Congenital Insensitivity To Pain With Anhidrosis In Two Brothers : Case reports

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Abstract-The first two cases of congenital insensitivity to pain with anhidrosis (HSAN4) in Saudi Arabia. Both diagnosed with congenital insensitivity to pain with anhidrosis based on both clinical and molecular analysis.

Index Term-Congenital insensitivity to pain with anhidrosis (CIPA), Hereditary insensitivity to pain with anhidrosis, Hereditary sensory and autonomic neuropathy type IV (HSAN4).

Introduction -

Congenital insensitivity to pain with anhidrosis (CIPA) is a rare hereditary an autosomal recessive pattern disease; however, the prevalence is unknown. It has two characteristic features: first is the inability to feel pain and temperature lead to multiple fractures, infections, and self-mutilation, including tongue and finger biting. The second element is decreased, or absent sweating (anhidrosis) leads to recurrent episodes of unexplained high-grade fever. The presentation of signs and symptoms of CIPA appear early, usually at birth or during infancy. [1] I am presenting two cases of CIPA as the first reported cases in Saudi Arabia, with differing Presentation to increase the awareness about the disease and its presentation.

CASE REPORT 1:

16 years old boy presented to a dermatology clinic with painless, large fissure in the right foot for one month. On further questioning, it was found that he was taken by his mother to the ER at King Fahad Armed Forces Hospital when he was three years old after they noticed painless swelling in his right knee which turned to be due to a fracture. The ER doctor put him in a cast, but he didn't cry; and when the cast removed later, it was found that his skin became black due to a strong cast and still, it wasn't painful.

Four months later, he presented to ER with painless, swollen left ankle which turned to be also due to a fracture. It took him seven months to heal.

Furthermore, his family reported that he bites his lips and fingers all the times and cause them to bleed, but he does not have any pain. Also, he doesn't like to go out in sunny days and prefers to stay in front of the air conditioner (heat intolerance). He always gets admitted to the hospital with recurrent infections and high-grade fever.

When he was 11 years old, his parents took him to Germany where he was diagnosed with congenital insensitivity to pain with anhidrosis (CIPA) based on clinical features in correlation with genetic studies in addition to thermoregulatory sweat test. He was having a slight developmental delay and was facing difficulties in the school and had IQ test done at King Fahad Armed Forces Hospital with scored only 60. Neonatal history: full term, born by cesarean section without complications .Family history: No consanguinity, No history of congenital disease running in the family. On Examination: His Left lower limb was shorter than the right one, he has lasting nail changes, since the age of 9. Both soles, toes, and ankles

have dry ulcers and fissures. There is swelling in both knees; he has normal hair and normal sense of temperature and normal sensation and motor functions. Investigations were done including Brain MRI which is Normal, Nerve conduction also typical Genetic study: mutation in NTRK-1 gene.

CASE REPORT 2

Eight-Year-Old male, presented to a dermatology clinic complaining of dryness in both feet for a long time. This is a child of non-consanguineous parents. Pregnancy was full-term with the uncomplicated cesarean section. He was kept in the hospital for five days due to cesarean section. In early infancy, he suffered from recurrent fever and irritability. Recently, he diagnosed as CIPA when he crushed his foot in the door knob followed by prolonged non-healing recurrent ulcers. Later, the mother feels that he has lost temperature sensation also. Developmentally, he is delayed. He set at one year, walked at two years, and his speech consists of words only. He has poor vision, and he uses eye refractive glasses. His hearing reported being normal. He was investigated in different hospitals and then finally a genetic testing was done from King Faisal Specialist Hospital -Riyadh. The gene NTRK-1 was tested, and he was found homozygous for GAA deletion c779-783 (one amino acid deletion) Family History: One brother now 16 years old has the same disease (CIPA), the above case
On Examination: The child was hyperactive. His comprehension was fair to good. He was thin, failure to thrive, with poor vision. His skin was dry and rough with hyperkeratosis. Motor examination showed normal tone, and his reflexes diminished. Power was 5/5. Gait examination was normal.

DISCUSSION

Congenital insensitivity to pain and anhidrosis caused by Mutations in the neurotrophic tyrosine kinase, receptor, type 1 gene (NTRK1). The NTRK1 receptor is found on the surface of cells, particularly neurons that transmit pain, temperature, and touch sensations (sensory neurons). [2].Hereditary sensory and autonomic neuropathies (HSANs) are categorized into five types. Loss of large myelinated is considered a main feature of the HSANs.[3].Type **ONE** (HSAN1) is the most common type of HSANs. In this type, begin as a distal sensory loss then distal muscle wasting and weakness and variable neural deafness occurred due to progressive degeneration of dorsal root ganglion and motor neurons[4]. Type **TWO** (HSAN2) is an autosomal recessive trait characterized by loss of pain, temperature, pressure and touch sensation lead to recurrent infections and fractures of hands and feet [5].Type**THREE** (HSAN3) (also known as familial dysautonomia or Riley-Day syndrome) is an autosomal recessive trait. Symptoms usually include irritability, tachycardia, hypertension, facial flushing, bronchorrhea, and diminished oral coordination thatmay cause in dysfunction swallowing and speech. The clinical features of this form are caused by sympathetic autonomic dysfunction. [6]

Type **FOUR** (HSAN4), Congenital insensitivity to pain with anhidrosis (CIPA) is another name for this kind. It is an autosomal recessive disease. Symptoms include generalized loss of pain sensation that causes multiple injuries, self-mutilation, and recurrent osteomyelitis. Also mutilation of the face and mouth due to loss of oral sensation. One of the distinct characters of HSAN4 is anhidrosis causing defects in thermoregulation and episodic of hyperthermia that may be associated with seizures. Usually, it is associated with a decrease in the intelligence quotient. [1] When we reviewed the literature, we found 39 published cases of CIPA in the Arab population. Table 1 summarizes the main features of CIPA in Arab cases. From this table, we can see that the cognitive functioning of children with congenital insensitivity to pain with anhidrosis (CIPA) has been shown to be in the mental retardation range (IQ range from 53.8 to 60). What is surprising is that there is six patient (14.6%) with average IQ. [7]. In the older child of our cases, molecular analysis revealed a mutation c.783_785delGAA, p.Lys261 del homozygous in NTRK-1 gene which has not yet been described as pathogenic in international databases. A deletion of three nucleotides in Exon 7 results in the loss of the amino acid lysine at the position of 261 in both alleles of the NTRK-1 gene. The homozygous appearance of this mutation stands in agreement with the autosomal-recessive trait of HSAN 4. While in the younger child of our cases, molecular analysis revealed a mutation c.783_785delGAA, p.Lys261 del homozygous in NTRK-1 gene. On the other hand, molecular analysis of the Emirati case reported that "a homozygous G3C (guanine3 cytosine) transversion of the 39 splice site in the first position of intron 4 and a C3A transversion at nucleotide 337 in exon 2 of the TRKA gene"[8]. In 2002, the genetic studies of the ten Palestine patients showed four out of ten patients had mutations in their genes.Three siblings patients of Bedouin Arab descent from the northern part of Palestine had a Pro-689-Leu mutation on the TrkA gene. While one case from Bedouin Arab from southern Palestine was found to have mutation 1926-1ns-T. This mutation was not found in the other two patients who were of the same origin.[7]Type **FIVE** (HSAN5) is described by the loss of pain, temperature sensation, but the another sensation is preserved.[9] In reviewing the literature, we found only one report about five related patients with HSAN5 from Saudi Arabia. The oldest one is 23 years old male, and the youngest one is ten months female. They were healthy looking with no dysmorphic features, normal sweating, normal intelligence quotient, normal neurological examination except for pain sensation. They had all the subsequent and complications of insensitivity to pain.[10]

Year of publication	No.	Origin	Gender	Age of presentation	Clinical features	Neurological examination	Consanguinity	R

Our cases	2	Saudi	Male	3years	-Repeatedly injury to feet, hand,tongue -Never complained after trauma since birth -Repeated fractures in knees and ankles - Hyperkeratosis of the soles with deep fissures -decrease IQ	-Generalized insensitivity to pain -normal sense of temperature and normal sense of fine touch and motor functions -Reflexes: normal	Absent	
			Male	6 years	-Never complained after trauma since birth -thick hyperkeratotic skin of the soles -hyperactivity -poor vision	- Generalized insensitivity to pain -start to lose sense of temperature and normal sense of fine touch and motor functions -Reflexes: diminished	Absent	
2013	3	Morocco	Females	At birth	-Psychomotor development delayed - Repeatedly injury to feet, hand. -Never complained after trauma since birth -Recurrent osteomyelitis of the right tibia at age of 10	-Generalized insensitivity to pain -Vibratory sensations: normal - DTR : absent	NR	
2010	23	Palestine	12 Female 11 Male	Mean 9 years 7 Months	-Mean IQ: 53.8	NR	NR	
2010	1	Algeria	NR	9Months	lesions of the SIB tongue and fingers with laxity	- Generalized pain insensitivity - Reflexes: normal - EMG: normal	Present	
2007	1	Egypt	Female	15 Months	-Bilateral corneal opacities. -Irregular defect in the lower lip. -Dystrophic toe nails. -Oval ulcer on sole of left foot.	- Impaired sensation on the extremities. - Brain MRI: changes of cortical brain atrophy at the frontoparietal region. - EEG: normal -Nerve conduction: normal	Present	
2002	10	Palestine	7 Female 3 Male	Mean 13 years	-6 normal IQ -4 moderate retardation -Unexplained fevers -Tongue-biting -Multiple skin wounds -Sepsis as a result of osteomyelitis.	- absence of touch sensationin 3 -Impaired temperature in 4 -Decreased vibration sense in 3 -Absent proprioception in 4	Present	[7]

2001	1	Emirates	Male	6 Months	- Self-mutilation of the right thumb - A large cracked lesion of the lip -Chronic ulcers of the right ear and right big toe - Osteomyelitis of the 3rd finger on the left hand developed by 5 years of age.	--CN function: normal. -Muscle tone ,power: reduced -Deep reflexes: preserved -Insensitivity to superficial and deep pain stimuli - Brain MRI: normal - CSF: normal	Present	[8]

Conclusions:

To the best of our knowledge, this is the first paper to report a case of congenital insensitivity to pain with anhidrosis (HSAN4) from Saudi Arabia. One of the most significant current findings from our cases that are careful medical attention and family care can decrease the complications of CIPA and improve the quality of life of the CIPA patient as it has been shown in our case of the young child.

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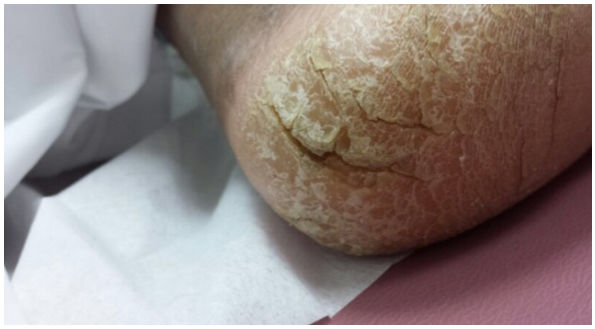

Figure 1: Photo shows a dryness and fissures in heel of left foot.

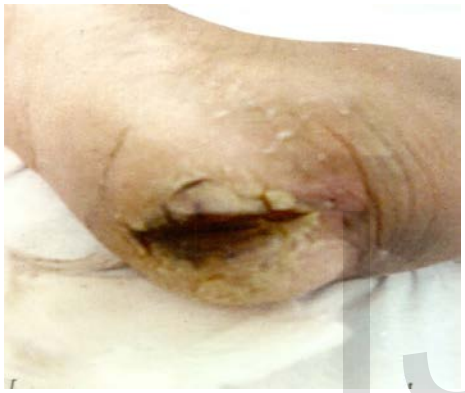

Figure 2: Photo shows alarge infected ulcer in RT foot

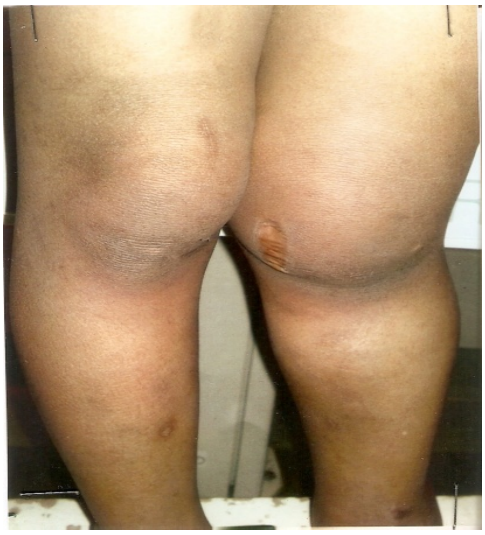

Figure 3: Photo shows swelling in left leg and multiple ulcers in lower limb