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НЕЙРОДЕГЕНЕРАЦИЯ СЕТЧАТКИ ПРИ БОЛЕЗНИ ГЕНТИНГТОНА

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Цель – исследовать морфологию сетчатки и выявить связи с клиническими данными при болезни Гентингтона (БГ).

Материал и методы. Было проведено одномоментное описательное исследование в группах субъектов с БГ и здоровых добровольцев, включавшее оценку параметров сетчатки методом оптической когерентной томографии (ОКТ).

Результаты. У пациентов с БГ количество ЦАГ (цитозин-аденин-гуанин) – повторов в гене белка гентингтина – определялось в пределах 38-56 повторов. Оценка по унифицированной шкале оценки БГ (UHDRS) составила 36,3±29,7 балла, длительность заболевания – 13,7±7,2 года. При исследовании слоев сетчатки методом ОКТ установлено снижение толщины комплекса ганглиозных клеток в макулярной зоне, средней толщины слоя перипапиллярных нервных волокон и их толщины в височном, нижнем и назальном квадрантах при БГ по сравнению с контролем. Обнаружена обратная корреляция между длительностью заболевания и толщиной слоя перипапиллярных нервных волокон в височном секторе.

Выводы. Локализация нейронных потерь указывает на специфический паттерн ретинальной дегенерации при БГ, схожий с болезнью Паркинсона и митохондриальными заболеваниями. Связь с длительностью заболевания подтверждает прогрессирующий характер изменений.

Ключевые слова: оптическая когерентная томография, болезнь Гентингтона, нейродегенеративные заболевания, сетчатка.

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RETINAL NEURODEGENERATION IN HUNTINGTON'S DISEASE

Abstract. The purpose was to analyze retinal morphology and to investigate the correlation with the clinical data in Huntington's disease (HD).

Material and methods. A cross-sectional study was performed to evaluate the retinal parameters in HD and healthy controls with the use of optical coherence tomography (OCT).

Results. The range of the CAG (cytosine-adenine-guanine) repeat expansion size was 38–56 repeats, the range of Unified HD Rating Scale motor scores (UHDRS) was 36.3±29.7, and disease duration was 13.7±7.2 years in HD patients. A significant decrease in the ganglion cell complex thickness, average, temporal, inferior and nasal retinal nerve fiber layer in HD subjects was revealed in OCT examination in comparison with control group. An inverse correlation between the disease duration and the temporal retinal nerve fiber layer thickness was found.

Conclusions. The localization of retinal thickness loss indicates a specific pattern of retinal neurodegeneration in HD, similar to Parkinson's disease and mitochondrial diseases. The association with the disease duration confirms the progressive nature of these changes.

Key words: optical coherence tomography, Huntington's disease, neurodegenerative diseases, retina.

Huntington's disease (HD) is a steadily progressing, fully penetrant neurodegenerative disease caused by a dominantly inherited CAG trinucleotide repeat expansion in the huntingtin gene [3]. The prevalence of this rare disease in the Caucasian race is 4.64-13.7 per 100 000 [2]. The pre-manifest and manifest stages are distinguished in the development of the disease, the age at the time of motor clinical onset correlates with the amount of CAG repeats [3].

The first study on retinal optical coherence tomography (OCT) in HD was announced in 2014 [4], showing peripapillary retinal nerve fiber layer (RNFL) degeneration. Shortly Kersten H. et al. [5], Andrade C. et al. [8], and Sevim D. et al. [7] presented a comprehensive analysis of retinal OCT parameters in groups of 8, 26 and 15 HD patients, respectively. Small group volume and insufficient data on pre-manifest HD requires further research. The purpose of this study was to analyze the OCT parameters of the retina and to investigate the correlation with clinical data in patients with pre-manifest and manifest HD.

Material and methods

A cross-sectional observational study was performed. Healthy volunteers were recruited in the control group. All HD patients had genetic confirmation of the diagnosis, CAG repeat length in the huntingtin gene was evaluated. Disease duration, UHDRS (Unified Huntington's Disease Rating Scale) motor scores and the stage of the disease were determined.

The thorough ophthalmological examination in all groups included the history taking, best-corrected visual acuity measurement (BCVA), intraocular pressure (IOP) measurement with Maklakov tonometry, biomicroscopy, indirect ophthalmoscopy. RTVue-100 spectral-domain OCT (Optovue Inc, Fremont, CA, USA) was used to analyze the peripapillary RNFL thickness (the average thickness and thickness in 4 quadrants) and the average ganglion cell complex (GCC) thickness.

Ophthalmic exclusion criteria: best corrected visual acuity below 0.9, spherical or astigmatic refractive errors more than 3 Diopters, intraocular pressure over than 22 mm Hg or the difference between the eyes more than 2 mm Hg, the vertical cup to disc ratio more than 0.4 according to the OCT, any significant optical media opacity, previous ocular trauma or surgery (including laser), any coexisting ocular diseases, the use of eye drops (excluding lubricants).

Neurological and other exclusion criteria: for the control group the Mini-Mental State Examination (MMSE) score less than 26, previous head trauma, diabetes, arterial hypertension and other systemic diseases with potential damage to the eye.

The statistical analysis was carried out using the SPSS 22.0 software package. Continuous variables are represented as arithmetic mean ± standard deviation. The Student's t-test for independent samples was used in samples with normal distribution and equal dispersion, remaining cases were compared with the Mann–Whitney U-test. The relationships were studied with Pearson correlation. The accepted significance level was 5% ($p<0.05$). There was a correlation between the right and left eye parameters, so the analysis was performed for the right eye of each patient.

Results

A total of 91 subjects, including 60 HD patients (60 eyes) and 31 control patients (31 eyes), were eligible for inclusion and exclusion criteria. In the HD group there were 29 pre-manifest and 31 manifest patients. The CAG repeats length varied from 38 to 56 (44.3 ± 3.8), the UHDRS motor scores in the manifest patients were 36.3 ± 29.7; the disease duration was 13.7 ± 7.2 years. Differences in age, gender, visual acuity and intraocular pressure between the main group and control were not significant (Table 1).

The HD patients showed a significantly lower thickness of the average GCC, the average RNFL, temporal, nasal and lower RNFL compared with controls (Table 2). OCT parameters of pre-manifest and manifest HD patients did not differ (Table 2). Average GCC thickness ($r=-0.66$, $p=0.003$) and temporal RNFL thickness ($r=-0.59$, $p=0.010$) were negatively correlated with UHDRS Motor Score. A significant but mild association ($r<0.50$, $P<0.05$) was found between structural parameters and CAG repeat length (table 3).

Table 1

Characteristics of the groups, M±m

Parameter	All HD patients (N=60)	Pre-manifest HD (N=29)	Manifest HD (N=31)	Controls (N=31)	p* HD vs. controls
Age, years	37,6±10,2	30,63±4,62	42,60±10,20	37,3±10,8	0,90
Females/males	24/20	7/14	17/6	15/16	0,599
Best-corrected visual acuity	1,0±0,0	1,0±0,0	1,0±0,0	1,0±0,1	0,26
Intraocular pressure, mm Hg	19,3±1,7	18,9±1,4	19,5±1,8	19,3±1,5	0,945

* t-test significance (Chi square test for gender).

Table 2

Retinal thickness parameters of the subjects, M±m

Parameter (μm)	All HD patients (N=60)	Pre-manifest HD (N=29)	Manifest HD (N=31)	Controls (N=31)	p* HD vs. controls	p** Pre-manifest HD vs. Manifest HD
Average GCC	84,9±7,8	85,36±6,43	84,70±8,66	93,8±5,2	<0,001	0,824
Average RNFL	96,07±9,4	99,86±8,74	93,74±8,96	105,7±7,5	<0,001	0,167
Temporal RNFL	69,4±15,1	69,29±12,41	69,44±16,67	86,8±6,9	<0,001	0,711
Superior RNFL	114,4±15,4	122,14±12,50	109,86±15,31	119,5±14,4	0,159	0,064
Nasal RNFL	73,5±10,5	76,43±7,62	71,86±11,65	80,5±12,9	0,016	0,274
Inferior RNFL	128,4±15,3	133,64±15,39	125,32±14,74	138,7±18,0	0,015	0,110

* t-test significance ** Mann–Whitney U-test significance.

Table 3

Correlation between structural parameters and markers of disease progression in Huntington's disease subjects

Parameter	CAG repeat length		Disease duration		UHDRS Motor Score	
	r	(p)	r	(p)	r	(p)
Average GCC	-0,487	0,001	-0,440	0,003	-0,657	0,003
Average RNFL	-0,389	0,014	-0,470	0,002	-0,433	0,082
Temporal RNFL	-0,134	0,409	-0,110	0,483	-0,590	0,010

Discussion

This is the first study that has identified a great potential of average GCC thickness and temporal RNFL thickness for discriminating pre-manifest HD. We studied the effects of HD on retinal morphology and evaluated the association between markers of disease progression and morphologic changes in the retina of 60 subjects with HD. Predominantly temporal RNFL loss characterize a specific parvocellular pattern of retinal neurodegeneration with parvocellular pathway lesion. Less pronounced but significant RNFL thickness reduction in the nasal and inferior quadrants was described for the first time. GCC degeneration and temporal RNFL thinning were associated with UHDRS Motor Scores increase. CAG repeat length showed mild inverse association with a number of OCT parameters.

According to the similarity of the pathogenesis of Parkinson's disease and HD La Morgia C. et al. suggested that the development of optic neuropathy in HD should have a parvocellular pattern with papillomacular bundle atrophy in contrast to Alzheimer's disease and glaucoma [6]. Our data support the hypothesis of La Morgia C. et al. [6] according to the most pronounced temporal RNFL loss in HD patients. This phenomenon could be explained by mitochondrial dys-

function in HD, causing the death of the most energy-consuming cells, in particular, ganglion cells [1,5]. It is consistent with experimental data suggesting an earlier lesion of cones than rods in the course of the HD progression [9].

Conclusion

Our results confirmed macular ganglion cells atrophy and its axons degeneration starting early in the course of the disease. Ganglion cells and RNFL thinning has a specific pattern of preferential parvocellular degeneration, probably associated with mitochondrial dysfunction. Clinical deterioration at the manifest stage of HD is accompanied by progressive retinal degeneration, CAG repeat length has a mild correlation with a number of OCT parameters. The association of OCT parameters with visual functions and vision-related quality of life in HD requires further research.

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СОЧЕТАНИЕ АНОМАЛИИ РАЗВИТИЯ ЗРИТЕЛЬНОГО НЕРВА И ГОЛОВНОГО МОЗГА (КЛИНИЧЕСКИЙ СЛУЧАЙ)

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С внедрением и развитием новейших диагностических методик возрастает актуальность качественной и количественной оценки поражения зрительного анализатора при друзах диска зрительного нерва (ДЗН). При диагностике друз ДЗН возможно выявление сопутствующих патологий.

В МНТК «Микрохирургия глаза» им. акад. С. Н. Федорова» г. Москва обратился пациент 50 лет, предъявляющий жалобы на эпизодическое затуманивание зрения и приступы головной боли. При постановке диагноза друзы диска зрительного нерва была выявлена сопутствующая врожденная неврологическая патология, которая стала случайной находкой на МРТ. Пациент был направлен на консультацию к нейрохирургу с целью уточнения диагноза, проведения возможного дальнейшего оперативного вмешательства и определения тактики лечения. Был поставлен диагноз артериовенозная мальформация глубинных артерий отделов левой теменной доли. Однако, сопоставив все риски, большие размеры артериовенозной мальформации, ее расположение в функционально важной зоне головного мозга, было принято решение о проведении наблюдения в динамике.

Ключевые слова: друзы диска зрительного нерва, артериовенозная мальформация.

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CLINICAL CASE OF THE COMBINED PATHOLOGY OF THE OPTIC NERVE AND THE BRAIN ABNORMALITIES

The urgency of the qualitative and the quantitative evaluation of lesions of the visual analyzer in drusen of the optic nerve disk increases with the introduction and development of the latest diagnostic techniques. If drusen are detected, it is possible to detect combined pathologies.