A patient between 20–30 years of age with jaundice and pain in joints and muscles

Jaundice and malaise are symptoms that would normally lead to admission to a hospital. The causes can be manifold; in the following we will present a case history with an unexpected etiology.

A previously healthy individual in the 20–30 years age bracket sought medical attention at the emergency unit late in the evening with malaise and generalised pain in muscles and joints. The symptoms had emerged in the previous few days. The patient complained of a slight cough, sore throat, flatulence but no abdominal pain. The patient reported an incident of pain in the lower part of the abdomen two weeks previously, and multiple occasions of vomiting one week before the contact, however the abdominal symptoms had passed before the visit to the emergency unit. The patient was unaware of any allergies, and did not use any kind of medication on a regular basis.

No definite diagnosis was made in the emergency unit, but a series of blood tests were performed for the general practitioner (GP) to follow up on the condition the following day.

The laboratory results were as follows: ALT 989 U/l (10–70), GGT 299 U/l (10–80) and ALP 143 U/l (35–105). CK, electrolytes, bilirubin, creatinine, BUN, uric acid and blood glucose were within normal ranges. The patient consulted the GP the following day, and the GP noted slight jaundice of the conjunctiva. However, the finding was uncertain and blood tests showed a normal bilirubin value of 10 μmol/l (9–25). AST was at 347 U/l (15–45). Clinical examination and auscultation of heart, lungs and abdomen provided no additional information.

After discussion of the case with medical staff at hospital admissions, the patient was admitted to the internal medicine ward on suspicion of liver failure.

At the hospital a thorough history was taken, and no specific hereditary conditions were noted. There were no unusual work-related or social exposures and the patient had not been abroad for the last 2 years. The patient had used no medication and did not abuse alcohol. The patient had eaten sushi for dinner the evening before the onset of joint pains. At admission the clinical examination of heart and lungs yielded no significant pathological findings, although a slight murmur was noticed over the right carotid artery. The patient did not present with a fever. The liver was noted as being slightly enlarged, the abdomen otherwise soft and with no tenderness. There was no blood in the stool and the rectal examination revealed nothing pathological. INR was 1.0 and albumin was 42 g/l (36–45). Ferritin and IgM were slightly elevated at 472 μg/l (30–400) and 2.3 g/l (0.4–2.1), respectively. AST was 295 U/l (15–45) and LDH 244 U/l (105–205). Electrolytes, arterial blood gas and CBC were all within normal ranges.

Autoimmune hepatitis was suspected in spite of the acute onset. To determine whether this was the case, blood tests for auto-antibodies were performed. Additionally, the patient was to be tested for infectious and toxic substances.

The tests showed no anti-smooth muscle antibodies, nor was there a positive ANA or anti-mitochondrial antibody titre, which cast doubt on the probability of an autoimmune hepatitis. Auto-antibodies of the following types were specifically screened for: DNA, RNP, Sm, SSA, SSB, Scl-70, CENP-B, Jo-1, fibrillarin, RNA polymerase III, Rib-P, PM-Scl, PCNA and Mi-2 to exclude the likelihood of an autoimmune hepatitis, lupus erythematosus, systemic sclerosis, polymyositis and mixed connective tissue disease. Levels of IgG, IgA, copper and iron were not elevated. The tests for Hepatitis A, B, C and Epstein Barr virus yielded negative results. A positive titre for cytomegalovirus IgG was discovered, however IgM was not present, making it unlikely that the infection was recently acquired.

Ultrasonography revealed the liver to be of normal size, but slightly hyperechogenic; however, no lesions, other pathology or parenchymal damage were detected.

No biochemical or microbiological cause of the liver failure had been found, and clinically the disease was in remission. Other causes were therefore suspected; however,
The patient was to be followed up by the GP.

Since the patient was showing signs of improvement and did not appear jaundiced, it was planned to discharge him from the hospital after two days. ALT had dropped to 604 U/l (10 – 70) and transaminase and lactate dehydrogenase were also returning to normal levels.

The diagnosis at discharge was unspecified toxic liver disease. It was assumed that the patient could have been exposed to a hepatotoxic material that could not be identified. The patient was to be followed up by the GP and he was scheduled for a visit to the hospital outpatient clinic.

The GP checked the transaminases one week after discharge, and these showed further improvement. Another consultation was scheduled one month later, during which the patient and GP in unison consulted various sources on the internet including UpToDate and the Norwegian Electronic Medical Handbook. The patient was curious as to the cause of the liver disease, and there was also a public health interest in finding any hepatotoxic agents in the local area.

Although some of the antibody tests were reperformed to reduce risk of a false negative, the results were unchanged. However, the patient had discovered other diseases online which could give rise to the symptoms concerned, among them hepatitis E.

The patient had no known contact with animals. Although there was no obvious route of transmission, the GP decided to test for this disease and sent the blood samples to the Norwegian Institute of Public Health. This test was taken two months after the initial visit to the GP. IgG and IgM against hepatitis E virus (HEV) were detected in two separate tests with two separate reagents. No HEV RNA was found in the subsequent PCR analysis.

The results of the tests were confirmed over the phone, and combined with the clinical findings the diagnosis of an acute HEV infection was established.

The patient showed no further symptoms of disease and was in good health.

Discussion
Hepatitis E is caused by the hepatitis E virus (HEV), a naked single-stranded RNA virus which is usually divided into four genotypes with different characteristics (1). Genotypes 1 and 2 are predominant in developing countries with poor sanitary conditions, where the contagion is passed on via the faecal-oral transmission route between humans. Outbreaks of these genotypes can occur both sporadically and in large epidemics, and are characterised by a staggering mortality rate of up to 25 % among pregnant patients (2).

In Europe however, genotype 3 is dominant, and infects a wide range of mammals, although the main reservoir seems to be porcine (1). The primary cause of hepatitis E infections in the human population is probably ingestion of contaminated food or direct contact with porcine faeces, although there are also well-documented cases of infection through blood products (3, 4). The incubation period varies from 2 to 8 weeks with an average of 40 days (5).

In otherwise healthy humans the HEV infection is usually asymptomatic. In patients who show symptoms, these are usually mild and non-specific. Symptoms disappear after a few days but can persist for a few weeks (6, 7), although serious infections also occur (8). The most common symptoms are jaundice, fatigue and fever (9). No increase in mortality has been described among pregnant patients infected with genotype 3 (1); however, the infection can become chronic in immunosuppressed individuals as well as cause an exacerbation of pre-existing chronic hepatitis with potentially serious consequences (5).

There are no official statistics regarding the prevalence or incidence of hepatitis E in Norway as it is rarely tested for. Hepatitis E is considered to be an infectious disease which is harmful to public health, and reporting of this disease to the Norwegian Surveillance System for Communicable Diseases (MSIS) was mandatory in the period from 1991 – 2002. As few as 24 cases were reported in the entire period (10), and in all these cases transmission of the disease had occurred outside of Norway. However, the Norwegian Institute of Public Health, reported in a personal communication that some cases have since been registered where transmission might have occurred in Norway.

In Europe the seroprevalence of anti-HEV IgG in the general population varies between 4.6 % and 16 % (1). In one study, HEV IgG was found in 9.3 % of the general population in Sweden (11). The prevalence is dependent on age, region, occupation and choice of diagnostic test. An approximation of the incidence of the disease can be obtained by studying the number of HEV RNA-positive blood donations. This was done in England in 2012 – 2013, where 0.04 % of 225 000 blood donations tested were found to be positive. The infections were of genotype 3 (4).

No registered drugs exist to treat hepatitis E, although treatments with ribavirin and pegylated interferon have both been attempted in cases of chronic HEV infection in immunosuppressed patients with promising results (12). No internationally approved vaccines against the disease exist. In China a vaccine with the trade name Hecolin has been shown to provide protection against genotype 4 which is predominant in China, although its efficacy against the remaining genotypes has yet to be determined (13).

In the case described in this paper, only IgG and IgM HEV antibodies were discovered, and no viraemia could be ascertained in the ensuing PCR analysis. This is scarcely surprising since the virus is typically removed from the bloodstream in about 5 weeks after infection (10) – and in this case the diagnostic blood test was performed about 2 months after admission.

This constitutes the first documented case of transmission of hepatitis E in Norway. The published literature can, however, be interpreted as pointing to a considerable number of unrecorded infections, and thus to an underestimated incidence rate of hepatitis E in Europe (1).

The patient has consented to the publication of this article.

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Litteratur

1652

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