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Clinical and Radiographic Evaluation of Ten Congenital Insensitivity to Pain with Anhidrosis Patients

Heba M. Gamal El Din [1*], Naglaa S. El Kilani [2], Mostafa I. Mostafa [3], Inas Sayed [4], Samira Ismail[5], Eatemad Shoreibah [6]

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azhardentj@azhar.edu.eg

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ABSTRACT

Purpose: This study was designed to introduce a standardized protocol for examination of congenital insensitivity to pain with anhidrosis patients. And also report the oro-dental manifestations in these patients. **Materials and methods:** In the current study, Oro-facial clinical and sensory examinations, as well as radiographic examination for ten CIPA patients were performed. **Results:** The Oro-dental findings were mainly missing teeth and soft tissue injuries. Radiographic examination revealed multiple congenitally missing teeth. **Conclusion:** A standardized protocol with Oro-facial clinical and sensory examinations, pulp sensitivity tests and radiographic examination should be considered as a primary diagnostic approach in patients with suspected Congenital insensitivity to pain with anhidrosis, instead of the more established but expensive molecular analysis and the invasive Sural nerve biopsy.

KEYWORDS

Anhidrosis,
Self-mutilation,
oro-facial injuries,
premature tooth loss.

INTRODUCTION

Hereditary sensory and autonomic neuropathies (HSAN) are a heterogenous group of disorders of the peripheral nervous system [(1)].

- Paper extracted from Doctor thesis titled: "Clinical, histopathological, radiographic evaluation with molecular characterization for congenital insensitivity to pain with anhidrosis patients."

1. Assistant Researcher of Oro-dental Genetics, Department of Oro-dental Genetics, Human genetics and genome research division, National Research Center, Cairo, Egypt
2. Professor and Head of Oral medicine, Periodontology, Diagnosis and Radiology Department, Faculty of Dental medicine for Girls, Al Azhar university, Cairo, Egypt
3. Professor of Oro-dental Genetics, Department of Oro-dental Genetics, Human genetics and genome research division, National Research Center, Cairo, Egypt
4. Researcher of Oro-dental Genetics, Department of Oro-dental Genetics, Human genetics and genome research division, National Research Center, Cairo, Egypt
5. Professor of Clinical Genetics, Clinical Genetics Department, Human Genetics and Genome Research Division, National Research Center, Cairo, Egypt
6. Professor of Oral medicine, Periodontology, Diagnosis and Radiology Department, Faculty of Dental medicine for Girls, Al Azhar university, Cairo, Egypt

* Corresponding author email: heba_mostapha85@hotmail.com

In 1993, five subtypes of HSAN were classified based upon clinical rather than genetic findings. Congenital insensitivity to pain with anhidrosis *(CIPA: MIM 256800)* [1] or hereditary sensory and autonomic neuropathy type IV (HSAN-IV) is an autosomal recessive disorder, described in 1932 as congenital pure analgesia [2].

Clinically, it is identified by the lack of pain sensation, anhidrosis and self-mutilating behavior [3]. The prevalence of this condition is 1 in 125 million newborns [4]. In Congenital insensitivity to pain, there is a failure of differentiation and migration of neural crest cells, leading to the complete absence of small myelinated and unmyelinated nerve fibers. As a consequence, patients have a loss of pain and temperature sensation. Furthermore, the sweat glands are not innervated, leading to anhidrosis. Moreover, since sweating plays an important role in maintaining normothermia under hot environmental conditions, thus anhidrosis disturbs homeostasis and increases susceptibility to recurrent febrile episodes [3].

CIPA is caused by a genetic mutation of the Neurotrophic tyrosine-kinase receptor (NTKR1) gene[5] which encodes the high-affinity nerve growth factor receptor TRKA. The NTRK1 gene consists of 17 exons and is located on chromosome 1 (1q21-q22)[6].

Owing to the characteristic self-mutilation in CIPA patients that usually results in oro-facial soft tissues lesions as well as premature tooth loss [7], the objective of our study was to introduce a standardized protocol, with Oro-facial clinical and sensory examinations, as well as radiographic and histological examination of dental tissues for those patients.

MATERIALS AND METHODS

A group of ten Egyptian patients suspected to have congenital insensitivity to pain with anhidrosis were selected from those attending the Outpatient clinic of the Oro Dental Genetics Department and Clinical Genetics Department, Human Genetics and Genome Research Division, National Research Center. All the procedure was explained to the patients' guardians and informed consents were signed after taking the approval of the Research Ethical Committee of the National Research Center.

All ten children underwent the following:

1. Detailed family history taking with pedigree analysis: to report any consanguineous marriages.
2. Clinical examination: Extra-oral examination to reveal the presence of any self-mutilative wounds or deep ulcers on the fingers, hands or feet. Also, comprehensive Oro-dental examination was carried out to check for any premature tooth loss or luxated teeth and reveal the presence of any self mutilative lacerations, traumatic ulcerations on the lips, gingiva, buccal mucosa, tongue…etc.
3. A standardized orofacial pain questionnaire was given to all the parents to collect information regarding the initial symptom of painlessness noticed in their children, behavior during immunizations or blood tests, sensory modalities and their reaction to other pain-related experiences as well as the past medical history of recurrent infections, self-inflicted traumatic injuries or eye problems.
4. Orofacial psychophysical tests to examine pain, thermal and mechanical sensations which includes: Division of the face bilaterally into six areas and evaluating the three branches of the trigeminal nerve.
5. Radiographic examination: Panoramic radiographs were taken for only five patients to reveal any abnormalities as well as exclude silent infection or any inflammatory processes.

RESULTS

Ten Egyptians (2 females and 8 males) of seven unrelated families were examined. Their ages ranged from three years to nineteen years. Our pedigree analysis was accordant with an autosomal recessive pattern. Consanguinity was present in all our families, and two families had more than one affected patient.

The answers given by the parents to the orofacial pain questionnaire were in compliance with the phenotype of CIPA and are summarized in table (1).

Table (1) *Summary of the answers given by the parents to the Oro-facial pain questionnaire.*

Patient no	1	2	3	4	5	6	7	8	9	10
Consanguinity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Family history	-ve	-ve	+ve	+ve	-ve	+ve	-ve	+ve	-ve	-ve
First symptom	Multiple ulcers.	White coating on the tongue along with fever.	Painless injuries.	Painless injuries	Painless injuries	Painless injuries	High fever episodes.	High fever episodes.	No crying with falls.	Tongue and cheek injuries.
Behavior during immunizations	No pain	No pain	No pain	No pain	No pain	No pain	No pain	No pain	No pain	No pain
Recurrent Fever episodes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sweating	Normal	Used to sweat at first, now no sweating	No sweating	No sweating	Normal	No sweating	No sweating	No sweating	No sweating	No sweating
Dry skin	Yes	Yes	Yes	yes	Very rough skin	No	Yes	Yes	Yes	Yes
Fractures	Limb fracture	Upper and lower limb fractures and a skull	Knee fracture, only noticed	Repeated limb fractures.	Lower limb fracture.	Repeated lower limb fractures	Painless fractures in both arms.	Lower Limb fractures	No	Lower Limb fractures
Recurrent infections	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Eye problems	Yes	No	No	No	No	No	Yes	No	No	No
Emotional pain	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Sense of smell	Very strong	Normal	Normal	Poor	Poor	Poor	undetermined	Normal	Normal	Normal
Taste	Normal	Normal	Normal	Normal	Normal	Normal	undetermined	Normal	Normal	Normal
Temp sensation	Present	Absent	Present	Present	Present	Present	undetermined	Poor	Present	Present
Itching sensation	Present	Present	Present	Present	Present	Present	undetermined	Present	Present	Present
Lacrimation	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Auto-amputation	Tip of the tongue	Tip of the tongue	The distal phalanges of three fingers as well as the tip of the tongue		Tip of the tongue		Distal phalange of one index toe as well as the tip of the tongue.	Three toes		

Extraoral examination revealed different self-inflicted injuries in all our patients varying from traumatic ulcerations in the skins, burns, and bone fractures to auto amputations of fingertips.

Intraoral findings are summarized in table no 2 and the most prominent findings are the large number of the missing teeth in our patients and the loss of the tongue tip.

Table (2): *The intraoral findings.*

Patient no.	Age	Number of missing teeth	Soft tissue injuries	Atrophic glossitis	Mouth opening	Xerostomia
1	11 yrs	22	Laceration of the lips. Traumatic ulcer in lower lip Loss of tongue tip.	Only in the anterior third of the tongue.	Limited	No
2	7 yrs	14	Loss of tongue tip, frictional keratosis on the lateral borders of the tongue.	Yes	Normal	No
3	7yrs		Loss of tongue tip.	Undetermined	Normal	No
4	19yrs		Undetermined	No	Normal	No
5	18yrs	15	Traumatic ulcer on the cheek Loss of the tongue tip Frictional keratosis on the lateral borders of the tongue.	Yes	Normal	No
6	7yrs	14	No	No	Normal	No
7	6yrs	13	Tongue injuries	No	Normal	No
8	4.2yrs	10	Tongue injuries	No	Normal	No
9	8yrs	14	No	No	Normal	No
10	9yrs	13	No	No	Normal	No

Radiographic examination was feasible in only five patients and the findings are shown in table (3).

Table (3): *The radiographic findings.*

Radiographic finding	**Number of patients**
Premature tooth loss	4
Congenitally missing teeth	5
Abnormal tooth shape	2
Impacted teeth	1
Normal jaw anatomy and bone density	3
Ridge atrophy	2

Table (4): *The results of the Oro-facial pain tests:*

Patient no	**Tactile sensation**	**Corneal sensation**	**Pain sensation**	**Thermal sensation**	**Taste**	**Pulp sensitivity test**
1	Normal	Absent	Hypoalgesia	Normal	Normal	Negative
2	Normal	Normal	Absent	Normal	Normal	Negative
3	Normal	Normal	Absent	Normal	Normal	Negative
4	Normal	Normal	Absent	Normal	Normal	Negative
5	Normal	Normal	Absent	Normal	Normal	Negative
6	Normal	Normal	Absent	Normal	Normal	Negative
7	Normal	Normal	Absent	Normal	Normal	Negative
8	Normal	Normal	Absent	Normal	Abnormal	Negative
9	Normal	Normal	Absent	Normal	Normal	Negative
10	Normal	Normal	Absent	Normal	Normal	Negative

DISCUSSION

Congenital insensitivity to pain with anhidrosis (CIPA) is a rare autosomal recessive disorder of the peripheral nervous system [8]. Self-mutilation is a prevalent finding in congenital insensitivity to pain with anhidrosis, it is secondary to the lack of pain perception and usually starts with the eruption of the anterior deciduous dentition [9]. Self-mutilation usually affects the Oro-facial region and limbs [7].

Thus, despite the rarity of the disease we aimed to work on congenital insensitivity to pain with anhidrosis and present the oral manifestations, in order to increase the scientific knowledge on congenital insensitivity to pain with anhidrosis and highlight the role of dentists in the early diagnosis of this disease, as well as introduce a standardized protocol for the diagnosis of these patients that is more conservative than skin or sural nerve biopsies and less costly than molecular analysis. This protocol includes oro-facial pain questionnaire, clinical, sensory and radiographic examination.

The first step in this protocol was to take a detailed family history with pedigree analysis to check consanguinity and to investigate if other family members were also affected. Analysis of the pedigrees of our patients was accordant with an autosomal recessive pattern. Consanguinity was present in all our families, and two families had more than one affected patient.

A standardized orofacial pain questionnaire was then given to all the parents and all the ten patients had a typical history of insensitivity to pain, absent or decreased sweating, and several symptoms commonly associated with CIPA, including fractures, high fever episodes, and painless self mutilative injuries (burns, wounds, bone fractures) from early childhood.

Oral self-inflicted injuries, varying from auto extraction of teeth, traumatic ulcerations in the oral mucosa and auto amputations of the tongue tip as well as severe biting injuries of the finger tips were found in nearly all the patients in our study.

Regarding the Oro-dental findings, missing teeth was the most commonly seen in our study, followed by the self-inflicted soft tissue injuries. Missing teeth is a frequent finding in CIPA patients [10-17]. The teeth are usually lost either by auto extraction or by prophylactic extraction in order to avoid further trauma.

Missing teeth was seen in 90 % of our patients and it was mainly in the lower anterior teeth. Self mutilative auto extraction was mainly the reason for the premature tooth loss in our study. This is in agreement with a previous study done in 1998 [11], in which missing teeth due to auto extraction was seen in more than one half of the subjects. However, this is in contrast with another study in 2002, in which auto extraction of teeth was not a common finding[18].

Among the different oral soft tissue injuries in our study, tongue injuries were the most frequent followed by the buccal mucosa then the lip injuries. This is in contrast with the previous report which reported that the lip injuries are more common than those of the buccal mucosa [18].

Tongue injuries typically start during the infantile period where infants painlessly thrust their tongue against the sharp edges of the erupting lower anterior teeth while sucking or nursing, and develop traumatic ulcers on the ventral surface of the tongue, which then usually progresses to amputation of the tongue tip by the age of two years [11].

Chronic tongue and cheek biting result in traumatic ulceration of the tongue and the buccal mucosa, which was also seen in our patients. Because of their lack of pain perception, patients are unconscious of these injuries and show no signs of discomfort. Also, one of the patients had limited mouth opening due to thick fibrous scar tissue in both the lips and the buccal mucosa, similar to previous reports [19, 20]. Atrophic glossitis was seen in two of our patients as well as in previous studies [11, 20, 21].

This phenomenon is apparently the result of an accumulative effect of the repeated tongue biting.

Congenital dental anomalies, such as enamel hypocalcification, enamel hypoplasia, and abnormalities of tooth shape or number were previously reported in CIPA patients. In our study, congenitally missing teeth were a remarkable finding in all the five patients examined radiographically, and four patients showed more than one missing tooth bud. This is in accordance with a recent study which also reported several congenitally missing permanent tooth germs in a Chinese patient affected with CIPA[7].

Abnormal tooth shape was also seen in our study. Taurodontism of upper molars was seen in the OPG of one of the patients, also the lower molars look rudimentary in the OPG of another patient. This is consistent with another report which showed short root anomaly of the standing teeth in the OPG of a Chinese patient with CIPA [14].

Since tooth size and proportions of the particular crown components (enamel, dentin and pulp) are derived from the neural crest development. Bearing in mind that neural crest dysfunction is present in CIPA, it is therefore reasonable to conclude that it might be the reason behind the distorted tooth dimensions [22].

The frequency of mandibular osteomyelitis is relatively high among CIPA patients, which may then lead to pathological fracture of the mandible. A previous study which examined 33 CIPA patients, reported that 6 patients out of the 33 had OM of the jaws [23]. All the osteomyelitis lesions of the jaws in CIPA patients were mainly found in the mandible, as in another study [6].

All the ten patients had normal touch, normal thermal cutaneous sensitivity and normal corneal sensations in all three branches of the trigeminal nerve bilaterally. Nevertheless all the patients showed no response to pinprick stimulation in all three branches of the trigeminal nerve bilaterally except for one patient who had mild pain. Also, all the patients showed negative response to the pulp sensitivity test. These results are in accordance with the phenotype of CIPA.

CONCLUSION

Owing to the wide spectrum of Oro-dental manifestations as well as the high frequency of mandibular osteomyelitis among patients affected with CIPA, it could be concluded that it is mandatory to include an oral and maxillofacial surgeon in the multidisciplinary team responsible for the long-term evaluation of these patients.

A standardized protocol with Oro-facial clinical and sensory examinations, pulp sensitivity tests should be considered as a primary diagnostic approach in patients with suspected Congenital insensitivity to pain with anhidrosis, instead of the more established but expensive molecular analysis and the invasive Sural nerve biopsy.

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