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Morphometric analysis of MRI images in children who suffered an ischemic stroke under the age of two years: a pilot study

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ABSTRACT

Morphometric evaluation of MRI images can provide important information about the exact lesion size and its localization in the brain, can guide therapeutic tactics and predict outcomes. At the same time, there are few relevant studies on morphometry in pediatric cohorts and its relationship to outcome data in the remote period of the disease. The aim of the present study is to establish morphometric characteristics of cerebral infarction in the acute period of the disease in a pediatric cohort of patients within a pilot study for further assessment of neural tissue recovery variants and comparison with cognitive function deficits in the residual period. Materials and Methods. The present work was prepared as part of the Psychological Dictionary Research Award competition and focuses on the first data from the morphometric analysis. An extended version of the clinical cohort including children from this study is presented in the published article "Voxel-based morphometry of brain MRI: first results in pediatric ischemic stroke cohort" (Korotkova et al., 2025). We analyzed brain MRI images obtained in the acute period of ischemic stroke in 21 children with the disease debut at the age of up to two years using software (RadiAnt DICOM Viewer, MRIcron, BrainVISA / Anatomist). Results: Qualitative and quantitative analysis revealed a predominance of left hemispheric (n = 10, 48%) middle cerebral artery pool (n = 19, 90%), subcortical localization (n = 15, 71%) with involvement of the internal capsule (n = 13, 62%). The volume of the infarct focus in the experimental sample varied significantly from 409 to 102192 mm3 (median - 2841 mm3) and occupied on average 2.9% of the total brain volume. The average lesion volume was significantly larger in the perinatal stroke group compared with the pediatric stroke group (10.4% vs 1.2%). Thus, brain regions considered important for future neurocognitive and motor development (internal capsule and thalamus) were involved in the ischemic infarct zone in more than half of cases (62%), which defines the importance of pilot morphometric MRI studies in studying the volume and localization of infarcts in young children.

Keywords: *perinatal ishemic stroke, pediatric ishemic stroke, MRI, brain morphometry, cognitive development, prognostic biomarkers*

Annotation

Morphometric evaluation of MRI images can provide important information about the exact lesion size and its localization in the brain, can guide therapeutic tactics and predict outcomes. At the same time, there are few relevant studies on morphometry in pediatric cohorts and its relationship to outcome data in the remote period of the disease.

The aim of the present study is to establish morphometric characteristics of cerebral infarction in the acute period of the disease in a pediatric cohort of patients within a pilot study for further assessment of neural tissue recovery variants and comparison with cognitive function deficits in the residual period.

Materials and Methods. The present work was prepared as part of the Psychological Dictionary Research Award competition and focuses on the first data from the morphometric analysis. An extended version of the clinical cohort including children from this study is presented in the published article "Voxel-based morphometry of brain MRI: first results in pediatric ischemic stroke cohort" (Korotkova et al., 2025). We analyzed brain MRI images obtained in the acute period of ischemic stroke in 21 children with the disease debut at the age of up to two years using software (RadiAnt DICOM Viewer, MRIcron, BrainVISA / Anatomist).

Results: Qualitative and quantitative analysis revealed a predominance of left hemispheric (n = 10, 48%) middle cerebral artery pool (n = 19, 90%), subcortical localization (n = 15, 71%) with involvement of the internal capsule (n = 13, 62%). The volume of the infarct focus in the experimental sample varied significantly from 409 to 102192 mm3 (median - 2841 mm3) and occupied on average 2.9% of the total brain volume. The average lesion volume was significantly larger in the perinatal stroke group compared with the pediatric stroke group (10.4% vs 1.2%). Thus, brain regions considered important for future neurocognitive and motor development (internal capsule and thalamus) were involved in the ischemic infarct zone in more than half of cases (62%), which defines the importance of pilot morphometric MRI studies in studying the volume and localization of infarcts in young children.

Introduction

The World Health Organization defines stroke as a clinical syndrome consisting of rapidly developing clinical signs of focal (sometimes global) cerebral circulatory collapse lasting more than 24 hours or resulting in death with no apparent cause other than vascular causes (Abiodun, 2018).

Since the 1990s, there has been an increase in the prevalence of pediatric stroke worldwide (Tan et al., 2022). In 2019, the global prevalence of ischemic stroke (hereafter referred to as IS) in children from birth to 19 years of age was 2,899,174 cases, with the highest incidence of IS in countries with low socio-demographic index (Institute for Health Metrics and Evaluation, USA). Frequency differences are due to both ethnic and genetic variability, as well as age ranges of the population examined in the studies (Sarecka-Hujar & Kopyta, 2020; Steiner et al., 2021). Compared to adult strokes, pediatric strokes are a distinct clinical entity with a unique etiology, a certain diagnostic order, and therapeutic approaches that are different from treating adult patients (Khalaf et al., 2018).

Strokes in children are associated with long-term neurological disability. Thus, the most common consequence of stroke is motor and cognitive impairment (Dunbar & Kirton, 2018; McKinney et al., 2018). Motor impairments include a combination of motor skills and coordination of movements (Zayed Higher Organization for People of Determination (UAE) & Ural Federal University, 2024) and sensorimotor impairments related to perception and movement control (Zayed Higher Organization for People of Determination (UAE) & Ural Federal University, 2024). Higher cognitive impairments include impairments in thinking, consciousness, attention, perception, memory, speech and language, learning, reading and writing, arithmetic skills (Zayed Higher Organization for People of

Determination (UAE) & Ural Federal University, 2024). Motor impairments, unlike cognitive impairments, are more likely to be noticed and corrected (Jordan & Hillis. 2011).

The main confirmatory method of diagnosing acute IS is brain imaging, which is crucial in the choice of reperfusion therapy as a treatment method, it facilitates specifying other subacute and chronic lesions of the brain matter and may be helpful in monitoring the patient's condition (Tedyanto et al., 2022).

Magnetic resonance tomography (hereinafter referred to as MRI) of brain is the gold standard for diagnosing acute IS in children (Dunbar & Kirton, 2018) and has a number of advantages: it has high image resolution (Lehman & Rivkin, 2014): thus, MRI without contrast is five times more sensitive and twice as accurate as computed tomography (hereinafter referred to as CT) without contrast (Tedyanto et al, 2022); MRI allows rapid differential diagnosis, including cases with stroke mimics (Nukovic et al., 2023). According to the recommendations of the Royal College of Paediatrics and Child Health, neuroimaging studies should be performed within one hour of the child's admission to the hospital if stroke is suspected in childhood (Royal College of Paediatrics and Child Health, 2017). Diffusion-weighted imaging (DWI) MRI is the most sensitive to ischemic changes in the brain substance, but it is also highly susceptible to motion artifacts and requires longer scans than standard T1- or T2-weighted images, making its use in pediatric samples very difficult.

There are two approaches to MRI image processing: qualitative and quantitative. Qualitative analysis of brain MR images includes assessment of the following parameters: localization of the infarction in relation to the cerebral hemispheres and lobes, involved arterial basin, affected internal structures of the brain, etc. Quantitative assessment includes morphometric analysis, which helps to determine the exact size of the brain volume and infarction, the amount of involvement of various structures and conductive pathways in the lesion focus. And one of the most common forms of morphometric analysis is voxel-based morphometry, which was proposed for the assessment of the brain structural changes by J. Ashburner and his colleagues (Ashburner & Friston, 2000). Voxel-based morphometry is a statistical method used to detect structural abnormalities in the brain and to measure its volume, in which a region of interest (ROI) or the infarction area (in case of IS) is defined on normalized MRI images.

Currently, most MRI studies of pediatric populations with ischemic stroke are of high quality and are based entirely on the interpretation of radiologists. Advances in neuroimaging software are making it possible to share MR image data online between clinical and research centres and between physicians and patients (Alhajeri, 2024). This, in turn, expands the possibilities of working with neuroimaging data and allows not only qualitative assessment of lesion localization in children with ischemic stroke (to determine the type, arterial basin involved, etc.), but also its morphometric quantitative evaluation (calculation of absolute and relative lesion volume).

Although morphometry indices have proved their importance for selecting treatment tactics (Craig et al., 2021; Ospel et al., 2024), assessing prognosis (Craig et al., 2021; Kong et al., 2018), and evaluating the effectiveness of rehabilitation measures (Arachchchige et al., 2021) after stroke in cohorts of patients with stroke debut at a typical age, this kind of studies on pediatric samples are sparse (Craig et al., 2018). For example, the keyword combination "morphometry AND ischemic stroke AND (pediatric OR perinatal OR neonatal)" showed 23 search engine publications, of which only 5 were directly related to the topic of morphometric analysis in pediatric samples (Al Harrach et al., 2019; Dinomais et al., 2015; Dinomais et al., 2016; Postic et al., 2024; Schnaufer et al., 2024). However, in all of these studies, the analysis included MRI data obtained already in the period of long-term effects (at the age of seven years and older), which does not allow us to judge the infarct volume in the acute stroke periods, the compensatory reactions and their connection with clinical symptoms. Sporadic work in this area in participant-limited samples has shown that

greater infarct volume is associated with poorer cognitive performance in children in the outcome period (Malone et al., 2022; Li et al., 2022).

Quantitative, morphometric processing of MRI brain images is a promising area in terms of finding predictive neuroimaging non-invasive biomarkers (as opposed to liquor and biopsy data, for example) that can be applied not only in academic research but also in clinical practice (Chalavi et al., 2012; Craig et al., 2021; Rebsamen et al., 2020). Further application of machine learning and artificial intelligence techniques may be also helpful in this research area (Sun, 2025).

Thus, morphometric studies with the analysis of MRI data obtained in longitudinal studies in the acute/subacute and outcome periods of childhood stroke, as well as their comparison with clinical data on the course of the disease and the results of assessment of the patient's neuropsychiatric developmental skills, may be of particular value. This determined the aim of the present study: to determine the morphometric characteristics of cerebral infarction in the acute period of the disease to assess the variants of neural tissue repair and to compare them with the emergence of the neurodevelopmental skills.

This Psychological Dictionary Research Award competition paper presents the first data from morphometric analysis in a cohort of children with ischemic stroke. An expanded version of the clinical sample, which included all children in this study, was included in the paper "Voxel-based morphometry of brain MRI: first results in pediatric ischemic stroke cohort" (Korotkova et al., 2025).

Materials and Methods

Research Design and Sample

The present study is the first phase of a prospective prognostic study. The participants of the experimental sample - children (n = 21, 15 boys and 6 girls, average age range 8.8±1.2 years) who have been suffering arterial IS since infancy and were selected according to the inclusion and exclusion criteria. Children with vascular malformations were included into the study in 2015-2019 period, the work was organized by the Regional Children's Clinical Hospital and Children's City Clinic No. 9 in Yekaterinburg, Russia.

Inclusion criteria were as follows: clinically confirmed diagnosis of ischemic stroke (ICD-10: "Brain Infarction", I63.0-I64.9); manifestation of ischemic stroke symptoms before the age of two years (including perinatal type of debut); confirmation of the IS diagnosis by brain MRI in the acute period; signed informed consent of parents and/or legal representatives of the child. The following exclusion criteria were followed: stroke manifestation at the age of over two years or fetal type of stroke debut; presence of signs of other cerebral circulatory disorders (hemorrhagic stroke, cerebral venous thrombosis, etc.); stroke confirmed in the acute period only by brain CT.

To assess the significance of the stroke debut age, we divided the experimental group into participants with perinatal (with diagnosis age of 0-28 days of life, n = 4) and pediatric (29 days-2 years of life, n = 17) debut of ischemic stroke.

Qualitative and quantitative MR-images processing

All MRI images were obtained with high-field CT scanners with power not less than 1.5T: HDxt Signa (General Electric Healthcare, USA) in the Department of Radiation Diagnostics and Endoscopy of the City Clinic "Children's Hospital №9", "Research Institute of Maternity and Infancy Care" of the RF Ministry of Health; ACHIEVA (Phillips Healthcare, Netherlands) in the Department of Radiology and Endoscopic Diagnostics of the Oblast Children's Clinic No. 1; Optima 450w (General Electric Healthcare, USA) in the Pediatric Department of Diagnostic Radiology of the Regional Children's Clinic (in Perm); Intera (Phillips Healthcare, the Netherlands) in MRI Clinic "Expert"; Aquilion 64 (Toshiba Medical Systems, Japan) in the Diagnostic Radiology Department of Tyumen Oblast Clinic No. 1; Magnetom Essenza and Magnetom Symphony (Siemens, Germany) in the Diagnostic Radiology Department of the Oblast Clinic No. 3 and the Medical Center "Park Med"; LCC Active

Shield Magnet and Cryogens (General Electric Healthcare, USA) in the Clinic "Demidov Central Hospital".

Qualitative and quantitative processing of brain MR images was conducted with the following software: RadiAnt DICOM Viewer (version 2021.1); MRIcron (version 1.0.20190902); BrainVISA/Anatomist (version 5.1.1).

The first step was to perform high-quality processing of MRI data. For this purpose, all images were opened in RadiAnt DICOM Viewer and viewed by a radiologist in slices to identify the exact boundaries of the infarct and its localization. The starting point was medical MRI reports, which helped to avoid errors and inaccuracies in determining the qualitative characteristics of the infarct. In case of doubt, the raw data and corresponding medical report were further checked by a specialist to confirm the accuracy of the primary clinical assessment.

The following factors were taken for qualitative analysis: stroke debut type (perinatal, pediatric), stroke type (cortical, subcortical, combined), affected hemisphere (left, right, both).

For quantitative morphometric processing, all MRI brain images were sequentially converted from DICOM to NIfTI format using the dcm2nii converter embedded in MRIcron, a tool-based cross-platform software that allows viewing and exporting brain images in NIfTI format. The conversion resulted in files with the extension .nii, whose name displays metadata (visualization mode, scan plane, etc.). For further morphometric processing, T1-weighted images in multi-echo sequence (MEMP), T2-weighted images in fast spin-echo sequence (FSE/TSE) and diffusion-weighted images in axial plane were taken as they are the most frequent and available in pediatric practice.

Morphometric analysis of MR images was performed using the Anatomist package included in the BrainVISA brain neuroimaging software platform (5.1.1). BrainVISA (Geffroy et al., 2011) is a software platform for morphometric analysis, which allows to calculate such morphometric indices as total intracranial brain volume, brain lesion volume and their ratio, detailed morphometry of individual cerebral structures. "The gold standard" is considered to be morphometric analysis based on manually extracted regions of interest (Chalavi et al., 2012). Images of both the whole brain and the infarct area (region of interest, ROI) of our patients were sequentially traced manually on all slices of T1- and T2-weighted images in axial projection in each patient for further quantitative analysis. The volume of the selected region of interest was defined through the MorphoStats function.

Table 1

Statistical analysis

Statistical data processing was performed using the following tools: free software development environment for statistical data processing and graphics Rstudio (version 2023.12.1); a set of open-source packages for the R tidyverse programming language (version 4.3.2); a set of open-source packages for the R rstatix programming language (version 4.3.3). Pairwise comparisons were performed with the help of Dunn's test using the dunn.test package (version 1.3.5).

Results

Qualitative and quantitative interpretation of MRI images

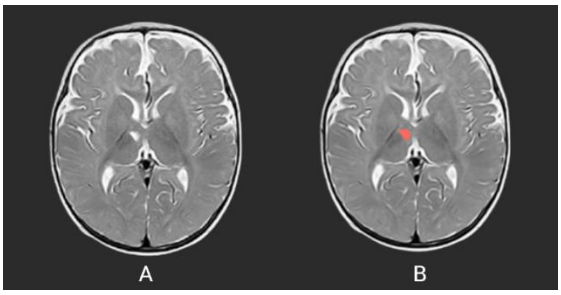
During data processing, the first step was a qualitative assessment of infarct localization (Table 1).

The results of qualitative processing of brain MRI in children with the early onset of arterial ischemic stroke (n = 21)

	Абс.	%
Number of participants	21	100
Infarct localization		
Cortical	1	5
Subcortical	15	71
Combined*	5	24
Capsula interna	13	62
Thalamus	5	24
Hemisphere		
Right	5	21
Left	10	48
Both	6	29
Lobe of the brain		
Frontal	15	71
Temporal	4	19
Parietal	11	52
Occipital	3	14
Insular cortex	6	29
Combined*	9	43
Damaged arterial basin		
Middle cerebral artery	19	90
Superior cerebral artery	2	10
Posterior cerebral artery	5	24
Anterior choroidal artery	12	57
Lateral lenticulostriate arteries	8	38
Combined*	18	86

Note. * - two and more damaged arterial pool; two and more brain lobes

The second step was quantitative morphometric assessment of MRI data. The infarct volume of each child was measured and brain MRI protocols were evaluated in case of suspected AI debut/verification in a child. T1-, T2-, and diffusion-weighted images in the axial plane were analyzed slice by slice by a pediatric radiology expert. Both total brain volume and the area of ischemic infarcts were defined as region of interest (ROI) and circled manually on each slice (Figure 1). Total intracranial brain volume and brain lesion volume were calculated in mm3 through the MorphoStats function.



The volume of brain tissue lesions in the studied cohort of children was also assessed in general and depending on the IS debut variant (perinatal, pediatric). The results of statistical data processing are shown in Table 2. Since the distributions of the analyzed parameters were not always normal, in addition to the average meaning and its standard deviation, Table 2 also presents data on the median and interquartile range (IQR) as it is recommended by N.M. Bulanov et al. (Bulanov et al., 2022).

Table 2

The results of morphometric analysis of brain MRI children with the early onset of arterial ischemic stroke in acute period

	Lesion volume, мм^3			Brain volume, мм^3			% of damaged brain tissues, %		
	M ± SD, median	min-max	IQR	M ± SD, median	min-max	IQR	M ± SD, median	min-max	IQR
n = 21	15144 ± 27447, 2841	409 - 102192	8977	888667 ± 27447, 982599	319474 - 1375100	662088	2.9 ± 5.7, 0.25	0.04 - 22.9	1.4
Perinatal stroke (n = 4)	42651 ± 41157, 42651	7427 - 102192	23928	375446 ± 53559, 367538	319474 - 447234	46718	10.4 ± 8.7, 8.3	2.3 - 22.9	5.4
Pediatric stroke (n = 17)	8671 ± 19758, 2774	409 - 83984	1178	1009424 ± 272279, 1032760	459026 - 1375100	334568	1.2 ± 3.1, 0.2	0.04 - 12.9	0.2

Note. IQR - interquartile range

The application of the nonparametric Mann-Whitney U-criterion showed a significant difference between age groups in brain volume ($p = 0.0003$), infarct lesion volume ($p = 0.009$) and relative lesion volume ($p = 0.006$).

Discussion

In the present study, we performed the first morphometric analysis of MR images of brain infarction in the acute period of the disease in a pediatric cohort of patients with the ischemic stroke debut before 2-year-old age, and assessed the difference in cognitive outcomes compared with typically developing children depending on lesion characteristics: disease age and infarct localization.

To obtain consistent data, we analyzed T1- and T2-weighted images and axial projection MRI images as they are frequently used to define the boundaries of anatomical soft tissue structures and to detect associated pathological changes (Jacobs et al., 2007) and they were the only ones available in all participants in the pediatric sample.

In children who suffered arterial IS at an early age, we observed predominance of left hemispheric localization of infarction (n = 10, 48%), involvement of subcortical structures in more than half of cases (n = 15, 71%), including the internal capsule (n = 13, 62%). In most patients of

our sample, the infarction lesion was located in the middle cerebral artery basin (n = 19, 90%).

The volume of infarct-involved brain tissue in the acute period of IS varied significantly from 409-102192 mm3 (median 2841 mm3) and occupied on average 2.9% of the total brain volume. While there was an apparent increase in total brain volume between the first and second year of life ($p = 0.0003$), differences were also found in infarct volume and in the ratio of infarct volume to total brain volume in perinatal and pediatric variants of stroke debut ($p = 0.009$ and $p = 0.006$, respectively).

The results of qualitative analysis of MRI images in the present study indicate possible involvement of many conductive pathways and cortical centers responsible for movement, fine and gross motor skills, cognitive domain, etc. in the infarct area. Quantitative evaluation of brain MRI data using the Anatomist package showed a significant variation in the volume of infarction in the acute period of the disease regardless of the debut age (perinatal/pediatric), which may result from different pathogenetic variants of IS, the course of nervous tissue repair processes affected by comorbidities, etc..

Conclusion

An international consensus of pediatric cerebrovascular specialists believes that, in the absence of contraindications and when available, brain MRI is of paramount importance to diagnose pediatric IS. Despite the fact that morphometric evaluation of MRI images can provide clinicians with important information both about the volume of the lesion focus and the involvement of conduction pathways and cortical centers in the focus of infarction and in the perifocal zone, at present such analysis is practically not performed either on the basis of medical institutions or for research purposes, and studies devoted directly to the morphometry of infarction in children are represented by single publications on a limited number of participants.

It is known that infarct localization not only determines the clinical presentation of the disease in the acute and outcome periods, but also influences the long-term prognosis of loss of higher neural function (Goldman-Yassen & Dehkharghani, 2021). Strokes localized in the middle cerebral artery basin often result in cognitive impairment - spatial neglect, constructive apraxia and loss of topographic memory (Yamadori et al., 1995). Left hemispheric strokes in infants are associated with probable verbal impairment (Westmacott et al., 2010).

The internal capsule is an important collector and conductor of white matter (Emos et al., 2023), along with the external capsule, radial vein and inferior thalamic radicle, the internal capsule is vulnerable to ischemia (Zhao et al., 2018). We chose the subcortical area of infarct localization as an area of special interest in the qualitative analysis of our own MRI image data not by chance. The subcortical type of stroke is known to be the most common (Corbetta et al., 2015), and it is subcortical and combined infarct location variants that may be predictors of worse cognitive outcome in a pediatric cohort of patients (Malone et al., 2022; Steiner et al., 2021). Westmacott et al. linked subcortical type of stroke to impairments in executive function, working memory, and attention in children (Westmacott et al., 2010).

The present study represents the first stage of evaluation of data on the localization and morphometry of IS infarcts that debuted in infancy. Comparison of the obtained neuroimaging data with the results of clinical presentation of neurological symptoms in the acute period, cognitive and motor outcomes of the disease at the age of 7-10 years at the next stages of the pilot study, including a larger cohort of children, will be the basis for the identification of complex prognostic markers that allow to determine with high accuracy the prognostically unfavorable variants of the infantile type of ischemic stroke debut, to get an idea of the mechanisms of neuroplasticity, and to identify the mechanisms of neuroplasticity of ischemic stroke.

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