Patient blood group impacts susceptibility to IVIg-associated hemolysis

What is this research about?
High-dose intravenous immunoglobulin (IVIg) is given to treat patients with immune and inflammatory diseases. It is usually an effective treatment that is well-tolerated. However, high-dose IVIg can cause an adverse reaction in which the patient’s red blood cells burst (hemolysis). The hemolysis is often mild and self-limiting, but it can become severe. Some patients who develop hemolysis may require transfusion of red blood cells to treat the resulting anemia.

IVIg is a drug prepared from donated plasma. It contains pooled antibodies from thousands of donors, and a minor population of these antibodies are thought to be involved in triggering red blood cell hemolysis. Antibodies recognize and bind to specific markers, called antigens, on the surface of the patient’s red blood cells. Binding of antibodies to antigens tags the red blood cells to be destroyed by the patient’s own immune system.

Antigens on the surface of red blood cells also determine a person’s blood group. Virtually no patients who develop IVIg-associated hemolysis are blood group O; people with blood group A, B, or AB are much more likely to have IVIg-associated hemolysis. This supports the idea that red blood cell antigens may play a role in susceptibility to IVIg-associated hemolysis. However, other factors are at play here, as not all A, B or AB patients develop hemolysis. In this study, the researchers sought to understand these factors to predict who is most susceptible to this serious adverse reaction.

What did the researchers do?
The researchers determined three plausible genetic risk factors that could make patients more susceptible to IVIg-associated hemolysis, then did genetic testing on 42 patients with blood groups A, B or AB who had received high-dose IVIg.

- **Blood group genetics.** Blood group is a genetic trait, like eye colour. Individuals who are blood group AB have both A and B antigens on their red blood cells and are genetically AB – they inherited both an A gene and a B gene from their parents. Individuals with blood group O did not inherit any A or B genes and have no A or B antigens on their red blood cells. Individuals who are blood group A may be genetically AA (they have two copies of the A gene) or AO (they have one copy of the A gene), depending on the genes inherited from each parent. Similarly, group B individuals may be BB or BO. There are also subtypes of group A blood; about 80 per cent of people have subtype A1 antigens and 20 per cent have subtype A2 antigens.

- **Secretor status.** As well as being found on red blood cells, A and B antigens can be secreted in soluble form into the bloodstream. Soluble A and B antigens have been found to protect against red blood cell hemolysis, but not everyone has these. Whether an individual is a “secretor” or “non-secretor” of soluble A and B antigens is based on whether they have the genes for a functional secretor protein.

- **Fcγ receptor.** This immune cell protein can be involved in red blood cell destruction. The researchers examined the number of copies of the Fcγ receptor gene each patient had, and looked for certain mutations within this receptor that might influence susceptibility to red blood cell hemolysis.

In brief...
Patients with blood group AB are more susceptible to a serious adverse reaction to high-dose IVIg, and would benefit from close monitoring for signs of hemolysis following treatment.
What did the researchers find?

- The incidence of hemolysis was highest for patients with AB blood who had the A1 subtype (group A1B). Of these 6 patients, all had IVIg-associated hemolysis. Having the O allele (i.e. being AO or BO) provided some protection against IVIg-associated hemolysis.
- Subtypes of group A (A1 or A2) seemed to influence risk: Of the 15 patients with an A gene who had hemolysis, none had the group A2 gene.
- Secretor status showed no correlation with IVIg-related hemolysis. Hemolysis occurred in 55 per cent of secretors and 36 per cent of non-secretors. There did not appear to be any difference in severity of hemolysis between secretors and non-secretors.
- There was no link between IVIg-related hemolysis and the copy number of the Fcγ receptor nor any tested mutations in the Fcγ receptor.

How can you use this research?

A patient’s ABO genetic make-up influences their susceptibility to IVIg-associated hemolysis. Having the O allele or the A2 subtype of group A blood seemed to protect against hemolysis. This may be related to antigen density - the amount of antigen on the red blood cell - which has been previously linked to the extent of hemolysis. People who are AO (or BO) have less antigen on the surface of their red blood cells than those who are AA (or BB). Group A2 is also known to have a lower antigen density than group A1.

While these findings are preliminary and limited by the small number of patients tested, they show that patients who are group A1B are at higher risk for IVIg-associated hemolysis. The results may seem to suggest that to minimize the risk of IVIg-associated hemolysis, IVIg treatment should be avoided in patients who are known to be blood group A1B. However, determining whether a patient is A1B, or indeed AA, AO, BB, or BO, requires genetic testing, which is not routinely done. Typing for AB is a routine test. Since A1B is the most common AB subtype, determining whether a patient who will receive IVIg is blood group AB is a practical approach to identifying those patients most at risk of IVIg-associated hemolysis.

IVIg is an effective treatment, and there are no effective alternatives to IVIg for many conditions in which it is used. These findings indicate that it would be prudent to monitor patients with blood group AB closely for any signs of hemolysis following high-dose IVIg treatment, and if necessary modify their treatment to prevent the development of severe hemolysis.

About the research team: This study was led by Dr. Donald R. Branch, a Canadian Blood Services scientist, and at professor in the departments of medicine, and laboratory medicine and pathobiology, at the University of Toronto. The study was conducted with collaborators from the University Health Network, Sunnybrook Health Sciences Centre, St. Michael’s Hospital, Mount Sinai Hospital, and the Hospital for Sick Children, all in Toronto, Institut Universitaire de Cardiologie et Pneumologie de Québec in Québec City, and international collaborators in Lund, Sweden, and Amsterdam, the Netherlands.

This Research Unit is derived from the following publication(s):

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