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Case Report

Amplified pain and complex regional pain syndrome in children: clinical cases and literature review

Vladimir M. Kenis

H. Turner National Medical Research Center for Children's Orthopedics and Trauma Surgery, Saint Petersburg, Russia;
North-Western State Medical University named after I.I. Mechnikov, Saint Petersburg, Russia

ABSTRACT

BACKGROUND: Musculoskeletal pain is a common reason for visiting pediatric clinics. Causes of chronic musculoskeletal pain include various inflammatory or noninflammatory conditions. Amplified pain syndrome refers to a wide range of conditions manifested by chronic pain, the common feature of which is central and/or peripheral sensory amplification of pain. Complex regional pain syndrome is characterized by spontaneously occurring or provoked by irritating stimuli pain of high intensity, disproportionate to the actual injury or other stimulus, and the presence of several concomitant vegetative and motor disorders.

CLINICAL CASES: This article presents three clinical cases of pediatric patients with chronic musculoskeletal pain and an analysis of the current literature on chronic pain in children.

DISCUSSION: Complex regional pain syndrome is more common in adolescent girls, and conflict or psychological trauma is a common trigger. Symptoms of disproportionate burning pain (causalgia) with trophic changes may indicate complex regional pain syndrome. To date, there are no generally accepted pharmacological treatments recommended for children with complex regional pain syndrome. Nonsteroidal anti-inflammatory drugs (ibuprofen) and paracetamol and their combination are commonly administered in cases wherein symptoms of chronic pain first appear.

CONCLUSIONS: Currently, a multidisciplinary approach, including physical, psychological, medical, and invasive methods, appears to be the most adequate treatment method for musculoskeletal pain. The use of analgesics should comply with approved protocols of pain management in pediatric practice.

Keywords: amplified pain; complex regional pain syndrome; children.

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Клинический случай

Амплифицированная мышечно-скелетная боль и комплексный регионарный болевой синдром у детей: клинические случаи и анализ литературы

В.М. Кенис

Национальный медицинский исследовательский центр детской травматологии и ортопедии имени Г.И. Турнера, Санкт-Петербург, Россия;
Северо-Западный государственный медицинский университет им. И.И. Мечникова, Санкт-Петербург, Россия

АННОТАЦИЯ

Обоснование. Боль в структурах опорно-двигательного аппарата у ребенка — одна из самых распространенных причин обращения к врачу. Причины хронической мышечно-скелетной боли включают широкий спектр воспалительных или невоспалительных состояний. Амплифицированный болевой синдром — это термин, который описывает широкий спектр состояний, проявляющихся хронической болью и характеризующихся центральным и/или периферическим сенсорным усилением боли. При комплексном регионарном болевом синдроме отмечают спонтанно возникающую или вызванную раздражающими стимулами боль высокой интенсивности, непропорциональную фактической травме или иному стимулу, при наличии широкого спектра сопутствующих вегетативных и двигательных нарушений.

Клинические наблюдения. В настоящей публикации представлены три клинических случая пациентов детского возраста с хронической мышечно-скелетной болью и анализ современной литературы, посвященной хронической боли у детей.

Обсуждение. Комплексный регионарный болевой синдром чаще встречается у подростков в возрасте 11–14 лет, девочки болеют чаще, чем мальчики. Конфликтная или психотравмирующая ситуация, как правило, служит триггером. Симптомы диспропорциональной жгучей боли (каузалгии) с соответствующими трофическими изменениями должны вызывать у практикующего врача подозрение на комплексный регионарный болевой синдром. На сегодняшний день не существует общепринятых фармакологических методов лечения, рекомендованных для детей с комплексным регионарным болевым синдромом. Нестероидные противовоспалительные препараты (ибупрофен) и парацетамол, а также их комбинация наиболее часто назначают в тех случаях, когда впервые появляются симптомы хронической боли.

Заключение. Комплексный мультидисциплинарный подход, включающий физические, психологические, медикаментозные и инвазивные методы, на сегодняшний день представляется наиболее обоснованным, при этом применение медикаментозных препаратов должно соответствовать утвержденным нормам и практике обезболивания в педиатрии.

Ключевые слова: амплифицированная боль; комплексный регионарный болевой синдром; дети.

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BACKGROUND

The etymological relationship between the Russian words for "pain" and "disease" is suggestive of an association between the two concepts. However, there are medical conditions wherein pain emerges as the fundamental aspect of the disease, defining its nature and serving as primary manifestation. In such cases, pain evolves from merely being a complaint or symptom to becoming a separate disease. Traditional clinical diagnostics defines pain as a primary indicator for identifying the underlying source, i.e., a disease or injury. Pain plays a pivotal role in localizing the pathological process, while a combination of clinical, laboratory, and instrumental methods are available to ascertain its specific nature. Therefore, a diagnosis of pain syndrome as a disease is primarily focused on pain assessment, and objective evaluations, both clinical and instrumental, should be regarded as a tool to rule out other potential diseases. This approach requires that a medical professional with expertise in a specific therapeutic area, including orthopedic surgery, maintain a high level of vigilance, demonstrate considerable patience, and be willing to interpret medical challenges. A mechanistic approach and "simple" explanations may not only prove ineffective in facilitating early diagnosis, but may also contribute to decision errors and the progression of the disease.

The concepts of acute and chronic pain are distinguished both terminological and temporal criteria. In population and clinical studies, the conventional approach of defining pain by its persistence is to categorize it as acute (up to 3 months) or chronic (more than 3 months). This facilitates the formal diagnosis, patient allocation to study groups, and use of treatment algorithms in relevant situations in real-world clinical practice. However, it is widely acknowledged among clinicians any such categorization is conventional. Initially, any chronic pain is preceded by an acute phase. Hypothetically speaking, any patient who seeks medical assistance for acute pain may ultimately develop chronic pain. However, this diagnosis can only be confirmed through repeated visits to the physician.

A musculoskeletal pain, specifically a sudden (acute) pain resulting from injuries and diseases, is one of the most common reasons for a child to visit a medical professional (a pediatrician, orthopedic surgeon, rheumatologist, or neurologist) [1]. The etiology of chronic musculoskeletal pain can be attributed to a multitude of inflammatory or non-inflammatory conditions such as arthritis, joint hypermobility, fibromyalgia, growing pains, complex regional pain syndrome (CRPS), etc.

A group of chronic pain syndromes of unknown etiology is generally described with the descriptive term "amplified pain syndrome" (APS). Amplified musculoskeletal pain syndrome (AMPS) is a term that describes a wide range of medical conditions characterized by chronic musculoskeletal pain. The underlying mechanism of these various subtypes is central and/or peripheral sensory pain amplification [2]. In APS, pain signals are amplified as a result of various factors, so that mildly painful or non-painful stimuli are perceived by the body as very painful. This leads to significant functional impairment, as the patient tries to avoid any situation that may cause pain [3]. The hallmark of CRPS is the occurrence of pain, which may develop spontaneously or in response to high-intensity stimuli and is disproportionate to the actual injury/stimulus. Another essential aspect of CRPS is the presence of a variety of concomitant vegetative and motor disorders [4].

It should be emphasized that the terminology used to describe pain syndromes is often confusing and contradictory. This is a result of the historical evolution of definitions, categorizations, and explanations of the same phenomena, which have varied across different clinical and scientific schools and periods. Consequently, there is considerable duplication and overlap in terminology. The absence of objective diagnostic criteria poses a significant challenge in establishing clear definitions of these historical terms. The causal relationship between the main concepts associated with chronic pain syndromes is illustrated in Figure 1. Chronic pain is typically determined by the temporal factor and defined as lasting for more than 3 months. Musculoskeletal location has been identified a specific determinant for chronic musculoskeletal pain, which can be associated with a wide range of causes such as rheumatic diseases, tumors, infections, inflammatory and non-inflammatory arthropathies, etc. Amplified musculoskeletal pain is distinguished from other chronic pain syndromes, once all other potential causes of pain have been excluded (although the search for the cause may not have been extensive enough to yield conclusive results). Moreover, it is hypothesized that an underlying factor is responsible for amplifying the pain perception in the central nervous system (CNS). CRPS may be considered a variant of APS with a distinctive clinical presentation and local symptoms.

CRPS is divided into two types. Type I CRPS (CRPS-I), formerly known as reflex sympathetic dystrophy, usually develops after an inciting event (a minor trauma or a bone fracture without apparent nerve injury). Type II CRPS (CRPS-II), formerly called causalgia, is an extremely uncommon occurrence in pediatric patients. It is a neuropathic disorder that results from a partial injury to a nerve or its branches. Historically, a variety of terms has been used to describe CRPS, such as reflex sympathetic dystrophy, reflex neurovascular dystrophy, algodystrophy, causalgia, and localized idiopathic pain, while the term "Sudeck atrophy" describes a combination of clinical and radiological signs.

Currently, there is a dearth of accurate, population-based data on the incidence of CRPS in children. The published

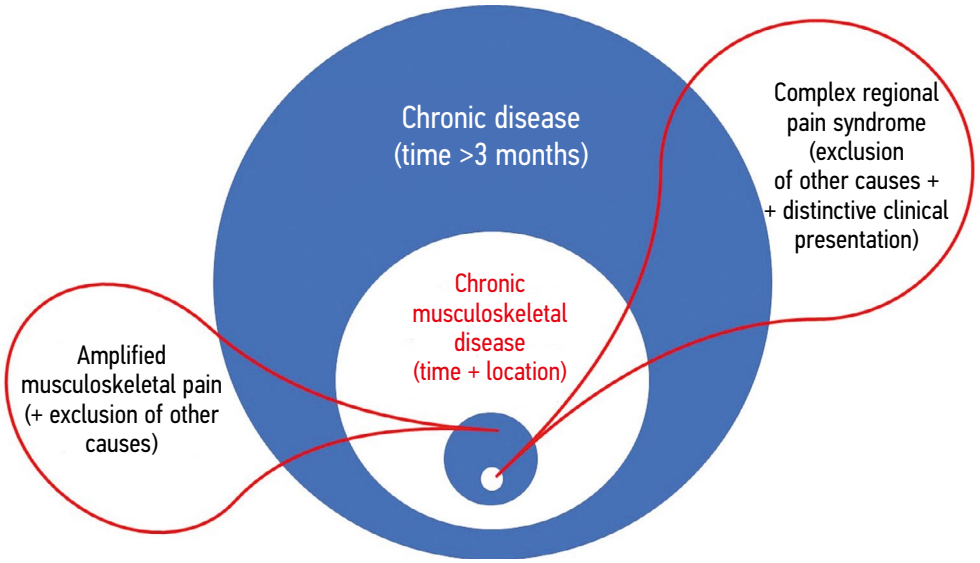

Fig. 1. Causal relation between the main terminological concepts describing chronic pain syndromes.

literature is largely comprised of case reports or case series [5, 6]. Among children under the age of 18 years, CRPS-I is more common in females, with a mean age of diagnosis at approximately 12 years. The lower extremities are more frequently affected than the upper extremities, with foot involvement being a particularly common occurrence [7].

The etiology and pathogenesis of CRPS remain unknown, although various hypotheses have been proposed based on studies conducted on adult patients. In many cases, CRPS develops after a relatively minor injury, most commonly a sprain, ankle twist, dislocation, or soft tissue injury. In some cases, no information on the injury can be obtained. Fractures have been reported to account for 5%–14% of the inciting events, while 10%–15% of cases of CRPS develop postoperatively [8].

Psychological factors and stress are significant contributors to the onset or progression of CRPS. Cruz et al. established an increased incidence of emotional distress, especially anxiety, in children with CRPS [9]. Logan et al. revealed that pediatric patients with CRPS were more functionally disabled, reported more physical symptoms (cardiovascular, respiratory, gastrointestinal, and urinary dysfunctions) than children with other pain conditions [10]. A greater prevalence of psychological and emotional school stress was observed in pediatric patients with CRPS, while school absenteeism was a common occurrence [11]. Stressful life events has been found to be more common in the CRPS group [12]. Furthermore, adverse family circumstances are frequently found to be a contributing factor. Sherry and Weisman [13] assessed 21 families with children diagnosed with CRPS, identifying two different types of families, where the type 1 showed high internal cohesion and organization and low levels of conflict, while type 2 showed high overt conflict and low levels of family cohesion and organization. The researchers identified a number of potential stressors in the lives of children, such as parental conflicts, serious school problems, and domestic violence. They concluded that CRPS is frequently a stress-related disease, and this factor must be taken into account when selecting therapeutic approaches for treating these children. Some children reported adverse psychological backgrounds, including psychological trauma and violence, only years later. The role of adverse childhood experiences in the development of amplification pain requires further investigation, but it may be an important factor [14].

Common clinical symptoms of CRPS in children include pain itself, high sensitivity to painful and non-painful stimuli, local vegetative symptoms, motor disorders, and trophic changes. Patients report a continuous pain in the affected limb, which persists even at rest and worsens with limb movement. In cases where the patient is able to recall the inciting event (such as a trauma, painful procedure, etc.), it becomes evident that there is a significant discrepancy the pain experienced and the underlying cause [3]. Most patients present with allodynia, defined as the experience of pain in response to a stimulus that is typically non-painful (i.e., tactile). Another common manifestation is hyperalgesia, i.e. a severe pain caused by a stimulus that would typically be perceived as moderately painful. Patients report experiencing a burning, fulgurant, stabbing, or like an electric shock-like pain. Limited range of motion in the affected limb is a hallmark of pediatric CRPS. Most children are unable or unwilling to bear weight on the affected limb because of the associated pain [15]. The absence of weight-bearing and forced immobilization may potentially contribute to the development of mild-to-moderate muscle weakness and muscle atrophy. The use of crutches or a wheelchair is frequently observed in such cases. It is crucial to initially rule out other potential causes of muscle weakness and atrophy, such as neuromuscular diseases. Vegetative changes

are evidenced by edema and mild swelling, temperature changes, hyperhidrosis, skin discoloration, cyanosis, cold intolerance, and macular and dry skin. Over time, trophic skin changes occur in the affected limb, e.g., hair and nails may grow faster or slower [16]. In their study, Agrawal et al. demonstrated that dystonia, primarily associated with a tonic flexion posture, was the most common movement disorder, followed by tremors and myoclonus [17].

A review of the published literature suggests that a number of mechanisms may be responsible for the development of CRPS. In central sensitization induced by peripheral tissue damage or nerve injury elicits a response process that occurs in the CNS, thereby reducing a pain threshold and increasing the length, severity, and location of pain [18]. Lebel et al. used functional magnetic resonance imaging (MRI), the most informative method for assessing the brain function, to evaluate CNS activation in 12 pediatric patients with CRPS. The abnormal activation of the sensory cortex, motor areas, emotion centers, and pain sensory areas was observed in response to stimuli applied to the affected limb vs. the intact one. These irregular patterns of CNS activation persisted even after the symptoms of the disease had been resolved. It is posited that the brain of patients with CRPS responds to normal stimuli in a manner that is different from that observed in healthy individuals [19]. It has been suggested that changes in small fibers (i.e., small fiber neuropathy, SFPN) may constitute a potential mechanism for CRPS. Acquired SFN is defined as damage to the small-diameter, unmyelinated peripheral nerve fibers that are responsible for pain signal transmission [20]. A study of 41 pediatric patients with chronic pain revealed definite SFN in 59%, probable SFN in 17%, and possible SFN in 22% of patients [21]. These findings suggest that SFN may represent a common pathogenetic mechanism underlying pediatric chronic pain syndromes. However, further studies are required to confirm this hypothesis.

Alexander et al. suggested that immune activation plays a role in the pathophysiology of CRPS. They reported a significant increase in plasma levels of cytokines and their soluble receptors in adult patients compared to controls [22]. Similarly, another study demonstrated an increase in cerebrospinal fluid levels of proinflammatory cytokines, namely interleukin-1β, interleukin-6 (but not tumor necrosis factor alpha) in adult patients with CRPS compared to controls [23]. Inflammation and peripheral sensitization (an increased sensitivity in the sensory system) may play a pivotal role in the early stages of CRPS after injury [24]. However, these processes themselves represent natural healing responses that are essential for the repair of damaged tissues. Pain is an adaptive response that is proportional to the provoking injury and tends to decreases during the phase of recovery. It is also reasonable to assume that certain sympathetic vasomotor responses, such as edema, hypothermia, or hyperthermia may be regarded as typical phenomena during the healing process. The severe pain, hyperpathia, allodynia, edema, and vasomotor changes observed in CRPS are characteristic of the early stages of severe trauma, suggesting that these symptoms and signs should not be considered abnormal. CRPS is a condition characterized by an abnormally increase in severity, extent, and duration of symptoms and signs of inflammation, sensory sensitization, and sympathetic responses. Neurogenic inflammation has been suggested to play a role in the early stages of CRPS [25]. Local elevations of proinflammatory cytokines have been demonstrated in adult patients early during CRPS [26].

A clinical diagnosis of CRPS is based on a comprehensive medical history and physical examination with neurological assessment. It is crucial to rule out other potential etiologies of chronic pain, including orthopedic, neurological, and rheumatic diseases. The anamnesis should include an assessment of the child's family, social, and school environment. A physical examination typically does not yield any notable abnormalities, apart from the aforementioned findings [27].

In the event that the diagnosis remains inconclusive, the initial examination will typically comprise a series of laboratory tests and imaging procedures, such as radiography, MRI, computed tomography (CT), and, where appropriate, scintigraphy and electroneuromyography (ENMG).

Fibromyalgia, joint hypermobility syndrome, myofascial pain, unrecognized local injury (fracture, sprain, dislocation), arthritis (including enthesitis-associated), spondyloarthropathy, leukemia, brain and spinal tumors, chronic relapsing multifocal osteomyelitis, Raynaud's disease, Fabry disease, erythromelalgia, perniosis, chronic compartment syndrome, peripheral neuropathy, progressive diaphyseal dysplasia (Camurati–Engelmann disease), idiopathic juvenile osteoporosis, thyroid disease (hyperthyroidism/hypothyroidism), vitamin D deficiency — this is not an exhaustive list of medical for which differential diagnostics with CRPS is required [3].

A basic laboratory testing protocol should include hematology, blood chemistry, C-reactive protein level, erythrocyte sedimentation rate, creatine kinase, and antinuclear antibodies. However, CRPS patients usually present with normal laboratory values. Imaging assessments typically demonstrate normal findings, although in those cases where the disease history is considerable or the degree of functional impairment is significant, secondary local osteoporosis may be identified, and MRI may indicate varying degrees of spinal cord edema [28].

There are currently no direct diagnostic methods for CRPS in either children or adults. However, a number of diagnostic criteria have been developed. The Budapest Criteria (Table 1) are the most commonly used [29], having demonstrated

Table 1. Budapest Criteria for complex regional pain syndrome

Criteria	Signs
Criterion 1	Long-term pain disproportionate to an injury
Criterion 2	At least one of four symptoms: • sensory: hyperalgesia and/or allodynia; • vasomotor: temperature asymmetry, and/or skin discoloration, and/or skin color asymmetry; • sudomotor: edema, and/or sweating changes, and/or sweating asymmetry; • motor/trophic: decreased range of motion, and/or motor dysfunction (weakness, tremor, dystonia), and/or trophic changes (hair, nails, skin)
Criterion 3	At least one sign of the following symptoms: • sensory: hyperalgesia (to pinprick) and/or allodynia (to light touch, and/or deep pressure, and/or joint movement); • vasomotor: temperature asymmetry, and/or skin discoloration, and/or skin color asymmetry; • sudomotor: edema and/or sweating changes; • motor/trophic: decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin)
Criterion 4	There is no other diagnosis that better explains the signs and symptoms

Note: two of the four criteria must be met for a diagnosis of CRPS.

high sensitivity (nearly 100%) and acceptable specificity (70%–80%) in adults, although they have not been formally validated in children.

The early diagnosis and treatment of CRPS are crucial [30, 31], and primary care physicians play an important role in preventing the development of CRPS and should be aware of the specific features of pediatric CRPS, such as gender (female), age (at approximately 12 years), injury site (lower limb) and side (left), and psychological and family problems. However, these features are not specific for CRPS. Although associated psychosocial problems can be identified through careful interview or specialized questionnaires, their routine use in all patients may not be appropriate in primary care settings.

This study presents three case reports of pediatric patients with chronic musculoskeletal pain and provides a narrative review of the literature, primarily comprising studies published after 2000. Additionally, it includes the most relevant publications of the previous decade on chronic pain in children, with the objective of raising awareness among physicians of this issue.

CLINICAL CASES

Patient 1

A 14-year-old female patient presented at the office of a pediatric orthopedic surgeon. She entered the office on crutches exhibited a series of expressive facial movements throughout the examination, indicating pain and distress. These movements were accompanied by changes in posture, the process of taking off her shoes before the examination. When asked about the purpose for the visit, the patient's mother mentioned a number of healthcare facilities they had previously visited earlier and emphasized that none of these facilities had been able to provide a satisfactory diagnosis or assistance. The medical history data indicated that approximately one year before at a sports camp during a sports dance training session, the patient twisted. She did not experience severe pain and continued training. On the following day, the patient experienced a recurrence of the pain, which subsequently increased in severity over the days. Upon returning from the camp, the girl informed her mother, who used home remedies with no improvement. In an emergency department, no evident of bone or ligament injury was identified. The patient was diagnosed with a sprain and discharged with standard recommendations. Over the next few months, the patient experienced worsening of pain, ankle and foot swelling. The treatment, which included electrical stimulation, compresses, and ointments with non-steroidal anti-inflammatory drugs (NSAIDs) proved ineffective. Instead, the pain worsened, thereby necessitating the use of crutches and the transition to online learning. Despite the use of various diagnostic modalities, including blood tests, X-ray, and MRI imaging, the underlying cause of the observed clinical presentation remained unclear. Since the onset of the disease, a variety ща medications, including NSAIDs, oral glucocorticoids, antibiotics due to suspected infection, multivitamins, and sedatives were regularly but unsystematically prescribed. Due to the recurrent physical symptoms of dyspepsia, abdominal pain, and heart pain in the heart, which also occurred with approximately the same severity before the foot injury, a number of assessments were performed and treatment modalities were attempted, yet no long-lasting results were achieved. The patient's mother consistently expressed regarding the potential adverse effects of various pharmaceutical agents. In direct conversation with the girl, her speech demonstrated a striking resemblance to her mother's description of the disease history. The mother's intervention

in the conversation was pervasive, with frequent corrections, instructions, and additions to the narrative, as though speaking on behalf of the girl. When asked about her activities at the sports camp where the injury occurred, the girl detailed her athletic achievements before the injury, the support she received from her friends on the sports team who visited her since she was home-schooled due to her inability to attend school. The patient said she wanted to return to school and resume sports training. The patient demonstrated difficulty in precisely localizing the pain. She provided a somewhat vague description of multiple regions in the ankle joint and foot areas, avoiding direct contact with the skin to prevent further discomfort. She reacted extremely emotionally to attempts to palpate the ankle joint and foot. It was also noteworthy that when her attention was deliberately switched to other objects (e.g., when assessing the range of motion in the knee joint or reporting the presence of pain), and concurrently, the physician's hands maintained contact with the previously identified painful areas, this did not elicit a markedly emotional pain response. After the examination, the girl put on a sock and a rather tight shoe, although before she had exhibited a notable reluctance to allow anyone to touch her foot. However, this did not negate the essence of the phenomenon of allodynia nor indicated that the pain was solely psychogenic in nature.

When asked directly in the presence of her mother about any potential negative or other psychological and emotional problems that may have arisen before or during the illness, the girl did not indicate any such problems. In a discussion with the girl's mother, it became evident that shortly before the onset of the disease, the girl's father, who had abandoned the family in her early childhood, had returned to them. The child was unable to accept this return, yet she demonstrated no outwardly negative reactions.

Following a consultation with a neurologist, the girl was diagnosed with CRPS and received pain relief medications, including a fixed-dose combination of ibuprofen and paracetamol (1 or 2 tablets depending on the pain severity, as needed, but not more often than once every 6 hours). Given the nature of the disease, the treatment course was 3 weeks. Additionally, the neurologist recommended amitriptyline, a consultation with a psychologist, subsequent sessions of psychotherapy, and rehabilitation treatment (physical rehabilitation, hydrotherapy). At the 3-month follow-up appointment, the patient presented without the use of crutches. Palpation and movements of the foot and ankle were observed to be painless. The mother reported without offering specific details, that the psychological situation within the family had been improved.

In this case, the patient and her mother needed to be informed that the painkiller (a fixed-dose combination of ibuprofen and paracetamol) and the antidepressant (amitriptyline) in this case should not be regarded as potentially harmful substances, but rather as treatment for the underlying disease. It was also crucial to clarify to the child and mother that in the context of CRPS, the motor function recovery should occur prior to pain relief, rather than afterwards, to effectively address kinesiophobia (fear of movements due to the painful feeling).

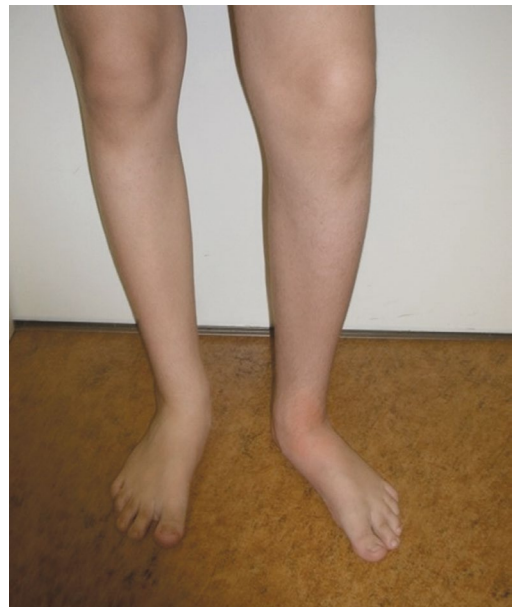

Fig. 2. Appearance of the feet in Patient 1: swelling, skin hyperemia, forced position of the limb.

Patient 2

A second clinical case is presented in a somewhat unconventional format, since the child was followed-up via written correspondence with the mother. A 15-year-old female patient permanently lived and studied abroad. The patient's parents were professional musicians, and the girl was learning the cello, demonstrating notable progress. Since the age of primary school, the child presented with intermittent pain in the legs and poor tolerance to physical activity. In adolescence, due to persistent symptoms, the child was examined by an orthopedic surgeon. Based on the radiography findings, bilateral *os tibiale externum* was diagnosed. The patient was offered surgical treatment, which was performed on the right leg. The suitability of the surgical procedure cannot be discussed retrospectively. However, it should be noted that there is no consensus in the literature on the optimal approach to the treatment of this medical condition. The postoperative and early recovery periods were unremarkable. The patient was able to resume her normal activities following the procedure, after which a similar surgery was performed on the left leg. In the early postoperative period, the child experienced pain and external changes in the foot, necessitating a medical consultation.

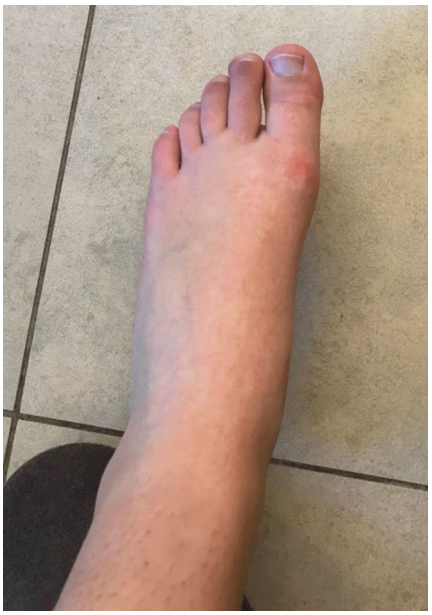

Fig. 3. Appearance of the foot in Patient 2: swelling and skin discoloration.

Having received no clear explanations, the parents elected to continue the standard rehabilitation treatment derived from the experience of the previous surgical procedure. However, despite this approach, there was no improvement in motor function, and the pain increased in severity. Consequently, following numerous consultations with medical professionals, and at the recommendation of a colleague, the girl's mother wrote a request for assistance. The fragment from the letter is presented in its original form, since it offers insight into the mother's perception of the situation with the child and the extent of her emotional involvement.

"Pain description: a persistent sharp pain in the entire left foot, and the tendons on both sides of the left leg. The entire leg (extending to the back) is highly tender and cannot be touched. She walks more slowly and avoids bearing weight on her left leg. The pain is less severe at night (the girl can sleep). The most severe pain occurs during excessive walking or any exercise. Four months ago, she could move her foot left, right, up and down with minimal discomfort. She demonstrated good recovery after surgery. Currently, she cannot move her foot in any direction due to pain. Purple spots often appear on the toes of her left foot due to pain and anxiety."

The mother was informed of the specifics of CRPS as a distinct medical condition and advised to consult with a pain management specialist. A video of the girl playing the cello on stage, walking without a limp in beautiful shoes, was sent several months later.

Surgical procedures on the foot are one of the most common triggers for the development of CRPS. In most cases, CRPS develops following minor surgeries performed for mild deformities that are not associated with significant initial pain syndrome. It is important for surgeons to recognize that even minor surgical procedures can potentially lead to significant complications.

Patient 3

Finally, Clinical Case 3 complements the presentation and illustrates the range of chronic musculoskeletal pain in pediatric patients. It concerns a 13-year-old female patient admitted to the Foot Pathology Department for examination and treatment. Over the past three years, she had been examined and treated by a range of medical specialists, including pediatricians, rheumatologists, and neurologists. The onset of symptoms occurred 3 years before, following an intercurrent viral disease, and was accompanied by pain and swelling in her legs, primarily affecting the ankle joints. The pain could occur in one or both legs concurrently, was not associated with a specific time of day, and was induced or aggravated by physical load. The efficacy of NSAIDs was found to be insignificant. The diagnosis established by the consulting physicians ranged from polyneuropathy to juvenile chronic arthritis. However, the pharmacological agents prescribed for the suspected diagnosis proved to be ineffective. During the online consultation, a diagnosis of CRPS was considered a potential explanation for the child's symptoms, based on the medical records which referenced a history of injury. The girl was admitted to hospital for assessments and conservative treatment. The medical history documented at the time of admission indicated that the child had no limb injury that could account for a temporal relationship comparable to that in the current clinical presentation. The psychosocial background of the family did not provide sufficient evidence to make an unconditional assumption of classic CRPS triggers. A review of the medical history demonstrated that at the age of 6, the patient was diagnosed with an astrocytoma located at the fourth ventricle base. After subtotal resection, the patient achieved a stable remission. Her mother reported that the girl had experienced difficulties with the motor function recovery following the surgical procedure. However, within a few months, she had fully recovered to her preoperative motor activity level. Furthermore, following the surgical procedure, the girl's emotional state changed significantly, and she became emotionally detached (as reported by her mother, "she stopped smiling"), while exhibiting increased susceptibility to whims and negative emotional reactions.

In recent years, the patient's inability to attend school due to leg pain resulted in her transitioning to home schooling and a significant reduction in her ambulatory activity within the home environment, except for essential activities (kitchen/toilet/bathroom). Despite this, her gait remained largely unimpaired. The girl explained her reluctance to walk

by the fear of pain. The assessments revealed no significant findings, although a decrease in bone mineral density was observed by bone densitometry (a Z-criterion of –1.8). As clinical examination conducted by various medical specialists (including orthopedic surgeons and neurologists) and CT, ENMG, and MRI scans demonstrated no factors that could be associated with the patient's clinical symptoms (the imaging findings are not provided in this case report). A diagnosis of APS was established. The brain tumor and subsequent treatment were suggested as an amplification factor. A bisphosphonate infusion (ibandronic acid 0.1 mg per 1 kg of body weight) was administered following the consent of the parents and the decision of the medical panel since the drug is not approved for patients under 18 years of age. At the two-day follow-up, the patients reported a reduction in pain severity from 9 to 7 points as measured by the visual analogue scale (VAS). It was recommended that the therapy be repeated at 3 months. Moreover, the patient received Ibuclin Junior 1 or 2 tablets depending on the pain severity, as needed, but not more often than once every 6 hours, for 3 weeks. One month after the treatment, the patient's pain syndrome persisted, though decreased in severity to a VAS score of 4 points. The parents reported an increase in motor activity and improved emotional state.

DISCUSSION

The primary objectives of CRPS treatment are to provide pain management and to enhance overall functioning, thereby improving the patient's quality of life. This is achieved through a comprehensive approach that integrates an intensive physical rehabilitation and cognitive behavioral therapy. This strategy may initially appear to conflict with the patient's intrinsic belief that rest is a means of symptom management. However, the choice of specific treatment methods remains unclear. A Cochrane review (2013) of treatment strategies for adult patients with CRPS highlighted a dearth of high-quality evidence-based studies to directly assess the efficacy of most treatments [32].

Physical rehabilitation is a cornerstone of treatment for children with CRPS [33], yet there is no consensus on the optimal length, intensity, or specific methodology. The most widely accepted treatment approach is based on a combination of physical rehabilitation and cognitive behavioral therapy [34]. The treatment is focused on providing the motor function recovery, enhancing the joint range of motion, improving exercise tolerance, and strengthening muscles, while also teaching the child to accept and manage pain [35]. Psychotherapy is an essential component of the multidisciplinary approach, and the efficacy of psychological treatments have been demonstrated in studies of children with chronic pain [36]. A Cochrane review (2014) [37] provides only limited evidence to support the efficacy of psychological methods in the assessment and treatment of pediatric patients with chronic pain.

To date, there is no consensus regarding pharmacological treatments for children with CRPS. NSAIDs and paracetamol are frequently indicated for the initial manifestations of chronic pain and are also used as an additional therapy to complement physical rehabilitation [38]. In a clinical study, 50 of 70 patients received NSAIDs, with 40% reporting a reduction in pain severity. Although this may initially appear to yield suboptimal results, it is crucial to emphasize that 55% of patients experienced persistent pain syndrome despite the combination treatment, which included physical therapy, transcutaneous electrical nerve stimulation, psychotherapy, tricyclic antidepressants, and sympathetic nerve block [39]. CRPS may be defined as a medical condition in which early inflammatory responses are not effectively suppressed. NSAIDs have been demonstrated to be an effective treatment option for pediatric patients with CRPS. Their mechanism of action involves the inhibition of peripheral sensitization, thereby suppressing the synthesis of prostaglandins [40].

The choice of a fixed-dose combination of ibuprofen and paracetamol as an analgesic in the presented case reports was based on the pharmacological characteristics of the drugs, specifically the combination of a classic NSAID (ibuprofen) and a central acting analgesic (paracetamol). This combination has been demonstrated to be highly efficacious in the treatment of chronic musculoskeletal pain in children, as it targets both the peripheral and central underlying mechanisms. A significant benefit of this fixed-dose combination is the availability of a pediatric dosage form (dispersible tablets) approved for children aged 3 years and older. Additionally, total doses of the active ingredients in the combination of ibuprofen and paracetamol are 1.5–2.5 times lower than those of monotherapies.

Amitriptyline and phenytoin have been used in pediatric CRPS, usually in addition to physical rehabilitation, sometimes in combination with gabapentin [41]. Gabapentin has been described as a drug of choice for the treatment of pediatric patients with CRPS [42]. These pharmaceutical agents were typically initiated at an early stage to facilitate physical rehabilitation, and their doses were tapered when symptoms subsided [43]. Small case series of oral glucocorticoids in CRPS in children did not show any significant clinical effect [44].

In their study, Petje et al. [45] evaluated the results of intravenous infusions of iloprost, a prostacyclin analogue. Despite pain relief, adverse reactions such as headache, nausea, vomiting, and decreased systolic blood pressure were reported in all cases. The authors do not recommend iloprost as a primary therapeutic option. Brown et al. [46] analyzed the treatment outcomes in 29 patients who had not responded to physical methods and cognitive behavioral

therapy. Both gabapentin and amitriptyline demonstrated efficacy in reducing pain and improving sleep, with no significant differences between the two. However, it was observed that the gabapentin group experienced ventricular conduction impairment, while amitriptyline was associated with Q–T prolongation. The use of bisphosphonates is also deemed appropriate, particularly during the early stages of CRPS [47, 48].

A paucity of data exists in the literature regarding the use of invasive treatments of children and adolescents with CRPS. The most commonly used methods included bolus sympathetic nerve blocks, epidural nerve blocks, and prolonged sympathetic nerve blocks, while spinal cord stimulation was less frequently used [49]. These invasive techniques have demonstrated efficacy in reducing pain syndrome and functional disorders in most patients. However, the level of evidence supporting the inclusion of invasive methods in the treatment program for CRPS in the pediatric population remains insufficient [50]. In a study by Donado et al. [51], prolonged epidural or peripheral nerve blocks in patients who had not responded to physical treatment and cognitive behavioral therapy resulted in a significant decrease in pain severity in most patients, although 39% of patients did not demonstrate clinical improvement in pain symptoms, and 43% had no functional improvement. It is important to recognize that invasive treatments for CRPS are associated with a risk of complications. Therefore, it is essential to carefully evaluate potential risks and benefits associated with these treatments. In general, the treatment outcomes in pediatric patients with CRPS are more favorable compared to adults. Many of them recover within a few months. A multidisciplinary approach has been demonstrated to be an effective method for achieving remission in most children; however, it should be noted that relapses are a relatively common occurrence. In their study, Sherry et al. [52] reported that 31% of patients experienced recurrent symptoms, which resolved after resuming the therapy. In a retrospective study of 32 pediatric patients with CRPS, 89% of them ultimately exhibited complete resolution of their symptoms. Relapses were documented in 7 children, but 6 of them also demonstrated the absence of further symptoms [53].

The case of a 12-year-old male patient with clinical CRPS, as reported by Japanese researchers, is noteworthy in terms of its potential implications for the early treatment of this medical condition [54]. The patient was referred to the clinic 2 days after a twist foot injury with a diagnosis of ankle sprain. Two days after the initial assessments, he reported an increase in pain extended to the entire foot. Additionally, the patient was unable to bear weight on the affected limb, experienced allodynia and hyperpathia. Oral paracetamol proved to be ineffective. At 5 days, the VAS score increased to 10 points, and CRPS was diagnosed. The treatment included celecoxib, pregabalin, and physical exercises to gradually increase tolerance to physical activity and movements that had induced pain at the onset of the disease (desensitization). On Day 11, the movement VAS pain score decreased to 5 points, and on Day 22, the patient reported a 2-point pain. Allodynia and edema completely resolved. Celecoxib and pregabalin were discontinued. On Day 35, the patients had no pain, and no relapses were documented at the 2-year follow-up.

Ankle sprains are certainly the most prevalent injury among physically active children and adolescents. One could reasonably hypothesize that the frequency would be comparable on the right and left sides. Interestingly, reported cases of CRPS in children following foot and ankle injuries were significantly more prevalent on the left side. The authors of the above-mentioned study suggested that the right hemisphere of the brain may be more susceptible to dysfunction such as CRPS.

The lack of comparative studies on the efficacy of treatment modalities and on the objective assessment of the treatment outcomes precludes the establishment of a standard treatment protocol for CRPS. Early diagnosis is of equal importance to the subsequent treatment. However, a longer course of the disease and its severe consequences are associated with late diagnosis [35].

Orthopedic surgeons are responsible for identifying the disease and determining the most appropriate treatment, which may vary depending on their experience and the availability of resources [55]. Unfortunately, there are no specific diagnostic scales developed for children and adolescents, so the criteria proposed for adults are used in this population [3].

Rastogi et al. identified several essential factors necessary for understanding chronic pain in children and prescribing appropriate treatment.

- All pain, whether acute or chronic, can be understood as a biopsychosocial phenomenon, with implications for both symptoms and treatment.
- Early use of a biopsychosocial approach is recommended to improve treatment adherence and clinical outcomes.
- The clinical course of complex pain syndromes may differ between pediatric and adult patients. Additionally, there are childhood-specific pain syndromes.
- An optimal multidisciplinary approach is based on the “three Ps” principle (pharmacological, physical, and psychological).
- There are no evidence-based guidelines for the treatment of complex pain in children. Medical professionals frequently have to rely on the adult studies, expert opinion, or clinical experience.

The authors highlight the challenges associated with treating complex pain, citing its potential to negatively impact on physical functioning, quality of life, mood, sleep,

family relationships, school attendance, and socialization. The problem for all parties involved (a child, parents, a medical professional) is the somewhat paradoxical yet crucial concept that functional improvement must precede a reduction in pain severity. This usually requires a multidisciplinary approach based on the "three Ps" principle (pharmacological, physical, and psychological), which focuses on both peripheral and central pain mechanisms [56].

What degree of vigilance should a medical professional maintain when treating a patient who experience an acute pain? What measures should be taken (or not taken) to prevent acute pain from escalating into chronic? It is evident that there is no definitive answer to these questions. Fortunately, an orthopedic surgeon typically faces clinical situations in which the source is readily apparent (trauma, deformity, etc.).

To what extent should one examine the specific details and circumstances that are not directly related to the emotional, social, psychological background in cases where the underlying cause of pain appears evident? It is crucial to bear this in mind and, where applicable, to avoid situations that contribute to the chronicity of pain, in particular, those associated with suboptimal pain relief. Oligoanalgesia is an emergency condition, in which patients are unable to communicate their pain sensations with sufficient clarity. However, in routine orthopedic practice, there are situations where pain relief is absent or inadequate, driven by the expectation of a brief, low-intensity injury or procedure [57]. Where is the borderline between concerns about potential adverse effects of pain relief itself (drug toxicity, allergy or individual intolerance, and the desire of both the medical professionals and patients to "do without pharmaceuticals")? In each specific case, it is essential to conduct a thorough examination of the initial circumstances and to take appropriate actions, while also considering the potential consequences. Meanwhile, the growing emphasis on painless treatment has been evident over recent decades. The extensive use of analgesics, particularly those available without a prescription, also has a detrimental impact. The "opioid crisis" defined as the misuse of potent addictive analgesics has been primarily prevalent in the United States in recent decades and has not yet been overcome. The phenomenon of athletes, medical professionals, and military personnel becoming addicted to painkillers as a result of has become a significant aspect of popular culture, thereby illustrating the relevance of this problem. A careful, thoughtful choice of pain management strategy for acute trauma should be based on two fundamental principles: first, a child should not experience pain when it can be relieved, and second, the use of analgesics should be strictly justified and the dosage should be carefully monitored.

The World Health Organization recommends two pharmaceutical agents for pain management in children aged 3 months and above: ibuprofen and paracetamol. This choice was based on an analysis of international data on the efficacy and safety in pediatric practice [58]. The combination of these agents offers certain advantages over monotherapy. Chang et al. demonstrated that the efficacy of a combination of paracetamol and ibuprofen in patients with acute pain was comparable to that of opioids and paracetamol [59]. Further research is required to elucidate the optimal treatment for chronic pain. However, the clinical examples presented herein illustrate the potential efficacy of this combination.

CONCLUSION

Pediatric CRPS is not a rare occurrence, rather it is frequently misdiagnosed. Currently, a substantial number of publications are focused on case reports and summarize knowledge on this problem. Adolescents between the ages of 11 and 14 are particularly vulnerable to the disease, with a higher prevalence among girls compared to boys. Some children are at higher risk of developing CRPS, including high achievers, leaders, and those successful in studies, hobbies, or sports. A conflict or psychological trauma typically serves as a trigger. A special emotional involvement of the child and parents in the situation is also evident, as indicated by providing a detailed history of the disease and its treatment (using the same terms, descriptive characteristics repeated by the parents), and peculiar emotional coloring of experiences (both children and parents seem to "cherish" the disease). It would be advisable for the medical professional to find an opportunity to discuss the situation with the parents and the child separately to gain a more comprehensive understanding of the potential psychological background.

A dissociation of the severity of symptoms and unassisted movements may be observed during examination, while local symptoms may be insignificant. The medical professional must be aware that the symptoms and disease may worsen following manipulations and procedures. This emphasizes the importance of a thorough examination and testing. It is crucial to avoid unnecessary immobilization, while invasive diagnostic and therapeutic manipulations (ENMG, nerve blocks, electrical stimulation procedures that can cause painful or unpleasant sensations) should be used with extreme caution. Classic symptoms of disproportionate burning pain (causalgia) and trophic changes should raise the suspicion of CRPS. This approach is the most effective method for preventing the onset of chronic pain conditions, which can result in serious functional limitations, depression, and long-term medical treatment.

Currently, standard treatment protocols for CRPS and APS in pediatric patients have yet to be developed, particularly given the lack of monotherapy for these medical conditions. In the current setting, the medical professional

has to choose from the available range of combinations of physical, psychological, pharmaceutical, and invasive methods. Meanwhile, the use of analgesics must adhere to the established standards and practices of pediatric pain management. The current evidence suggests that an integrated multidisciplinary approach to treatment is the most appropriate. However, further experience and knowledge are required to improve the outcomes.

ADDITIONAL INFORMATION

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AUTHOR INFORMATION

Vladimir M. Kenis, MD, PhD, Dr. Sci. (Medicine), Professor;
address: 64-68 Parkovaya str., Pushkin, Saint Petersburg, 196603, Russia;
ORCID: 0000-0002-7651-8485;
eLibrary SPIN: 5597-8832;
e-mail: kenis@mail.ru

ОБ АВТОРЕ

Владимир Маркович Кенис, д-р мед. наук, профессор;
адрес: Россия, 196603, Санкт-Петербург, Пушкин, ул. Парковая, д. 64–68;
ORCID: 0000-0002-7651-8485;
eLibrary SPIN: 5597-8832;
e-mail: kenis@mail.ru