15.10.3 Coeliac disease 2884

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section 15 Gastroenterological disorders 2884 15.10.3 Coeliac disease Peter D. Mooney and David S. Sanders ESSENTIALS Coeliac disease is a common disorder of the small intestine in which storage proteins in dietary wheat, rye, and barley (gliadin, secalins, and hordeins, usually referred to as ‘gluten’) induce an autoimmune enteropathy characterized by villous atrophy in genetically suscep- tible individuals. The prevalence of coeliac disease is 0.2 to 2% in populations with high consumption of gluten-containing foods. Females are more commonly affected than males (1.5–2:1), with typical presentation now in the forties. ‘Classical’ coeliac disease presented in childhood with malabsorption, but this is now rare. ‘Nonclassical’ presentations are now the norm, and highly variable, ranging from nonspecific ab- dominal symptoms to the consequences of malabsorption (e.g. an- aemia, osteoporosis) to nongastrointestinal symptoms (e.g. ataxia, dermatitis herpetiformis), and many have no symptoms at all. Diagnosis is made by serological testing for (usually) antitissue transglutaminase antibodies, which have excellent sensitivity and specificity, with confirmation by duodenal biopsy. Treatment is with a gluten-free diet, which constitutes a major chal- lenge for some people. Most patients (but not all) can eat pure oats. Complications include lymphoma, osteoporosis, and other auto- immune conditions. Patients have a normal life expectancy, although quality of life is adversely affected. Introduction Coeliac disease was first described in a mainly paediatric population with failure to thrive and symptoms of malabsorption. Several ap parently successful treatments such a ‘banana diet’ and the ‘Dutch mussel diet’ were described before its pathogenesis was elucidated. By the 1950s, it became clear that these treatments were effective because of the inadvertent exclusion of gluten from the diet. Willem Dicke, a Dutch paediatrician, identified that wheat and subsequently gluten was the trigger for coeliac disease. Subsequent work identi fied villous atrophy as the characteristic small-bowel lesion and gliadin antibodies confirmed an autoimmune pathogenesis. Once considered a rare condition, it is now apparent that coeliac disease is one of the most common autoimmune conditions encountered by physicians. It is also now clear that the presentation of coeliac disease is diverse and can be easily overlooked; although the rates of diagnosis for coeliac disease have improved, up to 75% of patients remain undiagnosed. Aetiology Coeliac disease is now recognized as a common autoimmune con dition characterized by a heightened immunological response to

ingested gluten in genetically susceptible individuals. Gluten is an umbrella term for the storage proteins found in wheat (gliadin), barley (hordein), and rye (secalin). There is a strong genetic component to coeliac disease, with first- degree relatives of an index case having a 5 to 11% chance of being affected. The pairwise concordance rate for monozygotic twins is 71.4 to 75%, compared to 9.1 to 11% in dizygotic twins. Second- degree relatives also appear to be at increased risk (approximately 2.5%), although there is uncertainty as to the exact prevalence in this population. The genetic heritage is further strengthened by the association with specific human leucocyte antigens (HLAs), with 90 to 95% of patients with coeliac disease carrying genes encoding HLA DQ2 (encoded by DQA1*05 and DQB1*02). The vast majority of the remainder carry the HLA DQ8 (encoded by DQA1*03 and DQB1*0302) haplotype. Other HLA associations have been re ported, such as the half DQ2 heterodimer usually in the form DR7 (DQB1*0201), but the true significance of these rarer HLA types is not clear. The appropriate HLA is required to develop coeliac disease. However, up to 35% of Western populations carry an HLA type compatible with coeliac disease, yet only 2 to 5% of these patient go on to develop the condition. Other genetic factors, mainly involved in T-cell regulation and inflammation, encoded by single nucleotide polymorphisms have been identified, although the risk associated with these genetic variations is small. Other environmental factors such as gastrointestinal infection, the composition of an individual's microbiome, or timing of gluten introduction in childhood have all been proposed, but the exact mechanism of the onset of coeliac dis ease is yet to be fully elucidated. Epidemiology Until the 1980s, coeliac disease was considered a rare condition, usually presenting in childhood with estimated prevalence rates of 1 in 4000 to 8000. However, data from large-scale screening studies in both adult and paediatric populations suggests that the estimated prevalence of coeliac disease in the United States of America and European populations ranges between 0.2 and 1.2%. Furthermore, some studies—particularly from Scandinavia—suggest that the true incidence of coeliac disease, along with other autoimmune condi tions, may be increasing. In common with other autoimmune con ditions, females are more commonly affected than males (1.5–2:1) Historically, coeliac disease was considered a disease of mainly Caucasian populations, but it is now apparent that coeliac disease is a global problem. Coeliac disease is more prevalent in areas where wheat is a staple crop, and areas such as Northern Africa and the Middle East have also demonstrated a prevalence similar to Western populations. However, clinicians from both the Indian subcontinent and China are now increasingly recognizing patients with coeliac disease. There are several hypotheses to explain this increasing prevalence, including improved detection and an increased con sumption of wheat in these ethnic groups as their diet becomes more westernized, or an increasing trend in all autoimmune diseases. A reduction in the burden of infective illness in these areas as they develop may also be having an impact. Some areas, however, do have a significantly lower prevalence of coeliac disease, for example, ethnic groups such as black Sahawari

15.10.3 Coeliac disease 2885 populations from sub-Saharan Africa and populations from the Far East appear to be at reduced risk. This may be in part due to reliance on other staple carbohydrate crops such as maize and rice, but there also appears to be a reduced prevalence of the HLA types associated with coeliac disease in these areas. Historical meta-analyses estimated that for every patient identi fied as having coeliac disease, seven to eight individuals remained undiagnosed. Diagnostic rates for coeliac disease are increasing, with a recent United Kingdom study estimating that the prevalence of diagnosed coeliac disease is now 0.24%, up from 0.14% a decade previously. Nonetheless, this would still suggest that 75% of patients with coeliac disease remain undiagnosed. Pathology Villous atrophy was identified as the characteristic lesion associated with

coeliac disease in the 1950s. As understanding grew, it became apparent that, in the presence of a positive serological marker, vil lous atrophy was diagnostic of coeliac disease. Various histological staging systems have been proposed, but the most widely used is the Marsh classification. These criteria, first reported in 1992, placed par ticular emphasis on the importance of the presence of intraepithelial lymphocytes in diagnosis and identified ‘preinfiltrative’ lesions in the absence of villous atrophy. In these criteria, a Marsh 1 lesion is described as elevated intraepithelial lymphocytes in the absence of villous atrophy, and a Marsh 2 lesion demonstrates crypt hyperplasia and raised intraepithelial lymphocytes. Finally, the ‘destructive le sion’ (Marsh 3) requires crypt hyperplasia, raised intraepithelial lymphocytes, and villous atrophy. These criteria have undergone further modification by Oberhuber to further subdivide the de structive lesion, grading the severity of the villous atrophy on the basis of the villous height-to-crypt depth ratio, into partial villous atrophy (3a), subtotal villous atrophy (3b), and total villous atrophy (3c) (Table 15.10.3.1). For a cast-iron diagnosis of coeliac disease, the presence of a Marsh 3 lesion is required. Figure 15.10.3.1 shows normal villi and villous atrophy. Marsh 1 and 2 lesions can be associated with a diagnosis of coeliac disease. A recent study randomized patients with Marsh 1 changes and a positive endomysial antibody (EMA) to a gluten-free or gluten- containing diet. Those who continued on a gluten-containing diet demonstrated deterioration in villous architecture, with reduced villous height-to-crypt depth ratio and a persistence of symptoms. Patients in the gluten-free arm noted a significant improvement in symptoms and no change in the villous height-to-crypt depth ratio. However, it is important to recognize that Marsh 1 and 2 changes are relatively nonspecific and are also associated with many other conditions including Helicobacter pylori infection, or as a result of nonsteroidal anti-inflammatory use. Coeliac disease is only subse quently confirmed on repeat gastroscopy and biopsy in 16 to 43.3% of patients. A list of differential diagnoses for Marsh 1 and 2 lesions is shown in Box 15.10.3.1, as a result of which a diagnosis of coeliac disease cannot be made based on the presence of increased intraepithelial lymphocytes alone. In these patients, a repeat gastroscopy and duodenal biopsy is recommended following a 6-week gluten chal lenge of 10 g of gluten (equivalent to four slices of bread) per day. HLA genotyping may also be useful in this situation as the absence of the HLA DQ2 and DQ8 haplotypes has a near 100% negative predictive value. Table 15.10.3.1 Marsh–Oberhuber classification for duodenal histology in coeliac disease Marsh–Oberhuber classification Description 0 Normal 1 Raised IELs (≥25 per 100 enterocytes)—a nonspecific finding that can be seen in coeliac disease 2 Raised IELs with crypt hyperplasia—a nonspecific finding that can be seen in coeliac disease 3a Raised IELs with crypt hyperplasia and partial villous atrophy 3b Raised IELs with crypt hyperplasia and subtotal villous atrophy 3c Raised IELs with crypt hyperplasia and total villous atrophy IELs, intraepithelial lymphocytes (a) (b) Fig. 15.10.3.1 Duodenal biopsy stained with haematoxylin and eosin showing (a) normal villous architecture and (b) total villous atrophy with elevated intraepithelial lymphocytes (March 3c).

section 15 Gastroenterological disorders 2886 Pathogenesis In genetically predisposed individuals, the immune reaction that leads to enterocyte damage is initiated by exposure to toxic peptides in gluten. These toxic peptides result from the partial proteolysis of ingested gluten by gastrointestinal enzymes. To date, at least 50 T-cell stimulatory epitopes in gluten proteins have been identified, although a unique 33-mer gliadin fragment is considered the most immunogenic peptide. Importantly, this 33-mer peptide is particularly resistant to further enzymatic degradation by gastric, pancreatic, and brush border peptidases because of its high content of proline and glutamine. Exactly how these partially degraded gliadin peptides are transported through the

small-bowel epithelium remains controversial. Both a paracellular route through tight junctions and epithelial transcytosis have been de scribed. Nonetheless, toxic gluten fragments enter the lamina propria and are deamidated by the enzyme tissue transglutaminase 2 (tTG- 2). This process increases the affinity of gluten for HLA DQ2 or DQ8 molecules, some of which remains bound to tTG-2, inducing a more rigorous gluten response when presented to CD4+ T helper-1 cells by antigen presenting cells. These activated CD4+ cells initiate the release of proinflammatory cytokines interferon-γ (IFN-γ) and tumour ne crosis factor-α (TNF-α) as well as interleukin (IL)-21, which stimulates proliferation of intraepithelial lymphocytes. Additionally, B cells are stimulated by type 2 T-helper cytokines to produce the characteristic autoantibodies seen in coeliac disease. It had previously been thought that coeliac disease was a disease of the adaptive immune system, but it is now apparent that the in nate immune system also plays an important role in the initiation of coeliac disease. Gluten peptides can elicit an innate immune re sponse indirectly by stimulating secretion of IL-15 or directly in macrophages and dendritic cells via receptors such as Toll-like re ceptor 4. This drives maturation of these cells and secretion of IL-1, IL-8, TNF-α, and monocyte chemoattractant protein-1 that serve to potentiate the adaptive immune response to gluten. Subsequently, under the influence of IFN-γ, matrix metalloproteinases are secreted by myofibroblasts, resulting in mucosal remodelling and villous at rophy. This in turn leads to the clinical symptoms of coeliac disease. Clinical features ‘Classical’ and ‘nonclassical’ presentations Until relatively recently, most patients diagnosed with coeliac disease were children presenting with symptoms of malabsorption: weight loss, chronic diarrhoea, or failure to thrive. A recent consensus document on nomenclature defines this presentation as ‘classical’ coeliac disease, and it remains relatively rare. With improved detection, it is now clear that coeliac disease is common, presenting most frequently in adulthood. Furthermore, a ‘nonclassical’ presentation is now more prevalent, and this pres entation is highly variable: patients may complain of nonspecific abdominal symptoms such as abdominal pain and bloating, al tered bowel habit, or they may have no gastrointestinal symp toms and present with consequences of malabsorption such as anaemia or osteoporosis. Furthermore, coeliac disease may be paucisymptomatic or present with symptoms not clearly associ ated with enteropathy such as ataxia or abnormal liver function tests. It is possible that undiagnosed coeliac individuals may ap parently be asymptomatic, although screening studies have shown subsequent improvements in quality of life, suggesting that those affected had accepted their premorbid state as normal for them. The commonly used term ‘coeliac iceberg’ is the best way to de scribe the manifestations of coeliac disease as they are understood today (Fig. 15.10.3.2). Case finding The protean manifestations of coeliac disease mean that a case- finding approach in at-risk groups is recommended by current national and international guidelines as the best method of case de tection. The aim of case finding is to identify patients at an early stage in their disease in order to alleviate symptoms and reduce the potential risks of developing complications of coeliac disease such as lymphoma, osteoporosis, or anaemia. Testing for coeliac disease is recommended in patient groups with a prevalence of coeliac disease greater than twice that of the general population. This has been demonstrated in multiple prospective case-finding studies for patients with classical symp toms or sequelae of malabsorption such as anaemia or osteopor osis. These same studies also demonstrate increased prevalence of coeliac disease in patients with more nonspecific symptoms, al though there is significant heterogeneity in the patient populations studied. Nonspecific abdominal symptoms The best evidence for testing for nonspecific abdominal symptoms is in patients fulfilling clinical diagnostic criteria for irritable bowel syndrome. Data from meta-analyses have demonstrated that irrit able bowel syndrome-type symptoms are common in patients with coeliac disease, affecting 38% of patients. Furthermore,

the preva lence of undiagnosed coeliac disease is 4.1% in those presenting with irritable bowel syndrome. Evidence for testing in patients with other abdominal symptoms is less compelling. A systematic review of diagnostic testing for coeliac disease demonstrated a wide range of coeliac disease preva lence in patients presenting with all abdominal symptoms from 2 to 13%. A meta-analysis of patients fulfilling the criteria for func tional dyspepsia showed no significant increase in coeliac disease compared to controls. However, dyspeptic symptoms are common in patients with coeliac disease and a gluten-free diet has been shown to improve dyspeptic symptoms in newly diagnosed coeliac patients. For this reason, case finding may be justified in patients with nonspecific dyspeptic symptoms, particularly for those with intractable symptoms where no other cause is apparent. Box 15.10.3.1 Causes of intraepithelial lymphocytosis (Marsh 1 and 2) • Coeliac disease • Helicobacter pylori infection • Drugs (NSAIDs, aspirin) • Small bowel bacterial overgrowth • Giardia • Gastroenteritis • Threadworm • Crohn's disease • Sarcoidosis • Idiopathic

15.10.3 Coeliac disease 2887 Extraintestinal presentations Identification of patients with extraintestinal manifestations of coeliac disease is important to avoid missed diagnoses. Case finding is justified in these groups as there may be an improvement in the extraintestinal manifestations on a gluten-free diet as well as po tentially reducing the risk of other known coeliac complications. Examples of this already discussed include patients with anaemia or osteoporosis, who may have subclinical malabsorption. Hepatitis Cryptogenic hepatitis is the most common hepatic manifestation of coeliac disease and testing patients with abnormal liver function tests with no clear cause may be justified. A recent meta-analysis of unex plained transaminitis demonstrated a pooled prevalence of coeliac disease 4% (1–7%), with 27% (13–44%) of newly diagnosed coeliac disease patients having abnormal liver function tests. Clinicians must, however, be wary of the association between coeliac disease and other autoimmune liver disorders such as primary biliary chol angitis, primary sclerosing cholangitis, and autoimmune hepatitis. These conditions should be excluded in patients with coeliac disease and abnormal liver function tests before a diagnosis of coeliac hepa titis can be made. Transaminitis resolves spontaneously on institu tion of an effective gluten-free diet within a year in most patients. Ataxia Idiopathic sporadic ataxia is another condition where case finding is recommended in the absence of gastrointestinal symptoms. In recent years, there has been increasing awareness of gluten ataxia as a distinct clinical entity. Studies have shown gluten-related anti bodies (including antigliadin antibodies) in 11.5 to 41% of patients with idiopathic sporadic ataxia. These patients may derive benefit from a gluten-free diet even in the absence of enteropathy, although up to a third of patients with ataxia and gluten-related antibodies have villous atrophy on duodenal biopsy. The reason for the associ ation between dietary gluten exposure and ataxia remain to be fully elucidated, but there is increasing interest in the role of tTG-6 anti bodies which are expressed in the cerebellum. Fatigue Unexplained fatigue may also be an indication for case finding for coeliac disease. Fatigue is an extremely common symptom in coeliac disease affecting 7–44% of patients with reduced fatigue in patients who report good adherence to a gluten-free diet. Testing for coeliac disease in patients with unexplained fatigue has an estimated preva lence of 0.8 to 3.3%. Other reasons for increased risk As well as patients with symptoms or obvious sequelae of coeliac disease, case finding is recommended in several groups where there is an increased risk of coeliac diagnosis. This includes patients with a first-degree relative who have an estimated 10% risk of developing coeliac disease. There is also significant cross-over between other autoimmune conditions and coeliac disease, particularly type 1 dia betes mellitus and autoimmune thyroid disease. Diagnosed

coeliac disease (25%) Classical symptoms (0.2%) Nonclassical symptoms (0.8%) The Coeliac Disease Iceberg HLA status DQ2:DQ8 positive patients (Up to 100% coeliac disease; Up to 35% general population) Villous atrophy equivocal normal mucosa Undiagnosed coeliac disease (75%) Untested or subclinical Potential coeliac disease Increased intraepithelial lymphocytes ± positive serology Healthy individuals HLA DQ2 or DQ8 positive of uncertain significance Fig. 15.10.3.2 The coeliac disease iceberg. Patients above the waterline have diagnosed coeliac disease. The majority of these patients now present with nonclassical symptoms. Patients under the waterline have either subclinical coeliac disease or have not yet been tested. Patients also under the waterline include those with potential coeliac disease (positive coeliac disease serology with normal or raised intraepithelial lymphocytes without villous atrophy) and those with HLA DQ2 or DQ8 who do not have any other markers of coeliac disease. Some of these patients may go on to develop coeliac disease although the trigger for coeliac disease is not yet fully elucidated.

section 15 Gastroenterological disorders 2888 Prevalence rates for coeliac disease in type 1 diabetes range from 2 to 10%. Screening for coeliac disease is currently recommended by Diabetes UK in children and adolescents with newly diagnosed type 1 diabetes, with repeat testing if symptoms develop. There is limited evidence that a gluten-free diet in patients with diabetes and coeliac disease may improve glycaemic control and reduce the risk of microvascular complications of diabetes. Screening for coeliac disease in patients with autoimmune thyroid disease is less clear cut, but may be recommended, particularly if large doses of replacement thyroxine are required, which may in dicate malabsorption of thyroxine. Estimated prevalence of coeliac disease is up to 7% in selected populations with autoimmune thyroid disease. There is also a well-documented link between coeliac disease and the congenital genetic defects of Turner’s syndrome and Down’s syndrome. The prevalence of coeliac disease in these pa tients ranges from 4.7 to 6.4% for Turner’s syndrome and 0.3 to 4.6% for Down’s syndrome. The reasons for these associations are not known, but clinicians should be aware of this potential association and have a low threshold for coeliac testing in these groups, particularly in children where coeliac disease as well as their genetic disorder may be contributing to growth retardation. Table 15.10.3.2 summarizes the patient groups where testing is currently recommended. Differential diagnosis The clinical presentation of coeliac disease is diverse and fre quently nonspecific, hence the potential differential diagnosis for coeliac disease is also broad. There are also differential diagnoses to consider for causes of villous atrophy, and these are particu larly important to consider in patients with villous atrophy in the absence of a positive serological test. In this cohort of patients, coeliac disease remains the most common cause, accounting for 28 to 44% of cases. A comprehensive list of the causes of small-bowel villous atrophy is shown in Table 15.10.3.3. The use of HLA genotyping can be useful in cases of seronega tive villous atrophy if it proves negative, but a thorough approach to investigating these patients to consider alternative diagnoses is required in all cases. Corroborative evidence such as a family history, evidence of functional hyposplenism, and response to a gluten-free diet should be considered. Adequate gluten intake at the time of duodenal biopsy also needs to be ensured as a reduced- gluten diet may be sufficient to normalize serology but insuffi cient to allow healing of the duodenal mucosa. In some cases, a gluten challenge may be appropriate. Historical evidence suggests that endomysial antibody may be negative in early disease or with lesser degrees of villous atrophy (Box 15.10.3.2). It must also be noted that wheat or gluten can induce symptoms in noncoeliac patients and self-reported sensitivity is not necessarily a result of coeliac disease. Table 15.10.3.2 Patient groups for whom case finding is advocated Gastrointestinal symptoms Estimated prevalence of coeliac disease (%)

Abdominal pain 1.6–3.2 Diarrhoea 3.9–5.4 Irritable bowel syndrome 4.1 Steatorrhoea 3.9–5.4 Unexplained abdominal symptoms 2–13 Potential malabsorption Anaemia 2.3–15 Osteoporosis or osteopenia 0–3 Vitamin D, ferritin, folate, vitamin
B12 deficiency (No prevalence data available) Weight loss 2.7–3.9 Groups with an increased risk of coeliac disease First-degree relative with coeliac disease 5–11 Type 1 diabetes 0.3–11.3 Autoimmune thyroid disease 2.9–3.3 Down's syndrome 0.3–4.6 Turner's syndrome 4.6–6.4 Others Prolonged fatigue (tired all the time) 0.8–3.3 Idiopathic sporadic ataxia 3.8–13.7 Unexplained subfertility 2.7–3.0 Elevated serum transaminases without other cause 4 Table 15.10.3.3 Causes of villous atrophy and negative coeliac serology Cause Condition Coeliac disease Infective Giardiasis Helicobacter pylori Helminth infestation HIV enteropathy Norovirus (chronic infection) Small intestinal bacterial overgrowth (SIBO) Tuberculosis Whipple's disease Immunological Autoimmune enteropathy Common variable immunodeficiency (CVID) Eosinophilic enteritis Graft-versus-host disease Drugs Nonsteroidal anti-inflammatory drug (NSAIDs) Olmesartan Miscellaneous Amyloidosis Collagenous sprue Crohn's disease Cryptogenic multifocal ulcerous stenosing enteritis (CMUSE) Ischaemic enteritis Lymphoma Mastocytosis Peptic duodenitis Radiation enteritis Tropical sprue Zollinger–Ellison syndrome

15.10.3 Coeliac disease 2889 Clinical investigation Serology Improved serological testing has been one of the main reasons for the increased awareness and diagnosis of coeliac disease, and ser ology should be the initial screening test of choice. Modern sero logical tests have excellent sensitivity and specificity in appropriate patient groups. Blood tests are much less invasive than a small-bowel biopsy and hence have increased the uptake of testing for coeliac disease, greatly improving our selection of appropriate patients for duodenal biopsy. Gliadin antibodies were the first widely available serological test, but these lacked the required sensitivity and specificity: they may be present in up to 12% of the general population and absent in cases of coeliac disease. For many years, therefore, the suspicion of coeliac disease was largely clinical. In the 1980s, endomysial antibody (EMA) testing was first de scribed and soon became commercially available. EMA tests detect IgA antibodies to antigens by direct immunofluorescence in monkey oesophagus or human umbilical tissue. Their drawbacks include the requirement for the development of multiple plates, which is labour intensive; the substrates are limited and are expensive, and the results are subjective. Subsequently, the enzyme tissue transglutaminase (tTG) was identified within the small-bowel endomysium as the key autoantigen in coeliac disease. Enzyme-linked immunosorbent as says (ELISAs) were subsequently developed, initially with guinea pig and then human recombinant tTG antigen. tTG assays are gener ally cheaper than EMA and may be more reliable as they provide a quantitative result. In general, tTG assays are more sensitive but less specific than EMA, particularly at low titres, but it is a weakness that there are a large number of commercially available tests, with their accuracy variable between manufacturers. Although gliadin antibodies have been superseded by EMA and tTG, more recently antideamidated gliadin peptide (DGP) as says have become available. As previously discussed, deamidated gliadin fragments have a higher affinity for HLA DQ2/DQ8 mol ecules and as a result DGP antibodies would be expected to have superior sensitivity and specificity compared to standard gliadin antibodies. Early studies of DGP antibodies showed high diag nostic performance, equivalent to conventional tests, with both IgA and IgG isotypes appearing highly sensitive and specific. However, meta-analysis in 2010 showed that although the IgA-based assay performed well, there was no diagnostic advantage conferred by the use of DGP. With the advent of accurate coeliac serology, the focus of case finding for coeliac disease has rightly focused on increased sero logical testing in at-risk groups. However,

it must be noted that the sensitivity of even the best assays of tTG, EMA, and DGP are not 100% and cases of seronegative coeliac disease do exist, particularly when a single serological test is used in the diagnostic algorithm. One common reason for seronegative coeliac disease may be IgA de ficiency. Selective IgA deficiency is present in 2% of coeliac patients (compared to around 0.2% of the general population) and may cause false-negative serology as standard tests are usually based on the IgA subclass of antibody. Immunoglobulin levels should be checked alongside standard serology and duodenal biopsy is recommended in IgA-deficient patients. It is important to recognize, however, that IgA deficiency is not the only cause of seronegative coeliac disease: the mean rate of tTG negative coeliac disease was 7% in 11 studies reported in a recent meta-analysis of IgA-tTG. For this reason a duodenal biopsy may still be warranted in patients with a high suspicion of coeliac disease but negative serology, particularly those with unexplained anaemia, diarrhoea, or weight loss. Furthermore, first-degree relatives of an index case, patients on immunosuppression, and those with early disease or refractory disease at diagnosis may also be at risk of sero negative coeliac disease. Endoscopy and duodenal biopsy Most coeliac patients are currently diagnosed on the basis of posi tive coeliac serology and a duodenal biopsy to confirm villous at rophy. Figure 15.10.3.3 shows magnification endoscopy of normal Box 15.10.3.2 Causes of seronegative coeliac disease • IgA deficiency • Self-imposed gluten-free or reduced-gluten diet • Steroid or immunosuppressant use • Lesser degrees of villous atrophy • Refractory coeliac disease • Early diagnosis • Family history with first- or second-degree relative (a) (b) Fig. 15.10.3.3 Magnification endoscopy showing (a) normal villi and (b) total villous atrophy.

section 15 Gastroenterological disorders 2890 villi and total villous atrophy. However, the 2012 European Society for Paediatric Gastroenterology, Hepatology and Nutrition guide lines suggest an algorithm for avoiding biopsy in a few paediatric patients with significant symptoms, very high antibody titres (tTG

> 10 × level of normal and positive EMA) and an appropriate genetic phenotype. Although this is understandable for a paediatric popula tion where endoscopic evaluation may require a general anaesthetic, duodenal biopsy to confirm diagnosis is still required in adult popu lations for several reasons. Firstly, although the performance of serology appears to be ex cellent, the studies into each test are invariably performed in high- prevalence populations. This ascertainment bias overestimates the performance of a diagnostic test. As we lower the threshold for serological testing, the disease prevalence within the tested popula tion will fall, and as a result the positive predictive value of the test will suffer; for example, in a recent cohort of 2000 patients with a prevalence of coeliac disease of 3.9%, the positive predictive value of tTG was only 28.6% despite sensitivity and specificity of greater than 90%. Secondly, a clinical response to a gluten-free diet is not diag nostic of coeliac disease, particularly in patients with irritable bowel syndrome symptoms which may be gluten sensitive in the absence of coeliac disease and Crohn’s disease that can be pseudo- improved by a gluten-free diet. The presence of villous atrophy on a duodenal biopsy gives concrete evidence of coeliac disease which is helpful for counselling patients, ensuring prescription of gluten- free foods, and assessing

improvement on a gluten-free diet. If patients do not respond to a gluten-free diet as expected, any un certainty in the initial diagnosis can make subsequent evaluation problematic. Finally, the diagnosis of coeliac disease has implications for first- degree relatives of an index case who have a 10% chance of diag nosis. It is difficult to recommend screening of relatives based on serology alone. Historical teaching suggested avoiding the duodenal bulb for bi opsy over concerns about confounding factors such as peptic duo denitis, Brunner's glands, and gastric heterotopia. Recent evidence, however, suggests that interpretation of duodenal bulb biopsies is feasible and that in up to 10% of patients with coeliac disease, vil lous atrophy may be confined to the duodenal bulb. Current inter national guidelines therefore recommend taking duodenal bulb biopsies as well as those from the distal duodenum in cases of sus pected coeliac disease. Management At present, the only proven treatment for coeliac disease is a gluten- free diet. This should result in the autoimmune cascade being turned off and restoration of normal villous architecture. However, the rate of healing of the small intestinal mucosa is highly variable with 35 to 66% of patients still having persistent villous at 2 years fol lowing diagnosis. Whether this is due to the natural rate of healing or persistent gluten exposure is not clear, but it is known that small amounts of gluten exposure can prevent mucosal healing and inten sive dietetic input may help mucosal recovery. The commonly used ways to assess adherence include patient- reported adherence, dietetic assessment, a validated adherence questionnaire, coeliac serology, or a repeat duodenal biopsy. None of these methods is without its drawbacks, but persistent villous atrophy on duodenal biopsy may have prognostic significance as it is associated with a higher incidence of non-Hodgkin's lymphoma and increased hip fracture risk. Patients should have access to a dietician to assess adherence in conjunction with repeat serology and gastroenterology input to assess for resolution of symptoms. Repeat duodenal biopsy should probably be reserved for patients with elevated serological markers, persistent symptoms, or nu trient deficiencies. Prognosis Older estimates of mortality in coeliac disease suggested a reduced life expectancy and increased risk of malignancy, but as the in creased prevalence of coeliac disease has become apparent, contem porary studies suggest that patients have a normal life expectancy and may be at reduced risk of cardiovascular disease. Quality of life may, however, be adversely affected by coeliac dis ease diagnosis. Studies looking at patients with coeliac disease on a gluten-free diet have shown this group to have a lower quality of life in both the short and long term compared to the general popula tion and patients with other chronic gastrointestinal conditions such as ulcerative colitis. Appropriate investigation and management of symptoms as well as support with a gluten-free diet may improve quality of life. Complications Lymphoma Historical estimates for lymphoma suggested a relative risk of 40 to 100 times that of the general population, but as detection of coeliac disease has improved, contemporary studies have shown only a modest risk for malignancy. A recent meta-analysis demonstrated a fourfold increased risk of non-Hodgkin

> lymphoma (including enteropathy-associated T-cell lymphoma) compared to the general population, with an estimated 1 in 2000 coeliac patients developing lymphoma per year. Evidence for the protective effect of a gluten-free diet against the development of lymphoma is circumstantial. Enteropathy-associated T-cell lymphoma is frequently diagnosed at the same time of or soon after the diagnosis of coeliac disease, before the patient can start an effective gluten-free diet. A recent large population- based study showed that persistent villous atrophy, which is more common in patients with poor adherence to a gluten-free diet, was associated with an increased risk of lymphoma with a hazard ratio of 2.26 compared to those who demonstrated mucosal healing on follow-up biopsy. Osteoporosis Osteoporosis is highly prevalent among coeliac sufferers, with 32 to 80% having reduced bone mineral density, and a strict gluten-free

15.10.3 Coeliac disease 2891 diet has been shown to improve bone mineral density. In a re cent study of 95 patients with newly diagnosed coeliac disease, there was a significant improvement in the mean bone mineral density independent of other risk factors and the effect of exercise. However, patients with silent or subclinical disease may not have metabolic bone disease to the same extent as those with classical coeliac disease. Current national guidelines recommend that patients are given lifestyle advice to ensure adequate calcium intake, avoid smoking and excess alcohol, and advice on adherence to a strict gluten-free diet. Baseline bloods for calcium, vitamin D, and alkaline phos phatase should be requested. Baseline DXA (dual-energy X-ray ab sorptiometry) to assess bone mineral density at diagnosis should be reserved for those with abnormal bloods or those at high risk of osteoporosis, which include those over the age of 70, recent weight loss of greater than 10%, a body mass index of less than 20 kg/m2, history of fragility fracture, and physical inactivity. A further DXA should be requested if there is a suspected fragility fracture or in cases of suspected poor adherence. Loss of bone density at a greater than expected rate should prompt measurement of vitamin D levels, a dietetic referral, consideration of repeat intestinal mucosal biopsy, and review of additional risk factors. Autoimmune disease Coexisting autoimmune conditions are common in coeliac dis ease. There is limited, conflicting evidence that a gluten-free diet may be protective in preventing development of other auto immune conditions. Circumstantial evidence comes from epi demiological studies looking at the age of diagnosis with coeliac disease compared to the numbers of patients suffering with other autoimmune conditions. In one study, older patients with coeliac disease appeared to have a significantly increased incidence of coexisting autoimmune conditions at diagnosis compared to younger coeliac patients, but two further studies showed no dif ference between age of diagnosis and levels of autoimmunity, and one demonstrated that patients younger than 36 at diagnosis ap peared to be at increased risk of other autoimmune conditions, al though those who were deemed adherent to a gluten-free diet had a significantly lower incidence of autoimmune conditions. The reasons for this paradox are unclear, but the authors concluded that patients diagnosed at an older age may have a less severe phenotype and may therefore be at reduced risk of developing other autoimmune conditions. Future developments At present, the only known treatment for coeliac disease is a gluten- free diet. Most patients with coeliac disease will have symptomatic improvement on gluten-free diet, but up to 30% will have persistent symptoms and—as previously discussed—many will have persistent villous atrophy. There may, therefore, be a clinical need for

novel treatments for coeliac disease. Several avenues are being explored, including oral enzymes to break down gluten into nontoxic frag ments, zonulin inhibitors to reduce paracellular uptake of gluten, and efforts to induce gluten tolerance through a therapeutic ‘vac cine’. A comprehensive list of potential therapeutic targets is shown in Table 15.10.3.4. FURTHER READING Aziz I, et al. (2015). Predictors for celiac disease in adult cases of duodenal intraepithelial lymphocytosis. J Clin Gastroenterol, 49, 477–82. DeGaetani M, et al. (2013). Villous atrophy and negative celiac ser ology: a diagnostic and therapeutic dilemma. Am J Gastroenterol, 108, 647–53. Ludvigsson JF, et al. (2014). Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. Gut, 63, 1210–28. Mooney PD, Hadjivassiliou M, Sanders DS (2014). Emerging drugs for coeliac disease. Expert Opin Emerg Drugs, 19, 533–44. Rubio-Tapia A, et al. (2013). ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol, 108, 656–76. Schuppan D, Junker Y, Barisani D (2009). Celiac disease from patho genesis to novel therapies. Gastroenterology, 137, 1912–33. Table 15.10.3.4 Potential therapeutic targets for coeliac disease Therapeutic target Mode of action Difficulties Gluten-specific proteases Degrade gluten into nontoxic fragments prior to entry into the duodenum Many glutenases are degraded in a gastric environment Even gastric stable glutenases in a perfect environment are unable to ensure gluten fully degraded prior to entry into the small bowel Zonulin inhibitor Regulate tight junction opening to prevent uptake of gluten into the lamina propria Not all gluten is transported through tight junctions—up to 90% of gluten may be transported through the epithelial cells via transcytosis Therapeutic ‘vaccine’ Promote T-cell gluten tolerance with repeated injections of subcutaneous gluten fragments Single drug in development only contains three of the many toxic gluten epitopes and only designed for patients with HLA DQ2 Tissue transglutaminase inhibitor Prevent deamination of gluten Tissue transglutaminase is involved in tissue homeostasis in multiple organ systems IL-15 inhibitor IL-15 secretion may be directly induced by gluten to initiate inflammatory cascade. May be crucial in the development of refractory coeliac disease Immunosuppression Therapeutic hook worm infection Suppress inflammatory immune response Only a single trial undertaken so far and has shown no benefit

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