Supplement Issue - 3rd International Symposium: Diverticular Disease of the Colon

DOI: http://dx.doi.org/10.15403/jgld-551

Pathogenesis of Diverticulosis and Diverticular Disease

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ABSTRACT

In this session different problems regarding the pathogenesis of diverticular disease were considered, including "Genetics", "Neuromuscular function abnormalities", "Patterns of mucosa inflammation", and "Impact of lifestyle". The patients affected by diverticular disease have clear genetic pattern, that might predispose to the occurrence of the disease as well as to its complications. Neuromuscular abnormalities may be recognized already at the stage of diverticulosis, and inflammation may explain symptoms occurrence in symptomatic uncomplicated diverticular disease (SUDD) or symptoms persistence after an episode of acute diverticulitis. Finally, lifestyle might also have an impact on symptoms' occurrence. Specifically smoking, but also obesity seem to play an important role, while the role of low-fiber diet and constipation is now under debate.

Key words: diverticular disease – acute diverticulitis – colonoscopy – genetics – fiber - low-grade inflammation – neuromuscular alteration – symptomatic uncomplicated diverticular disease.

Abbreviations: DD: diverticular disease; SCAD: segmental colitis associated with diverticulosis; SUDD: symptomatic uncomplicated diverticular disease.

GENETICS

Diverticular disease (DD) of the colon is a common disease with an increasing impact for the National Health Systems [1]. It is a complex disorder resulting from an interaction of multiple factors; however, the exact pathogenesis of this disease is not known. Gathered evidence suggests that genetic factors contribute to the development of DD [2]. Convincing data that support the role of genetic factors in DD come from monogenic disorders of connective tissue including Williams-Beuren syndrome, Coffin-Lowry syndrome and Autosomal Dominant Polycystic Kidney Disease where colon diverticula occur at a very early age [2]. A couple of epidemiological twin studies have also recently pointed to the significant role of inherited factors in the development of DD [3, 4]. Several small case-control studies have initially attempted to identify certain single nucleotide polymorphisms (SNPs), but were underpowered to provide significant findings [5, 6]. A larger case control study including 422 patients with diverticulosis and 285 controls found that variant rs3134646 in COL3A1 gene is associated with the risk of developing colonic diverticulosis in men [7]. However, the most important data on genetic predisposition of DD come from three very recent genome-wide association studies (GWAS) [7-9]. The first GWAS on Iceland population showed that variants in ARHGAP15 and COLQ genes were linked with uncomplicated DD and variants in FAM155A were associated with diverticulitis [8]. Additionally, 37 susceptibility loci with genome-wide significance were identified in a recent study from Maguire et al. [9] with replication of 8 loci. The largest GWAS study to date employed UK Biobank and imputed genotypes using 31 964 cases and 419 135 controls [10]. These associations were then replicated in a European sample of 3893 cases and 2829 diverticula-free controls and evaluated for risk contribution to diverticulitis and uncomplicated diverticulosis and identified 48 genetic risk loci [10]. The genetic data from all three GWAS studies clearly show that DD primarily is a disorder of intestinal neuromuscular function and of impaired connective fibre support, while an additional diverticulitis risk might be conferred by epithelial dysfunction related genes [8-10]. To date, there are no studies evaluating how identified

genetic risk factors could serve for clinical decisions making in DD prevention or management and these subjects are topics for future research.

NEUROMUSCULAR FUNCTION ABNORMALITIES

It has been hypothesized that in colonic DD higher intraluminal pressures in the affected segments may contribute to the production of pulsion diverticula [11]. However, data from rectosigmoid motor activity between controls and patients with DD were not univocal [12]. Further information was obtained by recording whole colonic motor activity for prolonged periods of time (24 hours or more) [13], and assessing visceral perception and compliance in the rectum and rectosigmoid area [14].

Colonic motility

In a previous study we recorded 24-h colonic motility in patients with asymptomatic DD and in healthy controls; patients displayed significantly increased motility in the segments with diverticula [15], an abnormal motor response to eating, and a significant increase of high-amplitude propagated contractions. In another 24-h study in patients with SUDD, compared to controls, patients had a significant increase of regular contractile patterns, with more than 80% represented by 2-3 cycles per minute pattern. More than one third of these patients (none of the controls) reported associated cramping lower abdominal pain during a regular contractile pattern [16].

Colonic sensory activity

By comparing data from symptomatic, asymptomatic patients with DD and controls, rectal perception of distention was increased in symptomatic patients compared to the other groups; rectal compliance curves were not different between the three groups [17]. In the sigmoid colon, perception was increased in symptomatic, but not in asymptomatic patients (before and after meals) compared to controls, with similar compliances in the three groups. The colonic response to eating was not different between groups. Thus, patients with symptomatic disease display increased perception of distention in both the affected (sigmoid) segment and in the unaffected rectum; this increase of perception is not due to an altered wall compliance. A further study showed visceral hypersensitivity in symptomatic patients possibly mediated by ongoing low-grade inflammation and upregulation of tachykinins [18].

In conclusion, neuromuscular dysfunction plays a paramount role in DD, but more investigations are needed to establish the true role of this dysfunction.

PATTERNS OF COLONIC MUCOSAL INFLAMMATION

Diverticulosis, namely the presence of colonic diverticula, is a common condition. In a recent population study 17.5% of participants had diverticula and the sigmoid was always involved [19]. An endoscopy study of all comers demonstrated 32.6% had diverticula, 71.4% of those aged ≥ 80 years [20]. The presence of inflammation, diverticulitis - macroscopic inflammation of diverticula with related acute or chronic complications is seen in 4% of those with diverticulosis (with an 11-year follow up) and 11% in younger patients (40-49 yrs) [20]. In the patients with acute inflammatory complications of DD, inflammation in the mucosa is evident and acute in nature. When complications ensue and diverticula break, an acute abdomen leads to surgical intervention and consequent surgical pathology shows full thickness and peritoneal inflammation. Segmental colitis associated with diverticula (SCAD), a unique form of mucosal or full thickness inflammation that looks similar with IBD, is observed in 11% of those with diverticulosis and 2% of patients investigated by colonoscopy [21-23]. This is a specific mucosal inflammatory process, confined to the sigmoid and descending colon. In SUDD, the site of inflammation is likely deep in the muscularis and may interact with nerves, as patients exhibit visceral hypersensitivity, and this may be mediated by ongoing low grade inflammation and upregulation of tachykinins [18]. However, in a community population with DD, there was no association between symptomatic diverticulosis (abdominal pain or diarrhoea) and serological (C-reactive protein) or mucosal inflammation – the inflammatory gradient was intact [19]. In small studies, macrophages have been shown to be increased in SUDD in 8 patients [24] and also lymphocytes were elevated in 10 patients [25], but when assessing every aspect of colon pathology in a community population of 127 subjects [21] and in an endoscopy population of 255 patients [26] no evident mucosal inflammation was noted.

DD shows a spectrum of pathological changes, which can be mucosal and/or neuromuscular. Other disorders may co-exist and the key to unravelling pathogenesis is in identifying triggers to inflammation. These include an aging gut, neuromuscular disorders, disordered immune reactivity and dysbiosis, genetics, diet, lifestyle and smoking [27].

IMPACT OF LIFESTYLE

Diverticular disease is called a disease of Western Cultures because of the rapid and continuous increase in incidence following the Industrial Revolution that has been largely attributed to changes in diet and lifestyle. Studies consistently indicate that low dietary fiber is associated with risk of incident diverticulitis [28, 29], although the association between fiber and asymptomatic diverticulosis is uncertain [30, 31]. In a large UK cohort, individuals who consumed more than 25 grams of fiber had a 40% decreased risk of hospitalization for diverticulitis [28], but two cross-sectional colonoscopy studies found no association between fiber intake and asymptomatic diverticulosis [30, 31]. Physical activity, especially vigorous activity, also decreases the risk of diverticulitis [32]. On the other hand, red meat consumption is positively associated with risk of diverticulitis (relative risk 1.2 for each serving of red meat) [33]. When considering diet as a whole, a Western dietary pattern (high in red meat and refined grains), increases risk of diverticulitis, whereas a prudent pattern (high in fruits, vegetables and whole grains) decreases risk [34]. Obesity, and central obesity in particular, is associated with risk of diverticulitis. In a prospective study, men with a body mass index (BMI) > 30 kg/m2 had a relative risk of 1.8 [35]. Weight

gain also contributes to the risk of diverticulitis [36]. Smoking is another risk factor especially for complicated diverticulitis (37,38). The importance of diet and lifestyle is demonstrated in a study that found that men who adhered to five healthy lifestyle factors (BMI 18-25 kg/m2, fiber intake > 23 g/day, red meat < 4 servings/week, two hours of exercise/ week and no smoking had a 75% decreased diverticulitis risk compared to men who did not adhere to any healthy lifestyle factors [39].

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