Journal of Pediatric Sciences

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Journal of Pediatric Sciences 2010;6:e59

How to cite this article:

Gonçalves JP, Neiva F, Antunes H. Mono-Symptomatic Cystic Fibrosis: a case report. Journal of Pediatric Sciences. 2010;6:e59

CASE REPORT

Mono-Symptomatic Cystic Fibrosis: a case report

Jean-Pierre Gonçalves[1], Filipa Neiva[1], Henedina Antunes[2]

Abstract:
Background and aim: Cystic Fibrosis (CF) is a monogenic disorder with heterogeneous phenotypic presentation. The diagnosis of typical cases is usually simple but in the atypical cases it is a clinical challenge and involves high clinical suspicion. In atypical cases, the sweat test may show border-line or normal values and the diagnosis involves the search for mutations in the CFTR gene, clinical features and follow-up.
Case report: We present a case of an adolescent boy affected by recurrent acute pancreatitis (AP) started at puberty, with normal sweat values, carrier of compound heterozygosity (I507del+IVS8(5T)). The I507del mutation is a severe CFTR mutation. In contrast, the IVS8(5T) mutation is not associated with clinical cystic fibrosis but, in compound heterozigosity with a more severe mutation, can be causative of mono- or oligo-symptomatic CFTR-related disorders.
Conclusion: This is probably the first case report of an atypical CF in a patient with the compound heterozygosity I507del+IVS8 5T. It confirms the challenges and difficulties for diagnosing atypical CF and highlights the role of CFTR mutations in the pathogenesis of idiopathic pancreatitis.

Keywords: Atypical Cystic Fibrosis; Compound Heterozigosity; I507del; IVS8(5T).
Received: *21/10/2010;* ***Accepted:*** *23/11/2010*

Introduction

Cystic Fibrosis (CF) results from mutations in the gene encoding the CF transmembrane conductance regulator protein (CFTR). Over 1000 CFTR mutations have been identified and have been archived on an online database [1]. It is a monogenic disorder and can present a heterogeneous phenotypic expression. The diagnosis in some patients is a clinical challenge, depending on a high clinical suspicion, especially in cases of atypical CF.

Patients with this type of CF in the sweat test may show normal or borderline values and the diagnosis is mainly based on clinical features and follow-up [2,3].

These cases have frequently compound heterozygosity in CFTR and an unusual presentation and/or late onset of symptoms, such like pancreatitis and infertility.

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Case Report

A 13-year-old Caucasian boy was referred with intense abdominal pain, in periumbilical region, colic-like, without irradiation, and vomiting with

16 hours of evolution. No past medical history was noted, but he did describe intermittent abdominal discomfort at least three per year. At the emergency room admission he was hemodynamically stable and constitutionally well (weight in the 10th percentile) without fever, anorexia or diarrhea. He was very complainant, assuming anti-pain (fetal) position, slightly dehydrated and the abdominal examination revealed epigastrium and periumbilical tenderness, but without abdominal defense. Laboratory findings showed amilasemia (448 U/L; normal range for age (NR) = 30 to 100 U/L) and lipasemia (1866 U/L; NR = 145 to 216 U/L). The remainder of his laboratory workup was normal, including serum cholesterol and triglycerides. The infectious serology for measles, parainfluenza, rubella, hepatitis virus A and B, cytomegalovirus, leptospira and mycoplasma were negative for recent infection. Simple abdominal radiography and abdominal ultrasound were normal.

He was admitted at the pediatrics department and conservative treatment (bowel rest, hydratation and analgesics) was pursued. Four days after admission he was symptoms-free, with normal serum amylase and lipase and discharged with the diagnosis of acute pancreatitis.

At ambulatory follow-up he made *a* magnetic resonance cholangiopancreatography, two different sweat tests that were normal and a genetic study for the most common CFRT mutations, in Portuguese population, which was negative.

In April 2006 he had a new episode of AP. An abdominal ultrasound (US) showed a hyperechoic pancreas consistent with edematous AP. Four days after admission he was symptoms-free and discharged with the diagnosis of idiopathic recurrent pancreatitis (RP). It was realized subsequently an endoscopic retrograde cho***l***angiopancreatography (ERCP) that was normal. With the same sample used in the previous genetic study and the collaboration of the Molecular Diagnosis Laboratory (Geneva University Hospitals) other mutations associated with RP were searched, namely in CFTR and *SPINK1* genes. The molecular genetic testing results showed a compound mutation in CFTR (I507del+IVS8 5T).

Attending this result we performed other studies to exclude other possible CFTR-related signs, including respiratory infection and function or azoospermia. The chest radiography, spirometry, semen analysis and ultrasonography of the vas deferens and the seminal vesicles were normal. Tests for pancreatic endocrine and exocrine function were also normal.

These data suggested a diagnosis of atypical CF mono-symptomatic.

To complete the genetic evaluation, the siblings and both asymptomatic parents were tested because they are potentially at risk of similar disease. This genetic study showed that the father and the two siblings are carriers of the severe CFTR mutation (I507del) and the mother is carrier of the mutation IVS8 5T.

Discussion

We report a case of a teenage boy with an atypical CF. This diagnosis was a clinical challenge. In fact inappropriate categorization of a patient with an atypical form can leads to an unnecessary burden of therapies and lifestyle restrictions.

The diagnosis of CF is a clinical decision supported by biochemical and genetic tests. A CF Foundation consortium (USA) attempted to provide definitive diagnostic criteria and despite their definition is imperfect it serves as useful foundation [4]. Our patient meets these criteria for CF, he has two CFTR mutations and a clinical feature consistent with CF (recurrent pancreatitis). It is an atypical case of CF because he has two normal sweat tests. Patients with atypical disease tend to present late in childhood

or as adults with less widely known complications such pancreatitis, congenital bilateral absence of the vas deferens (CBAVD) and azoospermia, or nasal polyps [5]. In our case study the unique symptom was pancreatitis, in fact pancreatitis is a rare manifestation of CF and may rarely be the presenting symptom in adolescent or adults patients (<2% of patients with CF) [6].

Patients with compound heterozygous CF gene mutations, unlike ΔF508 homozygotes, typically have pancreatic sufficiency and are frequently diagnosed at an older age due to the absence of onset pulmonary symptomatology. It is important to suspect a CFTR mutation in a patient with idiopathic pancreatitis. Our patient has a compound heterozygosity [I507del +IVS8(5T)]. The I507del mutation is a severe CFTR mutation. In contrast, the IVS8(5T) mutation is not associated with clinical cystic fibrosis but, in compound heterozigosity with a more severe mutation, can be causative of mono- or oligo-symptomatic CFTR-related disorders. Our report confirm that the presence of T5 allele with a severe CFTR mutation (I507del) is associated with non-classic CF. In males carriers of some types of T5 alleles in trans with a CFTR mutation are at higher risk of developing CBAVD [7], so it was important exclude this feature in our case.

The natural history of atypical CF is poorly understood because it is unclear when CF starts and develops, and what kind of prevention therapy is needed. However, in these patients periodic reviews are required because the effects of CFTR mutations may be cumulative [8].

Conclusion

This is probably the first case report of an atypical CF in a patient with the compound heterozygosity I507del+IVS8 5T.It confirms the challenges and difficulties for diagnosing atypical CF and highlights the role of CFTR mutations in the pathogenesis of idiopathic pancreatitis.

Similarly to the well described references, our report confirms that the presence of 5T allele with a severe CFTR mutation is associated with non-classic CF.

Finally, the effects of mutant CFTR can accumulate over the time, so patients with atypical CF require individualization on their therapy and a regular review of labels and follow-up.

Acknowledgments

The authors wish to thank Dr. Pedro Pereira who performed the ERCP and the Molecular Diagnosis Laboratory (Geneva University Hospitals), the Institute for Molecular and Cell Biology (Oporto University) and the National Institute of Health Dr. Ricardo Jorge that made the genetic study.

References

1. Cystic Fibrosis Mutation Database. htpp:// genet.sickkids.on.ca/cftr/app.

2. Boyle MP. Non-classic Cystic Fibrosis and CFTR-related diseases. Curr *Opin Pulm Med* 2003; 9:498-503

3. De Boeck K, Wilschanski M, Castellani C, Taylor C, Cuppens H, Dodge J *et al*. Diagnostic Working Group. Cystic fibrosis: terminology and diagnostic algorithms. *Thorax* 2006; 61:627-35.

4. Rosenstein BJ, Cutting GR. The diagnosis of cystic fibrosis: a consensusstatement. Cystic Fibrosis Foundation Consensus Panel. *J Pediatr* 1998; 132:589-95.

5. Stern R, Leroy W. The diagnosis of cystic fibrosis. *N Engl J Med* 1997; 13;336:487-91.

6. Choudari CP, Imperiale TF, Sherman S, Fogel E, Lehman GA. Risk of pancreatitis with mutation of the cystic fibrosis gene. *Am J Gastroenterol* 2004; 99:1358-63.

7. Groman JD, Hefferon TW, Casals T, Bassas L, Estivill X, Des Georges M *et al*. Variation in a repeat sequence determines whether a common variant of the cystic fibrosis transmembrane conductance

regulator gene is pathogenic or benign. *Am J Hum Genet* 2004;74:176-9.

8. Bush A, Wallis C. Time to think again: cystic fibrosis is not an "all or none" disease. *Pediatr Pulmonol* 2000; 30:139-44.