The ITP Support Association Platelet Reprint Series

No. 22 – Neonatal Alloimmune

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Title: **Neonatal Alloimmune Thrombocytopenia**

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Introduction

Readers of The Platelet will be very familiar with the condition of ITP (Immune Thrombocytopenic Purpura). This is a disorder in which the number of platelets is reduced largely as a consequence of an increased rate of destruction by the body's own immune system. This article will describe one of two other processes in which platelets are destroyed by different immunological mechanisms which can potentially lead to a misdiagnosis of ITP: Neonatal Alloimmune Thrombocytopenia (NAIT).

Platelet membrane structure

It is necessary to discuss the structure of the platelet membrane briefly to explain how the immune consumption of platelets works. Platelets are cells that are small in size but are complex in their function. Inside the platelet is cytoplasm which contains packages, or 'granules', of active molecules. The outside coating of the platelet is known as the 'membrane'. This is not only a structure to enclose the contents of the platelets but is an active biological structure that can change its shape and orientation allowing enhanced interaction with the blood vessel lining, other platelets and clotting factors. The molecules within the fluid or 'plasma' part of blood that act as bridges linking platelets to other structures include the proteins fibrinogen and von Willebrand factor. These proteins attach to the platelet via specific anchoring points. The various anchoring points, or 'receptors', on the cell surface are proteins with distinct chemical composition and shape. The specific nature of these proteins can be recognised by the body's immune system.

Role of the immune system

The immune system is designed to protect the body from invading bacteria or viruses. It is able to do this because it recognises the patterns of proteins on the surface of these infections as being different to its own tissues. The patterns recognised are called 'antigens'. Therefore it can distinguish between itself ('self') and foreign tissue ('non-self'). When exposed to non-self tissues it develops small proteins known as antibodies which attach to these tissues and help kill or remove them from the circulation. Over time the body's immune system is taught to recognise what belongs to itself and therefore prevent the production of antibodies against its own tissue.

The immune system in ITP – an auto-immune process.

The receptors on the platelet can be recognised by the immune system, they therefore act as antigens. However the immune system of the body does not attack these cells because it has been taught that these antigens represent 'self'. Therefore, normally platelets are able to survive in the circulation of the individual without being attacked by its own immune system. If, however, the immune system control mechanisms become faulty they may start recognising their own tissue as being foreign by mistake, that is it mixes up 'self' from 'non-self'. This results in the production and attachment of antibodies to the body's own tissues. These antibodies are termed 'auto-antibodies' (against self) and these antibodies are the ones that are attached to the platelets in patients with ITP. This mechanism represents an autoimmune process.

The immune system in NAIT - an allo-immune process

The receptors on the platelets in normal individuals all work in a similar fashion. However when the chemical composition of receptors from different individuals is compared in detail, it is possible to detect small differences in their chemical patterns. These differences generally do not influence the way the platelet works, however, they are different enough such that the immune system of the human can recognise that the platelets are different and have come from different individuals. Therefore if a platelet from one individual with one particular pattern of receptor structure is injected into the blood of another individual who has a different receptor structure the immune system of the individual which has received those platelets will recognise those platelets as being foreign. The immune system may respond in the same way as it would to an infection and develop antibodies which will attach to that platelet and remove it from the circulation. In this instance the body is attacking 'non-self' as apposed to 'self'. This is the process of allo-antibody production that is production of antibodies against a foreign receptor. This represents an allo-immune process.

Patterns of platelet receptors

Platelets have been recognised to have five different patterns of platelet specific receptor structure within which differences can be recognised by the immune system, that is there are 5 different antigen classes. These antigens, or potential targets for the immune system, are called the human platelet antigens; HPA 1a,1b; HPA 2a,2b; HPA 3a,3b; HPA 4a,4b; and HPA 5a,5b. Within each antigen class system, one structure is very common in the human population eg 1a and one very rare eg 1b. In each case an individual will recognise its own human platelet antigen as being 'self' but will recognise the alternative antigen as being foreign or 'non-self'. This leads to the potential to destroy those foreign platelets by the allo-immune process.

Allo-immune thrombocytopenia

There are two situations in which an individual can receive platelets other than those produced by its own bone marrow. One is the transfusion of platelets from a blood donor (see Platelet Reprint Article No. 23. *Post Transfusion Purpura*) and second, as discussed here, is the passage of platelets from the baby's circulation into the mother's circulation during pregnancy.

Neonatal alloimmune thrombocytopenic purpura

When a baby is developing in the womb it receives the nutrients and oxygen it requires to develop through the placenta. The placenta has a circulation of blood that passes into the baby and back out into the placenta. There is a barrier that prevents the mixing of blood with the mother's circulation but this barrier is able to allow the passage of small molecules in both directions. As early as 20 weeks of the pregnancy it is possible however, that small amount of blood can leak from the baby's circulation into the mother's circulation. This blood includes platelets.

The structure of the membrane of the baby's platelets is similar to that of an adult. They will contain the same types of membrane receptors. The specific human platelet antigens displayed on the membrane surface is inherited from either its father or mother. If the mother's HPA pattern is different to that of the father, the human platelet antigen pattern of the baby may be that of the father and therefore different to that of the mother. When small amounts of blood leak from the baby's circulation into the mother's circulation during pregnancy, the mother will recognise the baby's platelets as being foreign or 'non-self'. The mother's immune system will then develop allo-antibodies against these platelets and will destroy them within the mother's circulation.

These allo-antibodies can be small enough to cross from the mother's circulation across the placenta blood barrier into the baby's circulation. There they will recognise the baby's platelets as foreign and attach to them so reducing the numbers of platelets circulating in the baby's blood stream. The platelet count can drop to dangerously low levels whilst the baby remains in the womb, however there may be no sign of this until the baby is born. The platelet count is can be very low in the first few days and weeks after delivery. However as the antibodies from the mother's circulation are in time removed from the baby's circulation after delivery the destruction of the baby's platelets stops and the baby's platelet count will return to normal. The severity of the fall in

the platelet count can by quite marked and babies are at risk of severe bleeding episodes either before birth or following delivery. This may include bleeds into the brain.

Diagnosis is established by establishing the human platelet antigen pattern in the baby and comparing that with those of the father and the mother. This can now be done by DNA technology and is highly accurate. Emergency treatment of the low platelet count in the baby is the transfusion of platelets which are identical to those of the mother so they will not be removed by the mother's antibodies. The National Blood Service store platelets of specific human platelet antigen types which can be used in these circumstances. The mother is rarely used as an alternative donor of platelets. Newborn babies may alternatively have treatment administered such as intravenous immunoglobulin and random donor platelets. Once the baby has cleared the mother's antibodies, the thrombocytopenia resolves and will not recur in that baby.

If the parents have further children there will be a possibility that the problem may repeat itself. Investigations can identify future pregnancies that are at risk. There are medical interventions that can reduce the possibility of the mother developing antibodies against the baby's platelets, such as the use of intravenous immunoglobulin or corticosteroids administered to the mother. If there is a concern regarding the baby's platelet count, prophylactic transfusions of the appropriate platelets can in some circumstances be performed by injecting the platelets into the baby's circulation whilst still in the womb before delivery. This is performed in specialised obstetric units with close communication between the transfusion teams, haematologists and the obstetrician.

Differences from maternal ITP affected a newborn infant

Rarely, mothers with auto-immune ITP can pass antibodies from their circulation into the baby's circulation. On occasions these antibodies can remove platelets from the baby's circulation in the same way as the mother is affected. In this circumstance the pattern of the human platelet antigens are identical in the mother and the baby. Although the platelet count in the baby may drop as a result of these antibodies this tends to cause problems only after delivery and the thrombocytopenia is less severe than in the case of neonatal alloimmune thrombocytopenia. Nevertheless some babies do have bleeding complications and may require treatment in the first few days of life if the platelet count falls to a worryingly low level. This diagnosis is suggested when it is recognised that the mother's platelet count is often low or she has had a past history of ITP. In contrast, in cases of neonatal alloimmune thrombocytopenic purpura, the mother's platelet count is normal.