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DEVELOPMENT OF CONTRACTURES IN SPASTIC FORMS OF CEREBRAL PALSY: PATHOGENESIS AND PREVENTION

© ***O.A. Klochkova[1], A.L. Kurenkov[1], V.M. Kenis[2]***

[1] National Medical Research Center of Children's Health, Moscow, Russia;
[2] The Turner Scientific Research Institute for Children's Orthopedics, Saint Petersburg, Russia

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The origin of contractures in spastic forms of cerebral palsy (CP) is unclear. Tomorrow the early appearance and persistence of spasticity are not qualified as the main reason of growths disturbances, musculo-skeletal system deformations and secondary orthopedic complications. The latest investigations have shown prominent changes in the spastic muscles on the different structural levels and stages of muscle development. This study describes the histological, morphological, and biomechanical changes in the spastic muscles that play a pathophysiological role in the formation of CP contractions. The authors discuss the changes in the muscle fiber size, differentiation and elastic properties, degrees of the lengthening resistance in the bundles of muscle fibers, extracellular matrix proliferation, structural and mechanical changes, disturbances in gene expression and regulation in the tendons and muscle tissue, changes in the length and number of sarcomers, as well as the length and cross-section of the whole muscle.

Therefore, the movement limitations and contractions in CP do not depend on one universal mechanism. It is a combination of different structural changes in the muscles and the failure of the central movement and postural control.

Keywords: cerebral palsy; spasticity; contracture; muscle fiber; extracellular matrix; sarcomere; gene expression.

ФОРМИРОВАНИЕ КОНТРАКТУР ПРИ СПАСТИЧЕСКИХ ФОРМАХ ДЕТСКОГО ЦЕРЕБРАЛЬНОГО ПАРАЛИЧА: ВОПРОСЫ ПАТОГЕНЕЗА

© ***О.А. Клочкова[1], А.Л. Куренков[1], В.М. Кенис[2]***

[1] ФГАУ «Национальный медицинский исследовательский центр здоровья детей» Минздрава России, Москва;
[2]ФГБУ «НИДОИ им. Г.И. Турнера» Минздрава России, Санкт-Петербург

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Причины формирования контрактур при спастических формах детского церебрального паралича (ДЦП) до конца не ясны. В настоящее время раннее появление и персистенцию спастичности при ДЦП уже не рассматривают как основополагающую причину нарушения роста и развития опорно-двигательного аппарата, формирования вторичных ортопедических осложнений. В последние десятилетия результаты многочисленных экспериментальных и клинических исследований показали наличие значительных изменений в спастичных мышцах на различных структурных уровнях и этапах формирования мышечной ткани. В статье детально обсуждаются гистологические, гистохимические, морфологические, биомеханические изменения, выявленные в спастичных мышцах, которые имеют патофизиологическое значение для формирования контрактур по мере роста и развития ребенка с ДЦП: изменение размеров и дифференцировки мышечных волокон; уменьшение эластичности отдельного мышечного волокна и снижение сопротивляемости растяжению пучка волокон; пролиферация внеклеточного матрикса, измененного по структуре и механическим свойствам; изменение экс-

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прессии генов в сухожилиях и мышечной ткани, а также регуляции экспрессии генов, влияющих на состав внеклеточного матрикса; изменение длины и числа саркомеров в миофибриллах спастичных мышц; изменение длины и поперечного сечения целой мышцы.
Таким образом, ограничение двигательной активности, характерное для ДЦП, и формирование контрактур при спастических формах заболевания не могут быть объяснены одним универсальным механизмом, а представляют собой комбинацию структурных изменений в мышцах и разных нарушений центрального контроля движения и поддержания позы.

Ключевые слова: детский церебральный паралич; спастичность; контрактура; мышечное волокно; внеклеточный матрикс; саркомер; экспрессия генов.

Introduction

Spasticity can be defined as a rate-dependent increase in the muscle tone and increase in the reflexes to tension, a symptom of damage to the upper motoneurone [1]. The cause of this damage can be stroke, tumors, traumas of the brain and the spinal cord, neurodegenerative diseases, or infantile cerebral palsy (ICP).

Cerebral palsy, a result of non-progressive damage to the developing brain of a child in the perinatal period [2], remains the main neurological cause of disability in children [3]. The spastic forms of cerebral palsy account for > 80% of all cases [4]. Conventionally, the early appearance and persistence of spasticity in cerebral palsy is considered a leading cause of disruption of the growth and development of the musculoskeletal system as well as the formation of secondary orthopedic complications, such as contractures and dislocations in the joints [5]. Cerebral palsy symptoms concomitant to spasticity are muscle weakness, loss of selective muscle control, and reciprocal inhibition of muscle antagonists, perceptual disorders that also contribute to worsening functional deficiency and limiting of normal life. Most methods of treatment and rehabilitation for patients with cerebral palsy (exercise therapy, instrumental physiotherapy, plastering, orthotics, neurotomy, intrathecal baclofen therapy, injections of botulinum toxin, oral antispastic drugs, etc.) primarily aim to reduce the spasticity and prevent contractures [6, 7]. Thus, the annual efforts and costs for correcting spasticity and its consequences are enormous; however, the effectiveness of these measures is still unclear; further, an understanding of the true role of spasticity in the formation of contractures in cerebral palsy is also unknown.

A logical theory that explains the formation of contractures in cerebral palsy by the mechanism of "damage to the upper motoneuron → spasticity → restriction of movement in the muscle → prolonged muscle shortening and its inability to grow equally with bone → contracture" [8] is not fully confirmed by modern clinical studies [9, 10]. Therefore, even with successful elimination of spasticity in cerebral palsy after dorsal selective rhizotomy, the limitation of the volume of movements and contracture in the leg joints progresses during subsequent years of observation [11]. Increasing evidence shows that spasticity is not the only key factor in the formation and progression of contractures in cerebral palsy. This is a multi-step process that involves more complex and contradictory mechanisms of secondary adaptive changes in the muscles with central nervous system (CNS) damage and their primary role in the formation of contractures [12]. Clarification of these mechanisms is necessary both from the point of view of a fundamental understanding of pathophysiological processes and for making a reasonable choice of effective methods to prevent secondary deformities in cerebral palsy.

Here, we discuss the possible mechanisms for the formation of contractures and changes revealed in the muscles at different structural levels, with spastic forms of cerebral palsy.

Thus far, several international experts have conditionally divided most of the known muscle changes in cerebral palsy into the following three large groups [10, 12]:

1) histological and histochemical changes in the muscles (changes in the cell characteristics, types of myocytes, connective tissue content, and gene expression);
2) morphological changes (myocyte diameter, length of muscle fibers, length and cross section of the entire muscle, angle of attachment of muscle fibers to the tendon, as well as number and length of sarcomeres); and

3) biomechanical changes (disorders in the development of muscular effort, tension, and moment of force).

Changes in muscles with spasticity

Dimensions and differentiation of muscle fibers

The study of muscle biopsy samples appears the most logical method of determining the structural changes underlying the formation of contractures in spasticity; however, the methodological and ethical aspects significantly limit the use and interpretation of the results of this method [13]. The results of most such studies rely primarily on the evaluation of the structural changes in the muscles of various animal models and cannot be unequivocally transferred to humans. The results obtained in the study of intravital biopsy samples of muscles of spasticity patients are limited by the permissible dimensions of the tissue samples taken and the spectrum of the muscles studied.

Normally, histological examination of a healthy skeletal muscle is represented by a set of tightly packed muscle fibers that form closely adjacent polygons. The increased load on the muscle leads to hypertrophy of the muscle fibers, while the lack of load results in atrophy. Thus, as a rule, the size of the muscle fibers is an indicator of the muscle motor activity. Muscle biopsy samples obtained from patients with spasticity are characterized by an increased variability in the muscle fiber size, a large number of "round" and "bitten" rather than polygonal structures, and an increased volume of extracellular space [14–18]. However, such disorders are not specific for spasticity, they occur in several other neuromuscular pathologies and do not provide sufficient information regarding the degree of load on the muscle and the processes underlying contracture formation [19].

Ontogenetically, the muscle tissue undergoes various stages of "maturation" during which the embryonic and neonatal forms of myosin are replaced by "adult" ones, potentially during the entire period of childhood and early adolescence [20]. Expression and transformation of myosin are exposed to hormonal regulation and modulation due to muscle activity [21] and various external influences, especially mechanical stretching (flexibility of the skeletal muscles) [10]. Changes in the level of motor activity in cases of CNS damage and lack of weight loading disrupt the maturation of the "adult" forms of myosin [22].

The number of muscle fibers in the motor unit, the type of myosin in the fiber, and the synthesis of acetylcholine receptors are determined prenatally, to the greatest extent by the dimensions and activity of the innervating motor neuron [23, 24]. Early damage to the central motor neuron in cerebral palsy leads to a disorder in the differentiation of muscle fibers and neuromuscular transmission [20, 25]. Thus, a child with prenatal CNS damage can be born with an already impaired differentiation of muscle fibers as well as structural anomalies of muscle spindles and acetylcholine receptors. Further, the initial postnatal stages of motor development that are of decisive importance with respect to redistribution, appearance, and loss of innate neuromuscular interrelations will be affected [24, 26]. Thus, a survey of 21 children born premature with a low body weight and various injuries of the upper motoneuron showed a postnatal delay in the maturation of muscle fibers [27].

Most muscles contain the fibers of types 1 (slow) and 2 (fast) in their structure, the proportion of which depends on the basic function of the muscle. Thus, the salens muscle consists predominantly of slow fibers of type 1, ensuring the maintenance of a prolonged stable muscle contraction necessary for retaining the posture and balance, while the gastrocnemius muscle predominantly includes the fast type 2 fibers necessary for the development of active rapid contraction while running and walking and an effective rear thrust [28]. Chronic electric stimulation of the muscle can gradually transform it into a slow type [29–31] with all the relevant characteristics: an increase in the number and density of capillary distribution, the predominance of type 1 muscle fibers, increased endurance, and decreased strength. The opposite model with a chronic decrease in the muscle load due to immobilization [32, 33], tenotomy [34], and artificial weightlessness [35] led to a decrease in the size of the muscle fibers and predominance of fast type 2 fibers in the muscle. Thus, in the experiment, the chronic excess load on the muscle or, conversely, its inactivity reflected on the structure and type of muscle fibers. In biopsy studies, spasticity patients demonstrated increased proportion of type 1 fibers in the skeletal muscles [17, 25, 36] and, conversely, the predominance of

type 2 fibers [37]. Several investigators [14–16, 18] have reported a lack of significant change in the percentage of one or another type of muscle fibers in cases of spasticity. Thus, there is no consensus regarding whether the histological changes in the spastic muscle reflect its excessive or insufficient activity as well as excessive or insufficient innervation. These contradictory results may be attributable to the individual differences in the methods used for performing the experiments and interpreting the results of the biopsy examinations in human models. Nevertheless, the obtained data indicate that the structural changes in the muscles in spasticity, especially arising in the early perinatal lesions of the CNS, are not limited to the restructuring of the fibers due to the individualities of the mechanical load on the muscles. Significant contribution is made by violations at the early (embryonic) stages of aniage and maturation of the neuromotor apparatus and its subsequent ontogenetically innate transformation in conditions of impaired central innervation.

Changes in the mechanical properties of muscle fibers and extracellular matrix

The results of a study on passive mechanical properties of isolated muscle fibers and bundles of 5–50 fibers taken from spastic muscles (9 patients) and healthy muscles in persons without spasticity (21 patients) are interesting [38]. Using microtechnics, the authors compared the resistance to stretching of the individual muscle fiber and the muscle bundle. The logical result was that both spastic and non-spastic bundles of muscle fibers exerted greater resistance for stretching than the individual fibers of the corresponding muscles. This was because the fiber bundles contain an extracellular matrix represented by various types of collagen as well as proteoglycans and glycoproteins that provide additional resistance compared to a single muscle fiber. However, in healthy muscle tissue, the stretch resistance of a fiber bundle was 16 times greater than that of an individual fiber, while in a spastic muscle, this parameter differed only by a factor of 2. In addition, in spite of the lower stretchability of a single spastic muscle fiber compared to that of a non-spastic muscle fiber, the bunches of spastic fibers were more stretchable than those of healthy muscle fibers. A histological study of the sections of these muscles showed that the spastic muscles contained a considerably larger amount of extracellular matrix. Based on the obtained data, the authors concluded that, in spite of the fact that the spastic muscles contain more extracellular matrix, its "quality" and resistance to stretching are inferior to those of a healthy muscle. However, the very nature of quantitative and qualitative changes in collagen and other matrix components in spasticity require further investigation.

As mentioned above, R.L. Lieber et al. [38] as well as J. Fridén and R.L. Lieber [39] showed that the resistance to stretching of a single muscle fiber of the spastic muscle was higher than that of a healthy muscle fiber. These results suggested that in the presence of spasticity in the muscle fiber, the functioning of the structures responsible for maintaining the length of the sarcomer at rest and the stretch resistance is disturbed. One of the most likely causal factors is the giant protein of the cytoskeleton, titin [40]. Currently, there is no direct evidence of damage to spasticity by titin; however, indirect data suggest the likelihood of such a mechanism. Thus, titin is known to exist in various isoforms in the skeletal and cardiac muscles, determining the differences in the elasticity of these types of muscles [40]. Further, titin isoforms in the cardiac muscle are shown to change with ischemia [41]. Such transformation of titin isoforms in combination with a secondary change in the collagen expression against ischemia decreases the elasticity of the cardiac muscle and the formation of secondary (ischemic) cardiomyopathy. Thus, the possibility of transformation of titin in the skeletal muscle with spasticity into less elastic isoforms exists; however, such an assumption requires experimental confirmation.

Another possible mechanism for contracture formation in cerebral palsy that is actively discussed in the literature is a decreased population of satellite cells [42, 43].

Thus, the presented data indicate that the spastic muscle, although composed of fibers that are more "dense" and nonstretchable than those of the healthy muscle, contains an increased amount of extracellular matrix with significantly altered mechanical properties. The question regarding which of the following is the primary mechanism remains: the formation of an incompetent extracellular matrix and the compensatory attempt of the spastic

muscle to reduce the stretchability by compacting individual fibers or the primary compaction of muscle fibers against spasticity and compensatory changes in the composition and characteristics of the extracellular matrix.

Gene expression

In several studies on spasticity patients, there were changes in the gene expression in the tendons and muscle tissue as well as in the regulation of expression of genes that influenced the composition of the extracellular matrix [44, 45]. However, changes in gene transcription in the study of L.R. Smith et al. [45] were found both in the flexor muscles and in the extensor muscles of the spastic arm, indicating a similar transcriptional adaptation of the antagonist muscles, despite the prevalence of spasticity in the flexor muscles. In a later study by L.R. Smith et al. [46], in the biopsy specimens of the gastrocnemius and semitendinous/semimembranous muscles of patients with cerebral palsy, altered gene transcriptions were confirmed (in comparison with the biopsy specimens of healthy individuals), most of which were responsible for the increased production of the extracellular matrix, decreased metabolism, and activity of ubiquitin ligase in the muscles. The increased production of the extracellular matrix correlated with the degree of abnormality in the stretchability of the corresponding muscle fibers [46].

Thus, despite several questions and contradictions regarding changes in the regulation of gene expression in spastic muscles, most changes detected in cerebral palsy were related to increased synthesis of extracellular matrix proteins and/or a decreased muscle metabolism.

Connective tissue content

In addition to changing the shape and types of the muscle fibers, the accumulation of connective tissue fibers in the muscles as well as the retraction of the connective tissue of the articular capsules, was usually considered another mechanism for contracture formation in case of long-lasting spasticity in cerebral palsy [14, 18]. Several studies have revealed a significant correlation between the clinically assessed spasticity level and the amount of collagen in the muscle biopsy samples [18]. In contrast, A. Marbini et al. [36], M. Ito et al. [17], and L. Romanini et al. [15] have shown that the biopsy samples of spastic muscles contained a normal amount of connective tissue. J. Fridén and R.L. Lieber [39] as well as J. Rose et al. [16] also reported that about 50% of the biopsy samples from the muscles involved in "static and dynamic" contractures were regarded "normal" or as having minimal deviations. However, M. de Bruin et al. [47] described an increase in the connective tissue content along the vessels and nerves inside the spastic muscles and the absence of similar changes in other parts of the muscles; the authors interpreted this as a compensatory response to the increased load on these structures in spasticity.

Change in the length of the sarcomeres

The development of maximum muscle tension depends on the optimal overlap of actin and myosin fibrils owing to the repeated number of sarcomeres and their length [13, 28]. The growth of muscle fibers is because of the addition of new sarcomeres in response to stretching, load, and growth of the adjacent bones [48]. R.L. Lieber and J. Fridén [49] assessed the length of the muscle fibers and sarcomeres in the elbow flexor muscle of the hand (FCU — Flexor Carpi Ulnaris) in 6 patients with severe flexion contraction of the hand with spasticity and in 12 patients with damage to the radial nerve and normal innervation of FCU [49] during surgical intervention. With full flexion in the wrist joint, the length of the sarcomeres in the spastic muscles significantly exceeded that of the sarcomeres in the control group (3.48 ± 0.44 vs. 2.41 ± 0.31 microns); however, the length of the fibers was comparable in the two groups. This result could be explained either by a disproportionate growth of the muscle in comparison with the bone (the inability of the spastic muscle to add new sarcomeres during growth) or the loss of a part of the sarcomeres in case of CNS damage [49, 50]. In any case, increasing the length of sarcomeres leads to a reduction in the area of overlap of actin and myosin fibrils and a decrease in the muscle effort development by up to 40% of the norm; this could be a potential mechanism for reducing the muscle strength and activity in patients with cerebral palsy and, consequently, contracture development.

Change in the cross section and length of the whole muscle

The cross-sectional area of the muscle and the angle of attachment of the muscle fibers to the tendon are parameters that significantly affect muscular strength. The angle of attachment of the muscle fibers and the force developed per unit of the area of the cross section of the muscle increase with age and peak shortly after the completion of puberty [51]. In this regard, in studies using spastic muscle biopsies, the age of patients can significantly affect the results and interpretations. In a study by G. Elder et al. that involved a well-chosen control group, there was a decrease in the cross-sectional area of the leg muscles in cerebral palsy patients and a decrease in the strength of muscular effort developed per unit of cross-sectional area of muscle [52]. A. Marbini et al. also demonstrated hypotrophy and reduction in the cross-sectional area of muscle adductors and triceps muscles of the lower leg along with decreased angle of attachment of the muscle fibers to the tendon in patients with cerebral palsy [36]. In addition, preterm patients with cerebral palsy may not have the time to form a sufficient number of muscle fibers [53], potentially leading to an even greater reduction in the muscular effort.

However, the use of an isolated parameter of the transverse muscle size as a prognostic factor in reducing muscle strength seems too optimistic in the case of cerebral palsy. D. Damiano et al. found that the thickness of the quadriceps and lateral broad femoral muscle was compared with the force of arbitrary knee extension in patients with cerebral palsy and a control group created according to age [54]. Thus, the thickness of the muscle significantly influenced the strength of the developed muscular effort in healthy children and had limited contribution in the active movement in patients with cerebral palsy along with factors, such as lack of arbitrary control and the presence of pathological reflex activity. In addition, as in the case of other aspects of muscle changes in patients with cerebral palsy, the following question regarding the primary mechanism remains unanswered: is the decrease in the muscle volume and the associated decrease in muscle strength primary or is a decrease in the motor activity due to CNS damage and the resulting muscle hypotrophy primary? In either case, measurement of muscle thickness in each specific patient with cerebral palsy can be used for assessing the results of physical training and rehabilitation.

Changes in the length of the entire muscle in case of spasticity include both a shortening of the myogaster itself (by 10% for the medial gastrocnemius head — in a study on 15 cerebral palsy patients of prepubertal age) and lengthening of the tendon [55]. The shortened muscular part contains fewer sarcomeres, leading to decreased developing effort, while the elongated tendon part affects the biomechanics of movements. Skeletal muscles are known to have the ability to develop maximum force at a certain initial length [28]. Muscle shortening due to spasticity and the structural changes described above as well as the lengthening of the tendon-muscular complex due to overstretch/excessive surgical lengthening of the tendon, leads to suboptimal initial conditions for the development of muscular effort. The shortening of the spastic muscle and the forced position of the limb leads to hyperextension of the antagonist muscles and progression of their biomechanical incompetence.

Thus, the change in the length of both the spastic muscles and their antagonists and the violation of their biomechanical balance combined with the manifestations of pathological reflexes, synkinesia, causes progressive limitation of movement volume as well as the appearance and aggravation of contractures.

Conclusion

Despite the fact that in cerebral palsy the primary cause of motor disorders and secondary orthopedic complications is early CNS damage, several experimental and clinical studies reveal the presence of significant changes in the spastic muscles at different structural levels and stages of formation of the muscle tissue. The main changes in spastic muscle include the following:

- change in the size and differentiation of the muscle fibers;
- reduction in the elasticity of an individual muscle fiber and reduction in the resistance to stretching of the fiber bundle;
- proliferation of the extracellular matrix as well as altered structural and mechanical properties;

– change in the length and number of sarcomeres in the myofibrils of the spastic muscles;
– change in the gene expression in the tendons and muscle tissue as well as regulation of the expression of genes affecting the composition of the extracellular matrix;
– change in the length and cross section of the whole muscle.

These changes disrupt the mechanical properties of the spastic muscle and its interaction with muscle agonists and antagonists and lead to a change in the biomechanics of motion in cerebral palsy.

Thus, motor limitations and contracture formation in the spastic forms of ICP cannot be explained by a single universal mechanism and represent a combination of structural changes in the muscles and violations of the central control of movement and maintenance of posture. A consideration of all the described changes should be the basis for developing and selecting the optimal methods of rehabilitation and prevention of contractures in ICP patients.

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Information about the authors

Olga A. Klochkova — MD, PhD, Senior Researcher, Pediatrician, Neurologist. National Medical Research Center of Children's Health, Moscow, Russia. ORCID: 0000-0002-4079-3450. E-mail: klochkova_oa@nczd.ru.

Alexey L. Kurenkov — MD, PhD, Leading Researcher, Neurologist. National Medical Research Center of Children's Health, Moscow, Russia. ORCID: 0000-0002-7269-9100. E-mail: alkurenkov@gmail.com.

Vladimir M. Kenis — MD, PhD, Deputy Director for Development and External Relations, Head of Department of Pathology of the Foot, Neuroorthopedy and Systemic Diseases. The Turner Scientific Research Institute for Children's Orthopedics, Saint Petersburg, Russia. ORCID: 0000-0002-7651-8485. E-mail: kenis@mail.ru.

Ольга Андреевна Клочкова — канд. мед. наук, старший научный сотрудник, врач-педиатр, невролог ФГАУ «Национальный медицинский исследовательский центр здоровья детей» Минздрава России, Москва. ORCID: 0000-0002-4079-3450. E-mail: klochkova_oa@nczd.ru.

Алексей Львович Куренков — д-р мед. наук, ведущий научный сотрудник, врач-невролог ФГАУ «Национальный медицинский исследовательский центр здоровья детей» Минздрава России, Москва. ORCID: 0000-0002-7269-9100. E-mail: alkurenkov@gmail.com.

Владимир Маркович Кенис — д-р мед. наук, заместитель директора по развитию и внешним связям, руководитель отделения патологии стопы, нейроортопедии и системных заболеваний ФГБУ «НИДОИ им. Г.И. Турнера» Минздрава России, Санкт-Петербург. ORCID: 0000-0002-7651-8485. E-mail: kenis@mail.ru.