Sex and Gender Difference in Overlap Syndrome of Functional Gastrointestinal Disorder and the Effect of Genetic Polymorphism

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Introduction
Coexistent gastrointestinal symptom profiles and prevalence or associated factors for the overlap among non-erosive reflux disease (NERD), functional dyspepsia (FD) and irritable bowel syndrome (IBS) remain unclear. As little is known about sex or gender differences among patients with over functional gastrointestinal disorders (FGIDs) therapeutic approach is rather difficult.

Objectives
To evaluate the clinicodemographic features of NERD, FD, and IBS and their overlaps in the view of sex and gender difference and to assess the risk factors including genetic polymorphisms for NERD-FD-IBS.

Patients and Methods
Data collected from 494 FGID patients and 239 controls visiting the outpatient clinic of Gastroenterology at Seoul National University Hospital in Korea. Diagnostic criteria of FGID were based on the Rome IV. Risk factors including genetic polymorphisms of neurotransmitters and cytokines were evaluated.

1. Neurotransmitters that cause FGIDs
HTR3A C178T (serotonin gene), SLC6A4 (serotonin reuptake transporter), GNB3 C825T (G protein beta3 subunit), ADRA2C (Adrenergic receptors, adrenoceptor), CCKAR (Cholecystokinin, CCK), 5-HTTLPR (serotonin-transporter), Rs 25531 (serotonin-transporter)

2. Cytokines
TNFa 308G>A, IL10 592C>A, IL10 1082G>A

Results

Distribution of FGIDs
NERD 15.8%
NERD-FD 14.7%
NERD-IBS 2.9%
FD 12.3%
IBS-FD 7.0%
IBS 6.9%

Baseline characteristics and Distribution of FGIDs

<table>
<thead>
<tr>
<th>Variables</th>
<th>Healthy control (n = 239)</th>
<th>Non-overlap FGID (n = 255)</th>
<th>Overlap FGID (n = 239)</th>
<th>P value</th>
<th>Post-hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>35.1 (11.7)</td>
<td>35.1 (11.7)</td>
<td>35.1 (11.7)</td>
<td>0.907</td>
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</tr>
<tr>
<td>Sex (%)</td>
<td>149 (61.1)</td>
<td>98 (38.2)</td>
<td>51 (21.5)</td>
<td>0.001</td>
<td>a,b,c</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.4 (3.4)</td>
<td>25.4 (4.3)</td>
<td>25.4 (3.2)</td>
<td>0.843</td>
<td></td>
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<tr>
<td>Depression</td>
<td>3.7 (3.7)</td>
<td>3.7 (4.0)</td>
<td>3.7 (3.2)</td>
<td>0.732</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>5.1 (3.5)</td>
<td>5.1 (3.6)</td>
<td>5.1 (3.4)</td>
<td>0.332</td>
<td></td>
</tr>
</tbody>
</table>

Clinical characteristics of non-overlap and overlap FGIDs

NERD: IL10 1082G>A, no sex differences
IBS: GNB3 825C>T, no sex differences / IL10 592C>A, difference in men
NERD-FD: ADRA2A 1291C>G, difference in men and women
NERD-IBS: IL10 592C>A, difference in men
NERD-FD-IBS: SLC6A4 5-HTTLPR, SLC6A4 3609A>G, GNB3 825C>T
difference in men (GNB3 is different for both men and women)

Conclusion
Patients with overlap FGIDs should be a focus of attention due to their association with anxiety/depression and more severe symptoms, especially in women. Genetic polymorphisms seem to be pathophysiological factors of overlap FGIDs. (UN SDGs: Advancing human well-being 1)