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Rh Blood Group Positive Newborn of Rh Blood Group Negative Parents, Why, and How?

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ABSTRACT

The proteins of Rhesus (Rh) antigens are transmembrane proteins. The main antigens are D, C, E, c, and e, which are encoded by two adjacent gene loci. The presence or absence of RhD allele in a person is typed either positive or negative, represents by a suffix (+/-) after the ABO type. The antigenicity of Rh antigen is guarded by many factors, for example, the molecular weight of the antigen and the antigen being accessible to the antibody. Rh phenotypes can be identified by the presence or absence of the Rh surface antigens. The Rh antigen protein represented by 2 alleles at the specific gene locus. Rh-negative positive person can be homologous have 2 RhD alleles or heterozygous having RhD and Rhd alleles. Therefore, Rh positive parents can have Rh-negative children if both are Rh heterozygous. At the same time, Rh negative parent can have Rh positive children if both parents genotypically are positive but phenotypically are negative. They will test negative on antigenicity testing but on DNA testing they are actually RhD positive. Thus they will give the allele to their baby. If the baby expressed the RhD antigen on the surface will be phenotypically and genotypically positive.

Keywords: Rh blood group, ABO blood group, Newborn.

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HISTORICAL BACKGROUND

Drs. Philip Levine and Rufus E. Stetson in 1939 presented a 25 years mother who developed a stillborn due to hemolytic disease of the newborn [1]. The parents' blood group was O, therefore, the husband gave his blood to his partner to correct her anemia that resulted from blood loss during delivery [1]. Unfortunately, the mother had a severe reaction related to this transfusion. The researchers concluded that there might be an undiscovered antigen related to an unknown blood group on the father's Red Blood Cells (RBCs) not on the wife's RBCs. They couldn't name this blood group antigen at that time. One year later, two researchers published their blood-typing and cross-matching in 1940 [2], Simultaneously, Dr. Philip Levine and colleagues in 1941 published a possible theory about the disease which was called erythroblastosis fetalis was caused by Rh alloimmunization. Karl Landsteiner and coworkers published a method to identify patients for the antibody that caused transfusion reactions, known as Rhesus (Rh) [3].

The term "Rh" originally came from the Rhesus factor which was named by Karl Landsteiner and Alexander S as they believed it is similar to the antigen found on RBCs of the rhesus monkey. Subsequently, it was understood that the human factor is not similar to the rhesus monkey factor. However, the terms were already worldwide used and survived until the current time.

INTRODUCTION

The Rh blood group (RhBG) is the second most important of 36 known human blood groups after the ABO blood group. The RhBG composed of 49 defined antigens [4]. The most important of which are five antigens; D, C, c, E, and e. Of note, there is no d antigen. The capital letter represents a dominant allele while the small letter represents recessive allele. The presence or absence of RhD allele in a person is typed either positive or negative, represents by a suffix (+/-)

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after the ABO type. Antibodies to Rh antigens are mostly the cause of the aforementioned hemolytic transfusion reactions. The most antigenic of RhD and c antigens which imposed a risk of hemolytic disease of the fetuses and neonates.

There are two sets of naming for RhBG adopted by Ronald Fisher and coworker, and by Wiener. The Fisher-coworker one is commonly practiced, uses the CDE. This system was based on the theory that different genes control the production of each related antigen (e.g. D gene produces D antigen, and so on). The d gene was not actual but hypothetical.

The Wiener system used the RhHr naming. It was based on the theory of an allele gene at a single locus on each of the 2 copies of chromosome one. Each allele contributing to the production of multiple antigens. In this theory, a gene R is supposed to give rise to the Rh0, rh', and rh" (similar to the current system naming of the D, C, and E antigens) and the gene r to produce hr' and hr" (similar to current nomenclature of the c and e antigens) [5].

DNA testing showed that both theories are partially correct. The RhD gene produces a single antigen (anti-D) while the RhCE gene produces multiple antigens (anti-C, anti-c, anti-E, anti-e) [6, 7]. The proteins of Rh antigens are transmembrane proteins that have ion channels [8]. The main antigens are D, C, E, c, and e, which are encoded by two adjacent gene loci as mentioned above. Rh phenotypes can be identified by the presence or absence of this Rh surface antigen. The Rh antigen genotype that can only be identified by DNA analysis is not required for the patient treatment. The phenotype is usually of a clinical significance that may lead to an antigen-antibody reaction.

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The frequency of Rh-positive and Rh-negative blood group is around 94% and 6%, respectively [9]. The genotype of a child of Rh-negative parents will be definitely Rh-negative. However a child of Rh-positive genotype parents (homozygous or heterozygous) may have Rh positive or Rh negative, depending on the parents' specific genotypes [10]. The RhD genotype is inherited on the short arm of chromosome number one, p36.13-p34.3) with various alleles.

Testing for Rh antigen is assessing the antigenicity, not the gene itself. The antigenicity guarded by many factors for example, the molecular weight of the antigen, a minimal molecular weight of 8,000−10,000 Da weight and the antigen being accessible to the antibody.

The Rh blood group is complex and it is represented by DCEdec. An Rh positive means the individual possesses RhD (accessible to the antibody and molecular weight more than 8000 Da) Moreover, the positivity means the antigenicity (the phenotype) not the genotype (the gene).

DISCUSSION

Assuming both parents are actually having the two alleles for RhD (genotype) but the protein is not accessible or less than 8000 Da (no genetic expression) they will test negative but they will inherit their alleles to their child and the child might express the surface RhD (accessible to the antibody and the weight more than 8000 Da or genetically is expressed). The no accessibility of RhD (no expression) in the parents could be one of three reasons.

1. Weak RhD where RhD protein is altered in several ways, for example, the protein can be in the plasma not in the membrane therefore the parents will be phenotypically negative but genetically are positive (the RhD antigen is not accessible to the antibody during the testing). Weak D phenotype can give a negative reaction to anti-D reagent at immediate spin (IS), the negative reaction after 37^oC temperature of incubation, and finally positive reaction at anti-human globulin (AHG) phase. So this results from a quantitative difference in assessing the RhD antigen (small molecular weight or less number of RhD antigen). Practically this phenotype can be labeled as D positive when donating blood, while labeled D negative when receiving blood. However, this is a matter of some debate. Most "Weak D" patients can receive "D positive" blood without complications [11].
2. Partial RhD is due to a qualitative change in the RhD antigen. For example, the RhD protein can traverse the cell membrane where only part of it will be on the surface of the cell membrane. Thus, the parents despite being genetically positive they will be phenotypically negative (no antigen-antibody reaction). Therefore, this type of RhD phenotype is labeled Rh-positive but will receive RhD negative blood group [12].
3. Rhnull where the RhD protein is not detected. This is a very rare type of blood group and it is sometimes called the golden blood group. The RBCs lacking Rh blood group can have abnormal cell membranes such as stomatocyte which may lead to hemolysis. An example of this type the RhD antigen might disperse inside the plasma makes it very difficult to find (not accessible to an antibody during the testing.

CONCLUSION

Therefore the answer to the question of can Rh negative parents give birth to an Rh positive child is yes, Rh-negative parents can have Rh-positive children. When both parents have one of above three possibilities (genotypically are positive but phenotypically are negative), they will test negative on antigenicity testing but on DNA testing they are actually RhD positive. Thus they will inherit the alleles to their baby. If the baby expressed the RhD antigen on the surface and was not of one of the above three RhD phenotypes, will be phenotypically and genotypically positive. The answer is yes Rh-negative parents can give an Rh-positive baby.

CONFLICT OF INTEREST

The author declare that there is no conflict of interest.

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