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Insulin-like Growth Factor I (IGF-I) as a Predictive Factor of Retinopathy of Prematurity

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Abstract
Purpose: *To establish the reliability of insulin-like growth factor 1 (IGF-1) as a prognostic factor for the onset and progression of retinopathy of prematurity (ROP).*
Patients and Methods: *We examined 51 preterm infants with a birth weight ≤ 1500 g. and gestational age ≤ 32 g.w. Two samples of venous blood were taken for IGF-1 testing - the first sample: at birth and the second sample - two weeks thereafter. We used a radioimmunoassay test to detect serum levels of IGF-1 (nmol / l). Screening examinations for ROPwere performed with binocular indirect ophthalmoscopy and were documented with RetCam imaging system.*
Results: *51 prematurely born babies were included, 42 (82.4%) did not develop signs of ROP, and the remaining 9 children (17.6%) were observed with – ROP grade I (5 children) and ROP grade II (4 children). All cases with ROP showed a spontaneous regression without the need for treatment. The children were divided into two groups - without ROP and with signs of ROP. We did not detect a statistically significant decrease in IGF-1 serum levels in children with ROP in comparison to those who did not develop signs of the disease.*
Conclusion: *Blood IGF-1 levels were not found to be significantly differentbetween premature infants with ROP and those without, and we have not proven the reliability of IGF-1 as a prognostic factor for the onset and progression of ROP.*
Keywords**:** *insulin-like growth factor 1 (IGF-1), preterm infants, retinopathy of prematurity (ROP).*

I. Introduction

Retinopathy of prematurity (ROP) is a postnatal disorder ofretinal vessels that develops in the incompletely vascularized retina of preterm infants [1]. Although thisdisorder regresses in most patients, it can lead to severe visualimpairment. Developing countries, countries from Eastern Europe, South America, India and China are now victims of the third ROP epidemic. Thanks to the advances in neonatology and perinatal medicine in these countries, more and more premature infants, born with very low and extremely low birth weight survive. This in turn leads to a significant increase in the number of children with vision – threatening ROP. ROP is the main cause of childhood blindness in Bulgaria, Eastern Europe, nevertheless our ROP screening and treatment guidelines [2]. Therefore, methods of early diagnosis and timely treatment of this disease are sought.

Some models are based upon ground-breaking work by Smith, Hellstrom,Lofqvist, and colleagues, who have provided our current understanding of thepathophysiology underlying ROP.ROP develops in two phases, a hypoxic preclinical phase, during which slow postnatalgrowth can be used to predict risk, and a subsequent proliferative clinical phase. Thesephases result from alterations in serum insulin-like growth factor 1 (IGF-1), a somaticgrowth factor, and retinal vascular endothelial growth factor (VEGF), a hypoxia-inducedvasoproliferative factor necessary for normal retinal vascular development [3]. Serum IGF-1falls with premature birth from loss of maternal sources and poor endogenousproduction [4,5,6,7]. Importantly, IGF-1 plays a permissive role in VEGF-induced retinalvascular growth [8,9]. Therefore, low serum IGF-1 hinders retinal vessel development, withlocalized hypoxia and VEGF accumulation, as metabolic demands increase within thedeveloping retina. With increasing age and size, endogenous production of IGF-1 rises,permitting VEGF activity, and proliferative retinopathy develops.A lot of laboratory work supports this model [3,8,9,10,11,12]. Clinically, multiple investigators havedemonstrated that both prolonged early IGF-1 deficits and slow postnatal weight gain areassociated with a higher risk of subsequent severe ROP [4,13,14,15,16,17,18,19,20,21].

Purpose
To establish the reliability of insulin-like growth factor 1 (IGF-1) as a prognostic factor for the onset and progression of ROP, according to understandings that early IGF-1 deficitisassociated with a higher risk of subsequent severe ROP[4,13,14,15,16,17,18,19,20,21].

II. Patients And Methods

We examined 51 preterm infants with a birth weight ≤ 1500 g. and gestational age ≤ 32 gestational weeks (g.w.), treated in Neonatology Clinic, University Hospital „Maichindom", Sofia, Bulgaria (neonatal intensive unit in the capital of Bulgaria – Sofia). Two samples of venous blood were taken for IGF-1 testing (serum levels) - the first sample: at birth and the second sample - two weeks thereafter. We used a radioimmunoassay test to detect serum levels of IGF-1 (nmol / l), performed in Radioimmunoassay Laboratory, University Hospital "Akad. Ivan Penchev", Sofia, Bulgaria. Screening examinations for ROP were performed with binocular indirect ophthalmoscopy by ophthalmologists and were documented in Eye Clinic, University Hospital "Alexandrovska", Bulgaria.Examination of the retina was performed after pupil dilation with mydriatic combination of Phenylephrine 2,5% and Cyclopentolate 0,5%, the application of local anesthesia (0,5% Proxymetacaine Hydrochloride) and eye speculum. Retinal changes were documented with RetCam imaging system (Clarity Medical systems Inc., Pleasanton, CA, USA).

III. Results

51 prematurely born babies were included: 34 boys (66.7%) and 17 girls (33.3%). 42 infants (82.4%) did not develop signs of ROP, and the remaining 9 children (17.6%) were observed with – ROP grade I (5 children) and ROP grade II (4 children). All cases with ROP showed a spontaneous regression without the need for treatment. The children were divided into two groups - without ROP and with signs of ROP – TABLE 1.

TABLE 1. Serum levels of IGF-1 (two samples) and distribution by groups.

ROP	IGF-1	FIRST SAMPLE		SECOND SAMPLE	
		N	%	N	%
NO (WITHOUT ROP)	Extreme low value	13	31,0	16	38,1
	1-2,99	16	38,1	15	35,7
	3-5,99	7	16,7	9	21,4
	≥6	6	14,3	2	4,8
	Total	42	100,0	42	100,0
YES (WITH ROP)	Extreme low value	2	22,2	2	22,2
	1-2,99	2	22,2	4	44,4
	3-5,99	4	44,4	1	11,1
	≥6	1	11,1	2	22,2
	Total	9	100,0	9	100,0

To compare the two groups, we used a Wilcoxon Signed Ranks Test - comparing two dependent groups (repeated measurements). In its performance, we did not detect a statistically significant decrease in serum levels of IGF-1 in children who developed ROP, compared to those who did not develop signs of the disease – TABLE 2.

TABLE 2. Results ofWilcoxon Signed Ranks Test

ROP	N	FIRST SAMPLE vs SECOND SAMPLE	
		Z	p
NO	**42**	**-0,967**	**0,333**
YES	**9**	**-0,289**	**0,773**

IV. Discussion

ROP is an important cause of blindness in both developedand developing countries [22]. World Health Organization'sVISION 2020 programme delineates ROP as a preventabledisease that requires early detection and treatment to preventblindness and reduce inherent costs to the individual and community [23]. For this reason are created models for early prediction of ROP. These models are based on the pathogenesis of ROP-inhibition of vascularization in the early phase of ROP has been attributedto the hypoxic suppression of VEGF. A lack of IGF-1 in thisphase of ROP may also prevent normal retinal vascular growth.In phase II of ROP, pathologic vascular proliferation appearsto be associated with rising levels of VEGF and IGF-1 inducedby

hypoxia [4,5,6,7,8,9].Elevated VEGF and reduced IGF-1 levelswere reported in infants with ROP, though the severity of ROP was not specified [19].Hellström et al. [4] conducted a studymeasuring serum IGF-1 levels weekly and showed that lowserum IGF-1 levels correlated with later development ofROP. Hellström et al. also concluded that the mean IGF-1level at postmenstrual weeks 30 to 33 is a predictive factorof ROP, which is as important as the degree of prematurity [4].In 2006, Löfqvist et al. reported that the weight gain, weekly measured IGF-1 and IGF-binding protein 3 (IGFBP3) levels in serum of premature infants, were an early and reliable prognostic marker for ROP [13], and in 2009 they validated the method - the WINROP algorithm for the identification of premature babies in risk [14]. The proposed WINROP screening algorithm has a very high specificity in identifying high-risk infants for the development of ROP, as resultshave been shown in many studies [15,24,25,26,27,28,29,30]. This has led to the launch of the PREVENT-ROP study, which aims to establish the safety of the use of recombinant human IGF-1 (rhIGF-1) in the treatment of ROP [31].In another study, Peirovifar et al. [32] examined 71 preterm infants < 32 g.w. and theirdata demonstrated that at 6–8 weeksafter birth, the blood levels of IGF-1 and VEGF were notsignificantly different between premature infants withproliferative ROP and those without. In our study, the results are the same as theirs.The explanation of our negative results can be found in the fact that in our cohort, children showing signs of ROP have mild degrees – ROP Grade I and ROP Grade II - not needed treatment; unlike the mentioned studies of Hellström et al. [4] and Löfqvist et al. [13,14].

V. Conclusion

Serum levels of IGF-1 were not found to be significantly different between premature infants with ROP and those without, and we have not proven the reliability of IGF-1 as a prognostic factor for the onset and progression of ROP. It is necessary to carry out a larger study assessing the role of IGF-1 as a prognostic factor for the development and progression of ROPin Bulgaria, because advances in neonatal and perinatal medicine creates conditions for increased survivability of a growing number of children born prematurely.This determines the increasing number of children who are at risk of developing ROP and related early and late visual impairment and blindness. Widespread introduction of mandatory screening programs and conducting timely and effective treatment of ROP are key elements in reducing cases of preventable childhood blindness worldwide.

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