

Familial Diverticulitis: A Pilot Study Introducing an Innovative Survey Examining Risk Factors for Diverticulitis

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ABSTRACT

Objective: Diverticulitis has become increasingly prevalent in Western society. Risk factors for diverticulitis include age, diet, gut microbiota milieu, physical activity, obesity and genetics. Cases of familial diverticulitis are rare and widely understudied. In this paper, we report a case of a family who underwent sigmoidectomy for diverticulitis, while evaluating their risk factors for diverticulitis through the first questionnaire designed specifically for the disease entity of diverticulitis.

Methods: A retrospective chart review was performed of three family members who underwent a sigmoidectomy for diverticulitis. A comprehensive literature review was used to create a Diverticulitis Risk Factors Questionnaire and distributed to the family members.

Results: Common risk factors of the family members, identified through our Diverticulitis Risk Factors Questionnaire, included obesity, African American race, and a diet low in fiber and high in refined carbohydrates.

Conclusion: This pilot study introduces the first known questionnaire evaluating the genetic, clinical and lifestyle risk factors associated with diverticulitis.

INTRODUCTION

Diverticula are colonic outpouchings of the mucosa and muscularis mucosae where the vasa recti penetrate the colon wall. Diverticulosis is common in Western society. In 2004, diverticular disease accounted for 312,000 hospital admissions and was the most common inpatient gastrointestinal diagnosis ^[1]. Diverticulitis is a subset condition of diverticular disease characterized by inflammation of the diverticula, which is estimated to affect approximately 1-4% of patients in their lifetime ^[2,3]. Diverticulitis has become increasingly prevalent over the last couple of decades. In the United States from 1998 to 2005, hospital admission for diverticulitis rose by 26% and elective sigmoidectomy procedures rose by 29% ^[4]. In 2010, out of the 310,983 emergency department visits with the primary diagnosis of colonic diverticulitis, a little more than half of the patients (165,000 patients) were admitted ^[5]. All age groups have seen an increase in incidence, with people younger than 50 experiencing the greatest surge ^[6].

The etiology of diverticulitis is multifactorial. Common risk factors reported in the literature for diverticular disease include age, diet, gut microbiota milieu, physical activity, obesity and genetic factors ^[7-12]. Familial diverticulitis studies suggest that genetic predisposition may account for 40–53% of disease incidence ^[13-15]. Familial diverticulitis is widely understudied and only a few cases have been reported in the literature ^[16-21]. Thus, the identification of families with multiple affected family members provides an opportunity to investigate the genetic basis of diverticulitis. In this paper, we present the cases of three family members (mother, daughter and son), who underwent surgical intervention for different sequelae of diverticulitis. All family members completed a diverticulitis questionnaire in a pilot study to evaluate the genetic, clinical and lifestyle risk factors associated with diverticulitis. To our knowledge, this is the first study in which a survey is designed to investigate these risk factors associated with diverticulitis.

METHODS

IRB Review

The Johns Hopkins Medicine (JHM) institutional review board (IRB) determined that this study did not constitute human

subjects research under the DHHS or FDA regulations due to the study of three or fewer cases. They determined that IRB review was not required for the study and the authors were able to proceed with the project without further interaction with the JHM IRB. The authors adhered to the HIPAA Privacy Rule requirements for the use and disclosure of patient health information for this case report of three clinical cases.

Genetics, Clinical and Lifestyle Risk Factor Diverticulitis Survey Development

A comprehensive literature review was performed by searching PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) for papers published between 1946 and June 2016 using the following keywords: “genetics diverticulitis”, “familial diverticulitis”, and “risk factors for diverticulitis”. The first author and secondary authors reviewed all articles under the aforementioned searches to determine those journals with the best evidence. The most common genetic and lifestyle risk factors for diverticulitis were incorporated into the survey and organized into the following sections: family history, past medical history, medications, gastrointestinal history, dietary habits, and physical activity. Surveys included a combination of multiple-choice questions, Likert-type scale questions, and occasional free-text (**Appendix A**).

Case Report and Survey Completion

Cases of familial diverticulitis were identified within a family, of whom family members had the diagnosis of diverticulitis. All three family members were operated on by the same colorectal surgeon from August 2013 to June 2016. A retrospective chart review was performed in Epic Hyperspace® (Epic Systems Corporation, 2014) to collect demographic, social, perioperative and postoperative follow-up data. The surveys were distributed by paper format in September 2016.

RESULTS

Family Clinical Case Reports

The following cases are reported according to the patient's initial presentation during their surgical consultation and describes their subsequent diagnostic work-up and surgical management.

Mother

69 year old female with a history of hypertension and obesity (BMI 30.1 kg/m²), who was having diarrhea daily and an unintentional weight loss of 5-10 lbs over a 3-month period. A total of three colonoscopies were aborted by multiple gastroenterologists, and subsequently the surgeon, due to the inability of the colonoscope to traverse a near-complete sigmoid colonic obstruction. A computed tomography (CT) abdominal and pelvic scan showed a sigmoid colon mass with associated lymphadenopathy that was suspicious for malignancy. Given the known obstruction on endoscopy and suspicious mass seen on CT scan, the patient underwent a laparoscopic, converted to open low anterior resection with end-to-end stapled anastomosis and diverting loop ileostomy. Final pathology of the specimen was diverticulitis.

Son

51 year old male with a history of known diverticulitis treated in the past with antibiotics, nephrolithiasis, hyperlipidemia, and obesity (BMI 30.09 kg/m²), who presented to the Emergency Department with severe abdominal pain. A CT scan of the abdomen and pelvis showed microperforation associated with diverticulitis and he was admitted to the hospital for intravenous antibiotics. He previously had a colonoscopy, which showed a 3-4 mm diminutive polyp in ascending colon that was removed, as well as diverticulosis. A repeat CT scan did not show evidence of an abscess. The patient described constant abdominal pain and a change in bowel habits. Given his lack of resolution of symptoms after treatment for his diverticular microperforation, he underwent a laparoscopic sigmoidectomy.

Daughter

52 year old female with a history hypertension, mitral valve prolapse and obesity (BMI 44.21), who was initially diagnosed 8 years ago with a microperforation associated with diverticulitis on CT scan of the abdomen and pelvis. Her multiple episodes of diverticulitis were treated in the past with hospitalization for intravenous antibiotics and oral antibiotics as an outpatient. She lost 38 lbs in the year prior to surgery and had unresolving abdominal pain. She underwent a laparoscopic sigmoidectomy.

All family members did exceptionally well after surgery and have not had recurrence of their diverticulitis.

Survey Results

All family members were obese with a BMI>30, with the daughter being morbidly obese (BMI=44.21). Mother and son perceived a “healthy diet” as important, yet rated their diet as “somewhat healthy.” Both also described their past and current physical activity as “very active.” The daughter perceived her diet as “somewhat important” and rated it as “somewhat healthy.” She also reported her “childhood and physical activity” as “not active at all,” stating that she “sits for seven hours or more a day.” When rating the frequency of different food items in their diet, all members marked “high carbohydrates foods” as “eaten often/very often” and “vegetables and fruits” as eaten “rarely/never.” The sister and brother identified “insoluble fiber” as “eaten somewhat often,” while the mother identified it as “eaten rarely/never.” No family members reported usage of alcohol, tobacco, or

recreational drugs. **Table 1** summarizes survey results obtained from the family members. The family members felt that the survey was educational, in that it made them aware of potential modifiable lifestyle risk factors for diverticulitis.

Table 1. Diverticulitis risk factors questionnaire results.

	Mother	Son	Daughter
Clinical Factors			
Age (at time of surgery)	69	51	52
Race	African American	African American	African American
Body Mass Index (BMI)	30.1	30.09	44.21
Past Medical History	Hypertension, Obesity	Nephrolithiasis, Hyperlipidemia, Hernia, Obesity	Hypertension, Mitral Valve Prolapse, Obesity
Medication History	Acetaminophen – when needed	NSAIDs – when needed	Acetaminophen – when needed
Colorectal History	Bowel Obstruction	Diverticulitis (treated with antibiotics), Bowel Obstruction	Diverticulitis (treated with antibiotics)
Lifestyle Factors			
Occupation	Retired	Building Service Management	Tech Manager
Diet	Rated healthy diet as Important. Described current diet as Somewhat Healthy	Rated healthy diet as Important. Described current diet as Somewhat Healthy	Rated healthy diet as Somewhat Important for her. Described current diet as Somewhat Healthy
Foods eaten Often/Very Often	Soluble Fibers, High Carbohydrate foods	Red Meat, High Carbohydrate foods	High Carbohydrate foods, Sugary sweets
Foods eaten Rarely/Never	Fruits and Vegetables, Insoluble Fibers, Peanuts, Fast-Food	Fruits and Vegetables, Soluble Fibers, Nuts, Popcorn, Peanuts, Fast-Food	Fruits and Vegetables, Soluble Fibers, Popcorn, Peanuts, Fast-Food
Physical Activity	Very active as child. Moderately active today – does balance exercises 3-4 times a week for 3-5 h.	Very active as child. Very active today – does aerobic and strength exercises 5 or more times a week for 30 min.	Not active at all as child. Not active at all today – does not exercises regularly and sits for 7 h or more a day.
Tobacco, alcohol, rec. drugs	None	None	None

DISCUSSION

Cases of familial diverticular disease are rare and only a few have been reported in the literature. The first, published in 1946, presents a case of which seven out of nine sons were diagnosed with diverticulosis. According to the author, diverticulosis was not as prevalent at the time and was only found in 2-5% of the adult Caucasian male population. Interestingly, the sibling sample consisted of a varied range of BMIs, social status and living conditions^[18]. Omojola et al., described three Nigerian adult siblings who developed diverticulitis. There are very few cases of diverticulitis in Nigeria and thus the authors concluded this was suggestive of a genetic component of diverticulitis^[17]. In Holland, 15 and 18 years old siblings were diagnosed with diverticulitis^[16]. It is important to mention that both siblings suffered from joint hypermobility, which might be indicative of a collagen disorder and has been previously described as a risk factor for the development of diverticulosis. Other studies on familial diverticular disease include: two separate cases of diverticulitis in twins, three sisters in Italy and two young adult brothers^[19-22]. While these case studies demonstrate that there may be a genetic component to describing the etiology of diverticulitis, they are limited by their sample sizes and retrospective chart reviews of the patients. Descriptive patient characteristics are extracted from these retrospective reviews; however, no other statistical analyses may be performed on these studies with small sample sizes. The largest genetic studies are described by Gralund et al.^[13] and Strate et al.^[15].

A retrospective study in Denmark of 923 twins and 10,420 siblings showed that the proband concordance rate for monozygotic twins was twice as high as dizygotic twins. They also estimated that genetic factors contribute to 53% of the risk of developing diverticulitis^[13]. The strength of the study is that inpatient and outpatient diagnoses of diverticular disease were captured in the Denmark study; however, this retrospective study uses administrative data and does not readily distinguish between patients with uncomplicated diverticulosis versus diverticulitis and diverticular bleeding. Another retrospective study of 2,296 Swedish hospitalized twins with the diagnosis of “diverticular disease” found that the relative risk of developing diverticulitis, given one’s co-twin diagnosis of diverticulitis, is 7.15 for monozygotic twins and 3.2 for dizygotic twins^[15]. Both the Danish and Swedish studies consist of populations mainly consistent of Caucasian patients and thus these studies prevent the generalizability of the aforementioned findings to populations with different racial compositions. Yet the sample size for both studies was quite large. This paper involves prospectively collected data of 3 family members and is not reliant upon administrative data.

Multiple previous studies have shown an association between obesity and diverticular disease. Two large prospective studies exist. A study of 47,228 American males by Strate et al., found that men with a BMI>30 were 78% more likely to develop diverticulitis than males with BMI<21^[23]. The study was survey-based and designed to control for confounding factors, such as dietary fiber, fat and red meat intake, as well as the use of non-steroidal inflammatory medications, which are known risk factors for diverticulitis. A similar survey-based Swedish study found that obese women had a 33% increased risk of diverticulitis^[24]. Though strong in that

both survey-based studies had high response rates, in the acquisition of prospective data, there may have been recall bias in the self-reporting of weight, height and physical activity. The reason why obesity is a risk factor for diverticulitis remains unknown, although it has been hypothesized that it could be associated with cytokines secreted by adipose tissue that induce inflammation and differences in microflora between obese and lean individuals ^[23]. A common comorbidity shared by all family members in our case series was obesity. The mother had a BMI of 30.1, the son of 30.09 and the sister of 44.2 and all three required elective sigmoidectomy for diverticulitis. Lifestyle risk factors contributing to the development of obesity and diverticulitis include diet and exercise. Dietary risk factors for diverticulitis, described in the literature, include a low-fiber diet, red meat, popcorn, corn and nut consumption and a diet abundant in refined carbohydrates. For those patients who are obese, there is generally a lack of individual physical activity.

In 1971, Painter, et al., first proposed that diverticulosis is rare in African and Asian countries, in which high-fiber diets are common. They concluded that constipation and high intraluminal colonic pressures play a role in the development of diverticulosis ^[25]. Dietary fiber intake has since become one of the main modifiable risk factors for diverticular disease. However, some concerns have been raised due to geographical discrepancies in life expectancies that may have skewed these observations ^[26]. Animal experiments performed in rats and rabbits have supported the hypothesis that low-fiber diets play a role in the development of diverticulosis. However, it is important to emphasize the anatomical differences between rodents and humans, specifically the rodent's lack of *Taenia coli* and the fact that they have a tendency toward the development of diverticula in the cecum, as opposed to most humans who develop diverticular disease in the sigmoid colon ^[12]. Looking at diet in our family case series, the mother indicated that she "rarely/never ingested" insoluble fiber foods, such as wheat bran and whole grain cereal. The children both noted insoluble fiber as being consumed "somewhat often" in their diet. Vegetables and fruits, which have been shown to have high levels of cellulose (more than cereal), highly contribute to one's daily insoluble fiber consumption ^[27]. All of the members reported rarely/never eating vegetables and fruits and exhibited a diet low in insoluble fiber.

While it has been advised that patients with diverticular disease follow a high-fiber diet, they are historically told not to consume popcorn, corn, nuts, red meats, or diets high in refined carbohydrates. In 2008, Strate et al. analyzed the Health Professionals Follow-up Study cohort of US men followed from 1986 to 2004. Out of the 47,228 men surveyed for dietary information, there were 801 incident cases of diverticulitis. Popcorn, corn and nuts were not shown to increase the risk of diverticular disease ^[28]. In 2016, Cao et al. analyzed 46,461 men enrolled in the Health Professionals Follow-Up Study from 1986-2012. Seven hundred sixty-four incident cases of diverticulitis were identified. Men in the highest red meat consumption group had a multivariable relative risk of 1.58 of developing diverticulitis compared to the group of men who consumed the lowest quantity of red meat ^[29]. As was previously discussed, the Health Professionals Follow-up Study is a large prospective survey-based study of US male health professionals that comes with recall bias and lacks generalizability to women and other racial groups. A diet high in refined carbohydrates has also been named a possible risk factor, which all three family members reported having ^[25]. Both children reported "rarely/never eating" popcorn and peanuts, and the mother only reported "rarely/never eating" peanuts. The son is the only family member who reported consuming red meat "often/very often." When analyzing the dietary habits of the family members, it is important to note that the lack of insoluble fiber from their diets and high levels of carbohydrates might have increased their risk of developing diverticulitis.

In addition to diet, a lack of physical activity has also been linked to diverticulitis. Strate et al. showed that low physical activity and sitting for long periods during the day (more than 52 h a week) is associated with a higher risk of diverticulitis ^[30]. The mother and son felt that they regularly exercised. The daughter, however, stated that she was "not active at all", nor was she physically active during her childhood. Furthermore, she reported sitting for more than 7 h a day.

The family sample was of African American descent, of which this race is most commonly associated with an increased risk of diverticulitis ^[31]. Additionally, the brother and sister first developed symptoms of diverticulitis during their late forties, which has been one of the age groups with the highest increase in incidences of diverticulitis over the last few decades ^[6].

Finally, certain medications are associated with an increased risk of diverticulitis. Strate et al. reported that in a prospective cohort of 51,529 males, those who used NSAIDs at least two times a week had a 25% increased risk of developing diverticulitis ^[32]. Although, none of the family members reported frequent usage of medications, the mother and daughter reported occasional use of acetaminophen and the son reported occasional usage of non-steroidal anti-inflammatory drugs (NSAIDs).

The limitations of our study deserve discussion. Our sample size was low in this pilot study of a family of three patients. This was a retrospective study of three patients, who had been evaluated and managed by one colorectal surgeon. As such, our findings are not applicable to large populations, but should be considered a preliminary description of the clinical, genetic, and lifestyle risk factors for diverticulitis that could potentially be applied in appropriate settings. The benefit of this design is that it allowed the authors to create a questionnaire made specifically for the disease entity of diverticulitis, presenting a comprehensive overview of a high-risk population that has been lacking from prior studies.

While this discussion has examined the risk factors associated with diverticulitis, it is difficult to separate the nature versus nurture dichotomy behind the risk factors for diverticulitis. All three family members shared the following predispositions for diverticulitis: low-fiber diet and obesity. While there are familial and twin studies describing family members with diverticulitis,

this is the first study that introduces a questionnaire focused on the conglomeration of genetic, clinical, and lifestyle risk factors for diverticulitis. We hope to incorporate this questionnaire into our future clinical practice at a tertiary care referral center. In addition to educating the patient about modifiable risk factors associated with diverticulitis, this pilot study will expand to evaluate potential risk factors and how they interplay with familial diverticulitis and their potential to predict disease course and treatment.

CONCLUSION

This paper presents the case of three family members, who underwent elective sigmoidectomy for diverticulitis. Surveys according to known genetic, clinical and lifestyle risk factors were used to assess family members who underwent an operation for diverticulitis. To our knowledge, no such survey specifically designed to assess risk factors for diverticulitis exists. This diverticulitis survey may serve as a potential tool to make patients aware of modifiable risk factors for diverticulitis.

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