Tidsskriftet Tidsskrift for Den norske legeforening

# A man in his twenties from the Middle East with acute abdominal pain and jaundice

EDUCATIONAL CASE REPORT

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## A man in his twenties was admitted to the Department of Surgery for abdominal pain with intermittent worsening over 12 hours. Investigation revealed a disorder rarely seen in Norwegian hospitals.

*The patient was a man in his twenties from the Middle East who had lived in Norway for the past few years. He did not speak good Norwegian, so the case history was taken in English. He had been previously healthy, had no allergies and was not taking any drugs, medication or dietary supplements. There were no known diseases in the family.*
*The patient was referred from the primary care out-of-hours service with suspected gallstones. He came to the Emergency Department on foot, had a good level of fitness and his general condition was good. The abdominal pain was moderate, and he had mild low back pain. He reported no changes in bodily functions and had no relevant travel history.*
*He appeared to have normal hydration status and normal weight. The whites of his eyes were clearly jaundiced. Further clinical examination revealed blood pressure of 107/56 mmHg, regular pulse of 86 bpm, temperature of 37.3°C, respiratory rate of 20 breaths per minute and oxygen saturation of 97 %. Findings of the examination of the neck, heart and lungs were normal. He had direct pain on palpation under the right costal margin and a positive Murphy's sign. Findings of examination of the abdomen and lower extremities were otherwise normal. A stool guaiac test was negative.*
Based on the case history and clinical examination, biliary tract disease was suspected. The patient was referred for abdominal ultrasound.

*Blood samples were taken for screening, which found haemoglobin 11.7 g/dL (reference range 13.4–17.0), mean corpuscular volume (MCV) 88 fL (82–98), platelets 175 × $10^9$/L (145–390 × $10^9$/L), leukocytes 14.8 × $10^9$/L (3.5–10 × $10^9$/L), bilirubin 312 µmol/L (5–25), creatinine 80 µmol/L (45–90) and CRP 38 mg/L (< 5). The haematology instrument at the laboratory reported the presence of nucleated red blood cells in the blood sample, and therefore a blood smear was prepared.*
The biomedical laboratory scientist who took blood samples from the patient was trained in diagnostic haematology, including blood smears. The combination of anaemia, hyperbilirubinaemia and the finding of nucleated red blood cells raised suspicion of haemolysis. The biomedical laboratory scientist informed a clinician about the suspicion and recommended ordering more blood tests. Based on the findings of the blood smear, she recommended a urine sample for a test strip and microscopic examination.

*Supplementary blood tests found haptoglobin < 0.1 g/L (0.4–2.1), reticulocytes 128 × $10^9$/L (27.0–120 × $10^9$/L), ferritin 2,235 µg/L (30–400), vitamin $B_{12}$ 571 pmol/L (150–650). Lactate dehydrogenase (LD) could not be*

*analysed due to icteric serum. The blood smear was evaluated immediately, with the main findings being anisocytosis and poikilocytosis with bite cells and blister cells (Figure 1) as well as a few nucleated red blood cells.*

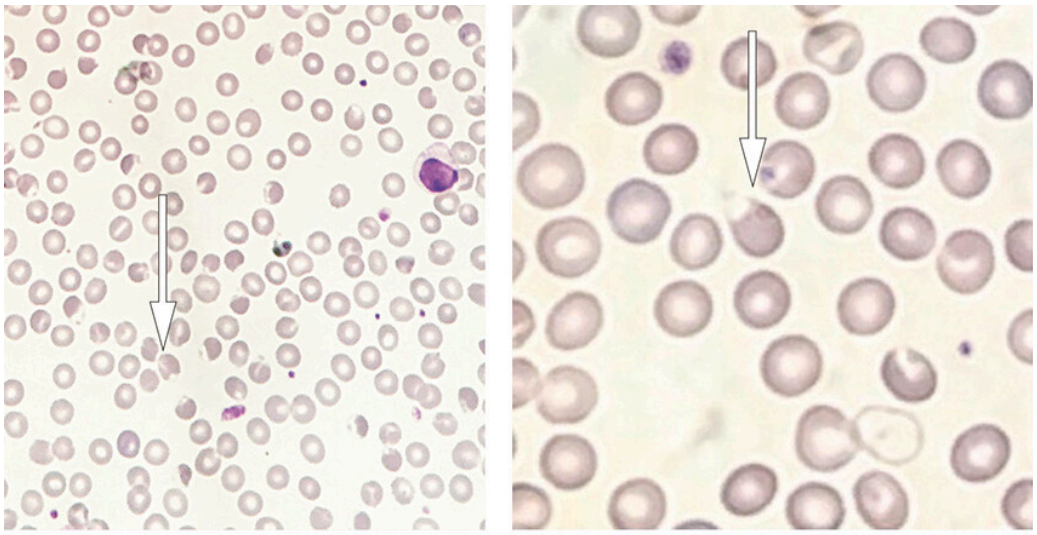


**Figure 1** May-Grünwald-Giemsa stained blood smear. The image shows bite cells (a) and blister cells (b) as a result of oxidative stress and acute haemolysis in the patient. Photo: Guro Archer Lauritzen

*The urine test strip was positive for leukocytes, albumin and blood. The urine sample was reddish-brown, and urine microscopy revealed some hyaline casts, granular casts and cellular casts. A few leukocytes and red blood cells were also found. The red blood cells had small inclusions called Heinz bodies (Figure 2).*

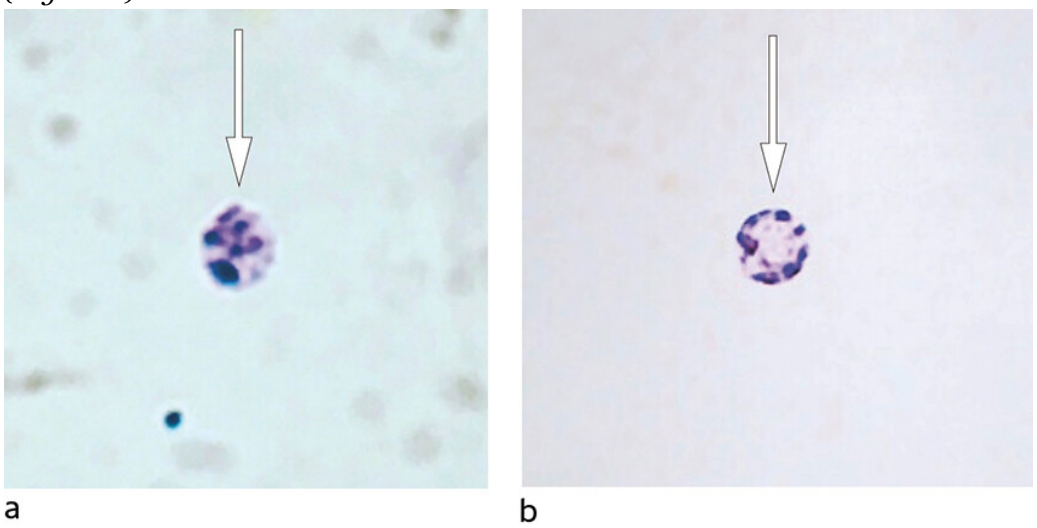


**Figure 2** Urinary sediment with Sternheimer-Malbin staining method. Urine microscopy revealed red blood cells with inclusions of Heinz bodies (a and b).

The diagnosis of haemolytic anaemia was suspected due to anaemia, increased reticulocyte count, elevated levels of lactate dehydrogenase, decreased or absent haptoglobin and elevated unconjugated bilirubin. Our patient had normocytic anaemia, which together with mild reticulocytosis, hyperbilirubinaemia and absent haptoglobin strengthened the suspicion of active haemolysis.

Blood smear is a useful diagnostic tool that is able to provide rapid and precise diagnostic clarification in conditions such as haemolysis. Anisocytosis means that there is variation in red blood cell size. Poikilocytosis means variation in red blood cell shape. Bite cells are red blood cells that have a 'bite' taken out of them. This 'bite' is a consequence of the macrophages in the spleen attempting to break down red blood cells with oxidative damage. A finding of nucleated red blood cells is often a sign of accelerated erythropoiesis. Reddish-brown urine raises suspicion of haemoglobinuria, and haemoglobin breakdown products in the urine (finding of blood on test strip) indicates intravascular haemolysis. The most notable finding of urine microscopy was Heinz bodies. These are precipitations of denatured haemoglobin (1–3). Heinz bodies in urine as well as findings of bite cells and blister cells in peripheral blood smear indicated that the patient's haemolysis was caused by oxidative damage to red blood cells.

*Abdominal ultrasound revealed a thin-walled gallbladder with no signs of concretions. There were no abnormal liver findings. Therefore, biliary tract disease was ruled out. The working diagnosis was haemolytic anaemia of unknown cause. The patient's clinical condition was stable, and he was admitted for observation without any further diagnostic or therapeutic activity.*

*The day after admission, the patient was found unresponsive on the bathroom floor. The cardiac arrest team was called, but he rapidly regained consciousness without intervention. He was reviewed by a doctor and transferred to the intensive care unit for further assessment. His haemoglobin levels had fallen from 11.7 g/dL to 10.4 g/dL. The doctor interpreted the current condition as a haemolytic disorder and suspected active autoimmune haemolysis with warm antibodies.*

*Treatment was initiated with intravenous methylprednisolone (Solu-Medrol) 100 mg once daily. A direct antiglobulin test (DAT), fibrinogen, d-dimer, cold agglutinins and serological tests for hepatitis virus, HIV and syphilis were requested. The patient was referred for CT scanning of the chest/abdomen/pelvis to rule out acute internal bleeding as an explanation of the loss of consciousness. CT revealed splenomegaly, with the largest anterior-posterior measurement being 14 cm (reference < 12 cm). There were no other abnormal findings.*

*Both D-dimer and fibrinogen were within normal ranges and, together with the absence of thrombocytopenia and helmet cells in the blood smear, thrombotic thrombocytopenic purpura (TTP) could be regarded as unlikely. The conclusion was that the patient's loss of consciousness was due to vasovagal syncope in connection with using the toilet.*

The most important next steps in the investigation of haemolytic anaemia consist of taking a thorough case history, clinical examination and extended haematological tests. Rapid onset of symptoms or jaundice raises suspicion of an acute haemolytic disorder in which the body's mechanisms for heme metabolism are overwhelmed, leading to accumulation of bilirubin in serum. Recent introduction of medication may indicate drug-induced haemolysis. Recent blood transfusions may raise suspicion of an acute or delayed

transfusion reaction. Positive family history may strengthen the suspicion of a hereditary cause of the haemolysis. Hepatomegaly/splenomegaly may be found in myeloproliferative or lymphoproliferative disease.

In addition to screening haematological tests, it is essential to request a blood smear as well as a direct antiglobulin test (DAT)/Coombs test. Blood smear will be able to elucidate life-threatening diagnoses such as thrombotic thrombocytopenic purpura, while the DAT/Coombs test is used to clarify whether or not the haemolysis is immune-mediated.

The direct antiglobulin test demonstrates whether the patient's red blood cells are coated with IgG, complement or both. In autoimmune haemolytic anaemia, the cause is generally autoreactive IgG (warm antibodies), and in that case the direct antiglobulin test is positive for IgG which is bound to the surface of red blood cells. However, there is another form called cold agglutinin disease, which means that the antibodies involved only bind to the red blood cells at temperatures lower than the body's core temperature. These antibodies are usually of IgM isotype and dissociate from the red blood cell surface on warming. The direct antiglobulin test may also be positive in this case because the red blood cells become coated with complement C3d, which remains attached to the red blood cells irrespective of temperature. The working diagnosis at this time was autoimmune haemolysis with warm antibodies. This was the basis for initiating steroid treatment.

*The patient was stable, and on day 3 the treatment was changed from intravenous methylprednisolone to the standard treatment for autoimmune haemolysis: oral prednisolone 1 mg/kg once daily. Despite this treatment, the patient's haemoglobin levels gradually fell, and on day 4 levels were 6.1 g/dL. The patient's general condition was good throughout, and his vital signs were normal. However, he developed dyspnoea on the slightest activity and reported a tendency to angina pectoris. Therefore, he received a transfusion of one unit of packed red blood cells. At this point, it became apparent that the direct antiglobulin test was negative, and cold agglutinins were also not found. Other microbiological and serological tests were also negative.*
*Since the direct antiglobulin test was negative, the working diagnosis of autoimmune haemolytic anaemia was rejected. Attention was now directed at finding alternative explanations for the haemolysis. Laboratory tests were reviewed with a focus on the urine findings. Analyses for paroxysmal nocturnal haemoglobinuria, haemoglobin electrophoresis and glucose-6-phosphate dehydrogenase deficiency had already been ordered. Bone marrow aspiration and biopsy were performed, and the patient's case history was reviewed in detail once more in conversation with an interpreter. It emerged that he had had an incident as a child in which his skin had turned yellow. Furthermore, prior to the current admission, he had consumed a meal consisting of broad beans.*
The patient's ethnicity, together with the case history details about a similar previous incident, raised a strong suspicion of glucose-6-phosphate dehydrogenase deficiency. The analysis for this disease came back five days after admission. Levels of the enzyme glucose-6-phosphate dehydrogenase were extremely low, 12 U/$10^{12}$ RBC) (reference range 200–400 U/$10^{12}$). Enzyme activity was <10 %, consistent with a severe enzyme deficiency. The

findings of haemoglobin electrophoresis were normal. The test for paroxysmal nocturnal haemoglobinuria was negative. Other blood and bone marrow tests did not indicate any other underlying disease. The steroid treatment was discontinued, and no further measures undertaken. The patient was discharged on day 7 in a good general condition and haemoglobin levels of 7.2 g/dL.

## Discussion

Glucose-6-phosphate dehydrogenase deficiency is the most common genetic enzyme deficiency worldwide. It is estimated that 400–500 million people have this disorder, which is most prevalent in the Mediterranean countries, Africa, Asia and the Middle East (1, 4).

Glucose-6-phosphate dehydrogenase is an essential enzyme for protecting red blood cells from oxidative stress (4). Patients are usually asymptomatic until they are exposed to an oxidative 'trigger', which may be a medicinal product or an intercurrent illness (4). Another classic trigger is the consumption of broad beans (Figure 3). The development of haemolysis following the consumption of broad beans (also known as fava beans) is called favism (1). The first case of favism in Norway was described in 1998 (5), but otherwise there are few reports on the disorder in Norwegian literature. A favism attack can lead to very severe and even life-threatening haemolysis. Signs and symptoms of the disorder can be explained by acute haemolysis with resulting anaemia and hyperbilirubinaemia. The patient may appear clinically unwell, pale and/or jaundiced, weak and short of breath. However, our patient was in a good general condition and not much affected by the haemolysis.

**Figure 3** Broad beans. Photo: edoneil/iStock

Most patients with glucose-6-phosphate dehydrogenase deficiency have no symptoms before they develop sudden episodes of acute haemolysis (1, 6). Acute intravascular haemolysis causes elevated plasma levels of haemoglobin, which binds to nitric oxide, among other things. Decreased concentrations of nitric oxide can cause vasomotor changes in veins and arteries and can result in symptoms such as abdominal pain. These vasomotor changes were the likely explanation for our patient's abdominal and back pain. Fever is not uncommon, but was not present in our case. The spleen may be enlarged due to extramedullary haematopoiesis, which was also seen in our patient. Urine is often dark. In our case, language challenges led to an imprecise case history being taken. This was particularly apparent when enquiring about bodily functions. The patient reported normal urination, while objectively dark brown urine was seen. Repeated conversations with an interpreter provided important information about events in childhood as well as recent consumption of broad beans, which led to the diagnosis.

In this case report, the biomedical laboratory scientist noticed the haemolysis pattern in the very first blood tests as well as on blood and urine microscopy. In consultation with a clinician, relevant diagnostic tests were ordered. To make a diagnosis of glucose-6-phosphate dehydrogenase deficiency, there must be a suspicion of the disorder. This suspicion can be raised by the combination of ethnicity, hereditary factors, previous similar episodes and relevant clinical and

biochemical features with a negative direct antiglobulin test with acute haemolysis. Other relevant differential diagnoses are thrombotic thrombocytopenic purpura, haemoglobinopathies, congenital red blood cell membrane defects such as spherocytosis and elliptocytosis, as well as paroxysmal nocturnal haemoglobinuria. Blood smear with findings of bite cells and blister cells strengthen the suspicion. Measurement of the activity of glucose-6-phosphate dehydrogenase in red blood cells can produce a definitive diagnosis.

The treatment of glucose-6-phosphate dehydrogenase deficiency consists mainly of removing triggers, whether that be infection, medicinal products or broad beans. Supportive treatment should be given in the form of intravenous hydration and blood transfusion at haemoglobin levels < 7–8 g/dL. Plasma haemoglobin is nephrotoxic and can cause acute kidney injury. Haemodialysis may be appropriate in cases of persistent kidney failure. However, most patients improve spontaneously without the need for extensive treatment.

Patients must be advised to avoid consuming broad beans in the future. They should also avoid medicinal products such as 4,4′-diaminodiphenylsulfone (Dapsone), fluoroquinolones, nitrofurantoin and sulfonylurea. Patients should be given detailed information about the disorder and urged to tell healthcare providers about this. Furthermore, they can be referred to the website for good patient information, which is also available in several different languages (7).

Microscopy of blood and urine are fundamental in the investigation of haemolysis. The case report illustrates the benefit of these simple and often undervalued examinations. It also illustrates the importance of taking a thorough case history and collaboration between biomedical laboratory scientists and clinicians.

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*The patient has given consent for the article to be published.*

*The article has been peer-reviewed.*

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Publisert: 2 May 2022. Tidsskr Nor Legeforen. DOI: 10.4045/tidsskr.21.0686
Received 29.9.2021, first revision submitted 23.12.2021, accepted 28.1.2022.