Familial clustering of recurrent pericarditis may disclose tumour necrosis factor receptor-associated periodic syndrome

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ABSTRACT

Objective. Although several causes of recurrent pericarditis have been identified, the etiology remains obscure in most cases. The tumour necrosis factor receptor-1 associated periodic syndrome (TRAPS) is the most common autosomal dominant autoinflammatory disorder and is caused by mutations in the TNFRSF1A gene encoding the 55-kD receptor for tumour necrosis factor (TNF)-α. Serosal membrane inflammation is a common feature of TRAPS, usually in the form of polyserositis. In addition, patients affected with recurrent pericarditis as the only clinical manifestation of TRAPS have been recently described.

Our aim was to investigate the possible involvement of mutations in the TNFRSF1A gene in a cohort of patients affected with idiopathic recurrent pericarditis.

Methods. Twenty consecutive patients diagnosed with idiopathic recurrent pericarditis were enrolled. Each patient underwent detailed examinations in order to rule out underlying diseases such as infections, connective tissue disorders and malignancies, and mutations of the TNFRSF1A gene were searched for by amplifying, using polymerase chain reaction (PCR), genomic DNA, and direct sequencing.

Results. TNFRSF1A mutations were found in 2 of the 20 patients. They were siblings, and they both carried a heterozygous low-penetrance R92Q mutation in the TNFRSF1A gene.

Conclusion. Familial clustering has been recently reported in up to 10% of patients with recurrent pericarditis, thus suggesting in some cases a possible genetic predisposition. Our study suggests that familial clustering may represent a clue for investigating mutations in the TNFRSF1A gene in these patients and eventually disclose TRAPS.

Introduction

Pericarditis may be caused by a wide spectrum of different conditions, most often including infections and autoimmunity. Although many causes have been identified, the etiology remains obscure in up to 85% of patients (1).

Recurrence occurs in up to 50% of patients with acute pericarditis (2). Tumour necrosis factor receptor-1 associated periodic syndrome (TRAPS) is the most common autosomal dominant autoinflammatory disorder and is caused by mutations in the TNFRSF1A gene (12p13), encoding the 55-kD receptor for tumour necrosis factor (TNF)-α (3). TRAPS is characterised by recurrent attacks of fever, typically lasting from 1 to 3 weeks. In addition to fever, common clinical features include peri-orbital oedema, a migratory erythematous plaque simulating erysipela with underlying myalgia, and arthralgia or arthritis. Serosal membranes inflammation is also a common feature, usually in the form of polyserositis (4, 5).

Patients affected with TRAPS typically do not respond to colchicine treatment, but are responsive to corticosteroid administration (6).

In addition, patients with TRAPS may present recurrent pericarditis as the sole clinical manifestation (4, 7) and, as we recently hypothesised, a poor response to colchicine treatment and/or a steroid dependence might be clues for investigating TNFRSF1A mutations (7).

In the present study, we have tested for mutations in the TNFRSF1A gene 20 additional patients diagnosed with recurrent idiopathic pericarditis.

Materials and methods

Patients

We enrolled 20 consecutive patients (9 males, 11 females) diagnosed with idiopathic recurrent pericarditis. Table I summarises the main characteristics of the cohort of the patients enrolled in the study. Each patient underwent detailed examinations in order to rule out underlying diseases such as infections, connective tissue disorders and malignancies.

Criteria for the diagnosis of recurrent pericarditis were: i) a documented first attack of acute pericarditis according to accepted diagnostic criteria: 1) chest pain 2) pericardial friction rub 3) ECG changes (typically widespread ST segment elevation, PR depression) 4) new or worsening pericardial effusion; a clinical diagnosis of acute pericarditis was made when at least 2 of these crite-
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Table I. Demographic, clinical and genetic characteristics of patients.

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age at testing/ Age at onset (yrs)</th>
<th>Sex</th>
<th>Mutations in TNFRSF1A</th>
<th>SAA (mg/L)</th>
<th>Diagnosis</th>
<th>Pt</th>
<th>Age at testing/ Age at onset (yrs)</th>
<th>Sex</th>
<th>Mutations in TNFRSF1A</th>
<th>SAA (mg/L)</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31/27</td>
<td>M</td>
<td>–</td>
<td>34</td>
<td>IRAP</td>
<td>11</td>
<td>43/39</td>
<td>F</td>
<td>–</td>
<td>4</td>
<td>IRAP</td>
</tr>
<tr>
<td>2</td>
<td>32/29</td>
<td>F</td>
<td>R92Q heterozygous</td>
<td>92</td>
<td>TRAPS</td>
<td>12</td>
<td>47/45</td>
<td>M</td>
<td>–</td>
<td>64</td>
<td>IRAP</td>
</tr>
<tr>
<td>3</td>
<td>38/34</td>
<td>F</td>
<td>R92Q heterozygous</td>
<td>78</td>
<td>TRAPS</td>
<td>13</td>
<td>56/54</td>
<td>F</td>
<td>–</td>
<td>8</td>
<td>IRAP</td>
</tr>
<tr>
<td>4</td>
<td>53/41</td>
<td>M</td>
<td>–</td>
<td>5</td>
<td>IRAP</td>
<td>14</td>
<td>44/44</td>
<td>M</td>
<td>–</td>
<td>48</td>
<td>IRAP</td>
</tr>
<tr>
<td>5</td>
<td>49/48</td>
<td>F</td>
<td>–</td>
<td>42</td>
<td>IRAP</td>
<td>15</td>
<td>36/35</td>
<td>M</td>
<td>–</td>
<td>23</td>
<td>IRAP</td>
</tr>
<tr>
<td>6</td>
<td>56/51</td>
<td>M</td>
<td>–</td>
<td>9</td>
<td>IRAP</td>
<td>16</td>
<td>26/5</td>
<td>F</td>
<td>–</td>
<td>6</td>
<td>IRAP</td>
</tr>
<tr>
<td>7</td>
<td>22/18</td>
<td>F</td>
<td>–</td>
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<td>IRAP</td>
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<td>21/21</td>
<td>F</td>
<td>–</td>
<td>58</td>
<td>IRAP</td>
</tr>
<tr>
<td>8</td>
<td>31/28</td>
<td>M</td>
<td>–</td>
<td>7</td>
<td>IRAP</td>
<td>18</td>
<td>32/28</td>
<td>F</td>
<td>–</td>
<td>184</td>
<td>N.K.</td>
</tr>
<tr>
<td>9</td>
<td>27/25</td>
<td>F</td>
<td>–</td>
<td>2</td>
<td>IRAP</td>
<td>19</td>
<td>37/36</td>
<td>M</td>
<td>–</td>
<td>2</td>
<td>IRAP</td>
</tr>
<tr>
<td>10</td>
<td>38/36</td>
<td>M</td>
<td>–</td>
<td>16</td>
<td>IRAP</td>
<td>20</td>
<td>42/37</td>
<td>F</td>
<td>–</td>
<td>36</td>
<td>IRAP</td>
</tr>
</tbody>
</table>

Pt: patient; yrs: years; SAA: Serum Amyloid A; F: female; M: male; IRAP: idiopathic recurrent acute pericarditis; TRAPS: tumour necrosis factor receptor-1 associated periodic syndrome; N.K.: not known.

ria were present ii) evidence of at least one recurrence (8).

Additional evidence of active inflammation was recorded in all cases and included detection of elevated C-reactive protein, as a confirmatory finding (1). Recurrence was documented by recurrent pain and ≥1 of the following signs: pericardial friction rub, electrocardiographic changes, echocardiographic evidence of pericardial effusion, and elevations in the white blood cell count or C-reactive protein or erythrocyte sedimentation rate.

In all patients, serum amyloid A (SAA) levels were also determined. All cases were Caucasians of Italian Ancestry, and all provided a written consent for genetic testing, in accordance with the Declaration of Helsinki and according to local Ethics Committee regulations.

DNA extraction

Mononuclear cells were purified from peripheral blood from healthy donors and patients (with informed consent) by density gradient centrifugation on Ficoll-Paque (Amersham Biosciences, Buckinghamshire, UK), using a Beckman GS-6R tabletop centrifuge (Beckman Coulter SpA, Milan, Italy). Cells were washed 2 X in phosphate buffered saline (PBS), re-suspended in RPMI 164 (Invitrogen Ltd, Paisley, UK) (buffered with sodium bicarbonate to pH 7.2) supplemented with 7.5% fetal calf serum (FCS) (Hyclone, Thermofischer Scientific Inc, SouthLogan, UT), plated in plastic flasks (Sarstedt AG, Numbrecht, Germany) and incubated overnight at 37°C in a humidified atmosphere with 5% CO2. Non-adherent cells, which consisted principally of peripheral blood lymphocytes (PBL), were centrifuged and re-suspended in fresh RPMI 164 supplemented with 7.5% FCS. Genomic DNA was isolated from peripheral blood lymphocytes of patients and healthy controls using QIAamp DNA mini Kit (Qiagen, Hilden Germany).

Genomic DNA amplification and mutation detection

The TNFRSF1A gene exons 2, 3, 4 and 6, which encode for the extracellular domain of the 55-kD receptor for TNF-α, were amplified by polymerase chain reaction (PCR) using Expand High Fidelity PCR System (Roche, Germany). PCR products were purified using Wizard SV Gel and PCR Clean-Up System (Promega, Madison, WI, USA). Sequencing was carried out on the ABI 373DNA analyser (Bio-Fab Research srl, Italy) using the same primers as those used in the PCR.

Results

Two out of the 20 patients tested (patients 2 and 3 in Table I) carried a heterozygous low-penetrance R92Q mutation in the TNFRSF1A gene. They were siblings. Their father also carried the R92Q mutation, but he was clinically healthy. Both were diagnosed with TRAPS based on poor response to colchicine treatment, on the duration of fever attacks (>2 weeks), and on their excellent responsiveness to corticosteroids (prednisone >25 mg/daily). The 2 patients are currently being treated with a combination of colchicine (1 mg/daily), indomethacin (75-150 mg/daily) and prednisone (>12.5 mg/daily). Despite the treatment, they have not achieved good disease control and still complain of 3-5 recurrences every year. Furthermore, they are characterised by persistently elevated SAA (>78 mg/L), which have been measured at least three times, including during symptom-free intervals. For this reason, they will soon start treatment with the tumour necrosis factor-α neutralising agent, etanercept.

The two patients were both characterised by adult disease onset, at the ages of 29 and 34 respectively. Another patient (patient 18), who does not carry any mutation in TNFRSF1A, was characterised by persistently elevated SAA levels and is currently considered as being affected by an unrecognised autoinflammatory disorder. No other patient carried mutations in TNFRSF1A gene, and all were diagnosed with idiopathic recurrent pericarditis since no other known causes of pericarditis were identified.

Discussion

Recurrent pericarditis may be isolated or associated with autoimmune rheumatic diseases, viral or bacterial infections, and neoplastic diseases (1). Although many causes have been identified, the
etiology of recurrent pericarditis remains obscure in most cases (8).

Recurrent pericarditis and other recurrent serositis, often in the form of polyserositis, are common in TRAPS (4, 5, 7); furthermore, patients with TRAPS presenting with recurrent pericarditis as the only clinical manifestation have been reported (4, 7). Dodè et al. (4) have recently described two patients presenting with recurrent pericarditis who carried the low-penetration mutations R92Q and P46L in TNFRSF1A gene. In addition we recently investigated 30 patients with recurrent pericarditis – all characterised by a poor response to colchicine treatment – for mutations in the TNFRSF1A gene; 4 out of 30 carried mutations in TNFRSF1A. Three of them, like the Dodè et al. cases, carried an R92Q mutation, and one carried a novel heterozygous ΔY103-R104 deletion in the exon 4, characterised by a six nucleotide heterozygous deletion (TACCGG nucleotide sequence) and causing the loss of the aminoc acids tyrosine and arginine at position 103 and 104, respectively (7). We therefore hypothesised that colchicine resistance and/or steroid dependence might be the clue for investigating TNFRSF1A mutations in patients of Mediterranean origin (7). The R92Q allele is common in patients of Mediterranean origin, and in a recent study its frequency in healthy Italian individuals was 2.25%. Moreover, in most of the R92Q patients, the mutation was inherited from one healthy parent (9). Nevertheless, its increased frequency among patients with periodic fever suggests that it is a low-penetration mutation rather than a benign polymorphism (10).

Although soluble TNFRSF1A serum levels in vivo do not seem to increase with attacks, monocytes from patients bearing the R92Q substitution show TNFRSF1A membrane staining and receptor shedding comparable to those in controls, thus suggesting that additional pathogenetic mechanisms may be operative in TRAPS (10).

Recently, Lobito et al. reported that the R92Q variant TNFRSF1A behaves like wild-type TNFRSF1A, with apparently normal folding, identical surface expression and TNF binding (11). The authors suggested that the pathogenesis of TRAPS in patients harbouring only the R92Q TNFRSF1A variant is probably different from that of patients carrying other mutations.

The R92Q allele may cause milder disease, and may often be associated with an oligosymptomatic course (5, 12). In addition, the low-penetration TNFRSF1A variant seems to contribute to atypical inflammatory responses in TRAPS, including cardiac diseases (myocarditis and pericarditis) (6, 7, 13, 14). Familial clustering of idiopathic pericarditis has been reported in one family (15), and Raatikka et al. reported one paediatric patient whose grandfather had recurrent pericarditis (16). Brucato et al. recently observed 6 patients out of 60 of whom one relative had – as in our 2 patients’ cases – a confirmed diagnosis of acute idiopathic pericarditis (17). In that study, familial occurrence of idiopathic pericarditis among relatives of patients with recurrent pericarditis was 10%. These data suggest a genetic predisposition in some cases of recurrent pericarditis. The author advocated further studies regarding the HLA system and other candidate genes, and suggested that counseling of patients with recurrent pericarditis should take into account familial clustering as well.

In our cohort, 2 siblings out of the 20 tested patients presented with recurrent pericarditis, and they both carried mutations in TNFRSF1A. This suggests that it may be interesting to investigate all familial cases of recurrent pericarditis for mutations in the TNFRSF1A gene, since familial clustering, in addition to poor response to colchicine treatment and/or steroid dependance (7), might represent an additional clue for investigating mutations in the TNFRSF1A gene and eventually disclose TRAPS.

References