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LETTER TO THE EDITOR

Gastrointestinal symptoms at diagnosis and during long-term gluten-free diet treatment in dermatitis herpetiformis patients

Dear Editor,

Dermatitis herpetiformis (DH) is a cutaneous manifestation of coeliac disease, a common gastrointestinal disease induced by dietary gluten.[1,2] At diagnosis, DH patients evince small bowel mucosal villous atrophy or at the least coeliac-type inflammation.[1,3] Despite this, obvious gastrointestinal symptoms are considered uncommon in DH, but evidence has lately challenged this view.[3,4] Furthermore, in up to 30% of coeliac disease patients gastrointestinal complaints have been shown to endure even during gluten-free diet (GFD),[5] but it remains unexplored whether such persistent symptoms occur in treated DH. This study aimed to elucidate DH patients' gastrointestinal symptoms at diagnosis and after long-term dietary adherence, and to investigate factors related to these symptoms.

The study cohort comprised 222 skin-biopsy proven DH patients with no prior coeliac disease diagnosis, that had answered to questionnaires previously.[4] Medical records were reviewed for clinical, serological and small bowel biopsy findings at DH diagnosis. Follow-up data on GFD treatment

TABLE 1 Demographic, clinical, serological and histological data of dermatitis herpetiformis (DH) patients with and without gastrointestinal (GI) symptoms at the time of DH diagnosis.

	GI symptoms ($n=91$)		No GI symptoms ($n=131$)		
	n	%	*n*	%	*p*-Value
Female	54	59	47	36	<0.001
Age at diagnosis, years, median (IQR)	38 (28–54)		37 (26–48)		0.282
Year of diagnosis					0.577
1970–1984	26	29	46	35	
1985–1999	34	37	46	35	
2000–2014	31	34	39	30	
Small bowel villous atrophy at diagnosis	64	85	69	72	0.036
Serum coeliac disease autoantibody positivity at diagnosis[a]	50	74	65	70	0.614
Extraintestinal symptoms other than DH[b] at diagnosis	20	22	9	7	0.001
Duration of skin symptoms before diagnosis, months, median (IQR)	10 (5–24)		12 (6–36)		0.201
Severity of skin symptoms at diagnosis					0.567
Mild	14	17	16	15	
Moderate	42	52	52	47	
Severe	25	31	42	38	
Use of dapsone after diagnosis	61	70	104	84	0.017
Skin symptoms at follow-up					0.724
Less than once a year	66	73	100	77	
1–4 times per year	14	15	18	14	
Once a month or more often	11	12	12	9	
Persistent gastrointestinal symptoms at follow-up	17	19	14	11	0.096

Abbreviation: IQR, Interquartile range.

[a]Serum IgA-class reticulin, endomysium, or transglutaminase 2 antibodies.

[b]For example anaemia, oral symptoms, articular symptoms, neurological symptoms and fatigue.

were gathered with disease-related questionnaire,[4] and by using validated Gastrointestinal Symptom Rating Scale (GSRS) and Psychological General Well-Being (PGWB) questionnaires.[6,7] Given that up to 30% of long-term treated coeliac disease patients report persistent gastrointestinal symptoms,[5] the 75th percentile value of GSRS total scores for our previously collected long-term treated coeliac disease cohort ($n = 129$)[8] was used for defining the GSRS cut-off value (2.47) for persistent symptoms.

As previously documented,[4] 41% out of the 222 DH patients had been experiencing gastrointestinal symptoms at DH diagnosis. Specifically, bloating or flatulence was reported by 39%, diarrhoea or loose stool by 32%, stomach pain by 22%, constipation by 7%, weight loss by 6%, heartburn by 4% and 22% reported unspecified gastrointestinal symptoms. Gastrointestinal symptoms were associated with female gender, presence of small bowel mucosal villous atrophy and other extraintestinal symptoms than DH at diagnosis, but not with skin symptom severity or persistence of skin or gastrointestinal symptoms (Table 1).

Out of the 216 DH patients with available data and following GFD, persistent gastrointestinal symptoms were detected in 14% of the patients after a median 25 years on GFD. These patients had more long-term illnesses, particularly gastrointestinal diseases, were more often current smokers and had a lower quality of life at follow-up than those without persistent symptoms (Table 2).

This study established that gastrointestinal symptoms, particularly abdominal bloating/flatulence and diarrhoea, are not uncommon in DH at diagnosis, and associate with the presence of small bowel mucosal villous atrophy. Interestingly, the presence of gastrointestinal symptoms at diagnosis was shown not to associate with duration or severity of skin symptoms. This inconsistency in clinical symptoms could be due to difference in immunological mechanisms, as cutaneous symptoms in DH arise from reaction directed towards

TABLE 2 Demographic, clinical and histological data of dermatitis herpetiformis (DH) patients with and without persistent gastrointestinal (GI) symptoms at follow-up.

	Persistent GI symptoms ($n = 31$)		No persistent GI symptoms ($n = 185$)		
	n	%	*n*	%	*p*-Value
Female	19	61	81	44	0.070
Age at diagnosis, years, median (IQR)	37 (30–49)		37 (27–52)		0.824
Small bowel villous atrophy at diagnosis	20	80	107	76	0.696
Age at follow-up, years, median (IQR)	67 (58–72)		65 (54–75)		0.617
Use of dapsone at follow-up	2	7	14	8	1.000
Skin symptoms at follow-up					0.984
Less than once a year	23	74	139	76	
1–4 times per year	5	16	26	14	
At least once a month	3	10	19	10	
Duration of GFD, years, median (IQR)	28 (16–35)		24 (14–35)		0.596
Adherence to GFD at follow-up					0.089
Strict diet[a]	22	73	135	73	
Dietary lapses less than once a month	3	10	38	21	
Dietary lapses more than once a month	5	17	12	7	
Long-term illnesses at follow-up					
Diabetes Type 1	0	0	5	3	1.000
Diabetes Type 2	7	23	18	10	0.031
Thyroid disease	7	23	24	13	0.158
Rheumatic disease	3	10	3	2	0.012
Hypertension	14	45	48	26	0.029
Other gastrointestinal disease[b]	7	23	12	7	0.003
History of malignancy	5	16	14	8	0.122
Smoking at follow-up	7	24	14	8	0.017
BMI at follow-up, kg/m^2, median (IQR)	25.7 (22.8–29.4)		25.4 (22.90–28.7)		0.783
PGWB total score at follow-up, median (IQR)	99 (90–111)		111 (102–119)		<0.001

Abbreviations: BMI, body mass index; GFD, gluten-free diet; IQR, interquartile range; PGWB, Psychological General Well-Being.

[a]No dietary lapses.

[b]Other gastrointestinal diseases than coeliac disease such as atrophic gastritis, peptic ulcer, oesophagitis, reflux disease, inflammatory bowel disease, collagen colitis, diverticulosis or irritable bowel syndrome.

epidermal transglutaminase (TG3),[9] while tissue transglutaminase (TG2) acts as the target antigen in small bowel mucosa.[2]

Surprisingly, presence of gastrointestinal symptoms at diagnosis did not associate with persistent gastrointestinal symptoms while of GFD, and nor did GFD strictness at follow-up, indicating that at least in a subset of patients, persistent symptoms are not related to DH. Instead, gastrointestinal symptoms on GFD were found to associate with comorbidities, life-style choices and poorer quality of life at follow-up.

In conclusion, this study confirmed that the gastrointestinal symptoms experienced by untreated patients with DH are similar in type to those in coeliac disease, and that the presence of gastrointestinal symptoms at diagnosis is not associated with the severity of skin symptoms or with the clinical resolution of DH on GFD. One in seven DH patients had persistent gastrointestinal symptoms despite long-term GFD. These symptoms are at least partly unrelated to DH but should not be overlooked as they impact the patients' quality of life.

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CONFLICT OF INTEREST STATEMENT

We have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data supporting the study findings are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The patients received a full written explanation of the study aims and provided written informed consent. This study was approved by the Regional Ethics Committee of Tampere University Hospital (R17043) and followed the ethical principles of the Helsinki Declaration.

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