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Case report

Surgical treatment of a patient with erythromelalgia (Mitchell's syndrome) using invasive spinal cord stimulation: A Clinical case

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BACKGROUND: Erythromelalgia is a rare hereditary disorder manifesting the basic triad of symptoms: *erythro* – redness, *melos* – limb, and *algos* – pain. It was first described by the American neurologist, S. Weir Mitchell in 1878. Clinical manifestations of the disease worsen the physical and psychological condition of the patient leading to reduced quality of life, increased morbidity and mortality. Currently, etiotropic therapy for erythromelalgia that demonstrates high efficacy in individuals with this pathology, has not been developed. Moreover, there is no consensus on treatment strategies for this category of patients, emphasized by the absence of clinical guidelines for the treatment of erythromelalgia. Treatment of patients with erythromelalgia is currently based on sequential pharmacotherapy in order to select the most effective therapy.

CLINICAL CASE: We presented the result of surgical treatment of erythromelalgia in a 15-year-old adolescent using invasive spinal cord stimulation.

DISCUSSION: Erythromelalgia remains an understudied condition with the lack of sufficient understanding of its etiology and pathogenesis. For the first time in Russia, a technique of invasive spinal cord stimulation was used in a pediatric patient with erythromelalgia, which resulted in a significant reduction of neuropathic pain, restoration of vasomotor regulation in the form of reduced edema and hyperemia.

CONCLUSIONS: In a patient with prolonged and pronounced refractory neuropathic pain caused by erythromelalgia, spinal cord stimulation was the only effective treatment technique alternative to symptomatic and drug therapy. Spinal cord stimulation should be considered as a method of treating neuropathic pain associated with pharmacoresistant forms of erythromelalgia.

Keywords: erythromelalgia; neuropathic pain; spinal cord stimulation; neuromodulation; Mitchell syndrome.

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Клинический случай

Хирургическое лечение пациента с эритромелалгией (синдром Митчелла) с применением инвазивной стимуляции спинного мозга. Клиническое наблюдение

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Обоснование. Эритромелалгия — редкое наследственное заболевание, проявляющееся основной триадой симптомов: *erythros* — покраснение, *melos* — конечность и *algos* — боль. Впервые описана американским неврологом S. Weir Mitchell в 1878 г. Клинические проявления заболевания ухудшают физическое и психологическое состояние, что приводит к снижению качества жизни, повышению уровня заболеваемости и смертности. В настоящее время высокоэффективная этиотропная терапия при эритромелалгии не разработана, не достигнут консенсус в стратегии лечения этой категории пациентов, отсутствуют клинические рекомендации по их лечению. Лечение пациентов с эритромелалгией в настоящее время основано на последовательной фармакотерапии с целью подбора наиболее эффективной схемы.

Клиническое наблюдение. Представлен результат хирургического лечения эритромелалгии у 15-летнего подростка с применением инвазивной стимуляции спинного мозга.

Обсуждение. Эритромелалгия остается и в наше время малоизученным заболеванием, этиология и патогенез данного состояния до конца не понятны. Впервые в России у пациента детского возраста с эритромелалгией применена методика инвазивной стимуляция спинного мозга, что обеспечило значительное уменьшение нейропатической боли, восстановление вазомоторной регуляции в виде уменьшения отека и гиперемии.

Заключение. У пациента с длительной и выраженной рефрактерной нейропатической болью, вызванной эритромелалгией, стимуляция спинного мозга оказалась единственной эффективной методикой лечения, ставшей альтернативой симптоматической и лекарственной терапии. Стимуляцию спинного мозга следует рассматривать как один из возможных методов лечения нейропатической боли, связанной с фармакорезистентными формами эритромелалгии.

Ключевые слова: эритромелалгия; нейропатическая боль; стимуляция спинного мозга; нейромодуляция; синдром Митчелла.

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BACKGROUND

Erythromelalgia is a rare hereditary disorder that is characterized by the basic triad of symptoms, namely *erythro* (redness), *melos* (limb), and *algos* (pain). It was first described by the American neurologist S. Weir Mitchell in 1878 [1].

Currently, the pathogenesis of erythromelalgia is underinvestigated. Most patients with erythromelalgia have an *SCN9A* gene mutation [2]. Several studies revealed that the *SCN9A* gene is located in the 2q24.3 locus of chromosome 2 and is responsible for the α-subunit formation of the closed sodium channel NaV1.7, which is widespread in the spinal ganglia neurons (nociceptors) that conduct pain signals and increase depolarization to enhance the signal [3, 4].

Patients with erythromelalgia are classified into patients with a primary form and an idiopathic form according to the *SCN9A* gene mutation. Additionally, secondary erythromelalgia can develop in the presence of the underlying disease (usually myeloproliferative, rheumatoid, or infectious), which is consistent with the concept of the polymorphic etiology of this pathology [5].

Experts from Europe and the United States of America reported the erythromelalgia incidence of 0.36–2.00 per 100,000 people per year. Primary erythromelalgia is more common. Erythromelalgia is detected approximately 2 times more often in females than in males [6–8].

The primary disease diagnosis is based on the history and clinical presentation. Erythromelalgia is a disease with multiple manifestations, which mainly include skin redness, swelling, and extremities soreness, more often the lower ones. Less commonly, the process is localized on the upper limbs, face, perineum, and genitals [9, 10].

Moreover, a local increase in the skin temperature is noted in the clinical disease presentation. Usually, the lesion symmetrically develops on both limbs; with daily disease activity with pain syndrome exacerbation at night, and seasonal activity with increased symptoms in warm months. Some patients develop a severe neuropathic burning pain syndrome that interferes with sleep and limits their motor activity [11, 12].

The most common complications of erythromelalgia are trophic disorders in the form of macerations and ulcerations [13].

Infection of soft tissues and sepsis occur in some cases, which can lead to lower extremity amputations [14].

Some patients may have mental disorders due to the constant and severe neuropathic pain [15].

A large number of patients with erythromelalgia are diagnosed with refractory hypertension, with frequent hypertensive crises with simultaneous neuropathic pain syndrome intensification [16, 17].

All these manifestations deteriorate the patient's physical and mental condition and reduce the quality of life, which leads to increased morbidity and mortality [18].

Increased manifestations of erythromelalgia are mainly triggered by an increased ambient temperature, wearing tight shoes, increased physical activity, and forced longtime limb position, causing a disorder of their tropism.

Currently, highly effective etiotropic therapy for erythromelalgia has not been developed, no consensus has been achieved on the treatment strategy for this category of patients, and there are no clinical treatment guidelines.

The main therapy for erythromelalgia is symptomatic and consists in cooling the extremities by wrapping them in wet cloths, using air conditioners and fans, and immersing the extremities in cold water for a long time, which often induces frostbite and the above-mentioned trophic complications.

The treatment of patients with erythromelalgia is currently based on consistent pharmacotherapy to select the most effective regimen. The therapy is aimed at alleviating the patients' condition induced by the main disease symptoms. Drugs from the groups of sodium channel blockers, antidepressants, anticonvulsants, antihistamines, prostaglandins, immunosuppressive drugs, aspirin, and topical drugs are mostly used. However, none of the drugs was fully effective, which led to polypharmacy in most patients. Some patients are resistant despite a wide range of drugs, and most often these are patients with primary erythromelalgia [19, 20].

The literature presents no systemic data on interventional treatment of erythromelalgia. Several clinical cases of adult patients with this disease have been described. The authors reported a positive effect of neuromodulation, clinical manifestation regression, and improved quality of life in the immediate and long-term postoperative periods [21, 22].

CLINICAL CASE

A 15-year-old patient with a previously diagnosed hereditary erythromelalgia was hospitalized in the Department of Spinal Pathology and Neurosurgery of the H.I. Turner National Medical Research Center for Children's Orthopedics and Trauma Surgery. The patient complained of hyperemia, burning pain, swelling in the feet and lower third of the lower legs, refractory hypertension with hypertensive crises up to 5 times a day, and subsequently increased pain. For the first time, clinical manifestations were recorded at the age of 4 years and were induced by physical exertion. They disappeared during the rest period. The disease course was slowly progressive, and cold therapy was first started using an air conditioner and a cold rubber water bag at the age of 11 years. Since then, decreased motor activity has been noted; however, the patient could not attend an educational institution. The child was examined by a geneticist, a neurologist, and a dermatologist. The hereditary nature of the disease has been established, considering erythromelalgia in the mother

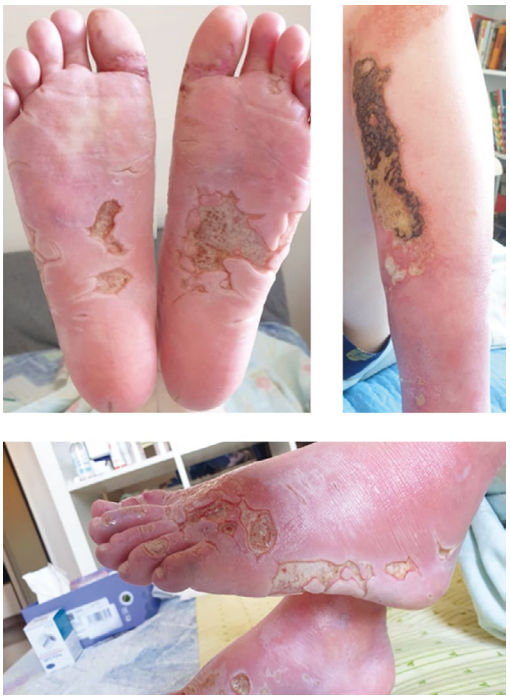

Fig. 1. Patient A. at the age of 14 years. Ulcerative skin lesion of the lower extremities

and grandmother. The patient began to receive effective pharmacotherapy at the age of 12 years. Hypertension and hypertensive crises were first registered at the age of 13 years. Over the subsequent period, several treatment regimens were tested using various combinations of non-steroidal anti-inflammatory drugs, antihistamines, opioids, antidepressants, systemic and local hormone therapy, antiepileptic drugs, and topical agents with lidocaine and silver. All therapy options were ineffective or had effect for no more than 4 h, after which the pain syndrome intensified. During the treatment, adverse reactions developed in the form of toxicoderma and skin ulcers of the lower extremities from the upper third of the lower leg to the feet (Fig. 1), which required surgical hospital treatment. Episodes of panic attacks with difficulty breathing appeared due to the condition deterioration and increased pain at rest and night, followed by sleep regression [20].

Patient examination revealed a forced sitting position on the bed with symptomatic cooling of the lower extremities with a cold rubber bag and air conditioning. Onychomycosis, hyperemic lower extremities from the middle third level of the leg, trophic foot ulcers in the healing stage, and post-ulcer scars of the lower legs and feet up to 15×5 cm^2 in size were noteworthy (Fig. 2).

Physical examination revealed no abnormalities in the cardiovascular, respiratory, and digestive systems. The neurological status included hyperesthesia from the middle third level of the lower leg, increasing in the distal direction. Pain neuropathic syndrome intensified in 20–30 min after a manual feet examination. Condition on the Karnofsky scale was 40%. The pain was rated at 8 points on a visual analog scale. Night sleep regression was first registered at the age of 14 years. Carbamazepine was prescribed at 200 mg twice a day, and hypertension was treated with Enap at 10 mg twice a day. Hypertensive crises occurred up to 5 times a day and were stopped by Concor and Capoten, and the maximum blood pressure was 160/110 mm Hg. Urinalysis and clinical and biochemical blood test results were within reference values. Magnetic

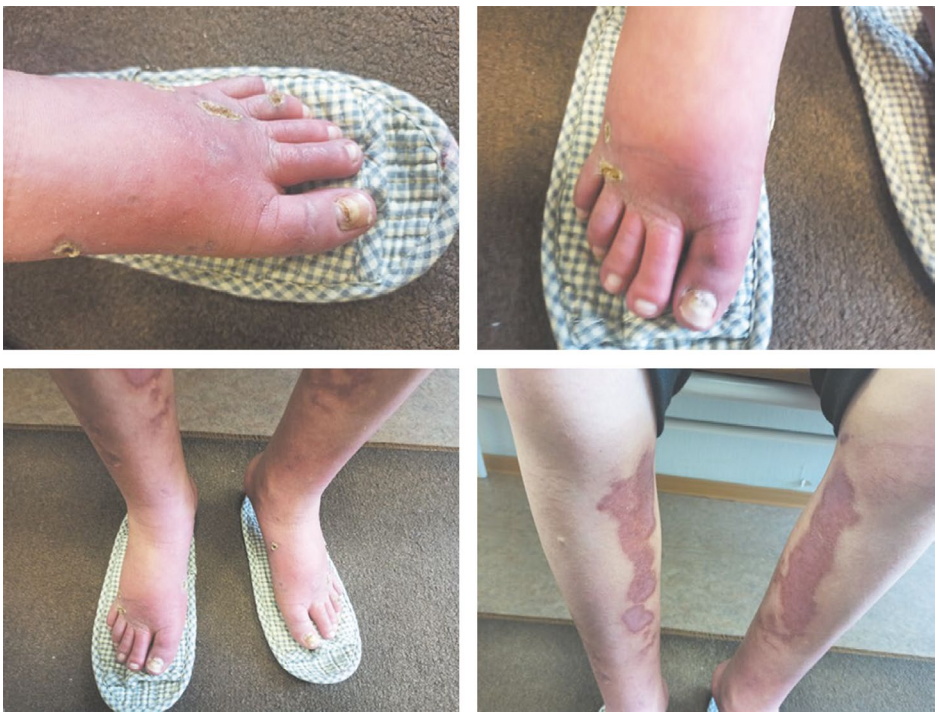

Fig. 2. Appearance of the lower extremities at hospitalization

resonance and computed tomography of the thoracic and lumbar spine revealed no pathology.

Electroneuromyography revealed signs of diffuse axonal motor fiber and, to a greater extent, sensory peripheral nerve fiber damage of the lower extremities, which are characteristic of manifestations of axonal, predominantly sensory, and polyneuropathy of the lower extremities. No disorders were registered in the functional activity of sensory and motor fibers of the upper and lower extremities.

Thus, a rare case of hereditary drug-resistant erythromelalgia with severe complications in the form of trophic skin disorders of the lower extremities, refractory hypertension with frequent hypertensive crises, panic attacks with respiratory failure, sleep regression, and motor activity limitation was diagnosed in the patient.

A multidisciplinary treatment approach for chronic pain syndrome was decided, considering the disease duration, the lack of symptomatic therapy effects, and the condition deterioration. Spinal cord stimulator implantation was planned as part of a multimodal treatment regimen.

The surgery was performed to implant a permanent eight-junction cylindrical epidural electrode. The electrode was placed at the Th_{11}–Th_{12} vertebrae level and the pulse generator was implanted in the right lumbar region using intraoperative radiography (Fig. 3).

Intraoperative neurophysiological monitoring was performed to position the electrodes to cover the sensory area of the lower legs and feet. The muscular activity of the lower extremities (*m. vastus lateralis*, *m. tibialis anterior*, *m. gastrocnemius*, and *m. abductor hallicis brevis*) was recorded when the epidural electrode was activated in the TriggeredEMG mode. The electrodes were placed in such a way that the maximum effect of the electric current accounted for the lower leg and feet region on both sides, which was manifested by the emergence of evoked activity on the electromyograms of the corresponding lower extremity muscles (Fig. 4).

The patient was in a horizontal position with a low flat pillow under his head for 2 days postoperatively to prevent electrode displacement. Stimulation started on a postoperative day 2 with constant tonic mode exposure with parameters of 4+ and 5–, pulse duration of 350 ms, frequency of 40 Hz, and the current strength of 2.1 mA (current strength range: 0.4–4.1 mA). The sensations of stimulation were described by the patient as a vibration that initially occurred in the lower legs with a gradual spread distally to the foot level. The patient did not feel the vibration in the feet, which is typical for sensory polyneuropathy manifestations, considering the electroneuromyography results. However, the current strength was not increased, and the cumulative effect of neuromodulation was observed, considering the data of intraoperative mapping during neurophysiological monitoring, indicating the conduction of

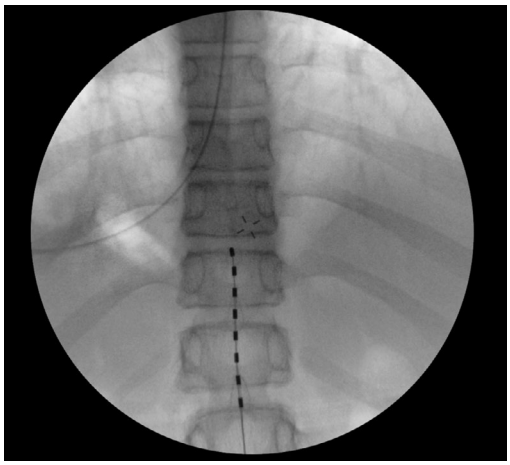

Fig. 3. Intraoperative radiography and the position of the eight-junction epidural electrode at the Th_{11}–Th_{12} vertebrae level

electric current when the epidural stimulator was connected to the lower legs muscles.

Improvement was noted on day 2 of stimulation in the form of an insignificant pain syndrome regression. Starting from day 3, the patient had a sensation of vibration in the feet, with a tendency to reduce skin hyperemia and extremity swelling. After 3 days of positive dynamics with constant tonic mode stimulation, a transition was made to the variable Burst mode. Further stimulation took place in the mode of 3 min operation and 3 min pause, with parameters of 5+ and 6–, the current strength of 1.1 mA (current strength range of 0.5–4.1 mA), the pulse width of 300 ms, basic frequency of 40 Hz, instantaneous pulses of 5, duration of 1 ms, and frequency of 500 Hz. The decision to change the stimulation mode to the Burst mode was due to the positive effect

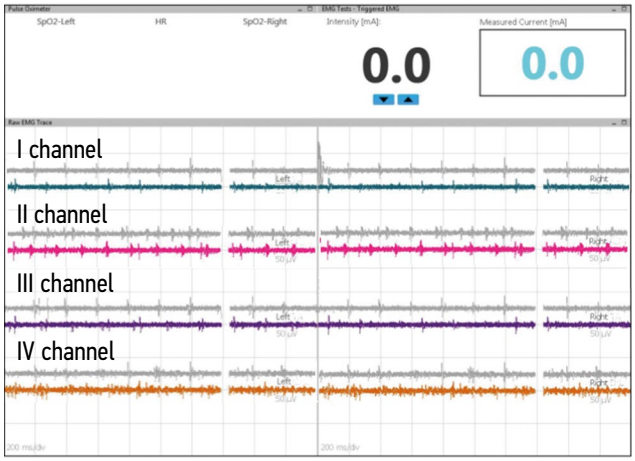

Fig. 4. Data of intraoperative neurophysiological monitoring using an epidural electrode with muscular activity registration of the lower extremities on the left and right: channel I: *m. vastus lateralis*, channel II: *m. tibialis ant*., channel III: *m. gastrocnemius*, and channel IV: *m. abd. hallucis brevis*. The muscular activity during the period of choosing the epidural electrode position is presented, and the muscular activity of the feet on both sides is recorded in presence of rhythmic stimulation with electrical impulses when the electrode is connected

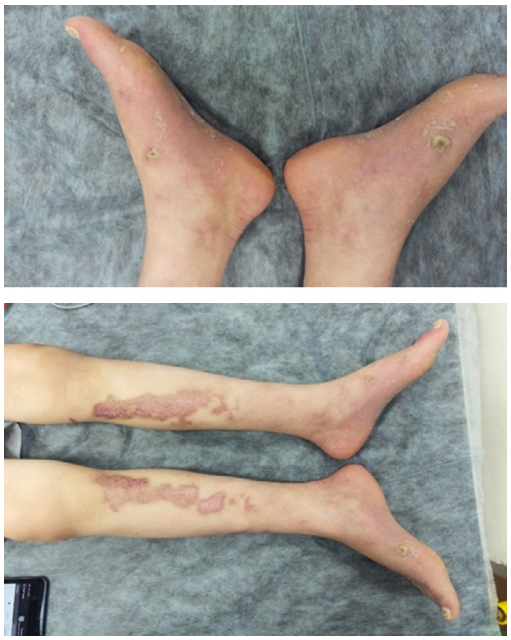

Fig. 5. Patient A. at 15 years old. The appearance of the lower extremities on day 7 of stimulation, regression of hyperemia, and leg and feet swelling

of stimulation on day 1 and the literature data on a more pronounced analgesic effect of this mode [23].

Pain, erythema, and edema started to noticeably decrease after 4 days of stimulation. On day 7, edema and erythema regressed (Fig. 5), the pain index on the visual analog scale decreased to 2 points, and the duration of sleep increased.

The therapeutic effect persisted 3 weeks after the start of stimulation, and the carbamazepine intake was discontinued. The patient's condition did not deteriorate thereafter. The patient experienced an increased incidence of hypertensive crises with simultaneous occurrence of shooting impulses in the lower extremities during stimulation, as well as pain syndrome intensification 2 months after the start of stimulation.

The child was hospitalized in the Cardiology Department for examination and antihypertensive therapy selection. Propranolol was prescribed at 1.875 mg/kg per day, and losartan at 12.5 mg once daily in the course of therapeutic measures. With antihypertensive therapy, the incidence and degree of arterial hypertension decreased, as well as the incidence of shooting impulses to the lower extremities, but without complete regression. The stimulation period was reduced and the pause period was increased, with the mode of 1.5 min of stimulation and 12 min of pause. The episodes of shooting impulses into the lower extremities almost completely disappeared after a change in the stimulation mode, and the analgesic effect was preserved. Pain in the sitting position was 2–3 points on the visual analog scale and up to 4 points in the supine position, with increased pain at night 6 months after the therapy initiation. The patient occasionally resorted to symptomatic lower extremity cooling. A positive vasomotor effect persisted in the form of the absence of significant swelling and skin hyperemia of the lower extremities. The Karnofsky index increased to 70%, the physical and emotional state significantly improved, and depressive symptoms and negative emotions associated with pain decreased.

DISCUSSION

Erythromelalgia, which was first described in 1878 and diagnosed by a characteristic triad of symptoms, remains an insufficiently studied disease nowadays, with no sufficient etiology and pathogenesis understanding [1–5]. The literature revealed no clear and reasonable strategies for the treatment of patients with erythromelalgia [20]. The presented clinical case describes a rare hereditary form of erythromelalgia resistant to combination pharmacotherapy with a constant progredient course and periods of exacerbation and remission. Over the past 3 years, the patient gradually developed severe trophic complications that required inpatient treatment, as well as concomitant arterial incurable hypertension and sleep regression, which, in combination, led to panic attacks and negative emotions associated with pain. The severe condition resulted in decreased motor activity; therefore, the quality of life significantly decreased. Considering the drug-resistant disease course, neurosurgical techniques aimed at nociceptive receptor blockade, and antinociceptive system strengthening were considered and applied. For the first time in Russia, the technique of invasive spinal cord stimulation was used in a pediatric patient with erythromelalgia, which significantly reduced the neuropathic pain and restored vasomotor regulation, namely reducing swelling and hyperemia, normalizing sleep, increasing motor activity, and generally improving the quality of life. A stable weakening of the manifestations of erythromelalgia for 6 months after surgical treatment was achieved using spinal cord stimulation. We may suggest a pathognomonic effect of spinal cord stimulation on the clinical manifestations of erythromelalgia with the main localization of the process in the lower extremities due to the regression of neuropathic pain syndrome and dyscirculatory disorders [3, 4]. In our case, the spinal cord stimulation technique surpassed in efficiency the traditional pharmacological treatment [5, 7, 12, 15, 16], which determines the interest in future research in the field of neuromodulation as part of a multimodal treatment regimen for patients with this complex and debilitating disease.

CONCLUSION

This study presented a clinical case of a patient with drug-resistant erythromelalgia with severe neuropathic pain, trophic disorders, and severe complications, which

necessitated inpatient treatment. The spinal cord stimulator implantation was part of a multimodal treatment regimen for a patient with this complex and debilitating disease based on the lack of effect from long-term symptomatic therapy and the deterioration of the child's condition. Regression of neuropathic pain syndrome and dyscirculatory disorders was achieved as a result of surgical treatment in the immediate postoperative period. Thus, spinal cord stimulation has become the only effective treatment method, an alternative to symptomatic and drug therapy, in a patient with prolonged and severe refractory neuropathic pain caused by erythromelalgia. Spinal cord stimulation should be considered as one of the treatment methods for neuropathic pain associated with drug-resistant forms of erythromelalgia.

ADDITIONAL INFORMATION

Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

Ethical considerations. The patient's representative provided written consent to the processing and publication of personal data.

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

All authors made a significant contribution to the study and preparation of the article, as well as read and approved the final version before its publication.

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