to normals, individuals with schizophrenia are insensitive to physical pain associated with illness and injury. In addition, insensitivity to pain of various sorts administered in experimental studies has been reported frequently in this population. This extensive and diverse literature of clinical and experimental reports suggests that many individuals with schizophrenia are less sensitive to pain than normal individuals. However, because the experimental studies-almost all of which were conducted before 1980 - suffer from a variety of methodological limitations, this research provides neither a satisfactory characterization nor an adequate explanation of pain insensitivity in schizophrenia. It is argued that this widely reported but currently neglected phenomenon has important implications for physical health, self-mutilation, homelessness, premorbid development, and affective flattening in individuals with schizophrenia.

Dworkin, R. H., W. C. Clark, et al. (1994). "Analgesia and Anhedonia - Pain Insensitivity and Affective Deficits in Schizophrenia." Psychosomatic Medicine **56**(2): 161-161.

Dworkin, R. H., W. C. Clark, et al. (1993). "Affective Deficits and Pain Insensitivity in Schizophrenia." Motivation and Emotion **17**(3): 245-276.

Affective deficits have long been considered a prominent feature of schizophrenia and play a central role in recent theory and research on the pathophysiology of this disorder. However, it has recently been argued that current approaches to the conceptualization and assessment of affective

flattening in schizophrenia are confounded by the social and neuromotor deficits that are also prevalent in this disorder. Insensitivity to pain in individuals with schizophrenia - a phenomenon that has been reported frequently but never systematically investigated - provides one approach to examining affective flattening unconfounded by social and neuromotor deficits. Two studies are described in which signal detection theory measures of thermal pain sensitivity were examined in patients with schizophrenia, mood disorder, and normal controls; in addition, in the patients with schizophrenia, the relationships between these measures and measures of affective deficits were examined. Patients with schizophrenia had significantly poorer sensory discrimination of painful thermal stimuli than control subjects, but did not differ from controls with respect to their response criterion for reports of pain; patients with mood disorder had a significantly higher (i.e., more stoical) criterion for reports of pain than controls. As predicted, among the patients with schizophrenia, higher response criterion was significantly correlated with greater affective flattening and less intense affective experience (as well as with fewer positive symptoms and poorer premorbid adjustment). The results of these studies suggest that pain insensitivity in schizophrenia may reflect affective as well as sensory abnormalities, and that pain insensitivity in schizophrenia may provide a method for studying affective flattening in this disorder that is relatively independent of the social and neuromotor deficits that confound existing measures of this symptom. Continued examination of the relationship between pain insensitivity and affective deficits in schizophrenia is also important because numerous clinical reports have suggested that pain insensitivity is detrimental to health and can have life-threatening consequences in individuals with this disorder.

Edwards-Lee, T. A., M. E. Cornford, et al. (1997). "Congenital insensitivity to pain and anhidrosis with mitochondrial and axonal abnormalities." *Pediatric Neurology* **17**(4): 356-361.

Hereditary sensory and autonomic neuropathy type IV, or congenital insensitivity to pain with anhidrosis (CIPA), is a rare clinical disorder with only 32 cases reported in the literature. There has been no consistent pathophysiologic defect of the sensory nerve detected by light microscopic examination, but a frequent finding of decreased small myelinated fibers and a uniform finding of decreased unmyelinated fibers by ultrastructural analysis has been reported. Muscle biopsy in a 2-year-old boy with congenital insensitivity to pain with anhidrosis indicated lipid droplet accumulation and reduced cytochrome C oxidase histochemically on light microscopy. Electron microscopic study showed almost absent small unmyelinated nerve axons within the muscle, increased microfilaments, and decreased microtubules in axons, some abnormally enlarged mitochondria, and normal-appearing motor endplates. Biochemical analysis of muscle mitochondrial enzyme function revealed cytochrome c oxidase function to be reduced to 35% of normal, with normal function of the other mitochondrial enzymes. (C) 1997 by Elsevier Science Inc. All rights reserved.

Emad, Y., A. El Yasaki, et al. (2007). "Arthritis in a child secondary to congenital insensitivity to pain and self-aggression. Why and when pain is good?" Clinical Rheumatology **26**(7): 1164-1166.

A 9 year-old female child presented with recurrent arthritis of ankles, left knee and unequal leg length. Clinical examination revealed mild valgus deformity in her left knee with grade 2 effusion, arthritis of both ankles and deformity in her left wrist. Examination of the affected joints showed no evidence of tenderness upon active or passive movements and the patient did not show any limping upon gait analysis. Past history of the patient revealed evidence of previous dislocation of her left hip and previous fibular fracture. Revision of her previous x-rays showed left hip dislocation, fracture left fibula and fracture of right metatarsal bone after repetitive trauma which pass unnoticed. Recent x-ray of her left knee showed osteochondral injury. Laboratory investigations were done to rule out common causes of childhood arthritis and revealed: ESR 12 1st hours, CRP negative, negative rheumatoid factor, and negative ANA. Neurological evaluation of the patient documented congenital insensitivity to pain and EMG studies confirmed evidence of sensory neuropathy. Traumatic arthritis resulting from congenital insensitivity to pain with self-aggression is rarely encountered in children but should be considered in the differential diagnosis specially if radiological features point to repetitive trauma with attempts of healing.

Erez, D. L., J. Levy, et al. (2010). "Assessment of cognitive and adaptive behaviour among individuals with congenital insensitivity to pain and anhidrosis." Developmental Medicine and Child Neurology **52**(6): 559-562.

Aim

Individuals with congenital insensitivity to pain with anhidrosis (CIPA) are reported to have mental retardation* but to our knowledge no detailed study on the subject has ever been published. The present study assessed and documented cognitive and adaptive behaviour among Arab Bedouin children with CIPA.

Methods

Twenty-three Arab Bedouin children (12 females, 11 males) with CIPA aged between 3 and 17 years (mean 9y 7mo, SD 4y 2mo) were assessed. They were compared with 19 healthy siblings of the affected children aged between 5 and 13 years (mean 8y 11mo, SD 2y 10m). All of the children in the comparison group, but only half of the CIPA group, were attending school. The children were evaluated using a standardized, non-verbal intelligence test, the Leiter International Performance Scale - Revised, and an adaptive behaviour questionnaire, the Vineland Adaptive Behaviour Scales, 2nd edition.

Results

Based on scores on the intelligence test and the adaptive behaviour scale, children with CIPA functioned in the mental retardation range (mean IQ scores: CIPA group 53.8, comparison group 83.32 [$p < 0.001$]; adaptive behaviour: CIPA group 68.1, comparison group 104.88 [$p < 0.001$]). IQ was significantly higher among the

children with CIPA aged up to 7 years 11 months than among the older children 73.83 vs 45.21 ($p < 0.001$).

Interpretation

As a group, the younger children with CIPA may be functioning above the mental retardation range. We propose that early intervention addressing these children's needs and developing an appropriate educational system, might improve their outcome.

Esteban-Garcia, A., E. Salinero-Paniagua, et al. (2004). "Hereditary sensory and autonomic neuropathies. The neurophysiological and pathological aspects of two cases with congenital insensitivity to pain." Revista De Neurologia **39**(6): 525-529.

Aim. Two patients suffering from congenital insensitivity to pain were studied. They corresponded to types IV and V of the 'hereditary sensory and autonomic neuropathies' (HSAN) classification. Case reports. The first case showed important autonomic dysfunctions, such as anhidrosis, hyperthermia, skin and bone trophic impairment, and mental retardation; the second one only exhibited alterations in pain and temperature sensibilities. In both, chronic indolent corneal ulcers were also present. Conventional neurophysiological evaluation of the neuromuscular system was normal, but an afferent disturbance of the blink reflex (BR) was evident in both. The sympathetic skin response was absent in the HSAN type IV case and normal in the HSAN type V. Notable reduction of the small myelinated fibres, associated to almost no unmyelinated fibres in the first case, were found in the sural nerve biopsies. Conclusions. So far there haven't been described BR abnormalities in patients with congenital insensitivity to pain, which should be related to a trigeminal sensory impairment, which could explain the corneal ulcers that suffered these cases. BR studies should be included in the neurophysiological evaluation of the suspected small fibre neuropathies even when there are no facial symptoms shown.

Facer, P., D. Atherton, et al. (2006). "A new syndrome of congenital insensitivity to pain diagnosed by skin biopsy and contact heat evoked potentials (CHEPS)." Journal of Neurology Neurosurgery and Psychiatry **77**(12): 1400-1400.

Fitzgibbon, G. J., H. Kingston, et al. (2009). "Haploinsufficiency of the nerve growth factor beta gene in a 1p13 deleted female child with an insensitivity to pain." Developmental Medicine and Child Neurology **51**(10): 833-837.

Pain insensitivity is mediated at the genetic level by the disruption of specific genes associated with neuronal development. Mammalian in vivo and in vitro studies have shown the nerve growth factor (NGF) gene to play an integral role in nerve maintenance and function. Pain insensitivity in humans can be attributed to hereditary sensory and autonomic neuropathies (HSAN) of which there are five classes (HSAN I-HSAN V). The human nerve growth factor beta gene (NGFB) located on chromosome 1p13.2 has been found to cause HSAN V within individuals homozygous for a point mutation in NGFB. Although heterozygotes

can display a milder phenotype, this has only been observed in adults. We report a karyotypically normal 5-year-old female with developmental delay, mild facial dysmorphism, and unsteady gait. Pain and thermal insensitivity were noted as were recurrent mouth ulcers, facial flushing, recurrent episodes of increased body temperature and unexplained sweating, indicative of a sensory neuropathy with mild autonomic involvement. Array comparative genomic hybridization (aCGH) analysis revealed a de-novo deletion within chromosome 1p13 of the child involving the NGFB gene. Sequence analysis of the homologous NGFB gene identified no mutation, implying that sensory neuropathy was caused by haploinsufficiency of the NGFB gene.

Galante, D., G. Pellico, et al. (2007). "Anesthesia for congenital insensitivity to pain with anhidrosis - Reply." *Pediatric Anesthesia* **17**(2): 192-192.

Garnier, M., P. F. Zaratin, et al. (2003). "Up-regulation of regulator of G protein signaling 4 expression in a model of neuropathic pain and insensitivity to morphine." *Journal of Pharmacology and Experimental Therapeutics* **304**(3): 1299-1306.

We hypothesized that the up-regulated expression of one or more members of the regulator of G protein signaling (RGS) family can cause an attenuation of signaling via Gi/Go-coupled opioid receptors, and thereby play a role in the development of hyperalgesia and accompanying insensitivity to morphine observed in animal models of neuropathic pain. Accordingly, we examined the mRNA expression of several RGS genes in a rat model of chronic neuropathic pain induced by partial ligation of the sciatic nerve. During the development of hyperalgesia, RGS4 was the only isoform examined whose mRNA levels increased significantly (up to 230%) in the lumbar spinal cord. In situ hybridization studies confirmed that RGS4 is present in the dorsal horn of the spinal cord where mu-opioid receptors (MORs) are also expressed. Overexpression of RGS4 in human embryonic kidney 293 cells stably expressing mu-opioid receptors predictably attenuated opioid agonist-induced inhibition of adenylyl cyclase. This inhibitory effect was overcome partially at high agonist concentrations, supporting the view that morphine insensitivity is promoted by RGS4 overexpression. These studies provide evidence that the up-regulation of RGS4 expression may contribute to changes in pain signal processing that lead to the development of hyperalgesia, and further affect its modulation by morphine.

Garnier, M., P. F. Zaratin, et al. (2003). "Up-regulation of regulator of G protein signaling 4 expression in a model of neuropathic pain and insensitivity to morphine (vol 304, pg 1299, 2003)." *Journal of Pharmacology and Experimental Therapeutics* **305**(2): 797-797.

Greco, A., R. Villa, et al. (2000). "The Gly571arg mutation, associated with the autonomic and sensory disorder congenital insensitivity to pain with anhidrosis, causes

the inactivation of the NTRK1/nerve growth factor receptor." Journal of Cellular Physiology **182**(1): 127-133.

Point mutations affecting the NTRK1/TRKA gene, encoding one of the receptors for the nerve growth factor (NGF), have been detected in congenital insensitivity to pain with anhidrosis (CIPA), a human hereditary sensory neuropathy characterized by absence of reaction to noxious stimuli and anhidrosis. To define the defect of NTRK1 in CIPA patients, we have introduced one of the previously reported mutations (Gly571Arg) into both the NTRK1 and the TRK-T3 oncogene cDNAs. The expression of the mutated constructs into COS1 cells revealed that the introduced mutation, while not affecting its correct membrane localization, rendered the NTRK1 protein unable to undergo activation upon stimulation with NGF. Similarly, the mutation abolished the constitutive activation of the TRK-T3 oncogene. Transfection into NIH3T3 and PC12 cells showed the loss of transforming and differentiating activity by the mutated constructs. Our results demonstrate clearly that the CIPA mutations cause the inactivation of the NTRK1 receptor, thus exerting a loss of function effect, and provide an experimental approach to distinguish functional mutations from genetic polymorphisms. *J. Cell. Physiol.* 182:127-133, 2000. (C) 2000 Wiley-Liss, Inc.

Greco, A., R. Villa, et al. (1999). "A novel NTRK1 mutation associated with congenital insensitivity to pain with anhidrosis." American Journal of Human Genetics **64**(4): 1207-1210.

Guidetti, M. S., B. M. Piraccini, et al. (1996). "Congenital insensitivity to pain with anhidrosis." European Journal of Dermatology **6**(4): 278-279.

A 1-year-old girl presented with dystrophic fingernails and ulcerating lesions and scars of the distal portion of the fingers. Since birth she had been suffering from recurrent episodes of hyperpyrexia, especially when the external temperature was high. Neurological examination revealed complete analgesia, the other sensory perceptions being normal. Evaluation of sweat gland activity using Minor's method showed almost complete anhidrosis. During the 2-year follow-up the patient undertook self-extraction of two of her teeth and developed painless fractures of the right tibia, resulting in a neuropathic arthropathy of the knee (Charcot joint). Clinical manifestations of congenital insensitivity syndrome usually appear at the time of tooth eruption. Dermatological signs include ulcerations and marked edema of the tongue and lips, periungual ulcerations, nail deformities and even severe finger mutilations.

Guo, Y. C., K. K. Liao, et al. (2002). "Congenital insensitivity to pain with anhidrosis - Case report." Journal of the Neurological Sciences **199**: S99-S99.

Guo, Y. C., K. K. Liao, et al. (2004). "Congenital insensitivity to pain with anhidrosis in Taiwan: A morphometric and genetic study." European Neurology **51**(4): 206-214.

Congenital insensitivity to pain with anhidrosis (CIPA) is characterized by

insensitivity to pain, anhidrosis, recurrent hyperpyrexia, mild mental retardation, and self-mutilating behavior. We report 2 brothers, aged 20 and 18 years, who suffered from phenotypes of CIPA. Both brothers had a branch site mutation in intron 7 (IVS7-33 T. A) of the neurotrophic tyrosine kinase receptor type 1 gene. The electrophysiological studies showed no significant abnormal findings in sensory evoked potentials, motor evoked potentials to transcranial magnetic stimulation, or heart rate variations; sympathetic skin responses were absent. Morphometric study of their sural nerve histopathology revealed normal myelinated fiber density, 8,082 fibers/mm² and 5,637 fibers/mm² (normal 6,141 B 421); decreased unmyelinated fiber density, 2,537 fibers/mm² and 2,211 fibers/mm² (normal 28,578 B 8,669); increased axon size, 4.41 +/- 1.59 μ m and 5.33 +/- 1.48 μ m (normal 3.73 +/- 1.45), and increased axon diameter (A)/myelin thickness (M) ratio (A/M), 3.47 +/- 1.42 and 2.70 +/- 1.07 (normal 2.49 +/- 0.93). Scatterplot analysis of the G ratio (axon diameter: fiber diameter) did not show consistent results in the relationship between axon size and myelin thickness. In conclusion, the neuropathy of our CIPA patients included a marked reduction of small myelinated and unmyelinated fibers and a relatively increased axon size. This is the first CIPA family encountered in Taiwan. Copyright (C) 2004 S. Karger AG, Basel.

Heggeness, M. H. (1994). "Charcot Arthropathy of the Spine with Resulting Paraparesis Developing during Pregnancy in a Patient with Congenital Insensitivity to Pain - a Case-Report." Spine **19**(1): 95-98.

This is a report of a 17-year-old female with congenital insensitivity to pain who was noted to develop significant truncal asymmetry during pregnancy. A dense paraparesis developed 10 days after delivery. Charcot arthropathy of the spine had resulted in severe destructive changes of both L3 and L4 with significant canal compromise. The patient made a complete neurologic recovery after anterior decompression and stabilization of the spine.

Herdem, M., S. Polat, et al. (1998). "Congenital insensitivity to pain with anhidrosis - A case report." International Orthopaedics **22**(2): 139-140.

We present a five-year-old girl with congenital insensitivity to pain with anhidrosis. A skeletal radiographic survey revealed several old fractures. Application of pilocarpine showed anhidrosis and nerve biopsy revealed a significant decrease in the number of myelinated and unmyelinated nerve fibres.

Hooley, J. M. and M. L. Delgado (2001). "Pain insensitivity in the relatives of schizophrenia patients." Schizophrenia Research **47**(2-3): 265-273.

The psychiatric literature contains anecdotal reports of diminished pain sensitivity in schizophrenia that date back to Kraepelin. Yet, the phenomenon of pain insensitivity in schizophrenia remains largely unstudied. For example, it is not clear if pain insensitivity is a consequence of the illness or if it is also present in the well relatives of schizophrenia patients. To explore this issue, we examined

pain thresholds and pain tolerances in healthy young adults. Compared with controls with no family history of psychopathology (n = 21), participants with a family history of schizophrenia (n = 32) showed elevated pain thresholds and pain tolerances to finger pressure. Pain insensitivity was also significantly correlated with elevated scores on measures of self-referential thinking, magical ideation, and perceptual disturbances. Finally, a sizeable minority (19%) of well relatives of schizophrenia patients showed extreme pain insensitivity compared to other participants. The pattern of findings suggests that pain insensitivity may warrant further exploration as a potential marker of underlying liability to psychosis. (C) 2001 Elsevier Science B.V. All rights reserved.

Hu, J., A. B. Zhang, et al. (2006). "Congenital insensitivity to pain with anhidrosis and progressing acro-osteolysis: a case report with 7-year follow-up." Chinese Medical Journal **119**(24): 2134-2137.

Huehne, K., C. Zweier, et al. (2008). "Novel missense, insertion and deletion mutations in the neurotrophic tyrosine kinase receptor type 1 gene (NTRK1) associated with congenital insensitivity to pain with anhidrosis." Neuromuscular Disorders **18**(2): 159-166.

Hereditary sensory and autonomic neuropathy type IV (HSAN IV) or congenital insensitivity to pain with anhidrosis (CIPA) is an autosomal-recessive disorder affecting the neurotrophin signal transduction pathway. HSAN IV is characterized by absence of reaction to noxious stimuli, recurrent episodes of fever, anhidrosis, self mutilating behaviour and frequent mental retardation. Mutations in the neurotrophic tyrosine kinase receptor type 1 (NTRK1) are associated with this disorder. We investigated NTRK1 mutations in five HSAN IV patients and one less typical patient with hypohidrosis, insensitivity to pain as well as motor- and sensory deficits in the peripheral nervous system. For the HSAN IV patients we identified a homozygous missense mutation (p.L572S), a homozygous deletion of 1985 bp (g.7335164-7336545del), a homozygous insertion c.722_723insC in exon 7 and two compound heterozygous mutations (p.Q558X + p.L717R). The less typical patient as well as one HSAN IV patient revealed no NTRK1 mutation. (C) 2007 Elsevier B.V. All rights reserved.

Igram, C. M., M. B. Harris, et al. (1996). "Charcot spinal arthropathy in congenital insensitivity to pain." Orthopedics **19**(3): 251-255.

Iijima, M. and N. Haga (2010). "Evaluation of nonnociceptive sensation in patients with congenital insensitivity to pain with anhidrosis." Childs Nervous System **26**(8): 1085-1089.

Congenital insensitivity to pain with anhidrosis (CIPA) is a rare, autosomal recessive disorder characterized by lack of pain and thermal sensation, anhidrosis, thermodyregulation, and mental retardation. Although nonnociceptive sensation, which is mediated by large-caliber myelinated A beta

fibers, is reported to be normal in CIPA patients, precise clinical assessments of this type of sensation have yet to be performed. The aim of this study was to evaluate peripheral sensory nerve function, including senses of touch/pressure, vibration, joint position, and two-point discrimination, in patients with CIPA by basic clinical neurological examination.

We examined touch/pressure sense, deep senses (vibration, joint proprioception), and two-point discrimination in 12 patients with CIPA (six males and six females aged 11-44) and 12 age- and sex-matched healthy controls. Touch/pressure sense was examined with Semmes-Weinstein monofilaments, vibration sense with a tuning fork, and two-point discrimination with a vernier caliper. Joint proprioception was assessed through subject recognition of passive movement of the great toe.

Perception thresholds of touch/pressure, vibration, and two-point discrimination were significantly higher ($p < 0.05$), and proprioception sensitivity was significantly lower ($p < 0.05$) in CIPA patients than in the healthy controls.

Our findings suggest that CIPA patients suffer from more widespread disturbances of sensation than has been previously recognized. Impairment may not be restricted to the types of sensation conducted by peripheral sensory A delta and C fibers.

Indo, Y. (2001). "Molecular basis of congenital insensitivity to pain with anhidrosis (CIPA): Mutations and polymorphisms in TRKA (NTRK1) gene encoding the receptor tyrosine kinase for nerve growth factor." *Human Mutation* **18**(6): 462-471.

Congenital insensitivity to pain with anhidrosis (CIPA), also referred to as hereditary sensory and autonomic neuropathy type IV (HSAN-IV), is an autosomal recessive hereditary disorder characterized by recurrent episodic fever, anhidrosis (inability to sweat), absence of reaction to noxious stimuli, self mutilating behavior, and mental retardation. The TRKA (NTRK1) gene located on chromosome 1 (1q21-q22), consists of 17 exons and spans at least 23 kb. TRKA encodes the receptor tyrosine kinase (RTK) for nerve growth factor (NGF) and is the gene responsible for CIPA. Defects in NGF signal transduction at the TRKA receptor lead to failure to support survival of sympathetic ganglion neurons and nociceptive sensory neurons derived from the neural crest. Thirty-seven different TRKA mutations, identified in patients in various countries, including nine frameshift, seven nonsense, seven splice, and 14 missense mutations, are distributed in an extracellular domain involved in NGF binding, as well as in the intracellular signal-transduction domain. Extensive analysis of CIPA mutations and associated intragenic polymorphisms should facilitate detection of CIPA mutations and aid in the diagnosis and genetic counseling of this painless but severe genetic disorder with devastating complications. In addition, naturally occurring TRKA missense mutations with loss of function provide considerable insight into the structure-function relationship in the RTK family. Further, molecular pathology of CIPA would provide unique opportunities to explore critical roles of the autonomic sympathetic nervous system as well as peripheral

sensory nervous system that transmit noxious stimuli in humans. *Hum Mutat* 18:462-471, 2001. (C) 2001 Wiley-Liss, Inc.

Indo, Y. (2009). "Nerve growth factor, interoception, and sympathetic neuron: Lesson from congenital insensitivity to pain with anhidrosis." *Autonomic Neuroscience-Basic & Clinical* **147**(1-2): 3-8.

Nerve growth factor (NGF) is a well-known neurotrophic factor essential for the survival and maintenance of sensory and sympathetic neurons. Congenital insensitivity to pain with anhidrosis (CIPA) is a genetic disorder due to loss-of-function mutations in the NTRK1 (also known as TRKA) gene encoding TrkA, a receptor tyrosine kinase for NGF. Patients with CIPA provide us a rare opportunity to explore the developmental and physiological function of the NGF-dependent neurons in behavior, cognitive, and mental activities that are not available in animal studies. Here, I discuss the significance of findings that patients with CIPA lack NGF-dependent neurons, including interoceptive polymodal receptors, sympathetic postganglionic neurons, and probably several types of neurons in the brain. They also exhibit characteristic emotional behavior or problems. Together, the NGF-TrkA system is essential for the establishment of a neural network for interoception and homeostasis that may underlie 'gut feelings'. Thus, NGF-dependent neurons play a crucial role in emotional experiences and decision-making processes. Prospective studies focused on these neurons might provide further insights into the neural basis of human emotion and feeling. (c) 2009 Elsevier B.V. All rights reserved.

Indo, Y. (2010). "Nerve growth factor, pain, itch and inflammation: lessons from congenital insensitivity to pain with anhidrosis." *Expert Review of Neurotherapeutics* **10**(11): 1707-1724.

NGF is a well-known neurotrophic factor essential for the survival and maintenance of primary afferent neurons and sympathetic neurons. NGF is also an inflammatory mediator associated with pain and itch. Congenital insensitivity to pain with anhidrosis is a genetic disorder due to loss-of-function mutations in the NTRK1 gene encoding TrkA, a receptor tyrosine kinase for NGF. Since patients with congenital insensitivity to pain with anhidrosis lack NGF-dependent unmyelinated (C-) and thinly myelinated (A delta-) fibers, and their dermal sweat glands are without innervation, they exhibit no pain, itch, signs of neurogenic inflammation or sympathetic skin responses. Based on the pathophysiology of congenital insensitivity to pain with anhidrosis, this article indicates how NGF-dependent neurons are essential for the establishment of neural networks for interoception and homeostasis, and play crucial roles in brain-immune-endocrine interactions in pain, itch and inflammation. In addition, it refers to involvements of the NGF-TrkA system in various disease states, and potential pharmacological effects when this system is targeted.

Indo, Y., S. Mardy, et al. (2001). "Congenital insensitivity to pain with anhidrosis (CIPA):

Novel mutations of the TRKA (NTRK1) gene, a putative uniparental disomy, and a linkage of the mutant TRKA and PKLR genes in a family with CIPA and pyruvate kinase deficiency." Human Mutation **18**(4): 308-318.

Congenital insensitivity to pain with anhidrosis is an autosomal recessive hereditary disorder characterized by recurrent episodic fever, anhidrosis (inability to sweat), absence of reaction to noxious stimuli, self mutilating behavior, and mental retardation. The human TRKA gene (NTRK1), located on chromosome 1q21-q22 encodes the receptor tyrosine kinase for nerve growth factor. We reported that TRKA is the gene responsible for CIPA and we developed a comprehensive strategy to screen for TRKA mutations and polymorphisms, as based on the gene's structure and organization. Here we report eight novel mutations detected as either a homozygous or heterozygous state in nine CIPA families from five countries. Mendelian inheritance of the mutations was confirmed in seven families for which samples from either parent were available. However, none mendelian inheritance seems likely for the family when only samples from the mother and siblings, (but not from the father) were available. A paternal uniparental disomy for chromosome 1 is likely to be the cause of reduction to homozygosity of the TRKA gene mutation in this family. Interestingly, a Hispanic patient from the USA has two autosomal genetic disorders, CIPA and pyruvate kinase deficiency, whose genetic loci are both mapped to a closely linked chromosomal region. A splice mutation and a missense mutation were detected in the TRKA and PKLR genes from the homozygous proband, respectively. Thus, concomitant occurrence of two disorders is ascribed to a combination of two separate mutant genes, not a contiguous gene syndrome. This finding suggests a mechanism responsible for two autosomal genetic disorders in one patient. All these data further support findings that TRKA defects can cause CIPA in various ethnic groups. This will aid in diagnosis and genetic counseling of this painless but severe genetic disorder. Hum Mutat 18:308-318, 2001. (C) 2001 Wiley-Liss, Inc.

Indo, Y., M. Tsuruta, et al. (1996). "Mutations in the TRKA/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis." Nature Genetics **13**(4): 485-488.

Ismail, E. A. R., N. Al-Shammari, et al. (1998). "Congenital insensitivity to pain with anhidrosis: Lack of eccrine sweat gland innervation confirmed (vol 13, pg 243, 1998)." Journal of Child Neurology **13**(12): 632-632.

Ismail, E. A. R., N. Al-Shammari, et al. (1998). "Congenital insensitivity to pain with anhidrosis: Lack of eccrine sweat gland innervation confirmed." Journal of Child Neurology **13**(5): 243-246.

Jarade, E. F., H. F. El-Sheikh, et al. (2002). "Indolent corneal ulcers in a patient with congenital insensitivity to pain with anhidrosis: A case report and literature review." European Journal of Ophthalmology **12**(1): 60-65.

PURPOSE. To report a case of bilateral corneal neurotrophic ulcer in patient with congenital insensitivity to pain with anhidrosis (CIPA) and review the literature.

CASE REPORT. A 6 year-old boy presented with bilateral central corneal sterile ulcer, decreased corneal sensitivity, moderately altered corneal reflex and normal tearing response. History taken, systemic evaluation and medical chart review were undertaken.

DISCUSSION. Fifty-two cases of CIPA have been reported worldwide. Fourteen cases had corneal involvement. The clinical picture of our patient is characteristic of CIPA.

CONCLUSIONS. Congenital insensitivity to pain with anhidrosis may present as neurotrophic corneal ulcer. We report herewith, this vision threatening corneal congenital abnormality. Early diagnosis and prompt treatment are mandatory to prevent corneal complications such as scarring and perforation.

John, D., M. Thomas, et al. (2011). "Neurotrophic Keratitis and Congenital Insensitivity to Pain With Anhidrosis-A Case Report With 10-Year Follow-up." *Cornea* **30**(1): 100-102.

Purpose: To report a rare case of congenital insensitivity to pain with anhidrosis.

Methods: A 3-year-old girl presented with watering in the right eye for 3 days. Slit-lamp examination showed an epithelial defect and hypopyon in the right eye and a corneal scar with thinning and vascularization in the left eye. There was bilateral reduced corneal sensation and evidence of self-mutilated lips and fingers.

Results: Neurological manifestations along with ocular features confirmed the diagnosis of congenital insensitivity to pain with anhidrosis.

Conclusions: Patients with congenital insensitivity to pain with anhidrosis are asymptomatic even when they develop corneal ulcer. Parents should be advised regular follow-up and prompt treatment because this is a vision-threatening corneal abnormality.

Kang, J. D. and H. H. Bohlman (2000). "Cervical disc herniation in a patient with congenital insensitivity to pain - A case report." *Spine* **25**(13): 1726-1728.

Study Design. A case report of a patient with a known diagnosis of congenital insensitivity to pain who developed a herniated cervical disc.

Objectives. To study the clinical manifestations of cervical radiculopathy in a patient with congenital insensitivity to pain and the long-term outcome after surgical treatment.

Summary of Background Data. There have been no reports in the English literature documenting such a patient.

Methods, Retrospective case report and long-term clinical and radiographic follow-up.

Results. This patient with a known diagnosis of congenital insensitivity to pain had neurologic motor weakness with "neck and shoulder pain." Clear radicular pattern could not be elicited. The patient underwent a successful anterior discectomy and fusion with long-term clinical and radiographic results.

Conclusion. Patients with congenital insensitivity to pain who develop a cervical disc

herniation may present with atypical symptoms not manifesting in the classic radicular pattern. Higher index of suspicion by the clinician must be practiced to make the appropriate diagnosis. Successful surgical outcome may be achieved in these patients.

Karkashan, E. M., H. S. Joharji, et al. (2002). "Congenital insensitivity to pain in four related Saudi families." *Pediatric Dermatology* **19**(4): 333-335.

Congenital insensitivity to pain (hereditary sensory and autonomic neuropathy [HSAN] type V) is a rare disorder of pain perception in which pain sensation is absent from birth, with no other neurologic deficits. We report five Saudi patients (three male and two female) age 10 months to 23 years who lacked pain sensation from birth but have normal appreciation of other sensory modalities. They are from four related families who are descended from one grandfather. The patients had sustained many painless injuries resulting in fractures and disfigurement, but otherwise are completely normal.

Karmani, S., R. Shedden, et al. (2001). "Orthopaedic manifestations of congenital insensitivity to pain." *Journal of the Royal Society of Medicine* **94**(3): 139-140.

Kawashima, N., M. O. Abe, et al. (2012). "Abnormal capacity for grip force control in patients with congenital insensitivity to pain." *Experimental Brain Research* **218**(4): 579-588.

Congenital insensitivity to pain (CIP), which is an extremely rare sensory neuropathy, is defined as the absence of normal responses to noxious stimuli. Although motor function is not directly impaired in CIP patients, it is likely that the sensory deficit affects the motor control system. In order to characterize motor capacity in CIP patients, we here measured grip force and acceleration of a held object in 12 patients with CIP and 12 age-matched able-bodied subjects. The results demonstrated that the grip force during the object grasp-lift-holding task was significantly greater, less reproducibility and greater fluctuation in the acceleration of the object in CIP patients than in normal subjects. Moreover, some patients showed absence of temporal coupling between the grip and load force, suggesting that anticipatory modulation of the grip force was at least partly impaired. As far as the authors know, this is the first study to characterize motor control ability in patients with CIP. The observed abnormal motor capacity can be at least partly attributed to a lack of sensory inputs mediated by A delta and unmyelinated C-, specifically C-tactile, fibers. The present results may provide information useful for the prevention of secondary injury and education for patients during the developmental stage.

Kilic, S. S., R. Ozturk, et al. (2009). "Humoral immunodeficiency in congenital insensitivity to pain with anhidrosis." *Neurogenetics* **10**(2): 161-165.

Congenital insensitivity to pain with anhidrosis (CIPA) is an autosomal recessive disorder caused by mutations in the neurotrophic tyrosine receptor kinase 1

(NTRK1) gene, which encodes the receptor for nerve growth factor. We report the clinical course of a 7-year-old girl with CIPA and proven NTRK1 mutation. In addition to recurrent dislocation of the left hip joint and avascular necrosis of the left talus, the patient also presented with recurrent infections secondary to hypogammaglobulinemia, a feature not previously known to be associated with CIPA. The patient was treated with regular administration of intravenous immunoglobulins. Conservative treatment of the recurrent left hip dislocation by cast immobilization and bracing was implemented to stabilize the joint. The implication of the immune system of the reported patient broadens the clinical phenotype associated with NTRK1 mutations.

Kim, J. S., Y. J. Woo, et al. (1999). "Congenital insensitivity to pain with anhidrosis : A case report." Journal of Korean Medical Science **14**(4): 460-464.

Congenital insensitivity to pain with anhidrosis (CIPA) is a very rare genetic disorder of the peripheral nervous system characterized by recurrent episodes of unexplained fever, generalized anhidrosis, insensitivity to pain and temperature, and accompanied by self-mutilating behavior and mental retardation, We report on a 16 month-old boy with CIPA who exhibited these characteristic clinical features. A sural nerve biopsy revealed markedly reduced numbers of unmyelinated and small myelinated fibers, consistent with the characteristic features of CIPA.

Kiuru, M., M. Kurban, et al. (2010). "A nonsense mutation in the SCN9A gene in congenital insensitivity to pain." Journal of Investigative Dermatology **130**: S94-S94.

Klein, C. J., M. Sinnreich, et al. (2003). "Indifference rather than insensitivity to pain." Annals of Neurology **53**(3): 417-418.

Klein, C. J., Y. Wu, et al. (2007). "Genetic heterogeneity in primary erythromelalgia and insensitivity to pain." Journal of the Peripheral Nervous System **12**: 44-45.

Kotsias, B. A. (2007). "The fakir of the fun fair and the congenital insensitivity to pain." Medicina-Buenos Aires **67**(2): 209-210.

Ku, A. S. W., C. R. Rodrigo, et al. (2005). "Anesthetic management of a child with congenital insensitivity to pain with anhydrosis." Journal of Oral and Maxillofacial Surgery **63**(6): 848-851.

Kuo, R. S. and M. F. Macnicol (1996). "Congenital insensitivity to pain: Orthopaedic implications." Journal of Pediatric Orthopaedics-Part B **5**(4): 292-295.

We report two children in one family with congenital insensitivity to pain, anhidrosis, and mental retardation with behavioural disturbance. Orthopaedic manifestations of this condition include recurrent fractures, osteomyelitis, and neuropathic joints. The differential diagnoses and difficulties in the management

of this rare disorder are discussed.

Kurban, M., M. Wajid, et al. (2010). "A Nonsense Mutation in the SCN9A Gene in Congenital Insensitivity to Pain." Dermatology **221**(2): 179-183.

Background: Congenital insensitivity to pain (CIP) (OMIM 243000) is a rare autosomal-recessive disorder. Clinically, CIP is characterized by insensitivity to all modalities of pain except neuropathic pain, and recurrent injuries frequently go unnoticed. CIP is caused by mutations in the SCN9A gene encoding for the Na1.7 channel. Methods: We analyzed the DNA from members of a consanguineous Pakistani family for mutations in the SCN9A gene through direct sequencing after performing linkage studies. Results: We identified a novel missense mutation designated R523X in all affected individuals. A screening assay ruled out the possibility of polymorphism. Conclusion: We identified a novel mutation in the Na1.7 channel leading to CIP, extending the spectrum of mutations in the Na1.7 channel, and enhancing our understanding of the physiology of pain. Copyright (C) 2010 S. Karger AG, Basel

Larner, A. J., J. Moss, et al. (1994). "Congenital Insensitivity to Pain - a 20-Year Follow-Up." Journal of Neurology Neurosurgery and Psychiatry **57**(8): 973-974.

The exact nosological status of "congenital insensitivity to pain" remains in doubt. Possible pathological correlates of this clinical syndrome include sensory neuropathy, central lesions at the level of the reticular formation or dorsal horn of the spinal cord, or a central indifference to, or asymbolia for, pain. The reassessment of two members of a kindred previously reported more than 20 years ago as having congenital insensitivity to pain indicated that they in fact had an inherited sensory and autonomic neuropathy. Prolonged follow up and morphometric analysis of sequential nerve biopsies may be necessary to definitively establish this diagnosis.

Larsson, E., R. Kuma, et al. (2009). "Nerve growth factor R221W responsible for insensitivity to pain is defectively processed and accumulates as proNGF." Neurobiology of Disease **33**(2): 221-228.

We have previously identified a homozygous missense (R221W) mutation in the NGFB gene in patients with loss of deep pain perception. NGF is important not only for the survival of sensory neurons but also for the sympathetic neurons and cholinergic neurons of the basal forebrain; however, it is the sensory neurons that are mainly affected in patients with mutant NGFB. In this report, we describe the effects of the mutation on the function of NGF protein and the molecular mechanisms that may underlie the pain insensitivity phenotype in these patients. We show that the mutant NGF has lost its ability to mediate differentiation of PC12 cells into a neuron-like phenotype. We also show that the inability of PC12 cells to differentiate is due to a markedly reduced secretion of mature R221W NGF. The R221W NGF is found mainly as proNGF, in contrast to wild-type NGF which is predominantly in the mature form in both undifferentiated and

differentiated PC12 cells. The reduction in numbers of sensory fibers observed in the patients is therefore probably due to loss of trophic support as a result of drastically reduced secretion of NGF from the target organs. Taken together, these data show a clear decrease in the availability of mutant mature NGF and also an accumulation of proNGF in both neuronal and non-neuronal cells. The differential loss of NGF-dependent neurons in these patients, mainly affecting sensory neurons, may depend on differences in the roles of mature NGF and proNGF in different cells and tissues. (C) 2008 Elsevier Inc. All rights reserved.

Lee, S. T., J. Lee, et al. (2009). "Clinical and Genetic Analysis of Korean Patients with Congenital Insensitivity to Pain with Anhidrosis." Muscle & Nerve **40**(5): 855-859.

Congenital insensitivity to pain with anhidrosis (CIPA) is a rare autosomal recessive disease characterized by anhidrosis, insensitivity to noxious stimuli, and mental retardation. Mutations in the NTRK1 gene are associated with the pathogenesis of CIPA. In this study, we performed a clinical and genetic analysis on the NTRK1 gene in four Korean patients with CIPA. All patients had typical clinical manifestations of CIPA, including anhidrosis, recurrent fever, absent pain perception, and developmental delay. Sequencing analysis revealed one predominant mutation, c.851-33T>A, in four affected alleles and three novel mutations, including c.287+2dup inverted perpendicular, c.2155G>A (p.Glu719Lys), and c.1218delC (p.Pro407ArgfsX), in each affected allele. For one patient, who was heterozygous for c.851-33T>A, another mutation could not be identified, suggesting that a possible hidden intronic or large genomic mutation may have been present. This study extends the spectrum of mutations in the NTRK1 gene and confirms that Korean patients with CIPA have the same genetic background as other ethnicities. *Muscle Nerve* 40: 855-859, 2009

Levy, J., T. Monos, et al. (2004). "Intranasal wood foreign body causing orbital cellulitis in congenital insensitivity to pain with anhidrosis syndrome." Ophthalmic Plastic and Reconstructive Surgery **20**(1): 81-83.

A 2-year-old boy with congenital insensitivity to pain with anhidrosis (CIPA) was referred with a 2-day history of left periorbital swelling and mucoid conjunctival discharge. Marked worsening was noted despite intramuscular ceftriaxone treatment for 3 days, with marked proptosis, conjunctival chemosis, and a frozen eye. Orbital cellulitis was suspected. Ceftriaxone was intravenously administered. Orbital computed tomography (CT) disclosed an inflammatory process in the medial aspect of the left orbit with ethmoiditis. Improvement was not noted after external ethmoidectomy and drainage of the intraconal abscess. Repeat CT showed a recurrent intraconal abscess. A revision external ethmoidectomy was performed, and a bent wooden match was removed from the posterior aspect of the ethmoidal sinus, after which significant clinical improvement was noted. In patients with CIPA, accidental or self-penetrated foreign bodies must be kept in mind when treating all types of wounds.

Lin, Y. P., Y. N. Su, et al. (2010). "Novel Neurotrophic Tyrosine Kinase Receptor Type 1 Gene Mutation Associated With Congenital Insensitivity to Pain With Anhidrosis." Journal of Child Neurology **25**(12): 1548-1551.

Congenital insensitivity to pain with anhidrosis (hereditary sensory and autonomic neuropathy type IV) is a rare autosomal recessive disorder caused by a defect in neurotrophic tyrosine kinase receptor and nerve growth factor, as reported in previous studies. This report is of a 6-month-old male infant with typical symptoms and signs of congenital insensitivity to pain with anhidrosis. He had a homozygous insertion mutation with c.2086_2087 ins C of neurotrophic tyrosine kinase receptor type 1 (NTRK1) gene with both parents as heterozygous carriers. This mutation may have a strong relation to hereditary sensory and autonomic neuropathy type IV Taiwanese patients. This is the youngest reported patient in Taiwan and first reported with congenital insensitivity to pain with mutation of NTRK1 gene inherited from the parents. Early diagnosis may provide appropriate medical care and education for these children and their families for better prognosis.

Ma, A. and A. Turner (2012). "A Life without Pain: Congenital Insensitivity to Pain Due to Compound Heterozygous Scn9a Mutation." Journal of Paediatrics and Child Health **48**(3): 285-286.

Machtei, A., J. Levy, et al. (2011). "Osteomyelitis of the mandible in a group of 33 pediatric patients with congenital insensitivity to pain with anhidrosis." International Journal of Pediatric Otorhinolaryngology **75**(4): 523-526.

Objective: To determine the frequency of mandibular osteomyelitis (OM) in patients with congenital insensitivity to pain with anhidrosis (CIPA) and to relate its appearance to possible risk factors.

Methods: The records of 33 patients were reviewed for data concerning events of jaw OM, oral trauma, maxillofacial interventions, or OM of long bones.

Results: Eighteen percent of the patients had mandibular OM. Of the six patients, preceding oral laceration was documented in one and tooth extraction in two. Seventy percent of the patients had OM of the limbs, but only 15% overlapped, having both jaw and limb OM. Half of the patients with mandibular OM had also OM of the limbs during the following year. There seems to be a correlation between high frequency of limb OM (at least 5 events per patient) and appearance of mandibular OM.

Conclusion: The incidence of mandibular OM is very high among patients with CIPA and can result in pathologic fracture and the need for open reduction and internal fixation. The reason for this phenomenon is presently not clear. Preventive and therapeutic strategy for CIPA patients should be undertaken to minimize this severe complication. (C) 2011 Elsevier Ireland Ltd. All rights reserved.

Mardy, S., Y. Miura, et al. (2001). "Congenital insensitivity to pain with anhidrosis (CIPA): effect of TRKA (NTRK1) missense mutations on autophosphorylation of the receptor

tyrosine kinase for nerve growth factor." Human Molecular Genetics **10**(3): 179-188.

Human TRKA (NTRK1) encodes the receptor tyrosine kinases (RTKs) for nerve growth factor (NGF) and is the gene responsible for congenital insensitivity to pain with anhidrosis (CIPA), an autosomal recessive disorder characterized by a lack of pain sensation and anhidrosis. We reported 11 putative missense mutations in 31 CIPA families from various ethnic groups. Here we have introduced the corresponding mutations into the TRKA cDNA and examined NGF-stimulated autophosphorylation. We find that wildtype TRKA precursor proteins in a neuronal and a non-neuronal cell line were differentially processed and phosphorylated in an NGF-dependent and -independent manner, respectively. Two mutants (L93P and L213P) in the extracellular domain were aberrantly processed and showed diminished autophosphorylation in neuronal cells. Five mutants (G516R, G571R, R643W, R648C and G708S) in the tyrosine kinase domain were processed as wild-type TRKA but showed significantly diminished autophosphorylation in both neuronal and non-neuronal cells. In contrast, R85S and (H598Y; G607V), detected previously as double and triple mutations, are probably polymorphisms in a particular ethnic background. The other putative mutant D668Y might be a rare polymorphism or might impair the function of TRKA without compromising autophosphorylation. Mutated residues in the tyrosine kinase domain are conserved in various RTKs and probably contribute to critical function of these proteins. Thus, naturally occurring TRKA missense mutations with loss of function provide considerable insight into the structure-function relationship in the RTK family. Our data may aid in developing a drug which targets the clinically devastating 'complex regional pain syndrome'.

Mardy, S., Y. Miura, et al. (1999). "Congenital insensitivity to pain with anhidrosis: Novel mutations in the TRKA (NTRK1) gene encoding a high-affinity receptor for nerve growth factor." American Journal of Human Genetics **64**(6): 1570-1579.

Congenital insensitivity to pain with anhidrosis (CIPA) is characterized by recurrent episodes of unexplained fever, anhidrosis (inability to sweat), absence of reaction to noxious stimuli, self-mutilating behavior, and mental retardation. Human TRKA encodes a high-affinity tyrosine kinase receptor for nerve growth factor (NGF), a member of the neurotrophin family that induces neurite outgrowth and promotes survival of embryonic sensory and sympathetic neurons. We have recently demonstrated that TRKA is responsible for CIPA by identifying three mutations in a region encoding the intracellular tyrosine kinase domain of TRKA in one Ecuadorian and three Japanese families. We have developed a comprehensive strategy to screen for TRKA mutations, on the basis of the gene's structure and organization. Here we report 11 novel mutations, in seven affected families. These are six missense mutations, two frameshift mutations, one nonsense mutation, and two splice-site mutations. Mendelian inheritance of the mutations is confirmed in six families for which parent samples are available. Two mutations are linked, on the same chromosome, to Arg85Ser and to His598Tyr;Gly607Val, hence, they probably represent double and triple

mutations. The mutations are distributed in an extracellular domain, involved in NGF binding, as well as the intracellular signal-transduction domain. These data suggest that TRKA defects cause CIPA in various ethnic groups.

Matsota, P., A. Pandazi, et al. (2009). "Anaesthetic management of a Greek patient with congenital insensitivity to pain and anhidrosis undergoing a scheduled orthopaedic operation." Archives of Medical Science **5**(1): 115-116.

Congenital insensitivity to pain with anhidrosis (CIPA) is a very rare hereditary syndrome worldwide due to certain gene mutations and histological appearances that affect the peripheral pathway of noxious stimuli transmission and the innervation of sweat glands. It is characterized by insensitivity to pain, anhidrosis, and heat intolerance. We describe the clinical features and the anaesthetic management of a 24-year old Greek man suffering from CIPA, who uneventfully underwent an internal osteosynthesis of the femoral bone under general anaesthesia. This is also the first reported case with congenital insensitivity to pain and anhidrosis in Greece.

Melamed, I., J. Levy, et al. (2004). "A novel lymphocyte signaling defect: trk A mutation in the syndrome of congenital insensitivity to pain and anhidrosis (CIPA)." Journal of Clinical Immunology **24**(4): 441-448.

Congenital insensitivity to pain with anhidrosis is a syndrome characterized by loss of pain and sensation. The condition frequently evolves into deep wounds and prolonged healing times. Anhidrosis is another prominent component of the disorder. Often associated with recurrent episodes of unexplained fever, it can result in patient mortality. Recent investigations point to Trk A, the high affinity receptor for nerve growth factor (NGF), as a candidate for the site of the mutation that causes the disorder. Functional NGF receptors, such as Trk A and the Trk family of tyrosine kinases, are essential for NGF signaling of human lymphocytes. In this study, we demonstrated that the presence of a trk A mutation in patient B cells results in a novel lymphocyte signaling defect. In these B cells, NGF failed to induce Trk A phosphorylation, cytoskeleton assembly, or MAP kinase activation. These abnormalities may explain some of the clinical features of the disease.

Minde, J., O. Svensson, et al. (2006). "Orthopedic aspects of familial insensitivity to pain due to a novel nerve growth factor beta mutation." Acta Orthopaedica **77**(2): 198-202.

Background Congenital insensitivity to pain is a rare hereditary sensory neuropathy.

Patients We present 6 patients from a family with a mutation in the nerve growth factor beta gene (NGFB).

Results 3 patients were homozygous with a mutilating arthropathy starting early in life, and 3 patients were presumably heterozygous; with a milder course starting in adulthood. All patients had normal mental abilities. In addition to absence of deep pain, the patients had impaired temperature sensation, but no autonomic

deficiency. Sural nerve biopsies showed a moderate loss of A-delta fibres and a severe reduction in C fibers. Clinically, the disorder most often affected the lower extremities, with an insidious progressive joint swelling or a painless fracture, but the spine could also be involved with gross and unstable spondylolisthesis. Fracture healing was uneventful, but the arthropathy was progressive, eventually resulting in gross deformity and instability. When treating patients with congenital disorders such as this one, it is important to consider the slowly progressive nature of the disorder, and the orthopedic operations should therefore be planned from a long-term standpoint. Arthrodesis, limb lengthening and spinal decompression or fusion are the only elective procedures that seem reasonable. Fitting of orthosis for joint protection is also demanding. To delay the development of neuropathic arthropathy, patient education is essential but difficult in the very young.

Interpretation The different expression between homo- and heterozygous subjects and the central role of nerve growth factor make this disease an interesting model system for studies of disease mechanisms and the molecular background to pain.

Minde, J., G. Toolanen, et al. (2004). "Familial insensitivity to pain (HSAN V) and a mutation in the NGFB gene. A neurophysiological and pathological study." Muscle & Nerve **30**(6): 752-760.

We have studied a large Swedish family with a mutation in the nerve growth factor beta (NGFB) gene causing insensitivity to deep pain without anhidrosis (hereditary sensory and autonomic neuropathy, type V; HSAN V). Painfree joint destruction and fractures were common. Peripheral nerve conduction was normal, but temperature thresholds were increased. Sural nerve biopsies showed a moderate loss of A-delta fibers and a severe reduction of C fibers. The three most severely affected cases were all born to consanguineous parents, and were homozygotes for the causal genetic mutation. Treatment of these patients is discussed.

Minde, J. K. (2006). "Norrbottnian congenital insensitivity to pain." Acta Orthopaedica **77**: 2-32.

Congenital insensitivity to pain is a rare hereditary neuropathy. We present patients from a large family in Norrbotten, Sweden with a mutation in the nerve growth factor beta gene (NGF beta). Using a model of recessive inheritance, we identified an 8.3-Mb region on chromosome 1p11.2-p13.2 shared by the affected individuals in the family. Analysis of candidate genes in the disease-critical region revealed a mutation in the coding region of the NGF beta gene specific for the disease haplotype. All three severely affected individuals were homozygous for the mutation. The disease haplotype was also observed in both unaffected and mildly affected family members, but in heterozygote form. We have identified 43 patients, 3 homozygous and 40 heterozygous. The homozygous patients have a severe congenital form with onset of symptoms at an early age, most often

affecting the lower extremities with insidious progressive joint swellings or painless fractures. Fracture healing was normal, but the arthropathy was progressive, resulting in disabling Charcot joints with gross deformity and instability. These patients lacked deep pain perception in bones and joints and had no protective reflexes, leading to gross bone and joint complications. They also had abnormal temperature perception but normal ability to sweat. There was no mental retardation. Clinically, they fit best into the group HSAN type V. Sural nerve biopsies showed a moderate loss of thin myelinated fibers (A delta-fibers) and a severe reduction of unmyelinated fibers (C-fibers). 14 of the 40 heterozygous adult patients had mild or moderate problems with joint deformities, usually with only slight discomfort. Treatment was conservative with (if needed) different kinds of orthosis and in three cases joint replacement. Nine patients had neuropathy, and nine patients had no symptoms.

In congenital disorders like these, it is important to evaluate the age and also the slowly progressive nature, when considering treatment. There is an increased risk of growth disturbances in the very young. The orthopedic operations should therefore be planned from a long-term point of view, but patient education and orthosis are cornerstones in the treatment-to delay the development of neuropathic arthropathy. Arthrodesis, limb lengthening and spinal decompression with fusions are the only elective procedures that seem reasonable. This Norrbotnian disease is also interesting as a model system for the study of pain.

Miranda, C., M. Di Virgilio, et al. (2002). "Novel pathogenic mechanisms of congenital insensitivity to pain with anhidrosis genetic disorder unveiled by functional analysis of neurotrophic tyrosine receptor kinase type 1/nerve growth factor receptor mutations." Journal of Biological Chemistry **277**(8): 6455-6462.

Congenital insensitivity to pain with anhidrosis (CIPA) is a rare genetic disease characterized by absence of reaction to noxious stimuli and anhidrosis. The genetic bases of CIPA have remained long unknown. A few years ago, point mutations affecting both coding and noncoding regions of the neurotrophic tyrosine receptor kinase type 1 (NTRK1)/nerve growth factor receptor gene have been detected in CIPA patients, demonstrating the implication of the nerve growth factor/ NTRK1 pathway in the pathogenesis of the disease. We have previously shown that two CIPA mutations, the G571R and the R774P, inactivate the NTRK1 receptor by interfering with the autophosphorylation process. We have extended our functional analysis to seven additional NTRK1 mutations associated with CIPA recently reported by others. Through a combination of biochemical and biological assays, we have identified polymorphisms and pathogenic mutations. In addition to the identification of residues important for NTRK1 activity, our analysis suggests the existence of two novel pathogenic mechanisms in CIPA: one based on the NTRK1 receptor processing and the other acting through the reduction of the receptor activity.

Miranda, C., S. Selleri, et al. (2002). "The M581V mutation, associated with a mild form

of congenital insensitivity to pain with anhidrosis, causes partial inactivation of the NTRK1 receptor." Journal of Investigative Dermatology **119**(4): 978-979.

Misery, L., M. Hermier, et al. (1999). "Congenital insensitivity to pain with anhidrosis: absence of substance P receptors in the skin." British Journal of Dermatology **140**(1): 190-191.

Miura, Y., M. Hiura, et al. (2000). "Complete paternal uniparental isodisomy for chromosome 1 revealed by mutation analyses of the TRKA (NTRK1) gene encoding a receptor tyrosine kinase for nerve growth factor in a patient with congenital insensitivity to pain with anhidrosis." Human Genetics **107**(3): 205-209.

Uniparental disomy (UPD) is defined as the presence of a chromosome pair that derives from only one parent in a diploid individual. The human TRKA gene on chromosome 1q21-q22 encodes a receptor tyrosine kinase for nerve growth factor and is responsible for an autosomal recessive genetic disorder: congenital insensitivity to pain with anhidrosis (CIPA). We report here the second case of paternal UPD for chromosome 1 in a male patient with CIPA who developed normally at term and did not show overt dysmorphism or malformations. He had only the usual features of CIPA with a homozygous mutation at the TRKA locus and a normal karyotype with no visible deletions or evidence of monosomy 1. Haplotype analysis of the TRKA locus and allelotyping analyses of whole chromosome 1 revealed that the chromosome pair was exclusively derived from his father. Non-maternity was excluded by analyses of autosomes other than chromosome 1. Thus, we have identified a complete paternal isodisomy for chromosome 1 as the cause of reduction to homozygosity of the TRKA gene mutation, leading to CIPA. Our findings further support the idea that there are no paternally imprinted genes on chromosome 1 with a major effect on phenotype. UPD must be considered as a rare but possible cause of autosomal recessive disorders when conducting genetic testing.

Miura, Y., S. Mardy, et al. (2000). "Mutation and polymorphism analysis of the TRKA (NTRK1) gene encoding a high-affinity receptor for nerve growth factor in congenital insensitivity to pain with anhidrosis (CIPA) families." Human Genetics **106**(1): 116-124.

The human TRKA gene encodes a high-affinity tyrosine kinase receptor for nerve growth factor. Congenital insensitivity to pain with anhidrosis (CIPA) is an autosomal recessive genetic disorder reported from various countries and characterized by anhidrosis (inability to sweat), the absence of reaction to noxious stimuli, and mental retardation. We have found that TRKA is the gene responsible for CIPA. We have studied TRKA in 46 CIPA chromosomes derived from 23 unrelated Japanese CIPA families, including three that have been previously reported, and identified 11 novel mutations. Four (L93P, G516R, R638C, and D668Y) are missense mutations that result in amino acid substitutions at positions conserved in the TRK family, including TRKA, TRKB, and TRKC. Three (S131 fs, L579 fs, and D770 fs) are frameshift mutations. Three (E164X, Y359X,

and R596X) are nonsense mutations. The other is an intronic branch-site (IVS7-33T-->A) mutation, causing aberrant splicing in vitro. We also report the characterization of eight intragenic polymorphic sites, including a variable dinucleotide repeat and seven single nucleotide polymorphisms, and describe the haplotypic associations of alleles at these sites in 106 normal chromosomes and 46 CIPA chromosomes. More than 50% of CIPA chromosomes share the frameshift mutation (R548 fs) that we described earlier. This mutation apparently shows linkage disequilibrium with a rare haplotype in normal chromosomes, strongly suggesting that it is a common founder mutation. These findings represent the first extensive analysis of CIPA mutations and associated intragenic polymorphisms; they should facilitate the detection of CIPA mutations and aid in the diagnosis and genetic counseling of this painless but severe genetic disorder with devastating complications.

Miura, Y., S. Mardy, et al. (2000). "Mutation and polymorphism analysis of the TRKA (NTRK1) gene encoding a high-affinity receptor for nerve growth factor in congenital insensitivity to pain with anhidrosis (CIPA) families (vol 106, pg 116, 2000)." Human Genetics **106**(5): 575-575.

Mobini, M., A. Javadzadeh, et al. (2009). "Neuropathic Osteoarthropathy in a Patient with Congenital Insensitivity to Pain." Archives of Iranian Medicine **12**(6): 599-602.

This report describes a 23-year-old man who presented with multiple joint deformities as a consequence of multiple painless intra-articular fractures. Blood counts, biochemistry, and nerve conduction velocity were all normal. X-ray studies showed joint destruction in hips, elbows and knees. We concluded that he is a case of congenital insensitivity to pain culminating in multiple charcot joints.

Nagasako, E. M., A. L. Oaklander, et al. (2003). "Congenital insensitivity to pain: an update." Pain **101**(3): 213-219.

Narita, M. and T. Suzuki (2003). "Changes in intracellular signaling in both brain and spinal cord associated with the insensitivity to opioid receptor-mediated responses under a neuropathic pain-like state." Journal of Pharmacological Sciences **91**: 15p-15p.

Neves, B. G., R. T. Roza, et al. (2009). "Traumatic lesions from congenital insensitivity to pain with anhidrosis in a pediatric patient: dental management." Dental Traumatology **25**(5): 545-549.

Congenital insensitivity to pain with anhidrosis is a rare autosomal-recessive disorder characterized by unexplained fever episodes, anhidrosis, pain insensitivity, self-mutilating behavior, and mental retardation. The lack of sensitivity to pain results in traumatic lesions, such as ulcers, fractures, burns, bites, scars, and digital amputations. Several methods have been suggested to treat these patients; however, appropriate management is difficult, especially

when the mutilation is particularly severe. This report describes the case of a 2-year-old female patient who had severe self-mutilating injuries to her tongue, hands, lips, and oral mucosa caused by biting. The patient presented digital amputation and also a premature loss of a permanent tooth germ during the treatment. The dental management is described and discussed. It is important to include the dentist on the multidisciplinary team to reduce the frequency and severity of the self-inflicted lesions in these patients, also to prevent complications.

Nilsen, K. B., A. K. Nicholas, et al. (2009). "Two novel SCN9A mutations causing insensitivity to pain." *Pain* **143**(1-2): 155-158.

The sensation of pain is important and there may be serious consequences if it is missing. Recently, the genetic basis for a channelopathy characterised by a congenital inability to experience pain has been described and channelopathy-associated insensitivity to pain has been proposed as a suitable name for this condition. Different mutations in the SCN9A gene causing loss of function of the voltage-gated sodium channel Nav1.7 have been reported in patients with this rare disease. Here we describe a woman with insensitivity to pain with two novel mutations in the SCN9A gene, coding for the Nav1.7 channel. We also discuss the finding of anosmia which apparently is a common feature in these patients. (C) 2009 International Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.

Nilsen, K. B., A. K. Nicholas, et al. (2009). "Two novel SCN9A mutations causing insensitivity to pain (vol 143, pg 155, 2009)." *Pain* **145**(1-2): 264-264.

Nolano, M., C. Crisci, et al. (2000). "Absent innervation of skin and sweat glands in congenital insensitivity to pain with anhidrosis." *Clinical Neurophysiology* **111**(9): 1596-1601.

Objectives: A case of a 10-year-old girl with congenital insensitivity to pain with anhidrosis (CIPA) is reported.

Methods and results: Parents referred several hyperpyretic episodes without sweating occurring since birth, and insensitivity to pain, noticed when the child was 2 years old. Her body had many bruises and scars, bone fractures and signs of self-mutilation. Neurological examination was normal except for insensitivity to pain. Her IQ was 52. Electrical and tactile sensory nerve conduction velocities were normal. The patient was unable to detect thermal stimuli. Histamine injection evoked a wheal but not a flare; pilocarpine by iontophoresis did not induce sweat. Microneurography showed neural activity from A-beta sensory fibers while nociceptive and skin sympathetic C fiber nerve activity was absent. No small myelinated fibers and very rare unmyelinated fibers were found in the sural nerve. Immunohistochemistry showed a lack of nerve fibers in the epidermis and only few hypotrophic and uninnervated sweat glands in the dermis.

Conclusions: The lack of innervation of the skin (C and A-delta fibers) appears to be the

morphological basis of insensitivity to pain and anhidrosis, and is consistent with the loss of unmyelinated and small myelinated fibers in the sural nerve biopsy.
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Ogata, M., N. Misago, et al. (2007). "A case of herpes zoster in a child with congenital insensitivity to pain with anhidrosis." British Journal of Dermatology **156**(5): 1084-1086.

Okuda, K., T. Arai, et al. (2000). "Anaesthetic management of children with congenital insensitivity to pain with anhidrosis." Paediatric Anaesthesia **10**(5): 545-548.

Congenital insensitivity to pain with anhidrosis (CIPA) is a rare sensory neuropathy, which affects patients' pain sensation and thermoregulation. There are several issues to consider when planning anaesthesia for those with this congenital disorder. Over a 20-year period, six patients with CIPA underwent 20 surgical procedures under general anaesthesia in our institution. We analysed our experience with these patients retrospectively. We conclude that patients with CIPA are able to undergo surgical procedures under general anaesthesia without major problems.

Okuno, T., A. Inoue, et al. (1990). "Congenital Insensitivity to Pain with Anhidrosis - a Case-Report." Journal of Bone and Joint Surgery-American Volume **72A**(2): 279-282.

Oliveira, C. R. D., F. A. dos Santos, et al. (2007). "Spinal Anesthesia in a patient with congenital insensitivity to pain with anhidrosis." Anesthesia and Analgesia **104**(6): 1561-1562.

Congenital insensitivity to pain with anhidrosis (CIPA) is a rare, hereditary, autonomic recessive disorder. The inability to perceive pain results from loss of nociceptive afferents, while anhidrosis is caused by loss of innervation to the sweat glands. Insensitivity to pain and mental retardation lead to self-inflicted injuries, corneal lacerations, painless bony fractures, joint deformities with consequent chronic osteomyelitis, and septic arthritis. There are only a few reports on the anesthetic management for patients with CIPA. We describe the anesthetic management of a young woman with CIPA receiving bilateral arthrodesis of the ankle.

Ozbarlas, N., F. Sarikayalar, et al. (1993). "Congenital Insensitivity to Pain with Anhidrosis." Cutis **51**(5): 373-374.

Congenital insensitivity to pain with anhidrosis is a rare disorder. Its primary clinical features include congenital analgesia, which leads to self-mutilation; inability to sweat, which leads to defective thermoregulation; and mental retardation. A five-year-old boy with consanguineous parents and no family history of the disorder presented with ulcerating lesions on both knees and elbows. His family had discovered the lack of sensation to pain and anhidrosis. Physical examination revealed ulcers on both knees and elbows, self-mutilation of the tongue, fingers, and toes: Sensation to touch was intact and lacrimation

was normal. Moderate mental retardation and analgesia were noted in an otherwise normal neurologic examination. The results of electromyographic examination were normal and the application of pilocarpine showed anhidrosis. A skin biopsy specimen was also examined.

Paduano, S., G. Iodice, et al. (2009). "Orthodontic treatment and management of limited mouth opening and oral lesions in a patient with congenital insensitivity to pain: case report." *Journal of Oral Rehabilitation* **36**(1): 71-78.

Congenital insensitivity to pain is a rare clinical syndrome characterized by dramatic impairment of pain perception since birth and is generally caused by a hereditary sensory and autonomic neuropathy with loss of the small-calibre, nociceptive nerve fibres. We report a 9-year-old case, with a generalized congenital insensitivity to pain. The patient was referred to our Department by a private orthodontist for severe limited mouth opening and multiple oral ulcers which greatly worsened after starting the orthodontic treatment. The management of his oral lesions of the limited mouth opening and of the orthodontic treatment are described. The management approach aimed to improve mandibular range of motion and associated stretching and a self-modeling mouthguard to avoid cheek self-biting. This protocol allowed continuing the orthodontic treatment to restore the occlusion. Finally, good occlusion, normal function and better quality of patient's life were achieved.

Park, T. J., Y. Lu, et al. (2008). "Selective inflammatory pain insensitivity in the African naked mole-rat (*Heterocephalus glaber*)." *Plos Biology* **6**(1): 156-170.

In all mammals, tissue inflammation leads to pain and behavioral sensitization to thermal and mechanical stimuli called hyperalgesia. We studied pain mechanisms in the African naked mole-rat, an unusual rodent species that lacks pain-related neuropeptides (e.g., substance P) in cutaneous sensory fibers. Naked mole-rats show a unique and remarkable lack of pain-related behaviors to two potent algogens, acid and capsaicin. Furthermore, when exposed to inflammatory insults or known mediators, naked mole-rats do not display thermal hyperalgesia. In contrast, naked mole-rats do display nocifensive behaviors in the formalin test and show mechanical hyperalgesia after inflammation. Using electrophysiology, we showed that primary afferent nociceptors in naked mole-rats are insensitive to acid stimuli, consistent with the animal's lack of acid-induced behavior. Acid transduction by sensory neurons is observed in birds, amphibians, and fish, which suggests that this transduction mechanism has been selectively disabled in the naked mole-rat in the course of its evolution. In contrast, nociceptors do respond vigorously to capsaicin, and we also show that sensory neurons express a transient receptor potential vanilloid channel-1 ion channel that is capsaicin sensitive. Nevertheless, the activation of capsaicin-sensitive sensory neurons in naked mole-rats does not produce pain-related behavior. We show that capsaicin-sensitive nociceptors in the naked mole-rat are functionally connected to superficial dorsal horn neurons as in mice. However,

the same nociceptors are also functionally connected to deep dorsal horn neurons, a connectivity that is rare in mice. The pain biology of the naked mole-rat is unique among mammals, thus the study of pain mechanisms in this unusual species can provide major insights into what constitutes "normal" mammalian nociception.

Parvari, R., J. Levy, et al. (2001). "Reply to the letter to the editor by Toscano and Andria - "Congenital insensitivity to pain with anhidrosis: An NGF/TrkA-related disorder"." American Journal of Medical Genetics **99**(2): 165-165.

Philp, R. (1997). "Pain + The insensitivity Tylenol has displayed with its TV ad is a blast at ballett." Dance Magazine **71**(5): 7-7.

Planas, M. E., P. Gonzalez, et al. (1992). "Noninvasive Percutaneous Induction of Topical Analgesia by a New Type of Drug Carrier, and Prolongation of Local Pain Insensitivity by Anesthetic Liposomes." Anesthesia and Analgesia **75**(4): 615-621.

We studied the duration of action and permeability of common analgesics and local anesthetics applied dermally via new carriers-transfersomes-in rats and humans. The therapeutic potential of analgesic transfersomes was evaluated in Sprague-Dawley rats subjected to heat and pressure stimuli. Results were compared with those obtained from administration of lidocaine-containing standard liposomes. In rats, subcutaneous injections of 2% lidocaine solution and of liposomal or transfersomal suspension resulted in a strong initial analgesic effect that decayed within 6-7 min. Characteristic withdrawal time is approximately 30 s. Dermally applied analgesic transfersomes, by contrast, increased heat stimulus reaction to >70 s, 130% longer than in controls that received a placebo or a standard aqueous lidocaine solution. In humans, we tested two groups of nine male and female volunteers, aged between 25 and 60 yr, for pain-suppressing activity assessed by the pinprick method. Each subject received a total of 0.5 mL of a transfersomal preparation containing 7% lidocaine or 4% tetracaine over a forearm area of 9 cm. We conclude that the effectiveness of dermally applied anesthetic transfersomes is similar to that of the corresponding subcutaneous injections of similar drug quantities and that optimally designed transfersomes offer a suitable and promising means for the noninvasive treatment of local pain with direct, topical drug application.

Potvin, S. (2011). "Pain insensitivity in schizophrenia." Douleur Et Analgesie **24**(3): 152-159.

For a century, schizophrenia patients were thought to be insensitive to pain. Despite some positive evidence, this idea is still controversial. However, it is clear that schizophrenia is not a pain insensitivity syndrome. On neurophysiological basis, our group has gathered evidence linking schizophrenia to deficient excitatory pain mechanisms. Further studies are required, especially because insensitivity to pain in schizophrenia seems to be associated with significant

functional consequences. To cite this journal: Douleur analg. 24 (2011).

Protheroe, S. M. (1991). "Congenital Insensitivity to Pain." Journal of the Royal Society of Medicine **84**(9): 558-559.

Raspall-Chaure, M., M. Del Toro-Riera, et al. (2005). "Congenital insensitivity to pain with anhidrosis associated with congenital myasthenic syndrome." Revista De Neurologia **41**(4): 218-222.

Introduction. Congenital insensitivity to pain with anhidrosis (CIPA) or hereditary sensory and autonomic neuropathy type IV (HSAN IV) is a rare autosomal recessive disorder featuring recurrent fever episodes, inability to sweat, absent response to noxious stimuli, self mutilating behavior and mental retardation. It has been associated with mutations in the NTRK1 gene, located in 1q21-22 and encoding a high-affinity NGF receptor. Case report. An 8-year-old boy, the first son of consanguineous parents, presented with hypotonia, episodic hyperpyrexia and global developmental delay since the neonatal period. In addition to these signs, typical of CIPA, he displayed some other not previously described in this disease, such as facial dysmorphism, a severe swallowing disorder and a myogenic EMG pattern, that led to the initial suspicion of a muscle disorder. Molecular genetics studies uncovered a mutation c.C2011T in exon 15 of the NTRK1 gene. Genetic counselling was possible in the following pregnancy of the couple, where the female fetus was found to harbour the mutation in heterozygosity. The subsequent diagnosis of a congenital myasthenic syndrome in this sister led to neurophysiological re-evaluation of the probandus, in whom a myasthenic pattern of muscle activation was also found. Conclusions. A patient with CIPA and congenital myasthenic syndrome is described. CIPA must be the first diagnostic hypothesis when assessing a patient with insensitivity to pain, anhidrosis and self-mutilation. Given the rather homogeneous presentation of CIPA, the occurrence of atypical myopathic manifestations should raise the suspicion of a concurrent disorder: The present consanguineous kindred illustrates a rare instance of transmission of two mutated alleles giving rise to two unrelated, infrequent neurological syndromes.

Redouani, L., C. Leaute-Labreze, et al. (2002). "Difficulty in the management of congenital insensitivity to pain." Archives De Pediatrie **9**(7): 701-704.

We report a case of hereditary sensitive neuropathy associated with insensitivity to pain in an infant

Case report. - The girl was born after a normal full term pregnancy. She was hospitalized in the neonatal period because of hypotonia and recurrent cyanotic episodes due to false passage. The diagnosis of insensitivity to pain was suspected at nine months of age, as parallel with dentition, multiple mutilations of the tongue and the fingers were observed. The diagnosis was confirmed by biopsy taken from the sural nerve which showed a rarefaction of small myelinated fibres whereas unmyelinated fibres remained unaltered. At the age of

six years, the general condition was good and the neurologic development was satisfactory, neurotrophic and urologic complications currently being the main problem.

Conclusion. - A multidisciplinary and specialized care associated with parental compliance was necessary to minimize the complications of this potentially severe disorder (C) 2002 Editions scientifiques et medicales Elsevier SAS.

Romero, M., R. Simon, et al. (2008). "Dental management of oral self-mutilation in neurological patients: A case of congenital insensitivity to pain with anhidrosis." Medicina Oral Patologia Oral Y Cirugia Bucal **13**(10): E644-E647.

Hereditary sensory and autonomic neuropathy type IV is a rare disease characterized by fever episodes, mental retardation of different intensity, recurrent episodes of fever secondary to anhidrosis, little or no perspiration and congenital insensitivity to pain. Oral self-mutilation is also a characteristic sign. In this article, we present the case of an infant, aged 22 months, who showed these clinical characteristics and was treated with a dental device to prevent the patient from injuring her tongue. This device consisted of two acrylic splints joined at the back in the posterior sector, it provided an anterior open bite and allowed the infant to breathe through her mouth.

The lesions of the patient had improved after using the device but the patient died due to the medical problem.

Neuropathies treatment is a great challenge for medical teams. Dentists should form part of these teams because of the bucal implications that may appear. Different appliances can be designed in order to solve the special problems each case may present.

Rosemberg, S., S. K. N. Marie, et al. (1994). "Congenital Insensitivity to Pain with Anhidrosis (Hereditary Sensory and Autonomic Neuropathy Type-Iv)." Pediatric Neurology **11**(1): 50-56.

Congenital insensitivity to pain with anhidrosis (CIPA, hereditary sensory and autonomic neuropathy type IV) is an exceedingly rare disease. Only 31 cases have been reported. We report a 4-year-old girl with CIPA and include a complete review of the literature. CIBA is a severe autosomal recessive condition that leads to self-mutilation in the first months of life and to bone fractures, multiple scars, osteomyelitis, joint deformities, and limb amputation as the children grow older. Mental retardation is common. Death from hyperpyrexia occurs within the first 3 years of life in almost 20% of the patients. Ultrastructural and morphometric studies of the peripheral nerves demonstrate a loss of the unmyelinated and small myelinated fibers. The actual physiopathologic mechanism of this developmental disorder remains unknown.

Rosenthal, S. H., K. A. Porter, et al. (1990). "Pain Insensitivity in Schizophrenia - Case-Report and Review of the Literature." General Hospital Psychiatry **12**(5): 319-322.

Rozentsveig, V., A. Katz, et al. (2004). "The anaesthetic management of patients with congenital insensitivity to pain with anhidrosis." *Pediatric Anesthesia* **14**(4): 344-348.

Background: Congenital insensitivity to pain with anhidrosis (CIPA, or hereditary sensory and autonomic neuropathy type IV) is a rare, autosomal recessive disease, related to a mutation in the TrkA gene, characterized by inability to sweat, insensitivity to pain and recurrent episodes of hyperpyrexia. There are two Bedouin tribes in Israel with different mutations of the TrkA gene: one in the southern region and the other in the northern region. The Soroka University Medical Center is the referral centre for the entire southern region of Israel. One in 4500 anaesthesia cases involves a patient with CIPA.

Methods: We reviewed 40 anaesthesia records of 20 patients with CIPA for anaesthetic technique and incidence of side-effects.

Results: Sixteen patients developed complications in the immediate perioperative period: mild hypothermia in one patient and cardiovascular events in 15 others with one case of cardiac arrest. These complications were unrelated to the anaesthetic drug administered. There were no events of hyperthermia or postoperative nausea.

Conclusions: Cardiovascular complications following anaesthesia are common in patients with the southern Israel variant of CIPA. Hyperthermia, previously recognized as a major concern in patients with congenital insensitivity to pain with anhydrous, was not seen in our patients. We conclude that cardiovascular involvement is frequently encountered in CIPA patients following anaesthesia and is the major concern in their anaesthetic management.

Russ, M. J., S. S. Campbell, et al. (1999). "EEG theta activity and pain insensitivity in self-injurious borderline patients." *Psychiatry Research* **89**(3): 201-214.

The principal aim of this study was to investigate possible neurophysiological underpinnings of self-injurious behavior in women with borderline personality disorder (BPD). Pain report and EEG power spectrum density during a laboratory pain procedure, a 4-min 10 degrees C cold presser test (CPT), were compared among four groups; female inpatients with BPD who do (BPD-P group, n = 22) and do not (BPD-NP group, n = 19) report pain during self-injury, female inpatients with major depression (n = 15), and normal women (n = 20). The BPD-NP group reported less pain intensity during the CPT compared to the other groups. Total absolute theta power was significantly higher in the BPD-NP group compared to the Depressed (P = 0.0074) and Normal (P = 0.0001) groups, with a trend toward being significantly higher compared to the BPD-P group (P = 0.0936). Dissociative Experience Scale scores were significantly higher in the BPD-NP group compared to the Depressed and Normal groups (maximum P = 0.0004), and significantly higher in the BPD-P group compared to the Normal group (P = 0.0016). Beck Depression Inventory and Sheehan Patient Rated Anxiety Scale scores were significantly lower in the Normal group compared to all patient groups. Theta activity was significantly correlated with pain rating (Pearson partial r = -0.43, P = 0.0001) and Dissociative Experiences Scale score

(Pearson partial $r = 0.32$, $P = 0.01$). (C) 1999 Elsevier Science Ireland Ltd. All rights reserved.

Safari, A., A. A. Khaledi, et al. (2011). "Congenital Insensitivity to Pain with Anhidrosis (CIPA): A Case Report." Iranian Red Crescent Medical Journal **13**(2): 134-138.

Congenital insensitivity to pain with anhidrosis (CIPA) is a rare disorder characterized by episodes of fever and the inability to sense of pain despite the fact that all other sensory modalities remain intact or minimally impaired. The patient also may exhibit the signs of self-mutilation, mental retardation and little or no perspiration. We present a 10 years old Iranian patient diagnosed with CIPA with the above-mentioned clinical characteristics. The prosthetic treatment and the subsequent six month follow-up are discussed. Follow-up of the patient revealed that, with the use of this prosthesis, the patient's oral function and esthetics were established and the mouth lesions improved. Therefore especial dental management of CIPA patients according to their mental status, age, oral and dental condition is essential for solving the specific problems each case may present and the full mouth teeth extraction should be considered as the last treatment.

Sandroni, P., D. P. Martin, et al. (2006). "Congenital idiopathic inability to perceive pain: A new syndrome of insensitivity to pain and itch with preserved small fibers." Pain **122**(1-2): 210-215.

Individuals vary widely in their sensitivity to painful stimuli. Some exhibit heightened reactions to pain (hyperpathia), while others show relative indifference. Although multiple factors may be responsible for these differences, varying sensitivities to pain also can be due to underlying differences in nociceptive neurophysiology. We present here the case of an individual with an apparent congenital inability to perceive pain. This patient appears to be different from other reported cases of insensitivity to pain described in the medical literature. He exhibited no evidence of an abnormality of the peripheral or autonomic nervous system and no apparent abnormality of the central nervous system other than isolated deficits in pain and temperature perception. Since pain is a subjective phenomenon, there is no definitive way to assess this patient's reported inability to perceive painful somatic stimulation, but available evidence suggests he has a defect in the supraspinal processing of nociceptive stimuli which renders him insensitive to pain. This raises the possibility of either deficient central nociceptive functioning or aberrant endogenous anti-nociceptive functioning. (c) 2006 International Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.

Sarasola, E., J. A. Rodriguez, et al. (2011). "A short in-frame deletion in NTRK1 tyrosine kinase domain caused by a novel splice site mutation in a patient with congenital insensitivity to pain with anhidrosis." Bmc Medical Genetics **12**.

Background: Congenital insensitivity to pain with anhidrosis (CIPA) is a rare

autosomal recessive genetic disease characterized by the lack of reaction to noxious stimuli and anhidrosis. It is caused by mutations in the NTRK1 gene, which encodes the high affinity tyrosine kinase receptor I for Neurotrophic Growth Factor (NGF).

Case Presentation: We present the case of a female patient diagnosed with CIPA at the age of 8 months. The patient is currently 6 years old and her psychomotor development conforms to her age (RMN, SPECT and psychological study are in the range of normality). PCR amplification of DNA, followed by direct sequencing, was used to investigate the presence of NTRK1 gene mutations. Reverse transcriptase (RT)-PCR amplification of RNA, followed by cloning and sequencing of isolated RT-PCR products was used to characterize the effect of the mutations on NTRK1 mRNA splicing. The clinical diagnosis of CIPA was confirmed by the detection of two splice-site mutations in NTRK1, revealing that the patient was a compound heterozygote at this gene. One of these alterations, c.574+1G > A, is located at the splice donor site of intron 5. We also found a second mutation, c.2206-2 A > G, not previously reported in the literature, which is located at the splice acceptor site of intron 16. Each parent was confirmed to be a carrier for one of the mutations by DNA sequencing analysis. It has been proposed that the c.574+1G > A mutation would cause exon 5 skipping during NTRK1 mRNA splicing. We could confirm this prediction and, more importantly, we provide evidence that the novel c.2206-2A > G mutation also disrupts normal NTRK1 splicing, leading to the use of an alternative splice acceptor site within exon 17. As a consequence, this mutation would result in the production of a mutant NTRK1 protein with a seven aminoacid in-frame deletion in its tyrosine kinase domain.

Conclusions: We present the first description of a CIPA-associated NTRK1 mutation causing a short interstitial deletion in the tyrosine kinase domain of the receptor. The possible phenotypical implications of this mutation are discussed.

Sasnur, A. H., P. A. Sasnur, et al. (2011). "Congenital insensitivity to pain and anhidrosis." *Indian Journal of Orthopaedics* **45**(3): 269-271.

Congenital insensitivity to pain and anhidrosis (CIPA) is a rare reported entity characterised by disturbance in the pain and temperature perception due to involvement of the autonomic and sensory nervous system. It is an autosomal recessive trait with several defects of the gene NTRK1 coding for the neurotrophic tyrosine kinase a nerve growth factor receptor on chromosome 1q21-q22. Traumatic fractures are common and, because of lack of pain, may go unrecognised for prolonged periods, resulting in nonunion or pseudoarthrosis. A Charcot joint may be the end result. Treatment complications are very common in these patients and range from infection to wound breakdown to failure of fixation. We report here a rare case of CIPA in a 9-year-old girl and her younger male sibling with generalised absence of pain, anhidrosis and its orthopaedic implications.

Sato, Y., Y. Tsuboi, et al. (2004). "Anti-apoptotic effect of nerve growth factor is lost in congenital insensitivity to pain with anhidrosis (CIPA) B lymphocytes." Journal of Clinical Immunology **24**(3): 302-308.

Congenital insensitivity to pain with anhidrosis (CIPA) is identified as a genetic disorder of mutations in the human TrkA known as high affinity receptor of nerve growth factor (NGF). NGF signal through TrkA promotes anti-apoptotic activity in hematopoietic cells including B lymphocytes. Here we studied the effect of NGF on anti-apoptotic activity by using human EBV-immortalized B lymphoblastoid cell lines (EB-LCLs) derived from a patient with CIPA and the associated carriers of CIPA. The TrkA(mt/mt) EB-LCL derived from the CIPA patient and the TrkA(wt/mt) EB-LCL derived from the carrier with the heterozygous TrkA mutation did not show any responses to NGF on anti-apoptotic activity. We concluded that this phenomenon is one of the pathogeneses of CIPA.

Schalka, M. M. S., M. S. N. P. Correa, et al. (2006). "Congenital insensitivity-to-pain with anhidrosis (CIPA): A case report with 4-year follow-up." Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontics **101**(6): 769-773.

Congenital Insensitivity-to-pain with anhidrosis (CIPA) is a rare disorder in which pain perception is absent from birth, despite the fact that all other sensory modalities remain intact or minimally impaired and tendon reflexes are present. The challenge in dentistry is to manage the self-mutilation behavior avoiding serious damages especially to oral structures, hands and fingers. A Brazilian case of CIPA is presented and discussed with clinical documentation of the oral-related problems over a 4-year follow-up. A conservative treatment (mouthguard-like appliance) was proposed with the objective to avoid full mouth extraction.

Schreiber, R., J. Levi, et al. (2003). "Impaired first phase insulin response to intravenous glucose tolerance test in children with congenital insensitivity to pain and anhidrosis." Diabetes **52**: A546-A546.

Schreiber, R., J. Levy, et al. (2005). "Decreased first phase insulin response in children with congenital insensitivity to pain with anhidrosis." Journal of Pediatric Endocrinology & Metabolism **18**(9): 873-877.

Nerve growth factor (NGF) and its receptor tyrosine kinase A (TrkA) participate in endocrine pancreas morphogenesis and insulin secretion in vitro. Mutations in the TrkA gene cause the syndrome of congenital insensitivity to pain with anhidrosis (CIPA). We hypothesized that CIPA may represent a natural model for impaired NGF effect on insulin secretion in humans. Glucose challenge tests were performed in seven children with CIPA. We calculated the first phase insulin response (FPIR), the second phase insulin response (SPIR) and glucose disposal rate. FPIR was impaired in four and borderline in two patients. SPIR and glucose disposal rate were within the normal range. Oral glucose tolerance test was normal in all patients. Low FPIR in CIPA suggests for the first time that the NGF-TrkA pathway may play a role in insulin secretion in response to glucose

challenge in humans. Additional studies on the clinical significance of NGF-TrkA effects on insulin secretion are required.

Schulman, H., V. Tsodikow, et al. (2001). "Congenital insensitivity to pain with anhidrosis (CIPA): the spectrum of radiological findings." *Pediatric Radiology* **31**(10): 701-705.

Background. Congenital insensitivity to pain with anhidrosis (CIPA) is an exceedingly rare, hereditary, sensory autonomic neuropathy (HSAN).

Aim. To evaluate the various skeletal manifestations and cranial CT features in children affected by CIPA.

Materials and methods. In the semidesert area of the Negev, the Bedouin tribes constitute a closed society where consanguineous marriages are the custom. This has resulted in a group of 20 children being affected by this rare autosomal recessive HSAN. The skeletal surveys and CT scans of these 20 Bedouin patients, 12 girls and 8 boys, ages ranging between 1 month and 8 years, were retrospectively analysed. Cranial CT scans were performed in ten children because of neonatal hypotonia and psychomotor retardation. The skeletal findings were classified as follows: fractures, joint deformities, joint dislocations, osteomyelitis, avascular necrosis and acro-osteolysis.

Results. All 20 patients had fractures of the extremities and acro-osteolysis of the fingers. Six had joint deformities. Three children had recurrent hip joint dislocations and another three had avascular necrosis. Ten patients presented with osteomyelitis of the limbs, acetabulum and scapula. The cranial CT scans disclosed mild brain volume loss with some ventriculomegaly.

Conclusions. CIPA is a severe autosomal recessive condition that leads to self-mutilation early in life and to fractures, osteomyelitis and limb amputation in older children. Mental retardation is common. Death from hyperpyrexia occurs in almost 20% of patients in the first 3 years of life.

Serratrice, G. (1992). "Congenital Indifference and Congenital Insensitivity to Pain." *Bulletin De L Academie Nationale De Medecine* **176**(5): 609-618.

Shaaban, H., A. Bayat, et al. (2002). "Necrotising fasciitis in an infant with congenital insensitivity to pain syndrome." *British Journal of Plastic Surgery* **55**(2): 160-163.

We present a rare case of necrotising fasciitis in an infant with congenital insensitivity to pain syndrome. The aetiology, diagnosis and management of necrotising fasciitis in children are compared with those in adults. In contrast to adults, children affected by necrotising fasciitis are usually previously healthy and have no predisposing factors. Early diagnosis, intravenous antibiotics and aggressive surgical debridement are mandatory for an optimal outcome. (C) 2002 The British Association of Plastic Surgeons.

Shatzky, S., S. Moses, et al. (2000). "Congenital insensitivity to pain with anhidrosis (CIPA) in Israeli-Bedouins: Genetic heterogeneity, novel mutations in the TRKA/NGF receptor gene, clinical findings, and results of nerve conduction studies." *American*

Journal of Medical Genetics **92**(5): 353-360.

Congenital insensitivity to pain with anhidrosis (CIPA), a rare and severe disorder, comprises absence of sensation to noxious stimuli, inability to sweat, and recurrent episodes of hyperthermia. It has a relatively high prevalence in the consanguineous Israeli-Bedouins. Clinical studies of 28 patients are reported here. Using the linkage analysis approach, we linked the disease in 9 of 10 unrelated Israeli-Bedouin families with CIPA to the TrkA gene, which encodes the receptor for nerve growth factor. In one family, linkage was excluded, implying that another gene, yet unidentified, is involved. Two new mutations in the tyrosine kinase domain of the TrkA gene were identified in our CIPA patients: a 1926-ins-T in most of the southern Israeli-Negev CIPA patients, and a Pro- 689-Leu mutation in a different isolate of Bedouins in northern Israel. Eight prenatal diagnoses were made in the southern Israeli-Negev Bedouins, two by linkage analysis and six by checking directly for the 1926-ins-T mutation. Three polymorphisms in the TrkA protein kinase encoding domain were also observed. *Am. J. Med. Genet.* **92**: 353-360, 2000. (C) 2000 Wiley-Liss, Inc.

Shea, K. G. and L. Showalter (2003). "Iliarov method of repair of Achilles tendon rupture in a patient with congenital insensitivity to pain - A case report." Journal of Bone and Joint Surgery-American Volume **85A**(9): 1816-1818.

Shorer, Z., S. W. Moses, et al. (2001). "Neurophysiologic studies in congenital insensitivity to pain with anhidrosis." Pediatric Neurology **25**(5): 397-400.

Thirteen patients with congenital insensitivity to pain and anhidrosis, carrying a mutation at the TRK-A gene, were studied. Neurologic examination revealed vestigial pain sensitivity, suggesting an incomplete involvement of the affected nerves. All 13 patients manifested normal electrophysiologic studies but striking absence of sympathetic skin responses. We suggest the use of the sympathetic skin response test in the clinical evaluation of patients suspected of having congenital insensitivity to pain and anhidrosis. (C) 2001 by Elsevier Science Inc. All rights reserved.

Sipahi, T., N. Okumus, et al. (1999). "Congenital insensitivity to pain with anhidrosis: report of a 68-day-old case." European Journal of Pediatrics **158**(3): 268-269.

Sliwa, J. A., D. Rippe, et al. (2008). "Charcot spine in a person with congenital insensitivity to pain with anhidrosis: A case report of re-diagnosis." Archives of Physical Medicine and Rehabilitation **89**(3): 568-571.

We report the case of a 43-year-old woman referred for evaluation of worsening gait. Her initial evaluation led to a diagnosis of a Charcot spine and 2 spinal stabilization surgeries. Because no clear cause for the Charcot spine could be determined from the patient's history or initial evaluation, an extensive diagnostic work-up was undertaken, which ultimately led to a diagnosis of congenital insensitivity to pain with anhidrosis (CIPA). This diagnosis was known and

confirmed by the patient's parents but was unknown to the patient and her treating physicians. Unique to this case is not only the significant medical implications and the value of the re-diagnosis and confirmation of this rare condition, but also the rarer occurrence of a Charcot spine in a person with CIPA.

Staud, R., D. D. Price, et al. (2011). "Two novel mutations of SCN9A (Nav1.7) are associated with partial congenital insensitivity to pain." European Journal of Pain **15**(3): 223-230.

Insensitivity to pain is a rare disorder that is commonly associated with Hereditary Sensory and Autonomic Neuropathies (HSAN I-V) resulting often in autonomic dysfunction and premature death. Very few individuals have been reported with pain insensitivity lacking such autonomic neuropathies. We performed genetic, neurologic, psychological, and psychophysical evaluations in such an individual (OMIM 243000) and her first degree relatives. Sequence analysis of genomic DNA revealed two novel SCN9A mutations in this index case (IC). One was a non-conservative missense mutation (C1719R) in exon 26 present only in the IC and one parent. Further sequence analysis of the child's DNA revealed a 1-bp splice donor deletion in intron 17 which was also present in the other parent and one sibling. Detailed psychophysical testing was used to phenotypically characterize the IC, her family members, and 10 matched normal controls. Similar to family members and controls the IC showed normal somatosensory functioning for non-nociceptive mechanoreception and warmth. However, she demonstrated diminished ability to detect cool temperatures combined with profound deficits in heat and mechanical nociception. Congenital insensitivity to pain in our IC was associated with two novel SCN9A mutations which most likely resulted in a Nav1.7 channelopathy. However, in contrast to individuals with other SCN9A mutations, the observed pain insensitivity was relative and not absolute, which may be consistent with hypomorphic effects of one or both mutations. The ability to sense at least some danger signals may be advantageous and ameliorate the otherwise increased morbidity and mortality of some individuals with congenital insensitivity to pain. (c) 2010 European Federation of International Association for the Study of Pain Chapters. Published by Elsevier Ltd. All rights reserved.

Suominen, P. (2007). "Anesthesia for congenital insensitivity to pain with anhidrosis - Reply." Pediatric Anesthesia **17**(2): 193-193.

Suriu, C., M. Khayat, et al. (2009). "Skoura - a genetic island for congenital insensitivity to pain and anhidrosis among Moroccan Jews, as determined by a novel mutation in the NTRK1 gene." Clinical Genetics **75**(3): 230-236.

Suriu C, Khayat M, Weiler M, Kfir N, Cohen C, Zinger A, Aslanidis C, Schmitz G, Falik-Zaccai TC. Skoura - a genetic island for congenital insensitivity to pain and anhidrosis among Moroccan Jews, as determined by a novel mutation in the NTRK1 gene. *Clin Genet* 2009; 75: 230-236. (C) Blackwell Munksgaard, 2008

Congenital insensitivity to pain with anhidrosis (CIPA) or hereditary sensory and autonomic neuropathy type IV is a rare, autosomal recessive neurologic disorder, characterized by absence of reaction to painful stimuli, mental retardation, self-mutilating behavior, anhidrosis, and recurrent episodes of hyperthermia. Mutations in the neurotrophic tyrosine kinase receptor 1, a receptor phosphorylated by nerve growth factor, have been documented in diverse ethnic groups. We identified the same novel nonsense mutation in two unrelated families of Moroccan Jewish descent, each with two affected siblings. This possible founder mutation may trace to the rural Jewish village in southern Morocco from where both these families originated. Genetic screening for the causative mutation among 300 unrelated Moroccan Jews did not reveal carriers for the causative mutation, thus excluding high risk for CIPA in this ethnic subpopulation.

Szoke, G., A. RenyiVamos, et al. (1996). "Osteoarticular manifestations of congenital insensitivity to pain with anhidrosis." *International Orthopaedics* **20**(2): 107-110.

We report the case history of a boy who suffered from congenital insensitivity to pain with anhidrosis. We discuss the orthopaedic disorders occurring in 21 cases reported in the literature.

Sztrihai, L., G. G. Lestringant, et al. (2001). "Congenital insensitivity to pain with anhidrosis." *Pediatric Neurology* **25**(1): 63-66.

Congenital insensitivity to pain with anhidrosis is an autosomal-recessive disorder resulting from defective neural crest differentiation with loss of the first-order afferent system, which is responsible for pain and temperature sensation. There is also a neuronal loss in the sympathetic ganglia. Lack of sweating, hyperthermia, and infections of bones are main features of the disorder; however, contradictory results have been published regarding eccrine sweat gland innervation. A 5-year-old male patient with typical clinical manifestations of congenital insensitivity to pain with anhidrosis is presented.

Immunohistochemistry with antibodies against S100 protein and neuron-specific enolase failed to reveal nerve fibers in the vicinity of the eccrine sweat glands. The roles of the nerve growth factor and tyrosine kinase receptor gene mutations in the pathogenesis of the disease are also discussed. (C) 2001 by Elsevier Science Inc. All rights reserved.

Tachi, N., K. Ohya, et al. (1995). "Muscle Involvement in Congenital Insensitivity to Pain with Anhidrosis." *Pediatric Neurology* **12**(3): 264-266.

A patient with congenital insensitivity to pain with anhidrosis, who had characteristic clinical features and biopsied sural nerve, is presented, Nerve pathology findings indicated a loss of the small myelinated and unmyelinated fibers, Biopsied muscle disclosed a marked variation in fiber size, some small fibers with central nuclei, and a small number of small angulated fibers, consistent with neurogenic and myogenic changes. Many patients with

congenital insensitivity to pain with anhidrosis had muscle weakness and absent or decreased deep tendon reflexes with normal nerve conduction velocity, We confirmed that lack of small myelinated fibers in motor neurons resulted in a striking change of muscle in our patient.

Tanaka, T., T. Satoh, et al. (2012). "Congenital insensitivity to pain with anhidrosis: a case with preserved itch sensation to histamine and partial pain sensation." British Journal of Dermatology **166**(4): 888-891.

Congenital insensitivity to pain with anhidrosis is a rare autosomal recessive hereditary disorder that is characterized by having both sensory neuropathy and anhidrosis. A 6-year-old Japanese boy presented with recurrent fever, lack of sweating, occult bone fractures and impaired pain sensation without mental retardation. Genetic analyses revealed compound heterozygous mutations in the NTRK1 gene that encodes TrkA, which is a receptor for nerve growth factor. While there were no apparent changes in the patient's dermal eccrine glands, the quantitative sudomotor axon reflex test with acetylcholine chloride revealed a complete loss of both the axon reflex-mediated and the directly activated sweat responses. On the other hand, the histamine prick test induced a normal weal response surrounded by a flare phenomenon. Notably, the patient felt both an itch sensation after histamine and a burning sensation after topical capsaicin application. Consistent with these findings, PGP9.5+ nerve fibre innervation of the papillary dermis was observed, although the fibres were completely absent around the eccrine glands. These findings suggest that there was a partial preservation of the nerve endings that express the H-1 receptor and/or TRPV1 in the upper dermis, even though there were mutations of the NTRK1 gene in this case.

Tellez, M. J., F. Axelrod, et al. (2009). "The R3 component of the electrically elicited blink reflex is present in patients with congenital insensitivity to pain." Pain **141**(1-2): 178-180.

To clarify whether the R3 component of the electrically elicited blink reflex is a nociceptive response we studied two patients with congenital insensitivity to pain due to the impaired development of A delta and C nerve fibers (hereditary sensory and autonomic neuropathy types III and IV). We postulated that if the R3 component is a nociceptive reflex, it should be absent in these patients. The R3 responses were elicited in both sides in both the patients at all intensities, strongly suggesting that the R3 component of the blink reflex is not a nociceptive response. (C) 2008 International Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.

Tomioka, T., Y. Awaya, et al. (2002). "Anesthesia for patients with congenital insensitivity to pain and anhidrosis: A questionnaire study in Japan." Anesthesia and Analgesia **94**(2): 271-274.

We investigated the anesthetic management of patients with congenital insensitivity to pain and anhidrosis (CIPA) in Japan. CIPA is a rare inherited

disease characterized by a lack of pain sensation and thermoregulation. Although lacking pain sensation, some patients do have tactile hyperesthesia. Thus, anesthetics are a necessity during operations. We also determined that because patients with CIPA have problems with thermoregulation, temperature management is a concern during the perioperative period and sufficient sedation is necessary to avoid accidental fractures. Additionally, it was found that the use of muscle relaxants does not present a problem, malignant hyperthermia is not associated with CIPA, and that the possibility of abnormalities in the autonomic nervous system must be taken into consideration. Therefore, patients with CIPA can be safely managed with anesthesia.

Topuz, S., O. Ulger, et al. (2011). "Prosthetic Rehabilitation of a Child With Transfemoral Amputation who had Congenital Insensitivity to Pain With Anhidrosis." Turkiye Fiziksel Tip Ve Rehabilitasyon Dergisi-Turkish Journal of Physical Medicine and Rehabilitation **57**: 366-368.

Congenital insensitivity to pain with anhidrosis is a rare autosomal-recessive disorder characterized by systemic anhidrosis, insensitivity to pain, mental retardation, osteomyelitis, and joint deformities which could result in amputations. Prosthetic rehabilitation is important in patients who had congenital insensitivity to pain with anhidrosis associated with amputation. In this case report, we discuss the effects of anhidrosis, insensitivity to pain and other symptoms on prosthetic fitting and rehabilitation. *Turk J Phys Med Rehab* 2011;57 Suppl 2: 366-8.

Toscano, E. and G. Andria (2001). "Congenital insensitivity to pain with anhidrosis: An NGF/TrkA-related disorder." American Journal of Medical Genetics **99**(2): 164-164.

Toscano, E., R. della Casa, et al. (2000). "Multisystem involvement in congenital insensitivity to pain with anhidrosis (CIPA), a nerve growth factor receptor(Trk A)-related disorder." Neuropediatrics **31**(1): 39-41.

Congenital insensitivity to pain with anhidrosis (CIPA), a rare autosomal recessive disorder, is characterized by insensitivity to pain, self-mutilating behaviour, anhidrosis and recurrent hyperpyrexia. It is a hereditary sensory and autonomic neuropathy, also classified as HSAN, due to a defect of the receptor for nerve growth factor. CIPA is the first human genetic disorder caused by a defect in the neurotrophin signal transduction system. This is the first clinical report of CIPA patients characterized on molecular grounds. The clinical phenotypes of our patients show that CIPA is characterized by a multisystem involvement besides the nervous system, including bone fracture with slow healing, immunologic abnormalities, such as low response to specific stimuli, chronic inflammatory state ending in systemic amyloidosis. The molecular characterization allows a better understanding of most of the clinical features.

Toscano, E., R. Della Casa, et al. (1999). "Multisystem involvement in congenital

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insensitivity to pain with anhidrosis (CIPA), a nerve growth factor receptor (TrkA) related disorder." American Journal of Human Genetics **65**(4): A346-A346.

Toscano, E., A. Simonati, et al. (2003). "Indifference rather than insensitivity to pain - Reply." Annals of Neurology **53**(3): 418-419.

Tsirikos, A. I., O. Haddo, et al. (2004). "Spinal manifestations in a patient with congenital insensitivity to pain." Journal of Spinal Disorders & Techniques **17**(4): 326-330.

Spinal manifestations in congenital insensitivity to pain are relatively uncommon and easily misdiagnosed. We report on a patient with absent protective pain sensation, who developed spinal neuropathic arthropathy. At age 11 years, he presented with a destructive lesion at the L1-L2 level, causing him tingling sensation in both lower limbs. He was treated with combined anteroposterior spinal fusion from T12 to L3 and had full recovery. Five years later, he presented with a long history of clicking in his low back, muscle weakness and paresthesia in both lower extremities during walking, and evidence of Charcot arthropathy at the L4-L5 level, resulting in junctional kyphosis and canal narrowing. Posterior spinal arthrodesis from L3 to the sacrum was performed, due to lack of patient and parental consent for combined anterior decompression/posterior fusion. The patient resumed normal muscle function and his previous level of activities. Spinal complications should be anticipated in this condition and create diagnostic and therapeutic dilemmas. However, surgical management can produce favorable clinical results.

Tuncbilek, G., C. Oztekin, et al. (2005). "Calcaneal ulcer in a child with congenital insensitivity to pain syndrome." Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery **39**(3): 180-183.

Congenital insensitivity to pain with anhidrosis (CIPA) is a rare hereditary sensory neuropathy, comprising congenital insensitivity to pain, anhidrosis, and mental retardation. We present a 4-year-old child with CIPA and a calcaneal ulcer who was treated with double opposing rotation flaps, which eventually healed.

Varshney, M., K. K. Girdhar, et al. (2009). "Anesthetic management of a pediatric patient with congenital insensitivity to pain." Pediatric Anesthesia **19**(5): 552-553.

Vital, A., D. Fontan, et al. (1998). "Congenital insensitivity to pain with anhidrosis. Report of two unrelated cases." Journal of the Peripheral Nervous System **3**(2): 125-132.

Two unrelated female cases of congenital insensitivity to pain with anhidrosis are presented. The first case was born from consanguineous parents. In both cases, onset of manifestation was observed in infancy with automutilation and recurrent fever. Both were mentally retarded. They underwent a peripheral nerve biopsy respectively at 3 and 33 years. A dramatic loss of unmyelinated fibers was observed in both cases. Myelinated fibers were also moderately reduced in

number, especially those of smallest diameter; this loss was more marked in the second patient who was adult when the peripheral nerve was studied. Clusters of regenerating myelinated fibers were seen in both cases. Such histological observations might suggest a slowly progressive disorder. The cases are discussed together with previous reports dealing with congenital insensitivity to pain.

Wenkert, D., W. H. McAlister, et al. (2003). "Dominantly-inherited congenital insensitivity to pain manifesting with recurrent fractures: A new entity." Journal of Bone and Mineral Research **18**: S388-S388.

Xu, J., R. J. Leo, et al. (2002). "Linkage studies of delta opioid receptor gene and pain insensitivity in schizophrenia." American Journal of Medical Genetics **114**(7): 878-879.

Xu, X. J., M. J. C. Puke, et al. (1993). "Up-Regulation of Cholecystokinin in Primary Sensory Neurons Is Associated with Morphine Insensitivity in Experimental Neuropathic Pain in the Rat." Neuroscience Letters **152**(1-2): 129-132.

We examined the distribution of mRNA for the peptide cholecystokinin (CCK) with in situ hybridization in adult rat lumbar dorsal root ganglia following unilateral section of the sciatic nerve, as well as the effect of systemic CI 988, a selective antagonist of the CCK type B receptor, applied alone or in combination with intrathecal (i.t.) morphine, on the self-mutilating behavior of rats (autotomy) after axotomy, a sign of neuropathic pain and/or dysesthesia. There was a dramatic increase in the number of neurons in dorsal root ganglia synthesizing the peptide cholecystokinin (CCK) after sciatic nerve section. Furthermore, the autotomy behavior of rats was significantly inhibited by chronic i.t. administration of morphine in conjunction with subcutaneous (s.c.) injection of CI 988. Neither i.t. morphine nor s.c. CI 988 alone produced a comparable effect on autotomy. Our results suggested that up-regulation of the mRNA for CCK in primary afferents after nerve injury may be related to the clinical phenomenon of opioid insensitivity. Thus, coadministration of CCK antagonists in combination with opioids may offer a new approach in treating neuropathic pain.

Yagev, R., J. Levy, et al. (1999). "Congenital insensitivity to pain with anhidrosis: Ocular and systemic manifestations." American Journal of Ophthalmology **127**(3): 322-326.

(PURPOSE)-P-: To report the incidence and severity of the ophthalmologic manifestations in patients with congenital insensitivity to pain with anhidrosis.
(METHODS)-M-: Fifteen Bedouin children with congenital insensitivity to pain with anhidrosis underwent complete ocular examination, including refraction and assessment of corneal sensation, and a detailed neurologic examination, including measurement of median nerve motor and sensory conduction. Patients with corneal ulcers were treated appropriately.
(RESULTS)-R-: In the 15 children (eight girls and seven boys, with a mean age of 3.75 +/- 2.67 years; range, 9 months to 9 years), corneal sensation was absent in both

eyes. Corneal opacities were present in 10 children, five of whom had bilateral corneal opacities. Corneal ulcers were found in seven children, two of whom had bilateral ulcers, and in three children the ulcers recurred. The corneal ulcers were characterized by very poor healing. The surgical procedures included four lateral tarsorrhaphies, two corneal patch grafts, and one penetrating keratoplasty. All the patients had self-inflicted injuries varying from skin ulcers, burns, and bone fractures to autoamputations of fingertips and tongues. Many patients showed delayed healing and repair of bone and skin injuries. All patients had attacks of hyperpyrexia, moderate mental retardation, and hypotonicity with absent superficial sensation to light touch. Results of median nerve motor and sensory conduction studies were within normal limits,

(CONCLUSIONS)-C-: The patients with congenital insensitivity to pain and anhidrosis and absent corneal sensation showed a marked tendency to develop corneal ulcers that healed poorly. Congenital insensitivity to pain and anhidrosis, although rare, should be considered in the differential diagnosis of neurotrophic keratitis, (C) 1999 by Elsevier Science Inc. All rights reserved.

Yotsumoto, S., M. Setoyama, et al. (1998). "A novel point mutation affecting the tyrosine kinase domain of the nerve growth factor receptor gene, TRKA, in a family with congenital insensitivity to pain with anhidrosis." Journal of Investigative Dermatology **110**(4): 615-615.

Yotsumoto, S., M. Setoyama, et al. (1999). "A novel point mutation affecting the tyrosine kinase domain of the TRKA gene in a family with congenital insensitivity to pain with anhidrosis." Journal of Investigative Dermatology **112**(5): 810-814.

A nerve growth factor receptor encoded by the TRKA gene plays an important part in the formation of autonomic neurons and small sensory neurons in dorsal root ganglia and in signal transduction through its intracytoplasmic tyrosine kinase domain. Recently, three mutations in the tyrosine kinase domain of TRKA have been reported in patients with congenital insensitivity to pain with anhidrosis, which is an autosomal recessive disorder characterized by recurrent fever due to absence of sweating, no reaction to noxious stimuli, self-mutilating behavior, and mental retardation. We examined the TRKA gene in five generations of a large Japanese family with many consanguineous marriages who live in a small remote island of the southern part of Japan. We found a novel point mutation at nucleotide 1825 (A-->G transition) resulting in Met-581-Val in the tyrosine kinase domain. Two of the three affected patients were homozygous for this mutation; however, the third affected patient was heterozygous. Further analysis revealed that the third patient was a compound heterozygote with the Met-581-Val mutation in one allele and with a single base C deletion mutation at nucleotide 1726 in exon 14 in the other allele, resulting in a frameshift and premature termination codon.

Zafeiriou, D. I., E. Vargiami, et al. (2004). "Self-mutilation and mental retardation: Clues

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to congenital insensitivity to pain with anhidrosis." *Journal of Pediatrics* **144**(2): 284-284.

Zhou, T. H., X. H. Ren, et al. (1997). "Retardation of pain development: a case of recovery from congenital insensitivity to pain." *Acta Anaesthesiologica Scandinavica* **41**(8): 1077-1079.

Congenital analgesia is a rare genetic disorder. We report here that a 12-year-old boy was able to recover from congenital insensitivity to pain. Neurological examinations revealed that there was a 'stocking' distribution of pain decrement on the lower extremities under the patient's knee joints. Magnetic Resonance Imaging (MRI) of his brain showed gyrus thinning with sulcus widening at both sides of the parietal lobe. Southern blot hybridization probed with cDNAs of various opioid receptors did not detect any significant abnormality. Our results suggest that this rare case may not be genetically determined.

Zlotnik, A., S. E. Gruenbaum, et al. (2010). "Risk of aspiration during anesthesia in patients with congenital insensitivity to pain with anhidrosis: case reports and review of the literature." *Journal of Anesthesia* **24**(5): 778-782.

Congenital insensitivity to pain with anhidrosis (CIPA) is a rare autosomal recessive disease, characterized by episodes of unexplained fever, anhidrosis, pain insensitivity despite intact tactile perception, self-mutilating behavior, mental retardation, and autonomic nervous system (ANS) abnormalities. We present a case series of three patients with CIPA who underwent semielective orthopedic surgery under general anesthesia complicated by intraoperative regurgitation, and subsequent aspiration in two of the three cases. All three patients were nil per os (NPO) for at least 8 h prior to surgery. Two patients had their airways maintained with a laryngeal mask airway (LMA), and one patient had an endotracheal tube (ETT). The patients with an LMA suffered aspiration of gastric contents and subsequently developed hypoxic cardiac arrest. Although the patient with an ETT in situ regurgitated intraoperatively, the presence of the ETT prevented aspiration and any further potential complications. We review the perioperative complications typically observed in patients with CIPA and discuss the risks of using an LMA in these patients. We recommend that patients with CIPA always should be considered as having a "full stomach", regardless of the duration of their NPO status, due to their coexisting ANS abnormalities. Therefore, rapid-sequence induction with an ETT should be utilized for the anesthetic management in every patient with CIPA.