Coeliac disease in the elderly

A quarter of all new patients diagnosed with coeliac disease are in their seventh decade or older. Coeliac disease presents with a wide range of symptoms. It is under diagnosed, especially in the elderly who may present with only iron deficiency anaemia. The mean delay in diagnosis in elderly patients is around 17 years. Early treatment is necessary to avoid potential associated complications.

Dr Michaela Birket GP registrar at The Marches Surgery, Westfield Walk, Leominster, Herefordshire, UK
Dr Atef Michael* Consultant Geriatrician and Physician, Russells Hall Hospital, Dudley, West Midlands, UK
***Email** michaela@doctors.org.uk

Coeliac disease is a relatively common condition thought to affect 0.3–1% of the population.[1] It is most common in the northern hemisphere with a prominence in Western Ireland and Sweden.[2] The true prevalence is difficult to estimate because many patients have few or no symptoms.

Although coeliac disease was previously believed to develop predominantly in children, it is now understood that the condition usually affects adults, with about 25% patients receiving their diagnosis after 60 years of age.[3]

Coeliac disease presents with a range of symptoms and signs (see box 1). Those once described as typical, including features of malabsorption such as diarrhoea and weight loss, are now considered uncommon.[4,5] As many as 80% of patients have no gastrointestinal symptoms,[6] and coeliac disease has also been reported in obese patients.[7]

Atypical symptoms and signs include iron deficiency anaemia; osteoporosis; idiopathic elevation of liver transaminases; and neurological symptoms, such as ataxia, peripheral neuropathy, mononeuritis multiplex, and myopathy.[8]

These symptoms present a diagnostic challenge to clinicians, and can easily lead to delayed or missed diagnosis.

Pathophysiology

Also known as coeliac sprue or gluten-sensitive enteropathy, coeliac disease is a malabsorption disorder of the small intestine that occurs in genetically susceptible individuals after ingestion of wheat gluten.[9]

It predominantly affects the small intestine; abnormalities are most marked proximally and decrease in severity with distal progression. In severe cases, the lesion may affect the ileum and

even the stomach and rectum.[10]

Flattening of the mucosa is variable, from mild and partial villous atrophy to total absence of villi. Classically, in untreated coeliac disease, there is a flat mucosa with no villi (total villous atrophy), but more usually there is a reduction in the normal villous height, resulting in a reduced villous height:crypt depth ratio. The thickness of the mucosa is usually increased because of crypt hyperplasia.[11]

An increased number of intra-epithelial lymphocytes is the earliest pathological change following gluten challenge, and a high count may be the only sign of gluten sensitivity.[12]

Genetics and environment

Coeliac disease is caused by both genetic and environmental factors (ie. gluten).

Genetic susceptibility is suggested by an approximately 70% concordance between monozygotic twins[13] and an association with certain type II human leukocyte antigens (HLA). The disease is associated with HLA DQ2 (HLA-DQA1*05-DQB1*02) in up to 95% of patients, while most other patients have HLA DQ8 (HLA-DQA1*03-DQB1*0302).[14–16]

Box 1: Symptoms, signs, and conditions that require serological testing[23]

Gastrointestinal

- Chronic or intermittent diarrhoea
- Unexplained nausea and vomiting
- Recurrent abdominal pain
- Weight loss

Neurological

- Ataxia
- Peripheral neuropathy
- Mononeuritis multiplex
- Myopathy

Other

- Iron deficiency anaemia
- Osteoporosis
- Cryptogenic hypertransaminasemia

Conditions

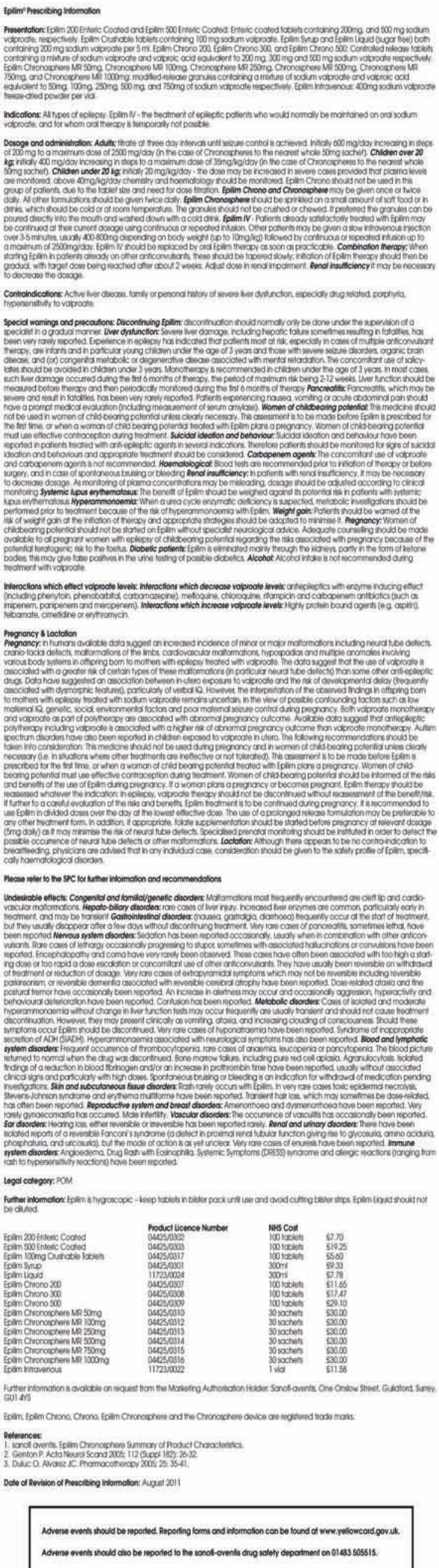
- Thyroid disease
- Irritable bowel syndrome
- Type 1 diabetes
- First-degree relatives of patients with coeliac disease

Coeliac disease is now thought to be mediated by an inappropriate T-cell driven immune response to ingested gluten[17] with a significant increase in the number of T-cell receptor +ve lymphocytes in the surface epithelium of the small intestine. The interplay between genetic (both HLA and other types) and environmental factors leads to the intestinal damage typical of the disease.[17]

Diagnosis

The gold standard in the diagnosis of coeliac disease is histology of a duodenal biopsy, which usually shows characteristic changes.[4] Findings include intraepithelial lymphocytosis, crypt hyperplasia and villous atrophy. Symptomatic and histological improvement on gluten withdrawal confirms the diagnosis.[18]

A positive anti-endomysial antibody (EMA) test identifies coeliac disease with a sensitivity of almost 90% and specificity of 100%.[19] Tissue anti-transglutaminase antibodies (tTGA) are less sensitive than anti-endomysial antibodies; however, the two tests combined identify coeliac disease with a sensitivity of over 95%.[20] As EMA and tTGA are IgA antibodies, these will be falsely negative in IgA deficiency. This is 10–15 times more common in coeliac disease patients than in healthy individuals. Overall, 2–3% of patients with gluten-sensitive enteropathy have selective IgA deficiency. Because these patients may not produce the IgA antibodies required to



Epilim® Prescribing Information

Presentation: Epilim 200 Enteric Coated and Epilim 500 Enteric Coated: Enteric coated tablets containing 200mg, and 500 mg sodium valproate, respectively. Epilim Crushable tablets containing 100 mg sodium valproate. Epilim Syrup and Epilim Liquid (sugar free) both containing 200 mg sodium valproate per 5 ml. Epilim Chrono 200, Epilim Chrono 300, and Epilim Chrono 500: Controlled release tablets containing a mixture of sodium valproate and valproic acid equivalent to 200 mg, 300 mg and 500 mg sodium valproate respectively. Epilim Chronosphere MR 50mg, Chronosphere MR 100mg, Chronosphere MR 250mg, Chronosphere MR 500mg, Chronosphere MR 750mg, and Chronosphere MR 1000mg: modified-release granules containing a mixture of sodium valproate and valproic acid equivalent to 50mg, 100mg, 250mg, 500 mg, and 750mg of sodium valproate respectively. Epilim Intravenous: 400mg sodium valproate freeze-dried powder per vial.

Indications: All types of epilepsy. Epilim IV - the treatment of epileptic patients who would normally be maintained on oral sodium valproate, and for whom oral therapy is temporarily not possible.

Dosage and administration: ***Adults:*** titrate at three day intervals until seizure control is achieved. Initially 600 mg/day increasing in steps of 200 mg to a maximum dose of 2500 mg/day (in the case of Chronospheres to the nearest whole 50mg sachet). ***Children over 20 kg:*** initially 400 mg/day increasing in steps to a maximum dose of 35mg/kg/day (in the case of Chronospheres to the nearest whole 50mg sachet). ***Children under 20 kg:*** initially 20 mg/kg/day - the dose may be increased in severe cases provided that plasma levels are monitored; above 40mg/kg/day chemistry and haematology should be monitored. Epilim Chrono should not be used in this group of patients, due to the tablet size and need for dose titration. ***Epilim Chrono and Chronosphere*** may be given once or twice daily. All other formulations should be given twice daily. ***Epilim Chronosphere*** should be sprinkled on a small amount of soft food or in drinks, which should be cold or at room temperature. The granules should not be crushed or chewed. If preferred the granules can be poured directly into the mouth and washed down with a cold drink. ***Epilim IV*** - Patients already satisfactorily treated with Epilim may be continued at their current dosage using continuous or repeated infusion. Other patients may be given a slow intravenous injection over 3-5 minutes, usually 400-800mg depending on body weight (up to 10mg/kg) followed by continuous or repeated infusion up to a maximum of 2500mg/day. Epilim IV should be replaced by oral Epilim therapy as soon as practicable. ***Combination therapy:*** When starting Epilim in patients already on other anticonvulsants, these should be tapered slowly; initiation of Epilim therapy should then be gradual, with target dose being reached after about 2 weeks. Adjust dose in renal impairment. ***Renal insufficiency*** it may be necessary to decrease the dosage.

Contraindications: Active liver disease, family or personal history of severe liver dysfunction, especially drug related, porphyria, hypersensitivity to valproate.

Special warnings and precautions: ***Discontinuing Epilim:*** discontinuation should normally only be done under the supervision of a specialist in a gradual manner. ***Liver dysfunction:*** Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and in particular young children under the age of 3 years and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation. The concomitant use of salicylates should be avoided in children under 3 years. Monotherapy is recommended in children under the age of 3 years. In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks. Liver function should be measured before therapy and then periodically monitored during the first 6 months of therapy. ***Pancreatitis:*** Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase). ***Women of childbearing potential:*** This medicine should not be used in women of child-bearing potential unless clearly necessary. This assessment is to be made before Epilim is prescribed for the first time, or when a woman of child bearing potential treated with Epilim plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment. ***Suicidal ideation and behaviour:*** Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. ***Carbapenem agents:*** The concomitant use of valproate and carbapenem agents is not recommended. ***Haematological:*** Blood tests are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding ***Renal insufficiency:*** In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring ***Systemic lupus erythematosus:*** The benefit of Epilim should be weighed against its potential risk in patients with systemic lupus erythematosus ***Hyperammonaemia:*** When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Epilim. ***Weight gain:*** Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it. ***Pregnancy:*** Women of childbearing potential should not be started on Epilim without specialist neurological advice. Adequate counselling should be made available to all pregnant women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus. ***Diabetic patients:*** Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies, this may give false positives in the urine testing of possible diabetics. ***Alcohol:*** Alcohol intake is not recommended during treatment with valproate.

Interactions which effect valproate levels: ***Interactions which decrease valproate levels:*** antiepileptics with enzyme inducing effect (including phenytoin, phenobarbitol, carbamazepine), mefloquine, chloroquine, rifampicin and carbapenem antibiotics (such as imipenem, panipenem and meropenem). ***Interactions which increase valproate levels:*** Highly protein bound agents (e.g. aspirin), felbamate, cimetidine or erythromycin.

Pregnancy & Lactation
Pregnancy: In humans available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers with epilepsy treated with valproate. The data suggest that the use of valproate is associated with a greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs. Data have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with dysmorphic features), particularly of verbal IQ. However, the interpretation of the observed findings in offspring born to mothers with epilepsy treated with sodium valproate remains uncertain, in the view of possible confounding factors such as low maternal IQ, genetic, social, environmental factors and poor maternal seizure control during pregnancy. Both valproate monotherapy and valproate as part of polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including valproate is associated with a higher risk of abnormal pregnancy outcome than valproate monotherapy. Autism spectrum disorders have also been reported in children exposed to valproate in utero. The following recommendations should be taken into consideration: This medicine should not be used during pregnancy and in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before Epilim is prescribed for the first time, or when a woman of child bearing potential treated with Epilim plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment. Women of child-bearing potential should be informed of the risks and benefits of the use of Epilim during pregnancy. If a woman plans a pregnancy or becomes pregnant, Epilim therapy should be reassessed, whenever this is indicated, in epilepsy, valproate therapy should not be discontinued without reassessment of the benefit/risk. If further to a careful evaluation of the risks and benefits, Epilim treatment is to be continued during pregnancy, it is recommended to use Epilim in divided doses over the day at the lowest effective dose. The use of a prolonged release formulation may be preferable to any other treatment form. In addition, if appropriate, folate supplementation should be started before pregnancy at relevant dosage (5mg daily) as it may minimise the risk of neural tube defects. Specialised prenatal monitoring should be instituted in order to detect the possible occurrence of neural tube defects or other malformations. ***Lactation:*** Although there appears to be no contra-indication to breastfeeding, physicians are advised that in any individual case, consideration should be given to the safety profile of Epilim, specifically haematological disorders.

Please refer to the SPC for further information and recommendations

Undesirable effects: ***Congenital and familial/genetic disorders:*** Malformations most frequently encountered are cleft lip and cardiovascular malformations. ***Hepato-biliary disorders:*** rare cases of liver injury. Increased liver enzymes are common, particularly early in treatment, and may be transient ***Gastrointestinal disorders:*** (nausea, gastralgia, diarrhoea) frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. Very rare cases of pancreatitis, sometimes lethal, have been reported ***Nervous system disorders:*** Sedation has been reported occasionally, usually when in combination with other anticonvulsants. Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants. They have usually been reversible on withdrawal of treatment or reduction of dosage. Very rare cases of extrapyramidal symptoms which may not be reversible including reversible parkinsonism, or reversible dementia associated with reversible cerebral atrophy have been reported. Dose-related ataxia and fine postural tremor have occasionally been reported. An increase in alertness may occur and occasionally aggression, hyperactivity and behavioural deterioration have been reported. Confusion has been reported. ***Metabolic disorders:*** Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur frequently are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Very rare cases of hyponatraemia have been reported. Syndrome of inappropriate secretion of ADH (SIADH). Hyperammonaemia associated with neurological symptoms has also been reported. ***Blood and lymphatic system disorders:*** Frequent occurrence of thrombocytopenia, rare cases of anaemia, leucopenia or pancytopenia. The blood picture returned to normal when the drug was discontinued. Bone marrow failure, including pure red cell aplasia, Agranulocytosis. Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations. ***Skin and subcutaneous tissue disorders:*** Rash rarely occurs with Epilim. In very rare cases toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme have been reported. Transient hair loss, which may sometimes be dose-related, has often been reported. ***Reproductive system and breast disorders:*** Amenorrhoea and dysmenorrhoea have been reported. Very rarely gynaecomastia has occurred. Male infertility. ***Vascular disorders:*** The occurrence of vasculitis has occasionally been reported. ***Ear disorders:*** Hearing loss, either reversible or irreversible has been reported rarely. ***Renal and urinary disorders:*** There have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria), but the mode of action is as yet unclear. Very rare cases of enuresis have been reported. ***Immune system disorders:*** Angioedema, Drug Rash with Eosinophilia, Systemic Symptoms (DRESS) syndrome and allergic reactions (ranging from rash to hypersensitivity reactions) have been reported.

Legal category: POM

Further information: Epilim is hygroscopic – keep tablets in blister pack until use and avoid cutting blister strips. Epilim Liquid should not be diluted.

	Product Licence Number	NHS Cost	
Epilim 200 Enteric Coated	04425/0302	100 tablets	£7.70
Epilim 500 Enteric Coated	04425/0303	100 tablets	£19.25
Epilim 100mg Crushable Tablets	04425/0317	100 tablets	£5.60
Epilim Syrup	04425/0301	300ml	£9.33
Epilim Liquid	11723/0024	300ml	£7.78
Epilim Chrono 200	04425/0307	100 tablets	£11.65
Epilim Chrono 300	04425/0308	100 tablets	£17.47
Epilim Chrono 500	04425/0309	100 tablets	£29.10
Epilim Chronosphere MR 50mg	04425/0310	30 sachets	£30.00
Epilim Chronosphere MR 100mg	04425/0312	30 sachets	£30.00
Epilim Chronosphere MR 250mg	04425/0313	30 sachets	£30.00
Epilim Chronosphere MR 500mg	04425/0314	30 sachets	£30.00
Epilim Chronosphere MR 750mg	04425/0315	30 sachets	£30.00
Epilim Chronosphere MR 1000mg	04425/0316	30 sachets	£30.00
Epilim Intravenous	11723/0022	1 vial	£11.58

Further information is available on request from the Marketing Authorisation Holder: Sanofi-aventis, One Onslow Street, Guildford, Surrey, GU1 4YS

Epilim, Epilim Chrono, Chrono, Epilim Chronosphere and the Chronosphere device are registered trade marks.

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Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk.

Adverse events should also be reported to the sanofi-aventis drug safety department on 01483 505515.

make a diagnosis, IgG EMA and tTGA must be checked when IgA deficiency is suspected.[21]

Negative serology does not rule out coeliac disease;[22] duodenal biopsies should always be performed if clinical suspicion is high.

NICE outlined the order for serology testing in guidance published in 2009 (see box 2).[23]

HLA analysis helps recognise high-risk groups and exclude coeliac disease in equivocal cases.[24] Coeliac disease is very unlikely when both HLA DQ2 and HLA DQ8 are absent.

The diagnosis of coeliac disease has been based on criteria of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition, revised in 1990. However, presentation can be muted or atypical in elderly patients. It can be hard to judge symptomatic relief after gluten withdrawal. The five forms distinguished are: classic, subclinical, latent, potential and silent.[25]

Elderly patients

A study reports that 34.1% of all new patients diagnosed with coeliac disease are in the seventh decade or above.[26] Swinson et al[27] demonstrated a bimodal distribution for age at adult diagnosis, with an initial peak in the fourth decade (predominantly women) and a later peak in the sixth and seventh decades (mostly men).

Hankey and Holmes[28] drew attention to coeliac disease being as much a disease of the elderly as of children, finding that 16% of their patients (19% of those aged 15 years and over) were diagnosed in their seventh decade and beyond. Cook et al[2] found that 12% (15% of those aged 15 years and over) were aged 60 or over at diagnosis.

Micronutrient deficiency is a common presenting clinical picture of intestinal malabsorption in the elderly; because symptoms of malabsorption are covert, diagnosis is often delayed, and nutritional deficiencies are more common and severe than in the young. As the elderly have less nutritional reserve than the young, these deficiencies are clinically more damaging.[29]

The mean delay in diagnosis of elderly patients is around 17 years.[30] Mortality rates increase with delay, suggesting that clinicians should be more alert to the possibility of coeliac disease in this population.[31]

Symptoms

Iron deficiency anaemia

This haematinic deficiency is the most frequent extra-intestinal manifestation of coeliac disease, occurring in approximately 39% of patients.[32]

Mandal et al[33] found that 1.7% of patients over 65 years of age presenting with iron deficiency anaemia have characteristic changes

of coeliac disease on duodenal biopsy. Up to 47% of adults with coeliac disease may have positive faecal occult blood tests.[34,35] When the faecal occult blood test is used to screen for cancer, coeliac disease should be considered as a differential diagnosis.

As iron deficiency anaemia is common in elderly people (13.5% of patients over 70 years)[34] and coeliac disease is often silent, all cases of unexplained iron deficiency should be considered for the diagnosis.

Box 2: NICE approach to serologic testing for coeliac disease[23]

Serological testing should be performed if the patient has symptoms or signs of coeliac disease:

- IgA tTGA is the first choice test
- If tTGA is equivocal, use the IgA endomysial antibody (EMA) test
- If tTGA is negative, check for IgA deficiency
- If there is IgA deficiency, offer IgG tTGA and/or IgG EMA testing
- If tTGA or EMA is positive, or if tTGA or EMA is negative but there is still clinical suspicion of coeliac disease, intestinal biopsy is done to confirm/exclude the diagnosis.

Malabsorption

Malabsorption may present with very few symptoms or the signs and symptoms of specific vitamin and nutritional deficiencies may be identified.

Most patients present with signs and symptoms of nutritional deficiency whereas gastrointestinal disturbance is the presenting complaint in around 20%.[36]

The most likely presentation is a combination of microcytic anaemia, past or present, a family history of the disease, and feeling tired all the time.[36]

Mandal et al found 21.4% of patients over 65 years presenting with chronic diarrhoea and iron deficiency anaemia will have coeliac disease.[34]

Osteoporosis

Because the diagnosis of coeliac disease is often delayed into adult life, many patients experience malabsorption for prolonged periods and consequently develop osteopenia or osteoporosis. One study[37] showed that 47% of women and 50% of men on a gluten-free diet had osteoporosis.

The cause of osteoporosis is likely to be calcium malabsorption leading to increased parathyroid hormone secretion, increased bone turnover, and cortical bone loss.[38] Stenson et al[39] found the prevalence of biopsy-confirmed coeliac disease to be much higher in patients with osteoporosis than those without it (3.4% versus 0.2%). Anti-tissue transglutaminase antibody levels correlated with the severity of osteoporosis as measured by T-score.

The authors recommend screening all patients with osteoporosis for coeliac disease.[40]

Neurological symptoms

Seizures related to calcification of the cerebral occipital lobe have been described in patients with coeliac disease.[40,41] In these cases, seizure control improved with anticonvulsants and introduction of a gluten-free diet.[42]

Seizure cases are rare in the UK and tend to present in childhood. Gluten sensitivity has also been found to be a cause of apparently idiopathic ataxia. Necropsy showed that the ataxia was a result of immunological damage to the cerebellum, to the posterior columns of the spinal cord, and to peripheral nerves.[43] A review by Hadjivassiliou et al[44] found ataxia and peripheral neuropathy to be the most common neurological manifestations of coeliac disease. Myopathy and hyporeflexia have also been described.[45]

Complications

Perhaps the most acknowledged complication of coeliac disease is the development of small bowel lymphoma. Lymphomas, mostly of T-cell type, and other malignant tumours of the small bowel, stomach and oesophagus, are associated with coeliac disease.[46]

West et al[47] found that people with coeliac disease have a 30% higher risk of gastrointestinal cancer and lymphoproliferative disease than the general population. However, the incidence of breast and lung cancer is decreased in patients with coeliac disease, for reasons so far unexplained. Prompt and strict dietary treatment has been

Key points

- One quarter of all new patients diagnosed with coeliac disease are in their seventh decade or older
- Coeliac disease may present with a wide variety or relative lack of symptoms in older people.
- Iron deficiency anaemia, malabsorption and osteoporosis are common presentations in the elderly
- The condition is often under diagnosed. The mean time of delayed diagnosis in the elderly is around 17 years
- The gold standard in diagnosis is the finding of characteristic histological changes on duodenal biopsy
- Patients with coeliac disease have a 30% higher risk of gastrointestinal cancer and lymphoproliferative disease than the general population.

found to decrease mortality in coeliac disease,[31] emphasising the importance of early diagnosis and institution of a gluten free diet.

I have no conflict of interest.

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