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Harderoporphyria in a Young Girl Suffering from Abdominal and Neurologic Pain: A Frequent Association?

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Abstract

Porphyria is a group of diseases in which substances called porphyrins build up, negatively affecting the skin or nervous system. The types that affect the nervous system are also known as acute porphyria, as symptoms are rapid in onset and last a short time. Symptoms of an attack include abdominal pain, chest pain, vomiting, confusion, constipation, fever, high blood pressure, and high heart rate. The attacks usually last for days to weeks. Complications may include paralysis, low blood sodium levels, and seizures. Attacks may be triggered by alcohol, smoking, hormonal changes, fasting, stress, or certain medications. If the skin is affected, blisters or itching may occur with sunlight exposure. Here we report on a girl of 12 years old with harderoporphyria suffering from recurrent abdominal and neurologic pain. The children was homoallelic for the CPOX missense mutation C.980A>G (p.H327R). After one year of follow up the girl still have for few days recurrent abdominal pain; then a diet was started (without meat, fruit and vegetables) which was followed by a low and gradual resolution of symptomatology.

Keywords: Childhood; Neurological involvement; Abdominal pain; Porphyria

Introduction

Porphyria is a metabolic disease caused by deficiency of specific enzymes of the biosynthetic way of heme. "Erithropoietic porphyrias" caused by hyperproduction of intermediate products of the synthesis of heme in the erithroid cells of the bone marrow, usually manifest it selves at birth or during childhood with skin photosensitivity. "Liver porphyria, with hyperproduction and sedimentation of porphyrins in the liver, mostly began symptomatic in adulthood rather than in children [1-3]. Hereditary Coproporphyria (HCP) is an autosomal dominant acute hepatic porphyria, results from mutations in the gene that encodes coproporphyrinogen III oxidase (CPO). HCP (Heterozygous or Rarely Homozygous) patients present with an acute neurovisceral crisis sometimes associated with skin lesions.

The intermediate products of the way are the precursors of "Porphyrin", "ALA", "Porphobirinogen" and the "Porphirins". In human beings these intermediary products do not carry out important physiologic tasks and, under normal circumstances, do not deposit in tissues in considerable amounts [1-19]. We report on a girl with abdominal and neurological pain suffering from harderoporphyria without any haematological or clinical sign of anemia.

Material and Methods

R. M. was born after a natural childbirth with a weighed of 2.810 gr; she manifested light asphyxia and jaundice at birth, for this reason she were recovered in UTIN, where she was in observation for three days. She came under our observation for the first time in November 2012, when she complained of having been suffering of stomach pains in her right hip and iliac fossa for about two months. The pain was linked to "skin hypersthia" with metameric distribution to the hip, the iliac fossa and the right lumbar region down to the root of the thigh. The pain was continuous with sudden exacerbations, especially during daytime, which hampered the patient's ambulation and obliged her in bed. At the recovery the clinical examination was normal: weight 52 kg (75% ile); height 168 cm (97% ile). The thoracic breathing was harsh and diffused; heartbeat was rhythmic and fine; abdomen was treatable, painful at deep palpation of the right iliac fossa. She did not present vomit or alteration of alvo or fever. Neurological examination was normal. The hematochemical tests were normal range and including emochrome with formula and reticulocyte

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count, urea, creatinin, total protein, bilirubin, AST, ALT, LDH, CPK, gamma gt, electrolites, PCR,VES, PT, PTT, fibrinogen, ATIII, immunoglobulin, cholinesterase, number of dibucain, D-dimer; urine test and urine culture; rotavirus and adenovirus research in faeces; B-HCG. Also the instrumental tests: echoabdomen, echo pelvis and echo gynaecologic, abdomen and pelvis MR, brain MRI, spine in toto MR, electromyography were normal. As the pain in the right iliac fossa persists the surgeons decide to do an exploratory laparoscopy. The laparascopy showed slight and non-specific signs of peritoneal inflammation and during the procedure appendix was removed (histological test: "folliculo-hyperplastic chronic appendix"). After appendicectomy the girl showed total disappearing of painful symptomatology and she resumed her normal life. After two months of total wellbeing, the girl comes back under our observation for the reappearance of pain in her left hip and iliac fossa and on the other side in her right thigh. The pain is always continuous with a rise in the daytime, resistant to FANS and forces the patient to stay in bed hampering her deambulation, there is no vomit or alvo alteration, appetite is good. There is no skin hyperestesia. Her right leg, though painful if palpated and after motion, does not show any signs of inflammation or edema. Morning and evening headache is present. The lab tests results are all still negative: emogram with formula and reticolocyte count, urea, creatinin, total protein, bilirubin, AST, ALT, LDH, CPK, electrolytemia, PCR, VES, PT, PTT, fibrinogen, ATIII, protein S, immunoglobulin, D-dimer, auto antibodies, cholesterole, triglyceride, apolypoproteine, ferritin, transferrin, vitamin B12, folic acid, tonsillar tampon for streptococcus B-emolitic, hidden blood in faeces, urinary and catecholamine and protoporphyrine calculation. At this moment brain MR shows absence of flow signs in the distal part of the transverse sinus, the sigmoid sinus and the gulf of the jugular in the left side in relation to a possible thrombosis. Even if the girl did not show any clinical signs of thrombosis, a heparin therapy was started. A further control after 4 days shows at MR a sign of flow is detected in the distal part of the transverse sinus, of the sigmoid sinus and of the gulf of the jugular on the left, with asymmetry of flow sign of the above-named vascular structures in the two sides with prevalence in the right one. After a few days the children manifested acute episodes of face edema, associated with photophobia, sweating and skin rash in the trunk that lasted for some minutes. In this moment a diagnosis of anxiety disorder was made. The girl comes again under our observation due to the presence of recurrent and persistent abdominal pains, resistant to the therapy. We decide to let the patient go on a free diet; this causes a worsening of abdomen symptomatology and the reappearance of neurological symptoms. In this phase urine, blood and faeces tests are carried out to determine the metabolites of porphyrine; then a diet was started (without meat, fruit and vegetables) which was followed by a gradual resolution of symptomatology. The tests that were carried out showed Porphobilinogen (urine) <0.20 mg/1 [0.0- 2.0 mg/dl]; total porphyrine (faeces) 27.4 mcg/g [<0.0- 4.0 mg/dl]; Pattern Porphyrine Harderocropo 38.2%. In this phase a diagnosis of "Harderoporphiria" was made. All the members of the family (proband mother and father and two brothers) were studied searching data from anamnestic history (example abdominal and/or neurologic abnormalities or photosensibility) and with samples for genetic studies. The children were homoallelic for the CPOX missense mutation C.980A>G (p.H327R) after one year of follow up the girl still have for few days recurrent abdominal pain.

Discussion

In our case the presence of abdominal pains and skin hyperesthesia, deambulation deficit, neurological symptoms, vasospasm of cerebral arteries, appearance of skin rush, face edema and photophobia, and the subsequent improvement of symptomatology after diet, alteration pattern porphyries have driven us to make a Porphyry diagnosis.

A deficit of human CPO, a mitochondrial enzyme, located on chromosome 3q11.2 [1] whom catalyses the stepwise oxidative decarboxylation of the heme precursor, coproporphyrinogen III to protoporphyrinogen IX, via a tricarboxylic intermediate known as 'harderoporphyrinogen; produced two phenotypically distinct disorders related to the deficient enzyme: HCP, including its homozygous variant form [MIM 121300] and harderoporphyria [3-6]. The molecular relationship between the single CPO gene and these two different phenotypes have not yet been defined and the biochemical basis remains unexplained.

In HCP, clinical penetrance is low and symptoms are very rare before puberty. Clinical manifestations of the disease are characterized by acute attacks of neurological dysfunction often provoked by drugs, fasting, menstrual cycle or infectious diseases [7,8]. Skin photosensitivity may also be present. Excretion of large amounts of coproporphyrin III, mostly in feces and urine is observed.

Biological not clinical patterns of our patients were similar to that observed Schmitt et al in 2005 and in the four harderoporphyric patients previously reported [6,10,11]. It must be emphasized that abdominal pain and neurological symptoms with transitory ischemic brain lesion, suggestive of acute hepatic porphyrias, have not been seen in harderoporphyric patients. Our patients have neurological and abdominal pain with a biology pattern of harderoporphyria. For this reason, these patients have never been treated by heme arginate injections, which is the main therapy used in acute hepatic porphyrias.

Harderoporphyria is a rare erythropoietic variant form of HCP, characterized by neonatal hemolytic anemia, sometimes accompanied by skin lesions and accumulation of harderoporphyrin in feces [6,10,11]. During childhood and adulthood a mild residual anemia is chronically observed. In our case the girl suffering from abdominal and cerebral pain, only one we find skin alteration, without any apparent clinical or ematological sign of anemia. No history of neonatal hemolytic anemia, but mild sign of jaundice. Schmitt report that harderoporphyric patients are iron overloaded. Two mechanisms could contribute to the hematological phenotype observed. Firstly, dyserythropoiesis occurring in bone marrow could be related to harderoporphyrin accumulation and/or heme deficiency in red blood cell progenitors. Furthermore, maturation arrest of erythroid precursors is known to stimulate intestinal iron absorption. Secondly, overproduction of porphyrins may account for hemolytic symptoms. Indeed, hemolysis of erythrocytes could result from photolysis of porphyrin-laden cells exposed to light in the dermal capillaries [11]. This intravascular hemolysis should worsen the anemia, but not participate to the iron overload, because intravascular hemolysis does not stimulate intestinal iron-absorption [16-19].

The pathogenesis of the neurological involvement in the Porphyries still remains not clear and it varies from the possible neurotoxin effect of Porphyries to the depletion of cofactors coming from the biosynthesis of eme to the vascular genesis. The pattern of porphyrin excretion in our patient showed that the major part of fecal porphyrin was harderoporphyrin, on the reversibility of the neurological injuries have been reported reversible vascular cerebral anomalies confirmed at MR and described as transitory cortical alterations. Our case highlights and confirms the further evidence

of the reversibility of the neurological damage demonstrating the vascular genesis of the disease.

Patients with homozygous HCP can have early-onset of manifestations, including abdominal pain and skin manifestations. These children, the offspring of heterozygous HCP parents, typically have less than 10% of normal CPOX enzymatic activity and have markedly elevated levels of urinary and fecal coproporphyrins during an acute attack. In 1955, Berger and Goldberg reported an 8-year-old boy, the offspring of first cousins, who had milk intolerance, riboflavin deficiency and rickets and presented with short stature, diarrhea and failure to thrive.

Hasanoglu et al. described a Turkish male infant, who presented with the Harderoporphyria phenotype including neonatal hyperbilirubinemia, hemolytic anemia, hepatosplenomegaly, and skin lesions when exposed to UV light. He was homoallelic for the CPOX missense mutation, c.980A>G (p.H327R), and had massively increased urinary uroporphyrins I and III (9250 and 2910 μM, respectively) and coproporphyrins I and III (895 and 19,400 μM, respectively). The patient expired at five months of age from an apparent acute neurologic porphyric attack. Our have the same genetic mutation of the children described by Hasanoglu, but with different clinical symptom and onset; in fact, our patients did not have any neonatal onset (started at the age of 9 years) and the other clinical signs different. Harderoporphyric patients reported to date [11] exhibited strictly identical clinical symptoms characterized by early onset of hemolytic anemia associated with chronic cutaneous manifestations. It must be emphasized that abdominal pain and neurologic symptoms, suggestive of acute hepatic porphyrias, have not been seen in harderoporphyric patients, thus our patients seem to have a different form of hardenocopro porphiria with sign of neurological and abdominal involvement and fecal harderoporphyrin without anemia. In the harderoporphyric family reported by Lamoril et al. [11], the parents were clinically asymptomatic but exhibited slightly abnormal fecal porphyrin excretion and an approximately 50% reduction in COX lymphocyte activity. In our family both parents and two brothers were asymptomatic without any neurological or hepatic alteration at the moment. In conclusion more studies have to be made to better clarify the association of harderoporfiria and liver and or neurologic manifestation.

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