A Case Series of Adenosine Deaminase 2-deficient Patients Emphasizing Treatment and Genotype-phenotype Correlations

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To the Editor:

Deficiency of adenosine deaminase 2 (DADA2) causes a vasculopathy with autoinflammatory features associated with mutations in CECR1. The phenotype of DADA2 varies from only cutaneous lesions to full-blown systemic disease with central nervous system (CNS) involvement and aneurysms in visceral arteries that may overlap with the spectrum of polyarteritis nodosa (PAN). 1-3

The Chapel Hill Consensus Conference (CHCC) 2012 defines PAN as a necrotizing vasculitis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, venules, or capillaries and not associated with antineutrophil cytoplasmic antibodies. 4 Now, with the discovery of DADA2, we know that monogenic disorders may cause a PAN-like vasculopathy. Thus, DADA2 should be classified under the group of “vasculitis with a probable cause” in CHCC 2012. 4

We herein present the characteristics of 6 DADA2 patients and their response to various therapies.

Three of our patients had been initially screened at the U.S. National Institutes of Health (NIH) because they had suggestive features for the CECR1 mutations. Subsequently, we screened 17 patients with suggestive features and identified 3 new cases. We have evaluated the course of these patients for a follow-up of median 8.5 years. All patients were Turkish and were followed in the departments of Rheumatology and Pediatric Rheumatology at Hacettepe University, Ankara, Turkey. Three (patients 2, 3, and 5) had been included in a previous paper. 2

Peripheral blood samples for DNA extraction were obtained. Sanger sequencing was performed to sequence 10 exons of CECR1 in NIH (n = 3) and Hacettepe University (n = 3). Primer sequences are available in the Appendix. PCR products were directly sequenced using ABI Prism 3130 Automated Sequencer (Applied Biosystems).

We defined 6 DADA2 patients from 5 families. The characteristics and treatment of patients are summarized in Table 1 and Table 2. There was consanguinity in 3 families (patients 1, 5, and 6). Homozygosity for the p.G47R mutation in CECR1 was detected in all patients. Five were initially diagnosed with systemic PAN fulfilling the 2008 Ankara or the American College of Rheumatology 1990 criteria. 5, 6 One (patient 1) was diagnosed with cutaneous PAN.

Table 1. The characteristics of patients with DADA2.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3, Sibling of Patient 2</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Fever</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Myalgia/arthritis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CNS</td>
<td>No</td>
<td>Stroke</td>
<td>Stroke</td>
<td>Stroke</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Skin</td>
<td>LR</td>
<td>LR, EN</td>
<td>LR, EN</td>
<td>LR, EN, necrotic ulcers</td>
<td>LR, EN, necrotic ulcers</td>
<td>LR</td>
</tr>
<tr>
<td>Eye</td>
<td>No</td>
<td>Strabismus</td>
<td>No</td>
<td>Optic neuritis</td>
<td>Strabismus</td>
<td>No</td>
</tr>
<tr>
<td>Hematological</td>
<td>No</td>
<td>No</td>
<td>MAS</td>
<td>No</td>
<td>Myelofibrosis</td>
<td>No</td>
</tr>
<tr>
<td>Immunological</td>
<td>Ig normal</td>
<td>Low IgM</td>
<td>Low IgM</td>
<td>Ig normal</td>
<td>Ig normal</td>
<td>Ig normal</td>
</tr>
<tr>
<td>Renal</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>FSGS, collapsing variant</td>
<td>AA amyloidosis</td>
<td>No</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Abdominal pain</td>
<td>Abdominal pain</td>
<td>Abdominal pain, bowel perforation</td>
<td>Abdominal pain, hypertransaminasemia</td>
<td>Abdominal pain, HSM, pancreatitis, amyloidosis</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>ANA 1/320</td>
<td>ANA 1/320</td>
<td>RF, LA-positive</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DADA2: deficiency of adenosine deaminase 2; CNS: central nervous system; LR: livedo racemosa; EN: erythema nodosum; MAS: macrophage activation syndrome; Ig: immunoglobulin; FSGS: focal and segmental glomerulosclerosis; HSM: hepatosplenomegaly; ANA: antinuclear antibody; RF: rheumatoid factor; LA: lupus anticoagulant; AA amyloidosis: secondary amyloidosis.
did not have any known immunological defect besides DADA2. Cavities were observed in his thorax computerized tomography, and tuberculosis was ruled out; thus, he was diagnosed as having necrotizing pneumonia. An autopsy could not be performed.

Patient 6 had received corticosteroids, azathiprinone, and methotrexate previously. She was stable in the last 4.5 years while being treated with colchicine only, which was started because she was a carrier for an MEFV mutation.

Currently, 3 of our living patients were stable (1 treated with colchicine, 1 with ETN, and 1 with MMF). Patient 3 had a mild activation while receiving FFP and patient 4 partially responded to ETN and plasmapheresis; however, his disease was still active.

There are a number of original features in this series. To our knowledge, this is the first report of DADA2 patients developing progressive and debilitating renal findings (FSGS, collapsing variant, and renal amyloidosis) and necrotizing pneumonia. In addition, response to FFP or MMF was not previously reported in DADA2.

There is no consensus on DADA2 treatment. Anti-TNF has proven useful in many patients including 2 in this series. In severe disease, hematopoietic stem cell transplantation and anti-interleukin 6 may be considered. It was also speculated that FFP support may help with the improvement of disease because DADA2 presents in the plasma; however, there is no previous report of its use. In 1 of our patients, FFP improved the disease activity for 8 months. On the other hand, his sibling had no significant response and the treatment was changed to ETN. Thus, FFP may be beneficial in selected cases for a certain period of time; however, probably not at the time of severe clinical features. Further, another drawback of FFP is the fact that it is a human product. In the patient with mainly cutaneous features, interestingly, MMF was very effective. It is interesting that 1 of our patients enjoyed prolonged remission; we are unable to comment on whether colchicine has any effect on her disease, though unlikely.

All our patients were homozygous for p.G47R mutation. Glycine encoded by codon 47 of CECR1 is conserved in all sequenced species. It was also speculated that FFP support may help with the improvement of disease because DADA2 presents in the plasma; however, there is no previous report of its use. In 1 of our patients, FFP improved the disease activity for 8 months. On the other hand, his sibling had no significant response and the treatment was changed to ETN. Thus, FFP may be beneficial in selected cases for a certain period of time; however, probably not at the time of severe clinical features. Further, another drawback of FFP is the fact that it is a human product. In the patient with mainly cutaneous features, interestingly, MMF was very effective. It is interesting that 1 of our patients enjoyed prolonged remission; we are unable to comment on whether colchicine has had any effect on her disease, though unlikely.

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APPENDIX 1. Primer pairs used in PCR and sanger sequencing.

<table>
<thead>
<tr>
<th>Primer Name</th>
<th>Primer Sequences, 5′–3′</th>
</tr>
</thead>
</table>
| **CECR1 exon-1** | F: CCA CAT GCA CAT AAA CCG AA  
R: GGT GCA GGT GGA TCA AGC CCA |
| **CECR1 exon-2** | F: AGA TCA GAG TTC CAC CCT TA  
R: CAG CCA CAA CCA CAG TAA TA |
| **CECR1 exon-3** | F: CCC TTT GTC TTC ACC ATT CTT  
R: TCT ATA GGT TTG TAC CAA GGG A |
| **CECR1 exon-4** | F: GGG ATA TGC AAG GTG GGT A  
R: CCT GAG TGG TCA ATT CAT GA |
| **CECR1 exon-5** | F: TCT CTC ACT GCT CAC CTG A  
R: CAG CCT AGT AGC TCT GCC T |
| **CECR1 exon-6** | F: CTC TCA GGG ATG ATC ACA ATG G  
R: GGA TGT CAG GGT ACC AAC A |
| **CECR1 exon-7** | F: CTG CTC CTG GTC ATT CTT AA  
R: AGT GAG ATA GAG CAC AGG AA |
| **CECR1 exon-8** | F: AAT AAA GCC ATA TCA TAC CTC TC  
R: CCT CCT GAA TAA CTT TAC TCA |
| **CECR1 exon-9–10** | F: GCT CAA GGT CTC ACC TCA C  
R: CCA CAT GGA GCT GAT TCA AG |

F: forward; R: reverse.