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SHORT REPORT

Symptoms of mast cell activation syndrome in functional gastrointestinal disorders

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ABSTRACT

Objectives: Mast cell involvement is evident in functional gastrointestinal disorders (FGID). FGID and mast cell activation syndrome (MCAS) are associated with multi-organ symptoms. An overlap has not been assessed.

Methods: MCAS symptoms were determined by questionnaires in 2083 FGID patients.

Results: The median number of MCAS symptoms ([IQR] (range 0–16)) was 6 [4–8] in all FGID, and in functional dyspepsia (FD) patients, 7 [5–9] in overlapping irritable bowel syndrome and FD (IBS+FD), 5 [3–8] in IBS and 5 [3–6] in non-IBS/non-FD ($p < .001$ *vs.* FD and IBS + FD) patients. MCAS symptoms in $\geq$2 organ-systems existed in 1773 (85%) of all patients.

Conclusions: MCAS symptoms are common in FGID warranting further mechanistic investigation.

Abbreviations: CI: confidence intervals; FD: functional dyspepsia; FGID: functional gastrointestinal disorders; GI: gastrointestinal; IBS: irritable bowel syndrome; IQR: interquartile range; MCAS: mast cell activation syndromesodds ratio OR

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KEYWORDS
Histamine; irritable bowel syndrome; functional dyspepsia; mast cell

Introduction

Patients with functional gastrointestinal disorders (FGID), including irritable bowel syndrome (IBS) or functional dyspepsia (FD), have a wide range of gastrointestinal (GI) and extra-GI symptoms. Extra-GI symptoms are not included in the diagnostic Rome criteria for FGID and are generally attributed to separate functional or somatisation syndromes [1]. Recent mechanistic studies have shown increased numbers and activation of mast cells and abnormal release of biogenic amines and pro-inflammatory mediators in FGID, which may contribute to the commonly reported multi-organ symptoms [2–6]. Mast cell activation syndrome (MCAS) shares substantial similar symptoms with FGID, but there is little data regarding an overlap of the syndromes. MCAS is defined by 'chronic, inappropriate, non-neoplastic mast cell activation resulting in multisystem inflammatory and allergic phenomena not fitting other defined allergic or inflammatory diseases', distinguishing the condition from mastocytosis with pathologic clonal markers [7]. Currently proposed diagnostic criteria include a symptomatic response to histamine receptor blockers or mast cell-targeting agents and potential biochemical markers, besides typical symptoms [7,8]. MCAS shows considerable overlap with the ambiguous entity of histamine intolerance [9,10]. This large exploratory study investigated the prevalence of symptoms associated with MCAS in FGID.

Methods

Successive male and female patients older than 18 years referred for evaluation of FGID were enrolled. FGID was classified according to Rome III definitions and grouped as FD, IBS, overlapping IBS + FD and non-IBS/non-FD [1]. Patients completed Rome III and standardised multi-organ symptom questionnaires documenting their symptoms in the preceding 6 months [11]. In the absence of a consensus on defining symptoms for MCAS, the 6 GI symptoms (abdominal pain, bloating, diarrhoea, constipation, nausea and epigastric/retrosternal burning) and 10 extra-GI symptoms (excessive tiredness, problems concentrating, headache, anxiety/depression states, skin rash, urticaria/pruritus, chronic sinusitis/rhinitis, irregular heartbeat, joint pain and myalgias) most commonly associated with MCAS were extracted from recent reviews [7,8]. The sum of GI and extra-GI symptoms comprised the MCAS score (range 0–16). In accordance with the most recent consensus criteria, typical symptoms involving at least two organ systems (GI, central nervous system, airways, cardiovascular, musculoskeletal or skin) were required for a diagnosis of MCAS. [8]. The probability of MCAS based on symptoms was compared across Rome III subgroups.

The median MCAS score was compared across Rome III subgroups using the Kruskal–Wallis test followed by between-groups comparisons by Dunn's pairwise comparison test. Bonferroni correction was applied for

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multiple comparisons. The association between MCAS (symptoms from two or more organ systems) and Rome III subgroups were analysed using multivariate logistic regression with adjustment for age and gender. Regression results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). A significance threshold of $p < .05$ was used.

Ethics Committee approval for the use of coded patient data was gained and the study was registered in ClinTrials.gov (NCT02085889).

Results

This study included 2083 FGID patients of mean age 39.7 ± 15.3 years (range 18–88), 1465 (70%) of whom were females. FD was diagnosed in 1214 patients (58%), IBS in 47 (2%), overlapping IBS + FD in 625 (30%) and 197 (9%) had neither FD nor IBS (non-IBS/non-FD).

The median [IQR] MCAS symptom score across all FGID patients was (6 [4–8]). It was higher in FD (6 [4–8]) and IBS + FD (7 [5–9]) than in non-IBS/non-FD (5 [3–6]) (both $p < .001$), but was similar in IBS (5 [3–8]) and non-IBS/non-FD ($p = .25$) and in IBS and FD (($p = .15$) (Figure 1). The same pattern of group differences was seen for the subgroups of GI and extra-GI symptoms (all $p < .001$) (Figure 1).

Using the cut-off of symptoms from two or more organ-systems, MCAS existed in 1773 (85%) of all 2083 FGID patients, in 1033 (85%) with FD, 36 (76%) with IBS, 557 (89%) with overlapping IBS + FD and 147 (75%) without IBS/FD. On multivariate analysis and compared to non-IBS/non-FD patients, FD (OR 1.8, 95% CI (1.2–2.6); $p = .002$), and IBS + FD (OR 2.6 (1.7–3.9); $p < .001$) were significantly and independently associated with an increased probability of MCAS (Figure 2). No significant association was seen for patients with IBS only (OR 1.1 (0.5–2.3); $p = .80$). The probability of

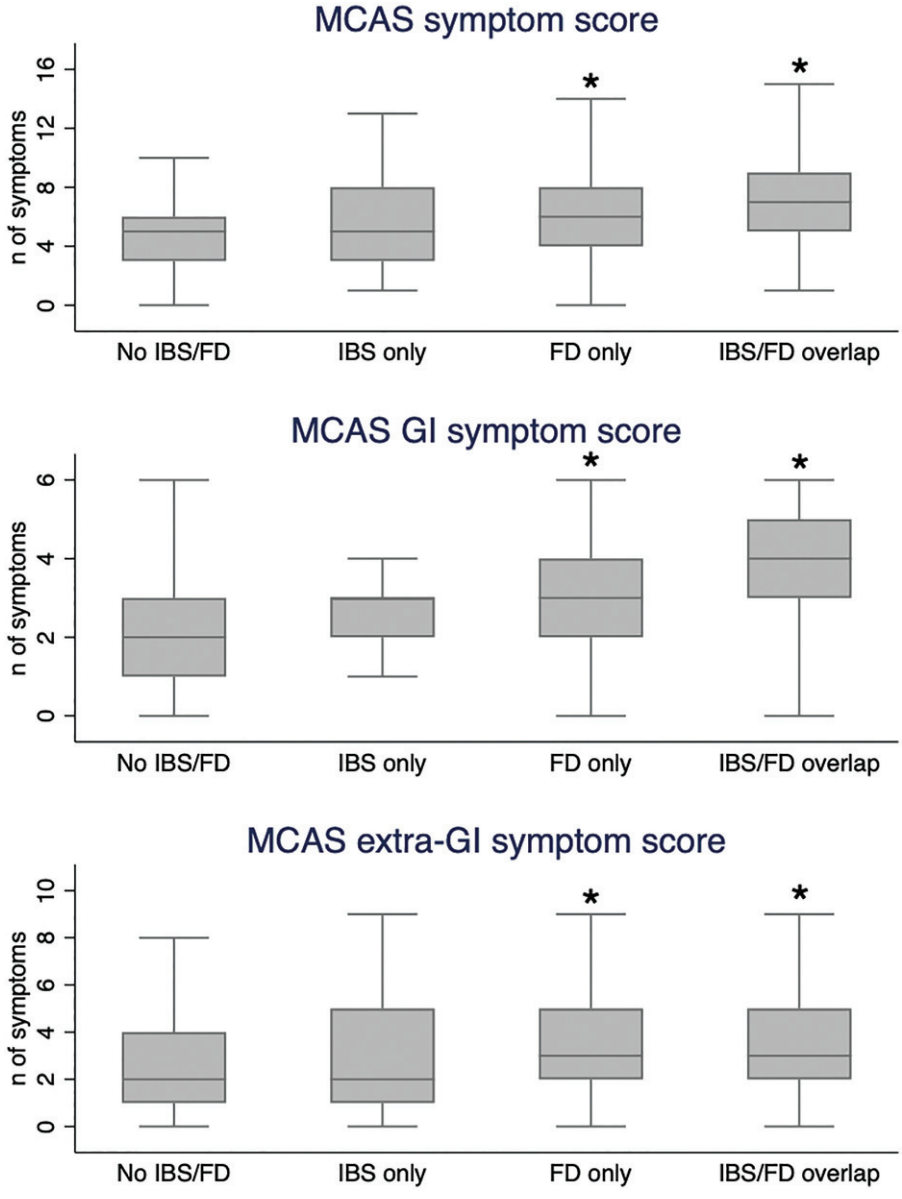

Figure 1. Box-whisker plots of medians, interquartile ranges and absolute ranges of the MCAS scores in 2083 patients with FGID (Total scores (top panel), GI symptom scores (middle panel) and extra-GI symptom scores (bottom panel) for FGID groups defined by the Rome III criteria. *$p < .001$; significance of the differences between patients without IBS + FD ant the other Rome III subgroups.

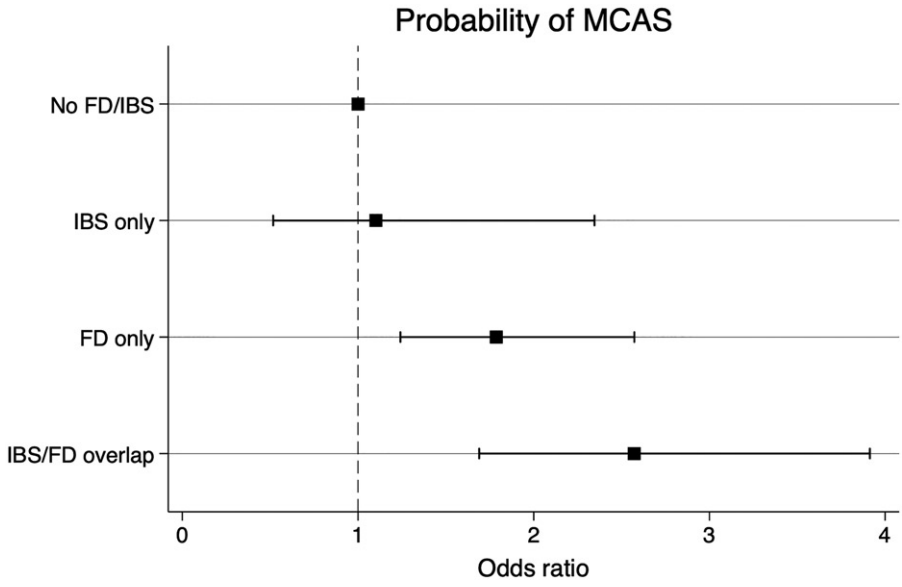

Figure 2. Forest plots of the probabilities (odds ratios [ORs] and 95% confidence intervals) of MCAS (symptoms associated with mast cell activation from two or more organ-systems) stratified by FGID subgroups. The reported ORs are age- and gender-adjusted.

MCAS was increased in females over males (OR 1.8 (1.4–2.3); $p < .001$), but was not associated with age (OR 1.0(1.0–1.0); $p = .13$).

Discussion

Symptoms associated with MCAS occur frequently in FGID. About 85% of 2083 patients had symptoms from two or more organ-systems, compatible with the diagnosis of MCAS, and a median of 6 symptoms typical of MCAS existed per FGID patient. The overlap between MCAS and FGID included both the classic GI symptoms of FGID and extra-GI symptoms. Patients with overlapping IBS + FD have a wider range of GI symptoms than isolated IBS or FD and consequently also show more overlap with MCAS GI symptoms. The greater probability of MCAS in females may be due to increased mast cell numbers and activation [12].

The overlap between MCAS and FGID suggests a promising avenue for further mechanistic investigation. Immune activation with downstream changes including hypersensitivity is observed in several of the overlapping functional syndrome, with increasing evidence for the involvement of mast cells and their mediators [2–6]. The number or activation of mast cells appears to be upregulated in IBS and FD and mast cell mediators are key modifiers of GI physiology [6]. Histamine is increased in supernatant from colonic biopsies and histamine receptors are upregulated in IBS patients [13,14]. Urinary levels of histamine reportedly correlate with IBS symptom scores [15]. Furthermore, mast cells are involved in symptoms related to extra-GI organs, including the brain, airways, musculoskeletal and skin tissues [3]. Consequently, mast cell dysfunction may contribute to GI and extra-GI symptoms in FGID. A few small treatment studies with antihistamines and mast cell stabilizers have been successfully performed in IBS patients, indicating potential for larger, confirmative studies [13,14].

Limitations to this explorative study include the extensively used but not externally validated questionnaires and an inevitable selection bias of the patients referred [11]. The association between GI and extra-GI symptoms of MCAS and FGID does not permit conclusions regarding causality. Studies with healthy controls are required to assess prevalence. The current, evolving definition of MCAS suggests the inclusion of biochemical parameters and the response to medication additionally to symptoms in the diagnosis of MCAS. These additional criteria need to be refined, but are important to prevent a widespread and uncritical classification of patients with FGID as MCAS due to the wide overlap of symptoms.

In conclusion, given the increasing importance of the mast cell and its mediators in functional syndromes, the overlap between MCAS and FGID deserves critical attention in the differential diagnosis of FGID.

Disclosure statement

The authors have nothing to disclose.

Author contributions

Study concept and design was formulated by CWS, AM. Acquisition of data was carried out by CWS, AM. Statistical analysis and interpretation of data was performed by SSO, CWS, AMD. Drafting and critical revision of the manuscript was done by CWS, SSO, AMD. Study supervision was carried out by CWS.

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