



# Congenital Insensitivity to Pain with Anhidrosis

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Congenital insensitivity to pain with anhidrosis (CIPA) is a rare autosomal recessive disorder. It is part of the hereditary sensory and autonomic neuropathy diseases (HSAN); specifically it is known as HSAN type IV. CIPA is characterized by the absence of reaction to noxious stimuli, the inability to sweat, hyperpyrexia, mild retardation, and self-mutilating behavior. Thus the name congenital, meaning present from birth; insensitivity to pain, meaning inability to feel pain; anhidrosis, the inability to sweat. This inability causes the hyperpyrexia or high fever because the individual isn't able to give off heat through sweating.

Many would feel that it would be a great thing not to feel physical pain. Pain though, is a way one's body tells it that something is wrong. An individual touching a hot stove would feel instant pain, forcing them to pull their hand away before causing too much damage. An individual with CIPA would keep their hand on the hot stove because they cannot feel it burning their hand. This is an important disease to study because by studying it, individuals can learn more about genetic diseases, how neurons and nerves work and communicate with the body and maybe find a cure for this disease.

CIPA is a fairly recently discovered disease. Within the past 10 years it has been found that CIPA is caused by a mutation to the TrkA (NTRK1) gene. This gene is responsible for encoding the receptor tyrosine kinase for nerve growth factor (6). Nerve growth factor is critical for the formation of autonomic neurons and small sensory neurons in the dorsal root ganglia. TrkA is part of the TRK proto-oncogene family and is expressed in neurons that sense temperature and noxious stimuli which is why a mutation to this gene causes the inability to feel pain (6). Mardy first reported that there is a lack of innervation with eccrine sweat glands which affects the individual's ability to sweat (4).

CIPA is a very rare disease; there are only around 60 documented cases in the United States

and around 300 worldwide (3). Since it is a genetic disease, CIPA is more likely to occur in homogeneous societies. While there may be very few reported cases, many studies have been done on these individuals. It is hard though, to get information on adults because many individuals do not live past the age of 25. Mardy was the first to study CIPA in-depth. Published in 1999 in the American Journal of Genetics, Mardy identifies the cause of CIPA, allowing for a better screening process in identifying individuals with this disease (4).

Another study was done by Guo, on two Taiwanese brothers, both diagnosed with CIPA. Guo basically studied myelination and axon thickness in the two brothers, comparing it to normal myelination. He first took DNA samples from the two brothers and mother. Then electrophysiological studies were done. Using an electromyograph, Guo tested motor conduction on the median, ulnar, tibial and perineal nerves. Then he took sensory conduction of the same nerves. Lastly, he did a sural nerve biopsy and counted the number of myelinated neurons, and compared axon size. The brothers were both male, ages 18 and 20. The 20 year old was slightly retarded while the 18 year old had a normal IQ (2).

The tests revealed a loss of small myelinated and unmyelinated fibers but normal large myelinated fibers in the sural nerve (2). It was also noted that the axon size was larger than normal in both patients. Guo discusses that there appears, like in many congenital diseases, no increase in the loss of small myelinated fibers with age. This study is interesting because it shows that the body tries to cope with less myelinated fibers by increasing the size of the axons. The only problem is that with CIPA there is a loss of the sensory nerves in the dorsal root ganglia. This is what causes the patient to lose the ability to feel pain.

Rosentsveig, looked at surgical records of 20 patients with CIPA. He studied anesthetic procedures done on patients with CIPA. It has been noted that patients with CIPA have a decreased peripheral and central norepinephrine activity (7). This can lead to hyperthermia and hypotension during the perioperative period. What was found was that there were no cases of hyperthermia in the 20 files looked at. One patient did go into cardiac arrest but that was unrelated to hyperthermia or hypotension. It was noted though, that there were many cardiovascular complications during surgery (7). This was unrelated to the anesthetic drug used, so a complete conclusion

was unable to be drawn from this study. Rosentsveig recommends that surgery “carries a significant risk of cardiovascular events” so special attention should be given to these patients when surgery is performed (7).

In a study done in 2002, Miranda studies a specific mutation to the NTRK1 gene, the gene responsible for this disease. It has been identified that there are at least 37 mutations among different ethnic groups (5). The mutation looked at in this study, was the M581V mutation, prevalent in Japanese families. The study found that the M581V gene suppresses the NTRK1 gene and thus is an important residue for receptor activity (5). It can account for some of the nerve growth factor effects, which is the main cause of the insensitivity to pain.

Probably the most documented case of CIPA was done on a Canadian woman named “Ms. C”. Her father was a physician and became aware of her disease when she didn’t respond to pain stimuli as a baby. “Ms. C” lived a relatively “normal” life, attending college at the McGill University in Montreal. When she was a younger, “Ms. C” received third-degree burns when she leaned on a radiator and also severed her tongue while chewing. Many tests were done on “Ms. C”. She did not respond to electric shock, boiling water, ice baths, pinched tendons, or histamine injections. No physical changes in her body were observed and she reported no pain. She also reported that she couldn’t remember ever sneezing or coughing. This could be attributed to the fact that coughing and sneezing are bodily functions which are caused by sensitivity and small pain to the throat and nose. Since she was unable to feel pain, her body did not respond to these stimuli either. Unfortunately, “Ms. C” died prematurely at the age of 29, from infections in her knees, hips and spine. An interesting note though, “Ms. C” reported painful sensations during her last months of life (3). The cause of this phenomenon is still unexplained.

Most children dream about being a superhero when they are young. CIPA patients can be considered Superman because they don’t feel physical pain but it is ironic that what gives them their “super powers” also becomes their kryptonite. Living with CIPA is not an easy task. Patients are forced to live a sheltered life. They must constantly be checked for scratches, bruises, bumps, anything that would indicate they are hurt. Before they eat, food must be checked to ensure it is not too hot. There are often dental and blood pressure problems which must constantly be monitored. Whenever they wake up in the morning CIPA patients must check their eyes to ensure that they did not scratch their retina while they

were sleeping. They must be kept within a relatively cool temperature so that they do not get a heat stroke. Even speaking and chewing can be dangerous as gum and tongue damage often occur. There is an endless list of checks that must be done throughout the day. Cuts that formed must be taken care of diligently because they have the possibility of becoming infected. There must be physical therapy to treat and manage neuropathic joints, bone infections and spinal curvatures (3). CIPA patients don’t realize how much damage they are doing to their body and must be refrained from dangerous and violent activities. Individuals with CIPA often associate their lack of pain with immortality, which is why many patients die prematurely.

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