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Navigating the Complexities of Sickle Cell Disease: An Expert Perspective

ReachMD Announcer:
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Here’s your host, Dr. Jennifer Caudle.

Dr. Caudle:
This is ReachMD, and I’m your host, Dr. Jennifer Caudle. Today, our discussion focuses on the pathophysiology, clinical presentation, burden, and unmet needs of sickle cell disease.

And joining me for our program today is Dr. Samuel R. Wilson. He’s an Assistant Professor of Medicine in the Division of Hematology at the University of North Carolina School of Medicine in Chapel Hill. Dr. Wilson, welcome.

Dr. Wilson:
Thank you.

Dr. Caudle:
So let's start with some background. What’s the cause and prevalence of sickle cell disease, both in the U.S. and on a worldwide scale?

Dr. Wilson:
So, sickle cell disease is a group of inherited disorders caused by a variant in the beta-globin gene, leading to the production of abnormal hemoglobin known as hemoglobin S.[1,2]

So, sickle cell disease occurs when a person inherits the hemoglobin S gene with a second variant beta-globin gene, such as another hemoglobin S or a hemoglobin C, D, or beta thalassemia mutation. And all of this leads to the underproduction of hemoglobin A.[3]

So people with homozygous hemoglobin S or sickle cell anemia, or SS, the most common form of sickle cell disease, produce mostly hemoglobin S. And under deoxygenated conditions, such as when our red blood cells deliver oxygen to our tissues, the hemoglobin S chains will polymerize, or create long chains of hemoglobin. And these chains are inflexible and impact the red cell shape, resulting in the characteristic sickled shape that we see in sickle cell. And thereby, this leads to abnormal red blood cell function, it leads to red blood cell breakdown or hemolysis, and ultimately leads to the various clinical manifestations that we see in sickle cell disease, including vaso-occlusion and anemia.[1,2]

In terms of its prevalence, sickle cell disease is among the most common inherited conditions globally, affecting more than seven million individuals worldwide, which is a lot.[1,4,5]

It’s more common in people descending from areas where malaria is or was endemic, with an incidence of 0.07 per 1,000 births in nonendemic areas but 10.68 per 1,000 births in African regions where there’s high malaria endemicity.[5,6]

And in the U.S., it impacts about 100,000 individuals, with higher prevalence in the Black or African-American population at one out of 365 births, and the Hispanic-American population at one out of 16,300 births.[5]

The most common genotype for individuals with sickle cell disease in the U.S. is hemoglobin SS, and this accounts for about 75.6 percent of the population.[7]

Now if we turn to disease burden, sickle cell disease has an annual global mortality of 376,000 individuals.[4]

In the U.S., sickle cell disease continues to be a source of early mortality among the Black American population, with a reduced overall life expectancy of 40 to 50 years compared to the national average of 70 years, which is a two decade gap. And the sickle cell disease annual death rate in the Black American population is much higher than in the global population, at 1.91 versus 0.4 per 100,000 population.[4,8]

Dr. Caudle:
I'd like to dive deeper into the pathophysiology of sickle cell disease. Could you explain the core processes of disease development and progression?

Dr. Wilson:
Of course.

So, one key pathophysiological process that we see in sickle cell disease is hemoglobin S polymerization, which leads to all the downstream of sickle cell disease symptoms.[1,9]

So, what is hemoglobin S? So, The substitution of glutamic acid for valine at the sixth position of the beta-globin chain leads to the formation of hemoglobin S.[1,3]

And when hemoglobin S is deoxygenated, it can form long polymers that are rigid and physically distort the shape of the red blood cells.[2,3]

This polymerization leads to sickling, impaired blood flow to tissues, and hemolysis.[2]

We also see increased adhesion-mediated vaso-occlusion as a result of sickled red blood cells, leading to aggregation of inflammatory cells such as neutrophils, platelets, and endothelial cells, and all of this contributes to impaired blood flow.[1,2]

And another disease mechanism is that the hemolysis-mediates endothelial dysfunction. So, free heme from hemolysis leads to depletion of endothelial nitric oxide reserves and the generation of oxygen-free radicals.[1,2]

There is sterile inflammation, and that also promotes vaso-occlusion.[2]

So if we take a look at each of these processes you have deoxygenation of abnormal hemoglobin S polymers leading to intravascular hemolysis, and then this contributes to the chronic vasculopathy, platelet activation, and pulmonary hypertension.[10]

Intravascular hemolysis has many downstream effects. For example, it can inhibit nitric oxide signaling, which can lead to vasoconstriction and inflammation, and as well it can amplify reactive oxygen species formation, which disrupts the redox balance.[2,10]

So we see that intravascular hemolysis leads to endothelial dysfunction due to the activation of sterile, or pathogen-free, inflammation, and this is triggered by the release of heme from hemolysis, and then you get the recruitment of inflammatory cells, and the production of cytokines that promote adhesion molecules on the endothelial and red blood cells.[10,11]

These intricate processes contribute to the vaso-occlusion and chronic inflammatory state in sickle cell disease.[2]

Dr. Caudle:
Thanks for walking us through the underlying disease mechanisms, Dr. Wilson. And with that in mind, how does the pathophysiology of sickle cell disease affect clinical presentation and comorbidities in these patients?

Dr. Wilson:
That's a really great question, because these disease pathways of vaso-occlusion, inflammation, and hemolysis underlie a wide range of sickle cell disease clinical manifestations and comorbidities that significantly impact our patients' lives.

So, vaso-occlusion, which is a hallmark of sickle cell disease, leads to acute pain, acute chest syndrome, hyposplenism, osteonecrosis, and nephropathy.[3]

And these inflammatory processes in sickle cell disease contributes to a hypercoagulable state, and the nitric oxide dysregulation due to intravascular hemolysis can cause pulmonary hypertension, priapism, leg ulcers, and cerebrovascular disease.[3]

When we look at these sickle cell disease comorbidities by age, we find some differences in presentation.

In a retrospective longitudinal cohort study of over 7,500 individuals with sickle cell disease, vaso-occlusive pain and infection were the most common symptoms across all ages. Now older adults between the ages of 46 to 64 had higher rates of cardiopulmonary disease and lower rates of vaso-occlusive pain than younger adults. A major limitation of this study, however, is that genotype information isn't included, which does differ by ages because of survival bias.[12]

Dr. Caudle:
For those just tuning in, you're listening to ReachMD.

I'm Dr. Jennifer Caudle, and today I'm speaking with Dr. Samuel R. Wilson about sickle cell disease, its underlying pathways, and disease burden on patients.

So now that we've discussed the symptoms and comorbidities associated with sickle cell disease, Dr. Wilson, can you elaborate on how these contribute to the disease burden experienced by patients?

Dr. Wilson:
Of course. So in terms of disease burden, sickle cell disease has a significant impact on our patients' quality of life.

A multi-country, cross-sectional survey assessing the impact of sickle cell disease on the daily lives of over 2,100 patients reported disrupted functioning in both the emotional and functional domains.[13]

For example, 62 percent avoided intense physical activity due to sickle cell disease. Now some part of this was probably due to the worry about exercise leading to symptoms occurring, like painful episodes for 58 percent, exhaustion for 55 percent, and dehydration for 48 percent.[13]

Patients also reported disruptions in daily functioning and relationships, such as in family and social life activities for 41 percent, household daily activities for 38 percent, sexual desire and/or activity for 32 percent, and their relationship with spouse or partner for 32 percent.[13]

Putting this into perspective, the baseline physical functioning health-related quality of life in sickle cell disease has been comparable to or worse than in chronic diseases such as cancer, cystic fibrosis, and obesity, which we understand has a huge impact on quality of life.[14]

And if we consider the economic burden, the impact on healthcare costs and utilization is substantial.

So, in a retrospective observational study analyzing electronic health record claims over a ten-year period, the annual incremental economic burden of sickle cell disease was estimated to be approximately three billion dollars, with inpatient costs accounting for 57 percent of the total and outpatient costs for 38 percent.[15]

Meta-analysis and systematic review of the literature found that there were varying rates in the number of annual emergency department visits, hospitalizations per patient per year, and rates of readmission in adults with sickle cell disease.[16]

Dr. Caudle:
And what are the current unmet needs in sickle cell disease screening?

Dr. Wilson:
Despite advancements in the understanding and management of sickle cell disease, there are unmet needs in screening.

For instance, ensuring universal newborn screening for sickle cell disease worldwide is and continues to be a major challenge. Many individuals born in regions without universal sickle cell screening or before its widespread implementation in areas such as the U.S. may have missed diagnoses. And globally, standardized protocols for screening adults are lacking.[17,18]

Dr. Caudle:
And what about unmet needs in treatments?

Dr. Wilson:
So in the past 30 years, we have had an expansion in treatment options for sickle cell disease, which is welcome. Yet, given the current morbidity that we see in sickle cell disease, despite the availability of these treatments, I'm eager for the development of additional disease-modifying treatments that are better tolerated, have fewer side effects, and improve the quality of life and morbidity in sickle

cell.

Now we've touched on the clinical repercussions of vaso-occlusive events in sickle cell disease, but it's also crucial to understand the benefits of increasing hemoglobin levels.

A systematic literature review with meta-analysis modeling demonstrated that an increased hemoglobin of one gram per deciliter or more decreased risks of strokes and silent cerebral infarcts by 41 percent, albuminuria by 53 percent, and mortality by 64 percent. It's important to note that the studies included in these meta-analysis covered all genotypes and included patients both with and without treatment with hydroxyurea or transfusions.[20]

Currently available treatments include disease-modifying and transformative therapies.

Disease-modifying treatments include transfusions and pharmacotherapies.[19,21,22]

Red blood cell transfusions reduce circulating hemoglobin S-containing red blood cells.[3,21]

And pharmacotherapies can target a number of mechanisms underlying the pathophysiology of sickle cell disease, such as:[19,21]

- Increasing the fetal hemoglobin, which prevents hemoglobin S polymerization
- or by reducing oxidative stress
- inhibiting P-selectin, which contributes to vaso-occlusion
- and inhibiting hemoglobin S polymerization.

Transformative therapies, such as hematopoietic stem cell transplant or gene therapy, replace the bone marrow stem cells with donor or edited stem cells that do not sickle.[14,23]

Each of these treatments has its limitations, including cost, tolerability, effectiveness, side effects, and thus a patient-centric approach should be utilized when determining the best treatment for each patient.

Dr. Caudle:
With these unmet needs in mind, what emerging therapies are on the horizon for sickle cell disease?

Dr. Wilson:
The emerging treatment strategies for sickle cell disease aim to target the various pathways involved in the pathophysiology of the disease.

An upstream target is pyruvate kinase activation, which aims to improve the red blood cell health and survival while simultaneously reducing hemoglobin S polymerization and red blood cell sickling. It does this by increasing ATP and decreasing 2,3-DPG.[24]

One strategy to inhibit hemoglobin S polymerization is by increasing fetal hemoglobin production. As we mentioned earlier, fetal hemoglobin interrupts hemoglobin S polymerization. So fetal hemoglobin production can be increased via pharmacotherapies or via gene therapy.[19,21]

Downstream of that, targeted strategies include novel therapies that target other aspects of sickle cell disease pathophysiology, such as inflammation, oxidative stress, and adhesion molecule expression.[24,25]

Each of these emerging treatment strategies has value, and an individualized treatment approach should consider the patient's goal of care and preferences through shared decision-making.

Dr. Caudle:
And as we conclude our discussion today, Dr. Wilson, what key points would you like to leave with our audience?

Dr. Wilson:
Thank you. So it's important to keep in mind that sickle cell disease is a group of inherited disorders caused by variations in the beta-globin gene.[2,14]

And a key process in the disease development is hemoglobin S polymerization. This leads to a cascade of pathologic processes, resulting in endothelial dysfunction, vaso-occlusion, and inflammation.[2,9]

These disease pathways underlie the sickle cell disease clinical presentation and comorbidities, including impaired health-related quality of life and a considerable annual mortality burden.[4,13,14]

Dr. Caudle:
Well, as those key takeaways bring us to the end of today's program, I'd lile to thank my guest, Dr. Samuel R. Wilson, for helping us shed light on the complexities of sickle cell disease and the ongoing efforts to improve care for these patients.

Dr. Wilson, it was great speaking with you today.

Dr. Wilson:
It was a pleasure talking with you as well. And thank you for the invitation.

ReachMD Announcer:
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