Epidemiology of Uninvestigated Dyspepsia and Functional Dyspepsia in Asia

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Functional dyspepsia (FD) is a group of gastrointestinal (GI) disorders that includes variable combinations of chronic or recurrent upper GI symptoms not explained by structural or biochemical abnormalities. FD accounts for a significant percentage of patients seen in primary care with abdominal symptoms. Although the criteria used to define FD can easily affect the prevalence in the general population, the prevalence of uninvestigated dyspepsia and FD diagnosed by the Rome III criteria is 5.3% to 20.4%, predominantly affecting females. The prevalence differs among geographical regions and races. Gene polymorphisms and early life events are also involved in the development of FD. The symptoms often alleviate and re-appear in the course of these entities. This information may introduce physicians to the detailed background of these patients and strategies for treatment.

Introduction

Functional dyspepsia (FD) is a group of gastrointestinal (GI) disorders that includes various combinations of chronic or recurrent GI symptoms not explained by structural or biochemical abnormalities.1 It is a syndrome, and the diagnosis can only be made based on patients’ self-reported symptoms and by the exclusion of structural diseases. The definition of the symptoms may differ by people, country, and geographical region. However, the pathophysiology of FD is now becoming clearer. The diagnostic criteria have been revised and are now more systematic.2,3 The Asian epidemiology of uninvestigated dyspepsia (UD) and FD diagnosed by the Rome III criteria will be reviewed in this paper.

Prevalence

Dyspepsia without organic disease is most prevalent in patients who visit medical institutes.4 A recent meta-analysis showed that the overall pooled prevalence of UD was 21%.5 However, this frequency became 5% to 12% when heartburn and regurgitation were excluded.6 In the Rome II definition,2 reflux symptoms were excluded from FD, and when irritable bowel syndrome (IBS) symptoms were present, FD was diagnosed as IBS. Therefore, the prevalence of FD is easily affected by the presence of heartburn or IBS symptoms. The prevalence of FD in Japan as defined by the Rome II criteria in subjects undergoing a health check-up was 13% when organic diseases were excluded.7
The prevalence of UD and FD in the general population diagnosed by the Rome III criteria has been reported to be 5.3% to 20.4% (Table 1). Only studies based on the general population and health checkups were selected here to obtain the true generalized prevalence in the community. A report from Japan showed that only 9% of patients examined by endoscopy due to dyspepsia symptoms had organic lesions, and 28% of patients with gastrointestinal symptoms without any specific lesions has no symptoms within 1 week after the endoscopy and before initiating medication. Furthermore, 21% of patients who visited a Japanese university hospital with abdominal symptoms had FD. In an Internet survey using a panel of volunteers registered with a survey organization, we elucidated the prevalence of UD and a history of childhood abuse in the population. The study subjects were selected using random computer screening to create an equal distribution by age, sex, and residential area. Age groups were equally stratified into five groups: 20s, 30s, 40s, 50s, and 60s and older. Using our age-stratified subjects’ data and the Japanese population census, the prevalence of UD in Japan was estimated to be 21.9%, and the percentage of subjects who consulted a medical institute with dyspeptic symptoms was only 5.7% of the population. An online survey is useful as a tool to estimate prevalence, especially in the general population, as long as we take the low response rate into account. As factors affecting the prevalence of FD, the investigation environment, the definition of symptom duration, and the meticulousness of organic disease exclusion are important. In the Rome II definition, the symptom duration of FD was defined as at least 12 weeks during the preceding 12 months, and in the Rome III definition, the symptom duration of FD was defined as at least 3 months with symptom onset at least 6 months before diagnosis. In Japan, people who have symptoms often consult a physician within 6 months of symptom onset. Therefore, the duration of symptoms does not often match the criteria for FD. Moreover, although structural disorders should be excluded to define FD, it is not easy to exclude them in a large-scale survey of the general population. The availability of examinations may be limited in general practice and differ even among hospitals. The characteristics of patients may also be different in primary care and tertiary care settings. In a report from Korea, the prevalence of FD defined by the Rome III criteria in primary clinics and tertiary care hospitals was 46.0%. Whereas, in a report from Japan, the prevalence of FD defined by the Rome III criteria in a general hospital was 2.1%. Therefore, when we evaluate the prevalence of FD, we should carefully take into account the background characteristics of the subjects analyzed.
Epidemiological Factors

a) Sex and subtype
The prevalence of upper gastrointestinal symptoms in the USA showed no significant differences between men and women. The surveys using Rome II or other than Rome definitions mostly showed no differences between males and females in the prevalence of dyspepsia. However, in Japanese men and women, the non-ulcer dyspepsia (NUD) rates were 11% and 26%, while in The Netherlands, they were 12% and 21%, respectively. These data indicate that dyspepsia is more prevalent in women. Furthermore, in a systematic review, dyspepsia had a different pattern of symptoms in men and women. Recent reports of UD/FD defined by the Rome III criteria also indicated a female predominance in Asia.

b) Geographical regions
The DIGEST study showed that the prevalence of UD in seven international sites was 41% of the general population, 60% in the USA, and 26% in Japan. A report from China showed that the prevalence of UD in the general population was 23.5%. Although these data suggest that the prevalence differs among geographical regions, the exclusion of organic diseases might not be complete, and the defined symptom frequency was different in the reports. The interpretation of symptoms may also be subtly different among geographical regions. Because the definition of FD differs in the Rome III and the Rome II criteria, it is not appropriate to compare the data directly.

c) Genetics and early life events
It has become clear that single nucleotide polymorphisms of genes are involved in many diseases, including malignant tumors, and psychosomatic diseases. Even in FD, these gene polymorphisms may be involved in susceptibility and development. Recently, genetics have been found to be involved in the development of functional gastrointestinal diseases (FGIDs). Holtmann et al showed that G-protein beta 3 (GNβ3) C825T polymorphisms are related to the development of FD. The odds ratio for upper abdominal symptoms associated with the CC genotype was 2.2 compared with the TC and TT genotypes. Homozygous GNβ3 825C carrier status is associated with unexplained upper abdominal symptoms. G-proteins are essential for stimulus-response coupling of receptors that are linked to intracellular effector systems, and this polymorphism is known to affect many kinds of diseases. It has also been reported that meal-unrelated dyspepsia in a US community study was associated with homozygous 825T or C alleles of GNβ3. Although GNβ3C825T polymorphism was not associated with FD subjects overall in the Japanese population, the GNβ3 subunit 825 TT genotype was interestingly associated with EPS-like dyspepsia. Another Japanese group reported that the GNβ3 subunit 825 TT genotype was associated with FD without Helicobacter pylori infection. A report from The Netherlands showed that FD in the tertiary referral setting was associated with the 825T allele of the GNβ3 gene. A recent meta-analysis showed that the genetic variant C825T in GNβ3 was significantly associated with FD under an additive model, and the association was race-specific.

We also examined the association between serotonin transporter (SERT) gene (SLC6A4) polymorphism and FD in Japan. The 5-HTTLPR L allele affects suscepti-
bility to PDS. A report from Korea showed that 5-HTTLPR S/S genotype was significantly associated with Helicobacter pylori-positive EPS status. However, other reports from the USA and The Netherlands did not show a relationship between SERT polymorphism and FD. These discrepancies may be related to the difference in the allele frequencies of 5-HTTLPR among races. The gene polymorphisms of the tetrodotoxin-resistant sodium channel NaV1.8, encoded by SCN10A, and the CC genotype of TRPV1G315C polymorphism were the only polymorphisms preventing the development of FD.

Although these data indicate the involvement of genetic factors in the development of FD, the odds ratio is maximally two to three. Therefore, environmental factors may also affect their development. Children of mothers with IBS have more non-GI, as well as GI, symptoms. Childhood abuse is associated with the development of dyspepsia, and the development and exacerbation of IBS. Further evaluation of how these genetic factors and other circumstantial factors interact is warranted in FD.

**Natural Course of FD**

The prevalence of FD itself is stable over 1 to 2 years. However, considerable turnover occurs, with approximately half of those with FD on the first survey not having these symptoms on the second survey. Halder et al prospectively examined the natural history of FGIDs in a US population. In a cohort followed for 12 years, approximately 20% had the same symptoms among people with symptoms at baseline, 40% had no symptoms, and 40% had different symptoms at follow-up. In UD, the disappearance rate of the symptoms between the initial and final surveys was 67%. The feature that symptoms shift among FGIDs and disappear might also be characteristic of FGIDs.

In a Japanese survey, the FD symptoms regressed in one-third of patients after they were told that they did not have an organic disease on endoscopy. These data indicate that an explanation of the condition can easily affect the symptoms of FD, and that building a favorable doctor-patient relationship is effective as one of the treatment strategies for FD.

**Conclusions**

FD represents one of the most prevalent conditions in patients who come to physicians with abdominal symptoms. Although the prevalence of UD/FD can be easily modified by the definition and studied population are often examined on UD but not FD, the data here demonstrated that the Asian prevalence of UD/FD is 5.3% to 20.4%. It is clear that we often see FD patients in the outpatient clinic after detailed examinations. The information presented here was intended to introduce physicians to a detailed background of these patients and the strategies for treatment. More studies on the prevalence of FD in the general population are warranted, as is the unraveling of the pathophysiology of FD.

**References**

53 Talley NJ, Weaver AL, Zinsmeister AR, Melton LJ 3rd: Onset and disappearance of gastrointestinal
