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Abstract

Background- Coeliac disease (CD) is well known to many clinicians as a diagnostic challenge, due to the diverse range of pre-diagnostic clinical manifestations. It is thought that this wide spectrum of signs and symptoms might be responsible for delays in diagnosis or misdiagnosis. The clinical presentation of CD has changed with traditional ‘classic’ symptoms of malabsorption being replaced by milder, atypical symptoms.

Objective- To document and analyze the clinical manifestations leading to the diagnosis of CD in a cohort of subjects previously studied at RPAH Allergy unit.

Methods- This retrospective cohort study examined the medical records of 105 adults previously diagnosed with CD. Data was collected in the following categories: pre-diagnosis signs; symptoms and precipitating events at initial diagnosis; length of time from onset of symptoms to CD diagnosis; associated disorders and family history; and GFD information sources and response to diet. Data was analysed using Excel and SQL Query Analyzer and the results were compared with the existing literature.

Results- Many subjects reported having gastrointestinal symptoms: bloating/wind (81.9%), diarrhea (72.4%) and abdominal pain (61 %). However a large proportion also had atypical features such as headaches (66.7%), fatigue (61%) and anemia (60 %). Eighty four percent of subjects experienced symptoms during childhood and in 71.5% of subjects it took more than 2 years to be diagnosed. A total of 84.5% of subjects were initially diagnosed with another condition to explain symptoms and 32% linked the onset of their symptoms to a precipitating event. Associated disorders were prevalent in 38.1% of subjects and 28.1% of subjects had relatives with CD. The main information source regarding the gluten free diet (GFD) was the Coeliac Society and for most subjects (86%) it took more than 12 months for symptoms to resolve on the GFD.

Conclusions- CD is now presenting more commonly with extra-intestinal symptoms. An increase in the awareness and recognition of atypical manifestations is necessary among physicians to reduce delayed or mistaken diagnosis, and to decrease long-term complications such as malignancies, osteoporosis and infertility.
Introduction

Coeliac disease is defined as a permanent intolerance to ingested gluten that results in immunologically mediated inflammatory damage to the small-intestinal mucosa \[1\]. It is one of the most thoroughly investigated and characterized forms of food-induced disease in humans \[2\]. Although there have been advances in the understanding of coeliac disease (CD), the exact mechanism that leads to mucosal damage remains uncertain. Most investigators now believe CD is caused by an abnormal cell-mediated immune reaction to gluten \[3,4\].

The current prevalence of CD among European Caucasians ranges from 1 in 250 (in Sweden) to 1 in 4000 (in Denmark) \[2\]. In Northern Ireland the prevalence is even greater with 1 in 122 \[5\]. CD in the USA continues to be regarded as rare. However recent studies using healthy blood donors for serological screening have challenged this theory with supportive evidence that suggests undiagnosed CD is probably as high as in several European countries \[6,7\]. In Australia the prevalence of CD remains unclear; however Hovell et al (2001) reported a 1 in 251 incidence of CD in a population survey in Busselton, Western Australia.

The true prevalence is probably underestimated, since active CD is now recognized to occur in asymptomatic individuals. These subjects have been classified as ‘silent’ coeliacs. Silent cases have no symptoms but the small intestinal biopsy shows villous atrophy \[9\]. The introduction of serological screening has allowed for an increase in the number of silent coeliac patients to be diagnosed. The identification of silent cases and the potential risk of malignancy in untreated CD is becoming a major topic of interest \[10\]. Screening studies have shown that for each case recognized on the basis of suggestive clinical symptoms, another six or seven are unrecognized \[11\].
This wide range in prevalence suggests that in addition to a genetic predisposition environmental triggers may play a role. Over the past decade, the epidemiology of CD has altered due to the increasing age at which CD is first diagnosed. CD is more common in females than males (3:1 respectively), in middle-age. It has is a strong familial basis with, some reports estimating a 10-12 % risk of first-degree relatives having the disease\textsuperscript{[12]}. The critical genetic factor thought to be responsible for this connection resides in the HLA region of chromosome 6.

Since the clinical presentation may be subtle with few diagnostic signs or symptoms, many cases remain undiagnosed. This is an area of concern as untreated CD can lead to long-term complications such as malnutrition, osteoporosis, reduced fertility and cancers of the gastro-intestinal tract (GIT). Holmes et al (1989) reported that the risk of developing cancer of the gastrointestinal tract is reduced to that of the normal population after following a gluten free diet (GFD) for 5 years.

Due to an improvement in screening tests, family studies, and awareness of the disease, it is now accepted that the presenting symptoms that characterize CD are more varied than those historically described. Classic symptoms seen traditionally in children were failure to thrive, abdominal pain, abdominal distention, soft/frequent/pale/foul-smelling stools, anorexia and irritability. Other associated clinical features are anaemia, delayed puberty, rickets and short stature\textsuperscript{[4]}.

However these days fewer patients present in early childhood with “classical” symptoms and are more likely to present later in adolescence and adult life with a variety of extra-intestinal symptoms. An increasing number of people are being diagnosed who have no GIT symptoms but present with signs such as nutritional deficiencies (iron deficiency anaemia, folate deficiency), osteoporosis or peripheral neuropathy\textsuperscript{[15]}. Typical symptoms in adults are diarrhoea, weight loss, abdominal pain, fatigue, irritability, lactose intolerance, childhood history of symptoms and recurrent mouth ulcers. Other
common presenting clinical manifestations are iron, folate and B12 deficiencies, infertility, bone pain or fractures and neurological problems \cite{4}.

A definitive diagnostic test for CD became possible in the 1960’s with the development of the peroral jejunal biopsy. This tested for architectural changes to the intestinal mucosa, specifically changes in the villous height to crypt ratio (villous atrophy) \cite{16}. Prior to this, the diagnosis of CD was entirely based on the presence of clinical features of malabsorption, the absence of infection and reduction of fecal fat excretion after gluten free diet (GDF) treatment \cite{3}.

The general acceptance of a specific set of diagnosing criteria developed by the European Society of Paediatric Gastroenterology and Nutrition (ESPGAN) significantly increased diagnostic awareness. Originally the criteria required three small bowel biopsies and a gluten challenge; however this has since been revised and simplified. To diagnose the condition, one biopsy is required to show villous atrophy while consuming gluten. Then to confirm the diagnosis, a second biopsy after 6 months on a GFD should demonstrate mucosal recovery \cite{17}. The introduction of various non-invasive blood tests (antigliadin, endomysial and transglutaminase) has made it possible to screen large populations. The diagnosis cannot be made on the presence of antibodies alone, however a biopsy is still considered necessary.

The IgA antiendomysial antibody (AEA) assays have very good predictive values (pv) for screening CD (98-100% positive pv and 80-95% negative pv) \cite{8}. The AEA antibody is directed against tissue transglutaminase, a component of human and primate connective tissue and is found in 95-100% of untreated patients with CD. AEA is more sensitive and specific for CD than

A number of diseases have been found to be associated with CD, especially those of autoimmune origin, such as rheumatoid arthritis, autoimmune thyroid disease, autoimmune hepatitis and insulin dependent diabetes mellitus \cite{19}. Auricchio & Viskorpi (1994) suggest that immune mechanisms
involved in associated diseases, may explain the coexistence of the disorders. Downs syndrome, cystic fibrosis and neurological dysfunction also show a connection with CD\textsuperscript{[20,21]}. Other conditions such as malignancies, osteoporosis and infertility are complications of long-term and perhaps inadequately treated CD.

Treatment of CD requires a lifelong removal of gluten from the diet. This involves avoiding wheat, rye, barley, triticale, possibly oats and many ingredients derived from these grains. Once gluten is removed from the diet the intestinal mucosa returns to normal in most individuals. Adherence to a GFD decreases the incidence of small-bowel lymphoma, slows down progressive bone mineral loss and decreases the likelihood of developing autoimmune disorders, nutritional deficiencies and infertility\textsuperscript{[22]}.

The diverse range of presenting manifestations seen in CD, make it a diagnostic challenge for clinicians. In 1994, Marsh reported that “the wide spectrum of signs and symptoms might be responsible for delayed diagnosis or misdiagnosis, which, initially is said to be as high as 60%”.

The Allergy Unit at RPAH has been conducting clinical research in people with CD for a number of years, providing an opportunity to review the natural history of this condition from information supplied when they were recruited. Some of the subjects studied presented with classic symptoms and were therefore diagnosed early, even before biopsies were available. On the other hand, many subjects experienced delays of many years while searching for an explanation for their symptoms. This study was designed to document and analyse the variation of pre-diagnosis histories, in an existing cohort of people with CD. Past symptoms, presenting signs, previous initial diagnoses and associated diseases have been collated. The emerging patterns have been discussed and then compared with the established literature.
Defining subjects-recruiting medical records

Review and recording of medical data

Pre-diagnostic signs, symptoms and precipitating events
Initial diagnosis and length of time to CD diagnosis
Associated disorders and family history
GFD information sources and time to relief of symptoms

Analyse and evaluate results

Compare with established literature

Figure 1 *Flowchart of Study Methodology*
Methods

This retrospective cohort study, examined the medical records of 105 adults previously diagnosed with CD. The subjects were members of the Coeliac Society of New South Wales who volunteered to participate in earlier studies conducted by RPAH Allergy Unit. These studies ran between the years 1994-1999 and investigated possible non-gluten food intolerances in CD and metabolic outcomes of the Australian gluten free diet. Permission to do the review was granted by the Ethnics Review Committee of the Central Area Health Service (RPAH Zone).

Defining Subject Group

The medical records of subjects involved in the following studies were obtained.

- Food Intolerance Study 1994-1997 (50 subjects)
- Asymptomatic Study 1995-1996 (10 subjects)
- Metabolic Study 1996-1999 (45 Subjects)

To be eligible for the above studies, subjects were to be within the ages of 18-75 and they had to have biopsy proven CD for a minimum of 1-2 years. The biopsy demonstrated damage to the villous architecture of the intestinal mucosa, which improved after dietary gluten withdrawal. All subjects were free of other significant concurrent diseases, such as cardiac, respiratory or renal disease. Their degree of compliance with the GFD was ascertained by direct enquiry from the dietitian (Kim Faulkner-Hogg) and a series of prepared questionnaires and food diaries.

Review and recording of medical data

The medical records of recruited subjects were reviewed and entered into a secure database at RPAH Allergy Unit. Dr Loblay conducted the initial medical history and examination. The information gathered in the interview consisted of symptomatic history (from childhood to present), previous diagnoses, biopsy results, some dietary data and personal and family history of associated diseases. Subjects were asked to bring with them a copy of their first 2-biopsy results. In 4 adult subjects initial
diagnosis was made in early childhood before biopsies were available, thus the biopsy results used for this study were obtained when re-diagnosed later as an adult. However the majority of subjects were able to provide copies of their original biopsies. In the initial interview there were specific questions asked regarding each of the above categories. These are listed below.

**Signs and Symptoms**
- Childhood, adolescent and adult symptoms
- Circumstances and symptoms of CD onset
- Duration of symptoms before diagnosis
- Continuing symptoms since diagnosis
- Typical symptoms such as gastro-intestinal complaints, skin disorders (Dermatitis herpetiformis), nutrient deficiencies, weight loss, food allergies and hayfever and psychological disturbances such as fatigue, headaches, stress and depression
- Hormonal and reproductive history including age periods began and menstrual history, childbirth, miscarriages, menopause and other hormonal problems.

**Previous Signs and Diagnosis**
- Other diagnoses made prior to CD
- Year and age of CD diagnosis.

**Biopsy and Dietary Data**
- Number and year of small bowel biopsies
- Histological outcome of biopsies. These were represented as either normal (N) or abnormal. The degree of abnormality was described as Total Villous Atrophy (TVA), Subtotal Villous Atrophy (STVA) or Partial Villous Atrophy (PVA).
- Degree of strictness of the GFD at each biopsy (Codex-GFD or NDG-GFD). The Codex-Gluton Free Diet was part of the WHO/FAO Codex Alimentarius Food Labeling Standard, which was used in Australia until to 1995. The final product, labeled under this standard,
can contain up to 0.3 % of protein from a gluten containing grain. No Detectable Gluten-
Gluten Free Diet (NDG-GFD) was introduced in 1995 as part of the new Australian Food
Labeling Standard. The final product can not contain detectable gluten (lower limit
0.003%). Ingredients such as wheat starch and malt were therefore excluded.

- Source of GFD information (Dietitian, GP, Naturopath)
- Length of time on GFD before feeling well.

**Family History**
- Family history of CD, associated diseases and other problems

**Result analysis and comparison with established literature**

Data was analyzed using the computer database SQL Query Analyzer and basic comparative statistics
were compiled. The results were tallied and graphed in an Excel database. Findings were evaluated and
assessed, then compared with a body

of established literature. To maintain patient confidentiality (e.g. name and contact details) the
database was password-protected and limited only to those involved in the study.
Results

Of the 105 medical records reviewed, 89 (85%) were from females and 16 (15%) were from males. The mean age (at interview) was 46.7 (range, 19-75 years) and the average length of time that people had had CD was 8.6 years (range, 1-29 years). The mean age at diagnosis for females was 36.8 years (SD 13.7, range 1.5-63 years) and males 41.3 years (SD 15.5, range 13-71). Six subjects were diagnosed as children, 4 of these were diagnosed before biopsies were available. These 4 subsequently returned gluten to their diets and were again re-diagnosed with CD as an adult (refer to Appendix 1, Table 1). The 2 other subjects diagnosed with biopsies at age 1.5 and 3 years remained on their GFD.

Symptoms Pre-Diagnosis

Frequent adult manifestations of CD were gastrointestinal complaints, including bloating/wind, diarrhoea, and abdominal pain. Common atypical signs of CD found in this subject group were headaches/migraines, anaemia and fatigue (refer to table 1).

Table 1. Adult manifestations of CD among subjects (n=103)

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloating/wind</td>
<td>81.9</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>72.4</td>
</tr>
<tr>
<td>Headaches/migraines</td>
<td>66.7</td>
</tr>
<tr>
<td>Abdominal pain/cramps</td>
<td>61.0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>61.0</td>
</tr>
<tr>
<td>Anaemia</td>
<td>60.0</td>
</tr>
<tr>
<td>Mouth ulcers</td>
<td>60.0</td>
</tr>
<tr>
<td>Constipation</td>
<td>32.4</td>
</tr>
<tr>
<td>Hayfever</td>
<td>32.4</td>
</tr>
<tr>
<td>Weight loss</td>
<td>28.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>27.6</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>23.8</td>
</tr>
<tr>
<td>Indigestion/heartburn</td>
<td>21.9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12.4</td>
</tr>
<tr>
<td>URTI</td>
<td>9.5</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3.8</td>
</tr>
</tbody>
</table>
These signs and symptoms were also the main contributing factors that led to the diagnosis of CD. Diarrhoea was reported as the main symptom leading to diagnosis (69.2% of subjects). Other manifestations that prompted subjects to seek a diagnosis are shown graphically in Figure 1 (over the page). One subject had no recorded data in this area.

At the time of diagnosis 21 (20%) subjects reported being anaemic as well as fatigued, while 25 (24%) subjects reported diarrhoea and abdominal pain/cramps. Only four subjects (3.8%) reported a combination of all four symptoms. These were the most frequently coupled manifestations among the cohort. One subject reported infertility and 3 had a history of miscarriage.

Eighty two (84%) subjects experienced symptoms during their childhood and/or teenage years, not including those subjects diagnosed as children. The most common childhood symptoms reported retrospectively were mouth ulcers, hives, diarrhoea and abdominal pain (see Table 2).

**Table 2. Retrospective Report of Childhood Symptoms (n=90)**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouth ulcers</td>
<td>31.4</td>
</tr>
<tr>
<td>Hives (urticaria)</td>
<td>30.5</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>24.8</td>
</tr>
<tr>
<td>Abdominal pain/cramps</td>
<td>19.0</td>
</tr>
<tr>
<td>Bloating/wind</td>
<td>11.4</td>
</tr>
<tr>
<td>Anaemia</td>
<td>10.5</td>
</tr>
<tr>
<td>Hayfever</td>
<td>10.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9.5</td>
</tr>
<tr>
<td>Constipation</td>
<td>8.6</td>
</tr>
<tr>
<td>Eczema</td>
<td>8.6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6.7</td>
</tr>
<tr>
<td>Delayed puberty</td>
<td>4.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.9</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>1.9</td>
</tr>
</tbody>
</table>
Figure 1. Manifestations leading to CD diagnosis (n=104)

- Diarrhoea: 69.2%
- Anaemia: 48.1%
- Bloating/wind/gas: 41.3%
- Fatigue: 39.4%
- Abdominal pain/cramps: 39.4%
- Weight loss: 37.5%
- B12 deficiency: 14.4%
- Folate deficiency: 13.5%
- Vomiting: 13.5%
- Stress/anxiety: 12.5%
- Nausea: 10.6%
- Constipation: 9.6%
- Mouth ulcers: 9.6%
- Dermatitis herpetiformis: 5.8%
- Depression: 4.8%
- Insomnia: 3.8%
- Headaches/migraines: 3.8%
- Miscarriage/infertility: 3.8%
- Osteoporosis: 1.9%
From the onset of symptoms, it took 10 or more years for 34 (32%) subjects to be diagnosed with CD. Twenty seven of these subjects experienced childhood and/or adolescent symptoms, while 7 reported no earlier symptoms. In 30 subjects (28.6%) a diagnosis of CD was given within a year of perceived symptom onset, while 23 (21.9%) and 11 (10.5%) subjects were diagnosed within 2-5 years respectively. A small group of 7 subjects (6.7%) reported lifelong symptoms before diagnosis (refer to Figure 2, over the page).

**Initial Diagnosis**

Prior to being diagnosed with CD, 87 subjects (84.5%) had been diagnosed with conditions that are now known to be clues for underlying CD. Among this cohort, disorders such as stress, anxiety and depression were the most frequent initial diagnoses (refer to Figure 3, over the page).

Subjects reported particular signs that were attributed to the mistaken diagnoses (refer to Appendix 2). Among them were nutritional deficiencies including anaemia (49.5%), B12 deficiency (16.2%), folate deficiency (10.5%) and calcium deficiency (4.8%) as well as thyroid disease (4.8%), and osteoporosis (0.95%) and infertility (0.95%).

**Possible precipitating factors leading to CD onset**

Prior to being diagnosed, 35 subjects (32%) related the onset of their symptoms to a specific event. The reported events were; periods of stress or anxiety (12.5%), followed by postpartum onset (11.5%) becoming ill while traveling (6.7%) and a sudden change in diet (1.0%) shown graphically in Figure 4.
Figure 2. Time from the onset of symptoms to diagnosis (n=105)

- Child/teen symptoms
  - <1 yr: 28.6%
  - >2 yrs: 21.9%
  - >5 yrs: 10.5%
- No previous symptoms
  - >10 yrs: 32.4%
  - Lifelong: 6.7%
Figure 3. Common initial misdiagnoses prior to CD diagnosis (n=87)

- Stress/anxiety: 18.4%
- Depression: 14.9%
- Irritable Bowel Syndrome: 13.8%
- Appendicitis: 13.8%
- Giardia: 11.5%
- Lactose intolerance: 6.9%
- Virus: 5.7%
- Gastroenteritis: 5.7%
- Salmonella/food poisoning: 4.6%
- Food allergies/intolerances: 4.6%
Figure 4. Possible precipitating factors leading to CD onset (n=33)

Among the whole cohort, 7 subjects had been turned down when donating blood because of low blood iron. Only 2 out of these 7 subjects underwent further investigations, which eventually led to the diagnosis of CD.

Concurrent Disorders in Study Subjects

Forty subjects (38.1%) reported having 1 or more disease that is reported in the literature as being associated with CD. Figure 5 graphically represents these diseases which have been diagnosed both pre (29%) and post (22%) CD (refer to Appendix 1, Table 2). Thyroid disease was most prevalent, with 10 subjects (25%) followed closely by Dermatitis herpetiformis with 9 subjects (22%). Of the whole cohort these conditions affected 9.5% and 8.6% of subjects respectively. Other diseases that exist concurrently in the subjects are listed in table 3
Figure 5. Concurrent disorders among subjects (n=40)

Family History

A total of 25 subjects had 1 or more relative with CD of whom 18 were first degree relatives. The most commonly reported disease was diabetes (of any kind). However in many cases the type of diabetes was not documented, thus the precise number of relatives with IDDM unknown. Most of the diseases listed in table 3 occurred in first degree relatives, with the exception of cancer of the GIT and diabetes. In 16 subjects, no family history was recorded; 2 of these were adopted, therefore past family history was unknown (refer to table 3).
Table 3.  
Family history of concurrent disorders

<table>
<thead>
<tr>
<th>Associated Disease</th>
<th>Number of subjects with 1 or more relative with the disease (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First Degree (%)</td>
</tr>
<tr>
<td>Coeliac Disease</td>
<td>18 (20.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14 (15.7)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>8 (9.0)</td>
</tr>
<tr>
<td>Irritable Bowel Syndrome</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Lactose Intolerance</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Thyroid Disease</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>4 (4.5)</td>
</tr>
<tr>
<td>Cancer of GIT</td>
<td>4 (4.5)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>1 (1.1)</td>
</tr>
</tbody>
</table>

**Information Sources**

The coeliac society provided all subjects with information about CD and the gluten free diet. Some subjects (36.5%) obtained additional information from other sources; 30.5% consulted dietitians, while others saw naturopaths (4%), nutritionists (1%) and GP’s (1%). Of the 32 subjects who saw a dietitian, 4 reported they were helpful, 7 reported they were unhelpful and in 21 no comment was recorded. The majority of subjects (86%) took 12 months or less for symptoms to subside on a GFD with most of these (58%) taking less than 3 months. Another 10% of subjects reported relief of symptoms after 12 months. Four percent reported no relief from the diet and another 4% had no recorded data on this subject (refer to appendix 3).
Discussion

This study assessed the pattern of clinical manifestations that led to the diagnosis of CD. It was designed to obtain a greater insight into the signs and symptoms that manifested in a cohort of coeliac subjects whose history had been thoroughly documented at the Allergy Unit.

There are several limitations of this study that should be addressed. Firstly the medical notes recorded by Dr Loblay are primarily based on the subject’s recollection of events, relevant data and symptom severity. This raises the question about the reliability of results, since they are strongly dependent on the ability of the subject to recall information from the past, especially regarding delays in diagnosis, childhood symptoms, family history and previous diagnoses. Apart from copies of the original biopsy results, other medical documents to support the subject’s recollections were limited.

Secondly, where vague information was recorded, assumptions were employed to categorize as many subjects as possible. For example, in some subjects the period of time from onset of symptoms to diagnosis required generalizing because the exact times were not recorded.

Thirdly, to be eligible for an earlier study the subjects had to have had continuing symptoms, while on a GFD. The subjects are also all members of Coeliac Society of NSW and predominately middle aged females. Therefore this sample of subjects is not necessarily representative of the entire Australian coeliac population. Nevertheless data obtained in this study describes this particular cohort of subjects and the following discussion compares their results with published literature.

For unknown reasons CD is predominantly reported in females [24]. Howdle (1994) suggests that women of childbearing age are more likely to develop symptoms and seek advice. Twelve of the cohort presented in this study felt that pregnancy precipitated the onset of symptoms leading to diagnosis.
The last decade has seen an expansion in the amount of literature describing the range of clinical manifestations in CD \cite{5, 26, 27, 31}. Traditionally CD was seen more commonly in children with “classic” textbook presentations such as diarrhoea, pot-bellies, muscle wasting, vomiting and growth retardation \cite{32}. Today full-blown malabsorption is rarely seen, although symptoms suggestive of small bowel disease are still common. A total of 25 subjects (24\%) in this study reported diarrhoea as well as abdominal pains at the time of their diagnosis (refer to table 1).

The most striking finding was the high incidence of atypical/non-classic manifestations (affecting 60\% or above of subjects). These included headaches, fatigue, anaemia and mouth ulcers. Mouth ulcers were found to be more frequent among this cohort (60\%) than in previous literature, for example Collin et al 1999 reported mouth ulcers affected only 10-40\% of CD patients. This study and others \cite{22, 26, 28} support the observation that more people are being diagnosed in adult life with subtle, extra-intestinal symptoms. The peak age of diagnosis is now estimated to be 40-50 years of age \cite{20}.

A large proportion of subjects (71.5\%) reported the onset of their symptoms began more than 2 years before their diagnosis (figure 2). Sanders 2002 and Green 2001 found similar results with the average duration of pre-diagnostic symptoms being 4.9 years and 11 years respectively. This shows that even despite an increase in the awareness and number of new cases being diagnosed, there is still an extensive delay in the recognition of silent CD. Some of the delay may be because patients do not seek medical attention, as they may not feel the symptoms are serious or they accept the chronic state of ill health as normal.

Iron deficiency anaemia is considered an important marker of silent CD. Bottaro (1999) supports this notion and reported anaemia as the most frequent extra-intestinal symptom of silent CD. In this study, 60\% of subjects reported being anaemic at some stage prior to CD diagnosis. Hin et al (1999) showed...
that over 80% of coeliac patients identified by serological screening did not have gastrointestinal symptoms, but over half had anaemia. This study also found an association between anaemia and fatigue (20% of subjects) at the time of diagnosis.

Among blood donors the prevalence of asymptomatic CD has been found as high as 1:266. In our study 7 people were informed of their low iron status while donating blood (leading only 2 subjects to CD diagnosis), but many more were told they were anaemic by physicians prior to diagnosis without further investigation. Perhaps if the connection had been more widely recognized, many subjects could have been diagnosed sooner.

In a large proportion of the cohort, a general lack of awareness of atypical symptoms lead to a variety of initial diagnoses and inevitably a delay in diagnosis (figure 3). The most common of these were stress/anxiety (18.9%), depression (12.6%), irritable bowel syndrome (IBS) (11.6%) and appendicitis (11.6%). The correlation with IBS is recognized by several investigators, in particular Green et al 2001 and Sanders et al 2001. Both found the presence of CD among people with IBS to be substantially higher than this study, 40% and 21% respectively.

Ventura et al (1999) suggests that prolonged exposure to gluten after the age of 15 can contribute to the development of autoimmune disease. Many subjects in this study were diagnosed with associated autoimmune diseases, the most frequent was thyroid disease (9.5%). The prevalence of thyroid disease in this cohort is comparable with previous studies. It has been reported that autoimmune thyroid disease occurs in 14-30% of patients with CD. Conversely, CD is reported to be more prevalent in people with autoimmune thyroid disease at 5-5.8%.
Insulin dependent diabetes mellitus (IDDM) is another widely recognized associated disease. A person with IDDM is 2-5% more likely to develop CD than the normal population \cite{34}. Only 1 study subject had IDDM which was diagnosed before CD.

Some subjects also reported other complications. The more common conditions reported were dermatitis herpetiformis (DH) and cancer of the gastro-intestinal tract (GIT) (29 subjects). Of the 40 people who reported a concurrent disorder, 22% had DH. However, only 8.5% of the whole cohort (105 subjects) had DH. Kennedy (2000) suggests 10% of adults with CD present with DH (otherwise known as ‘coeliac disease of the skin’). Six percent of subjects in this study reported cancer of the GIT. Likewise Howdle (1994) states approximately 5% of people with CD develop gastrointestinal malignancies (adenocarcinoma of pharynx, oesophagus and small intestine or lymphoma of small intestine), compared to 0.1% of the normal population.

Reduced fertility has also been reported in both men and women with untreated CD. Women suffer from an increased incidence of miscarriage, stillbirth and perinatal death \cite{32}. Our study showed only a small percentage of subjects had miscarriages (3.8%) or were diagnosed as infertile (1.9%) prior to their CD. In contrast up to 50% of women with untreated CD experience miscarriages or an unfavourable outcome of pregnancy. Martinelli (2000) reports women with undiagnosed CD seem to have approximately a 9-fold relative risk of multiple abortions and low birth weight babies compared to treated CD subjects.

It is well known that first-degree relatives of coeliacs have a higher incidence of CD than the normal population. Michalski and McCombs (1994) suggest, approximately 10% of first-degree relatives had CD and 20-30% of all relatives (total) were affected with CD. Our results show a higher prevalence among first degree relatives at 20.2%, similar to McElvaney et al (1992) findings at 17.8%. The
number of total relatives with CD in this study was 28.1%, thus consistent with Michalski and McCombs (1994) results. Diagnosis is often delayed in these cases because subjects are asymptomatic. This highlights the importance of periodic screening in family members of coeliac patients.

It is difficult to determine the exact time of onset of CD in most cases. However several subjects in this cohort related the onset of their symptoms to specific events, such as periods of stress (12.4%), post partum (11.4%) and travel (6.7%) (refer to Figure 4). Reports regarding perceived triggers of symptom onset is largely absent from existing literature.

This study demonstrates and emphasizes the crucial role of the Coeliac Society in providing coeliac patients with information regarding CD and the GFD. Dietitians need to be more equipped to effectively implement the GFD and hence reduce unsatisfied clients. The referral to dietitians should be a standard procedure, as the treatment for CD is a life-long strict GFD, which requires major dietary and lifestyles changes.
Conclusion

The results of this study show, that while some subjects were diagnosed due to classic symptoms, a large majority experienced atypical signs. Consequently, diagnoses were delayed or initially mistaken. A delay in diagnosis increases the probability of developing complications previously stated to be associated with untreated CD. To avoid delays in diagnosis a greater awareness of subtle manifestations of CD is necessary among physicians. Manifestations such as headaches, fatigue, anemia, stress/anxiety and depression, should be recognized as clues to undiagnosed CD, thus prompting further appropriate investigations. Perhaps non-invasive screening tests should be mandatory among high risk subjects presenting with ‘mild’ traditional symptoms, atypical signs, associated diseases and family history of the disease.
References


Appendix 2. Manifestations attributing to initial diagnosis (n=104)

% of Subjects

Manifestations

- Anaemia: 50.0%
- B12 deficiency: 16.4%
- Dermatitis herpetiformis: 10.5%
- Folate deficiency: 10.5%
- Thyroid Disease: 5.8%
- Calcium deficiency: 4.8%
- Osteoporosis: 1.0%
- Infertility: 1.0%
Appendix 3. Time to relief of symptoms on GFD (n=105)

- 0-3 mths: 56 subjects
- 3-6 mths: 17 subjects
- 6-12 mths: 10 subjects
- > 12 mths: 10 subjects
- No relief: 4 subjects
- n/r: 4 subjects