Irritable bowel syndrome might be associated with dry eye disease

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Abstract

Background A possible association between dry eye disease (DED) and irritable bowel syndrome (IBS) has been hypothesized based on the fact that they both share an inflammatory pathogenesis.

Methods Ninety-five patients with IBS and 276 healthy controls were enrolled in the study. All patients answered a questionnaire regarding DED symptoms and had a complete ophthalmic examination. DED signs were evaluated using Schirmer’s 1 and tear break-up time (tBUT) tests in both groups.

Results Female IBS participants presented significantly lower Schirmer’s test and tBUT (P=0.002 and P<0.001 respectively) than controls. Both diagnostic tests in male IBS patients were also significantly lower than in controls (P<0.001). 72% of IBS patients gave at least 3 positive answers to the questionnaire compared with 42% of the control group (P<0.01).

Conclusion Our results suggest a correlation between IBS and DED. DED symptoms can cause further complications in patients with IBS, and should be considered in their management. However, further research is needed to establish a possible pathophysiologic association.

Keywords Dry eye, irritable bowel syndrome, keratoconjunctivitis sicca

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Introduction

Dry eye disease (DED) or keratoconjunctivitis sicca (KCS) is the most common disease of the ocular surface. In 2007, the International Dry Eye Workshop defined it as "a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface" [1]. The prevalence of DED is estimated between 7.4 and 33.7% [2]. Most studies have found an increasing prevalence with aging and a greater prevalence among women probably due to their hormonal status [2,3].

Even though DED is considered as a condition of tear deficiency, either due to decreased lacrimation or excessive evaporation, its pathophysiology seems to be more complex. New concepts of its pathogenesis involve inflammation mechanisms mediated by T-cell lymphocytes [4,5]. It has been suggested that it is an inflammatory disorder, which affects both ocular surface and lacrimal glands. Desiccating stress, hyperosmolarity, proinflammatory cytokines released from the lacrimal glands and blinking abnormalities seem to contribute to inflammation of the ocular surface [6-8]. Loss of peptide growth factors and vitamin A, both necessary for cellular proliferation, migration, normal differentiation, immune modulation and ocular wound healing, might also contribute to ocular surface inflammation [9,10].

In some clinical disorders such as Sjögren's syndrome, the lacrimal gland becomes an important target of the immune system resulting in DED. The presence of focal lymphocytic infiltrates and the increased local production of proinflammatory cytokines are characteristic findings of lacrimal gland inflammation [11]. This finding has also been demonstrated by studies investigating the role of anti-inflammatory therapies such as topical 0.005% cyclosporine, corticosteroid therapy, and tetracycline in patients with DED [12-14].

Irritable bowel syndrome (IBS) is the most common gastrointestinal disorder [15]. It is defined, according to Rome III criteria, as recurrent abdominal pain or discomfort
for at least 3 days per month during the previous 3 months, associated with two or more of the following symptoms: improvement with defecation, change in the frequency and form or appearance of stools [16]. It affects 10-20% of adolescents and adults in western societies and is the most common cause of recurrent abdominal pain in children [17,18].

Despite the growing body of literature, IBS pathophysiology remains poorly understood. Recent studies suggest an inflammatory pathogenesis. Several investigators have demonstrated increased numbers of chronic inflammatory cells in the colonic mucosa of patients with IBS [19-21]. T-lymphocytes of the lamina propria are increased both in post-infectious and non-post-infectious IBS patients compared with controls. Mucosal mast cells are also increased, based on quantification methods [22]. Recent documentation of increased numbers of immune cells expressing CD25, a marker of immune cell activation, provides functional evidence of immune activation in IBS [23]. There is also a change in peripheral cytokine profiles in these patients. Abnormal interleukin (IL) -10/-12 ratio has been observed, suggesting a pro-inflammatory state [24].

In our case-controlled study we aimed to investigate the prevalence of DED in IBS compared with healthy subjects who visited our ophthalmology clinic for a regular visual acuity testing.

### Patients and methods

#### Patients

The study was conducted at the University Hospital of Ioannina Greece, a referral tertiary center for digestive and ocular diseases. Ninety-five patients with IBS, diagnosed according to Rome III criteria from September 2014 to January 2015 in the Hepato-Gastroenterology Unit, were consecutively included. One experienced gastroenterologist diagnosed all IBS patients before they were further tested for DED. 276 age- and gender-matched individuals without IBS, among the outpatients who had a routine visual acuity testing during the same study period in the Department of Ophthalmology, served as controls. Two ophthalmologists performed all ophthalmic examinations, both of whom were blinded to IBS status.

Patients with pre-existing ocular disease such as glaucoma or uveitis, disorders of the lid or nasolacrimal pathway, previous ocular surgery, and subjects using contact lenses were excluded from the study. We also excluded patients with ocular allergies, pterygium or blepharitis, because these factors may have an influence on dry eye test results (Table 1)[3,25].

For each patient we recorded gender and age. All patients had a routine ophthalmic examination, which included visual acuity measurement, external examination and slit lamp biomicroscopy. All patients were asked to answer a questionnaire regarding dry eye-related ocular symptoms, in the form of oral interview. It comprised 6 questions about itching, sand and burning sensations, red eye appearance, secretions, and discomfort in dry environments [26,27] (Table 2). Each question could be answered with either a “Yes” or a “No”. Positive answers to at least three questions of ocular symptoms questionnaire were considered as presence of DED. Additional diagnostic tests for DED, such as Schirmer’s test (ST) 1 and tear break-up time (tBUT), were used in this order.

The study was approved from the Institutional Review Board. Informed consent was obtained from all participating patients.

### Table 1 Consort flow diagram of patients enrolled

<table>
<thead>
<tr>
<th>Assessed for eligibility (n=402)</th>
<th>Excluded (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not meeting inclusion criteria (n=21)</td>
</tr>
<tr>
<td></td>
<td>Declined to participate (n=10)</td>
</tr>
<tr>
<td>Number of patients included (n=371)</td>
<td>Group 1 (n=95)</td>
</tr>
<tr>
<td>Group of patients with diagnosis of Irritable bowel syndrome</td>
<td>Group 2 (n=276)</td>
</tr>
<tr>
<td>Group of healthy patients who constitute the control group</td>
<td>Analyzed (n=95)</td>
</tr>
<tr>
<td>Excluded from analysis (n=0)</td>
<td>Analyzed (n=276)</td>
</tr>
<tr>
<td>Excluded from analysis (n=0)</td>
<td></td>
</tr>
</tbody>
</table>
Diagnostic tests

ST was performed under natural light without topical anesthesia. Standardized filter paper was placed in the lateral canthus away from the cornea and left in place for 5 min, while the eye was closed. The distance moistened was measured in mm. A reading of less than 5 mm was considered abnormal. It was only performed once in each patient.

Tear film stability was assessed using tBUT via a commercially available fluorescein test paper that came in contact with the bottom conjunctiva. The subjects were instructed to blink 3 times, and then to look straight-forward without any blink. Tear film was observed using a blue cobalt filter under wide lighting. The interval between the last blink and the appearance of the first corneal dry spot was measured. The last procedure was repeated 3 times and the mean value was recorded. A tBUT value less than 10 sec was accepted as abnormal.

Statistical analysis

We presented data separately for IBS patients and controls. Continuous variables are presented as mean ± standard deviation (SD, normal distribution), while non-continuous variables are presented as percentages. Normality was assessed with both the graphical inspection of the distribution and with the Shapiro-Wilk normality test. Statistical comparisons between groups were performed using the unpaired t-test or χ² test, as indicated. In case of unequal variances between subgroups the unequal variance assumption was employed, with the use of Welch t-test. Statistical significance for all comparisons was achieved if the P values from the corresponding statistical tests were below 0.05. All statistical analyses were conducted using the Stata Statistical Software Release 13 for Windows (College Station, TX, Stata Corp LP).

Results

Patients

The study group comprised 95 IBS patients and the control group 276 healthy participants. Demographic characteristics for IBS patients and controls are summarized in Table 3. Mean age was 49.8±15.36 for women and 58.28±15.47 years for men in the IBS group versus 51.9±16.64 and 55.8±19.25 years respectively in the control group. Both groups matched in gender (70.5% females in the IBS group vs. 67.3% in the control group). However, age difference between the sexes of the same group was greater in IBS patients (8.5 years) than in controls (3.9 years) (P=0.280 for female age, P=0.256 for male age, t-test).

Dry eye symptoms in IBS and healthy controls

More IBS patients gave three or more positive answers than healthy controls (Table 4). Specifically, 68 (72%) IBS patients gave at least three positive answers to the questionnaire compared with 116 (42%) healthy subjects (P<0.01, χ² test).

Table 2 Questionnaire of ocular symptoms related to dry eye disease

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you ever feel a foreign body or gritty or sandy sensation in your eye?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Do your eyes ever have a burning sensation?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Do your eyes ever feel dry?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Are your eyes ever red?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Do you notice much crusting on your lashes?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Do your eyes ever get stuck shut?</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 3 Comparison of demographic data between patients with irritable bowel syndrome (IBS) and controls

<table>
<thead>
<tr>
<th></th>
<th>IBS n=95</th>
<th>Controls n=276</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>67 (70.5%)</td>
<td>186 (67.3%)</td>
<td>0.564</td>
</tr>
<tr>
<td>Male</td>
<td>28 (29.5%)</td>
<td>90 (32.6%)</td>
<td>0.576</td>
</tr>
<tr>
<td>Age (F) (±SD, years)</td>
<td>49.8±15.36</td>
<td>51.9±16.64</td>
<td>0.280</td>
</tr>
<tr>
<td>Age (M) (±SD, years)</td>
<td>58.28±15.47</td>
<td>55.8±19.25</td>
<td>0.256</td>
</tr>
</tbody>
</table>

F, female; M, male; SD, standard deviation

Discussion

DED is an extremely common disorder that in various grades of severity affects a large part of the general population at one time or another. Millions of people experience symptoms of IBS each year. Both DED and IBS have an unclear pathogenesis, including a common theory of inflammatory pathogenesis.

Over the past few years several studies have shown that dry eye seems to be caused by inflammation mediated by T-cell lymphocytes [5]. A dangerous vicious cycle of inflammation develops on the ocular surface that may lead to ocular surface disease. The role of inflammatory cytokines and matrix metalloproteinases (MMPs) in the pathogenesis of dry eye seems to be very important for both the easier understanding of KCS and for the discovery of new therapeutic agents [7,28]. Increased production and activation of pro-inflammatory cytokines (IL-1,
inflammatory pathogenesis. Our study indicates that patients with IBS should be considered at increased risk of having DED. ST scores were significantly affected compared with healthy controls. tBUT test also yielded significantly lower results in IBS patients than in controls. In addition, all abnormalities in tear film production resulted in more common ocular complaints of dry eyes (more than 3 positive answers to the dry eye symptoms questionnaire) in IBS patients. Our results are supported by previous studies that demonstrated a relation between IBS and dry eye syndrome. Barton et al in 1999 [36] assessed the frequency of fibromyalgia and sicca complex (dry eyes and mouth) in secondary care patients with IBS. 33% of 46 IBS patients presented with sicca syndrome compared with only 6% in the control group, thus adding it to the list of extracolonic manifestations of IBS [36]. In a recent study concerning the prevalence and risk factors of DED in a female cohort, a high association between DED and IBS was found (P<0.0005). Vehof et al showed that four chronic pain syndromes including pelvic pain, chronic widespread pain, IBS, and dry eye were heritable and shared genetic etiologic factors in common biologic pathways, thus introducing the concept of pain hypersensitivity being a common pathogenetic mechanism [37,38].

Data concerning ocular changes in patients with IBS are limited, and dry eye is often overlooked in the context of IBS. This study aims to investigate the association between IBS and DED based on their inflammatory pathogenesis. Our study indicates that patients

Table 4 Schirmer’s 1 test, tBUT test, and questionnaire in IBS patients compared with healthy controls

<table>
<thead>
<tr>
<th></th>
<th>IBS</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean values (n=95)</td>
<td>Mean values (n=276)</td>
<td></td>
</tr>
<tr>
<td>tBUT (F) (±SD, sec)</td>
<td>7.21±3.15</td>
<td>14.39±6.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>tBUT (M) (±SD, sec)</td>
<td>7.69±3.60</td>
<td>14.02±6.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Schirmer’s test (F)</td>
<td>10.23 mm/5 min (SD±6.8)</td>
<td>13.46 mm /5 min (SD±9.17)</td>
<td>0.002</td>
</tr>
<tr>
<td>Schirmer’s test (M)</td>
<td>9.26 mm/5 min (SD±5.42)</td>
<td>14.16 mm/5 min (SD±9.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Questionnaire ≥3 positive answers (%)</td>
<td>68 (72)</td>
<td>116 (42)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

IBS, irritable bowel syndrome; tBUT, tear break-up time; F, female; M, male
of IBS. Our IBS patients presented a higher prevalence of DED compared with healthy controls. The fact that the score of all tests used for the evaluation of DED was worse in IBS patients than in controls, makes us believe that DED should be considered when treating IBS patients. However, further investigation should be done to establish their pathophysiological association.

References