Neurovisualization features of brain anatomy in children with spastic cerebral palsy revealed by magnetic resonance tractography

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ABSTRACT

Aim. To perform quantitative evaluation of the degree of white matter tract abnormalities in children with spastic cerebral palsy by magnetic resonance tractography to determine severity of the disease, as well as to carry out a dynamic assessment of treatment effectiveness.

Materials and methods. The study included 46 children (32 males, 14 females; average age 5.4 ± 1.1 years). The participants were divided into two groups. The experimental group consisted of 23 children with spastic cerebral palsy. The control group included 23 children without any neurological disorder. Examination of the brain was performed on the Siemens Essenza 1,5 Т system (Siemens, Germany) and included magnetic resonance tractography to reconstruct the major white matter tracts. The number of fibers, average fractional anisotropy value, apparent diffusion coefficient, and coefficient of myelination of major white matter tracts in the brain were calculated and analyzed.

Results. We found a significant difference in the above-stated parameters between the groups. The experimental group showed a decrease in the absolute number of fibers at the central and posterior segments of the corpus callosum, corticospinal tracts, and left inferior longitudinal fasciculus. Besides, we detected a decrease in fractional anisotropy at 2–5 segments of the corpus callosum and right lateral corticospinal tract, an increase in the apparent diffusion coefficient at 2, 4, and 5 segments of the corpus callosum and left lateral corticospinal tract, and a decrease in the myelination coefficient in all the examined tracts, except for superior longitudinal fasciculus. We revealed a positive correlation between the intensity of the motor disturbance and the coefficient of myelination at the anterior corpus callosum and inferior longitudinal fasciculus.

Conclusion. Magnetic resonance tractography is an informative technique for unbiased evaluation of white matter tract anatomy, as well the level and degree of motor tract damage. The most useful characteristics of white matter tract anatomy are the absolute number of fibers in the tract, fractional anisotropy, and coefficient of myelination. Some of them correlated with the intensity of motor disturbance, so they can be regarded as potential predictors of rehabilitation potential.

Key words: cerebral palsy, diffusion tensor imaging, tractography, fractional anisotropy, coefficient of myelination, neuroimaging, motor disturbance.

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

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Conformity with the principles of ethics. A written informed consent was obtained from parents of the children who participated in the study. The study was approved by the local Ethics Committee at Privolzhsky Research Medical University (Protocol No. 4 of 29.03.2017).
Нейровизуализационные особенности строения головного мозга у детей с детским церебральным параличом, полученные методом магнитно-резонансной трактографии

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РЕЗЮМЕ

Цель. Количественная оценка степени нарушений развития проводящих путей головного мозга у детей со спастическими формами детского церебрального паралича (ДЦП) методами магнитно-резонансной (МР) трактографии для определения тяжести заболевания, а также оценка динамики эффективности лечения.

Материалы и методы. Обследованы 46 детей 4–7 лет (средний возраст (5,4 ± 1,1) лет), из них 14 девочек (33%) и 32 мальчика (66%). Пациенты разделены на две группы. Исследуемую группу составили 23 пациента со спастическими формами ДЦП. В контрольную группу вошли 23 ребенка без неврологического дефицита. Исследование головного мозга проводилось на МР-томографе Siemens Essenza 1,5 Т (Siemens, Германия) и включало метод МР-трактографии. Были рассчитаны и обработаны: количество волокон, средний показатель фракционной анизотропии, коэффициент диффузии, коэффициент миелинизации основных проводящих путей головного мозга.

Результаты. Выявлена достоверная разница указанных выше показателей между пациентами исследуемой и контрольной групп. У детей с ДЦП отмечалось снижение абсолютного количества волокон в области центральных и заднего сегментов мозолистого тела, кортикоспинальных трактов и левого нижнего продольного пучка. Также определялось снижение показателя фракционной анизотропии волокон в области 2–5-го сегментов мозолистого тела, правого кортикоспинального тракта; повышение коэффициента диффузии в области 2, 4, 5-го сегментов и левого кортикоспинального тракта; снижение коэффициента миелинизации во всех исследуемых трактах, за исключением верхних продольных пучков. Выявлена положительная корреляция между выраженностью моторного дефицита и коэффициентом миелинизации в области переднего сегмента мозолистого тела и нижних продольных пучков.

Заключение. МР-трактография является информативным методом объективной оценки организации проводящих путей головного мозга, уровня и степени поражения моторных трактов. Наиболее информативными характеристиками организации проводящих путей являются абсолютное количество волокон в тракте, показатель фракционной анизотропии, а также расчетный показатель – коэффициент миелинизации. Некоторые из выявленных изменений коррелировали с выраженностью моторного дефицита, что позволяет рассматривать их как потенциальные предикторы реабилитационного прогноза.

Ключевые слова: диффузионно-тензорный имиджинг, трактография, фракционная анизотропия, коэффициент миелинизации, детский церебральный паралич, нейровизуализация, моторный дефицит.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Cerebral palsy (CP) is a neurological syndrome that includes a group of permanent disorders of motor development and posture retention [1]. The prevalence of this disease is quite high and, according to various authors, ranges from 2.2 to 3.3 cases per 1,000 newborns [2, 3]. Due to the severity of clinical presentation, early disability, and social maladaptation, timely diagnosis, treatment, and rehabilitation of patients with CP are of great social importance.

According to most authors, the diagnosis of CP is established on the basis of a combination of clinical and neuroimaging data, such as neurosonography (in the perinatal period) and magnetic resonance imaging [2, 4]. These basic techniques are used to assess the nature and localization of pathological changes in the brain, namely: white matter lesions in the form of periventricular leukomalacia (PVL), basal ganglia lesions, focal strokes, and various types of cerebral dysplasia [5]. Application of new MRI techniques, such as morphometry, tractography, spectroscopy, and functional MRI, has significantly increased the array of diagnostic information [6]. Diffusion tensor imaging (DTI) and magnetic resonance (MR) tractography have made it possible to accurately visualize the brain tracts that, according to some authors, are most often affected in patients with CP [7].

This technology is a mathematical three-dimensional reconstruction of tracts based on the direction of diffusion in each voxel of the brain. One of the main aspects of brain examination by the DTI method is to determine the value of fractional anisotropy (FA), i.e. the degree of co-directional movement of water molecules inside the white matter tracts. This parameter characterizes the degree of myelination of the brain tracts. Based on the FA maps, a three-dimensional reconstruction of the white matter tracts is performed using software [8]. The reconstruction is estimated taking into account symmetry, the length of tracts, and direction. It allows to identify the predominant side of the dysfunction, even with symmetrical white matter lesion according to structural MRI [9].

The aim of the research was to study disorders in brain white matter tract anatomy by MR tractography in CP patients of preschool age.

MATERIALS AND METHODS

The study encompassed 46 children aged 4–7 years (average age (5.4 ± 1.1) years), including 14 girls (30%) and 32 boys (70%). The experimental group consisted of 23 patients with spastic forms of CP, including 7 girls and 16 boys (the average age 5.4 ± 1.1 years). The diagnosis of cerebral palsy was established in children aged 9 months to 2.5 years.

Spastic diplegia (G80.1 according to ICD-10) was observed in 13 (56%) children, hemiplegic form of the disease (G80.2) – in 10 (44%) children. The average level of motor disorders in the patients with CP according to the Global Motor Function Classification System (GMFCS) [10] was 1.83 ± 0.5. The control group consisted of 23 children: 7 girls (30%) and 16 boys (70%). The average age was 5.6 ± 1.3 years. The children were treated for somatic pathology at the departments of the clinic, and had no motor deficits and organic disease of the nervous system, and, therefore, no neurologic deficit was observed. Indications for MRI, according to the referral from the neurologist, were headaches (in 6 patients) and delayed speech development (in 17 patients).

All the patients of the experimental group (with CP) underwent a complete physical examination, as well as a specialized clinical and neurological examination, including an assessment of the condition according to neurological questionnaires and scales, such as the modified Ashworth spasticity scale, the Visual Analogue Scale (VAS), the scale for assessing gross motor functions (Gross Motor Function Measure 88 (GMFM-88)), and the Manual Ability Classification System (MACS) for children with CP.

MRI was performed on the Siemens Essenza 1.5 T system (Siemens, Germany), using an 8-channel surface coil for the head. Structural images of the brain were obtained in the standard T1, T2, and FLAIR sequences in three mutually perpendicular planes. For MR tractography, the T1-weighted MPR (multiplanar reconstruction) sequences in the sagittal plane and the diffusion tensor echo planar pulse sequence in the axial plane were used, the number of diffusion directions was 20, and the diffusion factors were 0.1000 sec /mm².

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The data obtained by DT-MRI were processed using the BrainEx 2.2.0 program (NordicNeuroLab, Norway). The software automatically applied motion correction and eddy currents. Echo planar images were correlated with structural ones to perform a three-dimensional reconstruction of the tracts by anatomical landmarks.

The major white matter tracts were identified: segments of the corpus callosum (CC) (5 segments) (CC 1–5), right lateral corticospinal tracts (CSTr) and left lateral corticospinal tracts (CSTl), superior longitudinal fasciculus left (SLFl) and right (SLFr) and inferior longitudinal fasciculus left (ILFl) and right (ILFr) – a total of 11 localizations. The reconstruction was carried out according to the method of deterministic tractography [10].

In order to reconstruct the segments of the corpus callosum, the area of interest was placed on the corresponding segment, based on the scheme proposed by Hofer S. and J. Frahm [11]; for lateral corticospinal tracts, the area of interest was determined in the projection of the precentral gyri, for the superior and inferior longitudinal fasciculi – in the frontal and parietal, temporal and occipital lobes, respectively. For the reconstruction of the white matter tracts, the threshold of the fractional anisotropy index was 0.15, and the minimum fiber length was 20 mm.

For each selected fasciculus, the following parameters were obtained: the number of fibers, the fractional anisotropy index, and the diffusion coefficient. Derivative parameters were also calculated, such as the percentage of the number of fibers in the corpus callosum segments, relative to the total number of fibers in it, the laterality index (for paired tract fibers), as well as the myelination coefficient, which is a product of the number of fibers in the studied tract and the average fractional anisotropy value in it.

Statistical analysis of the obtained quantitative parameters in the tracts was carried out using licensed IBM SPSS v21 software (IBM SPSS, USA). The average values for the independent samples were compared using the Student’s t-test or the Mann–Whitney test, depending on the normality of the distribution of variables within the samples, to identify statistically significant differences between the groups. The Pearson’s correlation coefficient was used to assess the distribution of variables within the group of patients depending on the clinical form of CP and the degree of motor disorders (GMFCS score, GMFM 88 score).

The study was performed at the University clinic of Privolzhsky Research Medical University in the period from 2017 to 2019. The study was approved by the local Ethics Committee at Privolzhsky Research Medical University (Protocol No. 4 of 29.03.2017) and carried out with an obligatory written informed consent obtained from the parents.

RESULTS AND DISCUSSION

According to the results of the MRI study, in the patients of group 1 (with CP), a symptom complex was revealed, including three types of structural changes. The first type included glial changes in the white matter of the brain, predominantly of periventricular localization. Such changes were found in 19 (83%) out of 23 patients, including: minimally pronounced zones of periventricular gliosis in 9 (40%) patients; moderately pronounced zones of periventricular gliosis extending to adjacent structures in 2 (8%) patients; severe glial cysts in 7 (30%) patients; extensive zones of glial cysts combined with atrophic changes in 1 (4%) patient. Porencephalic cysts were observed in 2 (8%) patients. The second type which included changes in the ventricles of the brain was detected in 16 (70%) patients with CP.

Lateral ventricular asymmetry associated with periventricular leukomalacia was found in 6 patients; moderate dilation of the lateral ventricles – in 10 patients, including dilation of the posterior horns – in 7 patients. Signs of glial changes in the white matter of the brain and pathology of the cerebral ventricles were combined in 16 (70%) patients. The third type of the detected changes includes abnormalities of white matter tract anatomy in the brain structures. In the course of post-processing, the main white matter tracts in the brain were reconstructed (Fig. 1). Children from the control group (Fig. 2) had fairly even distribution of fibers over the segments of the corpus callosum (Fig. 2, a), as well as a symmetric number of fibers in the corticospinal tracts and superior and inferior longitudinal fasciculi (Fig. 2, b).

The patients with CP demonstrated a decrease in the absolute number of fibers in all segments of the corpus callosum (except for the anterior part), corticospinal tracts, as well as in the left inferior longitudinal fasciculus. Fractional anisotropy was significantly decreased in the central and posterior segments of the corpus callosum, the right lateral corticospinal tract, and the left inferior longitudinal fasciculus. The diffusion coefficient was significantly increased in the group of
patients with CP only in 5 out of 11 localizations. From the calculated parameters, the myelination coefficient was significantly reduced in all the studied tracts, except for the superior longitudinal fasciculus.

The percentage of fibers (%) or the laterality index (for symmetric tracts) significantly differed in the three segments of the corpus callosum. The results of statistical processing are presented in the Table.

Fig. 1. Typical changes in the major white matter tracts identified in the patients with CP: CST – corticospinal tract, SLF – superior longitudinal fasciculus; ILF – inferior longitudinal fasciculus; CC 1, 2, 3, 4, 5 – segments of the corpus callosum (here and in Fig. 2). Visually, an asymmetric decrease in the number of fibers in the corticospinal tract and the superior longitudinal fasciculus on the side of the lesion (Fig. 1, a) and a decrease in the number of fibers in the central and posterior central segments of the corpus callosum were detected (Fig. 1, b).

Fig. 2. Reconstructed major white matter tracts of the brain in the patients from the control group: a – fibers of the corticospinal tracts, superior and inferior longitudinal fasciculi; b – distribution of fibers in the segments of the corpus callosum

| Tract | Number of fibers, pc. | Fiber percentage (%) / laterality index | Fractional anisotropy (FA) | Myelination coefficient | Apparent diffusion coefficient (ADC) | p |
|-------|-----------------------|-----------------------------------------|----------------------------|-------------------------|--------------------------------------|---|
| CC1   | 1,594.2 (148.3)       | 0.393 (0.023)                           | 0.000                      | 0.07                    | 886.5 (66.7)                         | 92.0 (1.6) | 0.799 (St) |
|       | 2,028.4 (144.7)       | 0.280 (0.013)                           | 0.432 (0.007)              | 867.3 (69.8)            | 0.040 (M–W)                          | 1.2 (St)    |
Gliarial changes and changes in the cerebral ventricles have been well analyzed by many authors [5, 12, 13]. There is no consensus in the literature on the diagnostic significance of structural changes in the brain matter in patients with CP [14]. A few authors have identified and described changes in the corticospinal (motor) tracts, manifested both through a decrease in the number of fibers and a decrease in the fractional anisotropy index [15]. The authors associated changes in the characteristics of the corticospinal tracts, in particular, a decrease in FA, with motor impairments [6]. However, the degree of damage to the corticospinal tracts, established on the basis of a decrease in the fractional anisotropy index, does not always correspond to the severity of clinical manifestations in patients with CP [15]. No such correlation was found in this study either.

According to our data, abnormalities in the tract anatomy in the patients with CP were detected more often than described in the literature [15]. Changes in the corpus callosum (in all five segments) were observed in all patients with CP, regardless of the damage to other brain structures. Changes in the corpus callosum in patients with CP were described in the literature. In particular, its delayed development was studied, which was manifested through thinning and reduction of its volume in patients with CP, compared with healthy peers [16].

Also, according to the results of a systematic review by L. Mailieux et al. (2020), separate studies were identified that demonstrate a decrease in fractional anisotropy in patients with CP, mainly in the central regions [6]; similar data were obtained in our study. The nature of changes in the corpus callosum has not been sufficiently studied yet, and their role in the pathogenesis of CP is unclear. However, their association with impaired motor function can be traced quite clearly, because it is the motor areas of the cortex that are connected by commissural tracts of the central corpus callosum.

Among the patients of the CP group, a relationship between MR tractography data and impaired motor function was studied. A moderate positive correlation was found (significant at $p < 0.05$) between the GMFM 88 score and the myelination coefficient in the anterior segment of the corpus callosum (Pearson’s correlation coefficient $r = 0.54 – 0.61$).

### Table (continued)

| Tract | Number of fibers, pc. | $P$ | Fiber percentage (%) / laterality index | $P$ | Fractional anisotropy (FA) | $P$ | Myelination coefficient | $P$ | Apparent diffusion coefficient (ADC) | $P$ |
|-------|-----------------------|-----|----------------------------------------|-----|--------------------------|-----|------------------------|-----|-------------------------------|-----|
| CC2   | 729.4 (102.1)         | 0.024 | 0.164 (0.015)                          | 0.258 | 0.385 (0.01)            | 0.047 | 292.1 (43.1)          | 0.017 | 101.9 (2.9)               | 0.036 |
|       | 1,101.9 (115.4)       |     |                                         |     |                          |     |                        |     |                               |     |
| CC3   | 440.9 (99.5)          | 0.014 | 0.088 (0.013)                          | 0.362 | 0.368 (0.013)            | 0.036 | 173.2 (40.5)          | 0.016 | 112.6 (4.8)               | 0.052 |
|       | 817.3 (124.9)         |     |                                         |     |                          |     |                        |     |                               |     |
| CC4   | 228.7 (56.9)          | 0.000 | 0.041 (0.007)                          | 0.000 | 0.332 (0.013)            | 0.000 | 86.5 (25.2)           | 0.000 | 129.4 (4.6)               | 0.000 |
|       | 872.7 (140.6)         |     |                                         |     |                          |     |                        |     |                               |     |
| CC5   | 1,408.3 (157.1)       | 0.000 | 0.311 (0.022)                          | 0.027 | 0.411 (0.012)            | 0.000 | 609.1 (73.5)          | 0.000 | 112.1 (2.9)               | 0.000 |
|       | 2,678.1 (159.1)       |     |                                         |     |                          |     |                        |     |                               |     |
| CSTI  | 1,559.5 (87.6)        | 0.000 | -0.030 (0.859)                         | 0.089 | 0.381 (0.011)            | 0.147 | 598.8 (40.4)          | 0.000 | 90.9 (3.4)                | 0.015 |
|       | 2,314.3 (130.2)       |     |                                         |     |                          |     |                        |     |                               |     |
| CSTr  | 1,590.1 (112.2)       | 0.001 | -0.030 (0.859)                         | 0.089 | 0.379 (0.006)            | 0.039 | 608.8 (45.5)          | 0.000 | 87.9 (3.0)                | 0.052 |
|       | 2,251.4 (131.5)       |     |                                         |     |                          |     |                        |     |                               |     |
| SLFI  | 382.1 (44.3)          | 0.448 | 0.570 (0.279)                          | 0.102 | 0.320 (0.016)            | 0.209 | 131.2 (16.3)          | 0.489 | 79.5 (3.7)                | 0.582 |
|       | 421.3 (38.9)          |     |                                         |     |                          |     |                        |     |                               |     |
| SLFr  | 432.7 (64.8)          | 0.083 | 0.570 (0.279)                          | 0.102 | 0.346 (0.009)            | 0.059 | 153.6 (23.9)          | 0.077 | 82.0 (1.3)                | 0.422 |
|       | 543.9 (54.9)          |     |                                         |     |                          |     |                        |     |                               |     |
| ILFI  | 455.3 (47.8)          | 0.002 | -0.125 (0.400)                         | 0.116 | 0.354 (0.017)            | 0.067 | 172.0 (18.8)          | 0.001 | 92.3 (4.3)                | 0.854 |
|       | 685.8 (40.9)          |     |                                         |     |                          |     |                        |     |                               |     |
| ILFr  | 465.8 (51.6)          | 0.073 | -0.125 (0.400)                         | 0.116 | 0.369 (0.007)            | 0.052 | 175.8 (21.3)          | 0.049 | 96.1 (1.2)                | 0.012 |
|       | 585.8 (52.9)          |     |                                         |     |                          |     |                        |     |                               |     |

Note: *italics indicate selected average values in the group of patients with CP; the value of the standard error of the mean is indicated in parentheses; (St) – Student’s t-test was used, (M–W) – the Mann – Whitney test was used.*

$i$ indicates the median, the interquartile range is in parentheses.
correlation coefficient 0.51), as well as the myelination coefficient in the inferior longitudinal fasciculus (Pearson’s correlation coefficient 0.46 in the right fasciculus and 0.47 in the left fasciculus). The myelination coefficient, in our opinion, more accurately characterized disturbances in the tract anatomy, since its calculation takes into account a mutual change in two indicators: the number of fibers and the fractional anisotropy index.

There is a group of patients with CP, where signs of brain changes are not determined by structural MRI, and minor and / or symmetrical white matter lesions cannot fully explain the clinical presentation of the disease [14]. In our MRI study, changes in the white matter were absent in 4 patients (17%) with clinical signs of CP. Abnormalities in the anatomy of the white matter tracts in the corpus callosum were found in all these patients, regardless of the state of the white matter tracts of the brain. Thus, in the absence of MRI signs of white matter lesions, MR tractography is the only objective method to confirm CP in a child.

CONCLUSION

MR tractography is an informative method for unbiased assessment of brain white matter tract anatomy and the level and degree of damage to the motor tracts. The most informative characteristics of the tract anatomy are the absolute number of fibers in the tract, the fractional anisotropy index, and the calculated coefficient of myelination. Among the CP patients of the experimental group, a relationship was revealed between the MR tractography data and impaired motor function. A method was developed for assessing the condition of the tracts by calculating the myelination coefficient.

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Authors contribution

Klyuev E.A. – conception and design, collection and analysis of material, statistical interpretation of research results, drafting of the manuscript. Sheiko G.E. – collection and analysis of material, drafting of the manuscript, substantiation of the manuscript. Dunaev G.E. – collection and analysis of material, drafting of the manuscript. Lobanova E.V., Rasteryaeva M.V. – critical revision of the manuscript for important intellectual content. Sharabrin G.E. – conception and design, drafting of the manuscript, substantiation of the manuscript, final approval of the manuscript for publication, responsibility for the integrity of all parts of the article.

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