KRESSER INSTITUTE FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

Gut Pathology - Part Seven

Risk Factors for Intestinal Permeability

Genetic susceptibility	NSAIDs
Gender *(M)*	Gut pathogens
Inflammation	Nutrient deficiency
SIBO/dysbiosis	Stress
Alcohol consumption	

Risk factors for intestinal permeability are listed on this slide. Genetic susceptibility is certainly one, we know that 10 to 25 percent of first-degree relatives of inflammatory bowel disease patients have intestinal permeability, even in the absence of any other symptoms. Gender is a risk factor, estradiol regulates the epithelium formation, and occludin expression, which in turn affects the tight junctions. So females who tend to have higher levels of estradiol, like these female rats in studies are more resistant to tissue injury that's induced by acidosis, so it's thought that being male is actually one of the risk factors for intestinal permeability. Inflammation is another; inflammatory cytokines disrupt the tight junctions. SIBO, or dysbiosis, is a risk factor, SIBO has been associated with intestinal permeability in studies, and probiotics have been shown to decrease intestinal permeability by improving tight junction function and decreasing inflammation. It's well established that alcohol consumption, particularly significant alcohol consumption in a short period of time, disrupts the function of the tight junctions, and increases permeability. We know that NSAIDs like ibuprofen directly damage epithelial surfaces and lead to gut permeability. Gut pathogens such as C*lostridium difficile*, *E. coli*, and more, activate an inflammatory cascade that can modify or impair the function of the tight junctions. We know that several different nutrient deficiencies like vitamin A, zinc, long-chain omega-3 fats, vitamin D, and magnesium can increase barrier permeability, and we know that stress can affect occludin and zonulin levels, which would impact tight junctions and intestinal permeability.

Testing for intestinal permeability, as with SIBO testing, is not perfect, and there's no gold standard test. As of now, there are three common methods for assessing intestinal permeability: the lactulose-mannitol urine test, antigenic intestinal permeability screen, and direct zonulin measurement via serum testing. Just recently has the serum zonulin testing become more widely available and used in clinical practice. The lactulose-mannitol urine test and antigenic intestinal permeability screen have been historically what were used both in research and in clinical settings. There is still some disagreement on the utility and accuracy of serum zonulin testing for various

reasons that include discrepancies on which zonulin family peptides are actually being tested and reported in commercially available ELISAs and some instances that have shown inconsistencies or weak correlations in serum zonulin family peptide levels when compared to the lactulose-mannitol tests. Other markers under investigation include urinary D-lactate and fecal butyrate. The best approach is probably to use a combination of some of these things, but that may not always be practical. We'll discuss the ins and outs of various testing when we review the test section later.

The final pathology we'll discuss is autoimmunity. So I've touched on this already throughout the presentation, but specifically now with gut pathology we're referring to inflammatory bowel disease, and that is primarily Crohn's and ulcerative colitis. The difference between these two is that ulcerative colitis is restricted to the colon or rectum and affects only the superficial layer of the mucosa, whereas Crohn's can occur anywhere in the gastrointestinal tract and can affect all layers of the GI tract. These conditions are still not well understood, it's not for lack of effort, they've been studied extensively, and there are a lot of different competing theories about what causes them. There's a school of thought that they're caused by a mycobacterium that infects the intestine and leads to this kind of chronic inflammation. There is the more prevailing theory that they're caused by an autoimmune response to commensal gut bacteria, so anyone who has an IBD condition, it essentially attacks their own beneficial commensal gut bacteria, and then this causes persistent inflammation and tissue damage. In the old friends hypothesis, one of the theories is that commensal organisms that we co-evolve with, like hookworm, typically tune and regulate our immune system, that are no longer present in these highly sanitized environments that we live in, have actually predisposed us to this kind of autoimmune response, and that's one of the main causes or theories of IBD. As I mentioned before, Alessio Fasano and others believe that intestinal permeability is a pre-condition to developing inflammatory bowel disease and other autoimmune diseases, in which case that would be one of the major pathological mechanisms.

The risk factors for IBD are numerous, and include genetics, cigarette smoking, diet, physical inactivity, obesity, infections, antibiotics, NSAIDs, oral contraceptives, chronic stress, and sleep deprivation. Symptoms are pretty consistent with other gut dysfunction, but some that are less common in functional gut problems like IBS would be bleeding, abscesses, fistulas, B-12 deficiency because B-12 is absorbed in the terminal ileum, and that's often the area that's affected in Crohn's disease, and then extra-intestinal symptoms like skin conditions, arthritis, kidney stones, osteoporosis, macrocytic anemia, pulmonary involvement and eye disease, many of which are related to nutrient deficiencies that can be caused by IBD.

Testing for IBD is actually more straightforward and conclusive, typically, than testing for things like intestinal permeability and SIBO. IBD is often diagnosed by colonoscopy or endoscopy or capsule endoscopy, which is where you swallow a camera and it goes all the way through the intestinal tract taking pictures. It's a pretty expensive test, insurance doesn't typically cover it, and it's usually not used unless the suspicion is that the inflammation is in an area that can't be reached by an endoscope or colonoscopy. There are new markers for serum testing that can help to identify likelihood of IBD, and these include things like erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and then there are newer antibodies like ASCA and ANCA and anti-OMPC and anti-CBIR1. You can get these as a panel together from labs like Labcorp or Quest, and they can be helpful in identifying people that are more likely to have IBD, that you might be more likely to refer

to a colonoscopy if those antibodies are present. We're going to talk more about diagnostic algorithm for IBD later, when we talk in detail about that condition. There are also some really good stool markers for IBD that are on the Doctor's Data, Diagnostic Solutions Laboratory, and Genova Diagnostics stool tests that we're going to be teaching and discussing later, like calprotectin, lactoferrin and lysozyme. Significant elevations in the fecal versions of these markers can indicate different stages of IBD and can be helpful in differentiating between IBD and functional gut disorders like IBS.

Okay, that's it for now. Next we're going to dive into diagnosis and treatment of food intolerances and start looking at labs and specific cases.