Case report

Hereditary erythromelalgia in an adolescent.
Clinical observation of a rare disease

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BACKGROUND: Erythromelalgia is a severe, chronic, progressive disease with periods of exacerbation and remission. A triad of symptoms characterizes the disease: reddening of the extremities, a local increase in skin temperature, and pronounced neuropathic pain syndrome. There are sporadic works in the Russian literature that present data on erythromelalgia, particularly in children. The publications are descriptions of clinical observations with the assessment of the clinical picture of the patient regarding cutaneous manifestations and surgical care at the time of hospitalization, time spent in the hospital, and during the period of his chronic disease exacerbation.

CLINICAL CASE: A clinical case of hereditary erythromelalgia in a 15-year-old adolescent with a detailed description of the disease course since the initial manifestation is presented.

DISCUSSION: During three and a half years, despite early diagnosis and application of consistent pharmacotherapy including nonsteroidal anti-inflammatory drugs, antidepressants, anticonvulsants, antihistamines, opioids, hormonal therapy, local use of lidocaine, ointment with silver content, the disease was progressive, with the resistance of pain syndrome to the treatment, with periods of exacerbation and partial remission.

CONCLUSIONS: The presented clinical observations show the need to assess the patient as a chronic and intractable patient. Considering the lack of understanding of the apparent cause of this disease and its diverse manifestations in the clinical picture, a multidisciplinary approach with a search for new treatment methods, including neurosurgical techniques of chronic pain treatment, is required for patients with erythromelalgia.

Keywords: erythromelalgia; Mitchell syndrome; pain; limb redness; mutations in the SCN9A gene; Nav1.7 sodium channels.

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Клинический случай

Наследственная эритромелалгия у подростка. Клиническое наблюдение редкого заболевания

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Обоснование. Эритромелалгия — тяжелое хроническое прогрессирующее заболевание с периодами обострения и ремиссии. Для болезни характерна триада симптомов: покраснение конечностей, локальное повышение температуры кожи, выраженный нейропатический болевой синдром. В единичных работах отечественных авторов представлены данные о эритромелалгии, в частности, у детей. Публикации носят характер описания клинических наблюдений с оценкой клинической картины заболевания у пациента с точки зрения кожных проявлений и хирургической помощи на момент госпитализации в стационар, в период обострения хронического заболевания.

Клиническое наблюдение. Рассмотрен клинический случай наследственной эритромелалгии у 15-летнего подростка с детальным описанием течения заболевания, начиная с момента первичной манифестации.

Обсуждение. В течение трех с половиной лет, несмотря на раннюю диагностику и применение последовательной фармакотерапии, включающей нестероидные противовоспалительные средства, антидепрессанты, антиконвульсанты, антителамины, опиоиды, гормональную терапию, местное применение лидокаина, мази с содержанием серебра, заболевание протекало прогрессивно, с резистентным болевым синдромом к проводимому лечению, с периодами обострения и неполной ремиссии.

Заключение. Представленное клиническое наблюдение свидетельствует о хроническом течении и трудноизлечимом характере заболевания. С учетом отсутствия понимания четкой причины развития данного заболевания, разнообразных проявлений, к пациентам с эритромелалгией следует применять мультидисциплинарный подход с поиском новых методов лечения, в том числе с использованием нейрохирургических методик лечения хронической боли.

Ключевые слова: эритромелалгия; синдром Митчелла; боль; покраснение конечностей; мутации в гене SCN9A; натриевые каналы Nav1.7.

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BACKGROUND

Erythromelalgia was first described by S. Weir Mitchell in 1878 as a disease that manifests mainly as redness and painful extremities [1]. Erythromelalgia can be primary, idiopathic, and secondary, usually associated with myeloproliferative diseases [2].

Diagnostics are based on history and clinical presentation. The main disease signs are reddening of the extremities, a local increase in skin temperature, and severe neuropathic pain syndrome. According to the literature, the lesion develops symmetrically in both limbs, the exacerbation duration and pain syndrome severity are patient-specific, and there may be a permanent severe pain syndrome that prevents patients from sleeping [3, 4]. Trigger factors that induce disease exacerbation can be intense physical activity, an increase in ambient temperature, and the position of the affected limbs, leading to impaired trophism and blood circulation. The condition of the patient improves when the limb is cooled by immersion in cold water, wrapping in a damp cloth, cooling using an air conditioner or fan, and elevating the limb. Possible complications of symptomatic therapy are skin maceration, ulcers, and hypothermia of the limbs. Additionally, the development of mental disorders is noted in the presence of a long-term severe pain syndrome [5].

The etiology and pathogenesis of this disease have not yet been accurately examined. Genetic studies of patients with erythromelalgia revealed an SCN9A gene mutation responsible for the functioning of sodium channels Nav1.7, which, in turn, are present in the neurons of sensory and sympathetic ganglia [2, 6]. Patients with SCN9A gene mutations are classified to have the primary disease, and those without this mutation, with an unspecified etiology, have an idiopathic form.

The Russian literature presents single studies with data on erythromelalgia, particularly among children. Studies have described cases with an assessment of the clinical presentation of the disease in terms of skin manifestations and surgical care, with a description of the patient’s condition at the time of hospitalization and during an exacerbation of chronic disease [5, 7–9]. In the search for relevant studies in the Russian-language eLibrary database, only four articles were found, describing a clinical case of the disease. In the English-language databases Google Scholar, PubMed, and ScienceDirect for the period from 2000 to 2021, about 6000 articles were found. However, despite such a volume of English-language publications, clinical and practical recommendations for the management and effective treatment of patients with erythromelalgia have not yet been developed, and questions about the etiopathogenesis of this condition remain open.

There are no data on the interpretation of a patient with erythromelalgia as a chronic intractable neurological disease with persistent pain in the distal extremities and episodes of exacerbation in the form of increased pain and formation of trophic disorders of the soft tissues of the distal extremities. Herein, we present a clinical case of a patient with childhood erythromelalgia.

CLINICAL CASE

A 15-year-old male teen was admitted to H. Turner National Medical Research Center for Children’s Orthopedics and Trauma Surgery of the Ministry of Health of Russia with complaints of constant burning pain in the lower extremities, hyperemia, and swelling in the feet and lower third of lower legs.

History assessment reveals, according to the parents, that the above manifestations were first noted at the age of 4 years; during physical activity and elevated ambient temperature, the child began to complain of pain in the lower extremities, with complete regression at rest. The disease progressed progressively with increased frequency, duration, and severity of the pain syndrome. At age 11, the pain syndrome worsened with elevated ambient temperature and daily physical activities, which limited the child’s motor activity and interfered with school activities. Symptomatic therapy with an ice-cold rubber bag and limb cooling with an air conditioner was started. Since erythromelalgia was noted in the mother and maternal grandmother, the patient was consulted by a geneticist, and a diagnosis of hereditary erythromelalgia was made. A study for the presence of SCN9A gene mutations was not performed. Subsequently, he was examined by a neurologist and a rheumatologist. Taking into account the clinical presentation in the form of a pronounced neuropathic pain syndrome affecting the feet, differential diagnostics were performed, and Fabry disease was ruled out, the diagnosis of erythromelalgia was confirmed. At age 12, hyperemia, lower limb swelling, a constant pronounced pain syndrome at rest emerged. The patient was under the supervision of a psychiatrist and received a course of treatment with carbamazepine, pregabalin, gabapentin, and amitriptyline at the age-appropriate dose. In the process of selecting therapy, the most effective drug was amitriptyline, which caused incomplete regression of the pain syndrome for 4 h, followed by a relapse of the pain syndrome at a higher level. Since the beginning of 2020, at age 13, the patient lacked a full night’s sleep because of severe pain in the extremities, which aggravated at night. The amitriptyline therapy was performed for 6 months. At this time, a polymorphic exanthema developed over the entire surface of the skin, represented by roseola, papules, and vesicles (Figs. 1 and 2).

Treatment of skin rashes was performed under the supervision of a dermatologist, and toxicoderma was established. A decision was made to discontinue amitriptyline. Therapy of
skin rashes continued for 2 months; during the amitriptyline therapy, the patient experienced episodes of hypertension, with blood pressures up to 160/110 mm Hg, which worsened the neuropathic pain in the extremities.

Subsequently, only hypertension therapy, symptomatic therapy of the pain syndrome using an air conditioner, and an ice rubber bag were performed. The disease course was still progressive. In March 2021, at age 14, under the supervision of a dermatologist, hormonal therapy with prednisolone was started and performed for 3 months, but the patient’s condition deteriorated with increased limb pain at rest and at night, panic attacks with respiratory difficulty, and skin ulcers in the lower extremities (Fig. 3).

The patient was hospitalized at the combustiology department (St. Petersburg), hormonal therapy was canceled, and a repeated course of carbamazepine therapy was prescribed. During treatment, the skin ulcers healed, and pain syndrome slightly regressed. However, while taking carbamazepine, the frequency of hypertensive crises increased to several times a day, followed by an increase in neuropathic pain.

At the time of admission to the Department of Spinal Pathology and Neurosurgery of H. Turner National Medical Research Center for Children’s Orthopedics and Trauma Surgery, the condition was of moderate severity; with a forced position, the patient could sit on the bed with his legs bent at the hip and knee joints, the lower extremities were constantly cooled with an ice-cold rubber bag, and air conditioning. The child was of normosthenic physique. The skin was dry, pink, and clean, and turgor was preserved. Visible mucous membranes

Fig. 1. Patient A (13 years old). Appearance of the lower extremities after 3 months of amitriptyline therapy. Hyperemia of the feet and lower third of the lower legs

Fig. 2. Patient A (13 years old). Appearance of the lower extremities after 6 months of amitriptyline therapy; a generalized polymorphic exanthema is visualized

Fig. 3. Patient A (14 years old). Appearance of the lower extremities 3 months after the hormone therapy. Ulcerative lesions of the skin
were pink, moist, and clean. In the assessment of the hair and nails, there was alopecia; from age 14, onychomycosis of the nails of the feet was noted. Peripheral lymph nodes were unchanged. Local changes included brightly hyperemic legs and bluish-purple areas on the inner surfaces of the legs, on the rear surface of the feet, and in the area of the ankle joints. There were trophic ulcers at the healing stage and cracks on the plantar surface. Cicatricial changes were found in the middle and upper thirds of the lower legs up to $15 \times 5$ cm² in size (Fig. 4). Cardiovascular, respiratory, and digestive systems were normal. Neurological status showed clear consciousness, with 15 points on the Glasgow coma scale. The pupils were rounded and symmetrical ($D = S = 3$ mm). Pupillary reaction to light (direct and consensual) was preserved, with full eyeball movements. There was no nystagmus. The face was symmetrical. The hearing was preserved on both sides. There was no tongue deviation. Swallowing was not impaired, and phonation was preserved. Passive and active movements of the limbs were full and painless. Superficial abdominal reflexes were brisk and symmetrical. Muscle tone in the limbs ($D = S$), deep reflexes in the limbs ($D = S$), and strength of the limb muscles were preserved ($D = S = 5$ points). Sensitivity disorders of the hyperesthesia type at the level of the middle third of the lower leg, which aggravated in the distal direction, were registered. No pathological signs and meningeal symptoms were noted. Physiological functions were controlled, and diuresis was adequate to the water load. At 20–30 min after palpation and squeezing of the feet, the patient had an attack of increased hyperemia, swelling, and neuropathic pain. At rest, the intensity of the pain syndrome according to the visual analog scale was 8, and the general condition according to the Karnovsky scale was 40%. The patient was forced to use constantly an ice-cold rubber bag and a mobile air conditioner. According to the patient, he had no proper sleep for 1 year. He was constantly taking carbamazepine 200 mg two times a day, enalapril 10 mg two times a day, had increased blood pressure, and had supplemented therapy with Concor and Capoten.

According to laboratory studies, no pathological changes in results of the clinical blood test, biochemical blood test, and general urinalysis were noted. Computed tomography and magnetic resonance imaging of the thoracic and lumbar spine showed no pathological changes (Figs. 5 and 6).

Special attention should be paid to electroneuromyography of the upper and lower extremities according to the standard technique with the study of sensory fibers of the median, ulnar, superficial peroneal, and gastrocnemius nerves and motor fibers of the median, ulnar, deep peroneal, and tibial nerves. When stimulating the superficial peroneal nerve on both sides, sensory responses were not obtained (Fig. 7).

During stimulation of the sural nerve, sensory responses on both sides were significantly reduced, and the amplitudes of the sensory response were $0.3 \mu V$ on the right and $0.6 \mu V$ on the left. The rate of conduction along the sensory fibers of the sural nerve was reduced (40 m/s). When stimulating the motor fibers of the deep peroneal nerve, the amplitude of the $M$-response with $m. \ ext. \ digit. \ brevis$ on both sides was significantly reduced with $0.9 \ mV$ on the right and $1.1 \ mV$ on the left. During stimulation of the tibial nerve, the $M$-responses on both sides were slightly reduced ($8.8 \ mV$ on the right and $8.5 \ mV$ on the left). No conduction disorders were detected along the motor fibers of the peripheral nerves of the lower extremities on both sides. The conduction rate was normal ($50–56 \ m/s$), terminal and residual latencies
were normal, and the duration and shape of M-responses were not impaired (Fig. 8).

No disorders were revealed in the study of the sensory and motor fibers of the peripheral nerves of the upper extremities. The results of electroneuromyography indicated a diffuse lesion of predominantly sensory and, to a lesser extent, motor fibers of the peripheral nerves of the lower extremities of an axonal nature, typical for polyneuropathy.

Based on the history, the results of the physical examination, clinical and laboratory examination, neuroimaging, and neurophysiological research, the final diagnosis of angiotrophoneurosis, hereditary erythromelalgia (Mitchell’s syndrome), polyneuropathy of the lower extremities, predominantly sensory, trophic changes in the soft tissues of the lower legs and feet was established.

**DISCUSSION**

Erythromelalgia is a severe chronic progressive disease with periods of exacerbation and remission. It is associated with a decrease in the quality of life and increased mortality [10]. Owing to the insufficiency of knowledge and the lack of available objective diagnostic methods, in most cases, there is a long time interval between the disease manifestation and the final diagnosis. In the present case, hereditary erythromelalgia was diagnosed before the onset of the main symptoms based on his mother’s experience, who also had this disease, which was subsequently confirmed by a geneticist. For 3.5 years, despite early diagnostics and the use of consistent pharmacotherapy, including nonsteroidal anti-inflammatory drugs, antidepressants, anticonvulsants, antihistamines, opioids, hormone therapy, topical lidocaine, and silver ointment, the disease proceeded progressively, with pain syndrome resistant to well-known pharmacotherapy [11]. Additionally, there were periods of complications of the underlying disease, such as panic attacks with respiratory difficulty, hypertensive crises, and trophic skin lesions in the lower extremities. Trophic skin lesions in the extremities are the most common complication of the disease, which often leads to inpatient treatment, as in the case presented.

In a patient with erythromelalgia, neurophysiological examination revealed manifestations of axonal polyneuropathy.
of the lower extremities with a predominance of damage to sensory fibers, which is significant for the interpretation of pain syndrome and trophic disorders in the lower extremities. Persistent pain syndrome, which was noted in a patient with erythromelalgia, refers to the manifestations of neuropathic pain, which can occur with damage or dysfunction of the nervous system at different levels. Neuropathic pain occurs following impaired interaction between nociceptive and antinociceptive systems because of both primary damages to sensory fibers and sensitization of the central mechanisms of pain regulation [12]. In the occurrence of neuropathic pain, the role of peripheral nerves and roots of the spinal cord, which development is influenced by pain neurotransmitters, glutamate receptors, and sodium and calcium channels, are the most studied. Polyneuropathy with neuropathic pain is characterized by the involvement of thin and unmyelinated nerve fibers, and their dysfunction leads, in addition to pain, to a change in skin color and trophism. Dysfunction of fine fibers is detected in all patients with erythromelalgia [13].

Given the pronounced pain syndrome and the lack of pathognomonic treatment of erythromelalgia, such patients are mainly managed by neurologists and psychiatrists who use drugs to relieve neuropathic pain. Basic analgesic therapy includes anticonvulsants, antidepressants, cooling of the extremities, and avoidance of trigger factors that induce disease progression and exacerbation. To date, the treatment of these patients is performed in stages with the use of pharmacotherapy, choosing the most effective and efficient method. However, in the presented clinical case, neuropathic pain in the lower extremities was found to be resistant to any pharmacotherapy. Recently, in the case of ineffective pharmacotherapy for neuropathic pain of various etiologies, various neurosurgical methods have been used, which aimed at the blockade of pain receptors and strengthening the antinociceptive systems of the nervous system. It is advisable to consider these types of treatment for disorders and erythromelalgia.

**CONCLUSION**

The presented clinical case demonstrates the need to assess the condition of patients with hereditary and idiopathic forms of erythromelalgia as chronic and intractable. A neurologist and neurosurgeon should interpret the signs of this disease. Given the lack of understanding of the cause of this disease with various clinical manifestations, a multidisciplinary approach should be employed for patients with erythromelalgia, with the search for new methods of treatment, including the use of neurosurgical methods, for the treatment of chronic pain.

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**Author contributions.** V.G. Toriya wrote all sections of the article, collected and analyzed the data, and analyzed the literature. M.V. Savina performed the neurophysiological examination of the patient and staged editing of the text. S.V. Vissarionov and A.G. Bandurashvili performed staged and final editing of the text of the article and collected the data.

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