Editorial

Rh Disease Eradication

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The Rh disease has a long history starting form HDFN in 1609 and resulting in availability of Anti D immunoglobulin in 1966.

A French midwife, Louise Bourgeois worked at the royal court of King Henry IV and Queen Marie de Medicis in 1609 – She described the birth of twins. The first one had hydrops and died immediately. The second one, rapidly became jaundiced and, than developed neurological symptoms – kernicterus and died on the third day. In 1892, Ballantyne described a disease in newborn with icterus and odema.[1] In 1932 Diamond reported Erythroblastosis secondary to severe haemolysis, and cause was still unknown. In I938 Ruth Darrow from W&CH, Chicago identified the (antibody-related) pathogenesis. Another case involving Rh incompatibility was reported in 1939, although the Rh factor, a protein found on the surface of red blood cells, had not yet been discovered. This case was reported by an immune-hematologist, Philip Levine and physician, Rufus Stetson, who published their case in The Journal of the American Medical Association. This was a twenty-five year old woman who presented into a local hospital during her thirty-third week of pregnancy with labor pains and vaginal bleeding. She delivered a dead fetus with a weight of one pound and five ounces. The patient received a blood transfusion from her husband, as both had blood-type O. Ten minutes after completing the transfusion, the patient developed a chill and began feeling pain in her head and legs. Due to excessive vaginal bleeding hysterectomy was done, followed by another blood transfusion from a different donor. Throughout her entire visit, the patient received transfusions from 104 Type O blood donors. Remarkably, the mother showed no blood transfusion reaction to twenty-one of those donors. Further tests indicated that the patient's serum, or the plasma in the blood minus the clotting factors, specifically agglutinated her donors' cells—or rather, 80 percent of all her blood transfusions.

The two physicians tried to discover what was causing the patient's reaction. Initially, they assumed that temperature effected agglutination in the patient's blood, but they soon realized that temperature was not responsible.

A year later in 1940-41, Karl Landsteiner and Alexander S. Wiener coined the term "Rh factor" and described it as the cause of the iso immunization. They originally believed that Macacus rhesus, or Rhesus monkey, had the same red blood cell surface antigen (Rh) as the one found in human red blood cells. It was proven to be wrong later, as the composition of human sera and rhesus sera are different. However, the term "Rh factor" has continued to be used to describe these human antigens, and "anti-Rh" is used to describe human antibodies formed against the Rh factor.

When an Rh-negative mother carries an Rh-positive fetus, the most common form of Rh incompatibility occurs. If there is leakage from the fetal circulation into the maternal circulation the Rh-positive blood cells are released into the mother's bloodstream. This generates a process known as red-cell alloimmunization. This primary exposure of Rh-positive blood into the maternal circulation leads to sensitization, which results in the maternal production of Rh-positive antibodies called Rh immunoglobin G (IgG). The mother's IgG antibodies may pass through the placenta and attack the fetal red blood cells in a subsequent pregnancy.

The fetal effects of red-cell alloimmunization are known as hemolytic disease of the newborn, which is sometimes referred to as Rhesus disease. The Rh blood group system contains several antigens (i.e., D, C, c, E, e) - the Rh D antigen accounts for the majority of all cases involving Rh incompatibility since it is the most immunogenic.

Prevention remains the best treatment for Rh incompatibility. In 1967, Freda in the United States and Clarke in England published almost at the same time that alloimmunization to Rh (D) because of pregnancy could be prevented by the postnatal maternal administration of immunoglobulin preparations that

contained high titers of anti-Rh (D) antibodies The antibody Rh IgG, or RhoGAM, was first released in 1968, since then it has played a major role in decreasing Rh incompatibility. Initially it was made from the plasma of other Rh-positive mothers who had given birth to an Rh-positive child. Women who had usually high concentrations of "Big D" were reported to have made up to 80,000 dollars a year for selling their plasma. After the commercial production of this antibody the risk of Rh incompatibility has declined from 10 - 20 % to <1%. This measure alone prevents maternal Rh (D) sensitization in approximately 90% of cases; in contrast, in the absence of such prophylaxis, 12 to 16% of this Rh (D)-negative mothers becomes alloimmunized during each such pregnancy. The antibody is administered whenever there is probability of Rh-positive fetal cells entering the maternal circulation of an Rh-negative mother. It is normally administered at 28 to 32 weeks of pregnancy and again within 72 hours after delivery. In case of any sensitizing events as miscarriage, abruption, amniocentesis, or chorionic villus sampling may also need the administration of antibodies .

Once sensitization has occurred in the mother, Anti Rh (D) antibody is not effective in preventing the progression of the disease.

Current Situation

Rh (D) disease is the iso immunization by Rh antigen resulting in severe morbidity and mortality if not prevented and treated. Despite the advent of anti-Rh (D) immune prophylaxis, during last 50 years the burden of disease has only reduced by 50%.

Antenatal and postpartum prophylaxis policy can theoretically reduce the frequency of Rh (D) sensitization to 0.5%, whereas actually it has not done so globally. There are a lot of factors and barriers which need to be taken care of. Burden of disease varies across the globe as prevalence of Rh negative mothers varies widely. Unicef in 2008 gave a figure of 7.9% for Pakistan. In another study the prevalence varies as 4% and 11% in India and Pakistan respectively.[2] It has been reported as low as1.9% in China. In 2013 a systematic review determined that 50,000 fetal deaths and 114,000 avoidable neonatal deaths result annually due to failure to prevent RhD sensitization and 3/4 of these occur in South East Asia. In Pakistan 2008 data shows that 256000 mothers were not treated and 35840 were sensitized leading to Rh HDNS in 17920 fetuses.

A lot of barriers has been identified in this respect as: absence of routine blood typing, access and price of Anti-D immunoglobulin, injection not endorsed by government so difficult availability at rural level, lack of awareness in public and health care professionals. Huge population, lack of antenatal care and skilled birth attendants, high incidence of anaemia and blood transfusions or simply forgetting to give injection are additional factors adding to the list.

The way forward is to find practical yet simple solutions to stop this preventable disease.

- Awareness among public regarding impact of completely preventable disease
- Routine blood typing of all pregnant women –at the levels of BHU also
- Routine antenatal antibody screening where possible
- Enthusiastic involvement of government and health care providers
- Involvement of private sector, general physicians and donor agencies
- Easy access to Immunoglobulin when needed
- More focus on the subject in curriculum of HCP
- Establishment of linkages between HCP, local obstetrics societies, government and private sector
- Effective protocols and their implementation
- Enhancing quality of care and patient safety practices
- Monitoring, evaluation and feedback
- Generation of statistics/ data and research

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