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Relationship of Fibroblast Growth Factor 23 With Retinopathy of Prematurity Severity in Preterm Infants

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Abstract: Relevance. Retinopathy of prematurity (ROP) is among the primary causes of childhood blindness, particularly in countries with well-developed neonatal care systems. Emerging evidence points to the importance of hormonal regulators in angiogenesis, including fibroblast growth factor 23 (FGF23). However, its role in the pathogenesis of ROP remains poorly understood. Objective. To evaluate the association between serum FGF23 levels in the early neonatal period and the severity of ROP in infants born at a gestational age of less than 32 weeks. Materials and Methods. This study involved 38 preterm infants: 18 with confirmed ROP (main group) and 20 without signs of ROP (control group). All participants underwent ophthalmological assessment according to the ICROP-3 (2021) and ETROP classification systems. Serum FGF23 levels were measured by chemiluminescent immunoassay (CLIA) from umbilical cord blood collected immediately after birth. Results. The mean serum FGF23 concentration was significantly higher in the ROP group compared to controls (p<0б001). A strong positive correlation was identified between FGF23 levels and ROP severity (r=0б71). Elevated FGF23 levels may contribute to the pathophysiology of ROP in preterm infants and could serve as a potential early biomarker for identifying those at risk of developing severe disease.

Keywords: Retinopathy of prematurity, fibroblast growth factor 23 (FGF23), retinal angiogenesis.

Introduction: Retinopathy of prematurity (ROP) remains one of the leading causes of childhood blindness, particularly in the context of increasing survival rates among extremely premature infants [1,2]. According to WHO data, in countries with advanced neonatal care, the incidence of ROP among newborns with extremely low birth weight reaches up to 60%, while among infants with a gestational age of less than 28 weeks, the frequency of severe forms of the disease may exceed 30% [3,4,5]. Despite advances in early diagnosis and surgical treatment, the pathogenesis of ROP remains incompletely understood. Of particular interest are humoral mechanisms of angiogenesis, disturbances of which may play a key role in the development and progression of the disease.

One such mechanism involves the participation of hormones and growth factors, including VEGF, IGF-1, and the less studied FGF23 — fibroblast growth factor 23 — which regulates phosphate–calcium metabolism and vitamin D metabolism [6,7,8]. Given that phosphate and vitamin D deficiencies are common in extremely premature infants, investigating the role of FGF23 in the context of retinal angiogenesis is of particular importance. At present, there is a lack of data on the effect of FGF23 on the development of ROP,

which limits its potential clinical application as a biomarker.

Aim of the study. To assess the relationship between early neonatal FGF23 levels and the severity of retinopathy of prematurity in infants.

METHODS

The study included 38 preterm infants who were under inpatient observation in the Department of Premature Infant Care at the Republican Perinatal Center.

Inclusion criteria for the main group: gestational age <32 weeks; birth weight <1500 g.

Exclusion criteria: congenital malformations of the eyes or central nervous system; severe infections or sepsis; neonatal seizure syndromes; infants receiving systemic therapy with growth hormone or insulin; presence of significant somatic conditions affecting cytokine synthesis, such as FGF23 (e.g., pituitary insufficiency, Prader–Willi syndrome, etc.).

Based on the selection criteria, 18 preterm infants (36 eyes) with diagnosed ROP confirmed by ophthalmological examination were included in the main group. The mean gestational age in this group was 26.4 ± 1.8 weeks. The control group consisted of 20 preterm infants without signs of ROP during follow-up, matched for birth weight and gestational age.

Ophthalmologic assessment was carried out according to the International Classification of Retinopathy of Prematurity (ICROP-3, 2021) and additionally according to the ETROP criteria to determine indications for treatment. Each eye was evaluated separately.

Ophthalmic examination was performed by retinal inspection under pharmacological mydriasis using indirect ophthalmoscopy.

Serum FGF23 levels were determined by immunochemiluminescence assay (ICLA) using commercially available kits validated for neonatal use. Blood samples were collected from the umbilical cord immediately after birth. Measurements targeted the intact form of FGF23 (iFGF23), as this biologically active form regulates phosphate metabolism and active vitamin D production.

Clinical and anamnestic data included gestational age, birth weight, duration of oxygen therapy, feeding type, and presence of comorbid complications.

Data processing was performed using Statistica 10.0 software. Descriptive statistics were expressed as means (M) and standard deviations (SD). Differences between two groups were analyzed using the Student's t-test. Correlation analysis between FGF23 levels and ROP stage was performed using Pearson's correlation coefficient (r). A p-value of <0.05 was considered statistically significant.

RESULTS

Table 1 presents the distribution of retinopathy of prematurity (ROP) severity according to the ICROP-3 (2021) and ETROP classifications, analyzed per eye (n=36). The majority of cases were stage 2 and stage 3 (33,3% each), with a considerable proportion of aggressive ROP (16,7%). Zone II was the most frequently affected region (55,6%), and plus disease was observed in 61,1% of eyes.

Half of the eyes (50,0%) were classified as type 1 ROP, requiring active treatment. The mean gestational age of infants in the main group was 26,4±1,8 weeks.

Table 1. Distribution of ROP severity (ICROP-3, 2021 and ETROP) per eye (n=36) and gestational age.

Показатель	*n*	*%*
Stage 1	6	16,7
Stage 2	12	33,3
Stage 3	12	33,3
Aggressive ROP	6	16,7
Zone I	10	27,8
Zone II	20	55,6
Zone III	6	16,7
Plus disease	22	61,1
Type 1 (ETROP, requires treatment)	18	50,0
Type 2 (observation)	12	33,3
Regressing form / Stage 1	6	16,7
Mean gestational age, weeks (M±SD)	26,4±1,8	

Table 2. Mean FGF23 levels in the study groups.

Group	Mean FGF23 level (pg/mL) (M±SD)	p	*Reference values of FGF23 for newborns vary; however,*

Main group (n=18)	54,8±12,6	<0,001	*levels above 45–50 pg/mL are considered elevated.*
Control group (n=20)	33,1±9,4		

Table 2 presents FGF23 levels in preterm infants with and without retinopathy of prematurity (ROP). The mean FGF23 level in the main group was significantly higher compared with the control group (p<0,01). This finding may indicate the involvement of FGF23 in pathological angiogenesis or as a response to disturbances in phosphate metabolism in preterm infants.

Analysis revealed a positive correlation between FGF23 levels and the severity of ROP (r = +0,71, p<0,01), suggesting a potential compensatory or pathophysiological role of FGF23 in response to hypophosphatemia or altered vitamin D metabolism (Fig. 1).

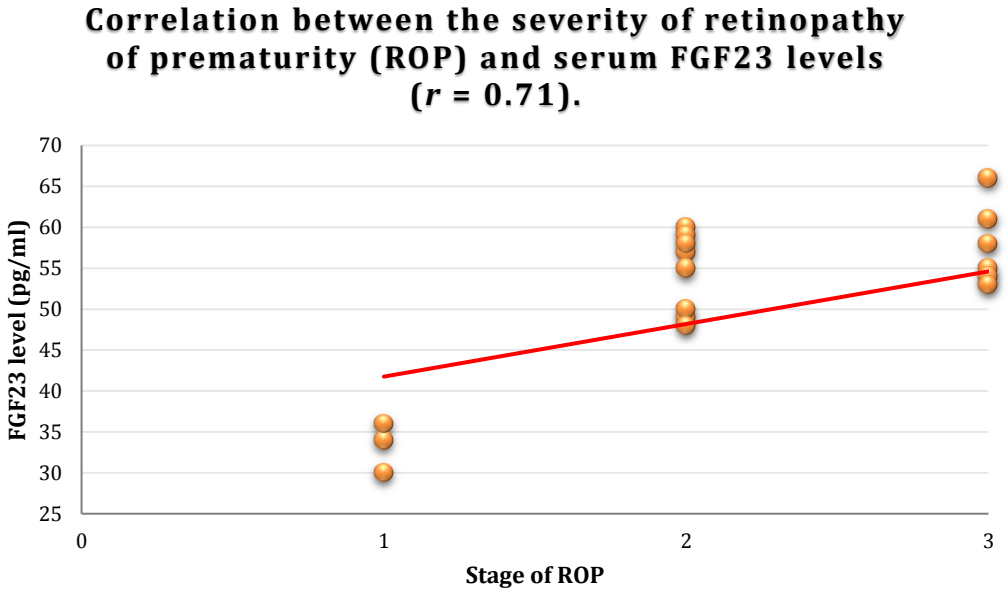

Figure 1. Correlation between the severity of retinopathy of prematurity (ROP) and serum FGF23 levels.

DISCUSSION

The present study demonstrated a statistically significant increase in FGF23 levels in newborns with retinopathy of prematurity (ROP) compared with the control group (p<0,001). This finding suggests a potential involvement of FGF23 in the pathogenesis of ROP, possibly through disruption of phosphate homeostasis and reduced vitamin D activity, both of which are critical for normal retinal angiogenesis. Since FGF23 is synthesized in response to hypophosphatemia, its elevation may represent a compensatory reaction to phosphorus deficiency, thereby exacerbating the imbalance of angiogenic signaling [2,6].

The positive correlation observed between FGF23 levels and ROP severity (r=0,71) supports the hypothesis of the pathophysiological significance of this biomarker. In infants with more advanced stages of the disease, FGF23 levels were higher, which may indicate its direct or indirect contribution to the progression of pathological angiogenesis. Unlike IGF-1, which exerts pro-angiogenic and protective effects, FGF23 is likely to influence angiogenesis indirectly - via systemic effects on mineral metabolism and regulation of active vitamin D metabolite synthesis.

CONCLUSION

A statistically significant positive correlation between FGF23 levels and the severity of retinopathy of prematurity was identified, suggesting that disturbances in phosphate metabolism and vitamin D regulation may contribute to disease pathogenesis. FGF23 may be considered a potential biomarker for the risk of ROP progression; however, confirmation in larger prospective studies is required.

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