Reminder of important clinical lesson

Elevated liver enzymes, anaemia and osteopaenia in a young woman

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Summary

A 23-year-old woman presented with elevated liver enzymes, anaemia and lower limb oedema. Iron-deficiency anaemia due to gynaecological problems was suspected. The patient was treated with iron supplements normalising the blood haemoglobin. Alcohol binge drinking was suspected to be the cause of elevated liver enzymes. After 7 years, the patient presented to our outpatient clinic with non-specific gastrointestinal symptoms. Blood tests revealed low levels of serum s-iron and elevated liver function tests. Abdominal ultrasound was normal. No signs of viral hepatitis or hereditary liver disease were detected. There was a marked elevation of tissue transglutaminase antibodies. A small intestine biopsy confirmed the diagnosis of coeliac disease. A bone density scan showed osteopaenia. Following a gluten-free, lactose-reduced diet, the gastrointestinal symptoms disappeared and s-transaminase activity and s-iron levels normalised.

BACKGROUND

The association between coeliac disease (CD) and elevated s-transaminase activity may be overlooked when patients present with non-specific symptoms. Alcohol abuse is often suspected to be the main reason for changes in liver function tests (LFTs), especially since binge drinking on weekends is becoming increasingly common among teenagers and young adults. Previous studies show that about 40% of patients with CD have elevated s-aspartate or s-alanine aminotransferase at the time of diagnosis.^{1,2} The prevalence of CD may be under-diagnosed if the non-symptomatic cases are included.³ Studies in the United Kingdom have found a prevalence of 1% in children and adults.⁴

CD is an immune disorder triggered by gliadin. The diagnosis is based on gliadin antibodies and histological changes in the small intestine. The classical symptoms include diarrhoea, abdominal pain, gaseous inflation and weight loss. Several patients suffer minor or no abdominal symptoms. The symptoms may not reflect the severity of the underlying disease. Even patients without symptoms may develop anaemia, osteoporosis, neurological changes or arthritis due to malabsorption. Other patients may present with elevated s-transaminase levels.

CD is associated with secondary osteoporosis due to malabsorption of calcium,⁵ changes in hormone status (parathyroid hormone)^{5,6} and cytokine interference. In CD, a decrease in interleukin-1, interleukin-6 and an increase in receptor activator of nuclear factor κ -B ligand/osteoprotegerin ligand ratio⁷ may lead to increased osteoclast differentiation. Further, in both osteoporotic patients and patients with CD, a decrease in insulin-like growth factor 1 (IGF-1) is observed.⁸ As IGF-1 stimulates bone formation, decreased IGF-1 levels may contribute to brittle bone status.

A study of 128 North Americans with CD found osteoporosis (T score < -2.5) in 34% at the lumbar spine, 27%

at the femoral neck and 36% at the radius.⁸ Osteopaenia (T score < -1.0 and > -2.5) was found in 38% at the lumbar spine, 44% at the femoral neck and 32% at the radius.⁹

Treatment of CD alleviates symptoms, improves the quality of life, corrects deficiencies in iron, vitamins and minerals and reduces the risk of intestinal T-cell lymphoma and osteoporosis.

CASE PRESENTATION

A 23-year-old woman consulted her general practitioner because of fatigue and lower-limb oedema. Her family history included sarcoidosis, but no known hereditary or autoimmune diseases. Blood tests revealed minor iron-deficiency anaemia and s-alanine aminotransferase levels two and a half times the upper level of normal values. Physical assessment revealed lower-limb oedema. The patient was referred to a haematologist. Repeated tests confirmed anaemia caused by iron deficiency with elevated s-transferrin levels and low levels of s-ferritin. Several months of treatment with iron supplements resulted in a normalisation of anaemia. Liver enzymes remained relatively stable. No signs of viral hepatitis were seen. An ultrasound of the veins in the lower extremities was normal. The patient was considered to have iron-deficiency anaemia due to gynaecological bleeding. Changes in LFTs were assumed to be the result of alcohol binge drinking on weekends.

At the age of 30, the patient graduated from medical school and initiated her internship. Owing to protracted symptoms with nausea and general weakness, her colleagues performed a general screening. Blood tests revealed s-alanine and s-aspartate aminotransferase levels to be more than twice the upper normal limit and reduced levels of iron. All other screening tests were normal. The patient lived a healthy lifestyle including regular physical

Figure 1 Macroscopic image of the duodenum: classical scalloping of folds and a 'cracked mud' appearance of the mucosa.

exercise. No regular medication was given and the alcohol intake was low. Retrospectively, the patient admitted non-specific gastrointestinal symptoms for years. The symptoms consisted of abdominal distension and intermittent diarrhoea. The patient was referred to the outpatient clinic. An initial examination revealed that the patient was slim and had minor lower-limb oedema. Chest x-ray, abdominal ultrasound and echocardiography were normal. No signs of viral hepatitis, autoimmune or hereditary liver diseases were detected. Marked elevation of IgA and IgG transglutaminase and s-antigliadin antibodies was observed. The patient underwent an upper endoscopy with duodenal biopsies. The endoscopy revealed classical scalloping of folds and a 'cracked mud' appearance of the mucosa (figure 1). The duodenal biopsy showed total mucosal atrophy, complete loss of villi, crypt hyperplasia and lymphocytic inflammation. The changes confirmed the diagnosis CD. On the basis of the modified Marsh classification, the patient was classified as 3C (Table 1).¹⁰

A bone density scan showed osteopaenia of the hip, a T score of -1.5 and normal bone mineral density at the spine (T score = 0.5).

A gluten-free and lactose-reduced diet was initiated. Vitamin and mineral supplements were administered. Gradually, LFTs and iron levels normalised. The non-specific gastrointestinal symptoms normalised, the lower-limb oedema disappeared and the patient gained about 10 kg of weight. A control dual-emission x-ray

absorptiometry (DXA) scan was not performed because of pregnancy.

INVESTIGATIONS

Diagnostic investigations

- ▶ Abdominal ultrasound
- ▶ Thoracic x-ray and echocardiography (systolic murmur and lower-extremity oedema)

Blood tests

- ▶ Viral hepatitis (adjusted according to exposure): hepatitis A—hepatitis A virus antibodies immunoglobulin (IgM anti-HAV); hepatitis B—IgM antibody to hepatitis B core antigen (anti-HBc), hepatitis B surface antigen and antibodies (HBsAg and anti-HBs Ag); hepatitis C—anti-hepatitis C virus antibodies (anti-HCV) and hepatitis C virus RNA, cytomegalovirus antibodies, Epstein-Barr virus antibodies, parvovirus antibodies
- ▶ Genetic disorders (adjusted according to familial history): Wilson's disease—urinary copper and ceruloplasmin
- ▶ Autoimmune liver diseases: anti-neutrophil cytoplasmic antibodies, smooth-muscle antibodies, anti-nuclear antibodies, anti-mitochondrial antibodies
- ▶ Immune deficiencies: common variable immunodeficiency syndrome, IgA, IgG and IgM
- ▶ Pregnancy
- ▶ CD: transglutaminase IgG and IgA
- ▶ Gastroscopy: CD and gastric disease

Investigations after diagnosis of CD

- ▶ Blood tests to detect malabsorption: vitamin D, calcium, iron, transferrin, ferritin, B-12 (cobalamin and homocystein or methylmalonate when necessary), zinc and magnesium levels.
- ▶ DXA scan to detect osteoporosis.

DIFFERENTIAL DIAGNOSIS

When patients are referred for elevated liver enzymes, the main diagnostic tools are often abdominal ultrasound and a range of blood tests.

The abdominal ultrasound may show benign changes such as gallstones or fatty liver disease. Findings such as an enlarged spleen, a small nodular liver or ascites may indicate cirrhosis. The abdominal ultrasound may also be important to identify potential malignant disease.

Blood tests are an important part of the diagnosis. Depending on the patient history, acute or chronic viral hepatitis should be considered. The present case mainly supports chronic viral hepatitis due to potential work-related exposure. Furthermore, acute hepatitis is often associated with a more marked elevation of the liver enzyme activity and a more rapid onset of symptoms. Genetic disorders should be suspected and Wilson's disease may sometimes present with mild symptoms. In other cases, Wilson's disease is asymptomatic or presents with acute liver failure. Hereditary haemochromatosis is not a likely diagnosis as iron levels are low. Autoimmune liver disease generally occurs in middle-aged women, but may be seen in younger patient groups. The diagnosis of autoimmune hepatitis with elevated IgG and a positive

Table 1 Modified Marsh classification of coeliac disease

Marsh type	Intraepithelial lymphocytes per 100 enterocytes	Crypts	Villi
0	<30	Normal	Normal
1	>30	Normal	Normal
2	>30	Enlarged	Near-normal
3a	>30	Enlarged	Partial atrophy
3b	>30	Enlarged	Subtotal atrophy
3c	>30	Enlarged	Total atrophy

Type 0: Normal mucosa.
Type 1: Infiltrative type.
Type 2: Hyperplastic type.
Type 3: Destructive type.

smooth-muscle antibody and primary biliary sclerosis with elevated IgM and mitochondrial antibodies generally requires a liver biopsy to confirm the diagnosis. Primary sclerosing cholangitis should mainly be suspected in patients with inflammatory bowel disease. In a number of patients, anti-neutrophil cytoplasmic antibodies are present, but the gold standard for making the diagnosis is endoscopic retrograde cholangiopancreatography. Additional tests may be considered when high levels of cholesterol or diabetes are suspected.

The diagnosis of alcohol abuse is often considered when patients present with non-specific symptoms and elevated liver enzyme activity. This diagnosis is important as relevant treatment and support may be life-saving. However, patients with alcohol abuse may suffer from other causes of liver disease. Furthermore, alcohol abuse may exacerbate liver disease. Making the correct diagnosis and the described potential diagnostic tests are important even when patients present with an 'obvious' alcohol problem.

TREATMENT

A life-long gluten-free diet (without wheat, barley and rye) was recommended and initiated. Initially, a 3-month lactose-free diet was also initiated until villi normalisation of the small intestine.

As a gluten-free diet requires a major lifestyle change, to improve compliance dietary counselling was offered.

The patient was recommended to take a vitamin supplement (calcium, vitamin-D, folate, zinc and multivitamin supplementation) for about 3 months until normalisation of the poor nutrient absorption.

Because of malnutrition for a long period of time the patient was offered bone mineral measurement by a DXA scan of the hip and spine, as osteoporosis is a well-known co-condition. The patient was found to be osteopaenic at the hip.

OUTCOME AND FOLLOW-UP

Although the patient had subclinical CD with atypical symptoms after a few months of gluten-free diet, she gained weight, had no lower-limb oedema, felt less abdominal distension and reported generally less tiredness and greater surplus energy in everyday life.

After 4 months of treatment, normalisation of liver enzymes, albumin, immunoglobulins, vitamins and minerals were observed. Serologically, the tissue transglutaminase antibody levels declined.

Follow-up after 1 year showed complete normalisation of tissue transglutaminase antibodies, liver enzymes and vitamins.

DISCUSSION

Although CD may lead to increased s-aspartate and s-alanine aminotransferase activities, for patients without the more characteristic symptoms such as diarrhoea, weight loss, anaemia and osteoporosis, this association may be overlooked.

A German research group published a case report of a middle-aged man who had had an ischaemic stroke followed by a subdural haematoma due to low vitamin-K-dependent clotting factor. The patient had elevated s-aminotransferases and tested positive for anti-gliadin

and anti-endomysium IgA antibodies. The histological examination of the small-intestine biopsy revealed signs consistent with CD. After initiation of a gluten-free diet, the liver enzyme levels normalised and the patient gained normal vitamin levels.¹¹

In 2003, a Canadian research group described a 34-year-old woman with diarrhoea and abdominal cramps for some weeks. Her liver enzymes had been elevated for 1 year. She was hospitalised as a result of increasing abdominal pain and weight loss of 13 kg. The laboratory tests showed malnutrition and increased s-transaminases. An abdominal CT scan showed intussusceptions without complete obstruction. The patient was serologically tested for CD and the results were positive. The duodenal biopsy confirmed the diagnosis of CD. After 4 months of a gluten-free diet, all the patient's symptoms had subsided and follow-up tests showed no evidence of intussusception.¹²

Osteoporosis due to CD is mentioned earlier in this report, and in 2008 Olmos *et al*¹³ published a systematic review and meta-analysis of the prevalence of fracture in patients with CD. This meta-analysis confirmed the hypothesis that the fracture rate is higher in this group than in the general population. Among patients with CD, 8.7% had experienced fractures compared with 6.1% in the control group.¹³

In conclusion, minor elevated s-aspartate and s-alanine aminotransferases and non-specific gastrointestinal symptoms often followed by anaemia and/or osteopaenia/osteoporosis might be signs of CD.

Learning points

- Elevated liver enzymes in successive blood samples must be evaluated. Diagnostic tests should be considered even when alcohol intake is found to be above the recommended limits.
- Atypical coeliac disease is difficult to recognise but essential to treat; so general practitioners and doctors in specialties other than gastroenterology should be aware of the symptomatic and non-symptomatic patients.
- Treatment alleviates symptoms and prevents long-term damage including potential malignant disease and osteoporosis/osteomalacia and thus decreases coeliac disease-induced increased fracture risk.

Competing interests None.

Patient consent Obtained.

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