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Factors Influencing the Type, Timing and Severity of Symptomatic Responses to Dietary Gluten in Patients with Biopsy-proven Coeliac Disease

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ABSTRACT

Background & Aim: There is a paucity of data reflecting the symptomatic responses to dietary gluten (SRDG) in patients with Coeliac Disease (CD). We aimed to determine the type, timing and severity of SRDG with reference to a range of disease-related factors.
Methods: Postal survey of 224 biopsy-proven patients including gluten-free diet (GFD) adherence, symptom checklist, ROME II criteria and The Hospital Anxiety & Depression Scale. Case-note review was also conducted.
Results: 26% of respondents were male. Full GFD adherence: n=159 (70%). Irritable bowel syndrome (IBS): n=50 (22%). Anxiety: n=30 (13%); Depression: n=33 (14%); Anxiety & Depression: n=72 (32%). Pruritus, fatigue and bloating were a more common SRDG in the partial/none GFD adherent group (p=ns). Co-existing IBS was associated with a greater prevalence of nausea and fatigue in response to gluten (p=<0.05). Fully GFD adherent patients are more likely to have SRDG <1hr than partial/none adherent (OR 4.8; p=0.004), as are a third of patients with co-existing IBS (OR 1.5; p=0.027) and those patients at risk of both anxiety and depression (OR 1.9; p=0.04). Inadvertent exposure to dietary gluten in the fully GFD adherent group is more likely to result in a severe SRDG in comparison to symptoms arising prior to consistent GFD adherence (OR 2.3; p=0.01). IBS sufferers are also more likely to rate their SRDG as severe in nature (OR 1.4; p=0.038).
Conclusion: Patients with consistent GFD adherence experience a SRDG faster and more severe in comparison to prior gluten exposure possibly demonstrating an adept immunological response. Anxiety and depression also enhance the speed of symptom onset and co-existing visceral hypersensitivity is a risk factor for severe reactions to dietary gluten.

K**ey words:** coeliac disease – symptoms – gluten-free diet – irritable bowel syndrome – gluten challenge – anxiety – depression – gluten.

INTRODUCTION

The patients with Coeliac Disease (CD) have a life defined by gluten. They tread a difficult tightrope where on one side lie the distressing physical symptoms born from dietary gluten exposure ranging from abdominal pain to headache to paresthesia [1] and on the other they encounter social obstacles and psychological challenges inherent to following a gluten-free diet (GFD) [2-4]. Despite the fact that gluten occupies such a pervasive force in the lives of coeliac individuals it is startling to acknowledge the paucity of data delineating the symptomatic responses to dietary gluten (SRDG) and the negative impact this has on our clinical effectiveness as a result [5].

With a greater appreciation of the type, timing and severity of SRDG the well documented delays to accurate diagnosis in patients with CD may be reduced [6] and the broad array of non-gastroenterology specialists the CD patient may consult with prior to accurate diagnosis [7] may be better equipped to speedily identify the condition and direct the coeliac to appropriate support. Coeliac disease is associated with a range of additional factors including gastrointestinal (GI) motor disturbances, particularly irritable bowel syndrome (IBS) [8], and psychological problems that include anxiety and depression [9]. We are yet to firmly grasp how these factors mitigate symptoms and to what clinical extent. Furthermore, the coeliac patient will live many years with his condition and it is important to understand the symptomatic repertoire the patient draws from in response to gluten so the healthcare provider is able to answer: Is this CD, or something else?

We completed a comprehensive survey of over 200 biopsy-proven CD patients concerning the type, timing and severity of SRDG and how these responses may be influenced by factors ranging from treatment (GFD adherence), co-morbid GI motor disturbances (IBS) and reduced psychological wellbeing i.e. anxiety and/or depression. In charting the character of SRDG we hope to improve our understanding of this critical area and suggest areas for improved clinical effectiveness.

METHODS

Study design

This was a cross-sectional postal survey.

Ethics

Written consent was obtained from all participants. This study received ethical approval from The National Health Service North Sheffield Research Ethics Committee in January 2009.

Participants

All patients with a diagnosis of biopsy-proven CD (classified as Marsh III or greater duodenal atrophy on histological examination) followed-up at Sheffield Teaching Hospitals NHS Foundation Trust within the last five years were invited to participate (n=450). All participants were over 18 years of age.

Data collection

GFD adherence was categorised as 'Fully Adherent' (everyday of the preceding 28 days) or 'Partial/None Adherent' for any level of adherence below fully adherent. We accept that the GFD is a significant undertaking due to the abundance of gluten-containing products in the Western diet that accidental dietary exposure may occur. It is these non-purposeful, accidental dietary exposures that permit patients who describe themselves as 'Fully adherent' to still comment on their SRDG. Symptoms on exposure to gluten within the last 28 days included: abdominal pain, diarrhoea, bloating, headache, itchy skin, insomnia, mouth ulcers, flatulence, fatigue, nausea, vomiting. Time to onset of first symptom following dietary exposure was categorised from within 1hr at regular increments to a maximum of 24hrs.

All patients were asked to rate the severity of their SRDG as 'mild', 'moderate' or 'severe'. In the fully GFD adherent group we also asked patients to rate the subjective severity of their SRDG whilst following a GFD in comparison to the severity of symptoms experienced prior to consistently following the diet. Patients were asked to rate their most recent SRDG as 'the same' severity, 'milder' or 'more severe' than symptoms experienced in the context of consistent and purposeful gluten exposure.

The ROME II Criteria [10] were used to determine the prevalence of IBS in the group with patients that satisfied two or more of the criteria deemed IBS positive. The Hospital Anxiety & Depression Scale (HADS) [11] is composed of 14 items; 7 relating to anxiety (HADS-A) and 7 relating to depression (HADS-D). Patients rated their feelings over the prior 7 days with each item generating a score for each subscale. A score of 7 or more for HADS-A demonstrates a risk of anxiety, for HADS-D a risk of depression.

All completed questionnaires were internally validated against medical records. Furthermore, additional information was gained from case-note review including disease duration and patient Method of Presentation at diagnosis (MoP): 'Typical' categorised as predominantly GI symptoms including abdominal pain, diarrhoea and bloating; 'Atypical' as non-GI symptoms ranging from headaches to fatigue and 'Screen-detected' in which patients were asymptomatic and diagnosed following investigation for deranged biochemical tests (anemia, for example).

Statistical analysis

When comparing two groups we used the Mann-Whitney U-Test and when comparing three groups or more we used the Kruskall-Wallis test. All tests were completed using SPSS v15.0 (IBM Surrey GU21 6EB, UK) and statistical significance was set at a P value of 0.05 or less.

RESULTS

Descriptive statistics

Completed questionnaires were received from 224 patients (response rate 49%) of whom 26% were male. Mean disease duration was 8 yrs (range 0.5-51 yrs); 159 patients (70%) reported full GFD adherence and 50 patients (22%) satisfied the ROME II criteria for IBS. We found a high proportion of patients (n=135, 60%) at risk of psychiatric co-morbidity: 30 patients (13%) at risk of anxiety (HADS-A >7), 33 (14%) at risk of depression (HADS-D >7) and 72 (32%) at risk of both anxiety and depression. Method of presentation was categorised as typical in 147 (65%), atypical in 41 (18%) and screen-detected in 36 (16%) patients.

Type of SRDG

Partial/none adherent GFD patients report more fatigue (55%), itchy skin (24%) and bloating (55%) than their fully adherent counterparts (39%, 14% and 40%, respectively). Patients with co-existing IBS report more IBS-type symptoms (abdominal pain, diarrhoea, bloating and flatulence) in response to gluten than the non-IBS group. However, the IBS group report greater fatigue (50% versus 40%) and nausea (50% versus 19%). Those at risk of anxiety and depression report more abdominal pain, headache, nausea, mouth ulcers and fatigue than all other groups categorised based on their risk of psychiatric co-morbidity. Based on MOP we observed that patients with a typical (GI) presentation were more likely to experience GI-related SRDG (abdominal pain, bloating and so forth), with the atypical (non-GI) group reporting headaches to a greater extent. Disease duration was not associated with a particular type of symptomatic response. See Table I for a summary of factors associated with the type of symptom response to dietary gluten.

Timing of SRDG

Fully adherent patients are more likely to report a SRDG within 60 mins of exposure in comparison to partial/none

TableI. Factors associated with type of symptomatic response to dietary gluten

		Symptom Type n=(%)				
		AP	Di	He	IS	In
GFD Adherence	Full (n=159)	82 (51)	82 (51)	33 (21)	23 (15)	6 (4)
	Partial/None (n=65)	33 (50)	33 (50)	16 (20)	16 (20)	5 (7)
	p =	ns	ns	ns	0.06	ns
IBS	Positive (n=50)	40 (80)	33 (66)	20 (40)	11 (17)	6 (12)
	Negative (n=174)	76 (44)	83 (48)	30 (17)	28 (16)	5 (2)
	p =	<0.001	0.027	0.0008	ns	0.03
Psychiatric Risk	None (n=97)	41 (42)	47 (48)	14 (14)	19 (19)	2 (2)
	HADS-A (n= 30)	19 (63)	15 (50)	8 (26)	5 (16)	2 (6)
	HADS-D (n=33)	14 (42)	15 (45)	7 (21)	6 (18)	0(0)
	HADS-A&D (n=72)	48 (66)	45 (62)	27 (37)	13 (18)	7 (9)
	p =	0.004	ns	<0.001	ns	0.04
MoP	Typical (n=147)	91 (62)	88 (59)	28 (19)	25 (17)	19 (13)
	Atypical (n=41)	25 (60)	26 (63)	21 (51)	8 (19)	8 (19)
	Screen-detected (n=36)	14 (38)	14 (38)	9 (25)	10 (27)	4 (11)
	p =	0.01	0.03	0.02	ns	ns
Disease duration	< 6yrs (n=134)	69 (51)	61 (45)	28 (21)	28 (21)	6 (4)
	> 6yrs (n=91)	49 (53)	59 (64)	24 (26)	12 (13)	5 (5)
	p =	ns	0.004	ns	ns	ns

Table I (continuation)

		Symptom Type n= (%)					
		MU	Bl	Fl	Fa	Na	Vo
GFD Adherence	Full (n=159)	17 (10)	64 (40)	41 (25)	63 (39)	39 (24)	28 (17)
	Partial/None (n=65)	12 (18)	36 (55)	23 (35)	37 (57)	13 (20)	6 (9)
	p =	ns	0.03	ns	0.018	ns	ns
IBS	Positive (n=50)	10 (20)	31 (62)	24 (49)	31 (62)	30 (60)	8 (16)
	Negative (n=174)	19 (10)	70 (40)	41 (23)	70 (40)	33 (19)	27 (15)
	p =	ns	0.008	0.0009	0.008	0.002	ns
Psychiatric Risk	None (n=97)	9 (9)	41 (42)	26 (27)	34 (35)	19 (19)	15 (15)
	HADS-A (n= 30)	2 (6)	14 (49)	9 (30)	12 (40)	5 (16)	3 (10)
	HADS-D (n=33)	4 (12)	12 (36)	9 (27)	15 (45)	5 (15)	3 (9)
	HADS-A&D (n=72)	14 (19)	37 (51)	24 (33)	43 (59)	27 (37)	15 (21)
	p =	0.05	ns	ns	0.001	0.016	ns
MoP	Typical (n=147)	19 (13)	80 (54)	50 (34)	72 (49)	42 (28)	26 (17)
	Atypical (n=41)	8 (19)	20 (49)	16 (39)	28 (68)	11 (23)	11 (23)
	Screen-detected (n=36)	4 (11)	13 (36)	9 (25)	13 (36)	4 (11)	4 (11)
	p =	ns	0.02	ns	0.01	0.04	ns
Disease duration	< 6yrs (n=134)	18 (13)	60 (44)	37 (27)	63 (47)	35 (26)	19 (14)
	> 6yrs (n=91)	12 (13)	43 (47)	29 (32)	40 (44)	20 (22)	17 (18)
	p =	ns	ns	ns	ns	ns	ns

AP: abdominal pain; Di: diarrhoea; He: headaches; IS: Itchy Skin; In: insomnia; MU: mouth ulcers; Bl: bloating; Fl: flatulence; Na Nausea; Vo vomiting ; GFD: gluten-free diet; IBS: irritable bowel syndrome; MoP> Method of disease presentation; HADS-A: anxiety; HADS-D: depression; ns: p = >0.05

adherent patients (OR 4.8, 95% CI 2.1-11; p=0.004). This relationship is illustrated in Fig. 1. Just under a third (28%) of patients with co-existing IBS report a SRDG within 60 mins in comparison to 14% of those without (OR 1.5, 95% CI 0.8-3.1; p=0.027). Being at risk of both anxiety and depression is associated with an onset to symptoms within 2 hrs of exposure in comparison to all other HADS groups (OR 1.9, 95% CI 1.0-3.6; p=0.04). MoP and disease duration were not associated with differences in the timing of SRDG.

Table II. Factors associated with perceived severity of symptomatic response to dietary gluten

		Perceived Severity n= (%)		
		Mild	Moderate	Severe
GFD Adherence	Full (n=159)	31 (19)	28 (17)	58 (36)
	Partial/None (n=65)	23 (35)	15 (23)	13 (20)
	p =	0.01	ns	0.01
IBS :	Positive (n=50)	11 (22)	9 (18)	22 (44)
	Negative (n=174)	43 (24)	34 (19)	39 (22)
	p =	ns	ns	0.038
Psychiatric Risk	None (n=97)	19 (19)	18 (18)	30 (31)
	HADS-A (n= 30)	10 (33)	5 (16)	8 (26)
	HADS-D (n=33)	6 (18)	8 (24)	7 (21)
	HADS-A&D (n=72)	20 (27)	13 (18)	28 (38)
	p =	ns	ns	ns
MoP	Typical (n=147)	42 (28)	25 (17)	49 (33)
	Atypical (n=41)	11 (26)	13 (31)	18 (45)
Screen-detected (n=36)	5 (13)	9 (25)	14 (38)	
	p =	ns	ns	ns
Disease duration:	< 6yrs (n=134)	33 (24)	25 (18)	39 (29)
	> 6yrs (n=91)	21 (23)	30 (33)	34 (37)
	p =	ns	0.014	ns

GFD: gluten-free diet; IBS: irritable bowel syndrome; MoP: Method of disease presentation; HADS-A: anxiety; HADS-D: depression; ns: p = >0.05

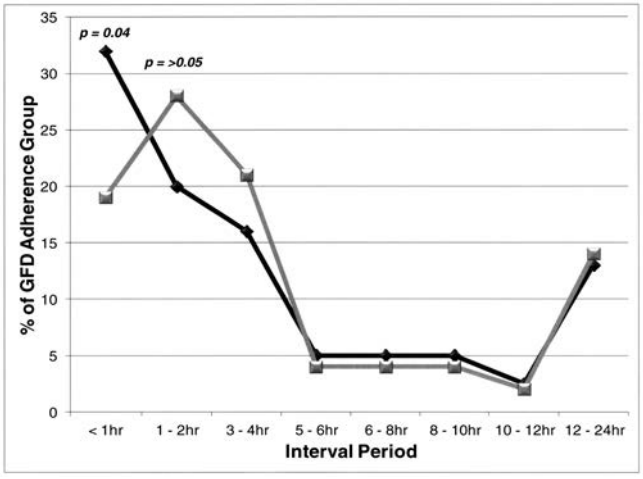

Fig. 1. Association between the onset of symptomatic response to dietary gluten and level of gluten-free dietary adherence.

Severity of SRDG

Thirty-six per cent of patients who regard themselves as fully adherent to a GFD but encounter a non-purposeful/accidental exposure to dietary gluten report a greater severity of symptoms than symptoms they experienced prior to following a GFD on a consistent basis (OR 2.3, 95% CI 1.2-4.6; p=0.01). Co-existing IBS was associated with a greater likelihood of reporting a SRDG as severe in nature in comparison to those without (OR 1.4, 95% CI 0.8-2.1; p=0.038). Indeed, just under half (44%) of CD patients with IBS rate their symptoms as severe. We found that risk of psychiatric co-morbidity, MOP and disease duration were not associated with differences in the reported severity of SRDG. These factors are summarised in Table II.

DISCUSSION

Our results are based on a comprehensive assessment of SRDG that has not been previously undertaken, consequently our results should be regarded as preliminary and subject to confirmation by future investigators. Furthermore, whilst the majority of respondents (70%) report maintaining a full GFD, 51% of these experienced an inadvertent exposure to dietary gluten in the previous 28 days underlining the difficulty coeliac patients encounter maintaining a GFD [12].

We report that in the context of consistent gluten avoidance, episodic exposure to gluten is associated with a speedier onset of symptoms that are more severe nature in comparison to those patients with chronic dietary gluten exposure. These findings may be mediated by local immunological activity within the intestine and further mediated by psychological processing of symptom experience within the brain.

T-cell responses to the immuno-dominant A-gliadin epitope have been reported to a significantly greater degree in coeliac individuals reintroducing dietary gluten following a two week GFD in comparison to chronic (non-GFD) gluten exposure [8, 9]; findings van Heel et al [13] assert why individuals with 'silent' CD experienced SRDG following a period of gluten abstinence as a consequence of The Atkins Diet. For the 'silent' coeliac this immune surge may bring symptoms to the surface for the first time, however, we report that individuals with established, hitherto symptomatic CD who predominantly abstain from gluten report symptoms faster than their non-adherent counterparts and crucially more swiftly in comparison to their prior experience of symptomatic gluten exposure. This may demonstrate that the immune system becomes more adept

in its response to gluten following a period of non-exposure that facilitates recovery and/or recuperation.

That individuals perceive a greater severity of symptomatic response is a phenomenon, which may represent a series of complex psychological responses that coalesce with feelings of failure and frustration. There are many social obstacles to overcome in order to achieve GFD compliance on a day-to-day basis (ref GFD problems) with considerable physician counselling and additional dietetic support required, especially in women who have been shown to express a higher degree of disease burden and a need for greater psychological support when undertaking the GFD [14].

The SRDG is not only physically unpleasant but psychically unwelcome and may be perceived as incredibly unjust if the individual has spent significant intellectual and emotional resources to maintain the GFD but poor food labeling and availability of GFD products has rendered them exposed to gluten despite such efforts.

That partially/none adherent patients report SRDG to a lesser severity than fully adherent patients may be representative of the reduced emotional 'loading' of the symptom response described above and also reflect a degree of immunological desensitization to on-going gluten-mediated symptoms to those chronically exposed to dietary gluten [15]. Co-existing IBS and the association with increased perceived severity of symptom may also reflect a state of heightened visceral sensitivity and serve to amplify the SRDG [16]. Those anxious and depressed patients are also more likely to report symptoms quicker may also reflect a state of heightened somatic vigilance that is characteristic of some depressive and anxious disorders [17]. Clearly a range of immunological, psychological and physical mechanisms are in play which are likely to be multi-dependent.

For both the physician and patient knowledge of the type, timing and severity of SRDG in the context of GFD adherence level is crucial.

Life with CD is a life dominated by the physical, social and psychological responses to gluten exposure and therefore all clinicians involved in the care of coeliac individuals must possess as detailed knowledge of the nuances of such responses as possible. These findings reinforce the need for extensive dietetic and social support in maintaining the GFD and identifying gluten-free products. Forewarning patients that symptomatic relief will be achieved by consistent GFD adherence but that episodic exposure may result in symptoms of novel severity and speed can also be incorporated into their long-term coping strategies. Armed with knowledge of how the character and severity of symptoms in the 'treated', GFD adherent coeliac occur may also avoid unnecessary investigation of a 'new-severe' abdominal pain in the coeliac who experienced grumbling abdominal pain prior to diagnosis and starting the GFD.

The individual patient will also have greater knowledge of his condition which may subsequently promote a sense of empowerment and coping in the longer-term. Forewarned that inadvertent dietary exposure is relatively inevitable and may lead to a more severe SRDG may reduce the emotional loading of such symptoms and, consequently, the potential distress they present to the coeliac individual on future exposure. Again, with reference to adequate counselling and dietetic support the coeliac patient with consistent inadvertent exposure or a social/occupational lifestyle that increases the risk of dietary gluten exposure may take the decision that 'grumbling' background symptoms associated with chronic gluten ingestion is favourable to the social and psychological efforts of maintaining a GFD and the physically and emotionally demanding experience of intermittent gluten exposure that may be unavoidable despite his best efforts.

A limitation to our methodology, a postal survey, was that we are unable to corroborate patient experiences of SRDG with objective evidence of changes to either small-bowel architecture or antibody profile. Whilst we report these findings based on a comprehensive assessment of a relatively large patient group, we recommend further studies to confirm our preliminary findings.

CONCLUSION

We have provided evidence that SRDG are far from static in the coeliac individual and that immunological, physical and psychological mechanisms may all potentially mediate the type, timing and severity of gluten-related symptoms. This evidence reinforces the need for adequate dietetic support and provides information that will be of great interest to both clinicians and patients alike.

Competing interests: None.

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