Case Report

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A challenging diagnosis of chronic osteomyelitis in a child with congenital insensitivity to pain: a case report

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Introduction: Congenital insensitivity to pain (CIP) is a rare condition where individuals are born with an inability to perceive pain. This can lead to various complications in the skin, skeletal system, and other bodily systems. Chronic osteomyelitis is one of the possible manifestations of CIP, which can be difficult to diagnose and treat due to the lack of pain as a diagnostic criterion.

Presentation: A 5-year-old boy with CIP developed chronic osteomyelitis in his right leg, presented with fever, claudication, swelling, and local heat for 2 months. He had a history of CIP since birth, diagnosed at 18 months of age. He also had a family history of CIP. He had previously suffered a shoulder fracture and had taken asthma medication for 1 year. He had experienced tonsillitis 2 months ago. On examination, he had hepatomegaly, enlarged lymph nodes in the groin, and a minor swelling on the right knee. He had an audible snapping sound during knee flexion. Blood tests showed increased inflammatory markers. Imaging studies confirmed presence of osteomyelitis, and bone biopsy revealed infection with *Staphylococcus aureus*. Treatment included vancomycin and cefotaxime.

Clinical discussion: Genetic factors behind CIP were discussed, highlighting challenges in diagnosis. Manifestations of CIP, diverse and age-related, include orthopaedic issues, ophthalmological effects, and thermoregulation disturbances. The patient's case is presented with unique features, necessitating a comprehensive diagnostic approach.

Conclusion: This case highlights the challenges faced in diagnosing osteomyelitis among CIP patients and emphasizes the need for other diagnostic criteria apart from pain.

Keywords: case report, chronic osteomyelitis, CIP, congenital insensitivity to pain, diagnostic challenges

Introduction

Pain is an inherent sensory process present in all advanced organisms, meant to identify potential or actual damage to body tissues[1,2]. Pain despite being a negative combination of sensory and emotional sensations has a very important role in controlling our behaviour and giving us a competitive advantage for survival[3]. However, in certain rare cases, some disorders can occur whereby elements of pain transmission may malfunction or even fail to develop[4]. An example of such a condition is congenital insensitivity to pain (CIP), which refers to a state where individuals are born with an inability to perceive pain[5].

The absence of the trophic role of nociceptive response, along with other unidentified mechanisms, gives rise to a pervasive and gradual impact of this condition on the skin, skeletal system, and other bodily systems[6–8]. Manifestations within orthopaedics concerning CIP include multiple issues like late diagnosis of fractures, nonunions, malunions, avascular necrosis, osteomyelitis, heterotopic ossification, and dislocations pertaining joints[9,10]. The causes of CIP can vary, with genetic factors playing a significant role. The condition is often associated with

HIGHLIGHTS

- A 5-year-old boy with congenital insensitivity to pain (CIP) presented with fever, leg swelling, heat, and claudication for 2 months, eventually diagnosed with chronic osteomyelitis.
- Diagnosis was challenging due to lack of pain perception, a key diagnostic criterion, necessitating use of other signs like swelling and inflammation.
- Imaging tests like X-ray, MRI, and bone biopsy confirmed the presence of osteomyelitis with *Staphylococcus aureus* infection.
- Treatment included antibiotics vancomycin, cefotaxime. Supportive lifelong care needed to monitor for infections and injuries.

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mutations in specific genes that are involved in the transmission of pain signals within the nervous system such as SCN9A and Nav1.7[11].

CIP does not have specific diagnostic criteria, but typically a combination of factors, including a history of unresponsiveness to pain, clinical examination, and neurological tests like Electroneuronography, are considered adequate, and the genetic test is the definitive confirmation. Regrettably, there currently exists no curative treatment for CIP, and the options available primarily focus on providing support and implementing preventive measures[12,13].

The present article describes a case study conducted on a 5-year-old child who had chronic osteomyelitis with preceding CIP since birth. This study aims to bring to the forefront the attention of medical practitioners and healthcare providers regarding the necessity of identifying alternative diagnostic criteria beyond pain in the diagnosis of chronic osteomyelitis among children affected by CIP.

Case presentation

We present a case of a 5-year-old boy who had been experiencing a fever and claudication in his right leg for a duration of 2 months. According to parent's report, the fever was with three peaks per day and responded to antipyretics. Intramuscular ceftriaxone was administered to him by a paediatrician for 8 days. While the symptoms showed partial improvement as noticed by his parents, they resurfaced after 10 days. These symptoms included fever, claudication, swelling, and heat in the right leg, without any redness.

During history taking, it was revealed that the child has had insensitivity to pain since birth. It was diagnosed in the child at 18 months of age after observing a lack of response to pain or acupuncture. As a result, the patient had a medical history of recurrent bruising. Additionally, the family history revealed that the mother's cousins also have insensitivity to pain. The patient had previously suffered a shoulder fracture and had been taking 'asthma medication', which was discontinued 1 year ago. Two months ago, the patient had experienced tonsillitis. However, there was no mention by the parents of any previous injury to the patient's leg. Besides, the child was delivered without complications through natural delivery and exhibited typical psychomotor development. At present, the child weighs 25 kg, measures 107 cm in length, and has a head circumference of 51 cm. At admission, the child's overall health appears to be good as there has been no fever spike over the past 10 days.

Upon examination, there was a minor swelling present below the thigh and on the right knee. Although there were no signs of inflammation or local heat, the child was experiencing some claudication. In addition, an audible snapping sound was heard during knee flexion. On examination of the nervous system, it was found that the child has a generalized absence of sensations such as pain, tingling, and heat, while the rest of the nervous system appears to be normal. Additionally, during the abdominal examination, hepatomegaly was observed 2 cm below the costal margin, while no splenomegaly was detected. Simultaneously, enlarged lymph nodes were noted bilaterally in the groin area. However, the cardiac and respiratory examination did not reveal any significant abnormalities.

Blood test: white blood cells (WBC) = 6700/μl, C-reactive protein (CRP) = 4.5 mg/dl, haemoglobin (Hb) = 10 g/dl, mean corpuscular volume (MCV) = 76 fl, erythrocyte sedimentation rate (ESR) = 60; Widal's test and Wright's test were negative; the circumference of the knee joint ($R = 28$ cm, $L = 27$ cm) and the circumference of the ankle joint ($R = 21$ cm, $L = 18$ cm).

An ultrasound of the knees was done, and an effusion of a small amount of cloudy content was found. Arthrocentesis could not be done. The bony surface of both sides of the knee joint was observed to be tortuous and irregular, and fluid infiltration was observed within the cellulite tissue in the right knee joint. Moreover, upon performing an X-ray of the right knee, it was found to have a bone lesion with a periosteal reaction. An MRI examination was conducted on the right knee and lower right thigh, revealing bone degeneration and fluid accumulation below the femoral epiphysis. There was also extensive oedema in the surrounding bone marrow and soft tissues, as well as a mild fluid collection behind the knee joint, indicating osteomyelitis. The remaining structures appeared normal.

Confirmation of chronic osteomyelitis was obtained via a bone biopsy of the right lower thigh. A sample of fluid from the lower thigh was cultured, which confirmed the presence of *Staphylococcus aureus* infection. Regarding management, the treatment for osteomyelitis involved administering a combination of vancomycin, 300 mg intravenously (i.v.) every 6 h, and cefotaxime, 1 g i.v. every 6 h, both continued for a duration of 14 days. Additionally, the patients were educated on the proper care for their child, as there is no definitive cure for this CIP condition. This included taking precautions to prevent injuries, actively checking for any injuries, and promptly seeking treatment for them. Subsequently, the child was discharged with careful monitoring to ensure the complete resolution of inflammation symptoms.

Discussion

Researchers have shown that CIP can be caused by mutations in the Sodium Voltage-Gated Channel Alpha Subunit 9 (SCN9A) gene that make the Nav1.7 protein non-functional. These mutations were found in various human populations, suggesting that they are not restricted to a single ethnic group or region[5]. Another one is variations in neurotrophic receptor tyrosine kinase 1 (NTRK1), which is a common genetic factor. Mutations and polymorphisms of this gene may impair sensory neurons' development and function leading to CIP[14]. We discussed the most common genetic causes of this condition, but many other rare variants can also lead to it. As mentioned in our presentation, it was noted that the mother's cousins also exhibit insensitivity to pain. Regarding the inheritance pattern, CIP is generally inherited in an autosomal recessive manner. However, it is important to mention that there are exceptions to this rule, such as SCN11A-CIP and ZFHX2-CIP, which are inherited in an autosomal dominant manner[11]. Unfortunately, we were not able to perform any genetic testing on the patient due to the limited resources in our country.

The manifestations of CIP are diverse and can be categorized as age-related. In neonates and young children, impaired temperature sensation may manifest as burns[15], and chronic otitis media can be observed[16]. In older paediatric patients, the presence of osteomyelitis and bone and/or joint deformities often necessitates

surgical interventions, which can, in some cases, involve extensive and profound amputations[17]. Ophthalmological effects are notable, with frequent absence of corneal sensitivity leading to common corneal ulcerations and, occasionally, neuroparalytic keratitis[18]. Thermoregulation disturbances, such as anhidrosis, may result in recurrent unexplained fever[14]. It is crucial to note that hyperpyrexia can be fatal if not treated[16].

In terms of development and intellectual aspects, children diagnosed with congenital insensitivity to pain with anhidrosis (CIPA) typically demonstrate significantly lower levels of cognitive and adaptive functioning when compared to their healthy siblings. Additionally, children with CIPA often exhibit a high frequency of ADHD symptoms. An interesting observation is the inverse correlation between intelligence quotient (IQ) and age among children with CIPA. As children with CIPA age, their IQ scores tend to decrease[19]. Another manifestation is anaemia, which has been reported in as much as 79% of CIPA patients[16]. It can also be noted that a few affected people suffer from neuropathic pain; however, this does not generally affect their daily lives[20]. Self-mutilating behaviour causing oral perioral injuries and injuries in extremities has also been observed[21].

In our specific case, the patient presented with a constellation of symptoms, including fever, leg pain, localized swelling, increased warmth in the right leg, and claudication. These symptoms were attributed to osteomyelitis. Remarkably, the patient showed insensitivity to pain, which is characteristic of the condition. Notably, the patient also exhibited typical psychomotor development, no ophthalmological effects and the perspiration was normal. Despite that chronic osteomyelitis can occur as a result of traumatic injuries, particularly during periods of civil unrest or war, or as a complication of surgical procedures, it is important to note that our patients did not have any of these circumstances or experience any impact from the ongoing conflict in our country[22].

Defining clinical diagnostic criteria for CIP remains a challenge as there is no established consensus. However, a definitive diagnosis necessitates observable evidence of the absence of nociception in a conscious individual of typical intellectual capacity. In cases involving intellectual disability, clinical diagnosis may pose increased complexity[11]. As assessment of the rest of the peripheral and central nervous system is typically normal, then the routine nerve conduction studies and electromyogram are typically normal[16]. Consequently, the sole diagnostic approach entails the application of painful stimuli, which we have undertaken.

During the evaluation of the patient's nervous system, notable findings included the absence of pain, tingling, and heat perception. However, the remaining aspects of the nervous system examination yielded results within the normal range. The diagnostic process for osteomyelitis involved the utilization of both X-ray and MRI imaging techniques.

The management of CIP entails a lifelong commitment, initially by parents and later by the patient himself, to maintain vigilant oversight for indicators of corneal damage, infections (commonly attributed to *S. aureus* and necessitating aggressive treatment), as well as potential bone and joint injuries[13]. Given the exceptional rarity of CIP, it is noteworthy that no disease-specific therapeutic interventions have received approval. Thus, it is recommended to primarily provide supportive care to patients and maintain regular follow-up assessments for the early detection of infections and emerging symptoms.

In response to the culture results confirming the presence of *S. aureus* in the lower thigh fluid sample, a treatment course was initiated, consisting of vancomycin and cefotaxime. Finally, given its genetic aetiology, the inclusion of family counselling and educational programmes concerning consanguineous marriages is a vital component of the management plan to ensure its efficacy[23].

Conclusion

CIP is a rare condition associated with severe bone problems. The findings presented in this case report hold particular significance for orthopaedic surgeons, emphasizing the intricate challenges associated with early diagnosis of osteomyelitis in children affected by CIP. By highlighting these difficulties, this study aims to prompt physicians to consider additional diagnostic criteria that are not solely reliant on pain, such as the presence of swelling and excessive heat, in order to enhance the detection process and ensure timely and accurate identification of these patients.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Consent

Written informed consent was obtained from the patient's parents for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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Author contribution

H.K.: is the first author contributed to drafting, reviewing, editing, bibliography, corresponding, and approved the final manuscript; R.A., D.A., and A.B.A.: contributed to drafting, reviewing, editing, and approved the final manuscript; N.M.: contributed to training, reviewing, and leading the process, and approved the final manuscript; J.M.: contributed to reviewing, supervising, and approved the final manuscript.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

Research registration unique identifying number (UIN)

I confirm that our article is a case report and does not involve a research study requiring registration in a publicly accessible database.

Guarantor

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