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HEREDITARY SENSORY MOTOR POLYNEUROPATHY

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Background. Congenital contractures are a heterogeneous group of diseases with different prognosis and different treatment modalities.
Clinical case. This article describes a family case of hereditary sensory motor polyneuropathy caused by the mutation of c.943G>A (p.Arg315Trp) in the *transient receptor potential vanilloid cation channel 4* (*TRPV4*) (NM_021625.4). The patient's clinical and neurological characteristics as well as the results of genetic and neurophysiological examinations are presented.
Discussion. Most often, mutations in the *TRPV4* lead to 3 main diseases: autosomal dominant hereditary sensory motor neuropathy, type 2C, scapuloperoneal spinal muscular atrophy, and congenital non-progressive distal spinal muscular atrophy with contractures. The present article describes in detail the differential diagnosis of hereditary sensory motor polyneuropathy to facilitate accurate verification of this disease by clinicians.
Conclusion. Patients with congenital multiple contractures need cooperative observation and examination by orthopedic surgeons and neurologists, including neurophysiological and genetic interventions in the examination plan for disease verification in order to optimize the treatment strategy and to predict the outcomes.

Keywords: arthrogryposis; sensory motor polyneuropathy; the gene *TRPV4*; DNA sequence.

НАСЛЕДСТВЕННАЯ СЕНСОМОТОРНАЯ ПОЛИНЕЙРОПАТИЯ

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Обоснование. Врожденные контрактуры — это гетерогенная группа заболеваний. Они характеризуются различным прогнозом для пациента, и для их лечения применяют разные методы.
Клиническое наблюдение. В статье описан семейный случай наследственной сенсорно-моторной полинейропатии, обусловленной мутацией c.943G>A (p.Arg315Trp) в гене *TRPV4* (transient receptor potential vanilloid

cation channel 4, NM_021625.4). Представлены клинико-неврологическая характеристика пациента, результаты генетического и нейрофизиологического исследования.

Обсуждение. Наиболее часто мутации в гене *TRPV4* приводят к трем основным заболеваниям: наследственной аутосомно-доминантной сенсомоторной нейропатии, тип 2C; скапулоперонеальной спинальной мышечной атрофии; врожденной непрогрессирующей дистальной спинальной мышечной атрофии с контрактурами. В статье подробно описана дифференциальная диагностика наследственной сенсомоторной полинейропатии, позволяющая практикующим врачам правильно верифицировать заболевание.

Заключение. Пациенты с врожденными множественными контрактурами нуждаются в наблюдении и ортопедов, и неврологов с включением в план обследования таких методов, как нейрофизиологический и генетический, что позволяет верифицировать заболевание, оптимизировать тактику лечения, а также прогнозировать его результаты.

Ключевые слова: артрогрипоз; сенсомоторная полинейропатия; ген *TRPV4*; экзомное секвенирование.

Congenital contractures represent a heterogeneous group of diseases with different etiology and clinical manifestations. They include isolated contractures affecting only one segment of the body and multiple contractures involving two or more body segments. The most common manifestation of isolated contractures is congenital clubfoot with an incidence of 1 per 500 live births [1]. In foreign literature, the general term "arthrogryposis" is used for the clinical description of multiple congenital contractures. Bamshad et al. classified arthrogryposis into three groups, namely, amyoplasia, distal forms of arthrogryposis, and congenital multiple contractures manifested by different syndromes caused by central nervous system lesions and various neuromuscular diseases [1]. According to Lowry et al., the incidence of arthrogryposis is 1 case per 3000 to 56,000 live births [2]. The most common type of arthrogryposis is amyoplasia, which is a sporadic, nonprogressive disease with an incidence of 1 per 10,000 live births [3].

Over the past 30 years, significant progress has been made in verifying various types of arthrogryposis and identifying genes responsible for the development of this pathology [3]. At present, more than 300 genes have been identified, which are associated with about 400 hereditary diseases manifested by congenital multiple contractures [4].

Clinical case

Patient A., who was the first pregnancy child and born at week 42 by natural delivery, was under our supervision. Birth weight was 3600 g. Clubfoot was diagnosed at birth. When examined at the age of 1.5 months, 30° flexion contractures of the knee joints, equinocavovarus deformity of the left foot, and equinoplanovalgus deformity of the right foot were revealed (Fig. 1). The child was diagnosed with arthrogryposis with lesions of the lower extremities, and conservative treatment was prescribed. The patient underwent staged plastering of the left and right feet using the Ponseti and Dobbs methods, respectively; and achillotenotomy was performed on both feet.

At the age of 6.5 months, the child was examined by a neurologist. The history revealed that the patient started to poise his head at 1.5 months old, turn over at 3.5 months, sit at 5.5 months, and babble at 4.5 months. Neurosonography indices are within the age norms. The child was sociable, performed tasks, and understood the speech spoken to him. He can pronounce up to 10 individual words. Cranial nerve examination revealed no abnormalities. The upper limbs had full active and passive movements. The muscle tone was physiological, and the muscle strength was up to five points. Biceps, triceps, and brachioradialis reflexes were symmetrical and low. External examination of the lower extremities revealed muscle hypotrophy of the lower legs and feet and varus deformity of the feet. Passive dorsal and plantar flexion of the feet was limited. The support on the entire foot was weak, and the patient could only stand with support for a short period. Muscle strength in the proximal parts of the lower extremities was reduced up to four points and in the distal parts up to two points. Hypotension, more pronounced in the muscles of the lower legs and feet, was revealed. Knee and Achilles reflexes on both sides were not activated. Based on the examination, the child was diagnosed with inferior flaccid paraparesis.

At the age of 7 months, surgery was performed on the right foot, namely, open reduction of the talus bone. Later, the child received two courses of rehabilitation treatment, including massage, exercise

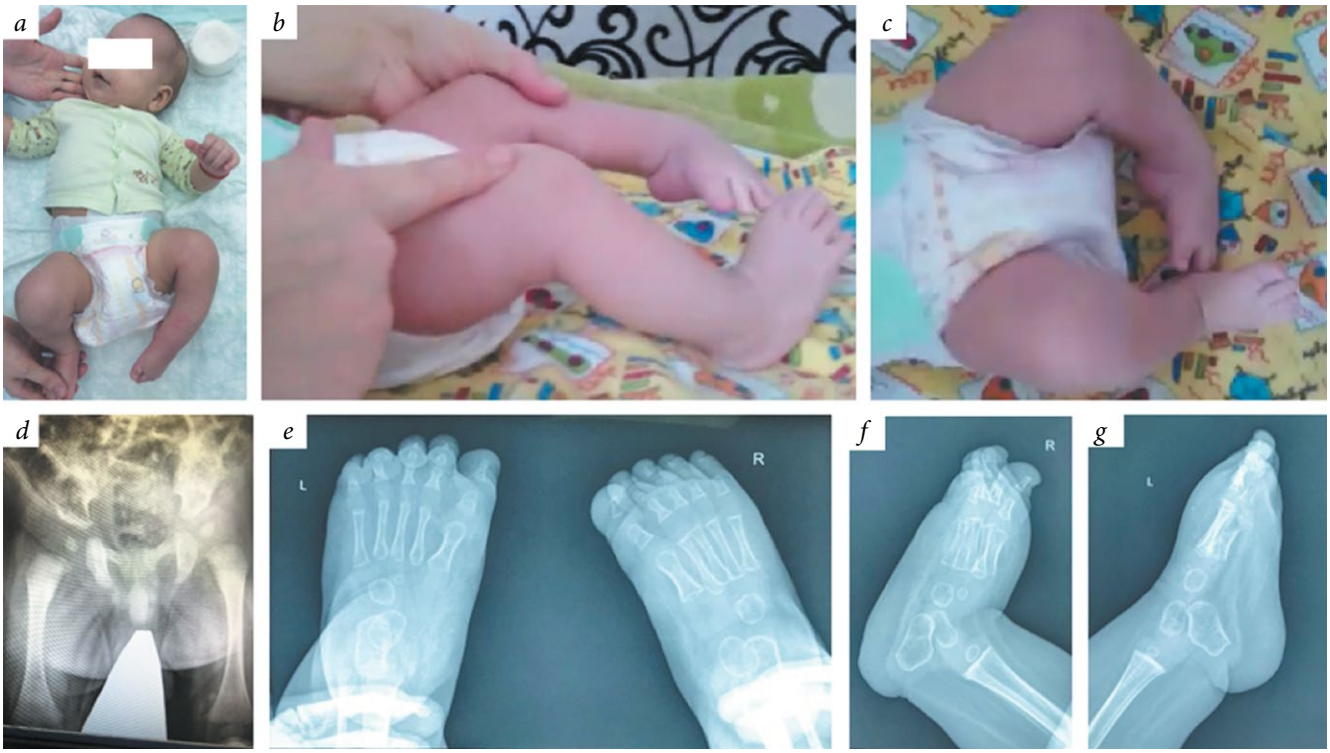

Fig. 1. Deformities of the lower extremities in patient A. (1.5 months old) prior to the treatment of (*a*–*c*) the limbs and (*d*) X-ray of the hip joints and (*e*–*g*) feet

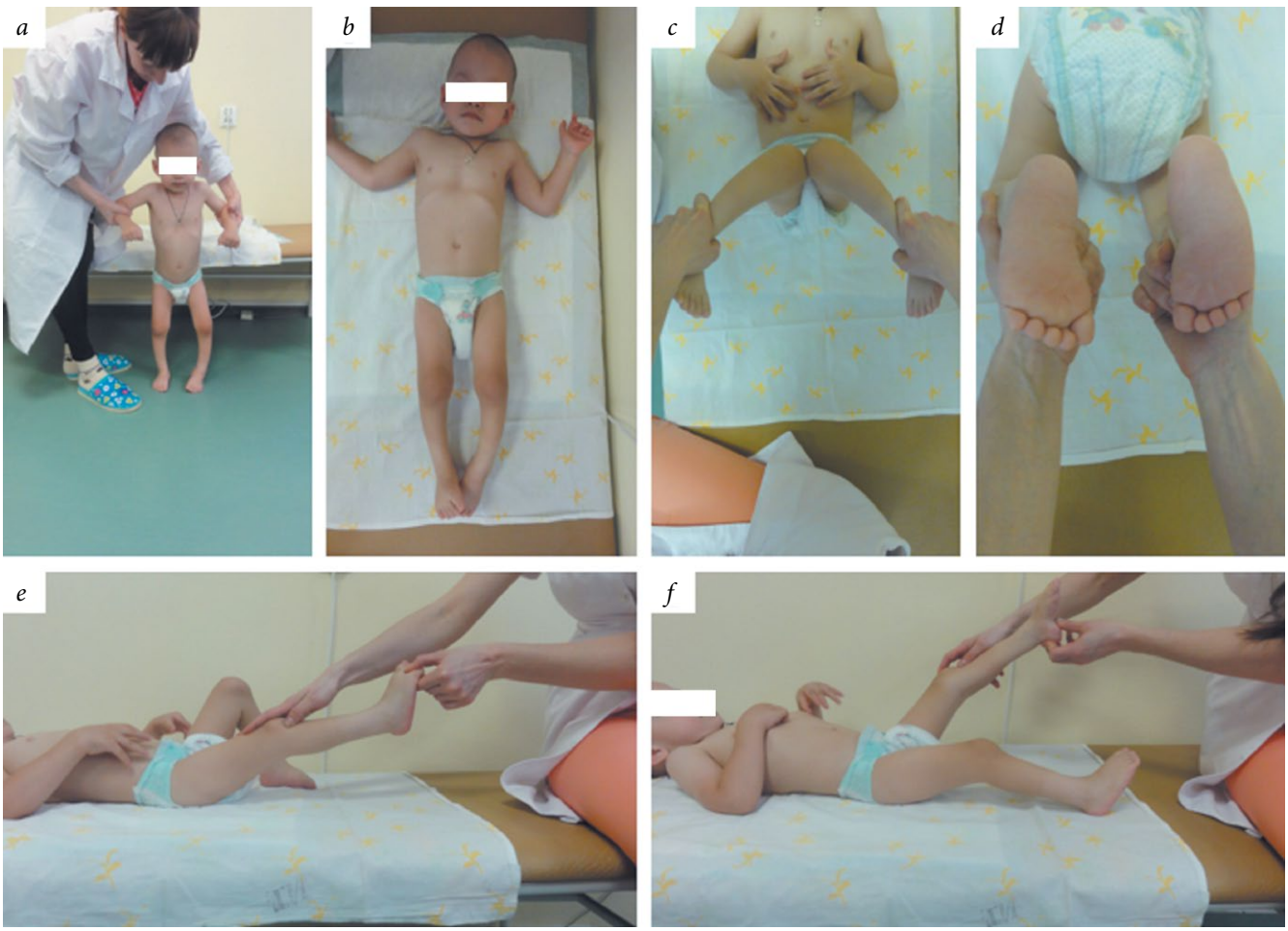

Fig. 2. Patient A.'s lower extremities at the age of 2 years after treatment: (*a*) standing view; (*b*) varus deformity of the lower legs; (*c*) rotational movements in the hip joints and (*d*) feet; (*e* and *f*) passive movements in the knee joints.

therapy, and physiotherapy (electrical stimulation of the lower extremity muscles and ozocerite application on the knee joints).

When examined at the age of 2 years, the child walked independently with support from both hands using the kneeboards and from the outer segment of the left foot. The boy was of proportional, normosthenic constitution, with satisfactory nutrition. The head was located in the midline, of normal size, and rounded shape. The face was symmetrical. The spine axis was correct. Movements in all parts of the spine were full and painless. The position and axis of the upper limbs were correct, with full movements in the joints, length D = S. In the lower limbs, length D = S. The axis of the lower limbs was varus. Movements in the hip joints revealed abduction of 55° on both sides, flexion of 130°, internal rotation of 45°, and external rotation of 60° on both sides. Movements in the knee joints revealed full flexion and extension up to 170° and 155° on the right and left, respectively. The right foot was in the middle position, and the left foot in the supination position, with the posterior part in the equinus position of 10° (Fig. 2).

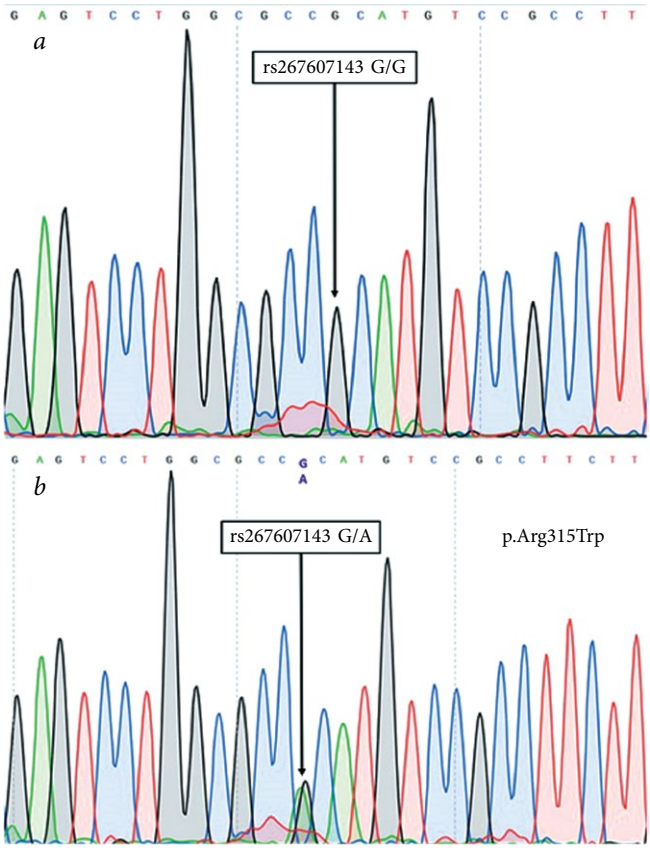

Fig. 3. Fragments of an electrophoretogram of DNA sequences corresponding to the region of the *TRPV4* gene where the mutation was detected (indicated by an arrow). (*a*) In a healthy mother, there are only normal G alleles. (*b*) The patient had a heterozygous carriage of two alleles (normal G and mutant A) at position rs267607143

The history revealed that the father of the child could not walk and moved using a wheelchair; he had deformities of the lower extremities from birth (clubfoot and flexion contractures of the knee joints). No pathology was noted in the upper extremities. During his childhood, his lower extremities were operated (with unknown nature of treatment). Currently, the father is professionally involved in sports (paralympic multidiscipline competition). His two brothers and the father's parents are healthy. The child's mother is healthy. On the maternal side, the anamnesis is not burdened.

Given the hereditary nature of the pathology, the child and his parents underwent a comprehensive examination.

To search for mutations, exome sequencing was performed in two family members — the proband and his father. Total DNA was isolated from whole blood samples obtained from the patients. The isolated DNA was used to construct libraries (KAPA Library preparation kit, KapaBiosystems, Wilmington, MA, USA). Exome enrichment was performed using the Nimble Gen Ez Cap Human v3.0 Exome Enrichment Kit (Roche, Madison, MI, USA) followed by sequencing on a Hiseq 2500 platform (Illumina, San Diego, CA, USA) in a pair-end reading mode with a read length of 100 bp. Bioinformatic processing of the results was performed as follows. Adapters trimming and filtering of low quality readings was performed using the Cutadaptand Trimmomatic program. Mapping of reads to the reference genome (GRch37/hg19) was performed using the BWA-MEM algorithm. The search for variations in nucleotide sequences was performed using a combination of GATK HaplotypeCaller + UnifiedGenotyper (to obtain a composite VCF file). For annotation, a combination of specialized algorithms, including SnpSift, ANNOVAR SIFT, PolyPhen2, MutationTaster, FATMM, CADD, DANN, Eigen, and AlamutBatch (splicing effect assessment, dbSNP, ClinVar, HGMD Professional databases) and BIC database were used.

Exome sequencing revealed a G>A missense mutation at position 943 of the *TRPV4* gene (transient receptor potential vanilloid cation channel 4 [TRPV4], NM_021625.4), which causes an Arg to Trp amino acid substitution at position 315 of

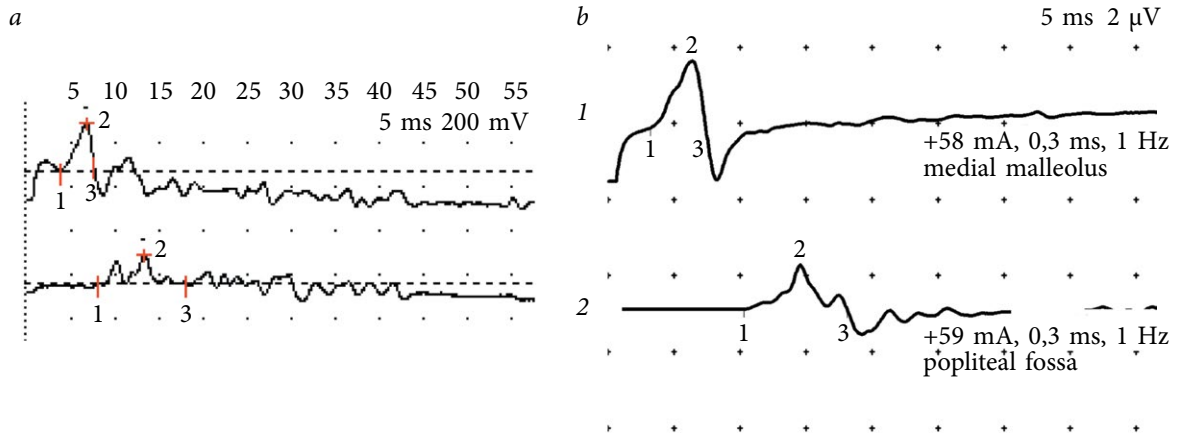

Fig. 4. M-answers with *m. abd. hall. brev.* when stimulating the tibial nerve: (*a*) in patient A., 1.5 years old, and (*b*) in patient A.'s father, 25 years old

the corresponding protein in the father and son. To confirm the potential mutations detected during the full exome sequencing, the child's father and mother were examined using the Sanger sequencing method using the ABI PRISM 3730 equipment (Applied Biosystems, Foster City, CA, USA), which confirmed the presence of heterozygous carriage of the identified mutation in the proband and his father. Meanwhile, such a mutation was not revealed in the child's mother (Fig. 3).

To determine the level of lesion, a neurophysiological examination was performed, which included electroneuromyography (ENMG) with an assessment of conduction and response parameters during stimulation of sensory fibers of the median, ulnar, and sural nerves and motor fibers of the ulnar, tibial, and peroneal nerves, and needle electromyography (EMG) of *m. tibialis anterior*, *m. vastus lateralis*, and *m. biceps brachii*.

When stimulating the sensory and motor fibers of the upper extremities, the amplitudes of sensory and motor responses (M-responses) were within the age norm, and conduction along the sensory and motor fibers of the upper extremities was not impaired. When the sensory fibers of the lower extremities were stimulated, the amplitudes of sensory responses were within the age norm, with a minor deceleration of conduction along the sensory fibers with a decrease in the impulse conduction velocity (ICV) to 38 m/s (age norm > 48 m/s). Stimulation of the tibial and peroneal nerves revealed a pronounced decrease in the amplitudes of the M-responses to 0.1–0.2 mV, an increase in the duration of the M-responses, and an increase in the polyphasy of the M-responses, which indicated damage to the peripheral motor fibers of the lower extremities by the type of myelinopathy and axonopathy. No denervation activity was detected when needle EMG was conducted on *m. tibialis anterior* and *m. vastus lateralis* at rest. When the potentials of motor units of increased amplitude and duration were activated, the EMG structure was hypersynchronous, which indicated chronic neurogenic changes in the muscles of the lower extremities. When conducting a needle EMG of *m. biceps brachii*, the parameters of the potentials of motor units were within the age normative indicators (Fig. 4*a*).

According to ENMG, the patient had signs of significant lesion of the motor fibers of the peripheral nerves of the lower extremities by the type of myelinopathy and axonopathy; the sensory fibers of the lower extremities were mildly affected by the type of myelinopathy, and chronic neurogenic changes in the muscles of the lower extremities were noted. Signs of damage to the sensory and motor fibers of the peripheral nerves of the upper extremities, as well as damage to the motor neurons of the spinal cord at the level of the cervical thickening, and primary muscle damage to the muscles of the upper extremities were not revealed.

ENMG performed to the father of patient A. (25 years old) revealed a pronounced decrease in the amplitudes of the M-responses during stimulation of the motor fibers of the lower extremities (0.1 and 4.7 mV for the M-responses upon stimulation of the peroneal and tibial nerves, respectively). Duration and polyphasy of M-responses were increased because of dispersion of impulse conduction. There were no sensory responses to stimulation of sensory fibers of the peroneal nerve, and those of the sural nerve were significantly reduced (2.3 μV).

The velocity of conduction of impulses along the sensory fibers of the sural nerve was reduced (38 m/s). When examining the upper extremities, the ICV by sensory and motor fibers was normal. In the study of the nerves of the upper extremities, the amplitudes of sensory and M-responses were within the normative values on both sides (Fig. 4*b*).

The ENMG data of the patient's father indicated a pronounced degree of myelinopathy and axonopathy type damage to the sensory and motor fibers of the peripheral nerves of the lower extremities. The changes were symmetrical and characteristic of sensory motor polyneuropathy manifestations of the lower extremities. During ENMG of the child's mother, no abnormalities were revealed.

Discussion

TRPV4, being an osmosensitive, chemosensitive, and mechanosensitive receptor, is involved in maintaining the influx of Ca^{2+} into the cell and also has high activity in the process of peripheral nerve maturation and plays an important role in stimulating neurogenesis, synaptogenesis, and axon growth [5–7]. The role of TRPV4 in cell maturation is not limited to neural tissue. Thus, blocking of TRPV4 in osteoclasts causes a decrease in their number and activity and an impairment of bone modeling [8].

The most common mutations in the *TRPV4* gene result in three diseases, namely, autosomal dominant hereditary sensory motor neuropathy — type 2C (OMIM# 606071), scapuloperoneal spinal muscular atrophy (OMIM# 181405), and congenital nonprogressive distal spinal muscular atrophy with contractures (OMIM# 600175). At the same time, cases of mutations in this gene have been described in several autosomal dominant skeletal dysplasias, such as metatropic dysplasia, Kozlowski's spondylometaphysial dysplasia, and brachyolmia, as well as cases of a combination of skeletal dysplasias and peripheral polyneuropathies [9, 10].

TRPV4-associated distal spinal muscular atrophy (nonprogressive, with contractures) is characterized by a benign course, a similar clinical phenotype, and neurophysiological signs of motor neuropathy. With this disease, the lower extremities are mainly affected (patients often have clubfoot); in addition, some of them have paresis of the vocal cords. Fleury and Hageman (1985) studied 21 patients from the same family with this pathology and found that the lower extremities of all the patients were predominantly affected. Of them, 15 had congenital contractures of the lower extremities, whereas the others did not have contractures but had nonprogressive weakness in the distal parts of the lower extremities [11].

Scapular-peroneal spinal muscular atrophy, caused by mutation in the *TRPV4* gene, includes progressive muscle weakness of the peroneal compartment and scapula muscles associated with vocal cord paresis or transient dysphonia. The literature described family cases of the disease with different disease courses in relatives [12, 13]. Berciano et al. (2011) monitored a mother and daughter with this pathology. The mother had sloping shoulders from birth and had weakness in the distal parts of the lower extremities at the age of 20 years; transient dysphonia appeared later. The daughter had contractures in the hip, knee, and ankle joints at birth, and at the age of 1.5 years, she underwent tracheostomy due to tracheomalacia. Flaccid paresis was registered in the upper extremities. The child's neurological symptoms did not progress. Based on the examination, distal spinal muscular atrophy was diagnosed in the mother and child [13]. DeLong et al. (1992) registered the phenomenon of anticipation in the study of a familial case of scapular-peroneal spinal muscular atrophy and muscle weakness that increased during life and found that the age of disease onset was directly proportional to the degree of disability [14].

Hereditary sensory motor neuropathy with an autosomal dominant mode of inheritance (CMT2C) is an axonal neuropathy with pathognomonic paresis of the vocal chords and the diaphragm [15–17]. However, these signs are not registered in all cases, which complicate the diagnostics of this nosology [18]. When the disease occurs in childhood, it progresses more severely, and shortness of breath develops because of laryngomalacia [16, 17].

Aharoni et al. in 2011 described a case similar to the one presented. The study monitored a girl with congenital knee joint contractures, clubfoot, and bilateral congenital hip dislocation. In addition to orthopedic pathology, the child had stridor and vocal cord paresis. Muscle weakness was predominantly noted in the lower extremities. The girl's brothers had similar clinical presentation, and the child's mother had a hoarse voice from an early age, but she had no orthopedic pathology. At the age of

30 years, her distal flaccid paresis began to progress. The neurophysiological examination of the girl and family members revealed signs of sensory motor polyneuropathy [19].

The literature describes cases of different pathologies in the same family, namely, sensory motor polyneuropathy and distal spinal muscular atrophy [9, 20].

Neurophysiological research is significant in the examination of patients with multiple congenital contractures. In most cases, in patients with congenital multiple arthrogryposis, motor neurons of the spinal cord are affected, which is manifested by neurogenic changes in the muscles of the upper and lower extremities. In this case, dysfunction of peripheral motor fibers, as a rule, has the nature of axonopathy and is manifested by a decrease in the amplitude of M-responses, whereas the conduction of peripheral nerves along the motor and sensory fibers and amplitudes of sensory potentials remain normal. In the clinical case presented, in addition to axonopathy of motor fibers, signs of peripheral nerve myelinopathy of the lower extremities were revealed in the form of a pronounced increase in duration and polyphasy of M-responses. A decrease in M-responses in severe myelinopathy may be due to both impulse conduction dispersion and secondary axonal disorders. The ENMG study in the boy's father revealed similar changes in the motor fibers of the lower extremities, which indicated myelinopathy (polyphasy, an increase in the duration of M-responses), whereas the degree of impairments in motor fiber conduction in the father (according to M-response amplitude, polyphasy severity, and M-response duration) was less compared with the degree of motor fiber disorders in the child.

In the differential diagnostics of the level of peripheral motor neuron damage, the study of sensory fibers is crucial. Signs of impaired function of sensory fibers indicate damage to peripheral nerves in sensory and sensory motor polyneuropathy. A decrease in the amplitude of sensory potentials is associated with axonopathy, and a decrease in ICV along sensory fibers is associated with myelinopathy. The absence of signs of damage to sensory fibers in the presence of motor fibers damage is a pathognomonic sign for lesion of the peripheral motor neuron at any level. Moreover, ENMG changes in motor neuron damage are the same, both at the anterior horn level of the spinal cord and in axonal motor polyneuropathy. Only the identification of progression of disorders along sensory fibers in the disease dynamics can help in such cases to accurately determine the level of damage during differential diagnostics.

Despite the young age and technical difficulties in registration, sensory potentials of the child being monitored were isolated during stimulation of the median and superficial peroneal nerves. The amplitudes of sensory potentials were normal, but there was a mild decrease in ICV along the sensory fibers of the lower extremities (36 m/s with an age norm of greater than 48 m/s). A decrease in ICV indicates a slowdown in impulse conduction in case of myelinopathy of sensory fibers. However, considering the patient's age and aspects of heat exchange in children, the influence of the registration conditions on the indicators of sensory responses (low skin temperature of the child's feet during the study) cannot be excluded.

During ENMG in the father, the potentials of the sensory fibers of the lower extremities were impaired, and the ENMG changes in motor and sensory fibers fully corresponded to the neurophysiological manifestations of sensory motor polyneuropathy of the lower extremities. There were no abnormalities revealed in the sensory and motor fibers of the upper limbs in both the child and father.

Thus, the clinical manifestations of the patient (congenital contractures of the lower extremities), the familial nature of the disorders (congenital contractures of the lower extremities and mutation in the *TRPV4* gene in the father and child), and the changes diagnosed by ENMG data in the father and child indicated an identical nature of the disorders. The abnormalities detected in the child with contractures of the lower extremities were manifestations of sensory motor polyneuropathy of the lower extremities with predominance in the degree of lesion to motor fibers and mild (progressive, considering changes in the father) lesion of sensory fibers, mainly of the myelinopathy type.

Conclusion

Patients with congenital multiple contractures require monitoring and examination by both orthopedists and neurologists to rule out various

variants of neuromuscular diseases. In addition to standard clinical, neurological, and X-ray methods, the examination protocol must include neurophysiological and genetic methods, which could verify the disease, optimize therapeutic approach, and predict its results.

Additional information

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

Ethical statement. All legal representatives signed informed consent to participate in the study and publish medical data.

Author contributions

E.L. Gabbasova, O.E. Agranovich, and *S.V. Sarantseva* developed the research design, analyzed the data obtained, wrote the text of the manuscript, and performed final approval of the article version.

A.E. Komissarov obtained the results and performed data analysis.

S.I. Trofimova, E.A. Kochenova, and *A.D. Slobodina* analyzed the data obtained, performed the literature review, and prepared the manuscript for submission to the journal.

M.V. Savina developed the research design, analyzed the data obtained, wrote the manuscript text, and conducted the neurophysiological research.

E.I. Shagimardanova and *L.Kh. Shigapova* prepared the material and performed the exome sequencing.

All authors made significant contributions to the research and preparation of the article and read and approved the final version before its publication.

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