Accepted Manuscript

Inflammatory Bowel Disease and Eating Disorders: A systematized review of comorbidity

L. Ilzarbe, M. Fàbrega, R. Quintero, A. Bastidas, L. Pintor, J. García-Campayo, F. Gomollón, D. Ilzarbe

PII: S0022-3999(17)30785-7
Reference: PSR 9405
To appear in: Journal of Psychosomatic Research

Received date: 21 June 2017
Revised date: 27 August 2017
Accepted date: 13 September 2017

Please cite this article as: L. Ilzarbe, M. Fàbrega, R. Quintero, A. Bastidas, L. Pintor, J. García-Campayo, F. Gomollón, D. Ilzarbe, Inflammatory Bowel Disease and Eating Disorders: A systematized review of comorbidity. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Psr(2017), doi: 10.1016/j.jpsychores.2017.09.006

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
INFLAMMATORY BOWEL DISEASE AND EATING DISORDERS: A SYSTEMATIZED REVIEW OF COMORBIDITY

Ilzarbe L¹, Fàbrega M², Quintero R³, Bastidas A⁴, Pintor L³, García-Campayo J¹,⁵,⁶,⁷, Gomollón F¹,⁶,⁸,⁹, Ilzarbe D¹⁰,¹¹.

1. Faculty of Medicine, Universidad de Zaragoza, Zaragoza, Spain.
2. Department of Child and Adolescent Psychiatry, Imperial College London, London, United Kingdom.
3. Psychosomatic and Liaison Psychiatry Unit, Department of Psychiatry and Psychology, Neuroscience Institute, Hospital Clinic de Barcelona, Barcelona, Spain.
4. Acute Inpatient Unit, Department of Psychiatry and Psychology, Neuroscience Institute, Hospital Clinic de Barcelona, Barcelona, Spain.
5. Department of Psychiatry, Hospital Universitario Miguel Servet, Zaragoza, Spain.
6. Aragón Health Research Institute (IIS Aragón), Zaragoza, Spain.
7. Network for Prevention and Health Promotion in Primary Care (RedIAPP), Madrid, Spain.
8. Inflammatory Bowel Disease Unit, Department of gastroenterology, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain.
11. Faculty of Medicine, Universitat deBarcelona, Barcelona, Spain.
EMAIL OF AUTHORS

Lidia Ilzarbe: lidilsim@gmail.com

Marina Fàbrega: m.fabrega-ribera@imperial.ac.uk

Rafael Quintero: rquintero@clinic.ub.es

Ana Bastidas: bastidas@clinic.cat

Luis Pintor: lpintor@clinic.ub.es

Javier García-Campayo: jgarcamp@gmail.com

Fernando Gomollón: fgomollon@gmail.com

Daniel Ilzarbe: daniel.ilzarbe_simorte@kcl.ac.uk

ADDRESS FOR CORRESPONDENCE

Daniel Ilzarbe Simorte
Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neurosciences, King's College London (PO85), 16 De Crespigny Park
London, United Kingdom, SE5 8AF
Phone: 020 7848 5312
Fax: 020 7708 5800
daniel.ilzarbe_simorte@kcl.ac.uk
ABSTRACT

Objective. Research has shown that there is an association between Inflammatory Bowel Disease, anxiety and mood disorders, however little is known about their association with Eating Disorders. In this paper we will present a case of a young female with a comorbid diagnosis of Inflammatory Bowel Disease and Eating Disorder, and then discuss the results from a systematic review of the literature, describing published cases of patients with the same condition.

Methods. A systematized review of the literature was conducted according to MOOSE guidelines. A computerized literature search of MEDLINE, PsycINFO and EMBASE, and a manual search through reference lists of selected original articles were performed to identify all published case-reports, case series and studies of Inflammatory Bowel Disease and Eating Disorders.

Results. Fourteen articles were included, encompassing 219 cases, including ours. The vast majority were females ranging from 10 to 44 years old. Anorexia Nervosa (n=156) and Crohn’s Disease (n=129) was the most frequent combination (n=90) reported in the literature. These cases present a poor prognosis because of corticoid refusal, medication abandon and/or deliberate exacerbation of IBD symptoms, in the context of trying to lose weight.

Conclusion. Recent evidence suggests there is a possible association between Inflammatory Bowel Disease and Eating Disorders, although the mechanisms involved in its ethiopathogenesis are still unknown. To be aware of this association is important because a delayed diagnosis of this comorbidity may lead to worse prognosis. Further research and a multidisciplinary approach could facilitate earlier diagnosis and provide therapeutic interventions.

KEY WORDS.

Anorexia Nervosa, Bulimia Nervosa, Crohn’s Disease, Eating Disorders, Inflammatory Bowel Disease, Ulcerative Colitis.
INTRODUCTION

Inflammatory Bowel Disease (IBD) is a group of conditions/disorders characterized by chronic inflammation of the gastrointestinal tract and episodes of relapses and remissions; especially in genetically susceptible individuals exposed to environmental risk factors. IBD comprises Crohn’s Disease (CD), Ulcerative Colitis (UC), microscopic colitis, indeterminate colitis and pouchitis. The prevalence of IBD may be increasing as a result of the low mortality, the earlier diagnoses and the longer duration of disease. The registered prevalence of CD varies from 0.6 to 322 per 100,000 in Europe, and from 4.9 to 505 per 100,000 in case of UC. Most studies showed a peak incidence in the second to fourth decade, with the highest incidence amongst 20 to 29 year old. There are not great differences between males and females.

The association between IBD and some mental disorders, especially anxiety and mood disorders, has been extensively studied. According to the meta-analysis by Neuendorf et al., the prevalence of anxiety and depressive disorders in IBD is 21% and 15% respectively. These rates increase up to 35% for anxiety symptoms and 22% for depressive symptomatology. However, other mental disorders have received sparse attention in literature. Especially, and despite the potential overlap in symptoms, the relationship between eating disorders (ED) and IBD has not been widely studied.

Anorexia Nervosa (AN) and Bulimia Nervosa (BN) have been the main diseases classically established as ED. Nevertheless, eating disorder not otherwise specified (EDNOS), which includes partial syndromes of AN and BN, has been the most commonly diagnosed till the recent publication of Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5). The point prevalence of EDNOS in a nation-wide community sample of young females was 2.4%. In the case of AN and BN, the lifetime prevalence amongst women range from 0 to 0.9% and from 0.9 to 1.5% respectively. AN has an overall incidence rate of 4.2-8.1 new cases
per 100,000 persons per year\textsuperscript{10}. In addition, AN presents the highest rate of mortality amongst all psychiatric illnesses, with a Crude Mortality Rate of 5.1 deaths per 1000 person-years\textsuperscript{8}.

There are some groups who have studied the role of diet in IBD\textsuperscript{11-13}. It has been reported that patients with IBD have strong beliefs about some food triggering IBD symptoms\textsuperscript{11}, which frequently drives them to avoid specific nutrients and/or reduce global intake. This may exacerbate malnutrition, and moreover it also may have an impact on their social life, as it usually involves events that include eating and drinking\textsuperscript{11}. Both, malnutrition and social isolation have been related with a significant reduction of quality of life in this population\textsuperscript{12}. In addition, there are common features in both ED and IBD (see table 1) which may lead to misdiagnosis. It has been reported mainly between IBD and AN\textsuperscript{14-21} due to the restrictive pattern\textsuperscript{13}, body mass index (BMI) reduction, predominance of females and similar age of onset\textsuperscript{2,22,23}. Apart from the overlapping symptomatology, both conditions can also coexist as described in the case below, making differential diagnosis more difficult (see table I).
Table I. Similarities and differences between the clinical presentation of inflammatory bowel diseases and eating disorders.

<table>
<thead>
<tr>
<th></th>
<th>IBD</th>
<th>ED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td>Ratio female: male</td>
<td>Higher in females&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>No differences&lt;sup&gt;2&lt;/sup&gt;</td>
<td>AN or BN: 5:1 to 10:1&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>CD: 0.34:1 to 1.65:1&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UC: 0.51:1 to 1.58:1&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Age of highest incidence</strong></td>
<td>CD or UC: 20-29 y/o&lt;sup&gt;2&lt;/sup&gt;</td>
<td>AN: 15-19 y/o&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BN: 20-24 y/o&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Common signs &amp; symptoms</strong></td>
<td>Diarrhoea Due to inflammation</td>
<td>It could be related to laxative abuse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea and vomiting Due to inflammation</td>
<td>It could be self-induced</td>
</tr>
<tr>
<td></td>
<td>Reduced appetite Secondary to abdominal pain and cramping, as well as inflammation</td>
<td>It can be present in AN</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight loss and malnourished (dehydration; anaemia; fatigue; amenorrhea in women)</td>
<td>Due to malabsorption</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Postprandial symptoms Bloating Abdominal pain</td>
<td>Feeling of fullness, meteorism or flatulence Post-meal pains of the epigastrium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constipation Due to inflammation (can lead to bowel obstruction)</td>
<td>Due to low food intake</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Differential signs and symptoms</strong></td>
<td>Fever Blood in stool Fistula Tenesmus Fear of abdominal discomfort from eating food</td>
<td>Body image distortion Fear to gain weight</td>
</tr>
</tbody>
</table>

Case reported in the literature about misdiagnosis and/or differential diagnosis between IBD and ED

| Final diagnosis of IBD: | Gryboski et al. 1968<sup>14</sup>                                      |
|                        | Metcalfe-Gibson et al. 1978<sup>15</sup>                                |
|                        | Hershman et al. 1985<sup>16</sup>                                       |
|                        | Jenkins et al. 1988<sup>17</sup>                                        |
|                        | Andant et al. 1999<sup>18</sup>                                         |
|                        | Blanchet et al. 2002<sup>19</sup>                                       |
|                        | Markella et al. 2010<sup>20</sup>                                       |

| Final diagnosis of ED:  | Tylec et al. 2014<sup>21</sup>                                         |

AN = Anorexia Nervosa; BN = Bulimia Nervosa; CD = Crohn’s Disease; ED = Eating Disorder; IBD = Inflammatory Bowel Disease; UC = Ulcerative Colitis.

There is a paucity of research looking at eating attitudes and behaviours in diet-related chronic health conditions<sup>24</sup> and autoimmune diseases such as IBD<sup>25</sup>. Satherley et al.<sup>13</sup> have recently reported higher prevalence of disordered eating symptoms in participants with IBD relative to healthy controls. Nevertheless, to our knowledge there is no previous review focusing on subjects with IBD fulfilling criteria for a diagnosis of an eating disorder. Thus, we present a case of a young female with a comorbid diagnosis of IBD and ED, and a systematized review of published cases of patients with the same condition.
Case report
A 20-year-old Caucasian woman, diagnosed with pancolonic and ileal CD at age 17, was admitted to the gastroenterology ward for autologous hematopoietic stem cell transplantation. She was corticodependent, intolerant to infliximab and required enteral nutrition at admission. She had been under exclusive enteral nutrition for 8 months. She had also history of Primary Sclerosing Cholangitis (diagnosed the previous year). She reported irregular menstruation since the age of 14 and six months of amenorrhea before admission in relation with weight loss (from 60 to 47.5 kg in the previous year; height=1.70 metres; BMI=16.4). She lived with her parents and her 24-year-old brother. She had abandoned her studies due to her health condition.

Once admitted, the patient was referred to the liaison psychiatry unit for mood lability. She presented fluctuating low mood with loss of interest in her self-care and anxiety symptoms related to her condition (i.e. unmanageable fear of leaving home due to difficult accessibility to bathrooms). At the age of 19 she had been diagnosed with adjustment disorder and started treatment with paroxetine 20 mg/day and alprazolam 0.25 mg/day.

During her admission, she frequently refused to eat due to early satiety, abdominal pain and nausea, despite the gastroenterologist’s recommendation of oral intake. In addition, she also hid prescribed medication and did not take it. Since the age of 14 she also reported a selective pattern of eating, progressive restriction of food intake, and feeling more comfortable using enteral nutrition. She did not describe body image disturbance or fear of gaining weight. Considering her BMI, the amenorrhea and the restrictive diet she was finally diagnosed with EDNOS.

METHODS
This systematized review was conducted according to the guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE). A computerized literature search of MEDLINE, PsycINFO and EMBASE was performed up to the 22nd of December 2016. Search strategy: “inflammatory bowel disease” OR “crohn's
disease” OR “ulcerative colitis” OR “microscopic colitis” OR “indeterminate colitis” OR “pouchitis” AND “eating disorder” OR “anorexia nervosa” OR “bulimia nervosa”.

The reference lists of the identified original articles and case reports were also searched manually for additional records. Studies were assessed by first author (L.I.), and when in doubt, the final decision was made in consultation with a second author. Some authors were contacted to obtain further information. No limitations were placed on language, publication date and publication status.

The following inclusion criteria were used: (I) any data reported about patients with a comorbid diagnosis of IBD and AN, BN or EDNOS. The exclusion criteria were: (I) cases reported with misdiagnosed IBD or ED, or uncertain diagnosis; (II) reviews and published conference abstracts. Case reports and case series were included given the limited number of published epidemiological studies addressing this comorbidity. Publications with cases reporting additional comorbidities were not excluded.

Data were extracted from eligible articles according to the inclusion criteria in a pre-specified Microsoft Excel spreadsheet. The following information was collected: (I) demographic characteristics (including age, gender, number of patients and country of origin); (II) clinical characteristics (including type of IBD, age of diagnosis of IBD, type of ED, age of diagnosis of ED, first diagnosis, initial symptoms and other comorbidities) and; (III) treatment (including drugs and procedures).

RESULTS

The search strategy identified 495 records, after removing 80 duplicates. 461 were excluded at first screening based on titles and abstracts, leaving 34 articles for full text review. Of them, we included 14 articles, excluding 20 articles for the reasons listed in Figure I. Amongst the 14 articles, there were two retrospective cohort studies, six case reports, and six case series (Table II).
Figure 1. Flowchart of literature search of comorbid eating disorders in inflammatory bowel disease.

Records identified through database searching (n=564) → Records identified through manual searching (n=11) → Records after duplicated removed (n=495) → Records screened (n=495) → Full text articles assessed for eligibility (n=34) → Studies included in qualitative synthesis (n=14) → Records excluded by title or abstract (n=461) → Full text articles excluded (n=20) - No case report (4) - Misdiagnosis (6) - Conference abstract (3) - Other comorbidities (2) - Other topics (5)
Table II. Cases reported in the literature with inflammatory bowel disease and eating disorder comorbidity.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Type of study</th>
<th>N</th>
<th>Sex</th>
<th>Age</th>
<th>ED</th>
<th>IBD</th>
<th>Other comorbidities</th>
<th>Corticotherapy</th>
<th>ED treatment</th>
<th>Psycho-social and environmental factors reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sreenivasan\textsuperscript{35}, 1984</td>
<td>Canada</td>
<td>Case report</td>
<td>1</td>
<td>F</td>
<td>17</td>
<td>AN</td>
<td>UC</td>
<td>Mitrail and aortic valves prolapse</td>
<td>Yes</td>
<td>NS</td>
<td>Overweight in childhood, disturbance of family relationships</td>
</tr>
<tr>
<td>Anonymous\textsuperscript{36}, 1985</td>
<td>USA</td>
<td>Case report</td>
<td>1</td>
<td>M</td>
<td>18</td>
<td>EDNOS</td>
<td>CD</td>
<td></td>
<td>Yes</td>
<td>Admission to psychiatric unit, and weekly psychotherapy sessions</td>
<td></td>
</tr>
<tr>
<td>Meadows &amp; Treasure\textsuperscript{36}, 1989</td>
<td>Australia</td>
<td>Case report</td>
<td>1</td>
<td>F</td>
<td>23</td>
<td>BN</td>
<td>CD</td>
<td>Glucose 6-phosphate dehydrogenase, early puberty</td>
<td>Yes</td>
<td>Yes</td>
<td>Psychological treatment</td>
</tr>
<tr>
<td>Mallet &amp; Murch\textsuperscript{37}, 1990</td>
<td>UK</td>
<td>Case report</td>
<td>1</td>
<td>F</td>
<td>13</td>
<td>AN</td>
<td>CD</td>
<td>Lactose intolerance, mild gastritis</td>
<td>No</td>
<td>NS</td>
<td>Admitted to psychiatric unit, behavioural regime and dietary regime</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>F</td>
<td>14</td>
<td>BN</td>
<td>UC</td>
<td>Lactose intolerance, obesity</td>
<td>No</td>
<td>NS</td>
<td>Overweight</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gryboski\textsuperscript{38}, 1993</td>
<td>USA</td>
<td>Case report</td>
<td>1</td>
<td>F</td>
<td>14</td>
<td>BN</td>
<td>UC</td>
<td>Lactose intolerance, early puberty</td>
<td>Yes</td>
<td>No</td>
<td>Best friend had BN</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>F</td>
<td>17</td>
<td>BN</td>
<td>CD</td>
<td>Lactose intolerance, obesity</td>
<td>Yes</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holaday et al.\textsuperscript{30}, 1994</td>
<td>USA</td>
<td>Case report</td>
<td>1</td>
<td>M</td>
<td>15</td>
<td>EDNOS</td>
<td>CD</td>
<td>Delayed puberty</td>
<td>No</td>
<td>NS</td>
<td>Divorced parents</td>
</tr>
<tr>
<td>Rickards et al.\textsuperscript{39}, 1994</td>
<td>UK</td>
<td>Case report</td>
<td>1</td>
<td>F</td>
<td>15</td>
<td>EDNOS</td>
<td>CD</td>
<td>Cyclical neutropenia</td>
<td>No</td>
<td>NS</td>
<td>Admitted to psychiatric unit, and weekly psychotherapy sessions</td>
</tr>
<tr>
<td>Blanchet &amp; Luton\textsuperscript{39}, 2002</td>
<td>France</td>
<td>Case report</td>
<td>1</td>
<td>F</td>
<td>25</td>
<td>AN</td>
<td>CD</td>
<td>Pancreatic fibrosis and focal pancreatic atrophy</td>
<td>No</td>
<td>NS</td>
<td>Admitted to psychiatric unit and psychotherapy</td>
</tr>
<tr>
<td>Baylé &amp; Bouvard\textsuperscript{31}, 2003</td>
<td>France</td>
<td>Case report</td>
<td>1</td>
<td>M</td>
<td>16</td>
<td>AN</td>
<td>CD</td>
<td>Obsessive Compulsive Disorder, Personality Disorder</td>
<td>Yes</td>
<td>NS</td>
<td>Admitted to psychiatric unit, and weekly psychotherapy sessions</td>
</tr>
<tr>
<td>Evert et al.\textsuperscript{32}, 2005</td>
<td>Germany</td>
<td>Case report</td>
<td>1</td>
<td>F</td>
<td>23</td>
<td>AN</td>
<td>CD</td>
<td>Pancreatic fibrosis and focal pancreatic atrophy</td>
<td>No</td>
<td>NS</td>
<td>Admitted to psychiatric unit, and weekly psychotherapy sessions</td>
</tr>
<tr>
<td>Culkin et al.\textsuperscript{33}, 2012</td>
<td>UK</td>
<td>Case report</td>
<td>1</td>
<td>F</td>
<td>36</td>
<td>AN</td>
<td>CD</td>
<td>Obsessive Compulsive Disorder, Personality Disorder</td>
<td>Yes</td>
<td>NS</td>
<td>Abused and neglected in childhood</td>
</tr>
<tr>
<td>Erdur et al.\textsuperscript{37}, 2012</td>
<td>Germany</td>
<td>Epidemiological cohort</td>
<td>1</td>
<td>F</td>
<td>-</td>
<td>AN</td>
<td>CD</td>
<td></td>
<td>NS</td>
<td></td>
<td>Individual and group therapy, art therapy, concentrative movement therapy and relaxation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>F</td>
<td>-</td>
<td>AN</td>
<td>UC</td>
<td></td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solmi et al.\textsuperscript{34}, 2013</td>
<td>Italy</td>
<td>Case report</td>
<td>1</td>
<td>F</td>
<td>26</td>
<td>AN</td>
<td>CD</td>
<td>Psychodynamic therapy</td>
<td>Yes</td>
<td>NS</td>
<td>Criticized at a ballet audition</td>
</tr>
<tr>
<td>AN = Anorexia Nervosa; BN = Bulimia Nervosa; CC = Collagenous Colitis; CD = Crohn's Disease; ED = Eating Disorder; EDNOS = Eating Disorder Not Otherwise Specified; F = female; IBD = Inflammatory Bowel Disease; M = male; NS = Not Specified; UC = Ulcerative Colitis; * = those using the disease to lose weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wotton et al.\textsuperscript{a}, 2016</th>
<th>UK</th>
<th>Epidemiological cohort</th>
<th>83</th>
<th>F</th>
<th>AN</th>
<th>CD</th>
<th>NS</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>62</td>
<td>F</td>
<td>AN</td>
<td>UC</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>32</td>
<td>F</td>
<td>BN</td>
<td>CD</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>22</td>
<td>F</td>
<td>BN</td>
<td>UC</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Our case</td>
<td>Spain</td>
<td>1</td>
<td>F</td>
<td>20</td>
<td>EDNOS</td>
<td>CD</td>
<td>Adjustment Disorder</td>
<td>Yes</td>
</tr>
</tbody>
</table>
A total of 219 patients, including our case, with a comorbid diagnosis of IBD and ED have been reported in the scientific literature (Table II). The vast majority were females, with only three cases reported on males. The mean ages ranged from 10 to 44. AN (n=156) and CD (n=129) were the most prevalent diagnosis amongst ED and IBD respectively. In fact, the comorbidity between them, AN plus CD, has been the most frequent combination reported in the literature (n=90) (see figure 2 for more details). The index diagnosis was IBD in 106 out of 211 patients, while ED was the first diagnosis made in 105 out of 211 (See figure II). There were no data on first diagnosis in 8 patients. ED were clinically diagnosed in case reports and in the two epidemiological studies they did not report any screening instrument (the cohorts were from subjects with ED).

Figure II. Distribution of comorbid eating disorder by diagnosis of Inflammatory Bowel Disease published in the literature (number of cases)

Clinical presentations were reported for seventeen patients with IBD and ED comorbidity: weight loss (n=16), abdominal pain (n=12), diarrhoea (n=7), anaemia (n=6), amenorrhoea (n=6), self-induced vomiting (n=5), bloody diarrhoea (n=5), asthenia (n=3), anorexia (n=3), nausea (n=3), vomiting (n=3), failure to thrive (n=2), hypoproteinaemic or edema (n=2), constipation (n=2), cachexia (n=1), early satiety (n=1), dizziness (n=1), dyspnoea (n=1), syncope (n=1), dysphagia (n=1) and sore throat (n=1). The two retrospective cohort studies did not report any sign or symptom.
Of the seventeen patients described in case reports or case series studies, five of them used the IBD symptomatology to potentiate weight loss (it was suspected in another case but not confirmed) with methods specified in 4 cases: 1) by taking laxatives; 2) by taking products with lactose despite being intolerant to it; 3) by combining both previous methods; and 4) by using stoma as a purging device. Improvement is reported only in one case, where AN symptoms improved after TNF-α therapy prescribed for CD. In contrast, severe impairment and fatal outcomes were reported for most of the patients: five patients required bowel resections, two patients developed toxic megacolon and one died as a result of occult perforation of the colon and severe cachexia. In relation to the treatment, enteral nutrition (n=4) and parenteral nutrition (n=6) were in general well tolerated. Lack of adherence to prescribed treatment was described in 6 patients. And among the 10 patients receiving corticosteroid therapy, another six of them showed concern or refusal to being treated with corticoids in relation to weight gain.

**DISCUSSION**

The main findings of our systematized review focused on comorbidity between IBD and ED are: 1) CD and AN are the two comorbid disorders more frequently reported; 2) epidemiologically, comorbid IBD and ED is mostly reported in young women; and 3) IBD symptoms have been reported to be used for potentiating weight loss in some cases.

Several reported papers that mention IBD and ED are focused on the misdiagnosis between CD and AN14-21, being the differential diagnosis sometimes difficult to establish. The first case with a comorbid diagnosis of IBD and ED was reported by Sreenivasan35 in 1984. Since then, other authors have reported cases with ED and IBD, and several studies screening ED in patients with IBD have been published24,25,27,40,41, the most recent one28 in 2016.

The scientific literature suggests that there is an association between ED and IBD, although more research is required to confirm this24,25,28. The direction of the relationship between IBD and ED also remains unclear; it is not known whether IBD leads to the development of an ED, if it is the reverse, or if the relationship is bidirectional. Wotton et al.28 observed a significant elevated risk of being diagnosed with Ulcerative Colitis (UC), five or more years after the first admission due to AN. They also reported on a higher risk of CD in patients diagnosed with AN,
and vice-versa, within the first year after an admission. Similar results were described in another study, where they found that the incidence and lifetime prevalence of CD were increased in patients with ED. Regardless of the direction of this link, comorbidity may lead to significant delays in diagnosis and complex therapeutic management. In our case, the patient showed abnormal eating behaviours since the age of 14, although the diagnosis of EDNOS was not made until she was 20. Although epidemiological studies did not report the age of the subjects, from the individual cases descriptions, it seems that this comorbidity should be especially considered in the differential diagnosis within younger patients. Additionally, the association between IBD and ED may also worsen the prognosis of both conditions and even threaten patient’s life as some examples found in this review.

Several risk factors have been hypothesized to relate ED with a diagnosis of IBD: delayed growth and puberty onset, preoccupation with dietary management, fear of abdominal discomfort from eating food, weight and body shape concerns, poor body image, poor emotional well-being, disease severity, body shame (e.g. use of colostomy or ileostomy bag), impaired personal relationships and physical limitations. With regards to ethio-pathogenesis theories that relate both diseases, some explanations have been raised focusing primarily in three aspects: 1) role of diet; 2) changes in body shape because of drug therapy for IBD; 3) immune-inflammatory pathogenesis.

Regarding the role of diet in patients with IBD, Hughes et al. has recently validated the Food-Related Quality of Life-29 questionnaire (FR-QoL-29). This questionnaire has been developed specifically for patients diagnosed with IBD to evaluate eating behaviours and dietary changes related with the disease and its consequences in terms of quality of life. Relative to this, some studies have suggested that these modifications in dietary patterns and gastrointestinal symptoms presented in patients with IBD may act as predisposing factors for ED. Some of these factors are:

- The subjective perception of patients of some aliments triggering their IBD symptoms although scientific evidence is not enough to support this relation.
- Dietary recommendations for IBD, which often include hyperphagic diets to compensate the malabsorption due to the disease and/or short bowel syndrome after massive bowel resections\(^3\); in order to avoid malnutrition and/or delayed growth in youngers\(^4\).

- The need of enteral or parenteral nutrition, required for treatment in some cases, may complicate the reestablishment of food intake, as the case we presented and other one reported in the literature\(^3\).

- Additionally, exacerbations of postprandial abdominal pain, early satiety, anorexia or nausea have been described in patients with upper gastrointestinal CD and weight loss, which could be specially exacerbated due to the delayed gastric emptying of solids shown in AN and CD\(^3\).

All this may lead to food avoidance behaviours, modifying normal eating habits and increasing weight loss\(^13,37,39\).

In relation to secondary effects of treatment, Meadows and Treasure\(^3\) were the first who proposed that changes in body shape due to corticotherapy, could explain a link between ED and IBD. The appearance of acne, moon face, oedema, and skin striae are frequent early adverse effects associated with a supra-physiological dose of corticosteroids, currently used to induce remission in CD\(^4\). These changes may modify the body shape of the patient and increase their weight, resulting in triggering restrictive and/or purgative behaviours to regulate it. This theory has been supported by other authors who have described similar cases\(^31,37,38\) in which patients refused prescribed corticosteroids. This time sequence, however, is not applicable to the cases where ED is the initial diagnosis\(^19,29,34,37-39\). Other drugs used for IBD treatment, as tacrolimus, have been reported to induce anorexia nervosa-like symptoms in children\(^5,45\).

In recent years, Solmi et al.\(^3\) have offered a novelty inmuno-inflammatory hypothesis suggesting that proinflammatory cytokines (IL-6 and TNF-α), which levels are increased in CD, may be involved in the maintenance of AN symptoms. These substances and hypothalamic neuropeptides have common ways in regulating hunger/satiety and energy expenditure. Over-expression of the IL-6 may contribute to increase levels of anorexigenic peptides (pro-opiomelanocortin and corticotrophin-releasing hormone) and decrease orexigenic peptides.
(neuropeptide Y, agouti-related, melanin-concentrating hormone, prepro-orexin)\textsuperscript{46}. Additionally, IL-6 facilitates satiety by stimulating leptin sensitivity at the hypothalamus. Likewise, TNF-α promotes the effect of anorexigenic peptides in inflammatory diseases as IBD\textsuperscript{34}. It has been also found increased levels of autoantibodies (autoAbs) against peptides related with appetite, body weight and suppression of food intake (α-melanocyte-stimulating hormone, oxytocin, vasopressin, luteinizing hormone-releasing hormone, adrenocorticotropic hormone) in patients with ED as well as in control subjects\textsuperscript{47}. Although these autoAbs are not sufficient to cause ED\textsuperscript{47}, it has been suggested that non-harmful autoAbs may become pathogenic and contribute to the development of ED by different mechanisms\textsuperscript{47,48}: 1) autoAbs may cross the blood-brain barrier and disrupt signalling at the MC4 melanocortin receptor, related with weight regulation; 2) autoAbs may also interfere with signalling on the MC3 melanocortin receptor of the arcuate nucleus, located outside the blood-brain barrier and associated with the control of food intake by substances such as neuropeptide Y (NPY); 3) autoAbs may block α-MSH function and suppress the production of IL-1 and TNF-α, inhibiting food intake; and 4) autoAbs may occupy serotonin-binding sites and increase its concentration, which is a common feature found in plasma of AN patients. In this regard, several studies have described similar features for patients with IBD. It has been found that disruption in MC1 melanocortin receptor signalling may lead to worsening of colitis in mice\textsuperscript{49}. In fact, one study showed a reduction of intestinal inflammation in murine models being treated with melanocortin-derived tripeptide α-MSH (KPV)\textsuperscript{50}. Lower plasmatic levels of NPY have also been found in patients with IBD than in control subjects, suggesting a key role of NPY in the development of IBD by interacting with other substances as serotonin and somatostatin\textsuperscript{51}. Likewise, serum serotonin levels may be associated and correlated with a higher pouch endoscopy inflammation in and cuffitis\textsuperscript{52}. Additionally, another study\textsuperscript{53} showed lower levels of acyl ghrelin IgG autoAbs in patients with AN than in healthy subjects. In contrast, ghrelin reactive autoAbs bind mainly to des-acyl ghrelin in control subjects. In case of IBD patients, serum ghrelin levels seem to be higher in active disease than in IBD patients in remission. These elevated levels correlate with severity of the IBD and the activity markers\textsuperscript{54}. These features suggest a possible link between gut and brain. However, it remains unclear whether these substances play a role in the pathogenesis or maintenance of ED\textsuperscript{34}. 


The main limitation of this review is inherent to the publication bias: there are few articles focused on this topic and they are mainly case series. Besides, it should be taken into account that frequently, published case reports are those with unusual presentations or outcomes due to their severity. At the same time, this could also support our view that less severe patients suffering this comorbidity could be underreported and/or underdiagnosed. It needs to be also highlighted that none of the publications included reported longitudinal prospective data and that only one author performed the article selection. Nevertheless, as a strength, to the authors’ knowledge this is the first review addressing this comorbidity, exhaustively reviewing all published data and suggesting plausible ethiopathogenic mechanisms underlying this association. Although literature is scarce and conclusions should be taken cautiously, it is a relevant topic in daily clinical practice and its interest is growing in latest years as reflected in recent epidemiological studies 24,25,27,28.

CONCLUSION

Recent evidence suggests a possible association between IBD and ED, and some theories and risk factors have been proposed in this regard. Nevertheless, the mechanisms involved in its ethiopathogenesis are still unknown. To be aware of this condition is important because a delayed diagnosis of comorbid IBD and ED may lead to worse prognosis. Considering our experience in the management of the case described above and the cases reported by other authors, there are some clinical implications that could be of interest for clinicians. First, ED diagnosis should be considered in patients with IBD. Second, multidisciplinary approach would be recommended in these complex cases to provide an adequate therapeutic intervention. Third, screening tools to evaluate eating attitudes and behaviours in patients with IBD could be used in daily practice, as for example the Eating Attitude Test – 2611.55. Further research, mostly prospective studies, is needed to firmly support this link, and to identify clinical and/or biological markers which could facilitate earlier diagnosis.

ACKNOWLEDGMENTS

We would like to thank Ellen Grimås for her contribution reviewing orthography and stylistic aspect of the writing.
FUNDING STATEMENT

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICTS OF INTEREST

M. Fabrega and D. Ilzarbe are grant-holders from Alicia Koplowitz Foundation. No other conflicts of interest.

ABBREVIATIONS

AN: Anorexia Nervosa

AutoAbs: Autoantibodies

BN: Bulimia Nervosa

CC: Collagenous Colitis

CD: Crohn's Disease

ED: Eating Disorders

EDNOS: Eating Disorder No Otherwise Specified

IBD: Inflammatory Bowel Disease

MOOSE: Meta-Analyses and Systematic Reviews of Observational Studies

UC: Ulcerative Colitis

REFERENCES


24. Quick VM, McWilliams R, Byrd-Bredbenner C. Case-control study of disturbed eating behaviours and related psychographic characteristics in young adults with and without diet-


HIGHLIGHTS

1. Symptomatology overlaps between inflammatory bowel disease and eating disorders
2. Comorbidity should be considered in the differential diagnosis
3. Crohn’s Disease and Anorexia Nervosa is the most frequent reported comorbidity
4. A delayed diagnosis of this comorbidity may lead to poorer prognosis
5. A multidisciplinary approach would be necessary to manage these cases