Human Pathology (2015) **46**, 277–283

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

Colonic spirochetosis is associated with colonic eosinophilia and irritable bowel syndrome in a general population in Sweden☆,☆☆

Marjorie M. Walker BMBS, FRCPath[a,*], Nicholas J. Talley MD, PhD[b], Linn Inganäs MSc[c,d], Lars Engstrand MD, PhD[d], Michael P. Jones PhD[e], Henry Nyhlin MD, PhD[f], Lars Agréus MD, PhD[c], Lars Kjellstrom MD[g], Åke Öst MD, PhD[h], Anna Andreasson PhD[c,i]

[a]*Anatomical Pathology, Faculty of Health and Medicine, School of Medicine and Public Health, University of Newcastle, Newcastle, 2308 NSW, Australia*
[b]*Faculty of Health and Medicine, University of Newcastle, Newcastle, 2308 NSW, Australia*
[c]*Center of Family Medicine, Karolinska Institutet, SE-141 83 Huddinge Stockholm, Sweden*
[d]*Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, SE-141 83 Stockholm, Sweden*
[e]*Psychology Department, Macquarie University, North Ryde, 2109 NSW, Australia*
[f]*Internal Medicine, Karolinska Hospital, SE-141 83 Huddinge, Sweden*
[g]*Internal Medicine, Aleris Sabbatsbergs Hospital, SE-113 24 Stockholm, Sweden*
[h]*Pathology, Aleris Medilab, SE-183 53 Täby, Sweden*
[i]*Stress Research Institute, Stockholm University, SE-106 91 Stockholm, Sweden*

Received 24 September 2014; revised 26 October 2014; accepted 27 October 2014

Keywords:
Irritable bowel syndrome;
Infective colitis;
Histopathology;
Eosinophils;
Colonic spirochetosis

Summary Irritable bowel syndrome (IBS) is a functional disorder defined by symptoms in the absence of overt pathology. Colonic spirochetosis (CS), defined by histologic observation of spirochetal strains of *Brachyspira* in colonic biopsies, is uncommon and considered of doubtful significance. We aimed to determine the prevalence of CS in the general population, identify subtle colon pathologies, and evaluate a link with symptoms of IBS. Colonoscopy was performed in 745 subjects (aged 19-70 years, mean age 51 years, 43% male) with biopsies (ileum and 4 colonic sites) from a random population sample, Stockholm, Sweden, who completed a validated questionnaire of gastrointestinal symptoms; IBS was identified by Rome III criteria. CS was identified by histology and immunohistochemistry. In a general population, 17 individuals (2.28%; 95% confidence interval, 1.2%-3.5%) were diagnosed as having CS by histology; 6 (35%) had IBS. CS was always present in the sigmoid colon, but only 14 rectal biopsies. Eosinophils were increased in colon biopsies in CS cases versus controls, in the transverse (P = .02), sigmoid colon (P = .001), and rectum (P = .0005) with subepithelial eosinophil clusters (P = .053).

☆ Competing interest: The authors report no conflicts of interest and are solely responsible for the content and writing of the paper.

☆☆ Funding/Support: This study was supported by the following institutions: Swedish Research Council; Ersta Hospital, Stockholm, Sweden; the Foundation Tornspiran, Stockholm, Sweden; AstraZeneca R&D, Sweden; and Ferring Läkemedel AB. Financial support was also provided through the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet.

* Corresponding author. Anatomical Pathology, Faculty of Health and Medicine, University of Newcastle, Newcastle, 2308 NSW, Australia.
E-mail address: marjorie.walker@newcastle.edu.au (M. M. Walker).

http://dx.doi.org/10.1016/j.humpath.2014.10.026

Lymphoid follicles (at any site) were present in 13 CS ($P = .0003$). There was a 3-fold increased risk of IBS in CS (odds ratio, 3.59; 95% confidence interval, 1.27-10.11; $P = .015$). Polyps and diverticular disease were similar in CS cases and controls. The prevalence of CS in a general population is 2% and associated with nonconstipating IBS. Colonic eosinophilia with lymphoid follicles may signify the presence of CS.

1. Introduction

Colonic spirochetosis (CS) was first described in 1967, when short spirochaetes adhering to the surface of colonic epithelium were shown by electron microscopy of rectal biopsies [1]. These were also noted at light microscopy to appear as a surface "blue haze or fringe" [1]. Subsequently, CS was also seen in the appendix [2] and a possible association with simulated appendicitis (ie, no histologic evidence of acute appendicitis) was observed in the original reports [2]. Since then, variable and inconsistent gastrointestinal (GI) symptoms have been described in uncontrolled studies of CS. In a Norwegian study in which CS was diagnosed by biopsy, symptoms on referral to the gastroenterologist included diarrhea, abdominal pain, constipation, and blood in the stools [3]. A recent review of 26 patients in North Carolina, United States, with CS presenting at endoscopy over a 5-year period noted that symptoms of diarrhea or alternating bowel habit (46%) and abdominal pain (31%) were most common [4]. However, these were all referral-based studies, and to date, no population-based studies have been performed to document the link, if any, between the infection and symptoms.

The epidemiology of CS is only sporadically described and varies worldwide; in studies based on culture of feces to demonstrate spirochetes there appears to be a lower prevalence in developed countries, United Kingdom (1.5%) [5], whereas in developing countries and rural areas, there is a higher prevalence, such as in the Arab Gulf (11.4%) [6] and remote North West Australia (32.6%) [7]. When detected by histology in biopsy samples, the prevalence of CS ranges from 0.4% in a study from Japan [8], 2.5% in Norway [3] to 16.5% in a Greek population [9]. This infection has a higher prevalence in homosexual men—from a specialist clinic, 30% had infection with a positive association with gonorrhea but not symptoms [10] and CS has also been noted in men with HIV infection [11].

Spirochetosis in the colon is defined by histologic observation of spirochetal strains of *Brachyspira* (*pilosicoli* or *aalborgii*) adherent to colonic epithelium, usually seen in biopsies taken at colonoscopy for investigation of GI symptoms. Microscopically, there are no definitive or consistent mucosal inflammatory lesions reported in association with spirochetosis [2,4,12], although a study from Italy suggested pathogenesis may be due to loss of colonic microvilli when biopsies were examined by transmission electron microscopy [13]. CS has also been suggested to be tentatively associated with hyperplastic and adenomatous polyps in a small number of cases [14,15]. Histology is said to be normal in most of these cases—however, this is on looking for overt active (neutrophil) infiltration, not subtle changes of innate inflammation (eg, increased eosinophil infiltration) [12]. We have previously described that in functional disorders, pathology is linked to innate immunity [16]. Increased numbers of lymphoid follicles and aggregates in colon mucosal biopsies have also been shown to be associated with persistent diarrhea of unspecified etiology [17].

A study in the general population could clarify any association of CS with histology and symptoms. The PopCol study is a unique epidemiologic study of GI symptoms with colonoscopy and biopsy in randomly selected subjects in Stockholm, Sweden [18,19]. The aim of this study was to investigate the prevalence of CS in a general population by identification through colon biopsy and to ascertain if there were links with subtle pathologies and symptoms in this group.

2. Materials and methods

2.1. Subjects

This article reports on 2 samples. The first consists of all individuals on whom colonoscopy with biopsies was performed (n = 745 subjects, aged 19-70 years, mean age 51 years, 49% male) and biopsies taken from the ileum and 4 sites in the colon as part of a population-based questionnaire and colonoscopy study in Stockholm, Sweden, the PopCol (Population-based Colonoscopy) study, which has previously been described in detail [19]. The sample population was sociodemographically similar to the background population, consisting of 49% men (Fig. 1). The 745 who underwent colonoscopy also completed a validated questionnaire of GI symptoms, the abdominal symptom questionnaire [20], and the Rome II questionnaire for functional bowel disorders [21]. The study was approved by the local ethics committee, Forskningskommitté Syd at Karolinska Institutet, Stockholm, Sweden, and all participants gave informed consent.

The second sample consists of the subset of sample 1 who had also histopathology performed and in whom spirochetosis was identified plus 1:1 age (±2 years) and sex-matched controls who were free of spirochetosis.