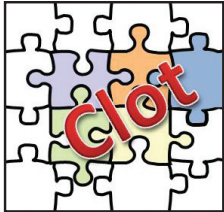


LOW IRON LEVELS AND BLOOD CLOTS IN HHT



"blood clot" jigsaw puzzle

You probably know that people with hereditary hemorrhagic telangiectasia (HHT) are often short of iron because of bleeding, particularly from the nose. Being short of iron is what makes you anemic. But how does this fit in with blood clots? The key messages from our recently published study¹ were:

1. It is surprisingly common for people with HHT to have blood clots – the rate appeared to be at least twice that of the general population.
2. People with HHT and lower blood levels of iron were at higher risk of blood clots. This did not mean low iron levels cause blood clots in HHT, it just seemed to make blood clots more likely. If people had taken iron tablets to keep iron levels normal, they were not at increased risk. The extra risk from low iron levels appeared to be due to higher blood levels of an important risk factor for blood clots, coagulation factor VIII.
3. Ferritin was not a good marker of iron deficiency because it was often high for other reasons in people who were short of iron.

We already know that people who bleed need a higher iron intake to balance their iron losses. The study just provides another reason to keep a close eye on iron levels. The big message for people with HHT is that they are at risk of blood clots, despite having a blood vessel/bleeding disorder; normal clot prevention measures should be used at appropriate times as in the general population.

Background

We all need the clotting system to work properly, to prevent excessive bleeding. But sometimes, instead of producing a small clot just where it is needed, the blood clotting process produces much a larger blood clot which can cause severe problems and even death. When blood clots form in the major veins they are called deep venous thromboses (DVT). These can break off and travel to the lungs, as pulmonary emboli (PEs). Treating these clots with blood thinning agents such as warfarin (coumarin) or heparin is standard medical practice. Even for people who have HHT, treatment with blood thinning agents may be needed if they also have blood clots. But it is obviously safer to prevent blood clots in the first place.

I think the best way to consider blood clot risks is by thinking of doing a jigsaw puzzle - you need many pieces in place before you can see the picture.

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We are all born with a few pieces in our "blood clot" jigsaw puzzle. Some people are born with more pieces than others, making them more prone to having blood clots at high risk times. By themselves, no one piece of the puzzle can be considered to cause clots, they just increase the risk.

Throughout life there are ways to fill in more pieces of the puzzle – having surgery, for example. Medical practice recognizes these times of higher clinical risk, and there are guidelines advising nurses and doctors when to use clot preventers like graded compression stockings, and/or low dose blood thinning injections. But many important blood clots happen at non high risk times, apparently out of the blue. You could think of them as happening to people who had lots of pieces in their jigsaw puzzle, although it wasn't realized.

Sometimes we can find a label or marker in the blood that means a person is at higher risk of having a blood clot. One example of this is the clotting factor, factor VIII ("factor 8") which you may have heard of because very low levels cause the bleeding condition hemophilia.

For some people, factor VIII levels are high at least 6 months after any illness, surgery or pregnancy – what we consider to be high "resting" levels. We do not know why resting factor VIII levels are high in some people - they do rise a little as people get older, but no genetic cause of high factor VIII levels has ever been identified. However, it is known that people with higher resting levels of factor VIII are at higher risk of having blood clots, both in the general population², and for people with HHT³.

This is where the new iron study comes in. ***Until this study, we hadn't realized that low blood levels of iron are a piece of the blood clot jigsaw puzzle for people with HHT.***

What does this mean for people with HHT?

1. The biggest new message for people with HHT is that they are at risk of blood clots, despite having a bleeding disorder, and that normal clot prevention measures, including low dose blood thinning agents, should be used at appropriate times as in the general population.
2. Prevention and treatment of iron deficiency anemia is already a big part of HHT medical practice. The CDC advises that people who are at risk of iron deficiency should eat a healthful diet that includes good sources of iron, and eating foods that help your body absorb iron better⁴. These include fruits or vegetables that are good sources of vitamin C. There are also recommendations on how iron supplements should be given. The CDC does not recommend people start iron supplements without consulting a healthcare provider⁴.

3. Even though the studies were of more than 600 people in total, the study still should be confirmed in other groups of people with HHT.*

What does this mean to people in the general population, without HHT?

At present, the study results cannot be extended to the general population; it may be that in terms of blood clots, low iron levels only matter for people with HHT. Further studies will need to be performed.

That being said, **iron deficiency is the most common nutritional deficiency and the leading cause of anemia in the United States.** Data from the UK National Blood Service shows that after operations, more blood transfusions are needed in people who had low iron stores when they went into hospital. The research is therefore a further reminder of the importance of iron, and while we wait to see if the link to blood clots is also seen in the general population, there are very good reasons for paying more attention to iron levels.

** Researchers considering looking back at their databases to see if the findings are true in other populations should take into account that the study showed the timing of samples for blood levels of iron really matters, and that a commonly used blood marker of iron deficiency (ferritin) cannot be used because it is elevated by too many other conditions, even if people are very short of iron.*

References:

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2. Kyrle PA, Minar E, Hirschl M, Bialonczyk C, Stain M, Schneider B, Weltermann A, Speiser W, Lechner K, Eichinger S. High plasma levels of factor VIII and the risk of recurrent venous thromboembolism. *N Engl J Med*. 2000 Aug 17;343(7):457-62.
3. Shovlin CL, Sulainam NL, Govani FS, Jackson JE, Begbie ME. Elevated Factor VIII in hereditary hemorrhagic telangiectasia (HHT): association with venous thromboembolism. *Thrombosis and Haemostasis* 2007;98(5):1031-9.
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CAN YOU TELL ME A LITTLE MORE ABOUT HOW THIS STUDY CAME ABOUT?

The study actually started back in 1999 when Dr. Shovlin realized that people with HHT seemed to be having a lot of blood clots. This had not been suspected before. After all, HHT is recognized and named as a bleeding disorder.

In 2000, Dr. Megan Begbie and Dr. Claire Shovlin set out to identify differences in blood from healthy people with HHT and age-matched controls. In clinic and study days at Hammersmith Hospital, people with HHT and their partners kindly gave blood samples for the research study which Dr. Begbie presented to the 4th HHT Scientific Conference in Tenerife in 2001. Later, they found an important difference - the HHT group had higher levels of factor VIII³. At the same time, Dr. Shovlin was running a busy HHT clinical service, supported by colleagues in Hematology. By 2006, the numbers were high enough to look at the differences between people with and without blood clots; this showed high factor VIII was linked to thrombosis risk, as in the general population.³

But there was an association between high levels of factor VIII and iron. This was very unexpected. Dr. Shovlin had only measured iron carefully because this was important to guide the clinical management of the patients she was reviewing with nosebleeds and anemia. At that stage, it was not clear whether the higher blood clot risks were with low iron levels due to bleeding, or the treatments for low iron levels.

By the end of 2009, an additional 200 people had been seen, and John Livesey, an Imperial College medical student, was recruited to the group to look at what factors were linked to

high factor VIII in this new group of HHT patients. John was told that the team had “found something” in the first series, but did not tell him what it was. That may sound odd, but it is very important that studies are genuinely replicated, without bias. John worked exceptionally hard during his Bachelor Science (BSc) project; he found the same results as were found in the first series. This was very impressive for a student and he was rewarded with the William Broadbent BSc Project student prize for Imperial College London. John also presented his findings at the 9th HHT Scientific Conference in Turkey last year.

For the final paper, patients seen up to January 2011 were included. Overall, the study showed that lower blood iron levels were associated both with higher blood clot risk and higher factor VIII levels. This was not because people with lower iron levels were older or younger. As expected, higher factor VIII levels were also associated with an increased risk of blood clots. Interestingly, high factor VIII and low blood iron fit into the same “slot” of the jigsaw puzzle - if factor VIII was in place in the jigsaw puzzle, low serum iron levels did not add any more.

The reason why this study is of importance for people with HHT, and potentially beyond, is that while it is not possible to lower high factor VIII levels directly (other than treating the reason(s) why the levels are high, or waiting for them to end), it is possible to prevent and treat low iron levels.