Pediatr Pract Res 2022; 10(3): 134-138
DOI: 10.21765/pprjournal.1182084

CASE REPORT
OLGU SUNUMU

Congenital Insensitivity to Pain with Anhidrosis Syndrome: A case report in Diyala province / Iraq

Konjenital Ağrı Duyarsızlığı ile Anhidrosis Sendromu: Diyala vilayeti / Irak'tan Bir Olgu Sunumu

Mohammad A. Al Chalabi[1], Jalil Alezzi[2]

[1]AlBatool Teaching Hospital / Diyala/ Baqubah/Iraq
[2]College of Medicine/University of Diyala

Abstract

Congenital insensitivity to pain with anhidrosis syndrome (CIPA); is a rare autosomal recessive disorder presenting with pain insensitivity, sweating inability, and intellectual disability. The incapability to sense pain and temperature often leads to recurrent severe and inadvertent self-inflicted harm; these can result in severe complications, as patients settle slowly from skin and bone harm. We present a case of a four-year-old boy with a diagnosis of CIPA, after repeated visits to the hospital emergency department for repeated chest and both ankle joint infections, which prompted further investigations. A four-year-old boy was admitted to Albatool teaching hospital for maternity and children in Baqubah, Diyala, Iraq because of recurrent chest and both ankle joints infection. He is the second child of consanguineous parents. His six-year-old sister is normal. The mother noticed early after birth that her child was suffering from high fever, he was not responding to pricking and injections, and he never sweats with intolerance to warm weather. Examination revealed mental developmental delay, absent upper and lower canine teeth, napkin and face dermatitis which was intractable to therapy, and deep pus discharging ulcers of both heels. Radiology of feet shows signs of osteomyelitis. There is a history of the same disease in two male cousins who died at age of three and five years respectively, the overall clinical context warranted a clinical suspicion of CIPA. Early diagnosis of this extremely rare disease is very important for the treatment and prevention of complications. This case report shows that a clinician should suspect to investigate for CIPA when managing kids with multiple inadvertent self-inflicted harms, anhidrosis, and pain insensitivity.

Keywords: CIPA, self-mutilation, osteomyelitis

Öz

Konjenital Ağrı Duyarsızlığı ile Anhidrosis Sendromu (CIPA); ağrıya duyarsızlık, terleme yetersizliği ve zeka geriliği ile seyreden, nadir görülen otozomal resesif geçişli bir hastalıktır. Acıyı ve sıcaklığı hissedememek, sıklıkla tekrarlayan şiddetli ve istemeden kendi kendine zarar vermeye yol açar; Hastalar deri ve kemik hasarından yavaş yavaş yerleştiğinden bunlar ciddi komplikasyonlara neden olabilir. Bu yazıda, tekrarlayan göğüs ve her iki ayak bileği eklemi enfeksiyonu nedeniyle hastanenin acil servisine tekrarlayan ziyaretleri sonrasında CIPA tanısı konan dört yaşında bir erkek çocuğu vakayı sunuyoruz. Irak'ın Diyala eyaletine bağlı Bakuba kentindeki Albatool Doğum ve Çocuk Eğitim Hastanesi'ne 4 yaşında bir erkek çocuk, tekrarlayan göğüs ve her iki ayak bileği eklemi enfeksiyonu nedeniyle yatırıldı. Akraba anne babanın ikinci çocuğudur. Altı yaşındaki kız kardeşi normal. Anne, doğumdan hemen sonra çocuğunun yüksek ateşi olduğunu, iğnelere ve iğnelere tepki vermediğini ve asla sıcak havaya karşı tahammülsüzlükten terlemediğini fark etti. Muayenede zihinsel gelişim geriliği, üst ve alt köpek dişlerinin yokluğu, tedaviye dirençli peçete ve yüz dermatiti ve her iki topuğun derin irinli ülserleri saptandı. Ayak radyolojisi osteomiyelit belirtileri gösteriyor. Sırasıyla üç ve beş yaşında ölen iki erkek kuzende aynı hastalık öyküsü vardır, genel klinik durum klinik CIPA şüphesini garanti etmiştir. Son derece nadir görülen bu hastalığın erken teşhisi, komplikasyonların tedavisi ve önlenmesi için çok önemlidir. Sonuç: Bu vaka raporu, bir klinisyenin, birden fazla istemeden kendi kendine zarar veren, anhidroz ve ağrı duyarsızlığı olan çocukları yönetirken CIPA araştırmasından şüphelenmesi gerektiğini göstermektedir.

Anahtar Kelimeler: CIPA, kendini yaralama, osteomiyelit

Corresponding Author: .Jalil I. Alezzi,
Address: College of Medicine / University of Diyala /Iraq
E-mail: jalilkadim@gmail.com

Başvuru Tarihi/Received: 29.09.2022
Kabul Tarihi/Accepted: 30.11.2022

INTRODUCTION

CIPA also known as hereditary sensory and autonomic neuropathy Type IV (HSAN-IV) is a very rare autosomal recessive disorder presenting with pain insensitivity, sweating inability, and intellectual disability. The cause of CIPA development is mutations in the neurotrophic tyrosine kinase receptor type 1 gene (NTRK1)).(1-7) This gene encodes the high-affinity receptor of nerve growth factor which is found on the 1q21-q22 chromosome. The incidence of the disease is 1 in 125 million newborns (2) so it is a very rare disease; there are only a few hundred cases reported in the world, 60 of them in the united states. The NTRK1 pathway is important for the preservation of autonomic sympathetic postganglionic neurons as it is in charge of skin innervation through sensory axons (8-13). Dearborn is the first one who described the pathology in 1932 as Congenital pure analgesia. Swanson 1963 described the First reference, in literature, to CIPA, and Fruchtman et al 2013 described clinical presentation including morbidity of the condition.CIPA is tremendously risky, and mostly the patient doesn't live over the age of 25. (5,8,10,14-18,19). The presentation of the disorder is with episodes of overheating due to warm ambient temperatures because these patients have absent or decreased sweating. Hypotonia improves with growth.(1,3,19-24) Pain perception is considerably reduced and autonomic nervous system functions are lost but the pressure and touch sensations are preserved which also causes poor healing of wounds and fractures with a tendency for chronic osteomyelitis and Charcot joints development. (17,24-26). Anhidrosis causes thick skin with the appearance of callosities, lichenification of the palms, and chronic dystrophic changes in the nails. There tearing is present, but corneal ulceration occurs from hypoesthesia. Almost all patients have behavioral and cognitive deficits (7-9,26). Only one case of CIPA was reported in Ninawa / Iraq (27).

Diagnostic Tests

The diagnosis of CIPA is based on the clinical presentation, pharmacological test (intradermic reaction to 1:10, 000 histamine) and neuropathological exam in electron microscopy and detection of mutations on the NTRK1 gene represents the last diagnostic step (12). A comprehensive workup is needed to reach the diagnosis. Though the controversial role of nerve biopsy, it has been stated that CIPA is accompanied by the loss of unmyelinated and reduction of small, myelinated fibers in the sural nerve, which could describe these manifestations. (13).Genetic counseling should discourage consanguineous marital relations, especially if there is a positive history of CIPA syndrome in the family (13).

Treatment

There is no definite treatment for the disease but surgical restoration is the only intervention for joint deformity in CIPA (13). Conservative treatment looked to be the best choice to preclude further complications caused by multiple surgeries. (Preventive measures such as local foot care and custom-fitted shoes can help minimize the risk of injury and avoid the need for radical surgeries. (14). Early diagnosis of CIPA could make parents more aware of risk factors, so, accidents could be avoided with continual alertness to the child's activities. Dentistry clinics play a big role in the prevention of injuries due to self-mutilation by the child(15), through the extraction of primary teeth which was recommended in the 1960s for the avoidance of self-mutilation. wearing of dental guards along with strict vigilance by the parents are better options available which t are more appropriate to the quality of life of the CIPA child. The aim of reporting this syndrome is to make physicians familiar with this condition and avoid unnecessary surgeries and even amputations, use conservative treatments, and make the diagnosis of this syndrome easier without extra laboratory requests.

CASE

A four-year-old boy was admitted to Albatool teaching hospital for maternity and children in Baquba, Diyala, Iraq because of recurrent chest infection and osteomyelitis of both ankle joints, He is the second child of consanguinous parents. His 6-year-old sister is normal. His mother noticed early after birth that her child was suffering from high fever, he was not responding to pricking and injections, absence of pain during intravenous line placement and he never sweat with intolerance to warm weather. Teething had started at seven months of age but because of recurrent finger biting and trauma to gum, his canine teeth had fallen at 2.5 years of age. At 10 months of age, he was admitted to the hospital after a febrile convulsion and stayed there for two weeks with a persistent fever. A thorough investigations were done including (CBC, CRP, ESR, urine exam and culture, blood culture, CSF examination and culture, echocardiography, bone marrow aspiration and culture, abdominal ultrasound, and brain CT scan) which were normal. Then three months later , he was readmitted because of a respiratory infection, and episodes of hyperthermia and unexplained fever recurred. At 2 years ofd age he had pneumonia and cellulitis of the right foot. In infancy, He was hypotonic, self-mutilation, and had neurodevelopmental delay which was misdiagnosed as a metabolic disease. At age of three years, the patient was diagnosed with right foot osteomyelitis. The child had a tongue laceration which was difficult to heal with delayed wounds healing in other parts of the body. The result of uric acid, serum glucose, liver, renal, and thyroid function tests, serum lactate, ammonia, creatinine phosphokinase level, and chromatography of amino acids all were normal. Nerve conduction velocity (NCV) was normal and brain MRI showed mild brain atrophy, but intradermal reaction to 1:10,000 histamine was positive. Although aggressive treatment started, his

foot condition shows no improvement so amputation was advised by an orthopedic surgeon. The parents refused this option, later the patient had a left foot infection which necessitates admission to the hospital again. A re-evaluation of the child is done. Examination revealed mental developmental delay with mild mental retardation, absent upper and lower canine teeth, napkin and face dermatitis which was intractable to therapy (**Figure 1**), deep pus discharging ulcers of both heel (**Figure 2**), swab send for culture which revealed staph aureus infection and resistant to a lot of drugs except meropenem), a deep scar in the right ear and skin changes of both legs (**Figure 3**), neurological examination was normal. The patient felt touch and pressure sensations but not pricking and heat. There was no hepatosplenomegaly or lymphadenopathy. ophthalmologic examination was normal. Immunological investigations were normal. Radiology of feet shows signs of osteomyelitis (Figure 4). There is a history of the same disease in two male cousins who died at age of three and five years respectively, one of them underwent below knee amputation. The diagnosis of CIPA was done and it must be confirmed by electron microscopic study of nerve biopsy and genetic tests which is not available in our center.

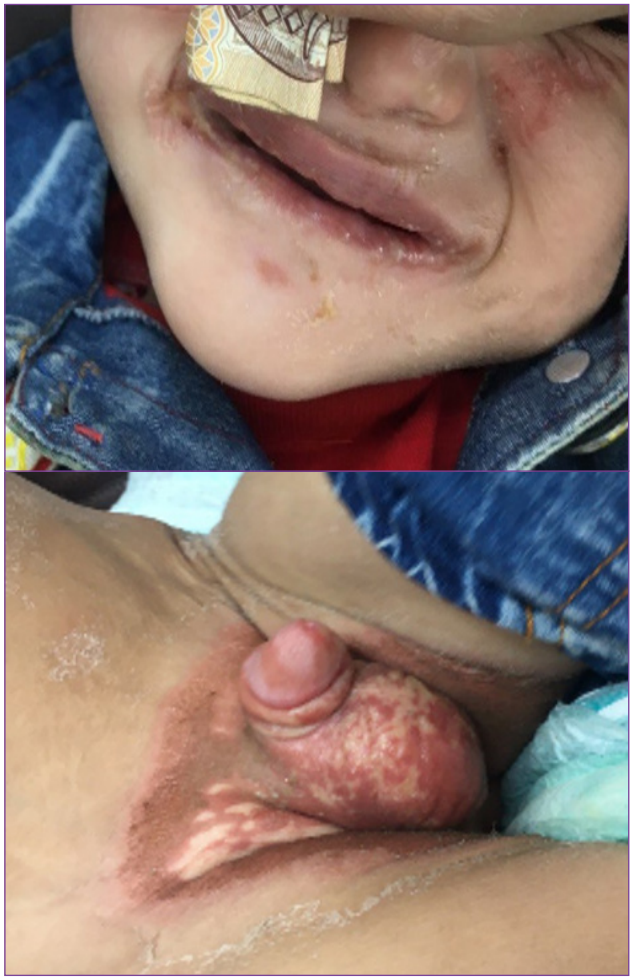

Figure 1. Dermatitis of the face and the napkin area not responding to treatment

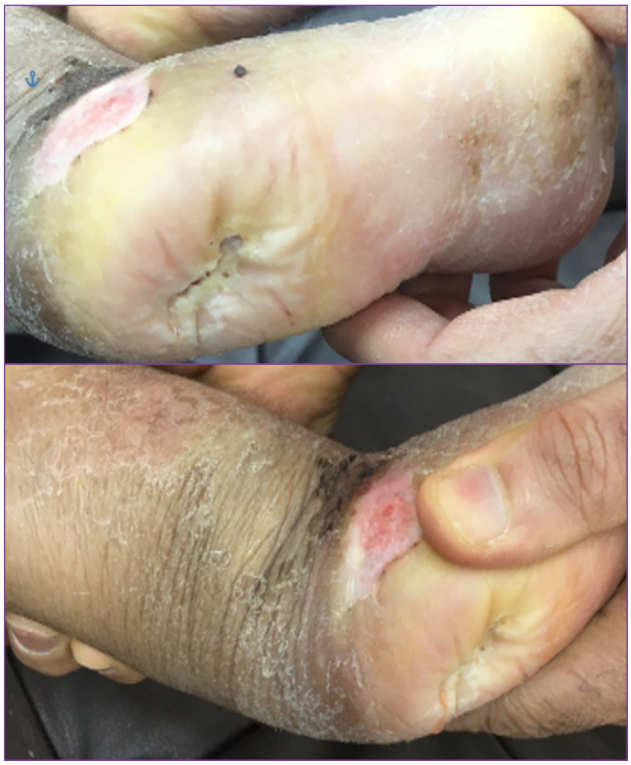

Figure 2. Deep pus discharging ulcers of both heels (osteomyelitis).

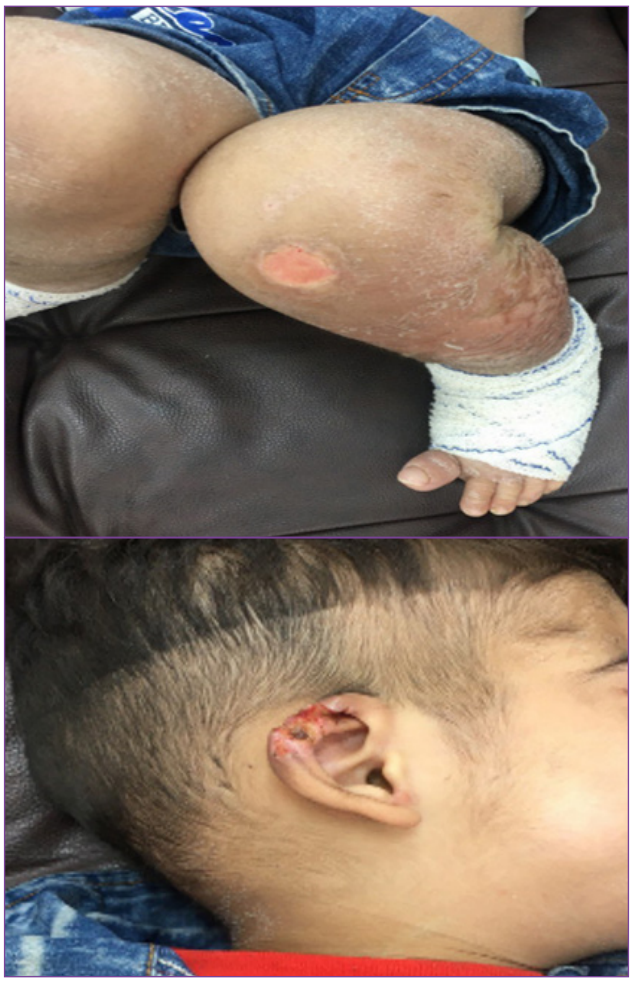

Figure 3. Skin and ear infection

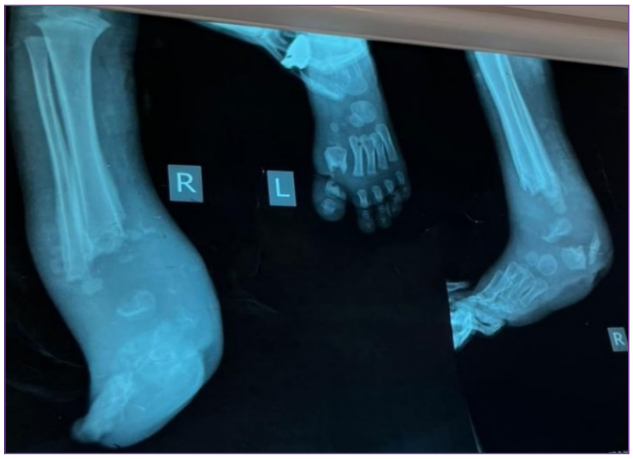

Figure 4. X-Ray of right and left ankle joints: shows nearly destructed joints by inhomogeneous bone sclerosis with the formation of sequestra (osteomyelitis).

DISCUSSION

Congenital insensitivity to pain with anhidrosis is an autosomal recessive disease caused by a mutation in the gene neurotrophic receptor tyrosinase 1 (NTRK1), which is located on chromosome 1q21-22. (16) It has been identified that there are at least 37 mutations among different ethnic groups(25). The major presenting feature of the patient was fever due to anhidrosis which is also common in other reports (22-24). Absence of pain sensation seen in all the patients leading to painless ulcers of mouth structures and extremities with unawareness of injuries produced by trauma or by self-mutilation so fingers and toes infection, scarring of lips and tongue are commonly detected (17,22-25). Self-harm behavior and mild mental retardation present in our patient which had been treated as developmental delay as reported in other literatures (22-24) .There is skin changes like skin dryness which presents as keratoderma in palmo-plantaris in the advanced state as reported by Daneshjou et al (9) The child had eczema, which was difficult to treat which is reported in other literitures (20,22). Chronic bone infections (osteomyelitis) as our patient suffered ,due to delayed healing as seen in other reports (19,22-26). The first sign of this syndrome is fever secondary to anhidrosis, which has recurrent presentation since neonatal period or from the first months of life.(18,22,23,24-27).The febrile seizures occur frequently as seen by our patient. sural nerve biopsy shows myelination defect and loss of small myelinated fibers and it was not performed on our patient due to unavailability of the test in our hospital and family compliance regarding performing the test outside the institution. Unfortunately in our country, we do not have the facility to confirm the diagnosis by genetic tests so we have to start treatment by clinical findings to make the patient's quality of life better. A heat stroke is very dangerous especially in our country so early diagnosis is important to prevent this complication .

CONCLUSION

Early diagnosis of this extremely rare disease is very important for the treatment and prevention of complications. Depending on clinical presentation and high suspicion is important in avoiding unnecessary investigations,early and proper treatment will prevent unnecessary amputation.

ETHICAL DECLARATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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