This Week in Hemophilia

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Closing the Gender Gap: Why Carrier Screening is Key for Women in Hemophilia Care
Link:
https://ashpublications.org/bloodadvances/article/doi/10.1182/bloodadvances.2024013866/517516/Proactive-Systematic-Hemophilia-Carrier-Screening

Hemophilia is an inherited bleeding disorder passed down through families, mainly affecting males, but women can carry the defective gene and may also experience symptoms. Identifying female carriers is critical as they may have low coagulation factor levels, leading to bleeding complications, and the study aims to address gaps in diagnosis and care for these individuals.

To conduct this study, the researchers systematically updated family pedigrees of male patients with hemophilia and reached out to female relatives for carrier screening. Genetic testing and factor level assessments were performed on obligate (certain) and potential carriers. This proactive approach also included inviting unscreened female relatives through letters sent to their families. The goal was to identify as many carriers as possible and provide them with early diagnostic care.

The results showed that about half of the 900 identified female relatives were confirmed as carriers, but a significant number remained untested. Among those tested, a substantial portion had low factor levels, indicating they were at risk for bleeding problems. Carriers with factor deficiencies were diagnosed earlier than those without, highlighting the importance of timely screening.

This study is crucial for improving the recognition and care of women with bleeding disorders, which has historically been overlooked. By identifying carriers early, women can receive appropriate treatment and make informed decisions about family planning and health management. The findings emphasize the need for systematic screening programs and better awareness among healthcare providers to ensure equal access to care for all individuals affected by hemophilia, regardless of gender.

Body fat and lean mass in people with hemophilia
Link: https://onlinelibrary.wiley.com/doi/full/10.1111/hae.15091

The study addresses an important gap in understanding body composition in people with hemophilia (PwH), specifically looking at differences in body fat and muscle mass based on hemophilia severity and age. This is significant because PwH, particularly those with severe cases, often experience joint problems that limit their mobility, which can lead to reduced muscle mass (called muscle atrophy) and higher fat levels. Understanding these body composition changes can help improve health management for PwH, as increased body fat and decreased muscle mass are linked to higher risks of heart and metabolic diseases.

To investigate this, researchers used a technology called dual x-ray absorptiometry (DXA), which is a highly accurate way to measure body fat, muscle mass, and visceral adipose tissue (VAT, which is fat stored around the organs). The study included 201 men with different levels of hemophilia severity—mild, moderate, and severe—divided into five age groups. By doing a full-body DXA scan, the researchers measured body fat percentage, muscle mass in the arms and legs, and VAT.

The results showed that PwH with severe hemophilia had significantly less muscle mass than those with moderate or mild hemophilia, particularly in the arms and legs. However, body fat percentage

and VAT were similar across all severity levels but increased with age. Older participants (40 years and older) had higher amounts of fat, while muscle mass didn’t significantly differ between age groups.

These findings highlight that PwH, especially those with severe hemophilia, are at higher risk for muscle loss due to reduced physical activity. The study's results contribute to a better understanding of body composition in hemophilia and suggest that maintaining muscle mass should be a focus in treatment plans, especially in older patients. This knowledge could help guide more personalized physical therapy and lifestyle interventions to manage health risks in PwH, particularly as they age.

Engineered FVIII variant for gene therapy
Link: https://www.nature.com/articles/s41467-024-51296-8

This study addresses a significant challenge in treating Hemophilia A through gene therapy: achieving durable and effective expression of factor VIII (FVIII), a key protein missing in those with Hemophilia A. While initial gene therapies showed promise by temporarily raising FVIII levels, they often resulted in a long-term decline in FVIII expression, limiting their effectiveness. This issue is important because stable and long-lasting FVIII production could eliminate the need for frequent FVIII infusions and improve the quality of life for people with Hemophilia A.

In this research, the authors investigated whether a modified version of FVIII, known as FVIII-QQ, could offer a better solution. This variant is engineered to resist inactivation by activated protein C (APC), which normally reduces FVIII's activity. By making FVIII-QQ more resistant to inactivation, the researchers aimed to maintain effective blood clotting even when the FVIII levels were low, which could allow lower doses of gene therapy and reduce potential side effects from the viral vectors used to deliver the gene.

The methods included testing this modified FVIII-QQ gene therapy in male mice with Hemophilia A. The researchers measured how long FVIII-QQ levels remained in the bloodstream and how effective it was in promoting clotting compared to standard FVIII. The results showed that FVIII-QQ provided stronger clotting effects than the standard FVIII, even at lower levels of expression. Importantly, FVIII-QQ did not cause increased risk of blood clots, which is a key safety concern.

These findings contribute to the broader goal of developing more reliable gene therapies for Hemophilia A. By demonstrating that FVIII-QQ can provide durable and effective clotting function at lower doses, this research suggests a potential path toward gene therapies that are both safer and more effective in the long term. If these results are replicated in humans, it could revolutionize the treatment landscape for people with Hemophilia A, offering a more permanent and manageable solution.