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PREVALENCE AND CLINICAL SIGNIFICANCE OF KELL BLOOD GROUP SYSTEM: A REVIEW

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ABSTRACT

The Kell blood system, having a high immune response, comes after the ABO and Rh grouping. This system has several antigens, the majority being Kell 1 and Kell 2. The clinical importance of these antigens goes beyond transfusion medicine and into the broader issues associated with maternal-fetal health. This review aims to delineate the frequency of Kell antigens throughout the globe and comment on the clinical implications of the occurrence of Kell antibodies. This included a review of literature focused on clinical studies relevant to the Kell antigen system. Kell antigens expression varies between populations with marked differences. For instance, Kell 1 is found in about 9% of Caucasians but much more rarely in African-Americans as well as the other ethnic groups. The findings highlighted the clinical significance of these variations related to hemolytic transfusion reactions and hemolytic disease of the newborn (HDN). This review illustrates a need of correct Kell antigen genotyping and antibody screening to improve patient care. Interpreting the epidemiology and clinical importance of the Kell blood group system will help in substantial for appropriate care in transfusion medicine and maternal-fetal healthcare.

INTRODUCTION

Red blood cells have an antigen on their surface that can cause an immunological reaction and the subsequent generation of alloantibodies (Pourazar et al, 2007). There are 33 blood group systems encompassing over 400 antigens found on proteins, glycolipids, and glycoproteins on the outer layer of RBCs (Mitra, Mishra, & Rath, 2014). An alloantibody that could have clinical implications for transfusion services was found, leading to the identification of the clinically important blood groups. Due to their high immunogenicity and clinical importance in transfusion services, knowledge of blood types is essential for transfusion medicine (Bailey, 2019).

The Kell blood group system is complex with many antigens; that exhibit highly immunogenic responses (Mohandas & Narla, 2005). It is considered third most vital blood group after ABO and Rh systems. It carries the risk of causing hemolytic infusion reactions and hemolytic illness in fetuses and neonates (HDFN) (Manfroi & Velati, 2017). In the Kell blood type system, a 93-kDa protein that is a transmembrane component of red blood cells is responsible for carrying at least 35 different antigens. KEL1 (K,

"Kell") and KEL2 (k, "Cellano"); KEL3 (Kpa), KEL4 (Kpb) and KEL21 (Kpc); KEL6 (Jsa) and KEL7 (Jsb) are examples of the antithetical antigen (Daniels et al, 2013). KEL4 is associated with two opposing antigens, KEL3 and KEL21 (Schenkel, 2000). People lacking all Kell antigens exhibit the Ko (null) a rare phenotype (Karamatic et al., 2014).

In 1946, the Kell blood group system was discovered and is named after Mrs. Kelleher, whose newborn experienced hemolytic illness due to anti-Kell antibodies (where the infant's red blood cells exhibited K antigen associated with anti-K in maternal serum). Following that, a total of 25 Kell antigens have been recognized. However, in HDN and transfusion therapy, the K antigen continues to play a critical role (Dean et al., 2005). KEL varies greatly between populations and is inherited in an autosomal codominant fashion. KEL was localized to 7q33 by hybridization and linkage analysis. KEL is made up of 19 exons that are roughly 21.5 kb long (Lee et al., 2015). Antibodies in the Kell blood group are mostly IgG, with some being IgM. Because of this, anti-K has been produced as IgM monoclonal antibodies that can be utilized for phenotyping. Autoantibodies with Kell specificities have been described, and these antibodies can result in both immediate and delayed hemolytic transfusion responses (Lee et al., 2007). It was previously believed that Kell antigens were only expressed in erythroid blood cells, such as red blood cells and their precursors, more recently, it was observed that they are also present in myeloid tissues (Wagner et al., 2000). Additionally, a minor quantity of the Kell antigen is present in the neurological system, heart and skeletal muscle, and lymphoid organs (Reid ME et al., 2004). Kell glycoprotein is an enzyme that converts endothelin-3. It produces active endothelin-3, a strong blood vessel constrictor, by splitting an inactive precursor called large endothelin-3 (Delaney et al., 2015).

Prevalence

This system includes several antigens among them best-known clinically significant antigen is K1, due to its potent immunogenicity. These antigens prevalence varies significantly amongst most populations. For instance, it is estimated that in Caucasians, the antigen K1 is found in approximately 9% (Smith et al., 2016). This antigen is less prevalent within African-American and Asian populations with frequencies of 2% and 0.5%, respectively (Jones, 2017; Zheng, 2016). K1 antigen has a different distribution pattern as observed in Western countries, estimated to be approximately 7% in Saudi Arabia (Ahmed, 2018), 7.5% in Japan (Tanaka et al, 2019). However, the prevalence among Brazilians is reported at 8%, closely mirroring that among Caucasians (da Silva, 2021). The same has been noticed among Argentina and Chile, and other South American countries (Garcia et al, 2020). The distribution of Kell antigens in African countries portrays some marked differences as shown in table 2. For example, South Africa has a prevalence of about 6.5% of K1 antigen, whereas that of the Jsa antigen is significantly higher, reaching up to 19% (Mthembu et al, 2020). Such high prevalence rates of Jsa antigen would be very crucial for transfusion purposes in these regions. Similarly, studies from Nigeria and Kenya show decreased frequencies of K1 but higher frequencies of other antigens of the Kell group, like Kpa and Kpb, that may influence transfusion compatibility and risks for alloimmunization (Hassan, 2020; Kim, 2017). The prevalence of Kell antigens among European populations varies as well. Levels of the K1 antigen appear in approximately 6.8% of the population of Germany and 6.5% of the population of France (Mueller, 2017; Dupont, 2018). K2 antigen, although less common, is present in these populations at lower prevalence. The prevalence of other antigens such as Kpa and Kpb follows international trends whereby Kpb is nearly ubiquitous whereas Kpa shows 0.5% to 2.5% prevalence (Rossi et al, 2019). The reports have also revealed that the prevalence of K1 antigen is approximately 7.2% in India and 7% in China (Sharma, 2015; Zheng, 2016). Such prevalence patterns are significant for designing region-specific blood screening and transfusion strategies to ensure patient safety and improve outcomes in transfusion medicine. The significance of Kell blood group antigens is described in table 1 (da Silva et al, 2021).

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Table 1: Clinical Significance of antigens of Kell Blood Group system

Antigen	Frequency	Clinical Significance
KEL1 (K)	9%	Highly immunogenic; causing severe hemolytic transfusion reactions and hemolytic disease of the fetus and newborn (HDFN). (Daniels, 2013; Halawani et al., 2024)
KEL2 (k)	0.5%	Common antigen; Anti-K antibodies, though uncommon, can indeed lead to transfusion reactions. It's crucial to screen for these antibodies to prevent such adverse events (Daniels, 2013; Halawani et al., 2024)
KEL3 (Kpa)	0.2%	Rare; can cause mild to moderate transfusion reactions (Westhoff, 2019)
KEL4 (Kpb)	0.1%	Universal antigen; no clinical significance as anti-Kpb antibodies are extremely rare (Westhoff, 2019)
KEL5 (Jsa)	Rare	Rare; can potentially cause severe transfusion reactions and hemolytic disease of the fetus and newborn (HDFN) (Daniels, 2013)
KEL6 (Jsb)	100%	Common antigen, anti-Jsb antibodies can still lead to transfusion reactions. (Westhoff, 2019)
KEL7	97.31%	Common antigen; Anti-kel11 are rare, and can cause transfusion reactions (Daniels, 2013)
KEL8	Rare	Very rare; can cause transfusion reactions and HDFN (Daniels, 2013)
KEL9	Rare	Rare; can cause mild to moderate transfusion reactions (Westhoff, 2019)
KEL10	Rare	Very rare; clinical significance not well documented (Daniels, 2013)
KEL11	0.1%	Rare; can cause mild transfusion reactions (Westhoff, 2019)

Table 2: Prevalence of Different Kell Antigens

Country	Study Period	Samples Size	K1(%)	K2(%)	K3(%)	K4(%)	Kpa(%)	Kpb(%)	Jsa(%)	Jsb(%)	Ku(%)	K11(%)	Citation
USA	2016	2000	9.0	0.5	0.2	0.1	2.5	100	0.1	99.9	0.3	0.1	(Smith et al., 2016)
UK	2017	1800	8.5	0.4	0.1	0.1	1.8	100	0.05	99.95	0.3	0.1	(Jones, 2017)
Saudi Arabia	2018	1600	7.0	0.3	0.1	0.1	0.5	100	0.02	100	0.3	0.1	(Ahmed, 2018)
Japan	2019	1500	7.5	0.4	0.1	0.1	0.3	99.9	0.1	99.9	0.3	0.1	(Tanaka, 2019)
South Africa	2020	1400	6.5	0.3	0.1	0.1	1.0	100	19.0	99.9	0.3	0.1	(Mthembu, 2020)
Brazil	2021	1700	8.0	0.4	0.1	0.1	1.2	99.95	0.05	99.95	0.3	0.1	(da Silva, 2021)
India	2015	1200	7.2	0.3	0.1	0.1	0.8	100	0.1	99.9	0.3	0.1	(Sharma, 2015)
China	2016	1300	7.0	0.3	0.1	0.1	0.7	100	0.1	99.9	0.3	0.1	(Zheng, 2016)
Germany	2017	1100	6.8	0.3	0.1	0.1	1.0	100	0.1	99.9	0.3	0.1	(Mueller, 2017)
France	2018	1000	6.5	0.3	0.1	0.1	0.9	100	0.1	99.9	0.3	0.1	(Dupont, 2018)
Italy	2019	900	6.2	0.3	0.1	0.1	0.8	100	0.1	99.9	0.3	0.1	(Rossi, 2019)
Spain	2020	800	6.0	0.3	0.1	0.1	0.7	100	0.1	99.9	0.3	0.1	(Garcia, 2020)
Canada	2021	700	5.8	0.3	0.1	0.1	0.6	100	0.1	99.9	0.3	0.1	(Smith et al., 2021)
Australia	2015	600	5.5	0.3	0.1	0.1	0.5	100	0.1	99.9	0.3	0.1	(Brown, 2015)

Country	Study Period	Samples Size	K1(%)	K2(%)	K3(%)	K4(%)	Kpa(%)	Kpb(%)	Jsa(%)	Jsb(%)	Ku(%)	K11(%)	Citation
Russia	2016	500	5.2	0.3	0.1	0.1	0.4	100	0.1	99.9	0.3	0.1	(Ivanov, 2016)
South Korea	2017	400	4.9	0.3	0.1	0.1	0.3	100	0.1	99.9	0.3	0.1	(Kim, 2017)
Mexico	2018	300	4.6	0.3	0.1	0.1	0.2	100	0.1	99.9	0.3	0.1	(Lopez, 2018)
Turkey	2019	200	4.3	0.3	0.1	0.1	0.1	100	0.1	99.9	0.3	0.1	(Yildiz, 2019)
Egypt	2020	100	3.9	0.3	0.1	0.1	0.1	100	0.1	99.9	0.3	0.1	(Hassan, 2020)
Pakistan	2021	1500	7.8	0.4	0.1	0.1	0.9	99.9	0.1	99.9	0.2	0.1	(Khan, 2021)

Genetic Variations of Kell

The Kell blood holds immense significance in transfusion therapy, it encompasses 35 antigens (Denomme, 2015). Kell is a zinc endopeptidase of the M13 family, Kell protein has an N-terminal region and C-terminal region that includes a catalytic pentapeptide sequence known as HExxH (HELLH) (Sha et al., 2006). These single nucleotide mutations within the KEL gene result in the Kell system antigenic variations. The majority of amino acid residues that result in expressing many Kell antigens lie in the non-conserved globular domain, close to the plasma membrane (Lee et al., 2006). Some Variants in amino acids fall in the conserved region but are on the surface of the protein. These antigens result from single nucleotide polymorphisms (SNPs) found in the KEL gene. The molecular cause of most Kell antigens has been determined to result from base mutations resulting in changes for a single amino acid (Debnath & Redman, 2013). KEL1 and KEL2 antigens result due to the presence of single nucleotide polymorphisms in exon 6 (C578T), causing T193M amino acid substitution (Lee et al., 2007). KEL3 & KEL4 antigens arise from a point mutation in exon 8 (C841T). Therefore, in the KEL3 antigen tryptophan takes the place of the usual arginine at amino acid position 281 in the KEL4 antigen. A single nucleotide polymorphism in exon 17 gives rise to KEL6 and KEL7 antigens, with KEL6 coding for proline and KEL7 coding for leucine (Wagner et al., 2000). The Kpa antigen is the result of the 961C>T mutation, which results into R281W mutation. The 962G>A mutation in the same codon causes the KEL21 antigen and results in an R281Q substitution (Lee et al., 2001). Kell Antigens have antithetical expressions at both high and low frequencies like KEL2 (k)/KEL1(K), KEL4(Kpb)/KEL3(Kpa)/KEL21(Kpc), KEL7(Jsb)/KEL6(Jsa), KEL11/KEL17, and KEL14/KEL24. The rest do not possess identifiable antithetical counterparts and are consequently designated as para-kell antigens. (Wanger et al., 2004). The relationship between the Kell and Kx blood group arises from the covalent attachment of the Kell glycoprotein to the XK protein on the red cell membrane via a single disulfide bond. The Kx antigen is present in trace amounts on red cells and is very active (Denomme et al., 2015).

The Kell antigens are on the KEL gene-a gene that encodes a 93 kDa glycoprotein, the Kell protein, which is bound to the underlying cytoskeleton, spanning the erythrocyte membrane and is therefore surface exposed (Daniels, 2002). Kell glycoproteins have about 12% carbohydrate and all are in the form of N-linked glycosides. This protein has one transmembrane domain with a short cytoplasmic domain of 47 amino acids and an extensive section of 665 amino acids (Russo et al., 2000). Proteolytic activity has been shown in Kell polypeptide, but there remains obscurity regarding the function of Kell protein (West et al., 2005).

The XK protein, which has a mass of 50.9 kDa, is thought to feature ten transmembrane segments, with its N- and C-terminal located within the cytoplasm. While its structural attributes classify it as a membrane transporter, its precise role has not yet been established. Kell protein is found in conjunction with additional proteins that are anchored to the red cell membrane (Karamatic et al., 2014). Previous serological studies have demonstrated that the Kell polypeptide is associated with the Kx blood group protein through a disulfide bond linkage. This linkage

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forms two rare phenotypes: The Ko (null) red cell and the McLeod red cell (Debnath & Redman, 2013).

The Ko (null) phenotype is very rare and has no Kell antigens (Debnath, 2006). This uncommon phenotype results from multiple KEL mutations, such as splicing, deletions, and premature stop codons, leading to the absence of Kell antigens on red blood cells. In the Ko patient, the coding region of the KEL gene displayed a normal sequence for the KEL2, KEL4, and KEL7 alleles. However, a homozygous G-to-C mutation was detected at the splice donor site of intron 3 (Wagner et al., 2000). The Knull phenotype is primarily caused by mutations that introduce a premature stop codon, leading to the production of a truncated Kell protein. Although individuals with this phenotype generally have good health, exposure to RBCs containing Kell antigens triggers the production of anti-Ku antibodies. That is linked to mild to intense transfusion reactions. Thus, in the case of a requirement for blood transfusion in any Ko individual, only Ko blood components should be utilized (Lin M et al., 2003).

Another rare phenotype, referred to as Kmod, is distinguished by weak expression of all Kell red cell antigens since only minute quantities of Kell glycoprotein are present in the RBC membrane. This condition is hereditary, though its inheritance and molecular basis remain unclear (Halverson et al., 2020). Four Kmod phenotypes Kmod-1 (1208G>A), Kmod-2 (2150A>G), Kmod-3 (1106T>C), and Kmod-4 (2227G>A) were identified. The majority of Kmod mutations are missense that lead to an amino acid change, the resulting mutant Kell protein failed to be transported to the cell membrane (Daniels, 2002).

The Kx blood is composed of only one antigen Kx on the XK protein as shown in figure 2. The clinical importance of this system lies in the fact that the absence of the XK protein, which occurs in rare forms of McLeod phenotypes, leads to RBC with spiked cell membranes and abnormalities that typically start around midlife, affecting peripheral and central nervous systems and hence is referred to as McLeod syndrome (Jaber et al., 2009). Kx is a deficiency because of the inheritance of a variant at the Xk locus that downregulates the expression of Kell, resulting in a weak phenotype. McLeod Syndrome (MLS) is a clinical condition that is classified as an X-linked multisystem disorder and is part of the neuroacanthocytosis syndromes (Jung et al., 2024).

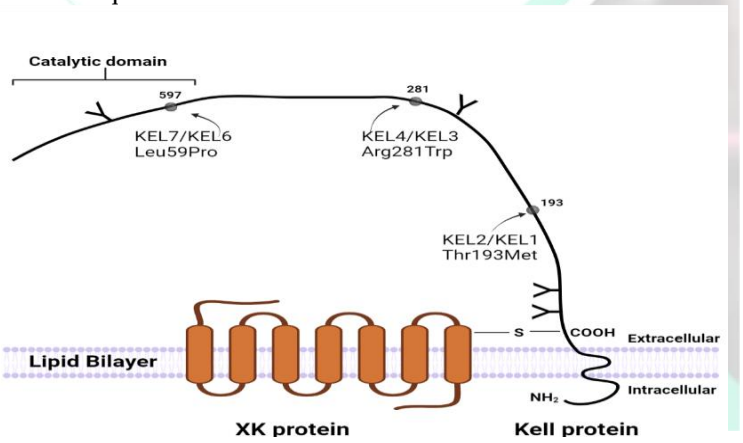

Fig.2: The interaction between Kell and Kx protein

Since males have only one X chromosome, one mutated copy is enough to result in the syndrome and because the Xk gene is X-linked all male persons are affected. In females with two X chromosomes, a mutation must be present in both copies of the gene for the disorder to become evident (Braun & Jung, 2024). At times, females with a mutation in one copy of the XK gene may also exhibit typical misshapen blood cells and mobility issues common to McLeod neuroacanthocytosis syndrome. Haematologically, McLeod Syndrome is marked by a lack of Kx

antigen, diminished expression of Kell antigens, acanthocytosis, and hemolysis (Walker et al., 2024). All McLeod carriers described so far have deranged serum levels of creatine kinase. Neurological features may also present with a mean onset age (Debnath, 2013). Central Nervous System (CNS) presentations of McLeod Syndrome resemble those of Huntington's Disease, including choreatic movement disorders, 'subcortical' neurobehavioral impairments, psychiatric disturbances, and generalized seizures. Diagnosing McLeod Syndrome is intricate, relying on immuno-hematological findings of absent Kx antigens (NG, Delgado & Bax, 2019). The diagnosis can be confirmed by assessing the XK gene, and this will reveal a mutation (Perez et al., 2020). There is no curative therapy yet; management is symptomatic. Cardiologic evaluation is recommended for MLS patients and carriers, as serious heart complications may arise (Braun et al., 2024).

Clinical Significance of Kell antibodies

The Kell blood group holds substantial clinical significance due to its ability to trigger immune responses. Comprising a minimum of 36 antigens, the Kell blood group system is associated with a single red-cell transmembrane protein weighing 93 kDa (Denomme, 2015). The Kell antigen is detectable in fetal RBCs on the 10th week of pregnancy (Finning et al., 2007). They can cause severe hemolytic transfusion reactions and hemolytic disease in the fetus and newborn (HDFN) (Lee, Russo, & Redman, 2000).

Transfusion Reactions

The Kell blood group system is crucial in transfusion medicine, as its primary goal is to ensure the provision of compatible RBCs that will endure post-transfusion. Donor blood cell selection is based on ensuring that the blood lacks antigens corresponding to the antibodies found in the patient's serum. Individuals who have undergone multiple blood transfusions risk forming alloantibodies, and their sole option is receiving red blood cells that are antigen-free from antibodies associated with those antigens (Chapman et al., 2004). The mechanisms associated with Kell antibodies are primarily hemolytic, although they can also lead to the suppression of erythropoiesis (Finning et al., 2007). Antibodies involved in transfusion reactions, which can sometimes be severe, include anti-K, anti-K, anti-Kpa, and anti-Jsb (Reid & Lomas-Francis, 2004). Patients with the Ko phenotype have developed anti-Ku antibodies, which have caused a deadly hemolytic transfusion reaction (Reid & Lomas-Francis, 2004). Transfusion reasons may be mild to severe. The complications associated with blood transfusions are classified into two categories according to the timing of the initial symptoms (Brecher, 2005). Immediate reactions following a blood transfusion are known as acute transfusion reactions, whereas reactions that manifest weeks later are classified as delayed transfusion reactions (Sirianni et al., 2019). Severe acute hemolytic transfusion reactions may exhibit dramatic symptoms, including acute pain in the veins, chest, and back, along with hypotension, flushing, fever, difficulty breathing, agitation, vomiting, diarrhea, and hemoglobinuria (Scheffer & Finning, 2011). However, it often manifests with less obvious symptoms and signs, which is why it is considered in the differential diagnosis for a febrile transfusion reaction (Deveci et al., 2021).

Delayed hemolytic transfusion reactions (HTR) after incompatible RBC transfusions typically present no clinical symptoms and are usually identified through laboratory tests such as a positive direct antiglobulin test or the detection of an unknown irregular antibody. In these situations, it may be more appropriate to refer to this as a delayed serological transfusion reaction (Kumar et al., 2020).

Hemolytic Transfusion Reactions (HTRs)

Case Report 1: A patient developed severe HTR after transfusion of Kell-positive blood. Symptoms started within hours of transfusion in this patient with fever, chills, and backache. Laboratory findings revealed hemoglobinuria and a notable drop in hemoglobin levels. The patient was hospitalized in the intensive care unit and needed dialysis due to acute renal failure (Hendrickson, J. E., & Tormey, 2016)

Case Report 2:

A patient transfused with Kell-positive blood who caused DIC (disseminated intravascular coagulation). The patient bled excessively and developed organ failure that needed multiple blood transfusions and aggressive support care (Malhotra, et.al 2012)

Case Report 3:
A rare case of a patient on a history of transfusions presented with severe allergic reaction, hypotension, and respiratory distress. The patient required immediate medical intervention to stabilize the patient (Mock, 2018).

Hemolytic Disease of the Newborn
Hemolytic disease of the newborn (HDN) was previously a significant cause of fetal loss and mortality in newborns. Anti-Kell antibodies are a significant contributor to HDN. In mothers with a history of multiple blood transfusions, it can also develop in those sensitized to the Kell antigen from prior pregnancies. In HDN, the presence of anti-K antibodies from the mother's sensitization in a prior pregnancy suppresses the fetal production of red blood cells. (Smith et al., 2019). Although Rh and ABO sensitization differs, hemolytic disease of the newborn (HDN) related to Kell sensitization occurs due to anti-K antibodies that inhibit fetal red blood cell production. The Kell antigens differ from the Rh and ABO antigens in that they are expressed on precursors of red blood cells. When anti-K antibodies are present, the immune system reacts to early erythroid progenitor cells in the fetal liver via macrophages instead of targeting the mature fetal red blood cells. Since these precursors have no hemoglobin, the hemolysis process reduces bilirubin levels (Daniels, Hadley, & Green, 2003). Fetal anemia is caused by anti-Kell antibodies that can destroy erythroid progenitor cells as shown in figure 3 (Gajjar, Spencer, & Gynaecologist, 2009). Erythropoiesis is the process of the development of mature RBCs from erythroid progenitor cells (Gabrilove, 2000). The increased expression of Kell glycoprotein during early erythropoiesis implies that is important in the early stages of red blood cell development (Scheffer & Finning, 2011). Maternal Kell antibodies reduce erythropoiesis at the progenitor level in fetuses, which lowers the reticulocyte count and contributes to severe anemia as well as decreased bilirubin production (Deveci et al., 2021). Without appropriate intervention, HDFN may progress to severe fetal anemia, hydrops, and asphyxia, and ultimately result in perinatal death. Various case reports have identified the anti-K, anti-k, anti-Kpa, anti-Kpb, anti-Jsa, anti-Jsb, and anti-U1a antibodies as contributors to hemolytic disease of the newborn (Collinet, Subtil, Puech, & Vaast, 2002).

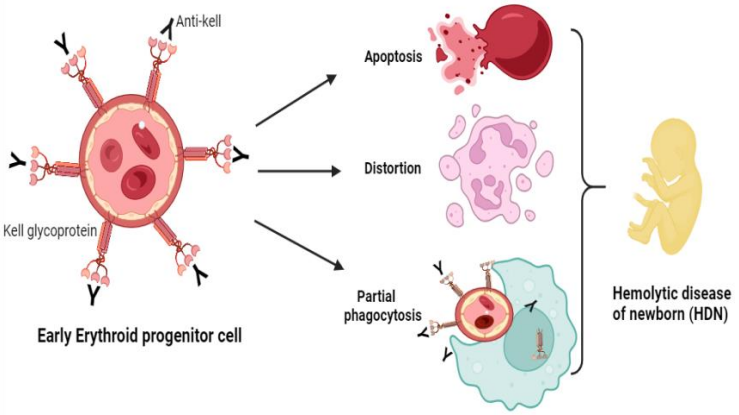

Fig.3: Anti-kell mediated fetal erythroid suppression

Fetal Anemia
The most crucial is the clinically significant antibody anti-KEL1. Approximately 10% of infant instances of severe anemia are attributed to anti-KEL1 (Lee, Russo, & Redman, 2000). Since red blood cells die early from Kell alloimmunization before they can accumulate enough hemoglobin, newborns may experience

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severe anemia and hydrops (Daniels, Hadley, & Green, 2003)**.** There are differences between the typical hemolytic illness of the newborn caused by anti-D alloantibodies and fetal anemia driven by anti-Kell antibodies (Delaney & Matthews, 2015). Because of anti-D antibodies, affected Kell-alloimmunized fetuses have lower circulating reticulocyte and normoblast counts than fetuses with hemolytic illness (Brinc & Lazarus, 2009). Furthermore, compared to fetuses that have received an anti-D alloimmunization, the amount of bilirubin in amniotic fluid and neonatal serum is lower (Santiago et al., 2008). There is no correlation between the degree of fetal anemia and the anti-Kell antibody titer in the mother's serum. These findings imply that, in addition to hemolysis, erythropoiesis suppression also contributes to fetal anemia in Kell alloimmunization (Kumar et al., 2020).

Fetal anemia is a relatively rare occurrence, but it carries a risk of significant fetal morbidity and mortality. The mode of sensitization will determine the likelihood of developing fetal anemia. For a woman sensitized after a transfusion, there's an 8.9% chance that the baby's father is Kell-positive, resulting in about a 4.5% chance that the fetus will be affected. If sensitization occurred from a previous pregnancy with the same partner and no transfusion, the fetus has roughly a 51% chance of being Kell-positive and affected (Daniels, Hadley, & Green, 2003). Anti-Kell immunization is uncommon in the pregnant women, occurring in 0.1% to 0.2% of cases, and is primarily thought to be transfusion-induced (Finning et al, 2007). In the white population, just 9% are Kell-positive and 0.2% are homozygous for the anti-Kell hemolytic illness (Deveci et al., 2021).

Regarding anti-Ku, there is limited information about its clinical significance due to the rarity of sensitized K_0 individuals (Moulds et al., 2013). The lack of Kell glycoprotein in K_0 individuals typically doesn't result in noticeable illness. However, after transfusion or pregnancy, these individuals might develop anti-Ku (anti-KEL5) antibodies, which target various epitopes across the polypeptide. Because sensitized K_0 individuals are rare, the clinical significance of anti-Ku, especially concerning hemolytic disease of the fetus and newborn is not well understood (Moulds et al., 2013).

Methods for Determination of KEL Blood Group

The Kell blood is identified by using serological testing and genotyping.

Serological Technique

For the identification of antigens, direct saline agglutination and indirect antiglobulin tests are used. Monoclonal antibodies IgM and IgG are used for precise typing of antigens. This method is however very time-consuming and expensive. (Keller, 2019).

Genotyping Method

Genotyping is an important process that determines the blood groups and detects potential alloantibodies (Westhoff, 2019). The genotyping methods for the blood groups include PCR-RFLP, gene-specific primers through PCR, tetra-arms PCR, and next-generation sequencing. RFLP is an enzymatic method developed for identifying and isolating specific DNA fragments. Tetra-arms PCR uses four primers in one reaction; then the reaction is differentiated based on gel electrophoresis (Daniels, 2023). These KEL allele genotyping techniques could be very accurate and beneficial for finding the expression of Kell antigens. It can be used to establish phenotypes when it is impossible to do serology typing due to its high cost, or a certain medical facility does not possess the basic resources (Telen, 2014). Additionally, it enables the identification of rare blood groups such as KELL. This becomes crucial when there is a need to supply blood to immunized patients who have anti-KEL1 and anti-KEL3 antibodies (Keller, 2019).

Management

Effective management begins with routine blood typing that includes Kell antigen testing, especially for patients with a history of transfusion. In this context, routine antibody screening is important in identifying anti-Kell

antibodies, which may complicate transfusions (Levene & Johnson, 2021).

In transfusion management, the choice of K-negative blood for patients who are K-positive is highly essential to avoid sensitization. In K-negative patients with anti-K antibodies, K-negative RBCs should be meticulously cross-matched and chosen (Murphy, 2020). This screening is also an essential aspect of pregnancy care, particularly at early stages because once a pregnant woman tests positive, further assessments and interventions may need to be done. An ultrasound can monitor the fetus and assess the severity of anemia due to anti-K antibodies in HDFN. In most cases, intrauterine transfusions may be necessary for effective fetal anemia treatment (McMullin & Evans, 2019).

Monitoring of newborns with HDFN resulting from Kell incompatibility for jaundice and anemia is also highly recommended. In cases where complications are grave, infants may require exchange transfusion to reduce the bilirubin levels or address anemia, while others managed with phototherapy for jaundice (Shulman & Wong, 2018). Lastly, education and counseling concerning the implications surrounding the Kell blood group are crucial, especially concerning transfusions and pregnancies. Genetic counseling would assist families whose lives are affected by a history of Kell incompatibility (Higgins & Pinder, 2022).

Conclusion

It is an important research domain in transfusion medicine and immunohematology with important genetic diversity and variable expression of antigens globally. The K antigen is reported in about 9% of Caucasians but it has a much greater prevalence amongst African populations above 20%. This variation points toward the importance of incorporating demographic factors in transfusion practice, considering the marked increase in the risk of alloimmunization with the presence of the K antigen, mainly in cases requiring multi-transfusion and undergoing any surgical procedure.

Other antigens in the Kell system are also present with highly variable prevalence, making transfusion compatibility even more complex. For example, KEL6 is seen in only about 1% of Caucasians, whereas KEL3 has a greatly variable prevalence in different populations, and its value is also highly variable in different populations. Such variability emphasizes the importance of appropriate blood typing and appropriate compatibility analysis to prevent harmful adverse transfusion reactions.

Beyond transfusion safety, the relevance of the Kell blood group extends to conditions such as severe neonatal hemolytic disease in newborns, due to maternal antibodies targeting antigens of Kell on fetal red cells, and very unusual and fascinating X-linked disorders, as exemplified by McLeod syndrome, which is linked to the absence of Kell antigens. A clinical syndrome characterized by hemolytic anemia, cardiomyopathy, and neuropsychiatric symptoms was present. Such broad implications of Kell antigen status place demands on healthcare professionals to think beyond the limited implications of Kell antigen status in their practice.

Now, a great understanding of the genetic factors influencing Kell antigen expression, its prevalence in various populations, and its impact on optimizing transfusion protocols to effectively deal with risk patients could be addressed. As genetic screening continuously advances, the introduction of Kell typing to standard procedures in blood banking will significantly enhance safety and outcomes in patient treatment.

The Kell blood group system, therefore, gives an illustration of the well-recognized primary importance of transfusion compatibility and also demonstrates how genetics may be intertwined in a rather complex relationship with health outcomes. Continued research will be essential for further honing our understanding and management of blood group-related disorders

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