A case report of hereditary coproporphyria with neurological, haematological and renal involvement☆

Acerca de un caso de coproporfiria hereditaria con afectación neurológica, hematológica y renal

This was a 29-year-old male, referred for investigations into recurrent attacks of epigastric abdominal pain radiating to the rest of the abdomen, associated with vomiting. The patient reported having had episodes of abdominal pain since the age of eight, self-limiting after lasting a few hours, without recognising any trigger and with no other associated symptoms. He had recently begun to notice paraesthesia and weakness in the upper limbs. He did not report any other relevant personal or family medical history, and he denied the use of any toxic substances or medication. On physical examination, the patient had jaundiced skin and mucous membranes and brownish skin lesions in sun-exposed areas; abdomen was painful in the epigastric region, without peritonism. Neurological examination detected distal and proximal weakness in the upper limb (4/5) and loss of vibratory sensitivity. Analyses showed: haemoglobin (Hb) 9.8 g/dl (11 g/dl between attacks); mean corpuscular volume 70 fl; lactate dehydrogenase 450 U/l; total bilirubin 2.6 md/dl (IB 2 mg/dl) (transaminases and cholestasis enzymes normal); haptoglobin 20 mg/dl; ferritin 150 mg/dl; transferrin saturation index 25%; creatinine 1.4 mg/dl and c-reactive protein 10.6 mg/dl (both normal between attacks); haemoglobinopathies with normal foetal Hb and HbA2; lead levels, antinuclear antibodies, anti-DNA and anti-transglutaminase negative. Gastroscopy with duodenal biopsies, ultrasound, computed tomography (CT) of abdomen with CT-angiogram and CT of brain were all normal. Electromyogram confirmed the existence of a predominantly axonal sensory-motor polyneuropathy and focal neuropathy of the ulnar and left median nerves. A porphyrin test was requested: (a) blood: erythrocyte porphyrin 7.2 μg/g Hb (normal up to 5 for Hb values of 12–17 g/dl); (b) 24-h urine (1.755 μg/24 h, normal <200 μg/24 h) (porphobilinogen (PBG) and delta-aminolevulinic acid (ALA) levels normal after resolution of the attacks); and c) stools: coproporphyrins 7.8 μg/g (normal <5 μg/g) (uroporphyrin, protoporphyrin and heptacarboxyporphyrin in range). As hereditary coproporphyria (HCP) was suspected, treatment was started with haemin, with good control of the abdominal pain. A genetic study confirmed the diagnosis of harderoporphyria (mutation of the enzyme coproporphyrinogen oxidase [CPOX] in homozygosis).

HCP is a type of hepatic porphyria characterised by the development of acute neurovisceral and skin symptoms, formerly called ''mixed'' porphyria.[1] Along with acute intermittent porphyria (AIP), variegate porphyria (VP) and delta-aminolevulinic acid (ALA) dehydratase (ALAD) porphyria (ADP) make up the group of acute porphyrias. The prevalence of HCP ranges from 2 to 5/million population, behind AIP and VP.

It is an autosomal-dominant disorder of incomplete penetrance caused by heterozygous mutations in the CPOX gene (enzyme of the haem group cycle) which typically occurs after puberty. Harderoporphyria is an extremely rare homozygous variant, starting in childhood and accompanied by haemolytic anaemia.

The neurovisceral manifestations occur episodically and include symptoms of dysfunction of the central, peripheral and autonomic nervous system, indistinguishable from those caused by other forms of acute porphyria. The attacks usually begin with abdominal pain as the most common symptom.[2] Renal failure and electrolyte abnormalities can be detected, associated with diarrhoea or oral intolerance, or with a syndrome of inappropriate secretion of ADH in hyponatraemia.[3] Motor weakness can progress to a flaccid quadriparesis or respiratory paralysis in fatal cases, and, in other cases, persist as peripheral neuropathy for months or years.

Chronic skin lesions and pigment changes in sun-exposed areas are seen in 20% of cases.[1,2] The concurrence of neurovisceral and skin symptoms means a differential diagnosis is necessary between HCP and VP, as the only acute porphyrias that cause both manifestations.

The nonspecific nature of the symptoms and the rare nature of this disorder often delay diagnosis. Acquiring a high degree of clinical suspicion is essential for early recognition and the association of symptoms is an important diagnostic tool for that purpose. As in our case,recurrent attacks of acute abdominal pain not attributable to other organic causes are a common reason for suspecting acute porphyria. When other neurovegetative symptoms are added, such as the neurological symptoms or dehydration and renal failure our patient presented with, the suspected diagnosis gains strength. Skin manifestations are only observed in two forms of acute porphyria, VP and HCP, so their concurrence with neurovisceral symptoms narrows the differential diagnosis. Lastly, although haematological alterations are not typical of porphyrias, harderoporphyria does have the distinctive feature of haemolytic anaemia, combined with an earlier onset in childhood. Although our patient reported attacks of abdominal pain since the age of eight, it is possible that incomplete penetration of the mutation had an influence on the more dormant expression of the disease, delaying its diagnosis until adulthood.

When acute porphyria is suspected, total porphyrins should be requested in urine, faeces and plasma, plus erythrocyte porphyrins, and, if increased, analysis of their fractions will help identify the subtype.[4] The increase in urinary PBG is highly specific for acute porphyria, but it returns to normal more rapidly than porphyrins. Measurement of faecal porphyrins is the most sensitive method once the symptoms have resolved; during the attack, coproporphyrins are increased, with predominance of coproporphyrin

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III in HCP, and coproporphyrin III and protoporphyrin IX in VP, while they remain normal or almost normal in AIP. The diagnosis is confirmed by genetic study of mutations in the CPOX gene.

Treatment should be started as soon as possible, with the bases being the identification and correction of the factors precipitating the attack and the administration of haematin derivatives.[5]

In conclusion, in cases of recurrent acute abdominal conditions not explained by other causes and associated with other neurovisceral and skin symptoms, the possibility of HCP should be investigated; the additional development of haemolytic anaemia narrows the differential diagnosis to the harderoporphyria variety. The association of symptoms is key to establishing the suspected diagnosis in acute porphyria and so enable early treatment.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Idiopathic ischaemic ileitis, with overt obscure digestive bleeding☆

Ileítis isquémica idiopática, con sangrado digestivo oscuro manifiesto

Idiopathic ischaemic enteritis is an irreversible lesion of the mucosa induced by intestinal ischaemia, without evidence of mesenteric artery occlusion.[1,2] It is considered to be caused by hypoperfusion of the mesenteric vessels, without an explanatory structural, obstructive or inflammatory cause. The most common form of presentation is an inflammatory stricture.

We present the case of a 59-year-old male with a history of hypertension, who denied alcohol or NSAID use or being a smoker. He had been assessed several times in Accident and Emergency for gastrointestinal bleeding manifested by melaena. Tests showed him to have iron deficiency anaemia (haemoglobin: 5.1 g/dl, total iron: 15 μg/dl and ferritin: 27 ng/ml). Endoscopic studies (two oesophagogastroduodenoscopies and one colonoscopy) were reported as normal. Video capsule endoscopy (VCE) showed an ulcerated inflammatory lesion in the proximal ileum which was generating a concentric stricture, with estimated residual lumen of 30% in that area (Fig. 1A); the VCE was retained at the level of the stricture (Fig. 1B) for 72 h. The patient had colicky pain and distension, but no vomiting. We performed a retrograde double-balloon enteroscopy but, as we were unable to reach the site of the stricture, laparoscopic surgery was scheduled. Local resection of the diseased segment was performed with end-to-end anastomosis, without intraoperative complications. Intraoperatively, the surgeons found a hard area of about 5 cm of fibrotic strictures with marked local inflammation, so Crohn's disease (CD) was suspected. Histopathology showed chronic inflammation of the ileum with submucosal and serous fibrosis, muscle hypertrophy and marked vascular congestion, compatible with active chronic ileitis of ischaemic aetiology (Fig. 1C and D), but no findings suggestive of CD or malignancy. Special staining methods were used on the tissue, such as Ziehl-Neelsen, methenamine silver, PAS and Gram, all of which were negative, as was immunohistochemistry for cytomegalovirus, ruling out infectious causes. Further tests were carried out, including nuclear antibodies (anti-cytoplasmic antibodies, which were negative), enabling systemic vasculitis to be ruled out. CT-angiogram of the abdomen showed no thrombi or other vascular lesions, ruling out mesenteric ischaemic disease, and faecal calprotectin was normal, making CD unlikely, as it has a high negative predictive value. The patient made a satisfactory recovery, with no new episodes of bleeding or anaemia after surgery. At the 12-month follow-up, the patient was asymptomatic and not on any medication.

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