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Preeclampsia may share cause with disorders such as Alzheimer's

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New research has identified a potential cause of and a better diagnostic method for preeclampsia, one of the most deadly and poorly understood pregnancy-related conditions in the world. The international team, led by researchers at Nationwide Children's Hospital, discovered that the disease may result from a collection of protein mishaps like those associated with Alzheimer's disease. Their findings, released today by *Science Translational Medicine*, have already led to an affordable, fast and accurate urine test that could revolutionize the diagnosis of preeclampsia in resource-poor nations.

"Preeclampsia is a very important health problem for women around the world, but for many years no one has understood why or how it happens," said Irina A. Buhimschi, MD, director of the Center for Perinatal Research in The Research Institute at Nationwide Children's and first author on the paper. "We were studying the urine of pregnant women with preeclampsia and noticed these improperly folded proteins, and that was the 'Eureka!' moment. It meant that preeclampsia could be similar to other protein misfolding diseases, such as Alzheimer's and mad cow disease."

Dr. Buhimschi's team is the first to characterize the range of misfolded proteins found in the urine of pregnant women with preeclampsia.

Preeclampsia is the leading cause of preterm delivery in industrialized nations and accounts for up to 75,000 maternal deaths worldwide each year. It is characterized by protein in the urine and often-asymptomatic

high blood pressure of no clear origin. When left untreated, the condition can progress to cause seizures, stroke, liver failure and death. Preeclampsia typically appears after the 20th week of pregnancy and only resolves upon delivery of the baby.

Dr. Buhimschi found that, in women with preeclampsia, the placenta was clogged with similar misfolded protein material to that found in the brains of people with Alzheimer's. To carry out their functions properly, proteins must fold themselves into precise three-dimensional structures. But misfolded proteins, which fail to morph into their intended shape, are unable to function correctly. These and other proteins try to travel to and from the mother and baby on what is essentially a busy highway, Dr. Buhimschi explained, but the misfolded proteins build up in the mother's body and in the placenta and cause a traffic jam.

To better understand the presence and importance of these proteins in the urine of pregnant women with preeclampsia, the team used a dye called Congo Red, which was known to bind proteins such as amyloid based on previous research done with other protein misfolding conditions. When this dye was used to test the urine of pregnant women, researchers found that it helped identify both the presence and future severity of preeclampsia.

The identified misfolded proteins include the amyloid precursor protein and enzymes and beta-amyloid, which are all associated with Alzheimer's. Additional proteins found that often misfold include ceruloplasmin, immunoglobulin- free light chains and SERPINA1, which build up in toxic quantities in protein conformational disorders. Interferon-inducible protein 6-16 (IFI 6-16), a protein not previously known to be associated with other misfolding diseases but that was uniquely found misfolded in the urine of women with preeclampsia, is known to help prevent cell death and, in breast cancer cells, is responsible for resistance to treatment. The team used computer

modeling to predict IFI 6-16's involvement in preeclampsia aggregates and is continuing research to determine the mechanisms behind this and other proteins' involvement in preeclampsia.

The studies resulting in this publication began seven years ago and have already led to a paper-based Congo Red Dot urine test for preeclampsia that won the international Grand Challenges for Development award, sponsored in part by the United States Agency for International Development. The project is now funded by a transition-to-scale grant from the Saving Lives at Birth consortium to determine whether the test improves preeclampsia diagnosis and reduces morbidity and mortality in resource-poor nations.

"In a way, we put the cart before the horse, getting the test in gear before we were able to formally publish all of the science behind it," Dr. Buhimschi said. "It was just a great opportunity to really help people with a simple, cheap, non-invasive and very accurate test."

The paper test currently being piloted is a more user-friendly version than the one in this publication, Dr. Buhimschi said, but it is based on the study's results regarding the ability of Congo Red dye to bind with the misfolded proteins in women's urine. "The test can help identify preeclampsia and predict its severity even before clinical symptoms appear," she explained. "These proteins aren't excreted in the urine of women who do not develop preeclampsia."

While pilot testing continues around the world and at The Ohio State University Wexner Medical Center, Dr. Buhimschi and her collaborators are working to better understand the profile of misfolded proteins present in women with preeclampsia.

"In most protein conformational disorders, there is a particular protein that is the key culprit," said Dr. Buhimschi, who also is a tenured

professor at The Ohio State University College of Medicine. "If we can figure out which protein is the most critical actor in preeclampsia, we could potentially use drugs that target protein misassembly for that particular protein. This would allow us to treat or even prevent preeclampsia symptoms in women who test positive on the Congo Red Dot test."

Understanding the range of mechanisms behind the pathophysiology of preeclampsia will be even more crucial to developing an effective treatment.

"The story is not over," Dr. Buhimschi said. "Preeclampsia may be more than one disease. Particular types may be associated with certain subtypes of protein collections. We want to figure out exactly how each misfolded protein collection affects pregnant women and what we can do about it."

More information: Buhimschi IA, Nayeri UA, Zhao G, Shook LL, Pensalfini A, Fuani EF, Bernstein IM, Glabe CG, Buhimschi CS. Protein misfolding, congophilia, oligomerization, and defective amyloid processing in preeclampsia. *Science Translational Medicine*. 16 July 2014, 6(245). stm.sciencemag.org/lookup/doi/ … scitranslmed.3008808

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