Isolated idiopathic chronic pancreatitis associated with a compound heterozygosity for two mutations of the CFTR gene

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SUMMARY
We report the case of a patient suffering from idiopathic chronic pancreatitis (ICP) and compound heterozygous for mutations G542X and S1235R of the cystic fibrosis transmembrane regulator (CFTR) gene. The patient had normal sweat test and no other clinical sign usually linked with a typical or moderate pathology (bronchiectasis, nasal polyposis, congenital absence of the vas deferens) of the CFTR gene. G542X is a severe mutation, which is usually found in classical cystic fibrosis when associated with other severe mutations. S1235R is a quite rare abnormality recently reported as being potentially pathogenic when combined in trans with a second CF mutation.

Our case is quite similar to the only other six patients in the literature in whom only the pancreas is affected and who bear a rare mutation with moderate effect. The history and the clinical features of our patient indicate an unambiguous isolated ICP in which the presence of the S1235R mutation — in trans with regard to G542X — is likely responsible for the ICP phenotype. This case could throw light on some of the as yet poorly known abnormalities of the CFTR gene in the ICP phenotype.

RÉSUMÉ
Pancréatite chronique idiopathique isolée associée à une hétérozygo en deux mutations du gène CFTR
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Nous rapportons le cas d’un malade souffrant de pancréatite chronique idiopathique (PCI) hétérozygote composite pour les mutations G542X et S1235R du gène CFTR. Le malade avait un test sudoral normal et pas d’autre signe clinique associé habituellement à une affection (bronchiectasie, polyposse nasale, agénésie des canaux déférent) associée aux mutations du gène CFTR. G542X est une mutation sévère rencontrée assez fréquemment — en association avec d’autres mutations sévères — dans des formes de mucoviscidose classique. S1235R est une anomalie assez rare, rapportée récemment comme étant potentiellement délétère quand elle est associée en trans à une autre mutation du gène CFTR. Notre cas est à rapprocher des seuls six malades de la littérature dont l’atteinte semble limitée au pancréas et porteurs d’une mutation rare à effet modéré. L’histoire et le tableau de la maladie chez notre malade évoquent de manière complète et sans ambiguïté une PCI isolée dans laquelle la présence de la mutation S1235R — en position trans par rapport à G542X — est très vraisemblablement responsable du phénotype de pancréatite chronique idiopathique. Ce cas peut contribuer à une meilleure connaissance d’une certaine spécificité d’anomalies — encore mal connues — du gène CFTR dans le phénotype de PCI.

Case report
A 33-year-old man was seen for painful epigastric syndrome associated with high levels of serum pancreatic enzymes: hyperamylasemia, 358 U/L (normal, 114-286); hyperlipasemia, 2460 U/L (normal, 114-286); hyperleucocytosis, 19.1 G/L (normal, 4-10). CT scan and MRI confirmed the diagnosis of acute pancreatitis (Balthazar stage E) with diffuse anomalies and calcifications and with inflammatory lesions prevailing in the small pancreas where there was duct dilatation. Cancer of the pancreas and autoimmune pancreatitis were excluded by two
endoscopic ultrasonographies and cholangio- and wirsungo-
MRIs according to usual clinical criteria. The clinical course was
favorable with parenteral nutrition.

The patient had had epigastric pain probably due to the
pancreas from the age of 10. His growth was normal and he had
no recurrent lung infections. The diagnosis of chronic pancreatitis
was made in 1991 when he had pain following a meal with fat
food and wine. About every 18 months thereafter, he had severe
attacks without any identifiable cause (no biliary history, no clear
metabolic disturbance, intermittent and moderate alcohol con-
sumption estimated at 5 drinks per week at any time). These
recurrent attacks required parenteral nutrition and intensive care.

A pancreatic CT-scan was performed one week after the most
recent episode which showed a favorable evolution of the acute
pancreatic lesions and, for the first time, showed parenchymatous
calculations of the uncinate process of the pancreas (figure 1).
Otherwise, the aspect of the liver, spleen, adrenal glands, gall
bladder, and the two kidneys was normal. Thoracic CT-scan did
not reveal any abnormal lung image. A bronchial fibroscopy and
an ENT and upper gastrointestinal endoscopy were normal.
Therefore, the hypothesis was localized chronic calcifying pan-
creatitis of an idiopathic nature.

A genetic study was carried out in the proband and in his
paternal grandparents, parents and his brother. First, 29
mutations including the most frequent in France were sought for
paternal grandparents, parents and his brother. First, 29
mutations including the most frequent in France were sought for
the presence of the S1235R mutation in exon 19 (T

Analysis of the TRY4 gene encoding for the cationic trypsinogen
gene did not show any mutation (C. Férec, Brest). The genetic
status of the proband and his kindred are given figure 2. There
were no other compound heterozygotes and no history of
pancreatitis in the family, even in the three children of the
proband.

Owing to the presence of two mutations, the patient under-
went a sweat test with chloride assay with a specific electrode
after pilocarpine stimulation (Exsudose, France). A value of 15
mmol/L (normal, < 40; abnormal, > 60) was obtained.

Discussion

Although it is known that a mutated gene is directly involved
in hereditary pancreatitis, an autosomal dominant disease, it is
difficult to assess the responsibility of genetic factors among
patients presenting an idiopathic chronic pancreatitis. The
problem with rigorous genetic studies targeting the CFTR gene
among ICP patients is especially: a) the need to rule out any link
with chronic excessive alcohol consumption; b) the great variabil-
ity of the CFTR gene in which, 1000 mutations (http:
//genet.sickkids.on.ca) have so far been described (with a
variable phenotype and often poorly understood effects); c) the
limitation of the exclusion rate of mutations in most cohort studies.
Among all reported ICP patients, a very small minority presents a
mutation on each CF allele.

Our attention was drawn more particularly to the 14
non-alcoholic ICP patients [4, 5, 7, 11, 12] presenting a
compound heterozygosity for two mutations in the coding
sequence of the CFTR gene. Table I lists all the available
biological and clinical data of the 14 patients to which we added
our case.

Patients n°1 and n°8 bear a CBAVD and the R117H mutation
which is very often responsible for this CFTR pathology. Patient
n°2 is a compound heterozygote for R117H and N1303K: her
phenotype is that of a moderate cystic fibrosis as shown by
respiratory signs and an abnormal nasal potential difference in
the context of a borderline sweat test. With a sweat test of 108
mmol/L and the presence of two severe mutations, patient n°3
resembles more a cystic fibrosis patient than an ICP patient.
Patient n°4 is debatable from two points of view: a) her status of
compound heterozygote for two mutations of the CFTR gene
including one (R75G) considered by some as a simple polymor-
phism [14], and by others as a mild mutation [15]; b) her clinical
features of pancreatic damage and nasal polyposis. Patient n°12
with a clearly positive sweat test and attacks of the respiratory tract
resembles a CF patient more than an ICP bearer.

Patients n°5, 6, 7, 9, 10, 11 [11, 12] and patient n°15 [our
report] show a symptomatology limited to pancreatic damage,
with no other clinical or biological signs usually present in a
phenotype of atypical cystic fibrosis (i.e. no lung damage, no
nasal polyposis, no sterility). Moreover they are compound
heterozygotes for two mutations of the CFTR gene. Therefore,
these 7 patients might have a mild CF mutation that could be
more specific of the occurrence of ICP. In five patients (n° 5, 9, 10,
11, 15) who bear a frequent mutation well known for its severity
(F508del or G542X), the involvement of the ICP phenotype could
lie in their “second” missense mutation, i.e. L997F in exon 19
(Patient n°5), I1027T in exon 17a (Patient no9), D1152H in exon
11, 15) who bear a frequent mutation well known for its severity
(F508del or G542X), the involvement of the ICP phenotype could
lie in their “second” missense mutation, i.e. L997F in exon 19
(Patient n°5), I1027T in exon 17a (Patient no9), D1152H in exon
18 (Patients n°10 and 11) and S1235R in exon 19 (Patient n°15); and
the presence of 2 of these 4 missense mutations in patient n°7
could actually strengthen this hypothesis but to date little is known
about the possible impact of his 5T allele on the phenotype
(possible sterility). In patient n°6, calling the mutation “more
pancreatic” is more debatable: the mutation 3849+10kbC>T

(intron 19) has been described quite frequently in various moderate phenotypes and the effect on the phenotype of the very rare frameshift mutation 3878delG (exon 20) is not known.

So, out of the fourteen CF alleles of ICP patients (no5, 6, 7, 9, 10, 11, 15), eight CF alleles (57%) have a mutation affecting the C-terminal part of the CFTR protein encoding for the CFTR protein region corresponding to the membrane spanning domain 2 (MSD2) and the nucleotide-binding domain 2 (NBD2). It is also the case for the 2 CF mutated alleles 3120G>A in exon 16 (patient n°13) and G1069R in exon 17b (patient 14), but we have no information about the presence or absence of other clinical features these patients could present. Whether an abnormality in the C-terminal domain of the CFTR protein could mean more specific damage to the pancreatic epithelium through unknown mechanisms still remains to be established.

Table I. – Review of the literature: patients with an idiopathic chronic pancreatitis and compound heterozygous for two mutations of the CFTR gene.

<table>
<thead>
<tr>
<th>Patient</th>
<th>CFTR no</th>
<th>PolyT genotype</th>
<th>Sex genotype</th>
<th>Age (years)</th>
<th>Sweat chloride (mmol/L)</th>
<th>Anamnestic features known to be associated with atypical CF</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>F508del/R117H</td>
<td>9T/7T</td>
<td>M</td>
<td>45</td>
<td>29 CBAVD</td>
<td>[4]</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>N1303K/R117H</td>
<td>9T/7T</td>
<td>F</td>
<td>n.a.</td>
<td>37 bronchiectasis, sinusitis, positive NPD</td>
<td>[5]</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>R1162X/2789+5G&gt;A</td>
<td>7T/7T</td>
<td>F</td>
<td>n.a.</td>
<td>108 chronic cough</td>
<td>[5]</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>I336K/R75Q</td>
<td>7T/7T</td>
<td>F</td>
<td>26</td>
<td>26 nasal polyposis</td>
<td>[7]</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>3849+10kbC&gt;T/3878delG</td>
<td>7T/7T</td>
<td>M</td>
<td>14</td>
<td>n.a. none</td>
<td>[11]</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>F508del/R117H</td>
<td>n.a.</td>
<td>M</td>
<td>45</td>
<td>29 CBAVD, smooth P. aeruginosa</td>
<td>[12]</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>F508del/I1027T</td>
<td>n.a.</td>
<td>M</td>
<td>32</td>
<td>59 none</td>
<td>[12]</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>F508del/D1152H</td>
<td>n.a.</td>
<td>M</td>
<td>8</td>
<td>62 none</td>
<td>[12]</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>F508del/D1152H</td>
<td>n.a.</td>
<td>F</td>
<td>15</td>
<td>32 none</td>
<td>[12]</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>F508del/P574H</td>
<td>n.a.</td>
<td>F</td>
<td>26</td>
<td>81 sinus surgery, S. aureus, S. maltophilia</td>
<td>[12]</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>F508del/3120G&gt;A</td>
<td>n.a.</td>
<td>F</td>
<td>40</td>
<td>n.a.</td>
<td>[12]</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>F508del/G1069R</td>
<td>n.a.</td>
<td>M</td>
<td>16</td>
<td>n.a.</td>
<td>[12]</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>G542X/S1235R</td>
<td>7T/7T</td>
<td>M</td>
<td>35</td>
<td>15 none</td>
<td>[this study]</td>
</tr>
</tbody>
</table>

n.a.: not available. CF: cystic fibrosis. CBAVD: congenital bilateral of vas deferens. NPD: nasal potential difference.
was linked to the particular haplotype 7T/12TG/M470, which our patient also bears. At the same time, Monaghan et al. [17] considered that S1235R — when combined with a second CF mutation — may be pathogenic.

In conclusion, among the 7 PCI patients so far reported as compound heterozygous for two mutations of the CFTR gene and bearers of a pathology limited to the pancreas, our patient, with his detailed clinical investigation showing the isolated nature of the pancreas damage, could be one of the most interesting cases of compound heterozygosity for two mutations of the CFTR gene, including one (S1235R), which is not very common in the different forms of cystic fibrosis. This could lead to an exhaustive analysis of the CFTR gene in well-defined ICP patients. In several cohorts studied so far, the question is whether the exclusion rate of mutations was too limited and thus underestimated in ICP patients who are compound heterozygous for 2 mutations of the CFTR gene. If so, this would deprive us of information about rare mutations which — like the S1235R mutation in the patient reported here — could explain more specifically the ICP phenotype.

REFERENCES