Insensitivity to Pain, Congenital, with Anhidrosis

Alternative Names
CIPA
Neuropathy, Congenital Sensory, with Anhidrosis
Hereditary Sensory and Autonomic Neuropathy IV
HSAN4
HSAN IV
Familial Dysautonomia, Type II

Record Category
Disease phenotype

WHO-ICD
Congenital malformations, deformations and chromosomal abnormalities > Congenital malformations of the nervous system

Incidence per 100,000 Live Births
Unknown

OMIM Number
256800

Mode of Inheritance
Autosomal recessive

Gene Map Locus
1q21-q22

Description
Congenital insensitivity to pain with anhidrosis is a rare autosomal-recessive disorder of the nervous system. Lack of pain sensation, painless injuries of the extremities and oral structures with self mutilation, fever secondary to anhidrosis (lack of sweating) during hot weather, mental retardation, and loss of unmyelinated and diminution of small myelinated fibers in sural nerve specimens are the main features of the disease. Infection and scarring of the tongue, lips, and gums occur frequently, and keratoderma palmo-plantaris is a typical feature in older patients. Chronic infections of bones and joints represent additional complications.

In congenital insensitivity to pain with anhidrosis the insensitivity to pain is associated with the defective development of the small, nociceptive neurons in the dorsal root ganglia. These nociceptive neurons and the cells of the sympathetic ganglia derive from the neural crest, and their survival is stimulated by the nerve growth factor through the neuronal tyrosine kinase receptor.

Molecular Genetics
Nerve growth factor supports the survival of sympathetic ganglion neurons and nociceptive sensory neurons in dorsal root ganglia derived from the neural crest and ascending cholinergic neurons of the basal forebrain. Mutations in the tyrosine kinase receptor A gene, described recently in patients with congenital insensitivity to pain with anhidrosis, correlate well with the defective development of the nociceptive neurons. Human tyrosine kinase receptor A is a receptor tyrosine kinase which is phosphorylated in response to nerve growth factor. The binding of the nerve growth factor to tyrosine kinase receptor A stimulates homodimer formation and activation of tyrosine kinase activity. Phosphorylated tyrosine residues in tyrosine kinase receptor A cytoplasmic domain serve as anchors for binding downstream signaling molecules.

Epidemiology in the Arab World
Kuwait
Ismail et al. (1998) described an 8-year-old girl who was 1 of 2 affected sibs from healthy first-cousin Kuwaiti parents. She first presented at the age of 24 hours with fever, which persisted for 8 weeks. Extensive investigations revealed no cause for the fever. Recurrent febrile convulsions occurred, with fever of 42 degrees C induced by environmental temperature in Kuwait. She had mild hypotonia and hyporeflexia, did not cry during blood sampling, had never sweated, and never developed sphincter control.
Pictures of the child demonstrated severe mutilation of the hands and feet as well as of the tongue and lips.

**Saudi Arabia**
Jarade et al. (2002) reported a case of a 6 year-old boy patient with congenital insensitivity to pain with anhidrosis. The patient presented a bilateral central corneal sterile ulcer, decreased corneal sensitivity, moderately altered corneal reflex and normal tearing response. Jarade et al. (2002) concluded that congenital insensitivity to pain with anhidrosis may present as neurotrophic corneal ulcer.

**United Arab Emirates**
Sztriha et al. (2001) detailed the clinical manifestations of a 5-year-old male patient analyzed by Mardy et al. (1999) and Mardy et al. (2001). The patient had typical clinical manifestations of congenital insensitivity to pain with anhidrosis. He was the only child for a consanguineous family from the United Arab Emirates with no history for other affected family members. He did not sweat nor respond to painful stimuli in a normal way from the time of birth. Immunohistochemistry with antibodies against S100 protein and neuron-specific enolase failed to reveal nerve fibers in the vicinity of the eccrine sweat glands.

**References**


**Related CTGA Records**
Neurotrophic Tyrosine Kinase, Receptor, Type 1

**External Links**
http://harvester.embl.de/harvester/AAH6/AAH62580.htm


http://www.orpha.net/data/patho/GB/uk-HSANIV.pdf

**Contributors**
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