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Genetic Peculiarities of Blood Group Distribution in Infants Born to Mothers With 0(I) Rh(+) Blood Group in Bukovyna Region

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Abstract

The article presents the analysis of distribution of the group (according to AB0 system) and rhesus characteristics (according to anti-D system) in infants born to mothers with 0(I) Rh(+) blood group in Chernivtsi region (Ukraine) during the period of 2013-2014. The relationship of the umbilical bilirubin level and hemolytic disease of the newborn (HDN) (erythroblastosis fetalis), the necessity of its careful monitoring during the first day of life of a newborn, especially in case a baby belongs to a certain risk group, has been analyzed. The issue concerning probable HDN occurrence from mothers with A(II) Rh(+) blood group which is dominant in this region has been touched upon. The tasks for further work in this direction of ecopathophysiology in the areas of gene penetration have been assigned.

Keywords: hemolytic disease of the newborn (HDN), jaundice form, blood group system: AB0 and Rh-factor, bilirubin concentration, alloimmunization, gene penetration.

Introduction

«Alloimmunization with erythrocyte antigens is a global population problem» depending on many factors, and gene geographic region first of all [1]. According to the data presented by A.E.Skudnytskyi the index of alloimmunization of the population in every certain area is constant. At the same time, genogeographic junctions, the areas of gene penetration serve as a source of unusual antibodies increasing the index of alloimmunization of a certain region on the whole [1].

Pregnancy as one of the main ways of alloimmunization is the major natural sensitizing factor of the population. Realization of immune conflict in AB0 system in mothers with 0(I) Rh(+) blood group and possible occurrence of HDN is a consequence of this process, and jaundice form is its most frequent manifestation [2].

Group erythrocyte antigens are divided into three large categories: 30 systems, 6 collections, two series. All of them are coded by allele or adjacent genes and do not depend on the antigens from other systems. In AB0 system blood groups possess distinct area conformities. For example,

A(II) group has two maxima – in Europe and South-Eastern Asia [3, 4]. This is the most spread blood group in Ukraine dominating over 0(I) group.

AB0 incompatibility of mother and fetus have been found to affect the activity of antibodies. It is an interesting fact that antibodies anti-A and anti-B of Ig G class together with blood serum are present in the first portion of colostrum of practically all recently confined women, it is cause by their formation in 95,7-98,0 % cases. Presence of these antibodies is a physiological phenomenon which is not connected with incompatibility of mother and fetus by the antigens of Ig M class of AB0 system [5].

Recently a tendency to transplacental alloimmunization has been outlined when a reverse synthesis of Ig G antibodies into Ig M antibodies becomes possible, and vice versa, Ig M into Ig G in re-immunized individuals [2]. Transplacental transfer of the antibodies of producing cells is hardly a rare phenomenon – it can explain their high frequency (19,5%) among male carriers [1].

An important feature of the Ukrainian population is a vast anthropological and cultural-ethnographic diversity of local territorial-ethnic regions [6]. It is highly relevant to the region of Northern Bukovyna which together with sub-Carpathian and trans-Carpathian lands were isolated from the rest of Ukrainian territory for a long time. First, these regions were annexed to already formed part of Soviet Ukraine during the World War II [7]. Second, modern increasing migration flows of Caucasian race (peoples of Northern and Central Europe, Armenian and Alpine groups) as well as cross population flows from Eastern Ukraine and Western part of Russia characterize the region of Northern Bukovyna as a polymorphic population area of gene penetration.

In recent years a growing tendency of newborns with the signs of hyperbilirubinemia of hemolytic character by AB0 system is indicative of a probable change of the sensitizing index by this sign.

In previous works we have examined certain peculiarities of HDN depending on the blood group of a newborn, level of umbilical bilirubin, and maternal blood group characteristics [8, 9].

The results of distribution of blood groups in the infants born to mothers with 0(I) Rh(+) in 2013 induced an interest to analogical examination of distribution of these determinants in 2014 with their further comparative analysis.

Materials and methods

Examination of maternal and umbilical blood (examination of infantile blood was conducted in case blood transfusion became necessary) to detect blood group by AB0 and Rh-factor (anti-D) systems was conducted on the base of the laboratory of Anaesthetic Department with beds for intensive care units (ICU), Municipal Clinical Maternity Home № 1, the town of Chernivtsi, Ukraine.

Examinations to detect blood group and Rh-factor were performed according to the Order № 164, the Ministry of Public Health of Ukraine dated 05.07.1999 «Instruction to Detect Blood Groups by AB0 system and Rhesus» [10].

Belonging to blood group of patients was detected by agglutination reaction by means of reagents: standard erythrocytes and monoclonal antibodies (coliclones anti-A, anti-B, anti-AB).

Standard erythrocytes were prepared in the laboratory of Chernivtsi Regional Center of Blood Service according to the instruction on taking and registration of blood received from donors in small doses to prepare standard erythrocytes.

Monoclonal antibodies were used – erythrotest-coliclones produced in Russian Federation, Moscow, "Hematolog" certified on the territory of Ukraine. Rh-factor was detected by means of anti-Rh0(D) Ig M reagent of the same firm.

The series and expiry dates were indicated on all the reagents.

The level of general bilirubin and its fractions as one of the main biochemical prognostic criteria for the development of HDN was detected in the umbilical and infantile blood.

Detection of bilirubin and its fractions was performed by means of the unified technique with Endrashyk's method with the set of reagents produced by "Filicit-Diagnostica" (Dnepropetrovsk, Ukraine). Photoelectrocolorimeter KFK-2 was use to measure optic density of solutions.

The study was conducted during the period of 2013-2014.

Results and discussion

It is ABO immunization is an often cause of severe hyperbilirubinemia [11]. According to medical protocols of advising newborns born to mothers with O(I) blood group and negative Rh-factor, irrespective of blood group, umbilical blood should be examined to find group and Rhesus characteristics as well as the concentration of general bilirubin.

The results of comparative analysis of the distribution of group and Rhesus determinants in infants born to mothers with O(I) Rh(+) blood group during two years of the study are presented in Table 1. According to genetic laws the embryo inherits genetic information from both parents to the same extent. Analysis of the results showed maximally possible reflection of maternal group signs.

Table 1: Comparative distribution of blood characteristics in infants born to mothers with O(I) Rh(+) blood group by ABO system during 2013-2014 (on the base of Maternity Home № 1, Chernivtsi)

	O(I)		**A(II)**		**B(III)**	
	Rh(+)	**Rh(-)**	**Rh(+)**	**Rh(-)**	**Rh(+)**	**Rh(-)**
2013 (n=569)	55,89% (n=318)	4,92% (n=28)	24,78% (n=141)	3,34% (n=19)	8,96% (n=51)	2,11% (n=12)
2014 (n=553)	48,10% (n=266)	6,51% (n=36)	28,57% (n=158)	2,17% (n=12)	13,20% (n=73)	1,45% (n=8)

Note: n – number of individuals for every category

In nature crossing of organisms with different blood groups results in negative consequences and even death of such species. In human population sensitization on the ground of this incompatibility is solved with pharmacotherapy, the number of individuals with A(II), B(III) AB(IV) blood groups dominate over O(I). According to one of the theories initially there was only one O(I) blood group – the rest appeared in the result of expansion of residential areas and adaptation to new ecological conditions [4]. L.Segurel et al. [12] state that blood groups, A and B, are not the result of convergence, they are characterized by general origin among distant relative species and are preserved under the influence of factors of selective stabilizing selection during millions of years. ABO was the first human gene which displayed polymorphism, that is, this gene possesses not only usual dominant and recessive alleles, but two dominant alleles A and B, and the third allele – O – recessive [12].

In the majority of cases occurrence of HDN is natural in case of combination of the maternal phenotype O(I) with A(II) and B(III) groups of the fetus. On the other hand, dominant belonging of the majority of the population in Bukovyna region to A(II) blood group results in the process of continuous competition between O(I) and A(II) blood group of newborns. Both genes A and B are dominant concerning O, but they lose their dominance towards each other.

According to our study in spite of dominance of A and B genes, children born to mothers with O(I) Rh(+) blood group approximately in half of the cases inherited group and Rhesus characteristics identical to maternal ones which is the evidence of minimal risk of isoimmunization. This fact is indicative of a positive genetic mechanism of natural selection by these characteristics. In case only group belonging is considered the number of newborns with O(I) blood group was 60,8% and 54,61% in 2013 and 2014 respectively, which was reliably more than a half of the cases of distribution from general amount. The range difference in 6,19% was just the difference of competitive genes: A(II) and B(III) blood groups and dominant Rh(+), when the studies of two years were compared.

Why are we talking about HDN increase in recent years where the process of isoimmunization plays “first fiddle”?

Let us consider ranges of umbilical bilirubin concentration level as a primary index in HDN screening (Table 2).

Table 2: Comparative distribution of umbilical bilirubin concentration (micromole/L) in infants born to mothers with 0(I) Rh(+) blood group in 2013-2014. (on the base of the Maternity Home, Chernivtsi)

	0(I)		**A(II)**		**B(III)**	
	Rh(+)	**Rh(-)**	**Rh(+)**	**Rh(-)**	**Rh(+)**	**Rh(-)**
2013 (M±m)	34,0 ± 0,71 (n=318)	36,70±0,71 (n=28)	38,70±1,32 (n=141)	40,9 ± 2,30 (n=19)	39,8 ± 1,66 (n=51)	35,7 ± 2,17 (n=12)
2014 (M±m)	35,0 ± 0,48 (n=260)*	36,8 ± 1,46 (n=34)*	40,7 ± 0,99 (n=158)	38,1 ± 3,81 (n=12)	40,3 ± 1,50 (n=71)*	37,4 ± 3,19 (n=8)

Note: * – the number of bilirubin definition differs from the number of group definition due to hemolysis of the serum;
M – mean arithmetic value of bilirubin concentration and its standard error m=(σ√n).

The data presented in Table 2 show that levels of umbilical bilirubin in all the groups of newborns are in rather narrow ranges: 35-40 micromole/L. The use of Kraskel-Wallis criterion to conduct statistical analysis was indicative of a reliable influence of both group and Rhesus factors upon the value of umbilical bilirubin ($p<0,01$) in 2014: in comparison of all the six possible group and Rhesus combinations between themselves as well as in comparison with 0(I) A(II) B(III) blood groups irrespective of Rhesus distribution [13].

The use of another criterion – U-Wilkinson's criterion – to compare infants with 0(I) Rh(+) blood group with five other variants of possible group distributions concerning bilirubin level, showed reliable differences only for diametrically opposite groups: A(II) Rh(–) ($p<0,05$) and B(III) Rh(–) ($p <0,01$) [13].

As a rule, HDN development occurs during the first 12-24 hours of baby's life, the process is characterized by rather quick course: it is confirmed by average statistical levels of bilirubin in the umbilical blood in the moment of birth and pathological ones on the second-third days of life. There may be a number of mechanisms of development of such pathology, but hemolytic conflict remains a primary one and not only by AB0 system [14].

It is noteworthy that neonatologists notice inconsiderable yellowness of the skin, at the same time, the concentration values of general bilirubin on the second-third days were higher than 270,0 micromole/L, with normal average statistical value within the range of 32,0-36,0 micromole/L in the umbilical blood of nine infants with A(II) Rh(+) blood group in 2014 and five in 2013. General number of hyperbilirubinemia cases in this group of the study is presented in the Table 3.

According to literary data severe HDN is considered with general bilirubin concentration higher than 340 micromole/L during the first 28 days of life. The priority in reaching critical values belong to infants B(III) Rh(+) blood group: in 2013 two children showed the concentrations higher than this limit on the second-third days of their lives. In 2014 only one baby was with analogical group characteristics and critical level of bilirubin in the first days of life. These signs are characterized by inconsiderable frequency of features concerning the number of newborns in the region studied.

Table 3: The number of hyperbilirubinemia in infants born to mothers with 0(I) Rh(+) blood group by AB0 system during 2013-2014. (on the base of the Maternity Home, Chernivtsi)

	0(I)		A(II)		B(III)	
	Rh(+)	Rh(-)	Rh(+)	Rh(-)	Rh(+)	Rh(-)
2013 (n=569)	6	---	32	7	10	---
2014 (n=553)	7	2	43	3	13	4

Note: n – the number of individuals for every category

According to literary data general bilirubin level in the blood higher than 86,0 micromole/L is considered to be critical in the first 24 hours of life [14].

There were 34 such babies from the general group (2014), but real number of them is unknown as monitoring of bilirubin level with normal value of its concentration is conducted only on the second-fifth days in case HDN develops or any other pathological process against the ground of HDN. It is the first 24-36 hours of life when attention should be drawn to the monitoring of general bilirubin detection in babies with A(II) and B(III) blood groups against the ground of general anamnesis of the mother.

Cephalocaudal development of HDN should be considered here as the CNS is its target. Every fourth-fifth infant with A(II) blood group from general number of such babies is at risk of hyperbilirubinemia. On the other hand, critical concentrations of general bilirubin are purely individual characteristics: 340 micromole/L may be critical for some individuals, and for others – 250 micromole/L.

Why do we have the right to speak about blood group distribution in newborns of the given region?

The matter is that Municipal Clinical Maternity Home № 1 gives medical aid not only to urban residents but to the population of district centers as well: Hertsa, Zastavna, Kitsman, Novoselytsia, Sokyriany and Khotyn districts occupying a wide area of Northern Bukovyna (six out of eleven districts).

The data presented report on the two-year study during 2013-2014. Naturally, to get a wider characteristic of distributions the study should be conducted during five years. They will present more comprehensive manifestation of dominant distribution and variations of group and Rhesus characteristics in newborns of this group in a temporal factor.

Naturally a question arises concerning genetic distribution of the determinants studied in babies born to mothers with negative Rh-factor. In addition, a tendency of HDN development has been noticed in infants born to mothers with A(II) Rh(+) blood group (15 babies in 2014), whose umbilical blood was not taken to detect group and Rhesus characteristics and who were not examined additionally as they were in satisfactory condition at birth.

Conclusion

HDN occurrence in infants born to mothers with 0(I) Rh(+) blood group is of certain priority due to rather big number of the pregnant with the above characteristics.

In spite of inconsiderable variations of general bilirubin in umbilical blood between groups, the development of HDN has individual characteristics. Bilirubin metabolism, its synthesis, metabolic processes and excretion are under genetic control. For example, polymorphism in glutathione-S-transferase gene (GTS) can promote the increase of general serum bilirubin level.

The infants with A(II) blood group born to mothers with 0(I) Rh(+) blood group, are most often at risk of HDN development due to its prevailing distribution in Bukovyna region.

Future studies can develop in several directions and the following ones may have priority:

- genogeographic distribution of infants born to mothers with 0(I) blood group and negative Rh-factor irrespective of the blood group;

- markers of HDN development in the pregnant (compete typology of blood group with the use of up-to-date gel-type technologies, examination of acute phase proteins belonging to α_1-, α_2- and β-globulin fractions);

- circadian distribution of bilirubin level concerning time of the day and time of the infant's life;

- formation of HDN at the expense of immune and non-immune factors.

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Генетические особенности распределения групп крови у новорожденных от матерей С 0(I) Rh(+) в Буковинском регионе

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Аннотация. В статье проведен анализ распределения групповых (за системой АВ0) и резусных характеристик (за системой анти-D) у новорожденных от матерей с 0(I) Rh(+) группой крови в Черновицком регионе (Украина), на протяжении 2013–2014 годов. Проанализирована взаимосвязь уровня пуповинного билирубина и гемолитической болезни новорожденных (ГБН), необходимость тщательного его мониторинга в течение первых суток жизни новорожденного, особенно в случае принадлежности ребенка к определенным группам риска. Затронут вопрос о возможном проявлении ГБН от матерей со А(II) Rh(+) группой крови, доминантной в исследуемом регионе. Определены задачи для дальнейшей работы в данном направлении экопатофизиологии в зонах генопенетрации.

Ключевые слова: гемолитическая болезнь новорожденных (ГБН), желтушная форма, системы групп крови: АВ0 и Rh-фактор, концентрация билирубина, аллоиммунизация, генопенетрация.