Can a polymorphism in the thalassemia gene and a heterozygote CFTR mutation cause acute pancreatitis?

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Abstract

The case of a 32-year-old black woman of African descent who suffered from repeated episodes of acute pancreatitis, initially triggered when flying on airplanes, is reported. She did not drink alcohol or smoke. Genetic analysis was negative for cationic trypsinogen, serine protease inhibitor Kazal type 1 and chymotrypsin C. However, hemoglobin F was elevated. Sequencing of the thalassemia gene revealed a novel alteration in the 5’ region indicative of a functional abnormality of the molecule. Sequencing the cystic fibrosis transmembrane conductance regulator (CFTR) gene revealed a heterozygote sequence variant. The combination of a hemoglobin gene mutation known for thalassemia in conjunction with the hitherto undescribed CFTR mutation is suggested to pave the road for initial and repetitive pancreatitis attacks. This will be discussed.

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Key words: Acute pancreatitis; Hypoxia; Flying; Thalassemia; Hemoglobin; Cystic fibrosis transmembrane conductance regulator; Hereditary persistence of fetal hemoglobin

Core tip: This is a discussion case with two genetic alterations, one in a pancreatitis-related gene and one in an unrelated gene that might influence the oxygenation in the pancreas.

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INTRODUCTION

Within the group of younger patients suffering from recurrent episodes of acute pancreatitis, those not drinking alcohol impose a special diagnostic challenge. Many of these patients, who were coined to suffer from idiopathic pancreatitis even without a family history, may have mutations in the genes known to be associated with this disease[1]. Among genes identified to convey the risk of developing pancreatitis are cationic trypsinogen (PRSS1)[2], serine protease inhibitor Kazal type 1 (SPINK1)[3], chymotrypsin C (CTRC)[4] and cystic fibrosis transmembrane conductance regulator (CFTR)[5], whereas mutations in the anionic trypsinogen gene[6] appear to be protective. Some who may be negative for genetic factors may have anatomical abnormalities, such as pancreas divisum or other branching disorders[7]. Still then, a small subgroup is left with no identifiable reason. Those may suffer from rare metabolic conditions or syndromes, however, normally present with other symptoms indicative of the underlying disease. Beyond those conditions, there are rather exotic reasons for suffering from acute pancreatitis. We here report on the combination of two hitherto undescribed mutations in both an extrapancreatic and a
pancreatic gene that might explain the repetitive attacks of pancreatitis.

**CASE REPORT**

**Previous history**

The 31-year-old black woman, who was brought up in Kenya but had been living in Germany for the last 8 years, presented with repeated episodes of acute abdominal pain which started in the middle epigastric region and would eventually radiate into the back, suggestive of acute pancreatitis. These episodes initially occurred after flying on regular commercial aircrafts. She was hospitalized eight years prior to this attack when 23 years old for cystitis and pyelonephritis when a diagnosis of acute pancreatitis was established *via* computer tomography. At that time, she also suffered from iron-deficient anemia [hemoglobin (Hb) 10.7 g/dL, mean corpuscular volume 69.4 μm, iron 28 mg/dL, ferritin 23 ng/mL].

**Recent history prior to referral**

Abdominal ultrasound and computed axial tomography scan were reported to be normal; endoscopic retrograde cholangiopancreatography showed a slightly irregular main pancreatic duct (grade 0); however, no pancreas divisum and no papillary abnormalities. No overt gallstones, microlithiasis or sludge was present. After the last episode, when the diagnosis of acute pancreatitis was established by laboratory tests (elevated serum amylase (14.7 U/g) were well within the normal range. Fecal elastase-1 (985 μg/g) and fecal chymotrypsin (14.7 U/g) were well within the normal range.

**Imaging**

The pancreas appeared almost normal on ultrasound. Notably, the echogenicity was slightly elevated towards a so-called “white pancreas” (Figure 1). There was a normal arterial blood supply to the pancreas. As the patient was slender, the transabdominal ultrasound had a good visibility: no gallstones, sludge or microlithiasis could be detected in the gallbladder or the bile duct all the way down into the pancreas.

**Hematological and genetic tests**

Since the history of present illness together with the ethnic background of the patient was pressing, we performed further analysis with regard to a possible hemoglobinopathy. The ordinary complete blood count with blood smear was normal.

Hemoglobin F was slightly elevated at 0.92%, suggesting a “hereditary persistence of fetal hemoglobin” (HPFH). Molecular analysis of the hemoglobins resulted in the finding of a heterozygous transition at -158 C → T within the S’ non-coding region of the γ-gamma globulin gene (HPFH Swiss). Sequencing of the γ-gamma globulin gene did not reveal any abnormalities. Other genetic abnormalities associated with HPFH [HPFH-1 (black), HPFH-2 (Ghana), HPFH-3 (Indian), HPFH-7 (Kenya)] could not be detected. Sequencing of the β-thalassemia gene revealed no abnormalities. Sequencing the CFTR gene revealed a heterozygote sequence variant (c.2882T>C; p.M961T (ATG>ACC). Sequencing of PRSS1, SPINK1 and CTRC did not reveal any additional mutations in these pancreatitis genes.

**Further course**

During a six year follow-up, the patient did not develop any further episodes of pancreatitis. According to our recommendation, she resisted from flying.

Figure 1  Transabdominal ultrasound depicting a pancreas (arrows) of normal size with slightly enhanced echogenicity.
Table 1  Laboratory values upon presentation to the pancreas outpatient clinic

| Parameter          | Unit       | Value  | Range  |
|--------------------|------------|--------|--------|
| WBC                | 10E9/L     | 4.5    | 3.6-11.0 |
| RBC                | 10E12/L    | 4.73   | 3.8-5.2 |
| Hb                 | g/dL       | 14.8   | 12-16   |
| Hct                |            | 43.9   | 35%-47% |
| MCV                | fl         | 92.9   | 80-100  |
| Na                 | mmol/L     | 139    | 135-144 |
| K                  | mmol/L     | 4.28   | 3.5-5.2 |
| Ca                 | mol/L      | 2.18   | 2.25-2.60 |
| Albumin            | g/L        | 56.4   | 35-52   |
| Blood glucose      | mg/dl      | 74     | 70-115  |
| Bilirubin (total)  | mg/dl      | 0.31   | 0.2-1.4 |
| Uric acid          | mg/dl      | 3.2    | 2.5-5.7 |
| Cholesterol        | mg/dl      | 173    | 130-260 |
| Triglycerides      | mg/dl      | 36     | < 200   |
| BUN                | mg/dl      | 18.8   | 16.7-45.8 |
| Creatinine         | mg/dl      | 0.7    | 0.6-1.1 |
| Alkaline phosphatase| U/L        | 80     | 55-160  |
| γGT                | U/L        | 9      | 4-18    |
| GPT/ASAT           | U/L        | 5      | 5-19    |
| GOT/ALAT           | U/L        | 13     | 5-15    |
| Cholinesterase     | U/L        | 4238   | 2800-7400 |
| HBA1C              |            | 1.51   | 1.2-4.6 |
| Zinc               | mmol/L     | 34     | 16-50   |
| Amylase            | U/L        | 183    | 25-115  |
| Lipase             | U/L        | 202    | 114-286 |
| Chymotrypsin       | U/g        | 14.7   | > 6     |
| Elastase-1         | μg/g       | 985    | > 200   |
| HbF                |           | 0.92   | < 0.5%  |
| HbA                |            | 92.73  | 87%-94% |
| HbA2               |            | 2.14   | 1.6-3.1% |
| Anomalous Hb       | Not detectable |
| ALA                | μmol/d     | 24     | 2-49    |
| Porphobilinogen    | μmol/d     | 6.6    | 0.5-7.5 |
| Total porphyrines  | μg/d       | 41.7   | < 145   |

WBC: White blood cells; RBC: Red blood cells; Hb: Hemoglobin; Hct: Hematocrit; MCV: Mean corpuscular volume; BUN: Blood urea nitrogen; GOT/ASAT: Glutamic oxaloacetic transaminase; GPT/ALAT: Glutamic pyruvic transaminase; HBA1c: Hemoglobin A1c; ALA: Alpha lipoic acid.

**DISCUSSION**

In adolescent and young adult patients presenting with signs of pancreatitis, associations with genetic abnormalities are pressing[11]. Even in sporadic cases, mutations in the genes known to cause hereditary pancreatitis such as PRSS1 have been reported. More recently, mutations in SPINK1 and CTRC have been reported in patients with idiopathic pancreatitis. Those were all normal/negative in this patient. The earlier history of present illness with flying to and from Kenya triggering the episodes of pancreatitis made us suspicious of other mechanisms underlying the etiology of her pancreatitis. The ethnic background led to further analysis of hemoglobinopathies, which revealed elevated hemoglobin F. Elevated fetal hemoglobin is not uncommon; it has been detected in around 10% of teenage high school students[13], a few of them with abnormalities. Amongst these, the γ-globulin gene (HPFH Swiss) alteration is most frequent amongst females, all of them described as of Caucasian origin[11]. Detailed studies of our young black female patient revealed this heterozygous transition at -158 C → T within the 5’ non-coding region of the γ-globulin gene (HPFH Swiss) (Table 2). No other abnormalities could be detected. Notably, the patient did not suffer from clinically overt thalassemia, not having the typical mutations in the hemoglobin A (β-chain). Since this particular variant is considered to be minor[15], this could not have been expected. Nevertheless, associations with rather complex hereditary traits have been described in these hemoglobinopathies[13].

Classical thalassemia is reported to be associated with acute pancreatitis; however, the etiology is biliary as gallstones are typical in these patients. Indeed, in a series of 43 juvenile patients with acute pancreatitis, 30 suffered from cholelithiasis caused by thalassemia[16].

Sequencing the CFTR gene revealed a heterozygote sequence variant that has not been described previously (Table 2). The pathophysiological meaning, especially in relation to pancreatitis, is therefore unknown.

Whereas neither of these heterozygote mutations per se might have been sufficient to cause or contribute to pancreatitis, it is suggestive that the minor alterations in two genes, one pancreatic (CFTR) and one extrapancreatic (hemoglobin), might have culminated in a two-step mechanism leading to pancreatitis: impaired hemoglobin,
causing a certain degree of oxygen deficiency which is known to cause pancreatitis, e.g., during iatrogenic ischemia or heart-lung machine usage, imposed on a heterozygote mutation in the CFTR gene. This two-hit hypothesis is speculative as we did not investigate the functional changes imposed by such a transition in the non-coding region in the hemoglobin and the CFTR mutation alone or in combination.

There is only one study reporting on a small series of patients with clinically overt thalassemia, gallstones and biliary pancreatitis; however, our patient did not have overt thalassemia or gallstones/sludge or microthrombosis.

The pathologic oxygen saturation of hemoglobin in thalassemia has been described. Hypoxemia and ischemia have been demonstrated to be able to induce experimental pancreatitis. Microcirculatory disturbances are today considered to play an important role in the exacerbation of acute pancreatitis. Reduced perfusion of the pancreatic gland leading to hypoxia and ischemia is a well-described mechanism causing or worsening pancreatitis. Even in sickle-cell anemia, the acute pancreatitis is considered to be caused by microvascular occlusion. Conversely, hyperbaric oxygen therapy has been demonstrated to ameliorate acute pancreatitis. The combination of an alteration in a gene altered oxygen saturation with a gene altering pancreatic secretion represents the rendezvous of two genes, each in itself not sufficient to induce thalassemia or pancreatitis, an extrapancreatic and an intrapancreatic. This is supported by the finding in our patient with pancreas divisum with CFTR or SPINK1 mutations, also conditions that on their own might not be sufficient to cause pancreatitis.

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