

**SPEAKER:** In Fabry disease, which is a lysosomal storage disease, there is accumulation of Gb3 in the lysosomes. And this is thought to be one of the reasons that we develop gastrointestinal symptoms in Fabry patients. Currently, there aren't great studies and great data on the cause of the gastrointestinal symptoms.

However, there are various theories as to the reason that patients develop these symptoms based on the etiology and other systems in the body, including the cardiovascular and the renal presentation. The thought behind gastrointestinal symptoms is that there is both vascular and neuronal, and possibly immunologic and inflammatory dysregulation that leads to the symptoms.

In terms of the vascular component, there is thought to be the accumulation of Gb3 in the endothelium and the vessel walls, which both leads to hypertrophy of the vessel walls, and also leads to abnormal signaling, leading to increased hypertrophy also. And so therefore, the thought is that because of these thickened vessel walls, you have decreased perfusion and decreased blood flow in the GI vessels.

With this decreased blood flow, therefore, you're going to have moments or possible issues with this ischemia and lack of blood flow to important GI organs. This is thought to cause some of the symptoms, including the abdominal pain, particularly when there's moments of higher stress, such as eating or exercise. If there's not enough blood flow to these areas, it can lead to possible intermittent ischemia and presentation of the GI symptoms.

The other thought process that may be-- the other thought behind the processes that might be leading to the gastrointestinal manifestations are nerve damage. Again, this is thought to be due to the Gb3 accumulation within the nerves, leading to nerve damage. This can be seen under the microscope if you do a colonoscopy and take biopsies. It's also been found in gastric biopsies with Gb3 accumulation in the nerves, which can then lead to damage of the nerves and abnormal functioning of these nerves, which we think leads to the neuropathies causing frequently the pain and the diarrhea that we see in these patients.

Additionally, newer studies are looking at inflammatory and immunology components, including nitric oxide and other pathways that might be altered due to this Gb3 accumulation, and therefore leading to presentation of the symptom.