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A 5-Year-Old Palestinian Bedouin Girl with Repeated Self-Induced Injuries to the Digits, a Diagnosis of Congenital Insensitivity to Pain, and Anhidrosis

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
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Patient: Female, 5-year-old
Final Diagnosis: Congenital insensitivity to pain and anhidrosis
Symptoms: Infection • swelling
Medication: —
Clinical Procedure: Joint fixation
Specialty: Neurology • Orthopedics and Traumatology • Pediatrics and Neonatology

Objective: Unusual clinical course

Background: Congenital insensitivity to pain with anhidrosis (CIPA), also referred to as hereditary sensory and autonomic neuropathy type IV, is a rare autosomal recessive disease caused by mutations in the NTRK1 gene. The inability to feel pain and temperature often leads to repeated severe and unintentional self-inflicted injuries; these can result in severe complications, as patients heal slowly from skin and bone injuries. This case report describes a 5-year-old Palestinian girl with self-inflicted injury to the digits, a dislocated distal inter-phalangeal joint of the left big toe, and a diagnosis of CIPA.

Case Report: A 5-year-old girl, a daughter of related Palestinian Bedouin parents, presented with a chronic unhealed wound over the planter surface of the left foot. Painless repetitive minor traumata over the same area badly affected wound healing and this led to wound dehiscence and dislocation of the distal inter-phalangeal joint of the left big toe. Surgical fixation of the dislocated joint along with intravenous antibiotics and close follow-up resulted in eventual improvement and near complete wound healing despite the obviously slow healing process. The girl also displayed evidence of unintentional self-inflicted injury, which within the overall clinical context warranted a clinical suspicion of CIPA. This was confirmed by genetic testing for the presence of a homozygous frameshift mutation in the NTRK1 gene (c.1842_1843insT; p.Pro615Serfs*12).

Conclusions: This case report shows that a physician should have a low threshold of suspicion to investigate for CIPA when managing children with multiple unintentional self-inflicted injuries, anhidrosis, and pain insensitivity, mainly through genetic testing to detect mutations in the NTRK1 gene.

Keywords: Hereditary Sensory and Autonomic Neuropathies • Manipulation, Orthopedic • NTRK1 Protein, Human

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Background

Hereditary sensory and autonomic neuropathy type IV (HSAN-IV) (OMIM# 256800), congenital insensitivity to pain with anhidrosis (CIPA), and congenital nociceptor deficiency, all refer to an autosomal recessive condition [1] manifested by painlessness; autonomic dysfunction, including markedly reduced sweating, alterations in temperature, vibration or proprioception sense; and variable degrees of intellectual disabilities that lead to musculoskeletal manifestations (eg, fractures, joint deformities, dislocations) [2,3]. Reports record a prevalence of around 1 in 25 000 individuals [4].

CIPA is mainly caused by mutations in the Neurotrophic Receptor Tyrosine Kinase 1 (NTRK1) gene that encodes tropomyosin-related kinase A (TrKA) as a receptor for nerve growth factor (NGF) [5]. NGF has a vital role in regulating peptide neurotransmitter/neuromodulator levels in mature sympathetic and sensory neurons [6]. Defective NGF is likely responsible for the clinical manifestations of this rare entity [7,8], with more than 100 mutations previously identified in the tyrosine kinase domain of the TrkA gene in CIPA patients [9]

Children with CIPA typically have varying degrees of developmental and intellectual disabilities, which, together with painlessness, lead to late presentation and diagnosis [8,10]. Severe orthopedic complications such as osteomyelitis, nonunion, avascular necrosis, heterotopic ossification, and fractures followed by callus formation are common [11-13]; they are sometimes the initial presentation prior to an established diagnosis, and can present as early as the first months of life [14]. Factors complicating orthopedic management of these patients are the presence of autonomic dysfunction, self-inflicted injury, and possible association with immunodeficiency [15,16], with resultant susceptibility to infections caused by aggressive pathogens such as *Staphylococcus aureus* [17,18].

Further manifestations that can complicate the anesthetic management are increased risk of gastric regurgitation and aspiration, hemodynamic instability, and poor temperature regulation [19]. Increased awareness among orthopedic physicians of this rare disorder and associated surgical challenges will improve the quality of care provided to these children. Standard orthopedic treatment with intensive follow-up and low threshold for repeat radiological imaging are important to avoid clinically unrecognized infections, deformities, and incomplete healing [17].

CIPA is a rare condition, and reports of this condition are limited to small case series and case reports; the majority of these are children of consanguineous parents [14,20]; however, consanguinity is not mandatory for diagnosis as there are a number of cases reported of children of unrelated parents [21,22]. This report is of a 5-year-old Palestinian girl with self-inflicted injury to the digits, a dislocated distal inter-phalangeal joint of the left big toe, and a diagnosis of CIPA.

Case Report

A 5-year-old female patient who was the daughter of a Palestinian Bedouin refugee initially presented for orthopedic evaluation after a protracted left big toe wound infection after a traumatic event 2 months earlier. Her parents reported that despite general practitioner management by wound suturing and regular dressing at that time, there was evidence of progressive unexpected soft tissue infection and poor healing, and she was subsequently referred to us.

Initial evaluation in our outpatient clinic revealed an underweight child with intellectual disability, mild dysmorphism, and evidence of self-inflicted injury in the form of damaged fingernails and bitten lips (**Figure 1**). Left foot examination revealed

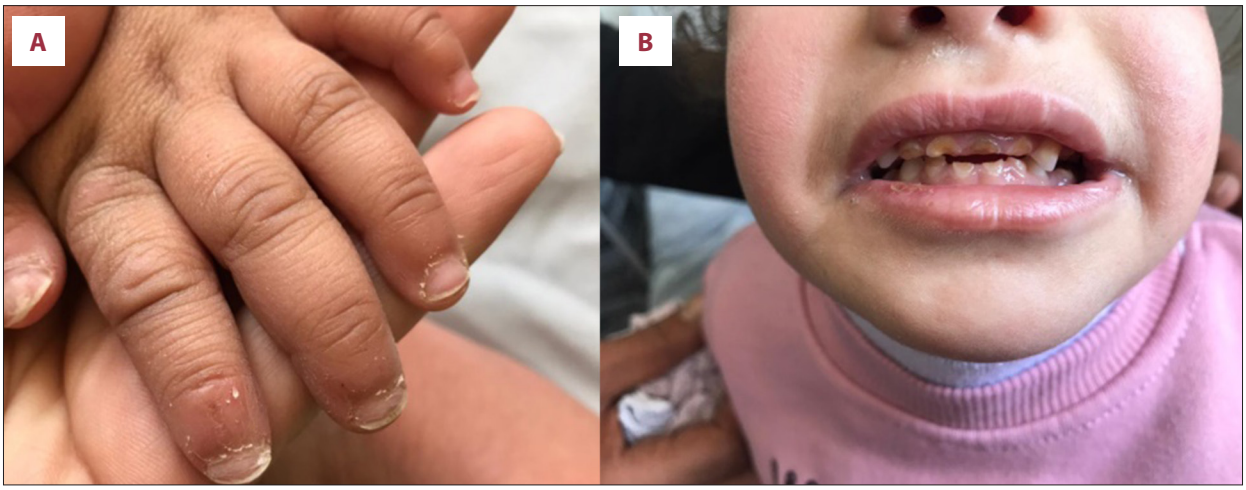

Figure 1. Evidence of self-inflicted injury. (**A**) Damaged fingernails. (**B**) Dentition eruption.

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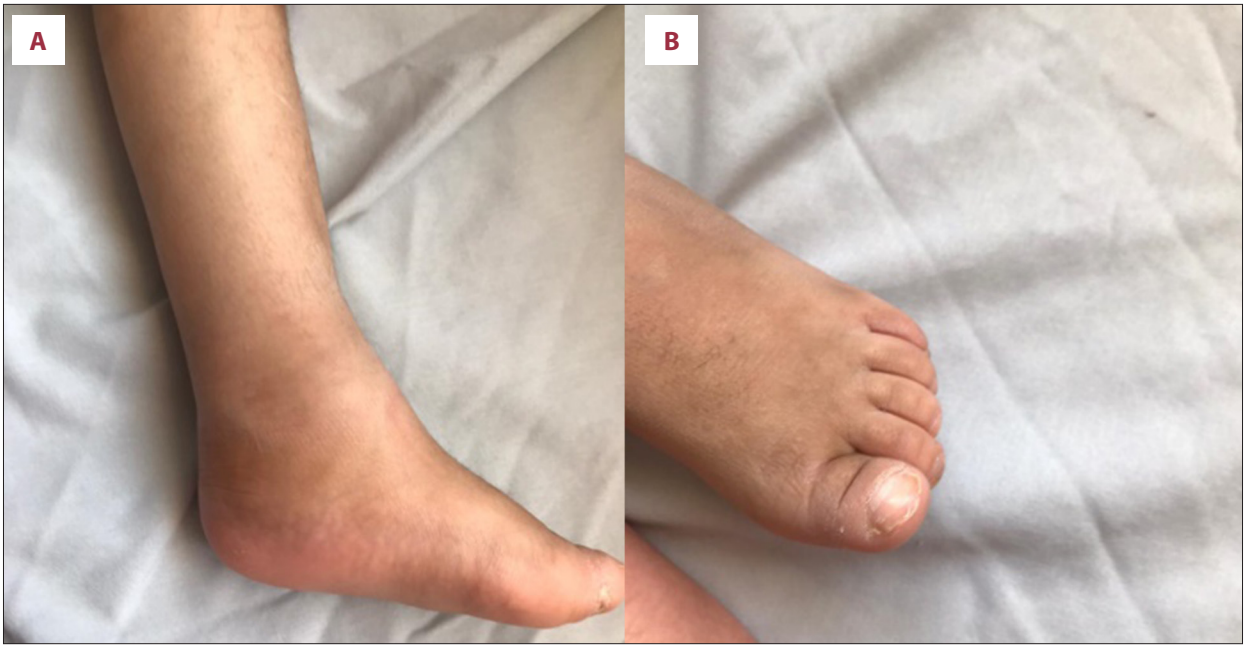

Figure 2. Healed wound 12 weeks after open reduction and k wire for open dislocated distal phalanx. (**A**) Lateral view of big toe. (**B**) Anterior view of big toe.

big toe swelling, hotness, and redness, with a deep wound on its planter aspect with bone exposure. Significantly, the patient displayed no indication of pain sensation during examination or wound dressing, allowing care without analgesics.

Laboratory evaluation was notable for elevated inflammatory markers; C-reactive protein (CRP) was 69 and erythrocyte sedimentation rate (ESR) was 45, with otherwise unremarkable liver function tests, thyroid function test, vitamin B12 level, random blood sugar, and complete blood count. An X-ray of the affected region showed a dislocated distal inter-phalangeal joint of the left big toe.

Given the constellation of clinical findings, CIPA was suspected and ultimately confirmed via genetic testing, which revealed a homozygous frame shift mutation in the NTRK1 gene (c.1842_1843insT; p.Pro615Serfs*12).

Considering the diagnosis of CIPA, management was tailored accordingly. The presence of infection and a dislocated distal inter-phalangeal joint of the left big toe required starting intravenous antibiotics followed by surgical fixation of the dislocated joint by means of K wire fixation under general anesthesia and circular casting for a total of 3 weeks, then the use of walking boots for an additional 4 weeks to decrease injured area mobilization and avoid repetitive trauma. Unfortunately, the pre-operative X-rays were not available.

Management continued by twice-weekly orthopedic clinic visits with monitoring for any new signs of infection or other orthopedic complications. These measures resulted in eventual improvement and complete wound healing throughout the first 3 months of management (**Figure 2**).

Despite the parents' awareness of their child's condition, poor adherence to clinical follow-up after the first 3 months of treatment led to worsening of the child's clinical condition. She subsequently presented 6 months later with left foot diffuse osteomyelitis of the talus, calcaneus, and distal fibula (**Figure 3**), in addition to right foot first metatarsal bone fracture, and callous formation (**Figure 4**).

Discussion

The overall clinical course of this patient shows the importance of early diagnosis and management of congenital insensitivity to pain with anhidrosis (CIPA), with the consideration of conservative management by cast immobilization as a cornerstone in the treatment of orthopedic complications when applicable.

Hereditary sensory and autonomic neuropathy (HSAN) is a group of genetically inherited diseases characterized by peripheral neuropathy [2,3]. It can affect sensory, autonomic, and motor nerves. HSAN involves 5 subgroups, which vary in mode of inheritance, genetic mutations, age of presentation, and clinical manifestations [2,3].

The patient described here presented the constellation of clinical findings seen in children with HSAN type IV/CIPA. This is

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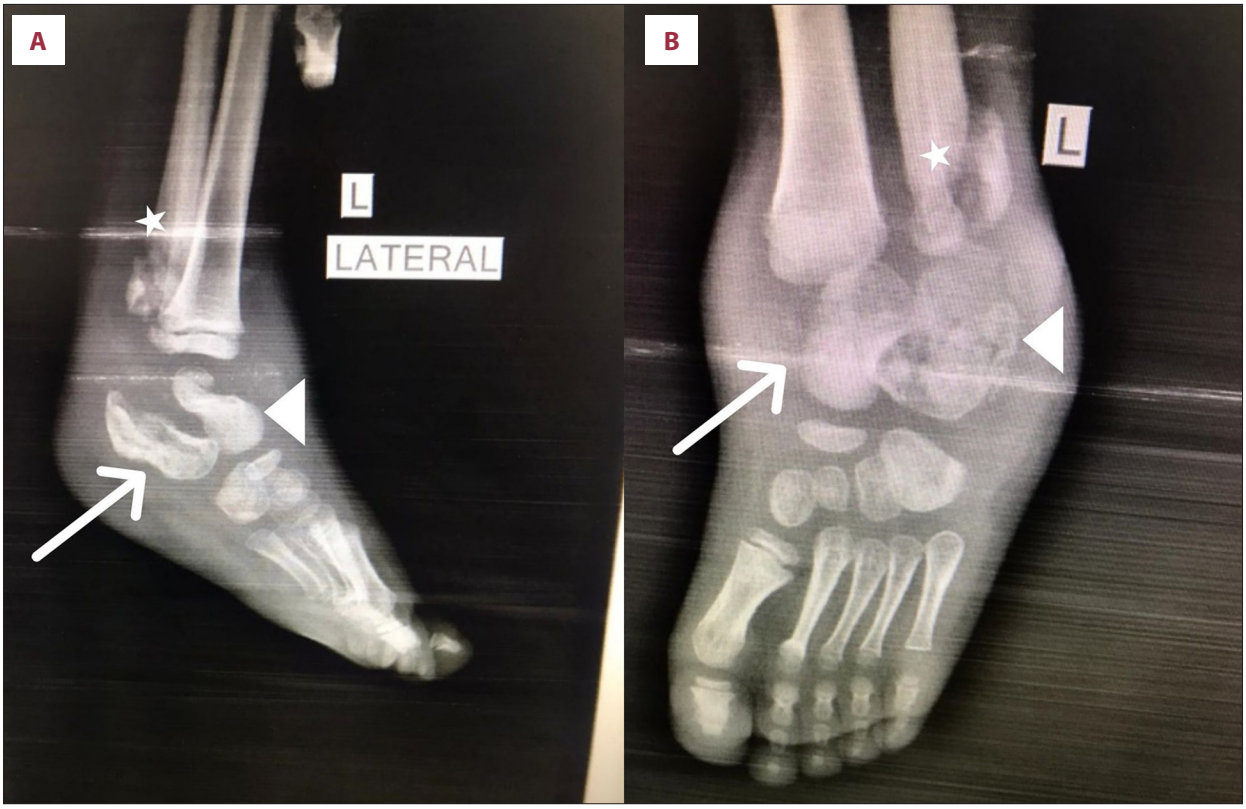

Figure 3. Left foot X-ray, diffuse osteomyelitis involving the talus (arrow), calcaneus (arrow head), and distal fibula (star). (**A**) Lateral view X-ray of the left foot. (**B**) Anterior-posterior view X-ray of the left foot.

characterized by the presence of a homozygous frameshift mutation in the NTRK1 gene that encodes TrKA, first described by Indo et al [5]. In addition to causing painlessness, and as TrkA signaling has a role in bone formation [6,23], lower TrkA signaling is linked to increased susceptibility to fractures [23].

HSAN type IV/CIPA is further classified into 3 different types depending on the clinical presentation: type A is characterized by multiple infections; type B is characterized by fractures, growth disturbances, and avascular necrosis, and type C is characterized by a combination of joint dislocations, fractures, and infections [3]. Type C best fits the patient described here.

The patient's lack of pain sensation not only contributes to increased risk of fractures and wound infections, but also interferes with adequate immobilization, leading to nonunion, micro-traumas, and neuroarthropathies [12]. These issues are further compounded by the presence of intellectual disability, impaired cognitive function, hyperactivity, and impulsivity [24], which all participate in repetitive injuries and poor healing in cases of bone fractures or joint dislocations.

In addition, CIPA patients may have recurrent corneal injuries leading to various degrees of visual disabilities [25]. The primary ophthalmic evaluation of our patient ruled out corneal involvement, and she was strictly educated about the importance of regular follow-up and quickly seeking medical advice if she had any vision symptoms.

While the clinical findings seem typical for the majority of patients, including ours, they are nonspecific, and diagnosing a patient with the disease is challenging and requires high clinical suspicion in the first place. Unusual complications following fractures and delayed wound healing in a child should alert the orthopedic physician to the possibility of CIPA.

Diagnosis is based on the clinical manifestations and confirmation with genetic testing, looking mainly for mutations in the NTRK1 gene. More than 100 different mutations had been previously reported around the world [7,9,26-28]. In the region from which our patient originates, nearly 89% of the cases show a similar mutation – the NTRK1 gene mutation (p.Pro615Serfs*12) [26].

Management of CIPA is mostly supportive with no disease-specific treatment, but frequent follow-up and evaluation for any signs of infection and unhealed injuries is the mainstay of management [16], as was applied to the described patient. While preventive measures aimed at minimizing exposure to injurious conditions and vigilance regarding skin hygiene are

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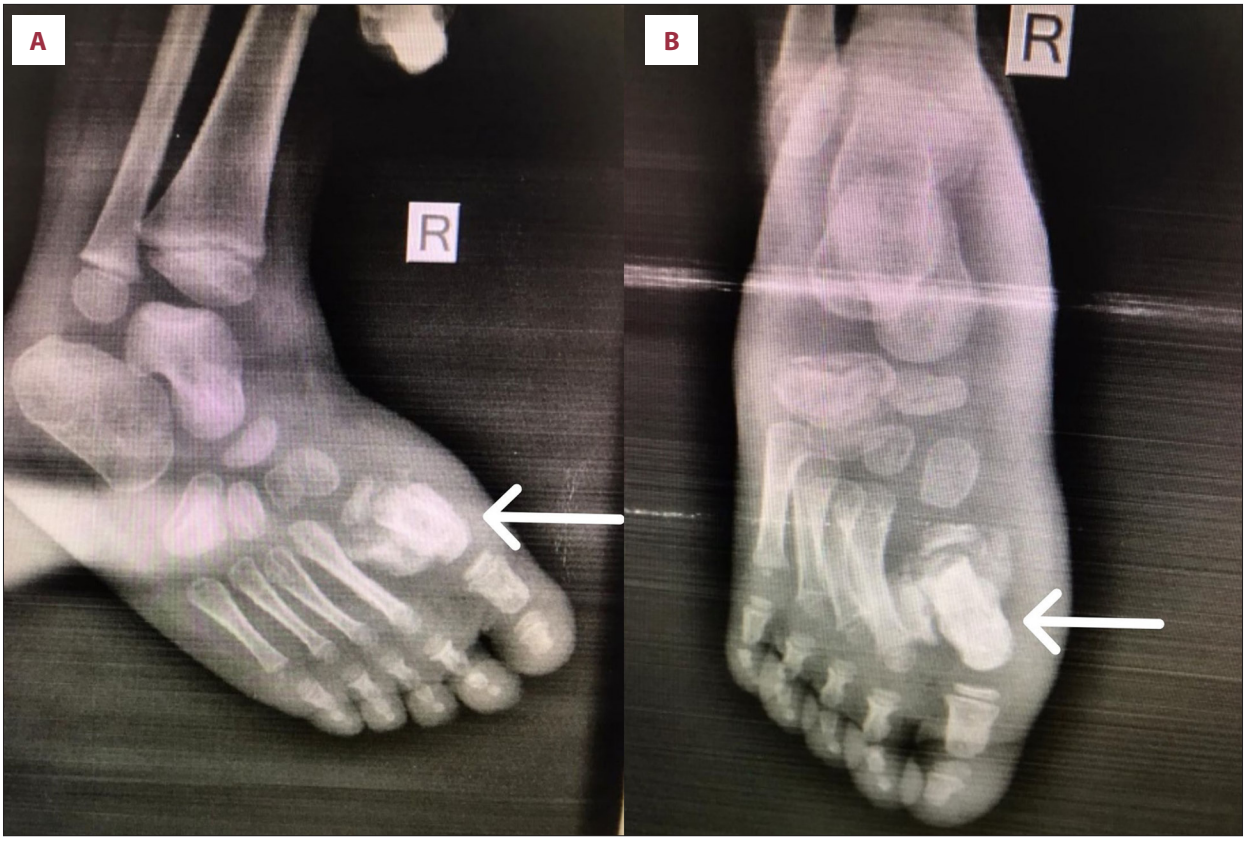

Figure 4. Right foot X-ray, first metatarsal bone fracture, and callous formation (arrow). (**A**) Lateral view X-ray of the right foot. (**B**) Anterior-posterior view X-ray of the right foot.

optimal, they were difficult to implement given intellectual disability and behavioral disturbances [8,24].

Although patients with CIPA have no pain perception [2,3], surgical intervention without anesthesia is not recommended as they still have a stress response to other stimuli such as endotracheal intubation and wound manipulations [19,29].

Significant implications arise with regards to orthopedic and anesthetic management [10,12,19]. While some reports have concluded that conservative treatment of fractures with closed reduction and cast immobilization was satisfactory and reported an increased incidence of infections after invasive corrective procedures [11], others have questioned this approach given the risk of complications arising from prolonged immobilization such as bed sores and osteopenia [12]. Regarding anesthetic management of patients with CIPA, in the report by Zlotnik et al, intraoperative and postoperative bradycardia was particularly increased [19].

Again, owing to the rarity of this disorder, various anesthetic complications are difficult to predict, and the possibility of perioperative aspiration and hyperthermia must be anticipated [19]. CIPA is a rare condition and well-defined orthopedic guidelines have not been formulated yet.

Last but not least, family counseling and education has a vital role in the continuity and effectiveness of management of those patients, and it influences the decisions of marriage between related family members by predicting the possibility of having affected offspring [14,20], especially knowing that it is a disease with high mortality. A recent report on CIPA from Jordan showed a high fatality rate, with 4 out of 7 cases experiencing early death [7].

To sum up, serious orthopedic complications owing to impaired pain sensation are by far the most serious yet preventable complications of CIPA, and it can be the initial presentation of the disease [3,14]. Trivial insults can lead to situations that are extremely difficult to manage if not detected in a timely manner [12]. Increased awareness of this condition among orthopedic physicians would improve the management of these patients.

In this case report, we highlight the diagnostic dilemma orthopedic physicians face when they encounter a previously undiagnosed child, and we stress that in cases of limb injuries, cast immobilization together with frequent clinical and radiological follow-up have a vital impact on preventing further complications that may develop due to repetitive unrecognized traumas.

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Conclusions

This report has shown that children who present with unintentional self-inflicted injury, anhidrosis, and pain insensitivity should be considered for investigation of mutations in the NTRK1 gene and CIPA, and we stress here the importance and effectiveness of cast immobilization in the management of a range of orthopedic complications.

Department and Institution Where Work Was Done

This case report was written at the Department of Orthopedics, Al-Safa Specialized Hospital, Jarash, Jordan.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part, after obtaining consent from the patient's parents.

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