EASILY MISSED?

New primary care series: Easily Missed?

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The series advisers of this new series explain why heightened awareness is needed of conditions that may be commoner than many doctors realise or may be missed at first presentation

Patients consult doctors with the expectation of an accurate diagnosis and advice on treatment. But in primary care, patients often present with undifferentiated symptoms without an immediately apparent diagnosis. For most conditions this doesn't matter because the symptoms either resolve or become worse in such a way that the patient returns before any harm is done.[1] In consultations, general practitioners work by using the probability that the collection of presenting symptoms reflects a specific diagnosis. A combination of knowledge, clinical experience, and sound judgment ensures that they usually get it right. The adage "common things are common" directly applies to diagnosis in primary care.[2] In horse racing parlance, it is usually better to bet on a 6-4 chance than a 66-1 outsider. This, however, assumes that the doctor has an accurate idea of the prior odds[3] and that no harm will result if a diagnosis thought to be less probable is made at a later consultation.

But what if the condition is commoner than some general practitioners think and that without timely diagnosis patients may come to harm? The new series "Easily Missed?" aims to highlight such diagnoses to raise awareness among general practitioners of conditions that we believe are under-recognised in primary care at first presentation. The series will include a wide range of conditions, including some that are common but under-diagnosed and others that are uncommon but so serious that they need to be thought of whenever there is any possibility of their existence. The series will aim to be relevant to all those working in primary care, not only in the United Kingdom.

The articles will be short and focused on diagnosis at presentation rather than treatment. The conditions described will fulfil four key criteria. Firstly, there will be evidence that the condition is commoner than most general practitioners realise or is often missed at first presentation. Secondly, the condition will be sufficiently common that the average full time general practitioner in the UK will encounter it at least once a year, or else be so serious that delayed diagnosis is likely to worsen prognosis substantially. Thirdly, the condition will have easily defined diagnostic features or diagnostic tests with known predictive characteristics. Fourthly, and most importantly, timely recognition will benefit the patient. As series advisers we welcome any suggestions for future articles on conditions that meet these criteria.

Osler said "Medicine is a science of uncertainty and an art of probability." Although uncertainty will always be with us in primary care, we hope the new series might teach us more about the art of probability.

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Interactive case report

A 38 year old woman with hypotensive shock at the onset of menstruation

This case was described on 14 and 21 February (*BMJ* 2009;338:b6, b246). Debate on the management of the patient continues on bmj.com (www.bmj.com/cgi/eletters/338/feb09_1/b6). On 7 March we will publish the outcome of the case together with commentaries on the issues raised by the management and online discussion from the patient and relevant experts.

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EASILY MISSED?

Coeliac disease

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This is a series of occasional articles highlighting conditions that may be commoner than many doctors realise or may be missed at first presentation. The series advisers are Anthony Harnden, university lecturer in general practice, Department of Primary Health Care, University of Oxford, and Richard Lehman, general practitioner, Banbury. If you would like to suggest a topic for this series please email us (easilymissed.bmj@bmjgroup.com)

The finding of iron deficiency anaemia is not consistent with the diagnosis of a functional bowel disorder, and other possibilities needed to be considered, including inflammatory bowel disease, colorectal cancer, and coeliac disease. Although patients with coeliac disease typically present with diarrhoea, weight loss, and anaemia, they may also present with extraintestinal symptoms, particularly adults, and the disease is much more common than previously believed.[1] Evidence is accumulating of substantial underdiagnosis in primary care, where several studies have suggested that as few as a quarter of patients with coeliac disease are recognised.[2-4]

Why is it missed?

In classic cases of coeliac disease, patients develop intestinal malabsorption with gastrointestinal symptoms, but atypical presentations are probably more common than this and often include few or no gastrointestinal symptoms, with patients having problems such as iron deficiency anaemia, osteoporosis, short stature, infertility, and unfavourable outcomes of pregnancy. These atypical presentations, combined with a low index of suspicion, contribute to underdiagnosis of the condition.

Why does this matter?

Coeliac disease is characterised by a lifelong intolerance to the gluten contained in wheat, rye, and barley and is a rather unusual combination of a food intolerance and an autoimmune disorder. The typical clinical features include tiredness, bloating, and loose stools, but when undiagnosed the condition can lead in childhood to serious developmental problems (such as short stature and retarded physical development) and in adults to potentially debilitating gastrointestinal symptoms, seriously affecting quality of life, and possible association with depression and reduced bone mineral density. Patients with coeliac disease are also more susceptible to small bowel malignancy (non-Hodgkin's lymphoma),[5] and up to 30% may have functional hyposplenism.[6]

HOW COMMON IS IT?

- 1% prevalence in general Western populations (possibly higher in Western Europe and Scandinavia)
- 3-6% prevalence in type 1 diabetes
- 5-10% prevalence in first degree relatives
- 10-15% prevalence in symptomatic iron deficiency anaemia
- 3-6% prevalence in asymptomatic iron deficiency anaemia*
- 1-3% prevalence in osteoporosis

* Pregnancy may unmask the effect of iron malabsorption, so testing pregnant women with moderate to severe anaemia is worth while

CASE SCENARIO

A 32 year old woman with fatigue and symptoms of irritable bowel syndrome has not responded to the usual treatment for the condition and has borderline iron deficiency anaemia. Her general practitioner requests tissue transglutaminase antibody (tTGA) testing, and the levels are found to be raised, leading to a diagnosis of coeliac disease.

Withdrawal of gluten from the diet not only protects against these complications but also substantially improves quality of life and restores normal nutritional and biochemical status.

How is it diagnosed?

Clinical

In children coeliac disease is associated with failure to thrive, chronic diarrhoea, and, less commonly, abdominal bloating and delayed puberty. In adults recurrent anaemia and chronic fatigue are the cardinal symptoms, which may be accompanied by weight loss, chronic diarrhoea, peripheral neuropathy, infertility, and arthralgia.[7-9] Iron deficiency anaemia and lower bowel symptoms are "red flag" symptoms for a diagnosis of colorectal cancer, and patients need to be investigated appropriately.

Groups at risk of coeliac disease include people with low bone mineral density and other autoimmune disorders, such as type 1 diabetes mellitus and autoimmune thyroid and liver disease; there are also associations between coeliac disease and Down's syndrome, Turner's syndrome, Sjögren's syndrome, and neurological problems such as ataxia and neuropathy. Because of the high prevalence of coeliac disease in first degree relatives of patients with the condition (most of whom carry the HLA markers DQ2 or DQ8) appropriate family members should be considered for screening with the tissue transglutaminase antibody test.[10]

Investigations

The optimal investigation for the diagnosis of coeliac disease is proximal small intestinal (duodenal) biopsy, which is generally preceded by serological testing. The test now recommended for use in primary care is the tissue transglutaminase antibody test; it has a sensitivity of about 95% and a specificity approaching 100% and is now replacing the previously used endomysial antibody test.[11 12] In patients with IgA deficiency IgG transglutaminase antibodies should be checked, particularly if the biopsy result is positive.

Clinicians should consider conducting a preliminary serological test in patients with symptoms suggestive of

KEY POINTS

Coeliac disease is relatively common in general Western populations

Patients at high risk include those with iron deficiency anaemia, first degree relatives with coeliac disease, autoimmune conditions such as diabetes mellitus and autoimmune thyroid disease, and infertility

The condition is underdiagnosed, partly because of a range of atypical and potentially confusing clinical presentations

Tissue transglutaminase antibody testing and duodenal biopsy represent the optimal investigations for diagnosis

Adherence to a gluten-free diet restores biochemical and nutritional status and protects against many of the complications of coeliac disease

coeliac disease, and testing for coeliac disease should form part of the investigations for patients thought to have irritable bowel syndrome.[13] Weight loss occurs in coeliac disease, although this can be associated with more serious gastrointestinal problems such as inflammatory bowel disease and cancer. Some patients with coeliac disease are of normal weight or even obese,[14] and the condition may develop in older patients.[15] Dermatitis herpetiformis is a skin manifestation of coeliac disease or gluten intolerance.

How is it managed?

The cornerstone of management is the exclusion of gluten from the diet, which restores the integrity of the villous lining of the small intestine, permits absorption of nutrients, and restores most aspects of health, as well as protecting against the development of malignancy.[10] Some patients with coeliac disease have relatively mild symptoms, but although the restrictions of a gluten-free diet may have less appeal, and the consequences of non-adherence are not known, dietary adherence is still recommended.

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A PATIENT'S JOURNEY

Coeliac disease and a gluten-free diet

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A woman who had symptoms of coeliac disease from childhood describes how her life improved markedly once the disease was diagnosed in her 20s

The day my physician gave me the most powerful tool that doctors have—a diagnosis—marked the point when my journey living with coeliac disease began. For years I had had chronic abdominal pain and vague gastrointestinal symptoms. As a child, I never slept on my stomach because it was always sore. When I was a teenager, my symptoms worsened (possibly related to an increasing reliance on pizzas). I was generally unwell and developed a chronic iron deficiency anaemia that was refractory to oral iron supplements. My physicians—general practitioners and gastroenterologists—would take a history then prescribe a therapeutic dose of barium (to both ends) to reassure themselves that they had not missed a diagnosis of inflammatory bowel disease.

As the barium cycle was repeated, I realised that medicine is the art not of making a diagnosis but of ruling one out, with special attention to the rare and deadly (I was once screened for acute intermittent porphyria). Once all medical diagnoses had been ruled out, two areas remained—functional and psychiatric disorders. My insistence that my symptoms did not fit

A DOCTOR'S PERSPECTIVE

Our understanding of coeliac disease has changed significantly. Coeliac disease is now known to be not simply a gastrointestinal malabsorptive disorder but rather a complex, multisystem autoimmune disorder. Delays in diagnosis of coeliac disease remain common, as many patients do not present with typical gastrointestinal symptoms of diarrhoea and abdominal pain. Instead, they present with atypical manifestations involving, for example, the haematological, rheumatological, or neurological systems, leading to a plethora of misdiagnoses. For coeliac disease, these atypical manifestations are now typical. Early diagnosis is important as people with untreated or poorly treated coeliac disease are at risk of developing serious complications, including osteoporosis and intestinal cancer. A gluten-free diet provides an effective treatment for coeliac disease. However, this diet is complex, costly, and challenging.

Mohsin Rashid, gastroenterologist

with a functional disorder only seemed to increase my physicians' conviction that I had a psychiatric disorder. As my symptoms persisted, frustration was mutual, and I became a "heartsink patient."

On the road to a diagnosis

My inspiration for considering the diagnosis of coeliac disease came when I was studying in Scotland. At that time, cheap bread and breakfast cereals had become my staples, and my symptoms had worsened. During a biochemistry lesson on coeliac disease I became intrigued by the similarity to my own symptoms. As a test, I switched from wheat based to rice based cereals, which had an immediate, though incomplete, effect.

Several months later when I saw my physician in Canada coeliac disease was added to the differential diagnosis. He recommended a diet containing gluten before yet another endoscopy to search for a diagnosis based on a biopsy. The diet brought a rapid return of my symptoms and wreaked havoc on my life. Faced with the choice of dropping courses and extending my degree programme or continuing a gluten-free diet without a biopsy, I chose to continue with my degree.

Undeterred, my physician recommended a wheat-free diet, for perhaps I had wheat sensitivity, not coeliac disease. After a single slice of wheat-free rye bread, my intestines challenged this hypothesis as well. Given that I would adhere to a gluten-free diet whether I was gluten sensitive or had coeliac disease, my physician eventually agreed that a biopsy would not change the management of my condition. He also could not deny that my anaemia of five years' duration had resolved with a gluten-free diet, and he diagnosed coeliac disease.

Life with coeliac disease begins

My physician advised that "all" I had to do was eliminate gluten from my diet. He also suggested that I join a support group. Meeting members of Coeliac UK and the Canadian Celiac Association has been an invaluable experience. I have discovered that I am not alone. Increased awareness, lobbying efforts, and more interest in the gluten-free diet are also starting to have an effect as more gluten-free products of a higher quality are becoming available in stores and restaurants.

Gluten is a protein in wheat, rye, barley, and triticale (a cross between wheat and rye) and is a contaminant introduced during the processing of most oats. I soon learned that reading labels is an art as wheat can masquerade as "durum," "semolina," or simply "starch." Everywhere I looked, there was hidden gluten. How could I know that most soy sauce is made out of wheat? I had to learn about how food is processed and cooked, to think about the ingredients and whether they might contain gluten. Grocery shopping took hours, as I had to read every label and often had to go to specialty food stores. Eating at restaurants introduced an added layer of complexity—and risk.

Gradually, I learnt about rice (I have seven varieties in my pantry, excluding rice noodles) and that by lunchtime, yesterday evening's leftovers are more palatable than sandwiches made of gluten-free bread. Baking was another matter, although fortunately, I enjoy cooking. Gluten is not an inert component of cereals. It functions as a binding agent and helps cakes and cookies to rise and retain moisture. Many of my kitchen experiments have produced flat, dry, crumbly products that bear no resemblance to their counterparts that contain gluten. Nearly a decade on, I have perfected a magic combination of rice flour, potato starch, tapioca starch, and xanthan gum (a binding agent), which reliably produces baked goods that earn compliments even from people who usually eat food made from wheat flour.

Coeliac disease has changed not only my life and my relationship to food, but also my relationship to my family. Whereas my parents felt helpless—suddenly feeling unable to feed their daughter safely when she came home—my grandmother has risen to the challenge. Her gluten-free bread rises and is the envy of my colleagues. I have to fight the rest of the family for her gluten-free Yorkshire pudding. For some, my gluten-free diet is overwhelming. They are afraid to

COMMON PRESENTATIONS OF COELIAC DISEASE

- Iron deficiency anaemia
- Osteoporosis
- Short stature
- Recurrent oral ulcers
- Dental enamel defects
- Chronic fatigue
- Increased liver enzymes
- Infertility

This is one of a series of occasional articles by patients about their experiences that offer lessons to doctors. The *BMJ* welcomes contributions to the series. Please contact Peter Lapsley (plapsley@bmj.com) for guidance.

WEB BASED RESOURCES FOR PATIENTS AND HEALTH PROFESSIONALS

- Coeliac UK (www.coeliac.org.uk)—A leading British support organisation for people with the disease
- Canadian Celiac Association (www.celiac.ca)—Non-profit, charitable organisation providing services and support to people with coeliac disease and dermatitis herpetiformis (information available in English and French)
- Canadian Celiac Association Resource Guide (www.celiacguide.org)—Information on coeliac disease, with printable pamphlets and links to other websites
- Celiac Stories (www.celiacstories.ca)—A book of narratives (in each chapter) by individuals with coeliac disease describing their road to diagnosis

feed me for fear of making me sick. Others are very adept at reading labels and discovering new products, sometimes triumphantly posting them around the world.

For me, the diagnosis of coeliac disease was a life transforming gift. My days of being in pain and frightened of the unknown were over. I had a condition that had a name. Even though it is at times financially and socially difficult, adhering to a gluten-free diet is certainly worth while. On the rare occasion when I do inadvertently ingest gluten, I am no longer writhing in pain wondering what caused it and whether it will end. Instead, I can usually identify the source of gluten that triggered the episode. Although I wonder how I lived so many years feeling constantly ill, I also take comfort now, knowing that these symptoms are temporary and I will soon return to my healthy, happy, gluten-free life.

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Competing interests: MR is a member of the Professional Advisory Board of the non-profit, charitable organisation Canadian Celiac Association.
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A PATIENT'S JOURNEY

Coeliac disease in childhood

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An 11 year old boy explains how coeliac disease affects him, and his parents tell of the obstacles to the diagnosis

Henry's perspective

I don't remember ever not having coeliac disease—my earliest memories of it are when I was in hospital and the staff gave me Jaffa cakes to eat before I was diagnosed and when I played with Lego while I was having a blood transfusion.

My nursery report says I said to my teacher after returning from being diagnosed, "I can't eat cup cakes anymore" so I guess I understood what had happened.

It is annoying not being able to eat cake and other foods at birthday parties and other celebrations, but most of the time I don't feel any different from other children. My primary school won't cook me a gluten-free lunch and has stopped letting me take a flask of hot soup in my lunch box, which I miss. I hope by the time I am older there will be more gluten-free foods like doughnuts. Bakeries smell so good. I often take my own food to barbecues, parties, aeroplanes, etc.

I am very rarely unwell but do get tummy aches every now and then. It is difficult to tell if this is because of my diet or just a tummy ache. The one thing I do really hate about having coeliac disease is the blood tests. I am not sure I will ever get used to them.

My aunt and two of my cousins also have coeliac disease, and they help my mum a lot, giving advice on what gluten-free foods are best and things like getting a breadmaker because the bread from them is really nice.

Many people don't understand what coeliac disease is. They think it's an allergy that I will maybe outgrow or don't even know what gluten is. I don't tell people unless I have to as I don't feel there is really anything wrong with me. I know there are lots of really sick children who spend a long time in hospital and can't do the stuff I do. If you have to have a disease this is an OK one.

I see Dr Ball at King's College Hospital every six months to check I am healthy and he is always very kind to me. He asks me questions about how I am getting on, school, all sorts of stuff.

I am a member of Coeliac UK (my mum joined) and they send a magazine, which has some useful information in it and stories of how people are diagnosed and how they feel. My mum uses the food directory sometimes to check if certain things are OK for me to eat.

She says I was a different boy before I was diagnosed—short, extremely pale, very whiny, often sick, very skinny but with a big round belly and I wouldn't eat anything. Now I am the second tallest in my class, love playing rugby, swim for my school, and eat masses (gluten-free of course!).

TWO PHYSICIANS' PERSPECTIVE

Henry provides a remarkable insight into the hindrances that coeliac disease present and the changes his family have made to ensure that he leads an active life. His case illustrates the importance of engaging the entire family in minimising the impact of diagnoses such as coeliac disease that require lifestyle changes. Additionally, Henry reminds those of us who are not exclusively paediatricians of the understanding that an 11 year old boy can have of a chronic illness and its treatment.

When Henry first attended our clinic (aged 3 years 8 months), he was pale and looked unwell, with a characteristically distended abdomen and small buttocks. His growth charts showed that he had moved from the 91st to the 50th and 25th centiles for height and weight respectively. Despite a family history of coeliac disease, his parents had struggled to convince healthcare professionals that anything was wrong. Finding that his haemoglobin level was so low (54 g/l; mean cell volume 55.2 fl) was quite a shock, and he was admitted for blood transfusion. Subsequent endoscopic jejunal biopsy and positive anti-tissue transglutaminase antibodies confirmed the diagnosis.

Coeliac disease can easily be missed on clinical grounds as symptoms may be quite subtle and severe anaemia is unusual as the presenting feature in a child. Coeliac disease should be considered in any child with recurrent abdominal symptoms that persist with no other explanation; it can now be reliably excluded in most cases with tissue transglutaminase antibody screening.

Faisal R Ali and Colin Ball, King's College Hospital, London

The parents' perspective

Henry was not 100% fit from about the age of 1. He was not thriving, he vomited often, was very pale, had bouts of being very whiny and tired, and wouldn't eat much. We just knew something was not right. We went to the general practitioner on several occasions but were told he was fine, which of course is what you want to hear, so we didn't argue.

However, with a family history of coeliac disease (Henry's aunt and cousin have it) and Henry's health continuing to decline, we just kept coming back to thinking that was what was wrong with Henry. Eventually we were begrudgingly referred to the paediatric team at King's College Hospital, London.

There stood Henry aged three and a half with his jeans meant for an 18 month old infant hanging off him, and Dr Ball said, "I think it's very obvious what the matter is." We have not looked back since.

That said, we did feel cross and let down by the various general practitioners we saw for not at least picking up Henry's extreme anaemia—caused by the coeliac disease.

Managing Henry's diet is not difficult; other than having his own bread, pasta, and biscuits, we all eat the same. We get the staples on prescription. Our surgery is very accommodating and has never questioned anything we ask for or the quantity. In the years since Henry was diagnosed gluten-free foods have come on so much, and all the supermarkets sell a wide range. They can also supply a list of all the gluten-free products they stock. It is a very healthy diet; not being able to eat most ready made products and fast food isn't a bad thing.

Of course there are times when Henry has to make do as no food options are available, but he is very relaxed about his situation and rarely complains. It is irritating that schools cater for various diets relating to personal choice and religion but not those required by a medical condition. People often do not understand the significance of the disease and lump it in with allergies or dietary choice.

Henry is a member of the charity Coeliac UK (www.coeliac.co.uk), whose quarterly magazine is very useful and keeps us up to date with new products, changes in research, case studies, recipes, and so on; Coeliac UK also works for people with dermatitis herpetiformis.

Henry's other cousin was diagnosed with coeliac disease last year, at the age of 18, so we are keeping a close eye on Henry's sister.

We rarely consider Henry to be unwell. He is as bright, healthy, and energetic as any child could be.

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Transnasal gastroscopy—lesson from a plumber

Transnasal oesophagogastroduodenoscopy (OGD) is a new technique for upper gastrointestinal endoscopy using a thinner endoscope passed through the nose rather than the traditional route through the mouth. These endoscopes are about 6 mm in diameter, similar to a bronchoscope. We have been using this method since July 2007. Because of its novelty, we organised a demonstration of the procedure for the local primary care physicians and other practitioners interested in endoscopy. We invited patients who have had previous gastroscopies orally and were on our follow-up list mainly for surveillance of Barrett's oesophagus.

I performed transnasal OGD on a patient who had previously undergone oral endoscopy three times. Those in the lecture room watched by video link. The procedure went well, and the patient said he found it less distressing than the oral method. He then said, "I am a plumber and want to give you some advice. I am used to passing similar tubes in my practice, and I think that if you rotate the tube in a semicircular way while passing it through the nose you will find it much easier to introduce." I could hear the audience laughing and thanked him for the advice.

Since then all the endoscopists in our unit have been practising the semicircular rotation of the endoscope as they introduce it through the nose. We feel it is easier to introduce and more comfortable for the patient. This shows that we can always learn from our patients who give sensible advice.

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