Eye tracking-based analysis of eye micromovements during a static fixation task in 6- to 13-year-old children who have undergone laser photocoagulation for retinopathy of prematurity

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Аналіз мікрорухів очей під час тесту на утримання погляду у дітей віком 6–13 років з ретинопатією недоношених після лазерної коагуляції з використанням технології айтрекінгу

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Abstract

Purpose: *To use eye tracking to determine the features of eye micromovements in a gaze fixation test in 6- to 13-year-old children who have undergone retinal laser photocoagulation (LPC) for retinopathy of prematurity (ROP).*

Methods: *A total of 125 children were included. Eye movements were recorded using the EyeLink 1000 Plus® (SR Research Ltd., Ottawa, Canada) eye tracker at a 2000-Hz sampling rate. The participant was asked to fixate gaze on the immovable central stimulus (a round dot-shaped target) for 10 seconds. The eye-tracking experiment was built in SR Research Experiment Builder, and Data Viewer® was used for data processing.*

Results: *In a static fixation test, statistically significant between-groups differences were found only for two characteristics. There was a significant difference between children that had undergone LPC for ROP and full-term emmetropic controls in average saccade amplitude (2.72 ± 1.63° versus 4.61 ± 2.20°, $p < 0.05$) and median pupil size (1269 (interquartile range, 1009-1443) versus 1987 (interquartile range, 1713-2325), $p < 0.05$).*

Conclusion: *In a static fixation test, average saccade amplitude was 1.7 times smaller (which corresponds to a reduction by 41.0%; $p < 0.05$) in the group of children that had undergone LPC for ROP compared to full-term emmetropic controls. Additionally, the median pupil size was 1.6 times smaller (which corresponds to a reduction by 36.1%; $p < 0.05$) in that group compared to controls. These findings indicate long-term changes in the visual system, which may affect fixation control and autonomic regulation.*

Keywords: *retinopathy of prematurity, retina, eye tracking technology, eye movements, saccades, children, laser photocoagulation, myopia.*

Резюме

Мета. *Виявити особливості мікрорухів очей під час тесту на утримання погляду у дітей віком 6–13 років з ретинопатією недоношених після лазерної коагуляції з використанням технології айтрекінгу.*

Методи. *Досліджено 125 дітей. У дослідженні використано айтрекер EyeLink 1000 Plus® (SR Research Ltd. ®, Канада) з частотою запису 2000 Гц. Учасники виконували фіксаційне завдання: протягом 10 секунд потрібно було утримувати погляд на центральному зоровому стимулі у вигляді круглої крапки без зміни положення мішені. Дослідження було запрограмовано у програмі Experiment Builder, а обробку отриманих*

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даних проводили за допомогою програмного забезпечення Data Viewer®.

Результати. *У тесті на утримання фіксації виявлено значущі міжгрупові відмінності за двома показниками. Середня амплітуда сакад була нижчою у дітей з ретинопатією недоношених після лазерної коагуляції (2,72±1,63°) порівняно з контрольною групою доношених дітей з еметропією (4,61±2,20°; p<0,05). Середній діаметр зіниці також був меншим у дітей після лазерної коагуляції — 1269 ум. од., міжквартильний інтервал (1009–1443 ум. од.) відносно контрольної групи — 1987 ум. од., міжквартильний інтервал (1713–2325 ум. од.); p<0,05.*

Висновки. *Встановлено, що у дітей із ретинопатією недоношених після лазерної коагуляції при виконанні завдання на утримання фіксації виявлено зменшення середньої амплітуди сакад у 1,7 раза порівняно з доношеними дітьми з еметропією, що відповідає зниженню приблизно на 41,0% (p<0,05). Середній діаметр зіниці в цій групі був меншим у 1,6 раза, або приблизно на 36,1% порівняно з контрольною групою (p<0,05). Ці результати свідчать про довгострокові зміни зорової системи, що можуть впливати на контроль фіксації та вегетативну регуляцію.*

Ключові слова: *ретинопатія недоношених, сітківка, айтрекер технологія, рухи очей, сакади, діти, лазерна коагуляція, міопія.*

Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative retinal disorder affecting premature infants due to abnormal vascular development. Abnormal vascular growth begins due to an immature retinal vasculature and effects of exogenic factors (hyperoxia, mechanical ventilation and unstable systemic hemodynamics), posing a risk of fibrosis, retinal tractional detachment and blindness, if not treated timely [1].

Prematurity, especially in children born at a weight <1500 g and/or before 32 weeks gestation, is a serious social and medical problem, as it is associated with the functional immaturity of multiple organ systems, including the visual system. These children frequently exhibit abnormal central nervous system (CNS) maturation, especially at the CNS sites responsible for visual integration, eye movement control, fixation and tracking [2].

Video-oculography systems (eye trackers) enable precise measurements of rapid gaze shifts (saccades) and phases of stable gaze fixation in children, and have been increasingly used in current eye movement studies [3]. Oculomotor patterns represent sensitive indicators of the functional status of the visual and cognitive systems, and can change due to neuropsychological or sensory abnormalities typical for preterm children or those with ROP [4, 5, 6]. In children with cerebral visual impairment, eye tracking studies can identify oculomotor dysfunction (abnormal fixation, smooth pursuit and saccadic movements), which is believed to be a key symptom of abnormal vision and may be associated with the features of the cognitive visual and learning functions [7]. An opportunity for investigation of oculomotor parameters in gaze fixation and prosaccade tasks and further analysis of these parameters enables assessing the latency, accuracy and stability of visual response and visual perception, which characterize the development of the prefrontal and subcortical oculomotor systems [8]. Eye tracking offers new opportunities for investigating the late sequelae of perinatal damage, particularly, visual control in infants with ROP. Additionally, it may become an objective tool for early diagnosis and neurovisual development monitoring.

It is reasonable to single out children with ROP (they have numerous neurological and ophthalmological issues) from all other preterm children. Although a vast number of studies have investigated retinal structural changes in ROP, the functional characteristics (particularly, oculomotor control) have not been sufficiently studied. Children with ROP are at an increased risk of developing ophthalmological abnormalities like strabismus [9], amblyopia, refractive errors [10, 11], contrast sensitivity abnormalities [9], etc. Functional effects of ROP on oculomotor control (including visual fixation and saccadic eye movements), however, have barely been studied.

The absence of data on the status of the oculomotor system in preterm children impairs our understanding of the mechanisms of oculomotor abnormalities and effects on the quality of life. Oculomotor abnormalities significantly affect child's cognitive development, learning and social integration [12].

The purpose of the study was to use eye tracking to determine the features of eye micromovements in a gaze fixation test in 6 to 13-year-old children who have undergone retinal laser photocoagulation (LPC) for ROP.

Material and Methods

This single-center open-label, non-interventional prospective study was conducted at State Institution "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine". One hundred and twenty-five 6- to 13-year-old children were included in the study and divided into five clinical groups of 19 to 34 individuals: group 1 (EMMET group; full-term emmetropic children without ophthalmological abnormalities); group 2 (MYOP group; full-term mildly to moderately myopic children without ocular comorbidity); group 3 (NROPP group; preterm children without signs of ROP); group 4 (ROPLC group; preterm children that have undergone LPC of the avascular retina) and group 5 (ROPRG group; children with spontaneous ROP regression).

Subjects underwent an ophthalmological and optometric examination (including clinical refraction, convergence, oculomotor balance and binocular vision status) before taking part in the study.

Baseline clinical details are shown in Table 1.

Median binocular best-corrected visual acuity (BCVA) (interquartile range (IQR)) was 1.0 (1.0–1.0) in most groups, but was lower in the ROPLC group. In groups 4 (ROPLC group) and 5 (ROPRG), median BCVA (IQR) was 0.95 (0.8–1.0) and 1.0 (1.0–1.0), respectively. Median uncorrected visual acuity (IQR) was the highest in the EMMET group, 1.0 (0.875–1.0), and low in the MYOP group, 0.3 (0.11–0.425), ROPLC group, (0.14–0.9), and ROPRG group, 0.6 (0.2–0.813). Refractive status in groups was in agreement with the grouping. Spherical equivalent refraction (SER) was myopic in group 2 (median SER [IQR] in the right eye and left eye was –1.875 D [–3.25 to –1.375] and –1.75 D [–3.125 to –1.125], respectively) and close to emmetropic in group 1 (–0.25 D [–0.25 to 0.5] and –0.125 D [–0.25 to 0.375], respectively). Additionally, median SER (IQR) in the right eye and left eye was –0.125 D (–0.75 to 0.5) and –0.25 D (–0.75 to 0.75), respectively, for group 3, –0.375 D (–3.5 to 0.5) and –0.625 D (–4.0 to 0.5), respectively, for group 4, and –1.125 D (–2.5 to –0.25) and –1.0 D (–2.0 to 0.125), respectively, for group 5.

This study was approved by the Bioethics Committee of SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine" (Meeting Minutes No.1 dated October 18, 2023), and followed ethical standards as outlined in the Declaration of Helsinki of the World Medical Association and relevant laws of Ukraine.

Before children were included in the study, their parents or legal guardians underwent a standardized questionnaire and provided children's clinical and history data required to determine whether the children met inclusion and exclusion criteria. Written informed consent was obtained from parents or legal guardians after provision of detailed information about aims, methods, risks and personal data processing.

Privacy was safeguarded through anonymization of data: each study subject was assigned a unique code to protect his or her identity. The storage, processing and analysis of the data obtained were done in compliance with the European Union General Data Protection Regulation (GDPR) and the Law of Ukraine "On the Protection of Personal Data".

Within the framework of this study, all subjects performed a single standardized eye tracking test. The test aimed to examine the features of eye micromovements in a gaze fixation test. Before beginning the experiment, the participants followed a standard eye-tracking calibration procedure, which consisted of fixating their gaze on nine points presented at random on the computer screen. The head was stabilized in a chin/head support. Figures 1 to 5 show the calibration and validation procedures and the procedure of eye tracker-assisted gaze fixation study. The participant was asked to fixate gaze on the immovable

Table 1. Clinical characteristics (age, refractive errors and visual acuity) of children in groups

Characteristic	EMMET (n = 19)	MYOP (n = 24)	NROPP (n = 37)	ROPLC (n = 23)	ROPRG (n = 26)	p
Age, years	8.5 (6.5– 12.5)	13 (10.0– 13.5)	8 (6.0– 9.0)	10.5 (8.5– 13.0)	12 (8.0– 13.0)	<0.001
UCVA OD	1 (0.875– 1.0)[2,4,5]	0.3 (0.11– 0.425)[1]	0.9 (0.8– 1.0)	0.65 (0.14– 0.9)[1]	0.6 (0.2– 0.813)[1]	<0.001
BCVA OD	1 (1.0– 1.0)	1 (1.0– 1.0)[4]	1 (1.0– 1.0)	0.8 (0.675– 1.0)[2]	1 (1.0– 1.0)	<0.001
UCVA OS	1 (0.9– 1.0)[2,5]	0.3 (0.185– 0.45)[14]	0.9 (0.7– 1.0)	0.9 (0.5– 1.0)[2]	0.6 (0.3– 0.850)[1]	<0.001
BCVA OS	1 (1.0– 1.0)	1 (1.0– 1.0)	1 (1.0– 1.0)	0.95 (0.8– 1.0)	1 (1.0– 1.0)	0.149
Refractive error (SE) OD, diopters	-0.25 (-0.25– 0.5)[2]	-1.875 (-3.25– -1.375)[1,4]	-0.125 (-0.75– 0.5)	-0.375 (-3.5– 0.5)[2]	-1.125 (-2.5– -0.25)	<0.001
Refractive error (SE) OS, diopters	-0.125 (-0.25– 0.375)[2]	-1.75 (-3.125– -1.125)[1]	-0.25 (-0.75– 0.75)	-0.625 (-4.0– 0.5)	-1 (-2.0– -0.125)	<0.001

Note. Data are presented as median (interquartille range). BCVA, best corrected visual acuity; EMMET, group of emmetropic children; MYOP, group of myopic children; NROPP, group of non-retinopathy of prematurity preterm children; OD, right eye; OS, left eye; ROP, retinopathy of prematurity; ROPLC, group of preterm children that have undergone laser photocoagulation; ROPRG, group of children with spontaneous ROP regression; SE, spherical equivalent. A one-way analysis of variance was used to compare normally distributed data among groups, followed by pairwise post hoc analysis with the Tukey-Cramer test. The Kruskal-Wallis test, followed by post hoc pairwise comparisons using Dunn's multiple comparison tests was used to compare data that were not normally distributed among groups. The superscript numbers indicate a significant difference, shown by post-hoc comparisons, versus EMMET ([1]), MYOP ([2]), NROPP ([3]), ROPLC ([4]), or ROPRG ([5]).

central stimulus (a 30-mm diameter round target placed against a neutral background) for 10 seconds. Eye movements were recorded using the EyeLink 1000 Plus® (SR Research Ltd., Ottawa, Canada) eye tracker at a 2000-Hz sampling rate. It has several mount combinations (e.g., Desktop Mount, Tower Mount and Long Range Mount), allowing experimenters to adapt it to specific requirements of a pediatric patient. The eye tracker provides spatial resolution of 0.01° of visual angle and average accuracy of 0.25°-0.50° of visual angle, which is important for the microdynamics of fixations and saccades.

The eye-tracking experiment was built in SR Research Experiment Builder (SR Research Ltd). This software has numerous preference settings to modify the parameters of stimulus presentation and data synchronization and recording. Stimulus material consisted of fixation dots that appeared in the center of the screen.

The following oculomotor parameters were assessed: average and median fixation durations, fixation counts, average and median saccade amplitudes, and saccade counts. Standard deviations of fixation duration and saccade amplitude and average pupil size were also analyzed.

Data analyses were performed using the EZR software (v. 1.68, Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R sta-

Рис. 1. Проведення учасником дослідження процесу калібрування айтрекеру в 9 точках.

Рис. 2. Процес валідації даних після проходження першого етапу калібрування.

Рис. 3. Демонстрація положення учасника дослідження під час калібрування з використанням підборідника та лобового фіксатора.

Рис. 4. Фіксаційна мішень під час проведення тесту на утримання погляду.

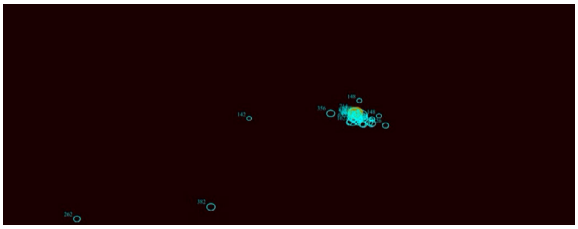

Рис. 5. Візуалізація фіксацій під час проведення тесту на утримання погляду (діаметр графічного маркера відповідає тривалості фіксацій), на фото дані пацієнта з групи 4 (РНЛК).

tistics (v. 4.3.1, R Foundation for Statistical Computing, Vienna, Austria) [13]. Mean and standard deviation (SD) were used to report normally distributed variables; median and IQR were used for non-normally distributed variables. A one-way analysis of variance was used to compare normally distributed data among groups, followed by pairwise post hoc analysis with the Tukey-Cramer test. The Kruskal-Wallis test, followed by post hoc pairwise comparisons using Dunn's multiple comparison tests was used to compare data that were not normally distributed among groups [14]. Spearman rank correlation analysis was performed to explore the association between quantitative variables. Evidence of a difference between the groups was determined via a two-sided critical region. Statistical significance was set at $P \leq 0.05$ for all analyses.

Results

The results and between-group comparisons are presented in Table 2.

Figures 6 and 7 show the distributions of average saccade amplitudes and mean pupil size, respectively, across study groups. Box plots show median values (middle bars), IQRs (boxes), and outliers, and dots are data points from individual participants.

Correlations between parameters

A correlation matrix was built, with correlation coefficients being calculated using Spearman's rank correlation test (Table 3). The table includes only the associations significantly different from zero ($p < 0.05$).

The correlation matrix (Table 3) analysis demonstrated that the closest associations were observed between the parameters structurally reflecting the same characteristic of eye-tracking data. Particularly, the fixation count was very strongly positively correlated with the saccade count ($r = 0.999$), and the minimum fixation duration was very strongly positively correlated with the fixation time ($r = 0.999$). There was also a strong correlation between the maximum fixation duration and the total number of registered samples ($r = 0.971$), as well as between the average saccade amplitude and the median saccade amplitude ($r = 0.799$).

Strong negative associations, however, point to the compensatory nature of the relationships among key parameters. Thus, the average fixation duration was negatively correlated with the saccade count ($r = –0.951$), which reflects the balance between the stability of gaze and the gaze shift frequency. A similar effect was observed between the total number of registered samples and the saccade count ($r = –0.864$), and between the fixation count and the standard deviation of fixation duration ($r = –0.857$).

Discussion

ROP is a serious vasoproliferative retinal disorder that may have late functional sequelae, even if treated early. LPC is an established treatment for severe ROP; it enables preserving the anatomy of the retina and preventing retinal detachment. Numerous studies, however, have demonstrated that children with ROP frequently develop visual and neurodevelopmental abnormalities, including oculomotor disorders and low fixation stability, irrespective of the treatment used [1, 15, 16, 17, 18, 19].

In the present study, eye tracking was used to examine eye micromovements during a static fixation task in 6 to 13-year-old children. This approach allows an objective assessment of fixation and saccade parameters which reflect the functional status of sensory motor vision control. Statistically significant between-groups differences were found only for two characteristics. There was a significant difference between children that had undergone LPC for ROP and full-term emmetropic controls in saccade amplitude ($2.72 \pm 1.63°$ versus $4.61 \pm 2.20°$, $p < 0.05$) and average pupil size (1269 (1009-1443) versus 1987 (1713-2325), $p < 0.05$).

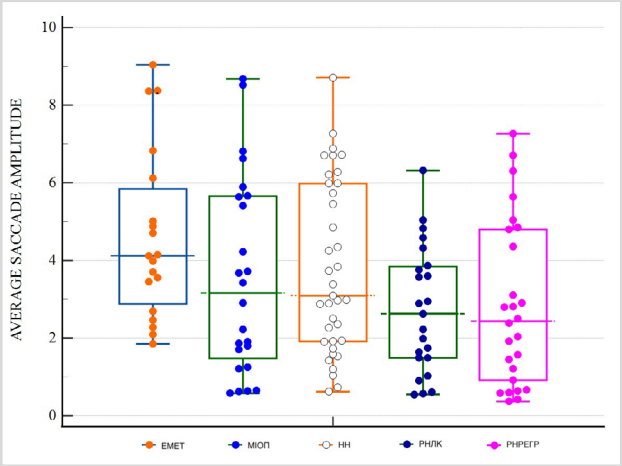

Рис. 6. Значення показника середньої амплітуди сакад в п'яти групах. Вказано медіану, міжквартильний інтервал, мінімальне та максимальне значення.

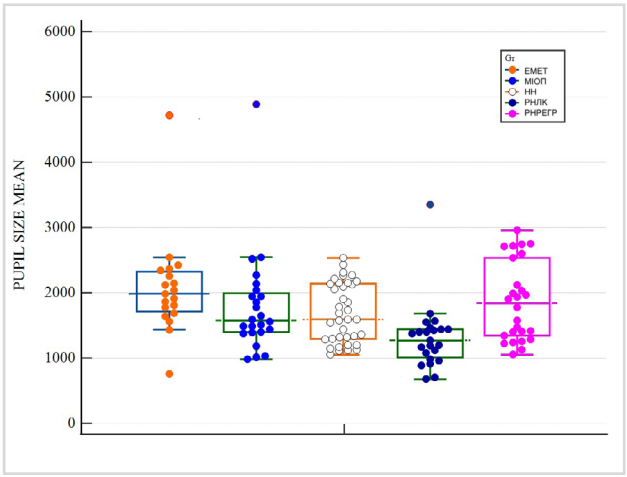

Рис. 7. Значення показника медіанного діаметра зіниці у п'яти групах. Вказано медіану, міжквартильний інтервал, мінімальне та максимальне значення.

Table 2. Characteristics and comparative analysis of eye micromovements for groups

Parameter	EMMET (n=19)	MYOP (n=24)	NROPP (n=37)	ROPLC (n=23)	ROPRG (n=26)	p
Average fixation duration (ms)	624.67 (525.18–885.29)	916.59 (647.05–1157.71)	784.71 (545.47–1249.44)	789.54 (573.10–1053.87)	804.43 (571.11–1216.22)	0.687
Average saccade amplitude (°)	4.61[4] ± 2.20	3.57 ± 2.54	3.80 ± 2.20	2.72[1] ± 1.63	2.84 ± 2.12	**0.030**
Blink counts	3 (1.25–5.50)	2 (1–3.50)	2 (1–5)	2 (2–5)	3 (1–4)	0.804
Fixation counts	15.53 ± 6.19	11.88 ± 5.68	14.89 ± 6.99	14.52 ± 5.78	14.38 ± 7.14	0.362
Maximum fixation duration (ms)	3028 (1838–4742.50)	3688 (2667–5143)	3144 (1686–4197)	2882 (1759.50–4472.50)	3106 (1746–5028)	0.670
Time point of maximum fixation duration (ms)	357647 (185786.25–638603)	188877 (140724–534825.50)	290545 (177868–445975.75)	324051 (199857.75–404830.25)	299507 (186187–453092)	0.539
Minimum fixation duration (ms)	72 (30.50–117)	136 (47–205)	104 (67–134.50)	96 (62–174.50)	97 (46–162)	0.331
Time point of minimum fixation duration (ms)	348325 (183797.75–642527.50)	183667 (139682–534758.50)	289651 (175313.50–441759.50)	322149 (198064.25–401139.25)	296656 (182605–447170)	0.536
Median fixation duration (ms)	366 (271–509)	426.50 (278–636.50)	372 (302.50–490.25)	518 (338.50–668.75)	386.50 (302–645)	0.471
Median saccade amplitude (°)	1.49 (0.98–3.08)	1.04 (0.61–2.27)	1.27 (0.86–2.50)	0.87 (0.64–1.62)	0.97 (0.59–1.56)	0.146
Average pupil size (conventional units)	1987.29[4] (1712.90–2325.07)	1576.23[4] (1396.76–1992.59)	1594.76 (1294.37–2139.71)	1268.55[1,2] (1008.98–1442.87)	1838.87 (1343.62–2537.41)	**<0.001**
Saccade count	14.68 ± 6.33	11.04 ± 5.71	14.19 ± 7.16	13.65 ± 5.80	13.46 ± 7.25	0.363
Standard deviation of fixation duration	781.06 (560.27–1034.16)	987.28 (788.01–1623.63)	904.79 (529.39–1345.65)	790.17 (546.62–1290.04)	867.23 (63.73–1403.07)	0.740
Standard deviation of saccade amplitude	4.88 (3.81–6.03)	3.73 (1.85–5.85)	3.89 (2.50–5.80)	3.12 (1.62–4.15)	3.34 (0.57–6.59)	0.089

Note: Normally distributed variables are presented as mean ± standard deviation, whereas non-normally distributed variables are reported as median (interquartile range). EMMET, group of emmetropic children; MYOP, group of myopic children; ms, milliseconds; n, number of patients; NROPP, group of non-retinopathy of prematurity preterm children; p, P-value; ROPLC, group of preterm children that have undergone laser photocoagulation; ROPRG, group of children with spontaneous ROP regression. A one-way analysis of variance was used to compare normally distributed data among groups, followed by pairwise post hoc analysis with the Tukey-Cramer test. The Kruskal-Wallis test, followed by post hoc pairwise comparisons using Dunn's multiple comparison test was used to compare data that were not normally distributed among groups. The superscript numbers indicate a significant difference, shown by post-hoc comparisons, versus EMMET ([1]), MYOP ([2]), NROPP ([3]), ROPLC ([4]), or ROPRG ([5]).

The most substantial changes in oculomotor parameters during a static fixation task were found in children that had undergone LPC for ROP. We, however, found no statistically significant differences compared to emmetropic controls in full-term myopic children, preterm children with no ROP or children with spontaneous ROP regression. This indicates that neither prematurity proper nor the presence of myopic refraction is definitely accompanied by abnormalities in the ocular motor parameters examined under conditions of a simple vision task. Taken together, these findings suggest that it is not myopia proper, but a combination of factors associated with unfavorable perinatal history, a severe ROP and the need for LPC has a key value in the development of the functional abnormalities found.

Table 3. Correlation matrix for parameters with statistically significant Spearman's rank correlation coefficients ($p < 0.05$)

Variable	Average fixation duration	Average saccade amplitude	Blink count	Fixation count	Maximum fixation duration	Time of maximum fixation duration	Minimum fixation duration	Time of minimum fixation duration	Median fixation duration	Median saccade amplitude	Average pupil size	Saccade count	Number of registered samples	Standard deviation of fixation duration	Standard deviation of saccade amplitude
Average fixation duration	-	-0.283	-0.625	-0.95	0.811	-	0.555	-	0.691	-	-	-0.951	-	0.903	-0.35
Average saccade amplitude	-0.283	-	-	0.243	-	-	-0.176	-	-0.521	0.799	-	0.239	-	-	0.927
Blink count	-0.625	-	-	0.596	-0.566	-	-0.559	-	-0.449	-	-	0.608	-	-0.592	0.229
Fixation count	-0.95	0.243	0.596	-	-0.76	-	-0.555	-	-0.629	-	-	0.999	-	-0.857	0.337
Maximum fixation duration	0.811	-	-0.566	-0.76	-	-	0.314	-	0.278	-	0.209	-0.77	-	0.971	-
Time of maximum fixation duration	-	-	-	-	-	-	-	0.999	-	-	-	-	0.194	-	-
Minimum fixation duration	0.555	-0.176	-0.559	-0.555	0.314	-	-	-	0.54	-0.224	-	-0.555	-	0.377	-0.23
Time of minimum fixation duration	-	-	-	-	-	0.999	-	-	-	-	-	-	0.187	-	-
Median fixation duration	0.691	-0.521	-0.449	-0.629	0.278	-	0.54	-	-	-0.436	-	-0.622	-	0.39	-0.535
Median saccade amplitude	-	0.799	-	-	-	-	-0.224	-	-0.436	-	-	-	-	-	0.629
Average pupil size	-	-	-	-	0.209	-	-	-	-	-	-	-	-	0.199	-
Saccade count	-0.951	0.239	0.608	0.999	-0.77	-	-0.555	-	-0.622	-	-	-	-	-0.864	0.333
Number of registered samples	-	-	-	-	-	0.194	-	0.187	-	-	-	-	-	-	-
Standard deviation of fixation duration	0.903	-	-0.592	-0.857	0.971	-	0.377	-	0.39	-	0.199	-0.864	-	-	-0.188
Standard deviation of saccade amplitude	-0.35	0.927	0.229	0.337	-	-	-0.23	-	-0.535	0.629	-	0.333	-	-0.188	-

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Small saccade amplitude found in children that had undergone LPC for ROP may reflect the features of the neural control of fixation and fixational eye movements, with this control involving particularly the superior colliculus [20]. Smaller values compared to controls (2.72 ± 1.63° versus 4.61 ± 2.20°) may be associated with an imbalance between fixation and saccade neurons, which reduces the efficacy of gaze switching. An additional mechanism may be insufficient signal integration in the nucleus raphe interpositus of the paramedian pontine reticular formation and cerebellum which are responsible for the accuracy and correction of saccadic movements [20, 21].

Lower median (IQR) values of the pupil size compared to controls (1269 (1009-1443) versus 1987 (1713-2325)) may be a consequence of changes in autonomic regulation, which are frequently seen in preterm children [22]. Visual brainstem structures (particularly, midbrain nuclei) are known to be involved in pupil control and the maintenance of visual fixation [23]. Therefore, the results obtained may reflect a combined effect of post-laser treatment local retinal changes and central control mechanisms on oculomotor activity, fixation stability and pupillary response.

There were no statistically significant differences between the groups in most parameters studied including average and median fixation durations, minimum and maximum fixation durations, fixation counts, saccade counts, and standard deviations of saccade duration and saccade amplitude. This may indicate a relative preservation of the major characteristics of fixational activity in children that have developed ROP. The absence of statistically significant changes, however, does not rule out the presence of more subtle abnormalities which may become apparent in more difficult tasks, including those with moving targets or increased cognitive loads.

Fixations are periods of time when gaze remains relatively stable on the object of interest, enabling a high spatiotemporal resolution of vision. Neurophysiologically, fixation is maintained by specific CNS structures. A key role in this process is played by the superior colliculus of the corpora quadrigemina, with the fixation neurons located in the rostral portion of the colliculus. These cells exhibit tonic activity during fixation and are inhibited during saccade initiation, enabling gaze switching [20].

The nucleus raphe interpositus of the paramedian pontine reticular formation integrates signals from the frontal and temporal eye fields, the superior colliculus and cerebellum, and also plays an important role in the process. The cerebellum (especially its vestibular portion and the flocculomodula cortex) controls correcting microsaccades and fixation stability during microscopic head movements [21].

Therefore, specific differences in saccade amplitude and pupil size may indicate a dysfunction of the integrated mechanisms that underlie fixation control and involve the oculomotor centers of the brainstem and cerebellum as well as autonomous visual pathway.

Atkinson and Braddick (2007) demonstrated that preterm delivery results in a cluster of deficits including visual spatial, visual motor and executive functions associated with dorsal stream dysfunction. Even in the absence of severe damage visible on magnetic resonance imaging (MRI), preterm delivered children showed worse results in attention and control tasks [24].

Our eye-tracking findings confirm similar relationships: small saccade amplitudes and small pupil sizes in children with ROP may reflect the vulnerability of the dorsal stream that provides the integration of spatial information with the control of targeted eye movements.

The association between immature brain structures and poorer eye movement performance in preterm born children indicates a possible involvement of oculomotor mechanisms in the formation of these changes. Shah and colleagues (2006) demonstrated that very low birth infants with impaired saccades, smooth pursuit, and binocular eye alignment at age 2 years had smaller occipital brain volumes at term equivalent, as measured by volumetric MRI than preterm infants without such abnormalities [30]. Thus, MRI data confirm that immaturity or structural changes in the central visual system may be associated with abnormal oculomotor control in preterm children [19–25, 30]. Therefore, eye tracking may be considered as a tool for assessing indirectly the functional status of the oculomotor system and a tool for predicting the late functional outcomes of preterm-born children.

Our findings are in line with the current view of ROP as a multifactorial condition that is not just an eye disease but involves a wider range of changes than local ophthalmic symptoms [20–28]. Eye tracking, when used in cohort studies of children with ROP, enables detecting the differences which cannot be always detected by customary ophthalmological techniques [29], which offers the potential for utilizing the methodology for monitoring late sequelae of ROP.

Therefore, LPC is a pathogenesis-based, required and vision-saving treatment for children with progressive ROP, but the very fact of having this procedure can be considered a high-risk marker of abnormal functional development of the visual system. Consequently, the children whose eyes have received laser photocoagulation for progressive ROP should have not only standard ophthalmological supervision, but also more vigilant multidisciplinary supervision including the assessment of the development of a healthy visual system and oculomotor and visual spatial functions, and timely checking the child's readiness for learning at school entry and other aspects of social adaptation.

Study limitations and prospects for future research

The present study has several limitations.

First, the study sample included only children aged 6 to 13 years, which prevents extrapolating the results to younger age groups.

Second, because there were significant between group differences in age, we cannot exclude completely the ef-

fect of age on oculomotor findings. The pattern of results, however, does not indicate that age was the major cause of the differences found, because only the group of children that had undergone LPC for ROP (but not other groups, particularly those including older children) showed statistically significant differences compared to emmetropic controls. Therefore, age should be considered as a potential factor that could influence the results.

Third, the participants of this study performed only a static fixation task, whereas more difficult tasks could be helpful in detecting additional features of oculomotor control.

We are going to conduct further research using dynamic fixation testing to enable the assessment of gaze shift strategies, fixational patterns, and accuracy of saccades in different directions. This would be helpful for better understanding of the mechanisms underlying late sequelae in the visual system in children with ROP and improve the prognostic value of eye tracking measures in this cohort.

Conclusion

During a static fixation test, average saccade amplitude was 1.7 times smaller (which corresponds to a reduction by 41.0%; $p < 0.05$) in the group of children that had undergone LPC for ROP compared to full-term emmetropic controls. Additionally, the median pupil size was 1.6 times smaller (which corresponds to a reduction by 36.1%; $p < 0.05$) in that group compared to controls. There were no statistically significant differences for other oculomotor parameters, which may indicate a relative preservation of basic characteristics of fixational activity in children that developed ROP. We, however, found no statistically significant differences compared to emmetropic controls in full-term myopic children, preterm children with no ROP or children with spontaneous ROP regression. The results obtained (1) indicate that it is in ROP children treated with laser that the most pronounced deficits in the oculomotor function are typical and (2) confirm the appropriateness of using eye tracking for the detection and further monitoring of these abnormalities.

Author Contributions

Artamonov OO – concept development, methodology, design, software; research, data collection, analysis and interpretation; manuscript preparation, writing, review; Katsan SV – concept development, methodology, design, analysis and interpretation of data; manuscript preparation, review. All authors read and approved the final version of the manuscript.

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Conflict of interest

The authors state that they have no conflict of interest that could influence their view on the subject matter or materials described and discussed in this manuscript.

Disclaimer

The opinions presented in this article are those of the authors and do not necessarily represent those of their institutions.

Ethical Statement

This study involved human subjects, was approved by the local bioethics committee, and followed ethical standards as outlined in the Declaration of Helsinki of the World Medical Association and the European Convention on Human Rights and Biomedicine, and relevant laws of Ukraine. Informed consent was obtained from all subjects or their representatives.

Data Availability Declaration

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Abbreviations

BCVA, best corrected visual acuity; EMMET, group of emmetropic children; LPC, retinal laser photocoagulation; NROPP, group of non-retinopathy of prematurity preterm children; OD, right eye; OS, left eye; ROP, retinopathy of prematurity; ROPLC, group of preterm children that have undergone LPC; ROPRG, group of children with spontaneous ROP regression; UCVA, uncorrected visual acuity.

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