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Metabolic Disorders Resulting From Rear Aggressive Retinopathy of Prematurely Born Babies.

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ABSTRACT

Subjects of the research were prematurely newborn babies with rear aggressive retinopathy and newborn babies with threshold retinopathy of II-III stages. The goal of the research is determination of the effect of acid-base blood composition and total antioxidant activity on development of rear aggressive retinopathy of prematurely born babies.

Keywords: rear aggressive retinopathy of prematurely born babies, acid-base balance, antioxidant activity parameters.

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INTRODUCTION

Since the Republic of Kazakhstan adopted international standards of L-test live birth on January 01, 2008 as recommended by the WHO (body weight starting from 500 g and gestational age – 22 weeks), sharp increase of retinopathy cases among prematurely born babies and thus number of babies blind from infancy should be expected.

Improvement of nursing method, development of intensive care and crisis care in perinatal medicine lead to significant increase of the survival rate among prematurely born babies, especially among those with extremely low body weight making 1.0-1.7% of the total number of prematurely born babies [1].

Fifteen millions of prematurely born babies come up every year, which is 8-10% of the total number of births. According to the WHO, 50,000 children all over the world become blind as a result of retinopathy. Retinopathy of prematurely boron babies is the main reason for blindness and hypovision among prematurely born babies and ranks first in the eye disability structure in economically developed countries.

According to the international classification, rear aggressive retinopathy of prematurely born babies is the most dangerous, fulminant and recalcitrant. This form of disease is characterized by rapidly progressive course, sudden vascular distention and tortuosity of amphiblestrodes in all quadrants of the eye-ground, localization of the process mainly in amphiblestrodes sections and absence of the process staging [2]. As a rule, rear aggressive retinopathy of prematurely born babies is revealed in a group of small prematurely newborns with heavy somatic condition [3].

The number of rear aggressive retinopathy cases among prematurely born babies, according to archive data, ranges from 7 to 24%, and the treatment efficiency is 45-72% [4,5,6].

According to results of the research of Kazakh Research Institute for Eye Disorders, the number of rear aggressive retinopathy cases among prematurely born babies for 2011 amounted to 6.06 % and increased by 2012 to 9.2 % .

Diagnostics and prescriptions for treatment of rear aggressive retinopathy of prematurely born babies are quite complicated [7, 8 and 9]. Diagnostics of the disorder is based mainly on instrument measurement methods (binocular ophthalmoscopy and digital retinoscopy). Identification of changes at the cellular level typical for rear aggressive retinopathy of prematurely born babies, which as a rule precede functional deviations. High disability rate among children with rear aggressive retinopathy stipulates the necessity to study metabolic disorders during births in order to justify correction and develop the treatment efficiency assessment criteria.

Archive materials contain individual publications on forecasting of development of rear aggressive retinopathy of prematurely born babies. Digital analysis of the retinal vessels condition allowed studying the peculiarities of formation of vascular disorders at early stages of rear aggressive retinopathy of prematurely born babies. Digital photo survey allowed revealing and systematizing diagnostics and forecast criteria of progression at early stages of the disorder [10].

There is a method for forecasting of development of rear aggressive retinopathy of prematurely born babies, which allows identifying baby's weight and gestational age by the time of birth. During the period of the second to the fourth weeks of life, Doppler survey of blood flow is carried out in the anterior cerebral artery in view of the resistibility index of the anterior cerebral artery. The resistibility index of the anterior cerebral artery exceeding 0.83 in at least two surveys, or one of the following signs: baby weight - 900 g or below, gestational age not exceeding 26 weeks by the time of birth are indicative of development of rear aggressive retinopathy of prematurely born babies [11].

It is established that there is direct correlation between thrombocytopenia and type 1 retinopathy of underborns in the first zone [12]. However, in archive materials there is no data on acid-base composition and parameters of total antioxidant activity of newborns with rear aggressive retinopathy of prematurely born babies.

Taking into consideration the abovementioned it perspective to study metabolic disorders of newborns with rear aggressive retinopathy.

Reference Materials and Applied Methods

Laboratory analyses, instrument measurements and statistical methods were used during the research.

Instrument measurements

- Indirect binocular ophthalmoscopy carried out in accordance with the standard procedure;
- Digital retinoscopy using *RetCam Shuttle* retinal pediatric system.

Laboratory analyses

- Identification of the acid-base balance parameters (pH, pCO2, pO2, BE).

Statistical methods

Calculation of obtained data was carried out using *SPSS Statistics* software. The criteria were used considering data distribution.

RESEARCH RESULTS

The following was found based on the performed research

- Clear relation between development of the rear aggressive retinopathy of prematurely born babies and fluctuations in blood gases (pO2) and (pCO2) $p \leq 0{,}001$.
- Respiratory alkalosis and hyperoxia are typical for babies with rear aggressive retinopathy during the neonatal period.
- Lactate values reflecting the level of tissue hypoxia made much difference in a group of babies with rear aggressive retinopathy. Each baby had significant fluctuations of lactate in blood and made up to 1.1 to 8.8 mM/l, averaging 2.6±1.9 mM/l. The comparison of lactate values among a group of babies with rear aggressive retinopathy, after a dispersion analysis, allowed identifying highly reliable discrepancies in lactate values ($F5 = 15.645$, $p \leq 0.001$).

Materials and methods of clinical instrument studies

Laboratory methods

Laboratory analyses included identification pH values in capillary blood using *ABL 800 Flex* device, partial gas pressure (pO2, pCO2), metabolites (Lac), deficient/ surplus bases (BE) throughout the period of artificial lung ventilation and oxygen therapy.

Procedure

For anesthetization's sake, newborns of postconception stage of over 30 weeks had 0.2-0.3 ml of 30% glucose solution administered in mouth 2 minutes before beginning of the procedure. Then 0.2-0.3 ml of 30% glucose solution was administered over again straight during the manipulation.

Scarificator injection follows preliminary warming up of the puncture point (for improvement of perfusion) and treating with antiseptic solution on the medial or lateral part of a heel at right angle towards of a sole. The first blood drop is removed by a sterile mop, next blood drops are collected avoiding air bubbles into a heparinized capillary tube, which is delivered to a lab [Roberts J.2004]. Provided correct carrying out of the procedure and safety of taking the capillary sample, the results shall correlate with the data acquired during arterial puncture. The highest compliance is with pH value (compared to the aerated blood pH below

0.02-0.05), moderate correlation for PaCO2 values (difference within the range of 1.3 millimeters of mercury to 7.5 millimeters of mercury) and the lowest one – PaO2, at an average, with the value lower in capillary blood by 24.2 millimeters of mercury.

This also included identification of the minimum and the maximum blood gas levels and their fluctuation levels. The total number of performed measurements is 190 (including 14 on premature newborns).

Clinical Study

Ophthalmological examination of premature newborns was carried out during 29 – 32 weeks of postconception stage in an intensive care unit for newborns and intensive care wards of the newborns pathology unit. The examination period was determined mainly by somatic Z-condition of babies. The examination frequency depended on the initial condition of amphiblestrodes and revealed signs of retinopathy of prematurely born babies. On the average, every child was examined two to eight times during stay in the newborns pathology unit.

Examination was carried out in conditions of the maximum mydriasis medicamentosus.

Binocular ophthalmoscopy of premature newborns was carried out in accordance with the standard practice.

Digital retinoscopy was carried out using *RetCam Shuttle* retinal pediatric system.

During examination of the eye ground of premature newborns, the condition of optic nerve head was taken into account (size, color, boundaries and form), as well as the vessel motion and size in the center and on the periphery. Once the first signs of retinopathy show up, the width and color of the avascular zone, presence of the demarcation line, axle, degree of proliferative modifications, local modifications of the macular zone and the area of papillomacular bundle were evaluated. The evaluation of the amphiblestrodes condition was carried out in accordance with the generally accepted international classification of retinopathy of prematurely born babies (1984) with amendments introduced in 2005, which provides separate consideration of the rear aggressive retinopathy of prematurely born babies and pre- 'plus' disease.

Statistical Methods

Descriptive statistics for the studied acid-base balance values among premature newborns was carried out in a group of children with rear aggressive retinopathy of prematurely born babies (inclusion criteria) and retinopathy of prematurely born babies II-III of the threshold stage (exclusion criteria). This included carrying out of acid-base balance values acquired during the examination using standard values among the both teams. The calculation was carried out using *IBM SPSS Statistics* software. The criteria were used with consideration of the data distribution.

RESULTS AND DISCUSSION

Data on the acid-base balance values of the blood composition of eight premature newborns with rear aggressive retinopathy and six premature newborns with threshold retinopathy of II-III stages was analyzed.

The examination revealed a number of factors making for development of rear aggressive retinopathy of prematurely born babies.

Comparison of the acid-base balance values (pH, pO2, pCO2) in the group with rare aggressive retinopathy of premature newborns and threshold retinopathy of II-III stages acquired during the research with standard values revealed significant violations (Table 1, 2 and 3).

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Table 1 – Comparison of pH values with standards values among newborns with rear aggressive retinopathy and threshold retinopathy of prematurely born babies of II-III stages

One-sample t-test						
	pH = 7.4 (standard)					
	t	Column of mercury	Significance (2-side)	Mean difference	95% confidence interval of mean difference	
					Lower boundary	Upper boundary
pH - Rear aggressive retinopathy	-4,913	147	,000	-,03649	-,0512	-,0218
pH - Threshold retinopathy	-2,182	47	,034	-,02521	-,0485	-,0020

Table 1 shows that pH values of children with rear aggressive retinopathy are reliably much different from the average standard value ($t = -4.913$, $df = 147$, $p \leq 0.001$). Newborns with threshold retinopathy have pH values reliably different from the average standard values ($t = -2.182$, $df = 47$, $p = 0.034$).

Table 2 – Comparison of pCO2 value with standard values among newborns with rear aggressive retinopathy and threshold retinopathy of prematurely born babies of II-III stages

One-sample t-test						
	Examined value = 40					
	t	Column of mercury	Significance (2-side)	Mean difference	95% confidence interval of mean difference	
					Lower boundary	Upper boundary
pCO2 - Rear aggressive retinopathy	-1,447	147	,150	-1,4770	-3,494	,540
pCO2 - Threshold retinopathy	-3,210	47	,002	-4,5437	-7,391	-1,696

Interpretation of obtained data of newborns with rear aggressive retinopathy shows that pCO2 values do not have statistically significant differences with average standard value ($t = -1.447$, $df = 147$, $p = 0.150$). While newborns with threshold retinopathy the pCO2 values are reliably different from the average standard value ($t = -3.210$, $df = 47$, $p = 0.002$).

Table 3 – Comparison of pCO2 values with standard values among newborns with rear aggressive retinopathy and threshold retinopathy of prematurely born babies of II-III stages

One-sample t-test						
	Examined value = 45					
	t	Column of mercury	Significance (2-side)	Mean difference	95% confidence interval of mean difference	
					Lower boundary	Upper boundary
pCO2 - Rear aggressive retinopathy	6,492	147	,000	14,1250	9,825	18,425
pCO2 - Threshold retinopathy	2,589	47	,013	8,9750	2,000	15,950

Interpretation of obtained data of newborns with rear aggressive retinopathy shows that pCO2 values are reliably much different from the average standard value ($t = 6.492$, $df = 147$, $p \leq 0.001$). Newborns with threshold retinopathy the pCO2 values are reliably different from the average standard value ($t = 2.589$, $df = 47$, $p = 0.013$).

Comparative evaluation of the acid-base balance values among the groups revealed that average values of compensated metabolic and/ or respiratory acidosis prevailed in the group of newborns with threshold retinopathy – pH 7.37, pCO2 35 millimeters of mercury, BE -5.28 mM/l, decompensated respiratory alkalosis was recorded in the average values in the blood plasm of newborns – pH 7.48, pCO2 37.6 millimeters of mercury, BE -4.98 mM/ l.

Newborns with rear aggressive retinopathy had hyperoxia; average pO2 value of the group amounted to 64.9 millimeters of mercury; among newborns with threshold retinopathy of II-III stages, normal oxygen conditions prevailed – average PO2 values amounted to 53.9 millimeters of mercury ($p \leq 0.001$). Fluctuations in pO2 values in the group of threshold retinopathy were not recorded; pO2 values made up to 196 millimeters of mercury only once. Newborns with rear aggressive retinopathy had the highest pO2 values - 218 millimeters of mercury and the lowest pO2 values – 32.1 millimeters of mercury during the respiratory support. So, the fluctuation range of the partial oxygen pressure in blood of such prematurely born babies was the highest. Newborns with rear aggressive retinopathy had this value averaging 185.9 millimeters of mercury, newborns with threshold retinopathy – 49.5 millimeters of mercury ($p = 0.050$).

Average pCO2 values of newborns with rear aggressive retinopathy amounted to 37.6 millimeters of mercury, newborns with retinopathy of II stage – 35 millimeters of mercury. Reliable difference in pCO2 values were revealed ($t = 2.028$, $df = 47$, $p = 0.048$). Newborns with rear aggressive retinopathy had the highest pCO2 values - 85 millimeters of mercury and the lowest pCO2 values – 11.4 millimeters of mercury during the respiratory support. With regard to fluctuations of values similar situation with pO2 was observed: the range of fluctuations of partial pressure of carbon dioxide in the first group amounted to 73.6 millimeters of mercury and was higher than that in the group with threshold retinopathy of prematurely born babies, where pCO2 value amounted to 43.4 millimeters of mercury.

Lactate values reflecting the degree of tissue hypoxia had significant difference in the group of children with rear aggressive retinopathy. Each child had significant fluctuations in lactate in blood and ranged from 1.1 to 8.8 mM/ l averaging 2.6±1.9 mM/ l. Comparing lactate values inside the group among children with rear aggressive retinopathy, during the dispersion analysis, revealed highly reliable discrepancies in lactate values ($F5 = 15.645$, $p \leq 0.001$). However comparison of lactate values of children with threshold retinopathy, during the dispersion analysis, did not reveal significant discrepancies in lactate values ($F5 = 0.297$, $p = 0.909$), neither discrepancies were revealed in the group with threshold retinopathy ($F5 = 0.297$, $p = 0.909$).

So, it can be assumed that the acquired data is indicative of the vital role of increase of lactate content in development of rear aggressive retinopathy.

Results of the Ophthalmological Examination

Rear aggressive retinopathy of prematurely born babies was found on 16 eyes of eight babies during the initial ophthalmological examination. The peculiarity of this form of disorder was characterized by the fact, that the pathological process proceeded symmetrically on both eyes in all cases. The postconception stage for the date of the examination averaged 30±1.67 weeks.

Distinguishing features of this form of disorder are:

- Eye pupil rigidity on mydriatics;
- Expressed constriction of amphiblestrodes arterial vessels;
- Expressed ischemic edema of amphiblestrodes with distinctive blanching of the peripapillary zone.

Central vessels are deeply expanded and coiled. Deep expansion and tortuosity of vessels was recorded in all four quadrant of the eye ground. Throughout the circuit there is numerous presence of arteriovenous shunts. In all cases at the boundary of the forepart of the first and/ or the second zone there are exudative and proliferative elements at the boundary of the avascular zone, first of all in nasal quadrant of the eye ground. Wide avascular zone with no formation of the demarcation line in temple quadrant. During next examinations, the dynamics of vascularization of the vascularization amphiblestrodes remained at the same level, as well as deeply coiled arteria and expanded veins in the central zone of the rear pole of the eye

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ground, which ended up into corkscrew coiled arteria - venous shunts. Wide avascular zone was limited by protruding axle with expressed massive extrarenal fibrovascular proliferation of muddy-gray color with numerous preretinal bloodstrokes of different degree (Figures 1 and 2).

Figure 1 – Ophthalmological picture of a baby with rear aggressive retinopathy

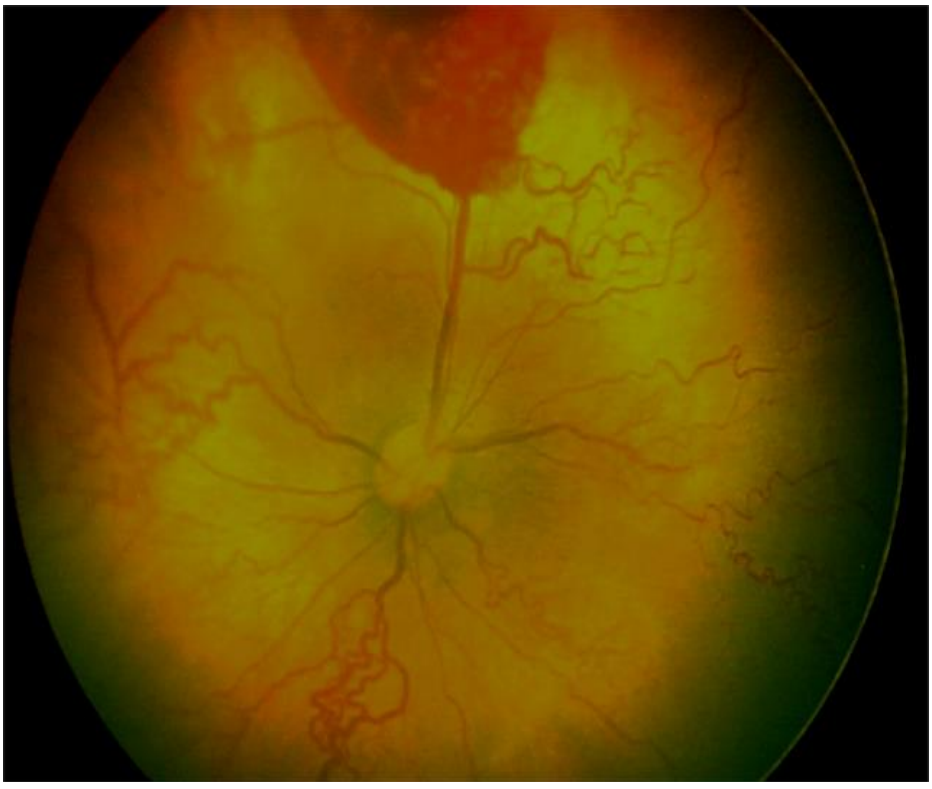

Figure 2 - Ophthalmological picture of a baby with rear aggressive retinopathy

During the ophthalmological examination of children with threshold retinopathy of prematurely newborns of II-III stages, the monitoring was carried out until the necessity in laser treatment. The number and

frequency of the ophthalmological examinations depended in the condition of the eye ground – presence of immature vascularization of amphiblestrodes or signs of retinopathy of prematurely born babies of different severity degrees.

The following was revealed as a result of dynamic monitoring in all cases:

- demarcation axle with following formation of a crest of vivid pink color and extraretinal proliferation;
- coiled vascular collaterals beyond the demarcation axle;
- retinal hemorrhage of different degree was found in the shunt area in 78% of cases;
- presence of ischemic avascular zones beyond the demarcation axle;
- duration of the pathological process was 6 to 9 hour meridians.

All children in both groups passed transpupillary laser coagulation of avascular zones of amphiblestrodes. The volume of laser coagulation of avascular zones of amphiblestrodes depended on the severity of the clinical retinopathy process of prematurely born babies. The number of coagulate depended on the length of an axle and width of the avascular zone and amounted to 119 to 1,569 averaging 529.48±376. Direct dependence between the length of the demarcation axle with extraretinal proliferation and the number of coagulates (Mann-Whitney test, $z = 4.433$, $p < 0.01$, $T = 78$) were revealed.

Case monitoring following lasercoagulation of amphiblestrodes was carried out on the 7-14 and 30th day. The case monitoring revealed treatment efficiency indicators by the 7th day after the laser coagulation of amphiblestrodes:

- decrease of the vascular activity in the rear pole of the eye;
- disappearance of tortuosity; normalization of the calibre retinal vessel and the initial regress of arteriovenous shunts;
- the continuing growth of retinal vessel in the laser concretion zone (former avascular zone);
- by the 14th day – dispersion and disappearance of retinal hemorrhage, initial applanation of the demarcation axle and change in its color into grayish.
- by the 30th day – disappearance of the axle, complete regress of the extraretinal vasoproliferation.

Regress of the retinopathy disorder among newborns amounted to 93.5%, with aggressive forms of the disorder – 83%.

DISCUSSION

The performed examination revealed clear relation between development of the rear aggressive retinopathy of prematurely born babies and high concentrations of additional oxygen, as well as fluctuations in blood gas values. During the respiratory support, significant difference of oxygen and carbon dioxide partial pressure levels was recorded in blood of prematurely born babies. Children with rear aggressive retinopathy are characterized by the condition of respiratory alkalosis and hyperoxia, which is indicative of the leading role in formation of the disorder. Because rear aggressive retinopathy of prematurely born babies is an integral part of the prematurity symptom group, the level of pathological changes on the eye ground of prematurely born babies directly proportional to the severity of their somatic Z-condition.

CONCLUSIONS

1. There is clear relation between development of the rear aggressive retinopathy of prematurely born babies and fluctuations in blood gas values (pO_2) and (pCO_2) $p \leq 0{,}001$;
2. Newborns with rear aggressive retinopathy are characterized with the condition of respiratory alkalosis and hyperoxia during the birth period;
3. Lactate values in blood of children with rear aggressive retinopathy have significant fluctuations; the dispersion analysis reveals highly reliable discrepancies in the lactate values ($p \leq 0.001$);

4. The ophthalmoscopic image shows that during the performed monitoring of the rear aggressive retinopathy of prematurely born babies there are exudative-proliferative element revealed in all cases at the boundary of the forepart of the first and/ or the second zone.

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