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ORIGINAL ARTICLE

Family screening and the psychosocial implications of coeliac disease

Zachary Gauci, Abigail Attard, John Schembri, Pierre Ellul

Background

Screening of first-degree relatives of patients with coeliac disease is recommended, though evidence on the frequency of repeat screening is lacking. Diagnosis of a chronic condition can have psychosocial implications. The aims of this study were to determine the proportion of first-degree relatives of patients who were screened and diagnosed with coeliac disease, as well as to determine the impact of the condition on their quality of life.

Methods

Patients diagnosed histologically at Mater Dei Hospital in Malta, between May 2009 and December 2018, were asked regarding family screening and a questionnaire was used to assess the effects of coeliac disease on their quality of life (n=96, 79% female, mean age: 46, 29.2% asymptomatic).

Results

11.4% of tested first-degree relatives were diagnosed with coeliac disease, despite only 31.7% (165/520) of first-degree relatives having undergone routine screening at least once and only 3.1% (16/520) having undergone multiple screening tests.

77% of index cases felt that other people do not understand their dietary needs. 38.5% avoid social activities because of their dietary requirements. 76% experience difficulty in finding something suitable to eat when not at home. Importantly, 83.3% claimed significantly increased costs.

Conclusion

The prevalence of CD in first-degree relatives of index CD patients is higher than that of the general population. However, a greater emphasis needs to be employed in ensuring serological screening of the at-risk groups.

Zachary Gauci* MD MRCP
Department of Medicine
Mater Dei Hospital
Msida, Malta
zachary.gauci@gov.mt

Abigail Attard MD MRCP
Department of Medicine
Mater Dei Hospital
Msida, Malta

John Schembri MD FRCP MSc
Department of Gastroenterology
Mater Dei Hospital
Msida, Malta

Pierre Ellul MD PhD FRCP MSc
Department of Gastroenterology
Mater Dei Hospital
Msida, Malta

**Corresponding Author*

Introduction

Coeliac disease (CD) is a chronic autoimmune condition precipitated by the intake of gluten, a protein present in wheat, barley and rye. CD occurs in approximately 1% of the Western population. The availability of serological investigations testing for CD, as well as awareness of potential complications of the condition, contribute to this increasing prevalence as a result of improved diagnosis.[1] Despite this, due to the paucity of symptoms in some patients, which if present may be non-specific, CD is likely to be under-diagnosed and the true prevalence of the condition is probably higher.

The prevalence of CD in first-degree relatives is around 10%, with significantly greater prevalence values in monozygotic twins, families with multiple members affected, or siblings who have the same HLA susceptibility alleles.[2]

The British Society of Gastroenterology (BSG) and the National Institute for Health and Care Excellence (NICE) guidelines recommend active case finding in certain clinical situations, including in first-degree relatives of patients with CD.[2-3]

Lifelong adherence to a gluten-free diet (GFD) can affect the patient's quality of life (QOL) including psychologically, socially and financially.[4]

The aims of this study were:

- To identify the proportion of first-degree relatives of patients previously diagnosed with CD who were screened and found to be affected by CD
- To determine the patients' perception of the effects of CD on their life

Materials and Methods

Patients diagnosed with CD at Mater Dei Hospital in Malta, between May 2009 and December 2018, were recruited. The patients were identified through the histopathology department. The inclusion criteria were age above 16 years and a histological confirmation of CD. Patients who did not have biopsy-proven CD were excluded from the study.

Patients were contacted during the year of 2019 and were consented for participation in the study. Patients were interviewed. They were asked about the clinical symptoms or pathway that led to investigations for CD. In those who were asymptomatic, the reason for CD screening was ascertained. The patients' clinical case notes were reviewed.

The next part of the questionnaire focused on family screening of first-degree relatives (parents, siblings and offspring). The number of first-degree relatives was ascertained, as well as whether any of them were known to suffer from CD and whether they underwent opportunistic screening via serology and subsequent endoscopy. For those in whom family screening did take place, the year of initial screening and whether a positive result was obtained was recorded for each first- degree relative. For those family members who were screened and initially tested negative, it was enquired whether screening was ever repeated at a later date and if so, the year during which subsequent screening was carried out was noted. First-degree relatives who underwent opportunistic screening in view of their positive family history were included. It was also enquired if any first-degree relatives had undergone coeliac serology testing in view of gastrointestinal symptoms and if any of them were diagnosed with CD.

The second part of the unvalidated Quality of Life (QOL) questionnaire focused on assessing the patients' perception of some of the psychosocial effects of CD on their life.

The following four questions were asked:

1. Do you feel that people don't understand your dietary needs or think that you're exaggerating?
2. Have you ever avoided social activities or felt less able to integrate with others because of your dietary requirements?
3. Do you find difficulty in finding something suitable to eat when you are not at home?
4. Do you feel that you have significantly increased expenses due to coeliac disease[4]?

The patients` response was graded on a 5-point Likert scale (never, rarely, sometimes, often, always).

RESULTS

Index Cases

One hundred and eight patients (108) met the inclusion criteria. Twelve of these patients were excluded because they have since become deceased (*n*=2), or because they could not be contacted (*n*=10). The majority of the patients diagnosed with CD were female (79%).

The current mean age of the patient population was 46 years (range: 18-80 years). The time that had elapsed from diagnosis varied between 6 months and 10 years (Figure 1).

The majority of patients (70.8%) that were diagnosed were symptomatic. The most common symptoms that patients complained about were abdominal pain (29.2%), diarrhoea (21.9%) and bloating (20.8%). Figure 2 demonstrates the various symptoms that the patients experienced.

Figure 1: Time elapsed from initial coeliac disease diagnosis of index case

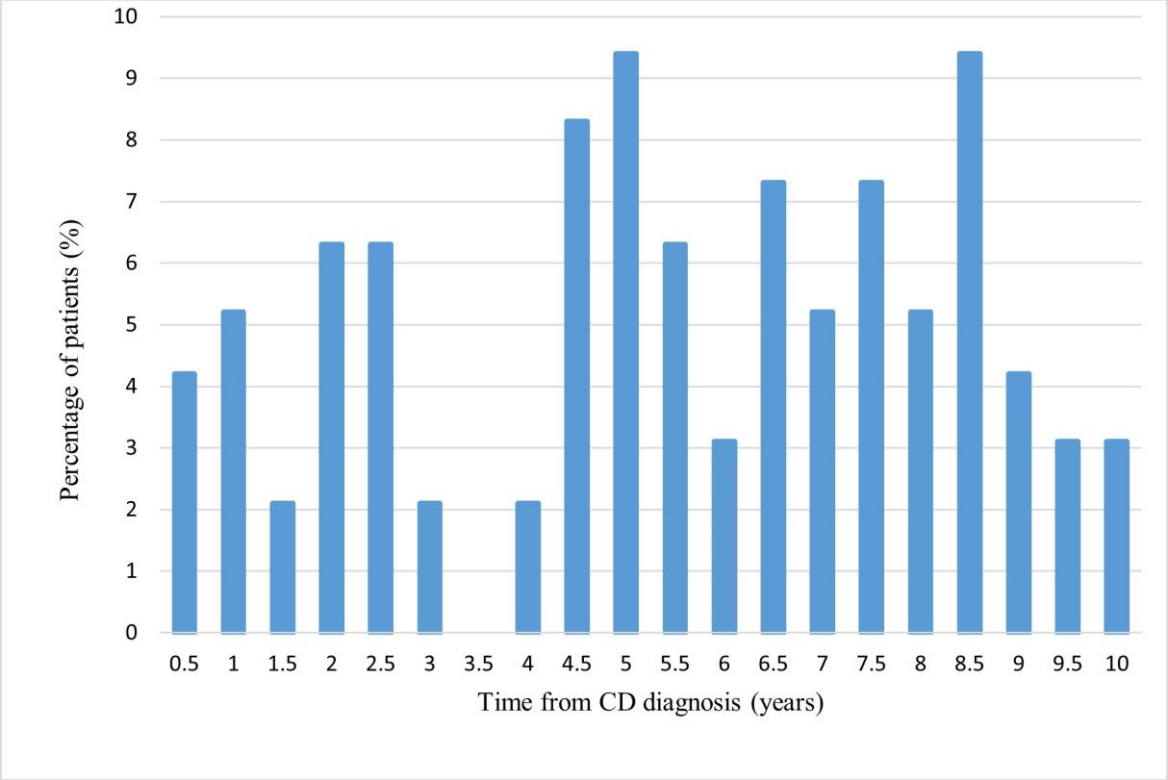
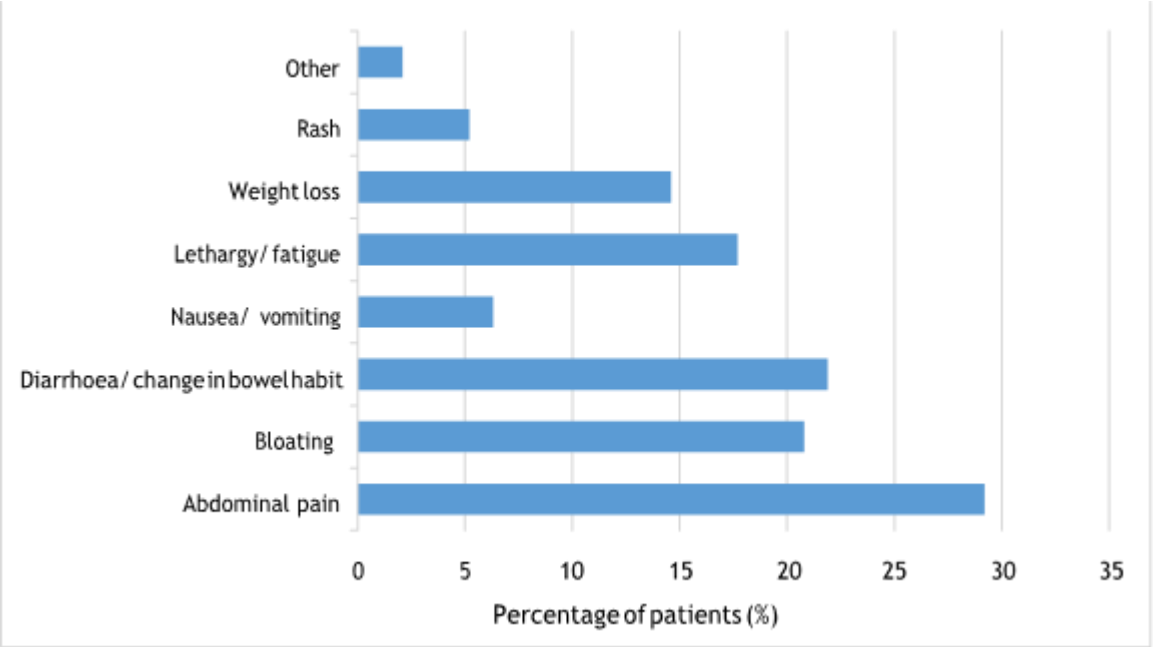


Figure 2: Symptoms reported by index cases



In the asymptomatic group, the reasons for performing serological blood investigations for CD were:

- Screening in view of a family history (14.3%) or other autoimmune conditions (7.1%),
- Osteoporosis diagnosed on dual-energy X-ray absorptiometry (DEXA) scanning (17.9%)
- Investigation of asymptomatic iron deficiency anaemia (60.7%).

The serological blood test that was performed was an anti-tissue transglutaminase antibody (anti-TTG Ab) which also included routine IgA levels as to identify those with IgA deficiency. Histology confirmed the diagnosis in all patients. The majority of patients had a histological classification of Marsh 3 (96.9%) (Table 1).

Screening of Relatives

The total number of first-degree relatives of index cases was 520 and 31.7% (165/520) of these were screened by means of a serum anti-TTG at least once in their lives. In this sub-group, 9.7% (16/165) of the individuals screened, were tested more than once. Thus overall, only 3.1% (16/520) of all first-degree relatives had multiple screening tests for CD following diagnosis of their first-degree relative.

The total number of relatives diagnosed with CD was 20. This accounts for 11.4% of all first-degree relatives who were tested, half being diagnosed prior to our index case due to gastrointestinal symptoms and /or anaemia (*n*=10) and the rest being diagnosed through routine screening after the index case was diagnosed (*n*=10/165; 7 female). Two families had 3 affected members in all, including the index case. In the screened group, the majority (90%; *n*= 9/10) were found to be positive the first time they were screened. Similarly, from the first-degree relatives who had already been previously diagnosed (i.e. before the index case) with CD, 7 out of 10 patients were also female.

The majority of patients undergoing screening (72.7%), underwent screening by means of anti-TTG antibody testing within 12 months from the diagnosis of the index case. Within the next 2 years, 12.7% were screened while the rest (14.6%) were screened more than 4 years after the index case.

Table 1: Marsh Classification of the index cases

Marsh Type	Percentage of study population (%)
1	2.1
2	1.0
3a	35.4
3b	37.5
3c	24.0

Table 2 shows the time interval between each screening for those individuals who were screened more than once (*n*=16). From those who were found to have CD upon initial screening, 60% (*n*= 6/10) were screened within the same year of diagnosis of the index case while 30% (*n*=3/10) were first screened 2 years following diagnosis of the index case. The remaining patient (*n*=1/10, 10%) initially tested negative when screened the first time but was then found to have CD 6 years from diagnosis of the index case when she was screened for the second time.

There was no statistical difference in the type of first-degree relatives that had undergone screening between parents (34.3%; *n*=48/140), siblings (24.6%; *n*=64/260) and children (44.2%; *n*=53/120).

Table 2: Time interval between each screening for those patients screened more than once

Time interval between each screening	Percentage of people screened more than once (%)
Yearly screening	25.0
2-year	18.8
3-year	31.3
4-year	6.3
5-year	0.0
6-year	12.5
Other*	6.3

**Initially screened after 2 years, then on a yearly basis*

Patient Response to Questionnaire

The patients' responses to the four questions asked in our questionnaire are summarised in Table 3.

In response to our first question, the majority of patients felt that at least sometimes, people did not understand their dietary needs or thought they were exaggerating (77%).

Similarly, more than a third of patients (38.5%) often or always avoided social activities or felt less able to integrate with others because of their dietary requirements.

Quite importantly, 76% of patients expressed at least some kind of difficulty in finding something suitable to eat when not at home.

With regards to economic terms, a significant proportion of patients (83.3%) stated that their expenses have significantly increased due to CD.

Table 3: Patient responses to questionnaire

Question (Q)	Never (%)	Rarely (%)	Sometimes (%)	Often (%)	Always (%)
Q1. Do you feel that people don't understand your dietary needs or think that you're exaggerating?	15.6	7.3	30.2	26.0	20.8
Q2. Have you ever avoided social activities or felt less able to integrate with others because of your dietary requirements?	22.9	9.4	21.2	17.7	20.8
Q3. Do you find difficulty in finding something suitable to eat when you are not at home?	10.4	13.5	25.0	26.0	25.0
Q4: Do you feel that you have significantly increased expenses due to coeliac disease?	7.3	9.4	19.8	22.9	40.6

Discussion

CD is a relatively common, chronic autoimmune condition estimated at occurring in approximately 1% of the population. There is a significant genetic basis for the development of the condition with a strong association with the HLA-DQ2 and HLA-DQ8 gene loci with more than 95% of affected individuals expressing the HLA-DQ2 or DQ8 haplotype.[5] This explains the high prevalence in family members of the affected individuals, particularly in first-degree relatives with HLA DQ2/DQ8 positivity and especially so if they are HLA-DQ2 homozygous.[6-7]

A significant proportion of these patients are asymptomatic or have symptoms secondary to, as of yet, clinically undetected CD. Due to the high prevalence of undiagnosed CD in first-degree relatives of affected individuals, routine screening of this cohort is routinely advised by various guidelines.[3,8-9]

A systematic review and meta-analysis reported a pooled prevalence of CD of 7.5% amongst first-degree relatives and 2.3% in second-degree relatives.[10] In studies, known familial tendencies usually vary from 4 to 15%[11-19] though a recent retrospective study quoted a higher proportion with 44.4% of screened first-degree relatives having been diagnosed with CD.[20]

In our study, less than a third of relatives had undergone screening (31.7%). Screening was done through anti-TTG IgA antibodies, which also included routine IgA levels to identify those with IgA deficiency. Subsequently, CD was confirmed by means of duodenal biopsies. In our study group, from those relatives who were tested, 11.4% of them were diagnosed with CD. Recall bias might be a source of error. Patients might have forgotten if their relatives had been screened and/or tested and furthermore, they might not be fully aware of their relatives' screening or their relatives might not have divulged the results to them. The relatively small community might act against this as most families are very close together. However, our first-degree relatives' rate of CD is consistent with international data. When screened, most of the first-degree relatives were screened within a year of diagnosis of the index case (72.7%). This might be due to the fact that patients and relatives tend to be more concerned at diagnosis. Furthermore, patients are usually advised to inform relatives about screening at diagnosis and not subsequently. Another limitation to our study was the inability to contact patients either due to lack of contact details or the patients not answering their phone despite multiple attempts.

The majority of index patients with CD (79%), as well as their relatives diagnosed with CD (70%), were female. Amongst all first-degree relatives, the highest proportion screened was that of the index cases' children (44.2%) followed by parents (34.3%) and siblings (24.6%). Some patients with young children expressed the intention to screen their sons and daughters at a later date as they were deemed to be too young to be screened at the time of this study. It is not generally recommended to use IgA anti-TTG antibody screening for children younger than four years old due to immaturity of the immune system.[21]

Evidence suggests that screening of high-risk groups such as relatives of the index case is beneficial.[22] However, evidence for the frequency of repeated testing in those who are initially negative is limited. Some institutions carry out repeat screening via anti-TTG testing every two years.[17] The 2019 European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other

gluten-related disorders recommends that it would be reasonable to screen at-risk family members every 3 to 5 years though acknowledging that testing frequency has not been clearly defined.[23]

In this study, only 3.1% of all first-degree relatives were screened more than once, though most patients were diagnosed during the first screening episode.

HLA typing, which has not been routinely performed in this cohort of patients, has previously been suggested as an option in order to determine those family members with initially negative anti-TTG who have predisposing DQ2/DQ8 alleles and focus on follow-up screening for them.[17] HLA typing has a relatively high negative predictive value for CD. Therefore, CD is very unlikely to develop in those patients with negative anti-TTG and negative HLA typing. However, positive HLA typing is also present in patients who will never develop CD and this might lead to unnecessary fear and anxiety of developing CD.[24-25]

This study also sought to obtain information on the impact of a diagnosis of CD on the patient. The accredited Coeliac Disease Assessment Questionnaire (CDAQ) was used as a reference in order to guide us in adapting questions to include in the questionnaire.[4,26] A total of 4 focused questions were chosen in order to keep the interview brief and keep the patients focused. The 4 questions dealt with the psychological, social and financial impact of the condition on their daily lives. Thus, though we made use of an unvalidated questionnaire that we developed, the questions that we asked were all obtained from the accredited CDAQ.

The first question focused on the psychological effect of the disease due to the patients' perception of stigma or lack of understanding by other people. The results show that the majority of Maltese CD patients felt that this is still an issue and that awareness and understanding of the condition is poor among the general public. In fact, 20.8% replied that they always feel that the general population does not understand their dietary needs and believes that their dietary needs are an exaggeration. Only 22.9% reported that they either rarely or never felt this way.

The second and third questions assessed the effects of the condition on the affected individuals' social lives. A significant proportion of patients claimed that their dietary needs drive them to avoid social activities and make them less able to integrate with others. More than a third of them avoided social activities on a regular basis and 76% of patients expressed at least some kind of difficulty in finding something suitable to eat when not at home.

The last question emphasised the financial implications of their dietary requirements. In Malta, patients with biopsy-confirmed CD are entitled to make use of the National Coeliac Scheme in which patients are entitled to a monthly monetary voucher which can be exchanged for a number of gluten-free products.

Despite this, 63.5% of patients have noted that their diagnosis has substantially increased their financial burden. This concern has also been recently highlighted by a study on the cost and availability of GFF in the United Kingdom.[27]

In conclusion, the prevalence of CD in first-degree relatives of index CD patients is higher than that of the general population. However, our local screening rates are still low and a greater emphasis needs to be done as to ensure adequate screening through serological testing. Future studies should also focus on the frequency of testing of first-degree relatives.

Summary

What is already known about the subject

- The prevalence of coeliac disease (CD) in first-degree relatives is elevated when compared with the general population at about 10%, due to a strong association with the HLA-DQ2 and HLA-DQ8 gene loci.
- Screening of first-degree relatives of patients with coeliac disease is recommended, though evidence on the frequency of repeat screening is lacking.
- Lifelong adherence to a gluten-free diet can affect the patient's quality of life including psychologically, socially and financially.

What are the new findings?

- In our Maltese study group, 11.4% of tested relatives were diagnosed with CD, such a percentage being consistent with international data.
- Less than a third of first-degree relatives of Maltese patients with CD were found to have undergone screening (31.7%) at least once, with only 3.1% having been screened more than once.
- The majority of interviewed Maltese patients felt that living with CD had a detrimental effect on their quality of life including perceived stigma due to lack of awareness of the general population, limitation of social activities and financial burden.

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