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PROGRESSING NEMALINE MYOPATHY IN A PATIENT REPEATEDLY OPERATED ON THE SPINE: CLINICAL CASE AND LITERATURE REVIEW

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Objective. To present a clinical case of a patient with spinal deformity associated with myopathy, which was initially undiagnosed and assessed as secondary myopathy after performed spinal surgeries.

Material and Methods. Study design: clinical observation and review of the literature. A 51-year-old female patient has been repeatedly operated on for scoliotic deformity of the spine with progressing neurological disorders. Clinical and complex radiological assessment (spinal telemetry in sitting position, CT, MRI) of the pathology was performed. In connection with the atypical course of the disease, a pathohistological study of muscle tissue fragments was performed with their fixation in a solution of 10 % neutral formalin. After histological processing, the fragments were embedded in paraffin and stained with hematoxylin-eosin by the Masson trichromic method and by the PTAH method. The preparations were examined using the Pannoramic MIDI II BF hardware and software complex to obtain digital images using the Whole slide imaging technology in the Single layer and Extended focus modes and an AxioScope.A1 stereomicroscope with a digital camera.

Results. Two patterns of distribution of nemaline rods of various density and configuration stained dark blue (by PTAH) were identified in sarcoplasm of parts of muscular tissues: diffusely throughout the myocyte and forming clusters of various sizes in transverse sections, and as filamentous structures — in longitudinal ones. Extensive fields of fatty degeneration, transformation of fibers into lipocytes, contracturely changed fibers, pictures of myophaga and areas of fibrosis of the interstitial space associated with residual myocytes were noted. Intramuscular nervous conductors were subjected to complete involution, singular nervous fibers were deformed, internal space was fibrotic. Neuromuscular spindles had unusually increased connective tissue capsule filled with lipocytes. Arterial vessels had fibrosis of t. adventicia and t. media, narrowed or obliterated lumen, and venous vessels were thin-walled and tortuous, which causes their permeability and can cause hemorrhage. The revealed changes in myocytes with the presence of nemaline rods are characteristic of primary nemaline myopathy.

Conclusion. The atypicality of clinical manifestations, primarily of the neurological status in scoliosis, requires excluding neuromuscular disease by conducting a histopathological examination of the surgical material.

Key Words: scoliosis, neuromuscular scoliosis, congenital myopathy, nemaline rods, fatty degeneration.

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A nemaline myopathy is a group of genetically distinct hereditary myopathies. Their common histopathological manifestation is the formation of filamentous structures in the muscle tissue. This is reflected in the name of pathology (from the Greek nema – thread). Two independent groups of researchers led by Shy and Cohen were the first to report on the disease in 1963. Later, many genetic varieties of this condition were found. Depending on the gene and mutation in it, nemaline myopathy may have both autosomal dominant and autosomal recessive inheritance. Nowadays, the incidence of pathology has not been determined. However, according to many geneticists, it is one of the most common congenital myopathies, reaching a frequency of 1: 50,000 [1, 2].

In most cases, spinal deformities associated with myopathy are diagnosed in childhood. Due to the progressive unfavorable disease course, a small number of patients live into adulthood. The features of deformities in adults are the mixed nature of pathogenetic mechanisms (fusion of degenerative changes), polymorphism of clinical manifestations, changes in bone density, and concomitant diseases [3].

Study design: clinical observation and review of the literature.

A 51-year-old female patient I. was admitted to the clinic of the National Ilizarov Medical Research Centre for Traumatology and Orthopaedics (Kurgan) with a diagnosis: scoliosis; condition after surgery; vertebrogenic thoracic myelopathy; lower gross spastic paraparesis, upper mild mixed paraparesis; pelvic organ dysfunction; vertebrogenic pain syndrome. Secondary diagnoses: recurrence of chronic gastritis; gastroesophageal reflux disease; bronchial asthma of mixed genesis, controlled; respiratory failure 0; stage 1, risk 2 hypertension; congestive heart failure 0; neurogenic bladder; established osteoporosis of mixed genesis; myelopathy, spas-

tic tetraparesis; neurogenic pelvic organ dysfunction.

At admission, the patient complained of progressive weakness of limbs and trunk muscles, inability to move independently, decreased sensitivity of the skin of the trunk and limbs, impaired urination and defecation, painful spasms of the muscles of the face, neck, and trunk, difficulty swallowing.

At the age of 13 (1981), the patient was newly diagnosed with spinal deformity. After 2 years, when falling on the corner of the table, the patient first manifested neurological symptoms such as lower extremity paraparesis, which gradually regressed in partially and independently manner. From the age of 30, the woman periodically had transient paresis of the muscles of the upper and lower extremities, progressing under conservative treatment with neurotropic drugs. The patient was followed up by an orthopedist for scoliotic deformity; genetic analysis and other instrumental diagnostic methods of myopathies were not performed. At the age of 39, due to the progression of the scoliotic deformity and the onset of constant back pain, the patient underwent reconstructive and stabilizing surgery on the thoracic and lumbar spine using transpedicular fixation. After the surgery, neurological disorders appeared (lower gross mixed paraparesis, pelvic organ dysfunction). The patient used a walker to move. A positive dynamics with partial regression of neurological symptoms was observed against the background of rehabilitation treatment. Twelve years later, when the patient was 51, the surgical hardware was partially dismantled due to surgical hardware instability and fractures of the T7 and T8 vertebrae (proximal level of spine fixation). Later, compression fractures of the T10 and T11 vertebrae were diagnosed against the background of systemic osteoporosis. In this regard, vertebroplasty of T6, T7, T10, and T11 vertebrae was carried out. During the same period, the woman noted a gradual progression of weakness in the legs, trunk muscles, and upper limbs.

In 2010, the patient underwent electroneuromyography. Indirect signs of radiculopathy were found, mainly in the roots of C4–C8 and L4–L5 with secondary muscular dystrophy. In 2020, a patient underwent a genetic analysis. No chromosomal abnormalities were found. The woman was followed up by a neurologist in the home area with a diagnosis of "secondary myopathy after spine surgery".

Neurological status of the patient at admission: conscious, in contact, oriented to place and time. Pupils D = S, light reflex preserved, no nystagmus. The eyes have a full range of motion. The palpebral fissures and nasolabial folds are symmetrical. The tongue when sticking is in the midline; no deviation. No signs of dysarthria and aphasia. No meningeal signs were found. Movements in the upper extremities are limited; muscle strength is up to 4 points on the left and up to 3 points on the right. Elbow jerk reflex: D = S. The tone in the hands is not changed. Muscle hypotrophy of the upper extremities is not detected. Movements in the lower extremities are severely limited. Tendon reflexes are high. The tone in the legs is reduced. Muscle strength of the right lower limb – 0 points, of the left lower limb – up to 2 points. Hypotrophy of the muscles of the thighs, calves, and feet. Clonoids in the feet on both sides. The kinesthesia is sharply reduced. Abdominal reflexes are activated. Mosaic hypesthesia of the skin of the extremities and trunk. Stretch symptoms are negative. Urination is by the type of retention; defecation – with a laxative agent. The patient does not move independently. She sits down with the use of auxiliary devices. The woman can sit without support for a short period.

X-ray and CT revealed scoliotic deformity of the spine with the presence of a posterior bone block at the level of T4–L5 vertebrae, the condition after vertebroplasty, elements of the surgical hardware of the L5 vertebra, osteoporosis, degenerative changes of the spine (Fig. 1).

According to MRI findings, there was no obvious organic pathology of the spinal cord in the cervical, thoracic, and lumbar spine (Fig. 2).

Due to the discrepancy between the clinical picture and the diagnosis of secondary myopathy after spine surgery, as well as considering the anamnesis and neurological status data, the question arose on the diagnosis of primary myopathy. The presence of foreign bodies of the L5 vertebra and the patient's desire to remove surgical hardware elements were indications to perform a procedure with intraoperative removal of paravertebral muscles for morphological study. A histopathological study of muscle tissue fragments was performed with their fixation in a solution of 10 % neutral formalin. After histological processing, the fragments were embedded in paraffin and stained with hematoxylin-eosin by the Masson trichromatic method and by the PTAH method. The preparations were examined using the Pannoramic MIDI II BF hardware and software complex to obtain digital images using the Whole slide imaging technology in the Single layer mode and Extended focus (3DHISTECH, Hungary) mode and an AxioScope.A1 stereomicroscope with a digital camera (Carl Zeiss GmbH, Germany).

Results

The surgical specimen had fragments where typical muscle tissue was absent while macroscopic observation. Dense fibrous and fatty tissue prevailed. There were fields with extensive fat replacement of myocytes and significant connective tissue fragments visualized in paraffin sections under microscopy; preserved muscle fibers were few in number (Fig. 3a). Most of the arterial vessels had pronounced fibrosis of the middle coat and almost complete obliterated lumen (Fig. 3b). The venous vessels were often tortuous and thin-walled, which could cause hemorrhages. Neuromuscular spindles had an unusually enlarged connective tissue capsule filled with cells similar to lipocytes (Fig. 3c). Fragments of tissue with myocytes of various sizes and degrees of transformation into fat cells were noted; internal nuclei were visualized; fragments of fibers changed in terms of contracture

were observed (Fig. 3d). Intramuscular neural conductors with signs of complete involution: there were no nerve fibers alone or they were severely deformed, the internal space was fibrotic (Fig. 3e). In a variety of muscle fibers, nemaline rods stained dark blue (by PTAH) were observed. There were two distribution patterns of pathological structures: diffuse distribution of nemaline bodies over the entire area of myocytes in the form of small inclusions (Fig. 3f, top left) and myocytes, where nemaline rods formed conglomerates of various shapes and densities, their clusters (Fig. 3f, fiber below). At large magnifications, dark blue short segments of nemaline threads could be identified on longitudinal sections (Fig. 3g).

Discussion

Nemaline myopathies are a set of genetic pathologies with similar clinical manifestations. They are characterized by a pronounced disruption of the muscle tissue structure with the formation of abnormal thread-like or rod-shaped structures in it. Meanwhile, it is possible to reliably identify the etiology of nemaline myopathy (the gene responsible for its development and defect nature) only in half of the cases. This fact indicates the incomplete study of this disease [4, 5].

The reasons for the nemaline myopathy onset are genetic defects leading to the abnormal formation of structural proteins in the muscle tissue. These are mainly sarcomeric proteins. As a result, the processes of muscle contraction, and sometimes their formation, are disrupted. It results in the occurrence of congenital forms of this condition. To date, it has been possible to identify 7 genes whose mutations are responsible for the development of nemaline myopathy. Yet, as mentioned above, they cause only half of all cases of the disease. Additionally, there is a form of pathology with a delayed onset. It affects mainly adults. As more detailed studies have shown, the pathology is most often caused by acquired autoimmune disorders, and not by genetic factors [4, 5].

In addition to the classification created based on modern genetics data, nemaline myopathy is also divided by its phenotypic manifestations: congenital (typical, intermediate, and severe) and juvenile forms. The relationship between these two classification systems is rather arbitrary. Different mutations of the same gene can cause the development of severe and typical congenital or juvenile forms of the disease [1, 4–6].

There are 7 types of nemaline myopathy, differing in types of genetic mutations (*NEM-1–NEM-7*).

The form manifesting in childhood (as in our example) accounts for about 12 % of cases. It is represented by relatively untroubled motor development in early childhood. At the end of the 1st or beginning of the 2nd decade of life, distal and proximal muscle weakness develops. It starts to progress slowly in patients.

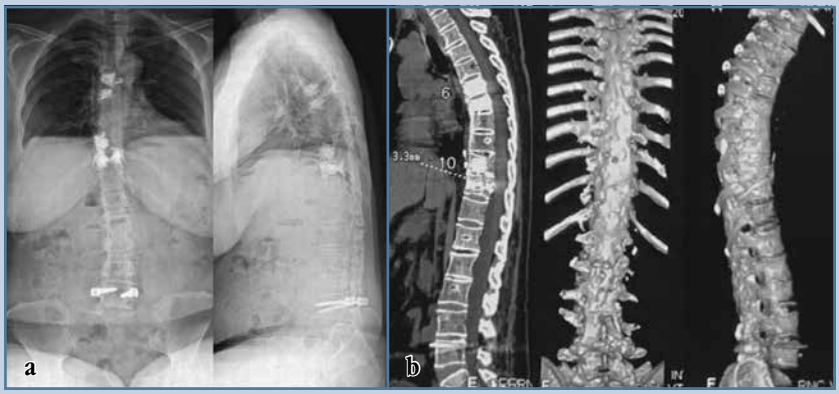

Fig. 1
Spondylograms in front and lateral projections **(a)** and CT data **(b)** of patient I., 51 y.o., upon admission to hospital

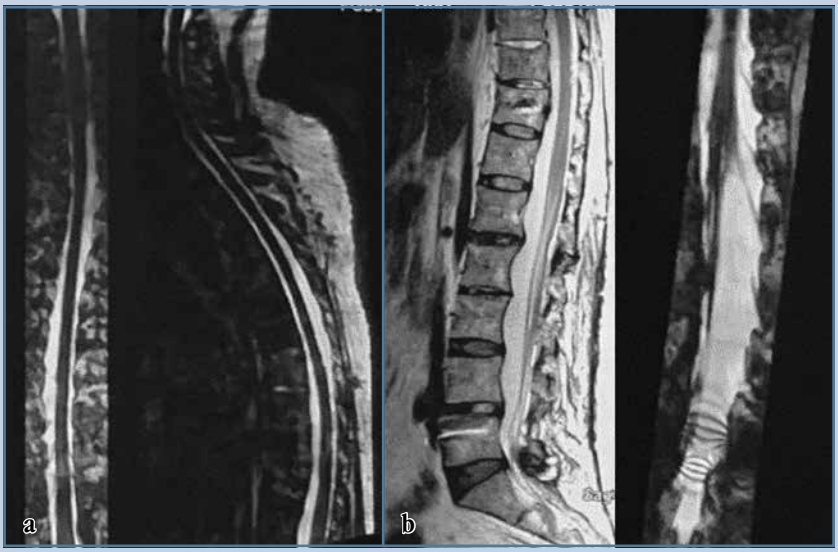

Fig. 2
MRI of the cervicothoracic **(a)** and lumbar **(b)** spine of patient I., 51 y.o., upon admission to hospital

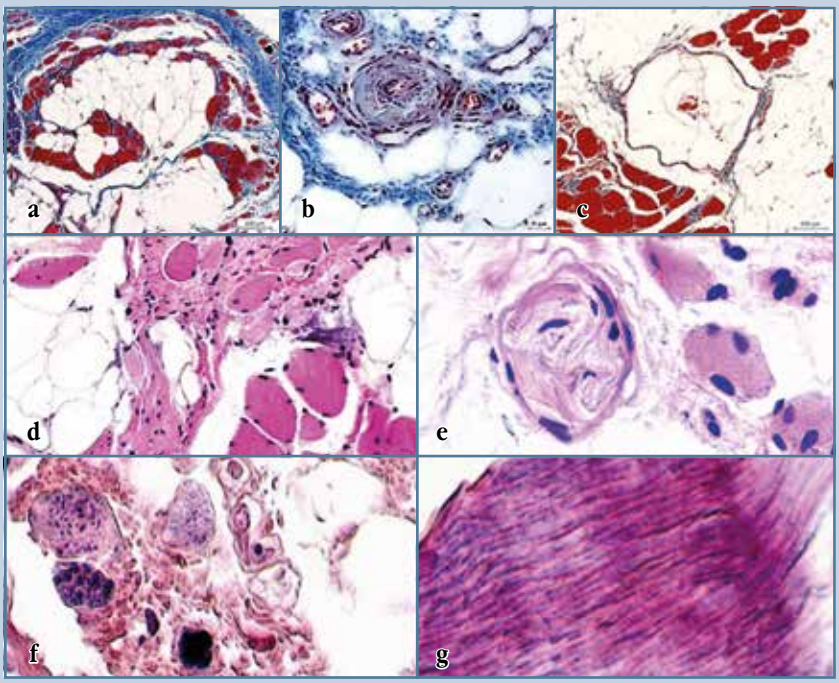

Fig. 3
Fragments of paraffin sections of paraspinal muscles in nemaline myopathy: **a** – preserved muscle fibers are framed by adipocytes; **b** – obliteration of the vessel lumen, severe fibrosis of the middle coat; **c** – neuromuscular spindle with enlarged connective tissue capsule, preserved myocytes, massive fat involution of muscle fibers; **d** – stages of replacement of myocytes with fat cells, variability of fiber diameters and internal nuclei; **e** – intramuscular nerve stem with lost histological structure, with mass degeneration of nerve fibers, only the perineurium is preserved; **f** – myocyte with diffuse distribution of nemaline rods (top) and conglomeration of nemaline bodies in myocyte (bottom); **g** – dark blue nemaline threads. Stain: **a–c** – Masson's trichrome; **d, e** – hematoxylin-eosin; **f, g** – PTAH. Magnification: **a, c** – 250x; **b** – 788x; **d** – 500x; **e, f** – 1150x; **g** – 3500x

The facial muscles, heart, and respiratory muscles are not affected [4, 6].

In an analysis of 143 patients with nemaline myopathy, Ryan et al. [7] show that in six patients the disease developed at the age of 41 to 59. Meanwhile, four people had symptoms for 20 years before the diagnosis. The disease manifested in adolescence in 19 patients.

The histopathological examination in nemaline myopathy is characterized by increased variability in the diameters of myocytes with a bimodal distribution on the histogram; internal nuclei, their increased number, fibrosis of endo- and perimysium, necrosis of muscle fibers [8], which is reflected in the study. Nemaline rods can be distributed both diffusely and in the form of irregular clusters in the cytoplasm of myofibrils. They are mainly found in small myocytes [8]. Electron-microscopic analysis reveals rod-shaped or egg-shaped structures; nemaline bodies have a lattice structure similar to Z-discs. It is supposed that the reason for the development of pathological structures is the lateral expansion of Z-discs. The electron-dense material of nemaline rods can extend from the Z-disc into the sarcomere, which reaches the adjacent Z-disc, – streaming [8]. Thin strands of actin are connected to the lattice structure of nemaline rods [8]. A thin strand is the main component of the sarcomere. Muscle weakness occurs at this level of contraction in nemaline myopathy. The *NEM 2* gene encodes the nebulin protein. Mutations are the main cause of myopathy. They were detected in 66.7 % of cases. *ACTA1* encodes the α-actin protein, mutations that cause 15–25 % of diseases. Proteins encoded by these genes are implicated in the formation of muscle tone and contraction. The role of nuclear defects in nemaline myopathy has been studied. An imbalance of collagen causes fibrosis of the vascular wall and, as a result, occlusion of the lumen. The role of collagen types I, III, IV, VI, XV, and XVIII in providing hemostasis has been identified. Fibrosis and vascular obliteration may be one of the reasons for the initiation of the pathological process in the muscles [4, 8–10].

Myocytes of people with nemaline myopathy have typical filamentous formations. However, these structures can also occur in other diseases [9, 10]. In this regard, to make a correct diagnosis, it is required to conduct a morphological examination of biopsy slices of the affected muscles, molecular genetic tests, and take into account clinical symptoms. Prenatal diagnostics, amniocentesis, chorion biopsy, and carrier screening are also of great importance.

During MRI screening, the selective lesion of different muscle groups forms a certain pattern. This helps in choosing a genetic analysis after the diagnosis of nemaline myopathy is made by the results of a muscle biopsy. For some types of nemaline myopathy (mutation of the *ACTA1* gene, *NEB* mutations), the specificity of muscle damage is determined: femoris, anterior tibial muscles, soleus, or gastrocnemius muscles; there is no specific pattern of muscle damage described for others. Additionally, the degree of muscle change is defined by the severity of the clinical manifestations of the disease [4, 6, 11].

The most affected muscles of the lower extremities – femoris or calf muscles are recommended as a material for morphological examination [4, 11]. The disease progression with damage to the

trunk muscles, as evidenced by the formation of spinal deformity, may suggest the informative value of studies of paravertebral muscles (intraoperative material), which is reflected in the presented observation.

No papers have been found regarding the features and course of spinal deformities in nemaline myopathy.

According to the literature [3, 12], a feature of the neuromuscular scoliosis outcomes in adults is an extended flat arch of the thoracic and lumbar spine with a pronounced twisted pelvis, the presence of hyperkyphosis or hyperlordosis of the spine with corresponding disorders of the trunk balance. These patients suffer from severe neurological manifestations of the underlying disease; they are limited in movement and verticalization in a sitting position. Some of the diseases are followed by pronounced changes in the respiratory, cardiovascular, and urinary systems. Patients experience difficulty in eating and digestion; there are signs of progressive hypotrophy of trunk and limb muscles, joint contractures, and osteopenia.

A retrospective analysis of the presented clinical case shows that the primary disease manifested in adolescence in associated with spinal deformity. Already at that woman's life period, the remitting course of the disease with episodes of neurological disorders could suggest its neuromuscular nature. The procedure performed to correct spinal deformity worsened the neurological status in the form of a persistent decrease in muscle strength and sensitivity of the lower extremities. Neurological manifestations were regarded as postoperative changes. Further progression of paresis of the muscles of the lower extremities and trunk is also regarded as a consequence of instrumental fixation of the spine. This is primarily due to the development of structural instability associated with a decrease in the vertebral density and the formation of compression fractures of the vertebrae. The procedures performed to remove the surgical hardware and vertebroplasty did not change the neurological deficit and the physical function of the patient. Even the specific diagnostic tests performed at that time (ENMG and genetic analysis) did not reveal the cause of the disease.

The constant progression of the disease with the addition of weakness of the muscles of the upper extremities, painful spasms, and difficulty swallowing has allowed the authors to presuppose a different etiology, conduct a morphological examination of the muscles and make a diagnosis.

After discharge from the hospital, the patient underwent repeated genetic analysis of frequent mutations in the *PLOD* gene and regions of the *FKBP14* gene (responsible for Ehlers – Danlos Syndrome). According to its results, pathogenic and probably pathogenic variants were not found.

Conclusions

Neurologic examination and history taking are necessary components in the work-up of patients with spinal deformities. The detection of neurological disorders is an indication for consultation by a neurologist and a geneticist.

MRI of the trunk muscles (primarily of the lower extremities) does not always reflect the degree of morphological changes in the muscles.

A negative result of a genetic test does not exclude the genetic nature of the disease, since it is currently impossible to detect all gene mutations.

Histopathological examination of a muscle biopsy sample is a reliable diagnostic test for neuromuscular diseases.

The collection of specimens during procedures in patients with neurogenic spinal deformities promotes clarification or, as in the above clinical case, establishes the etiology of the underlying disease.

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