EDS and the Gut

This article aims to provide an informal summary, for nonphysicians, of an important scientific paper reviewing gastroenterologic aspects of the Ehlers Danlos Syndromes. I have added comments based on my own experience as a medical generalist, working with EDS patients over the last 15 years. At the end, I make some general comments about the management and mismanagement of gut problems in people with EDS.

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Introduction

In early 2017, a series of articles on various aspects of the Ehlers Danlos Syndromes were published, in a special issue of the American Journal of Medical Genetics (AJMG).[1] These were the result of an effort over several years by the International Consortium on Ehlers Danlos Syndrome. One of these dealt with "gastroenterologic involvement in the Ehlers Danlos Syndromes." Like the other articles, it is written for doctors and researchers, not for the public or for patients with EDS. Its intent was to provide a review of the scientific literature on the subject, editorialized by suitable experts. My aim here is to summarize the material in that article that is relevant for people who have EDS or a similar condition. I am not a gastroenterologist, but a "medical generalist" who has been working closely with EDS patients for about 15 years. I have added my own comments, based on that experience. I hope some of what is below will be helpful to people with EDS looking for good treatment for "gastroenterological problems", or as I would prefer to say, trouble with their guts.[2]

Where are the American gastroenterologists?

The AJMG paper is co-authored by five physicians. Two are senior gastroenterologists at medical schools in London. Two are pediatric gastroenterologists at the Children's Hospital of Wisconsin. One is a physical medicine and rehabilitation specialist at Memorial Hospital in South Bend, Indiana.

Comment: *The lack of a representative expert in adult gastroenterology from the USA is noteworthy. It fits with my failure to find any gastroenterologists from the USA in attendance at recent American conferences on EDS. Gut problems in EDS have been reported in gastroenterology journals for over 30 years, and one of the types of EDS can cause death due to bleeding or rupture of the gut: yet gastroenterologists are taught little or nothing about these conditions in their training, or later. Ehlers Danlos Syndromes are not rare: I estimate there are at least 20,000 people with these conditions in North Carolina.[3] So there is a quite reprehensible lack of interest in them by medical specialties. This is why I write articles about EDS for patients – because only if they learn more about their condition than their doctors, can they have a chance of pressing for better medical care.*

Defective connective tissue in the gut

The AJMG paper summarizes a number of studies showing that in several, well-known gut disorders, there are abnormalities of the connective tissue in its walls, when seen at the microscopic or the chemical level. If some of these abnormalities cause the disorders, then this is one factor that could explain an association of EDS with gut disorders, since a major underlying feature of EDS is just such abnormalities of connective tissue.

Comment: *There's a strong tendency, among doctors and patients with EDS, to assume that all its manifestations are due to "loose tissues," whether those are the ligaments (that hold joints together), or connective tissue in general, which includes the skin, the membranes and sheaths that hold together soft organs such as the liver or the brain, and the webs that permeate the insides of firmer organs like muscles and bones, to provide structure and play various other supportive roles. This assumption is very dubious. Several of the common features of EDS, for instance anxiety, or dysautonomia (see later), have no plausible basis in physical looseness of connective tissues at the macroscopic level (meaning perceptible to unaided vision and touch). However, they may possibly be due to much subtler, but still "mechanical" defects, such as alterations in the fluid that surrounds all cells (the extra-cellular matrix or ECM) affecting the ease with which certain molecules can diffuse through it. Indeed, the simplest explanatory model for all the manifestations of EDS would be one based on an abnormality at this level, present in all tissues and organs, but only have perceptibly damaging effects on a few.*

Structural gut disorders in EDS

A "structural" medical disorder is an abnormality in the physical layout of an organ, at the level at which it can be seen by the naked eye. A dislocated shoulder is a structural disorder. So is a tight place (stenosis) in a blood vessel, or a slipped disc (herniated nucleus pulposus) in the spine. There are reports of structural disorders in people with hEDS, including diverticulosis of the colon, rectocele and rectal prolapse. But no studies show how common these are, or whether they respond to treatment any differently in the presence of hEDS.

Comment: *There are very few case reports of reversible structural gut disorders in EDS, meaning organs whose "layout" changes depending on what position the patient is in, and what's in the gut. This is important, because if the connective tissues that give shape to the abdominal organs were abnormally loose, this could produce visceroptosis, which is a displacement of a whole organ (or more than one). So for instance, if the connective tissues supporting the stomach were loose, it could drop down in the abdomen, and would be much more prone to do so if it were full of food. Such a drop could stretch or kink its blood vessels and/or its nerves, which could interfere with its function in digesting food and passing it on to the intestine beyond it. I have seen one case in which a kidney, in a patient with hEDS, was tethered so loosely in the abdomen that it caused various problems and required surgery to attach it back to its proper place. I have also seen a patient with hEDS whose bladder was so mobile that it could be seen, under an ultrasound scan, to "wander" all over the pelvis, depending on the patient's position. Since almost all x-rays and scans are done with patients lying on their backs, such reversible disorders may evade detection because the organs would then return to their normal positions when the patient lies down for the scan.*

Functional gut disorders in EDS

Several studies in the AJMG review show that "functional" gut disorders (see comment below) are very common indeed in EDS.[4] The studies showing this are convincing because of the very high correlations found, and because they come from different clinic populations in several different countries. An extraordinary finding from one study, based on patients at a gastroenterology clinic in England, was that a full one third of unselected patients turned out to have hypermobility-type Ehlers Danlos Syndrome (hEDS), using the standard diagnostic criteria used in 2014. In these hEDS patients, the disorders were mainly of the stomach and esophagus, i.e. abdominal discomfort after eating, and esophageal reflux (causing pain in the lower chest, and sometimes regurgitation of food up into the mouth); bowel problems (cramps, diarrhea, constipation) were rather less common. In a study from the Mayo clinic, patients with EDS were investigated for symptoms that sounded "functional" using methods designed to show abnormalities of gut movement. About a third of patients did have abnormal movement patterns in the stomach or colon, and/or reflux (food coming back up the esophagus from the stomach).

Other studies used standard criteria to assign particular kinds of functional gastrointestinal disorders (FGIDs) to patients with abdominal complaints who also had hEDS. These patients did indeed have recognizable types of FGID such as irritable bowel syndrome (IBS), rectal evacuatory dysfunction, functional constipation, and postprandial distress syndrome. (The latter was the most common.)

Comment: *A "functional" disorder is the contrary of a structural one: the pieces of the organ are all there and in the right positions, but they are not working properly together. Most "imaging studies," like x-rays, CT and MRI scans, only show structure, not function, because they take the equivalent of "still pictures" not movies; they therefore will not directly detect functional disorders, though they may sometimes pick up late effects of functional disorders on structure. (For instance, a muscle that isn't moving – a functional disorder – will slowly become smaller, i.e. a structural change.) And movement – moving food down the tube that is the gut - is only one part of its overall function: to digest and absorb food. So even a test that does detect movement, as does an ultrasound scan, cannot detect these other aspects of gut function. Most gut symptoms, such as abdominal pain, nausea, bloating, constipation and diarrhea, are due to functional disorders. The studies above, and other studies, show that gastrointestinal problems are so common in EDS that it might make more sense to regard them, not as complications of EDS, but rather as a routine component of EDS.*

In EDS, the gut can be too tight or too loose, in different areas

Studies show that in EDS, movement of the gut in pushing its contents along, can be either increased, or reduced, from one segment to another.

Comment: *This presumably is what accounts for the alternation between constipation and diarrhea that patients often report: the muscles that propel its contents may be either overactive, or inert. In another example, the stomach may be flaccid, yet the valve at its lower end may be too tight: a dysfunctional combination that prevents the stomach emptying, leading to bloating, nausea and vomiting. This observation may explain my impression, from seeing EDS patients going*

through investigations by gastroenterologists, that their tests are rather less accurate in the EDS group than in the general population. The standard tests often show nothing wrong when further evaluation eventually detects a problem that the earlier tests would normally have shown up. Sometimes the definitive test is when the patient has surgery, and at last a doctor can actually look at the organs, in full light, and handle them, without relying on shadows on a screen, or images seen through a tiny tube. In several cases, the surgeon has been very surprised to see major abnormalities that were not suspected before surgery: for instance, a gall bladder enlarged to a five-inch-long sausage-like tube, or a stomach that was as flat and inert as a plastic sandwich-bag. I suspect that the misleadingly-normal tests done before these revelations, were wrong mainly for the reason noted in a previous comment. - The abnormalities of movement were changing, depending on time and the patient's position, sometimes increased and sometimes reduced; but the scans "caught" the organs when they were resting in their normal locations and in their "normal" shape and size. In particular, if any imaging study is done after the gut has been rested, and emptied (for instance by emptying the colon with laxatives or enemas, or emptying the stomach by withholding food overnight before a test), it may revert to its normal dimensions even though, when full of food and working to move it, that part of the gut may be <u>either</u> distended because of the laxity of its wall, <u>or</u> constricted by overactive muscle constriction.

Dysautonomia, POTS and gut problems

A striking finding of many of the studies reviewed in the AJMG paper, is that the presence and severity of gut symptoms in people with hypermobile joint conditions is strongly associated with a variety of other symptoms, outside of joints. These may include widespread pain, exhaustion, dizziness, faintness, sensitivity to temperature changes, "brain fog" and problems with bladder control. The authors of several of the studies suggest these symptoms are likely due to dysautonomia (disordered functioning of the branch of the nervous system that manages involuntary processes such as heart rate, blood flow and digestion). One expression of dysautonomia that is routinely seen in hypermobility is "orthostatic intolerance" (exhaustion, faintness and other symptoms when sustaining an upright posture); one type of this condition is known by its acronym, POTS.

Comment: *These findings confirm that EDS and similar conditions are essentially <u>multisystem</u> disorders, and when problems in one body system are severe, other systems or organs tend to be severely affected too. Some of these connections may be explicable as disorderly function of the autonomic nervous system, since this controls function in a number of body systems. But there may be other processes going on that have similarly wide-ranging effects, which researchers are only just beginning to suspect. One is the possibility that in EDS, several different organs may be damaged by subtle auto-immune processes (see below). This interweaving of illness through different body parts and functions is what's implied in the obscure medical adage, true of many chronic medical conditions: "When you're sick, you're sick."*

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Celiac disease and inflammatory bowel disease: common in EDS

Celiac disease is intolerance of foods containing gluten due to an auto-immune process in the wall of the intestines. Its prevalence in the general population is thought to approach one in a hundred, and it causes a variety of symptoms, but most cases go undiagnosed. Two studies have looked at a possible association of celiac disease with hEDS. One study checked hEDS patients for celiac disease and found it in 5 out of 31, or 16%. The other study worked the other way round: patients with celiac disease were checked for hEDS, and its was found in 4 of 13, or 30%. These are small samples, and the studies need corroboration by larger surveys, but the size of the associations are still striking. They suggest some causative link between celiac disease and hypermobility conditions, raising the possibility of connections with other auto-immune diseases of the gut. This is indeed suggested by the finding of high numbers of people with hypermobility syndromes among patients with both Crohn's disease, and ulcerative colitis, both of which are auto-immune diseases.

Comment: *There may be connections between EDS and auto-immune conditions that go beyond the gut. There is evidence that orthostatic intolerance, including POTS, may sometimes be due to auto-immune damage in the autonomic nervous system. There is also evidence of similar damage to sensory nerves causing widespread pain of the sort that many people with EDS have. A variety of symptoms in EDS can go through periods of worsening, then remission, over months and years. These recall the exacerbations and remissions seen in well-known auto-immune conditions like rheumatoid arthritis. It seems that the earlier auto-immune conditions are diagnosed and treated, the lower the chance that they will worsen and cause new problems later, as studies of celiac disease have shown. So in the future, with better ways to both diagnose and treat the auto-immune concomitants of EDS in childhood, some of its long-term complications may perhaps be averted.*

Different types of EDS

It is well known that people with vascular-type EDS (vEDS) are at serious risk of suffering ruptures or hemorrhage of various internal organs, as well as blood vessels. The mortality for such events approaches one in three. Other types of EDS such as Tenascin-X deficiency also have specific patterns of vulnerability to organ ruptures, including hernias.

Comment: *This is the main reason why it's important to identify the very small number of people with a hypermobility condition who have these rare, but very serious, disorders. While a non-geneticist may <u>suspect</u> them, these conditions need to be investigated and confirmed by geneticists, usually through specific genetic tests. Note that these are very different tests from those available to the public, such as "23andMe", which geneticists advise are of no practical use in diagnosing hypermobility conditions.*

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Conclusions

The AJMG review concludes: "Current literature suggests an association between all subtypes of EDS and GI symptoms. This association is common and has hitherto been underestimated. The group observed that evidence for GI symptoms to be included as a major EDS diagnostic criterion is compelling . . . (But) specific evidence-based guidelines for the management of EDS patients with GI symptoms are not yet available."

But the authors also write, "There are anecdotal reports of global improvement . . . following patient-led "trial and error" diet-based interventions, as well as through the use of enteral nutrition via nasogastric feeding, percutaneous endoscopic gastrostomy/jejunostomy feeding, and total parenteral nutrition." They also mention, with favor, anecdotal benefits in some hEDS patients of the FODMAPS diet, which has some support as a treatment for irritable bowel syndrome (IBS).

Comment: *These sketchy conclusions are noteworthy for two tellingly-contradictory opinions. One is, that we don't have evidence to support particular management strategies for the gut disorders that people with EDS have. But the other is the acknowledgement that some patients benefit from invasive and potentially risky procedures, like having their food supplied via tubes surgically inserted into their abdomens, or into their veins. Gastroenterologists are naturally very reluctant to advise such procedures in the absence of proper studies showing they are worth the risks in EDS patients. They therefore withhold these treatments until a patient has lost so much weight from inability to feed themselves, that the treatment plan looks like "starvation under medical observation," which is unacceptable on several grounds. When such a decision is finally taken – often after the patient has been pleading for it for some time – the patient is now in such a debilitated state that the risks of the procedure are magnified, compared to having done it when they were less emaciated. An added dilemma is over the long term plan for someone who has required feeding by tube or intravenous infusion. It is quite unknown whether this is, in any particular case, a brief requirement or a lifelong necessity, or how to decide whether or when to try weaning the patient from the artificial feeding. Because of these unknowns, there are wide areas of controversy over these decisions. The frequent lack of clear test findings to explain the patient's food intolerance adds another twist: the tendency is to fall back on a diagnosis of "eating disorder" when the organic basis of a condition can't be proved. This would seem to argue strongly against treatment by a surgical procedure that carries significant medical risks. The patients with this predicament are typically young women, a group in whom eating disorders are genuinely very common. Thus the stage is set for fierce disputes among gastroenterologists and psychiatrists, with no good evidence to decide between them, about a patient who will literally starve to death unless some way is found to overcome the unknown block to feeding and digestion. It is to be hoped that the research will soon help us with these very wrenching decisions.*

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Footnotes

[1] The International Consortium on the Ehlers-Danlos Syndromes published its findings in a series of articles in a special issue of the American Journal of Medical Genetics in March 2017. The article may be found by internet search on "*Fikree A, Chelimsky G, Collins H, Kovacic K, Aziz Q. 2017. Gastrointestinal involvement in the Ehlers–Danlos syndromes. Am J Med Genet Part C Semin Med Genet 9999C:1–7*". However, only the one-paragraph abstract is available without charge. The website accessed by this search item gives details of how to obtain the full article and the charge for this.

[2] Professional groups love to have fancy language to denote what they do, even if the fancy language isn't quite accurate. "Gastroenterology" is from the Greek, meaning "the science or study of stomachs and intestines," which doesn't mention medical diagnosis or treatment at all, and sounds like a term for a special kind of biologist. Also, the term seems to exclude the bits above the stomach, namely the mouth and the esophagus, although gastroenterologists generally include these as fair game for their attentions. The British are rather less in love with jargon as evidence for competence. As a British doctor who is also half-Greek, I prefer the good Old-English term, "gut," to refer to the tube that goes from the mouth to the anus, and I enjoy saving myself six syllables each time I substitute it for "gastrointestinal tract."

[3] Estimates for the prevalence of Ehlers Danlos Syndrome were widely divergent, even before they were all made out-of-date by the new diagnostic EDS criteria put forward in early 2017. Since we now have new definitions of these conditions, it will be years, or very likely decades, before anyone does the big surveys, using the new definitions, to identify people with EDS and count them in populations. Geneticists used to say the Ehlers Danlos Syndromes as a whole had a prevalence of around one in 5,000. They nowadays suggest the figure may be more like one in 500. Some French experts claim a better figure is one in forty! In this field of wildly undisciplined estimates, I offer my own, based on this observation. When I see a young patient with hEDS, or with what is now to be called Hypermobile Spectrum Disorder, who is at a high school, in about half the cases I will later be asked to see another patient who is a student at the same school. Simple arithmetic based on this suggests the prevalence of these conditions to be at least one in 500. I therefore endorse this figure, which is also commonly thrown out (with no apparent evidence whatever) by geneticists who have realized that their earlier espousal of "one in 5,000" was a ludicrous under-estimate. Given the population of North Carolina is a little over ten million, this gives 20,000 as a ballpark figure for the number of people in our State, with EDS or a related condition, that is bad enough that they are seeking care for it.

[4] A good summary of "functional gastrointestinal disorders" is online at *https://www.med.unc.edu/ibs/files/educational-gi-handouts/What%20Is%20Functional%20GI.pdf*. This summary, from the Center for Functional GI and Motility Disorders at the University of North Carolina, is also interesting for its display of the institutional biases of the discipline of gastroenterology in North America. Specifically, in its section on Treatment, it devotes two paragraphs to listing medications for FGIDs, (one of which, Zenlorm, was actually removed from use in the USA in 2007 because of its potentially-fatal side effects). There follows just one sentence on psychological treatments, and not a word about dietary manipulations, which is odd since most people with these conditions are well aware that some foods are good and some bad for them.