JESSICA J. KANDEL, MD: Hello. I'm going to be talking today about new clues to understanding lymphatic disorders in children. To disclose, we're going to be discussing the off-label uses of FDA-approved agents, including propranolol for vascular anomalies. All the patient photographs were obtained and are shown by consent.

What are lymphatic disorders in children? They are congenital errors in development of the lymphatic portion of the vascular system. And they include lymphatic malformations, congenital lymphedema, and congenital accumulations of lymph fluid, ascites-- which is fluid within the abdomen, or pleural effusions. Almost nothing is known of their pathobiology.

The next question a doctor would ask is which of these lymphatic disorders are clinically important. And we'd answer, those which exert systemic effects, which make the whole child ill. These can include mass effects from lymphatic malformations that cause occlusion of the aerodigestive tract. That is the part of your body that does breathing-- the airway, and swallowing-- your esophagus, or that impedes your vision.

Lymphatic malformations can also cause circulatory derangement-- swelling or fluid accumulation. And when this happens, the normal coagulation system can become disordered, so that the child has a coagulopathy and is very prone to having these areas super infected.

This study is an example of stasis. The MRI-- MRA in this case-- demonstrates really diffuse involvement of the child's tissues. The whitish spongy areas that you can see are those which are involved with lymphatic malformation. And this particular child has required numerous procedures for infection of the affected tissues.

Very valuably for our line of research, transgenic mice have been developed that mimic human lymphatic malformations. On the right-hand side of the two little mouse embryos, you can see one that looks very swollen and pale compared to the other. And this one has a lymphatic malformation. If we look at the tissues from the normal mouse, which light up brightly with colors, indicating the presence of normal lymphatic structures, we see that these are absent from the tissues of the mutant mouse.

This helps us begin the biologic characterization of human lymphatic anomalies. So we began to study human samples from patients that had undergone surgery or other interventions for their lymphatic malformations. What we found was that a protein called Notch was activated in the involved tissues and was expressed in the exact same places that we found markers from lymphatic malformations.

Here in green are erratic lymphatic vessels that are malformations. And they are lighting up because they express a protein that indicates they're lymphatic in origin. In the lower panel we see Notch in red expressed in the same places. So this was an example of misexpression of this Notch protein in lymphatic malformations, and was very similar to the mouse I showed you in the slide before. And this was actually a very important clue as to the nature of these lymphatic malformations.

They allowed us to go ahead and do more detailed characterization of the lymphatic malformations. We were able to isolate and characterize two types of cells from patients with these disorders. One were progenitor-like cells. And others were more differentiated lymphatic endothelial cells. We were then able to take these two types of cells and characterize their responses to a series of drugs. We were also able to take these cells and see whether they would form a lymphatic malformation when injected into mice. That is, would they recapitulate the clinical disorder. And in fact they did.

In the top panels in this slide you can see just controls in which no cells or their carrier substance were injected, and no malformation forms. In the lower three panels you can see we have injected the progenitor cells. And they form erratic channels similar to human lymphatic malformations. This meant we had a mouse model that we could use to test interventions on.

We also-- as I mentioned-- took the cells and exposed them to a series of drugs. And what we found somewhat to our surprise was both the lymphatic progenitor cells and the endothelial cells were very sensitive to a very old and familiar drug called propranolol, which is a beta blocker that has been used in childhood for about 30 to 40 years.

With this information we were able to offer options to families that previously had not had any. Our patient with a lymphatic anomaly was in the hospital again with a severe infection. Because his lymphatic malformation affected his skin, we were able to use our new insights and offer his parents treatment with a topical eye gel that is a cousin of propranolol, called timolol, and noticed almost immediate healing of his skin lesions. His parents asked that he be started on oral propranolol. And he did begin this. And we noted almost immediate shrinkage of his lesion with healing of his eruptions. And two weeks later the patient returned able to ambulate for the first time in three years. He had had such significant healing of his malformation. So this was a very exciting application of our basic observations.

In another case-- also around the same time-- we were referred a fetus, then at 33 weeks gestational age, who had a lymphatic malformation involving the lower face and neck. After discussion of their options, his parents were offered propranolol as a treatment. Fortunately this has been used very widely in maternal fetal medicine for many years, so we're well aware of the dosing and the risks and benefits.

And they decided to begin this. Serial MRIs of the infant showed that the baby grew, but the mass did not. And so the airway way became clear, which was also a very good result. The baby was confirmed to have an open airway shortly before delivery, and was actually delivered uneventfully with very good Apgar scores, and has not had any respiratory or feeding issues. The baby still has a little beard-like remnant of a lymphatic malformation, which you can see as the white projection beneath the chin, but has otherwise done well, and has been maintained since birth on propranolol.

And in the last case, we had a patient with lymphatic dysfunction that is without a defined malformation, but with collection of lymphatic fluid within the abdomen, edema, and ascites. He was 19. He had a life-long history of this edema and ascities, and was transferred to the intensive care unit after developing infection after surgery.

After he had recovered from surgery, he elected a trial of propranolol. Cells that were recovered from fluid we needed to remove from his pericardial space-- the space around his heart-- appeared to be lymphatic progenitor cells, which expressed beta adrenergic receptors-- which are the target of propranolol. After the patient began medication, a month later his weight was five kilograms below his baseline, and he needed to buy clothing in a smaller size because his edema had resolved so significantly. This was another very encouraging result.

Just in summary, patients with lymphatic disorders can benefit from recent research. The emergence of our biologic understanding has revealed new targets for treatment. We are beginning to define which patients may respond to propranolol. And I'd like to acknowledge my colleagues in this work, among them Sonia Hernandez, a vascular biologist at the University of Chicago Medicine, and the Vascular Anomalies Group, also at the University of Chicago.

Thank you very much.