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ACUTE PANCREATITIS UNCOMMON MANIFESTATION OF CYSTIC FIBROSIS? A CASE REPORT

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(Original scientific paper)

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Abstract

The pancreas is one of the primary organs affected by dysfunction of the cystic fibrosis transmembrane conductance regulator protein. While exocrine pancreatic insufficiency is a well-recognized complication of cystic fibrosis (CF), symptomatic pancreatitis is often under-recognized and occurs approximately in 20% of patients with CF and almost exclusively in pancreatic sufficient people. This is a case of acute pancreatitis in a ten-year-old boy in whom cystic fibrosis was suspected. Ten year old boy presented with stomach pain and vomiting for three days. On physical examination afebrile, conscious, dehydrated, occupies a forced position in bed. Abdomen was very painful on palpation epigastrically and periumbilically without organomegaly. Blood tests: Glycose= 8,4..11,4mmol/l, amylase= 147..222..660..800U/L, lipase=141..288..465..501U/L. Urine test positive for ketones, amylase in urine= 481..1302..8667U/L. Ultrasound and CT of abdomen with normal findings. The child was treated with parenteral rehydration, Amp. Ceftriaxon, Amp. Pantoparzole and subcutaneous somatostatin. Due to the persistence of elevated pancreatic enzymes, a sweat test was performed with high chloride values of 93..90 mmol/l. Chest X ray with normal findings. Tracheal aspirate was negative. Control laboratory analyzes with low inflammatory markers, but still with elevated pancreatic enzymes. Due to positive sweat test on two occasions and the manifestation of acute pancreatitis, CF was suspected and a blood sample was sent for genetic analysis. Symptomatic pancreatitis is uncommon manifestation in CF because it occurs exclusively in pancreatic sufficient CF patients. Newborn screening and improved panels of DNA mutation techniques are revealing more rare and nonclassical pictures of the disease, generally associated with pancreatic sufficiency and with an increased risk of developing pancreatitis.

Key words: *Cystic fibrosis, Acute pancreatitis, CFTR mutation, CFTR related disorders*

Introduction

Although the gene responsible for cystic fibrosis (CF) was identified more than twenty years ago, the relationship between genotype and phenotype in CF is still challenging and a matter of debate. CF is characterized by wide variability of clinical expression with regard to disease severity and rate of progression. This is caused, at least in part, by the large number of different mutations affecting the CFTR (cystic fibrosis transmembrane conductance regulator) gene, the existence of modifier genes and environmental factors, such as viral or bacterial pathogens, that influence disease phenotype (WHO, 2001; Welsh MJ et al., 2001). Soon after the CFTR gene was discovered, it became clear that dysfunction of CFTR in a single organ was associated with clinical phenotypes distinct from CF. For example, CFTR mutations have been identified in infertile males with no evidence of CF lung disease (Dumur V et al., Anguiano A et al., 1992; 1990; Patrizio P et al., 1993).

Even in 2010, CF remains in essence a clinical diagnosis (WHO, 2001; Welsh MJ et al., 2001; De Boeck K et al., 2006). It may also be defined either in molecular genetic terms as a disease caused by the presence of two CF-causing mutations one in each parental CFTR gene or in physiological terms as a disorder of electrolyte transport across epithelial membranes resulting from absence or abnormality of the CFTR protein. For the majority of affected individuals, there is little or no difficulty in diagnosing their condition as CF. The classical clinical syndrome is well known and easily recognised when an individual's signs and symptoms are being diagnosed. Moreover, even before the molecular basis of the disease was understood

patients were readily identified by their clinical presentation and a confirmatory sweat test documenting a sweat chloride concentration above 60 mmol/L. Eighty five percent of CF patients require pancreatic enzyme supplementation to digest food. These CF patients are termed “pancreatic insufficient” (CF-PI). The cystic fibrosis transmembrane conductance regulator (CFTR) gene encodes CFTR protein that functions as cyclic AMP-dependent chloride channel allowing the passage of anions and secondarily water into the lumen of pancreatic ducts. Luminal chlorides are exchanged for bicarbonates. The lack of CFTR channel or its disrupted function (being the consequence of CFTR gene mutations) results in reduced volume of more acidic secretion. It has been suggested that such a situation leads to the precipitation of highly concentrated protein-containing secretion with obstruction and organ damage. The intensity of this process determines the progression of the disease. Steatorrhea is the significant symptom of classical form of CF. Fifteen percent of CF patients do not require pancreatic enzyme supplementation and hence, are termed “pancreatic sufficient” (CF-PS). (Castellani C et al., 2009; Accurso FJ et al., 2008)

Most atypical CF patients can be confidently diagnosed with the help of reliable sweat tests and/or genetic analysis. These individuals usually present later in their lives with pancreatic sufficiency and milder respiratory disease. Currently, over 1700 mutations and polymorphisms have been identified in the CFTR gene. Because different mutations or variations in the CFTR gene are associated with a wide spectrum of clinical phenotypes or even associated with no disease at all, the demonstration of mutated CFTR genes in an individual does not predict with certainty, only at best with probability, this person’s prognosis [ECFS, 2006; CFF, 2007]. No doubt interactions with other genes and environmental factors substantially modify the clinical picture in each individual (Accurso FJ et al., 2008). Similarly, demonstration of an abnormal sweat test or abnormal potential difference across epithelial membranes might be helpful in assigning an individual to a CF or non-CF category.

Diagnostic criteria for CF are one or more of the phenotypic features of the disease or CF in a sibling or a positive immunoreactive trypsin (IRT, a neonatal screening test), in association with at least one other feature. The additional features includes a positive sweat test result on two occasions, a CF-causing mutation in each CFTR gene or an abnormal nasal potential difference(NPD). (Farrell PM et al., 2008; , Castellani C et al., 2008) A sweat chloride concentration above 60 mmol/L and/or the presence of 2 clinically relevant CF-causing mutations is uniformly accepted as diagnostic for the classical form of the disease (Welsh MJ et al., 2001; , De Boeck K et al., 2006; Rosenstein BJ et al., 1998; Farrell PM et al., 2008). However, this strict definition has obvious flaws. Patients with particular genotypes combining two CF-causing mutations may have a sweat chloride value in the intermediate range (30–60 mmol/L). The difficulty occurs when patients present with clinical symptoms suggestive of CF and a sweat chloride value in the intermediate range. Among these subjects, the subset with abnormalities in NPD measurement or 2 identified CFTR mutations has, on average, more severe lung disease (Goubau C et al., 2009) However, their disease symptoms are milder than those in subjects with a sweat chloride concentration above 60 mmol/L. Therefore, it is appropriate from a physician’s and also from a patient’s perspective to categorise these individuals differently from subjects with the classical life-shortening form of CF. Neonatal screening only identifies subjects at risk of being CF in whom the diagnosis needs to be further substantiated by a positive sweat test or by other physiological tests of CFTR function (e.g. NPD or intestinal current measurement (ICM)). The example of the p.R117H mutation demonstrates clearly that it is inappropriate to rely solely on IRT results and mutation analysis (Thauvin-Robinet C et al., 2009). There is a need to qualify patients who do not meet the diagnostic criteria of CF, but for whom there is evidence of CFTR dysfunction. . However, even among these individuals, there is a broad range of clinical phenotypes and disease severity. A CFTR-related Disorder (CFTR-RD) is defined as: a clinical entity associated with CFTR dysfunction that does not fulfil the diagnostic criteria for CF. Three main clinical entities illustrate these phenotypes: CBAVD (congenital bilateral absence of the vas deferens) with CFTR dysfunction, acute recurrent or chronic pancreatitis with CFTR dysfunction and disseminated bronchiectasis with CFTR dysfunction.

Case report

We report a case of a ten year old boy presented with stomach pain and vomiting for three days. On physical examination afebrile, conscious, dehydrated, occupies a forced position in bed. Abdomen was very painful on palpation epigastrically and periumbilically without organomegaly. Initial laboratory tests: Le= 8.09…4.17, Er= 4.33…4.11, Hgb= 123…112, Hct= 32.7…29.31%, Tr= 248…201, Amylase= 111,21…147 U/L, ALKP= 219 U/L, CRP<0,2, LDH= 238 U/L, Urine: Aceton +++. Abdominal ultrasound

with with several enlarged ileocecal lymph nodes. Control urine analysis with normal findings. Blood gass analysis : pH : 7,38 ; PCO2: 37,7 kPa; BE: - 2,5 mmol/l ; HCO3: 22,2 mmol/l; PO2: 75,9 kPa ; O2sat.: 94,4 %. Na=138...139...142...138 mmol/l, K=3,6 ...3,8...3,4....4 mmol/l, Ca=2,33... 2,34 ... 2,30 ... 2,46 mmol/l, P= 1,32...1,26...0,86 ...1 ,50 mmol/l, Cl=108...106,,,107 ...101 mmol/l, Mg= 0,79...0,80 ... 0,75 ...0,83 mmol/l , Urea= 2,7...4,3 mmol/l - Creatinine= 46,7...50,2 umol/l, glucose: 11,41 mmol/l – Total proteins= 68...67...66...74 g/l, Albumines=46...44...43...47 g/l - total bilirubin = 6,5... 6,4... 3,8 ... 4 umol/l; dir. bilirubin =2,7 .... 2,8 ... < 1,8 ...1,8 umol/L; indirect bilirubin = 3,8 ...3,6 ....2,2 umol/L, AST = 14... 27 ... 20 ...17 ...17 ....25 U/L, ALT = 11... 24...20....13 ...12... 19 U/L, GGT =11...11...10 ...11...10 ...12 U/L, LDH= 175...187...163...190...195...180 U/l, AlkP= 168...167 U/L. Control amylase = 171...222...502...315...332...660...800 - Lipase= 141...123....288...176...251....465...501, Urine amylase : 481...1302...524....1103....8667 - IEPH: IgA= 0, 88 g/l ;IgG= 10, 56 g/l IgM=1, 13 g/L. After admission the child was treated with parenteral rehydration, Amp. Ceftriaxon, Amp. Pantoparzole and subcutaneous Somatostatin. Abdominal CT with normal findings. Due to the persistence of elevated pancreatic enzymes, a sweat test was performed with high chloride values of 93..90 mmol/l.Chest X was with ray with normal findings. Tracheal aspirate was negative. Control laboratory analyzes with low inflammatory markers, but still with elevated pancreatic enzymes - serum amylase = 918 U/L, Lipase= 786 U/L – Urine amylase : 3225 U/L. Due to positive sweat test on two occasions and the manifestation of acute pancreatitis, CF was suspected and a blood sample was sent for genetic analysis. The basic 11 mutations have been made and all are negative. The child was released to home treatment with Caps. Omeprazole and hygienic-dietary regimen of nutrition. At the first and only control (because the child was not brought to the second scheduled control) amylase and lipase with normal values and elevated chlorides in sweat test = 93 mmol/l.

Discussion

A CFTR-related Disorder (CFTR-RD) is defined as: a clinical entity associated with CFTR dysfunction that does not fulfil the diagnostic criteria for CF. Three main clinical entities illustrate these phenotypes: CBAVD (congenital bilateral absence of the vas deferens) with CFTR dysfunction, acute recurrent or chronic pancreatitis with CFTR dysfunction and disseminated bronchiectasis with CFTR dysfunction. CF-causing mutations, p.F508del being the most common, that generally have <2% of normal CFTR function lead typically to pancreatic insufficiency in homozygotes. In contrast, CF patients with genotypes producing ~5% of normal CFTR function often have pancreatic sufficiency (Chen JM et al., 2009). In the human exocrine pancreas, CFTR is predominantly expressed at the apical membrane of the ductal and centroacinar cells that line small pancreatic ducts where it controls cAMP-stimulated HCO^-_3 secretion into the duct lumen (Poulsen JH et al., 1994; Ko SB et al., 2004; Park HW et al., 2010). The major role of CFTR in pancreatic ducts is to dilute and alkalinize the protein-rich acinar secretions, thereby preventing the formation of protein plugs that predispose to pancreatic injury (Chen JM et al., 2009). Stimulated by findings that both idiopathic chronic pancreatitis (ICP) and CF pancreatic disease show early ductal plugging resulting from inspissated secretions, chronic pancreatitis is a known cause of falsepositive sweat tests (Welsh MJ et al., 2001) and CF patients occasionally suffer from pancreatitis, in 1998 two groups simultaneously reported an association between CFTR mutations and ICP (Cohn JA et al., 1998; Sharer N et al., 2010). About 30% of patients with ICP or recurrent acute pancreatitis are found to carry CFTR mutations. No specific CFTR mutations are associated with ICP, but rare or private class 4 or class 5 mutations (Welsh MJ et al., 1993; Zielenski J et al., 1995) are generally found in these patients. Almost 18% of subjects with ICP had common CF-causing mutations, whereas ~2% were compound heterozygotes who had a CF-causing mutation plus a milder CFTR allele (Noone PG et al., 2001). Combined data from these earlier studies indicated that ~18% of subjects with ICP had common CF-causing mutations, whereas ~2% were compound heterozygotes who had a CF-causing mutation plus a milder CFTR allele (Noone PG et al., 2001). Two studies analyzed all CFTR exons and flanking regions in 78 well-defined ICP patients. These studies demonstrated that the risk of ICP increases to 6.3, 2.4, and 37 times that of normal with a CF-causing mutation, the IVS8-5T allele, and a CF-causing mutation plus a milder allele in trans, respectively (Audrézet MP et al., 2002; Cohn JA et al., 2005). More recent studies corroborating these findings suggest that CF carriers exhibit slight CFTR dysfunction (i.e. individuals with 50% of normal CFTR function account for most CFTR-related attributable risk, because they represent 3% of the population in many countries [Bishop MD et al., 2005; Cohn JA et al., 2005; Weiss FU et al., 2005; Keiles S et al., 2006; Tzetis M et al., 2007). SPINK1 (encoding serine peptidase inhibitor, Kazal type 1, a trypsin inhibitor secreted by the pancreas) is one of the three ICP susceptibility genes involved in the pathway of

premature trypsinogen activation and inactivation (Chen JM et al., 2009). Gene-gene interactions have been documented in individuals who inherit both low-penetrance SPINK1 variants and CFTR mutations in ICP. Coinheritance of the common SPINK1 N34S allele (de Cid R et al., 2010) and at least one abnormal CFTR allele accounts for 1.5% (1/67), 4% (1/25), 5.1% (2/39) and 7.7% (3/39) of the total patients analyzed, respectively, in four studies in which all the CFTR and SPINK1 exons were analyzed and the diagnosis of ICP was unambiguous (Noone PG et al., 2001; Audrézet MP et al., 2002; Weiss FU et al., 2005; Tzetis M et al., 2007); a total of ~4.1% of ICP patients were double heterozygotes of SPINK1/CFTR variations. In particular, a synergistic effect was observed between a CFTR compound heterozygote genotype and the SPINK1 p.N34S allele. Pancreatitis risk is increased ~40-fold with two CFTR mutations, 20-fold with p.N34S, and 900-fold with both CFTR and SPINK1 mutations (Noone PG et al., 2001). Recent work has identified a mutation in carboxypeptidase A1, primarily in childhood pancreatitis (Witt H et al., 2013) The PRSS1 gene encodes for cationic trypsinogen— autosomal dominant, with 80% penetrance. p.R122H and p.N291 are the most common mutations (80%). The CTRC gene encodes for CTRC, which acts as a defense mechanism against intrapancreatic trypsin autodigestion by catalyzing rapid trypsin degradation. A loss of function mutation has been identified in patients with CP (Ravi Kanth V et al., 2014; LaRusch J et al., 2015). A higher frequency of mutations in the CFTR gene in patients with idiopathic CP (upward of 30% in the group and representing a 2- to 6-fold increase above the control population) was first demonstrated in 1998 (Sharer N et al., 1998; Cohn JA et al., 1998). There is an up to 40-fold risk for pancreatitis in individuals with compound heterozygote CFTR mutations (Noone PG et al., 2001). In patients with CF, pancreatitis occurs in 20% of those who are PS. To evaluate genotype-phenotype correlations, the Pancreatic Insufficiency Prevalence score was developed and validated to determine severity in a large number of CFTR mutations. Specific CFTR genotypes are associated with pancreatitis. Patients who carry genotypes with more mild phenotypic effects have a greater risk of developing pancreatitis than patients carrying genotypes with moderate-severe phenotypic consequences at any given time (Ooi CY et al., 2011)

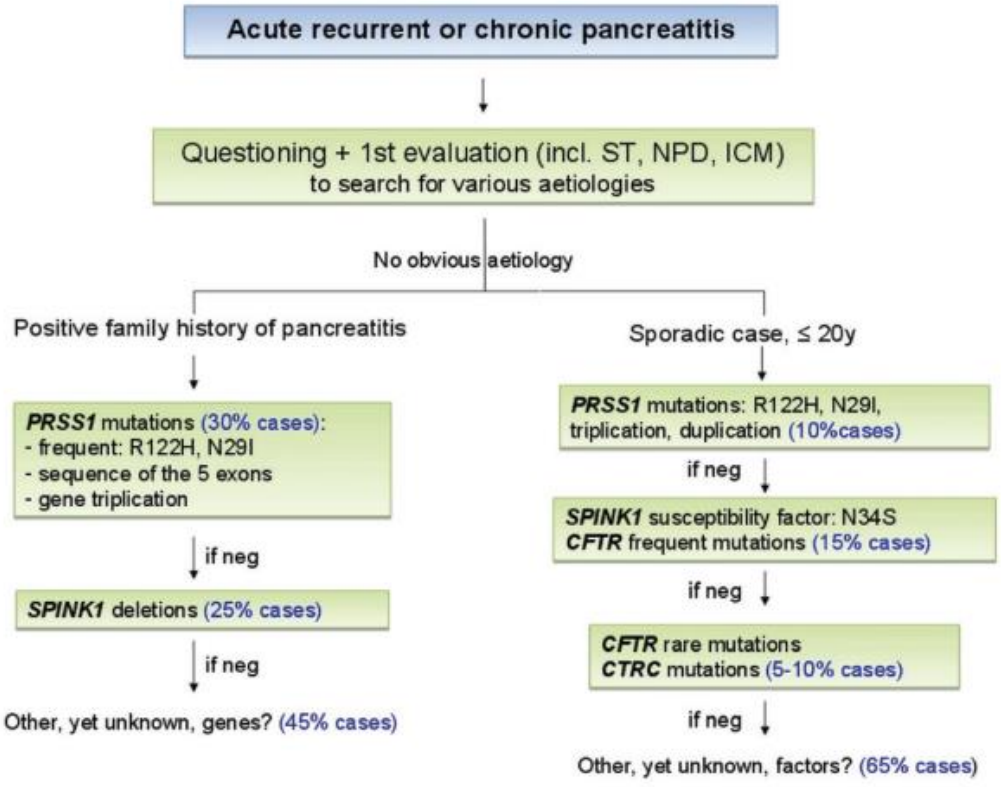

Figure 1. Diagnostic algorithm for acute recurrent or chronic pancreatitis. Summarize clinical, functional, and genetic diagnostic testing in patients presenting with acute recurrent or chronic pancreatitis. Abbreviations: PRSS1 (cationic trypsinogen); SPINK1(Serine protease inhibitor Casal type 1), CTRC (chymotrypsin C).

Conclusion

Symptomatic pancreatitis is uncommon manifestation in CF because it occurs exclusively in pancreatic sufficient CF patients. Newborn screening and improved panels of DNA mutation techniques are revealing

more rare and nonclassical pictures of the disease, generally associated with pancreatic sufficiency and with an increased risk of developing pancreatitis. But the diagnosis of a limited number of CFTR-RD patients is not clear-cut. A grey zone exists between CFTRRD and CF. If we are very close to the criteria required to identify these individuals as CF patients, the preferred option is to designate them as CFTR-RD and to follow them at least once a year. Some of these CFTR-RD patients will never meet the criteria to be classified as CF. In the case of other CFTR-RD patients, some years later these individuals will progress to a diagnosis of CF and will require follow-up in CF centres. Thanks to advances in science and our knowledge of CFTR dysfunction in CF and CFTR-RD patients, there is confidence that the diagnosis and treatment of these disorders will improve.

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