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Case Report

A case report and insightful review of congenital insensitivity to pain with anhidrosis

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ABSTRACT

We present a case of a 9-month-old male, born to a third-degree consanguineous marriage, presenting with a month-long history of mild to moderate fever occurring 3-4 times daily. The child remained active during afebrile periods and exhibited no associated symptoms. Physical examination revealed pallor and multiple abrasions on bilateral fingers, with stable vital signs. Extensive investigations for infectious and hematological conditions were negative. Notably, the child did not cry during IV insertion and the fever developed after sun exposure. A detailed CNS examination revealed an absence of sensation to crude touch, pain and temperature, leading to further tests which confirmed the diagnosis of congenital insensitivity to pain with anhidrosis (CIPA). This case underscores the importance of considering CIPA in children with unexplained fevers and insensitivity to pain, particularly in consanguineous families and highlights the need for regular follow-ups and supportive management.

Keywords: Anhidrosis, Comprehensive care, Congenital insensitivity to pain with anhidrosis, CIPA, Hereditary sensory and autonomic neuropathy type IV, Insensitivity to pain, NTRK1 gene mutation, Self-inflicted injury, Temperature dysregulation

INTRODUCTION

Congenital insensitivity to pain with anhidrosis (CIPA), also classified as hereditary sensory and autonomic neuropathy type IV (HSAN IV), is an extremely rare autosomal recessive disorder presenting early in infancy. This condition results from mutations in the NTRK1 gene, which encodes the high-affinity receptor TrkA for nerve growth factor (NGF), a critical component for the development and survival of sensory and sympathetic neurons.[1-3] The condition is most prevalent among specific populations, notably Israelites and Japanese population.[4] However, global incidence estimates vary widely, with some sources citing an incidence as low as 1 in 125 million newborns, reflecting its rarity outside of certain founder populations.[5] Early diagnosis, genetic confirmation and coordinated multidisciplinary care are vital to improving quality of life and reducing morbidity of patients diagnosed with CIPA. A multidisciplinary approach is required for management of patients diagnosed with CIPA. This paper presents the case of a 9-month-old male child with pyrexia of unknown origin later was diagnosed with CIPA.

CASE REPORT

A 9-month-old male child, second born of a third-degree consanguineous marriage, presented with complaints of fever for the past month. The fever had an insidious onset and was intermittent in nature, with documented axillary temperatures ranging from 100°F to 101°F. The patient experienced intermittent fever occurring 3-4 times daily, without accompanying rigors or chills. The child remained active during the afebrile periods and the fever did not subside completely with over-the-counter medications. Additionally, there were no associated symptoms such as rash, ear or eye discharge, excessive crying while passing urine or seizures. The child had no history of vomiting,

excessive irritability, lethargy, refusal to feed, cough, cold or increased respiratory activity. There was no reported history of contact with tuberculosis, recent travel, loose stools, decreased urine output, blood transfusions, malignancy in the family, animal contact or exposure to unpasteurized milk. Moreover, there were no bony pains, swellings, bleeding from any site, history of recurrent infections or oral ulcers.

The child was born full-term via normal vaginal delivery, weighing 2.5 kg, with no neonatal intensive care unit stay. Developmental milestones were appropriate for age. Immunizations were up to date as per the National immunization schedule, with no special vaccines taken. The child was exclusively breastfed until 6 months of age, followed by complementary feeding.

On presentation, the child was afebrile with a heart rate of 116/min, respiratory rate of 30/min, blood pressure of 92/60 mmHg, capillary refill time of less than 3 seconds and SpO_2 of 98% on room air. Conjunctival pallor was noted. There were no evidence of lymphadenopathy, clubbing, icterus or peripheral edema. Multiple abrasions were observed on bilateral fingers. There were no signs of vitamin deficiency, external markers of tuberculosis or infective endocarditis. Respiratory examination revealed equal air entry bilaterally with breath sounds heard on both sides. Cardiovascular examination showed normal heart sounds (S1, S2) with no murmurs. The abdomen was soft and non-tender with no hepatosplenomegaly. Neurological examination revealed a Glasgow Coma Scale score of 15/15, normal tone in all four limbs, 5/5 strength on bilateral upper and lower extremities, reflexes 2+ at all joints and no signs of meningeal irritation.

Differential diagnoses included infections such as enteric fever, tuberculosis, rickettsial fever, malaria and Epstein-Barr virus, autoinflammatory conditions; malignancies such as leukemia and hematological conditions like sickle cell anemia and thalassemia.

The child had two previous hospital admissions. During the first admission from April 2nd to April 6th, 2024, the child received IV antibiotics and was discharged on oral antibiotics. During the second admission from April 16th to April 18th, 2024, the child received IV antibiotics and dexamethasone. The child was subsequently referred to our hospital. Investigations revealed negative results for Dengue, PSMP (PC3-secreted microprotein), Typhi dot IgM, blood culture, Weil-Felix test, urine routine microscopy, urine culture, Koch's workup, HHH ELISA (HIV, hepatitis B and C ELISA) and HPLC/sickling test (High-performance liquid chromatography). The 2D echocardiogram and abdominal ultrasound were also within normal limits.

A workup for pyrexia of unknown origin (PUO) was conducted and broad-spectrum antibiotics were empirically added. However, it was noticed that the child did not cry during IV insertion and sampling. Upon further investigation, the mother reported that the child did not cry during deep intramuscular injections for routine immunizations and that she had never noticed the child sweating. Interestingly, the mother reported that the child developed fever after spending time in the sun, which did not subside with antipyretics but did subside with cold water sponging. A detailed CNS examination revealed an absence of sensation to crude touch, pain and temperature. The patient was suspected to have CIPA and a whole exome sequencing was sent which confirmed the diagnosis. After stabilization, the child was subsequently referred to his paediatrician, dentist, dermatologist, Orthopedics and geneticist.

DISCUSSION

CIPA, also classified as hereditary sensory and autonomic neuropathy type IV (HSAN IV), is an extremely rare autosomal recessive disorder presenting early in infancy. This condition results from mutations in the NTRK1 gene, which encodes the high-affinity receptor TrkA for NGF, a critical component for the development and survival of sensory and sympathetic neurons.[1-3] The pathophysiology is that the NTRK1 gene mutation disrupts NGF signaling, leading to the loss of NGF-dependent neurons, particularly unmyelinated C fibers and small myelinated Aδ fibers. These nerve fibers are responsible for transmitting nociceptive (pain), thermal and itch sensations and their absence results in analgesia and anhidrosis. In addition, defective innervation of sweat glands causes complete or partial anhidrosis, which impairs thermoregulation and often results in hyperpyrexia, as exemplified in the patient described in our case study.[3,8,9]

Clinical features

Clinically, patients with CIPA typically present with an inability to perceive pain and temperature, a hallmark feature noticeable from infancy. This profound sensory deficit leads to recurrent self-inflicted injuries, as patients are unaware of harmful stimuli. Common manifestations include biting wounds, oral scalds, severe bruxism and corneal ulcerations, all of which reflect the absence of protective pain responses.[2,8]

Due to the lack of pain perception, patients frequently suffer from multiple fractures, joint dislocations and chronic osteomyelitis, often resulting from repetitive, unnoticed trauma.[8,9] Anhidrosis is another key clinical feature which leads to episodes of unexplained fever and dangerous hyperpyrexia, particularly during infancy or in hot climates, as inability to regulate body temperature through sweating impairs thermoregulation.[6,8]

Neurologically, many individuals with CIPA also experience cognitive impairments and developmental delays, which may compound the challenges in early diagnosis and management.[3,10] Dermatological manifestations are common and may include xerosis (dry skin), palmoplantar hyperkeratosis, skin fissures and

frequent infections. Lip scarring is also often seen, resulting from circumoral dryness and repetitive trauma due to the lack of discomfort.[11,12]

Diagnosis

CIPA is established through a combination of clinical evaluation, pharmacological testing, neuropathological examination and genetic analysis. Histamine and sweat tests are useful in identifying autonomic dysfunction, which is a hallmark feature of the disorder. Electrophysiological studies, such as nerve conduction studies (EMG), along with skin biopsy, are employed to rule out other forms of hereditary or acquired neuropathies and help narrow the differential diagnosis.[6] Definitive diagnosis is achieved through genetic testing, with the identification of pathogenic mutations in the NTRK1 gene, which is considered the diagnostic gold standard for CIPA.[13,14] In addition, electron microscopy of nerve biopsies may reveal the absence or marked reduction of small unmyelinated (C fibers) and thinly myelinated (Aδ fibers) nerve fibers, further supporting the diagnosis.[15]

Management

There is currently no curative treatment for CIPA. Therefore, management is primarily supportive and requires a comprehensive, multidisciplinary approach. A key focus is injury prevention, as patients are prone to unrecognized trauma due to their inability to feel pain. This includes the use of protective gear, specialized orthopaedic care and, in some cases, surgical interventions such as osteotomy or even amputation for non-healing or severely infected fractures.[8,9] Dental care is another critical component of management. Due to the high incidence of oral trauma and caries, patients require frequent dental check-ups to monitor and treat unnoticed injuries. Preventive measures and early interventions are essential to preserve oral health and function.[2]

Regulating body temperature is vital, especially in children, as anhidrosis puts them at risk for life-threatening hyperthermia. Management strategies include the use of cooling vests, avoidance of hot environments and maintaining proper hydration to help prevent overheating.[8] Patients should be monitored regularly by a team of specialists, including paediatricians, dentists, ophthalmologists and dermatologists. This ensures early identification and prompt treatment of complications such as infections, dental deformities and vision problems.[15]

Genetic counselling plays a crucial role in family planning. It is important to educate families about the autosomal recessive inheritance pattern of CIPA and to discourage consanguineous marriages. Prenatal diagnosis is available through genetic testing for NTRK1 mutations in at-risk pregnancies, providing options for early intervention and informed decision-making.[6,15] Daily evaluations by caregivers and parents are essential, as affected children may not recognize or communicate injuries. Preventive orthopaedics strategies such as special footwear, periods of non-weight bearing and modification of physical activities help reduce the risk of fractures and joint damage.[8,9]

Prognosis

Although historically considered to have a poor prognosis, many individuals with CIPA now survive beyond early childhood due to improved supportive care and early recognition of complications. However, recurrent infections, trauma and hyperpyrexia continue to pose life-threatening risks.[8,15]

CONCLUSION

CIPA is a devastating and complex neurogenetic disorder marked by insensitivity to pain and anhidrosis. Early diagnosis, genetic confirmation and coordinated multidisciplinary care are vital to improving quality of life and reducing morbidity. As our understanding of CIPA's pathophysiology expands, future therapeutic interventions may target specific signalling axis, offering hope for more specific treatments.

This case report illustrates the diagnostic workup and management of a patient with CIPA. Diagnosis of CIPA is established through a combination of clinical evaluation, pharmacological testing, neuropathological examination and genetic analysis. Although considered a poor prognosis for most patients, supportive care and early recognition of complications are vital for survival. As our understanding of CIPA evolves, so too will our ability to provide targeted and effective treatments that improve outcomes for individuals affected by this disorder.

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