A Monogenic Disease with a Variety of Phenotypes: Deficiency of Adenosine Deaminase 2

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ABSTRACT. ***Objective.*** Deficiency of adenosine deaminase 2 (DADA2) is an autosomal recessive autoinflammatory disorder associated with *ADA2* mutations. We aimed to investigate the characteristics and ADA2 enzyme activities of patients with DADA2 compared to non-DADA2 patients.

Methods. This is a descriptive study of 24 patients with DADA2 who were admitted to the Adult and Pediatric Rheumatology, Pediatric Haematology, and Pediatric Immunology Departments of Hacettepe University. All *ADA2* exons were screened by Sanger sequencing. Serum ADA2 enzyme activity was measured by modified spectrophotometric method.

Results. Twenty-four patients with DADA2 were included: 14 with polyarteritis nodosa (PAN)-like phenotype (Group 1); 9 with Diamond-Blackfan anemia (DBA)-like features, and 1 with immunodeficiency (Group 2). Fourteen PAN-like DADA2 patients did not have the typical thrombocytosis seen in classic PAN. Inflammatory attacks were evident only in Group 1 patients. Serum ADA2 activity was low in all patients with DADA2 except one, who was tested after hematopoietic stem cell transplantation. There was no significant difference in ADA2 activities between PAN-like and DBA-like patients. In DADA2 patients with one *ADA2* mutation, serum ADA2 activities were as low as those of patients with homozygote DADA2. ADA2 activities were normal in non-DADA2 patients. *ADA2* mutations were affecting the dimerization domain in Group 1 patients and the catalytic domain in Group 2 patients.

Conclusion. We suggest assessing ADA2 activity along with genetic analysis because there are patients with one *ADA2* mutation and absent enzyme activity. Our data suggest a possible genotype–phenotype correlation in which dimerization domain mutations are associated with PAN-like phenotype, and catalytic domain mutations are associated with hematological manifestations. (First Release September 15 2019; J Rheumatol 2020;47:117–25; doi:10.3899/jrheum.181384)

Key Indexing Terms:
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POLYARTERITIS NODOSA PURE RED CELL ANEMIA

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Deficiency of adenosine deaminase 2 (ADA2) enzyme (DADA2) is an autosomal recessive autoinflammatory disease associated with mutations in *ADA2* encoding the ectoenzyme ADA2[1,2]. The ADA2 enzyme is essential for endothelial stability and a factor defining the macrophage subsets[3]. It is a dimeric protein secreted in the extracellular environment mostly expressed by monocytes and other cells of the myeloid lineage[4,5]. It has 4 domains: the signal sequence, the dimerization domain, the putative receptor-

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binding (PRB) domain, and the catalytic domain[4]. Dimerization of ADA2 monomers is required for full enzymatic activity and the dimer gets stabilized by interacting with the cell-surface glycosaminoglycans (GAG)[6]. The PRB domain is responsible for the binding of ADA2 to specific receptors while the catalytic domain is important for the catalytic function of the enzyme[6].

The more common phenotype of DADA2 is vasculopathy and stroke[7,8,9]. The hematological and immunological findings of DADA2 include Diamond-Blackfan anemia (DBA)–like phenotype[7,10,11], lymphopenia[12], neutropenia[9,11,13–17], pancytopenia[10,11,15], Coombs positive hemolytic anemia[10], autoimmune cytopenia[2,9,11,16,18], hemophagocytic lymphohistiocytosis[2,19], cellular immunodeficiency[12], and hypogammaglobulinemia[2,7,11,19].

Herein, we report the features of a cohort of patients with DADA2 from Hacettepe University, Ankara, Turkey. We also investigate the diagnostic potential of serum ADA2 activity measurement. In addition, we compared the laboratory test results of polyarteritis nodosa (PAN)–like DADA2 patients and non-DADA2 PAN patients.

MATERIALS AND METHODS

Patients. This is a descriptive study consisting of two DADA2 cohorts (n = 24) from Hacettepe University (Ankara, Turkey), which is a tertiary referral hospital in a country with high consanguinity rate. There is a strong collaboration between different departments of the medical school.

Group 1 included 14 DADA2 patients with the PAN-like phenotype. We have also included PAN patients (n = 60) who were negative for *ADA2* mutations. We compared the results of basic laboratory tests [hemoglobin (Hb), white blood cell (WBC) count, thrombocyte count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)] during active disease between PAN-like DADA2 patients and non-DADA2 PAN patients. For patients with DADA2, the response to etanercept (ETN) is defined as absence of any disease-related symptoms and normal acute-phase reactants (APR) without increase in doses of concomitant therapies such as corticosteroids.

Group 2 included 10 patients with DADA2, 9 diagnosed with DBA in their primary centers (the pediatric hematology departments from 5 different centers in the country) and referred for molecular workup and followup to our center. They were diagnosed with DADA2 and evaluated in our center at least once at the time of this study. These 9 DADA2 patients with DBA-like phenotype were among the 60 patients in our national DBA registry, all of whom had been tested for *ADA2* mutations. One patient was diagnosed in the Department of Pediatric Immunology when she was screened for immunodeficiency genes in a panel.

Twelve patients with DADA2 had been included in previous papers[2,19,20] and 2 other papers, including 2 patients from Group 2, have been submitted.

The serum ADA2 activity was also investigated in a group of patients who had features mimicking DADA2 (n = 89). This group included patients with systemic vasculitis other than PAN (e.g., Behçet disease), cytopenia (due to reasons other than DBA; e.g., myelodysplastic syndrome), immunodeficiency (e.g., CD4 deficiency), or a history of stroke or thrombosis (due to reasons other than DADA2; e.g., glial tumor). These patients were not tested for *ADA2* mutations because their diagnoses were already confirmed. In addition to these patients, ADA2 activity was tested in 5 DBA and 3 PAN patients who did not have *ADA2* mutations.

Written consent from the patients was obtained according to the Declaration of Helsinki. The study was approved by the ethics committee of Hacettepe University (GO 15/721).

Total ADA (tADA) and ADA2 activity assays. Two ml of venous blood were taken from patients, parents, and controls, and centrifuged at 1500 g for 15 min. Serums were separated and stored at –80°C until the analysis was performed.

Serum tADA and ADA2 activities were measured by making the total reaction volume half of the spectrophotometric method described by Giusti and Galanti[21]. This method is based on measuring the ammonia released during the conversion of adenosine to inosine, by the Berthelot reaction. A 21-mM adenosine solution in 50 mM phosphate buffer, pH 6.5 was used as substrate for tADA activity. Added to the test tubes was 0.1 mmol/l erythro-9-(2-hydroxy-3nonyl)adenine (EHNA), pH 6.5, an ADA1 inhibitor, in the presence of 21 mM adenosine for ADA2 activity[22]. A 15-mM ammonium sulfate standard stock solution was prepared in ammonia-free distilled water and then freshly diluted to 75 μM during the working day with 50 mM phosphate buffer, pH 6.5 and used as standard for the assay. Serum sample (25 μl) and 21 mM adenosine solution were mixed for tADA assay. For the ADA2 assay, 25 μl of serum sample, 21 mM adenosine, and 0.1 mM EHNA (at the final volume) were mixed. Then the reaction tubes were incubated at 37°C for 60 min in a water bath. After that, the reactions were stopped by phenol/nitroprusside (106 mM phenol; 0.17 mM sodium nitroprusside) solution. The serum samples were added to the blank tubes. Then alkaline hypochloride (11 mM NaOCl; 125 mM NaOH) solution was added to all test tubes, mixed, and incubated at 37°C for 30 min in a water bath. All samples were studied in double. The blue-violet color formed at the end of the experiment was measured at 628 nm using Shimadzu UV-1700 spectrophotometer. The results were calculated after subtracting sample blank values from sample values and reagent blank values from standard values. The results were expressed as U/l at 37°C. One unit of the tADA or ADA2 was defined as the amount of enzyme required to release 1 μmol of ammonia per min under standard measurement conditions. Percentage contributions of ADA2 activities to the tADA activity (ADA2%) were also calculated.

Genetic analysis. Fourteen PAN-like DADA2 patients (Group 1) were diagnosed with Sanger sequencing of 10 *ADA2* exons at the National Institute of Health (n = 3) and Hacettepe University (n = 11). The same method was used for checking *ADA2* mutations in the patients of the PAN cohort (n = 60). Primer sequences are presented in Supplementary Table 1 (available from the authors on request). PCR products were directly sequenced using ABI Prism 3130 Automated Sequencer (Applied Biosystems). *MEFV* gene variant analysis was also performed in these 14 patients with Sanger sequencing. Twelve variants [E148Q, P369S, F479I, M680I(G-C), M680I(G-A), I692del, M694V, M694I, K695R, V726A, A744S, R761H] were tested in *MEFV* in our Department of Medical Genetics.

In Group 2, one patient was diagnosed with whole exome sequencing and 8 were diagnosed with Sanger sequencing of *ADA2* exons. One patient from the Department of Pediatric Immunology was diagnosed with an immunodeficiency gene panel analysis[23]. This panel included 266 genes that were analyzed with targeted next generation sequencing. Analysis was performed by Ion Reporter 5.6 Software.

Statistics. Statistical analysis was performed using the SPSS software (version 21.0; IBM Corp.). The variables were investigated using visual (histogram, probability plots) and analytic (Kolmogorov-Smirnov) methods to determine the normality of distribution. The data of descriptive analysis were expressed as the median, minimum, and maximum values. Categorical variables were compared with the chi-square test or Fisher's exact test where appropriate. The Mann-Whitney U test was used to compare the non-normally distributed continuous data between 2 groups.

RESULTS

Demographic and clinical characteristics of patients with DADA2 (n = 24). The median (min–max) ages at symptom onset and diagnosis were 3.5 years (1 mo–35 yrs) and 14 years (1.6–45 yrs), respectively. Male/female ratio was 1:1.

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Group 1 included patients with PAN-like features (n = 14; Table 1 and Table 2). One also had severe anemia and pancytopenia. Group 2 included 9 patients with DBA-like features and 1 patient with immunodeficiency (Table 3).

There was parental consanguinity in 15 patients (62.5%). There was an affected sibling in 2 families.

Clinical and laboratory characteristics of patients in Group 1 (n = 14). The main features of Group 1 patients are summarized in Table 1 and Table 2. All patients had recurrent episodes of fever, abdominal pain, and elevated APR. The APR were also increased in all during active disease.

Nine patients (64.2%), 5 adults and 4 children, fulfilled the Ankara 2008[24] and the American College of Rheumatology criteria[25] for PAN.

There was proteinuria in 8 patients. It was in the nephrotic range in 3 [patients with focal segmental glomerulosclerosis

Table 1. Characteristics of adult patients with DADA2 in Group 1 (PAN-like phenotype).

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Sex	Male	Male	Female	Female	Male	Male
Consanguinity	First degree	None	None	None	First degree	None
Current age, yrs	–	–	25	24	49	21
Age at symptom onset, yrs	19	4	7	11	35	2
Age at diagnosis, yrs	22	22	21	21	45	17
ADA2 mutation	p.Gly47Arg/ p.Gly47Arg	p.Gly47Arg/ p.Gly47Arg	p.Gly47Arg/–	p.Gly47Arg/ p.Gly47Arg	p.Gly47Arg/ p.Gly47Arg	p.Gly47Arg/ p.Gly47Val
Serum ADA2 activity, U/l	–	–	1.69	1.01	–	1.03
Myalgia/arthralgia	Yes	Yes	Yes	Yes	Yes	Yes
Neurological findings	None	Optic neuritis, unilateral deafness, stroke	Hemorrhagic stroke, intracranial hemorrhage in putamen	Mononeuritis multiplex	Ischemic stroke in mesencephalon, diplopia	Hemorrhagic stroke, ischemic stroke, lesion in pons and bilateral thalamus, peripheral neuropathy, diplopia
Dermatological findings	Livedo reticularis, erythema nodosum, necrotic ulcer	Livedo reticularis, erythema nodosum, necrotic ulcer, RP	Livedo reticularis, erythema nodosum, RP	Livedo reticularis	Livedo reticularis, erythema nodosum, RP	Livedo reticularis
Ophthalmological findings	Strabismus	None	None	None	None	Nystagmus, intranuclear ophthalmoplegia
Hematological findings	Myelofibrosis	None	None	None	None	None
Immunological findings	Normal Ig	Normal Ig	Normal Ig	Normal Ig	Low IgM	Low IgM
Renal findings	AA amyloidosis, proteinuria	Proteinuria, hypertension, FSGS, collapsing variant	Proteinuria, hypertension	Proteinuria	Proteinuria	Proteinuria
Gastrointestinal findings	Recurrent abdominal pain, pancreatitis, HSM, amyloidosis	Recurrent abdominal pain, hypertransaminasemia	Recurrent abdominal pain, HSM	Recurrent abdominal pain	Recurrent abdominal pain	Recurrent abdominal pain, hepatomegaly
Arterial aneurysms	None	Hepatic artery and bilateral renal artery aneurysms	Renal artery aneurysm	None	Superior mesenteric artery, hepatic artery, and bilateral renal artery aneurysms	None
Pathological investigation	Amyloidosis in renal and duodenal biopsies; small vessel vasculitis in skin biopsy; normocellular bone marrow biopsy with lymphocytic aggregates and fibrosis	FSGS, collapsing variant	Increase in mesangial matrix and total sclerosis in 5 glomeruli; medial thickening in some arteries consistent with hypertension in renal biopsy	Vasculitis involving medium-size arteries	Nonspecific	Nonspecific
Previous treatment	CS, CYC, IVIG, FFP, colchicine, tocilizumab	Colchicine, CS, FFP, CYC, AZA, iliomedin, ETN	Colchicine, CS, AZA, CYC, MMF	Colchicine, CS, MTX, AZA	Colchicine, CS, RTX, CYC, ETN	Colchicine, enaksaparin
Current treatment	–	–	ETN	Colchicine	ETN	ETN
Exitus	Yes	Yes	No	No	No	No

Ankara 2008 criteria for children and ACR 1990 criteria for adults. PAN: polyarteritis nodosa; ADA2: adenosine deaminase 2; DADA2: deficiency of ADA2; AZA: azathioprine; CS: corticosteroid; CYC: cyclophosphamide; ETN: etanercept; FFP: fresh frozen plasma; FSGS: focal segmental glomerulosclerosis; GN: glomerulonephritis; HSM: hepatosplenomegaly; Ig: immunoglobulin; IVIG: intravenous Ig; MTX: methotrexate; MMF: mycophenolate mofetil; RP: Raynaud phenomenon; RTX: rituximab; ACR: American College of Rheumatology; AA amyloidosis: reactive amyloidosis.

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Table 2. Characteristics of pediatric patients with DADA2 in Group 1 (PAN-like phenotype).

Characteristics	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14
Sex	Female	Female	Male	Male	Male	Female	Male	Male
Consanguinity	First degree	None	None	First degree	First degree	First degree	None	First degree
Current age, yrs	18	15	19	20	17	7	13	18
Age at symptom onset, yrs	6.5	3.5	8	3.5	14	1.5	4	12
Age at diagnosis, yrs	14	10.5	15	17.5	14	3	9	17
ADA2 mutation	p.Gly47Arg/ p.Gly47Arg	p.Gly47Arg/ p.Gly47Arg	p.Gly47Arg/ p.Gly47Arg	p.Gly47Arg/ p.Gly47Arg	p.Gly47Arg/ p.Gly47Arg	p.Gly47Arg/ p.Gly47Arg	p.Gly47Arg/–	p.Gly47Arg/ p.Gly47Arg
Serum ADA2 activity, U/l	0.46/0.46[a]	–	1.44/1.43[a]	0	0.11	0.55	1.37/1.37[a]	2.6
Myalgia/arthralgia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Neurological findings	Peripheral neuropathy, minimal atrophy in the distal extremity	Peripheral neuropathy, ischemic stroke, lesion on the pons and the medial crus cerebri, 3rd cranial nerve palsy	Peripheral neuropathy, ischemic stroke, left cerebral cortical and subcortical lesion, reduction in the calibration of the right posterior cerebral artery	Sensorimotor axonal type of polyneuropathy, mild dysfunction in the central sense pathways in the right of SEP	Sensorimotor axonal type of polyneuropathy, spinal cord atrophy, bilateral extension in MEP and SEP	Ischemic stroke, acute ischemic lesion in the right nucleus ruber neighborhood, 6th cranial nerve palsy	Ischemic stroke, ischemic lesion in the right ponto mesencephalic junction, 6th cranial nerve palsy	None
Dermatological findings	Livedo reticularis	Livedo reticularis, erythema nodosum, RP	Livedo reticularis	Livedo reticularis	Livedo reticularis	Livedo reticularis	Livedo reticularis	Digital ischemia and ulcer, RP
Ophthalmological findings	None	Strabismus	None	None	None	Strabismus	Strabismus	None
Hematological findings	None	None	Macrophage activation syndrome	None	None	None	None	Lymphopenia
Immunological findings	Normal Ig	Low IgM	Low IgM	Normal Ig	Normal Ig	Normal Ig	Not checked	Normal Ig
Renal findings	None	None	None	Proteinuria, hypertension, testicular torsion	None	None	None	Proteinuria, hypertension
Gastrointestinal findings	Recurrent abdominal pain, abdominal MRI normal	Recurrent abdominal pain	Recurrent abdominal pain, intestinal perforation, and ileostomy at the age of 8	Recurrent abdominal pain, abdominal MRI normal, hepatomegaly	Recurrent abdominal pain, abdominal MRI normal, hepatomegaly	Recurrent abdominal pain	Recurrent abdominal pain	Recurrent abdominal pain, diarrhea, HSM, stenosis in superior mesenteric artery
Arterial aneurysms	None	Hepatic artery microaneurysm	Hepatic artery microaneurysm	None	None	None	None	Microaneurysms in bilateral renal arteries and superior mesenteric artery
Pathological investigation	Necrotizing vasculitis lobular panniculitis in medium-size vessels	Vasculitis involving medium-size arteries	Vasculitis involving medium-size arteries and small arteritis in the ileal resection material	Mesangial proliferative GN	Nonspecific	Nonspecific	Nonspecific	None
Other findings	–	–	–	–	Core myopathy (verified with muscle biopsy)	–	–	Dilated cardiomyopathy and dilated left coronary artery
Previous treatment	NSAID, colchicine, MTX, CS, MMF	Colchicine, MTX, CS, CYC, AZA, MMF	Colchicine, CS, CYC	Colchicine, CS	Colchicine, CS	Colchicine, CS, AZA	CS	CS, CYC
Current treatment	ETN	ETN	ETN	ETN	ETN	ETN	ETN	ETN
Exitus	No	No	No	No	No	No	No	No

[a] The first value was before ETN treatment; the second value was after ETN treatment. ADA2: adenosine deaminase 2; DADA2: deficiency of ADA2; PAN: polyarteritis nodosa; AZA: azathioprine; CS: corticosteroid; CYC: cyclophosphamide; ETN: etanercept; GN: glomerulonephritis; HSM: hepatosplenomegaly; Ig: immunoglobulin; NSAID: nonsteroidal antiinflammatory drugs; MEP: motor evoked potentials; MRI: magnetic resonance imaging; MTX: methotrexate; MMF: mycophenolate mofetil; RP: Raynaud phenomenon; SEP: somatosensory evoked potentials.

Table 3. Clinical and laboratory characteristics of patients with DADA2 in Group 2 (Diamond-Blackfan anemia–like and immunological phenotype).

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Sex	F	F	M	M	F	F	F	F	M	F
Current age	7 y 6 m	6 y 2 m	4 y 4 m	25 y	5 y 5 m	3 y	4 y	16 y 5 m	6y 1 m	8 y
Age at symptom onset	1 m	4 m	40 d	6 m	6 m	4 m	4 m	3 m	5 m	7 y
Age at diagnosis	5 y 6 m	4 y 1 m	2 y	22 y	3 y 8 m	20 m	3 y	16 y	5 y	7y 3m
ADA2 mutation	p.Phe207Ser/ p.Asp454His	p.Gly358Arg/ p.Gly358Arg	p.Ile210 Thrfs*57/ p.Arg49 Alafs*13	p.Tyr482Cys/ p.Tyr482Cys	p.Tyr227fs*27/ p.Tyr227 fs*27	p.Gly358Arg/ p.Gly358Arg	p.Tyr456Cys/ p.Tyr456Cys	p.Arg306Ter/ p.Arg306Ter	p.Arg306Ter/ p.Arg306Ter	p.M465fsX/ p.M465fsX
Serum ADA2 activity, U/l	0.34	2.14	0.91	–	–	0.52	–	1.24	–	0.125
Neurological	Ischemic stroke	–	–	–	–	Myopathy, lactic acidosis	–	–	–	PRES
Hematological	PRCA	PRCA	PRCA	PRCA	PRCA	PRCA	PRCA	PRCA	PRCA	Neutropenia, anemia, leukopenia
Immunological	Low IgA, Low IgG, Low CD19	Normal	Low IgA, Low IgG, Low IgM	Low IgA, Low IgG, Low CD19	NA	Low IgM	Low IgM	Low IgM, Low IgA, Low CD19	Low CD19, Normal Ig	Low IgM, Low NK and CD19+ cells
Hepatosplenomegaly	–	SM	SM	HM, SM	–	–	SM	–	–	–
Other findings	–	Short neck, synorphy, low hair line, depressed nasal root, bilateral clinodactyly	–	Inguinal hernia (operated)	Small right orbita, low–set ears, epicanthus, anteverted helix, broad forehead, down–slanting palpebral fissures	–	–	–	–	Recurrent skin infections due to neutropenia (treated with recurrent granulocyte infusions)
Steroid response of PRCA	+	–	–	+	+	–	–	+	+	–
HSCT	–	–	–	Yes	Yes	–	–	–	–	–
Outcome	Alive, on steroid, transfusion independent	Alive, transfusion dependent, on chelation	Alive, transfusion dependent, on chelation	Alive, post HSCT	Alive, post HSCT	Alive, transfusion dependent, on chelation	Alive, transfusion dependent, on chelation	Alive, remission	Alive, remission	Alive, recurrent skin infections

HSCT: hematopoietic stem cell transplantation; PRCA: pure red cell aplasia; ADA2: adenosine deaminase 2; DADA2: deficiency of ADA2; HM: hepatomegaly; SM: splenomegaly; NA: not available; PRES: posterior reversible encephalopathy syndrome; Ig: immunoglobulin; NK: natural killer cells.

(FSGS), amyloidosis, and mesangial proliferative glomerulonephritis], while mild proteinuria was present (~180–200 mg/day) in 5. Proteinuria improved in all with ETN except 2, who died soon after DADA2 diagnosis.

In the PAN cohort without *ADA2* mutations (n = 60; M/F = 1.4), there were 37 children (61.5%) and 23 adults (38.5%). The median (min–max) thrombocyte count of PAN patients was 440 (180–726) × 10^9/l, whereas it was 333 (129–502) × 10^9/l in PAN-like DADA2 patients (p = 0.009). There was no significant difference between these 2 groups in Hb, WBC count, ESR, and CRP levels.

Clinical and laboratory characteristics of patients in Group 2 (n = 10). The clinical and laboratory characteristics of patients in Group 2 are summarized in Table 3.

The hemogram findings at diagnosis of pure red cell aplasia (PRCA) in patients 1–9 revealed a median Hb level of 4.3 g/dl (2.02–6) with a reticulocyte count of 0.2% (0.17–0.57%). Median WBC and platelet counts were 9.7 × 10^9/l (5.1–11.3) and 345 (204–690) × 10^9/l, respectively. PRCA was diagnosed with paucity of erythroid precursors in the bone marrow aspirate in an otherwise normocellular bone marrow in these patients. Parvovirus PCR was negative in all (peripheral blood).

Patient 10 had an afebrile convulsion during followup while she was taking ETN and still neutropenic. The magnetic resonance imaging was compatible with posterior reversible encephalopathy syndrome (PRES), while fungal abscess, encephalitis, or a vasculitic feature of DADA2 were excluded. ETN was discontinued because it has been implicated in PRES.

Serum tADA, ADA2, and ADA2% enzyme activities. Serum tADA and ADA2 activities were analyzed in 123 individuals: 16 DADA2 patients, 10 family members (parents/siblings) of DADA2 patients (all heterozygotes for *ADA2* mutations), 3 PAN and 5 DBA patients who did not have *ADA2* mutations, and 89 diseased controls (described above).

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The median (min–max) ADA2 activities were 1.03 (0–2.6) in PAN-like DADA2 patients (n = 10); 0.91 (0.34-2.14) in DBA-like DADA2 patients (n = 5); 14.84 (13.05-27.13) U/l in PAN patients without *ADA2* mutations (n = 3); 19.01 (15.39-39.19) U/l in DBA patients without *ADA2* mutations (n = 5); 10.43 (7.95–15.07) U/l in heterozygote family members of DADA2 patients (n = 10); and 22.27 (13.08–57.35) in the diseased control group (n = 89). Thus, serum ADA2 activity was within normal range in PAN and DBA patients who did not have *ADA2* mutations and other diseased controls (n = 89; Figure 1). There was no significant difference between PAN-like and DBA-like DADA2 patients regarding ADA2 activity (p = 1).

The ADA2% was 19.62 (0–75.29) in PAN-like DADA2 patients (n = 10) and 15.96 (5.86–20.61) in DBA-like DADA2 patients (n = 5). However, ADA2% was 72.66 (57.32–93.7) in heterozygote family members (n = 10), 78.88 (72.03–96.18) in DBA patients without *ADA2* mutations (n = 5), 77.57 (75.36–85) in PAN patients without *ADA2* mutations (n = 3), and 83.78 (37.76–100) in the diseased control group (n = 89). ADA2% was decreased in patients with DADA2.

ADA2 deficiency was identified in all patients with DADA2 but one. Patient 4 from Group 2 had ADA2 measurement after hematopoietic stem cell transplantation (HSCT) and ADA2 activity was normal.

In 3 patients (Group 1) who had responded to ETN, serum ADA2 activities remained very low subsequent to the treatment (range of pretreatment and posttreatment ADA2 activities 0.46–1.44 U/l and 0.46–1.43 U/l, respectively). At the time of the first evaluation of ADA2 activities, the disease was active in these patients. They had inactive disease under ETN for ≥ 6 months at the time of the second check of enzyme activities.

ADA2 activities of unaffected heterozygous parents were about half the activity of the control subjects, although these individuals were asymptomatic (Figure 1). However, in two DADA2 patients with one *ADA2* mutation, ADA2 activities were as low as the activities of DADA2 patients with biallelic mutations.

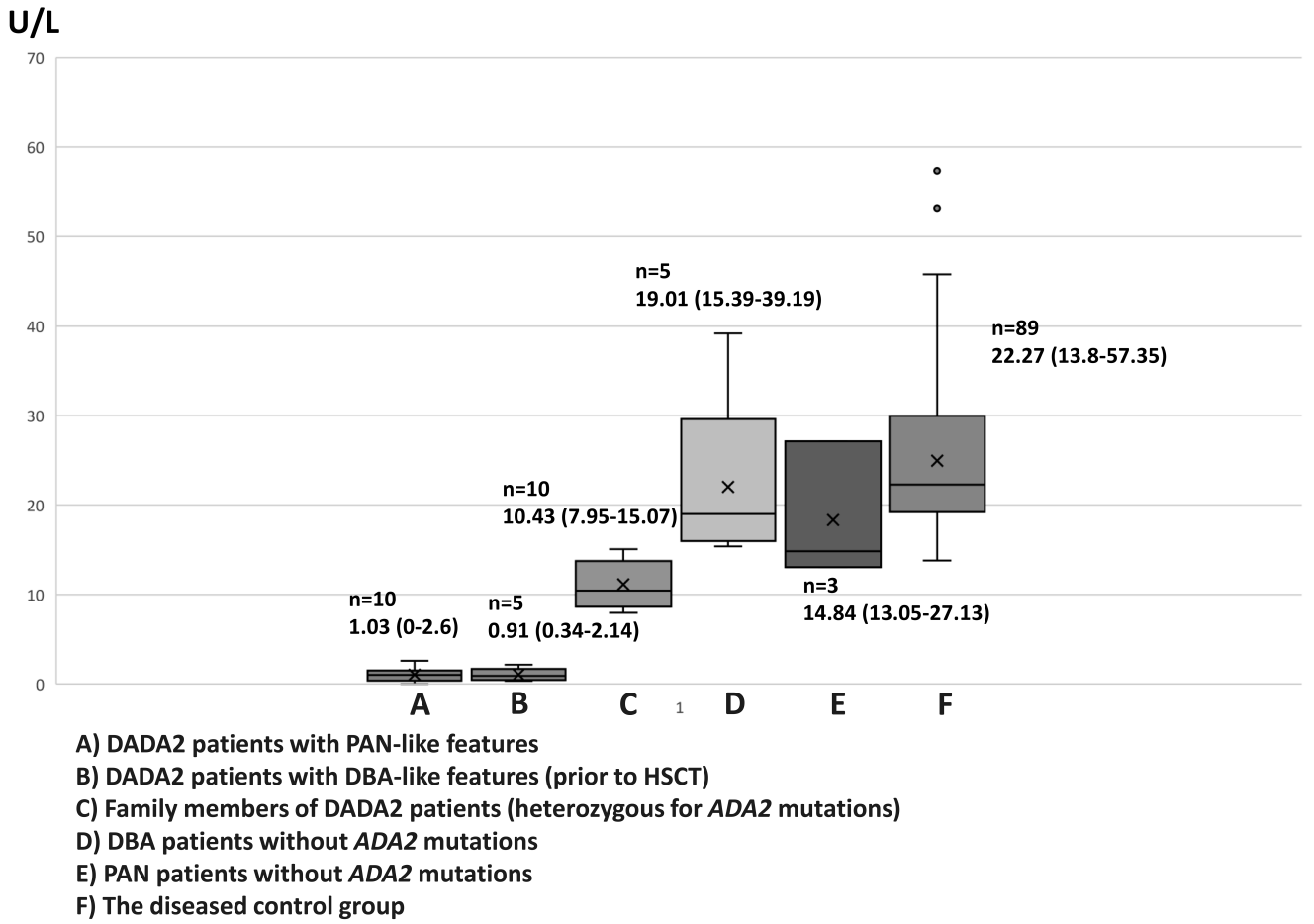

Figure 1. Adenosine deaminase 2 (ADA2) activities in patients with deficiency of ADA2 (DADA2), family members of DADA2 patients who were heterozygous for *ADA2* mutations, Diamond-Blackfan anemia (DBA) and polyarteritis nodosa (PAN) patients without *ADA2* mutations, and diseased controls. HSCT: hematopoietic stem cell transplantation.

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Molecular workup. All DADA2 patients had *ADA2* mutations. In Group 1, eleven were homozygous for G47R mutation in *ADA2*, two were heterozygous for G47R, and one was compound heterozygous for G47R and G47V (Table 4). These mutations affect the dimerization domain of ADA2 enzyme. *MEFV* variant analysis (in all Group 1 patients) revealed heterozygosity for E148Q in 2 patients.

The heterogeneous spectrum of *ADA2* mutations in Group 2 patients were affecting the catalytic domain of ADA2 enzyme (Table 4).

Treatment: Group 1. All patients were refractory to corticosteroids. All responded to ETN except 2 who died soon after DADA2 diagnosis and 1 who is stable while taking colchicine.

Among pediatric patients, the patient with a previous diagnosis of cutaneous PAN (Patient 7) responded to mycophenolate mofetil and had been stable for 1 year; then her disease flared and ETN was started. Fresh frozen plasma (FFP) was tried in 2 siblings (Patients 8 and 9) while they were waiting for the approval of biologics; one did not respond while the other was stable while receiving FFP. Subsequently, ETN was started in both. All pediatric patients are currently stable while taking ETN.

Among the adult patients, 3 currently are stable while taking ETN. FFP was administered to 2; none responded. One adult patient has been clinically stable for the last 7 years while taking colchicine only; anti–tumor necrosis factor (TNF) treatment has now been suggested. Two patients died soon after DADA2 diagnosis; one before the initiation of ETN, the other 3 weeks after the initiation of ETN.

Treatment: Group 2. Four (44%) of 9 patients with DBA-like phenotype responded to corticosteroid treatment. HSCT was performed in 2 patients (one responsive, the other refractory to corticosteroid). Two patients after HSCT and another 2 after 2-year corticosteroid treatment achieved remission and required no transfusions thereafter. Four patients (refractory to corticosteroid) are currently in a transfusion program, along with iron chelation treatment with deferasirox. None of the 9 patients with DBA-like features has received ETN. In Patient 10, the neutropenia did not resolve with corticosteroids, cyclosporine, and immunoglobulin therapy. ETN offered temporary benefit with an increase in neutrophil count for a 2-week period, but it failed to resolve the neutropenia. Neutropenia did not respond to FFP, either. Matched unrelated donor transplantation was planned for severe persistent neutropenia because no matched family donor was found.

Outcome: Group 1. Eleven patients are clinically stable with normal CRP on ETN. All of these patients reached clinical and laboratory remission within the first month of ETN and they have not experienced any disease flare so far while using ETN. One patient is stable while taking colchicine only with normal APR (checked every 3 mos). Two adult patients (Patients 1 and 2) died soon after DADA2 diagnosis.

The disease course in Patient 1 was complicated with myelofibrosis and secondary amyloidosis (renal and intestinal). He was resistant to the immunosuppressive treatments and FFP, and died of necrotizing pneumonia 2 months after DADA2 diagnosis. Tuberculosis was ruled out. The family did not consent to autopsy.

Patient 2 did not respond to various immunosuppressive therapies and FFP, and developed resistant digital ulcers and FSGS (collapsing variant) while he was taking immunosuppressives and iloprost. He died despite the initiation of ETN and plasmapheresis.

Outcome: Group 2. Four patients are in remission while taking no treatment (2 after HSCT; 2 after 2-year corticosteroid treatment). One patient who responded to corticosteroids is still receiving corticosteroid treatment. No relapse has been observed in the aforementioned 5 patients. Four patients who did not respond to corticosteroid treatment are currently in a transfusion program. Patient 10 still has severe neutropenia refractory to treatment.

Table 4. Molecular results of *ADA2* gene analyses in patients with DADA2 from Group 1 and Group 2.

Group No.	Patient No.	Mutation Position	Mutation Type	Affected Domain of ADA2 Protein
1	1, 2, 4, 5, 6–12, 14	Exon 2: c.139G>A; **p.Gly47Arg**	Homozygous missense	Dimerization
1	6	Exon 2: c.139G>A / Exon 2: c.140G>T; **p.Gly47Arg/p.Gly47Val**	Compound heterozygous missense	Dimerization
1	3, 13	Exon 2 c.139G>A; **p.Gly47Arg**	Heterozygous missense	Dimerization
2	1	Exon 4: c.620T>C/Exon 9: c.1360G>C; **p.Phe207Ser/p.Asp454His**	Compound heterozygous missense	Catalytic
2	2, 6	Exon 7: c.1072G>A; **p.Gly358Arg**	Homozygous missense	Catalytic
2	3	Exon 4: c.629delT/Exon 2: c.144_145ins; **p.Ile210Thrfs*57/p.Arg49Alafs*13**	Compound heterozygous Del/ins_ frameshift and non-sense	Catalytic
2	4	Exon 10: c.1445A>G; **p.Tyr482Cys**	Homozygous missense	Catalytic
2	5	Exon 4: c.680-681delAT; **p.Tyr227fs*27**	Homozygous deletion-Frameshift non-sense	Catalytic
2	7	Exon 9: c.1367A>G; **p. Tyr456Cys**	Homozygous missense	Catalytic
2	8, 9	Exon 6: c.916C>T; **p.Arg306Ter**	Homozygous non-sense	Catalytic
2	10	Exon 9: c.1392_1393insG; **p.M465fsX**	Homozygous missense	Catalytic

ADA2: adenosine deaminase 2; DADA2: deficiency of ADA2.

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DISCUSSION

To our knowledge, this is the first study reporting the whole DADA2 spectrum with PAN-like, hematological, neurological, and immunological presentations.

The definition of DADA2 changed the diagnosis for a significant number of patients who had been originally diagnosed with classic PAN. Further, PAN-like features with recurrent fever and abdominal pain attacks in DADA2 might have suggested the co-occurrence of familial Mediterranean fever (FMF) and PAN. Thus, our patients with PAN-like DADA2 had been tested for *MEFV* mutations and the results had not confirmed an FMF diagnosis. Two of them were heterozygous for E148Q, the frequency of which is around 6% in a healthy Turkish population[26,27].

We have suggested that low to normal thrombocyte count in DADA2 may help in differentiating from PAN where thrombocytosis is expected. Thrombocytosis in classic PAN generally occurs as a reactive change due to inflammation[28]. The absence of thrombocytosis in PAN-like DADA2 is interesting. It also remains unknown how DADA2 causes DBA-like anemia. ADA2 may have a role in hematopoietic process besides its inflammation-associated effects.

In our patients with DBA-like DADA2, the corticosteroid responsiveness was 44%, while it is around 80% in classic DBA patients in the literature[29]. On the other hand, hepatosplenomegaly, which was present in 4 out of 9 patients with DBA-like DADA2, is not a feature of DBA, which is a bone marrow failure syndrome[29]. Additionally, compared to classic DBA[29], dysmorphic features were more subtle in DADA2 and immunologic abnormalities were common.

Proteinuria was observed in more than half of patients with PAN-like DADA2, mostly as mild asymptomatic proteinuria in the absence of a renal disease. This may be caused by endothelial dysfunction or chronic inflammation[30]. Its improvement with ETN suggests a predominant role for inflammation in the pathogenesis of proteinuria.

The catalytic domain of ADA2 was affected in DBA-like patients while the dimerization domain was affected in PAN-like patients in our cohort. Mutation in the dimerization domain can impair the dimer formation and interaction with GAG, leading to decreased ADA2 activity. However, catalytic domain mutations probably cause conformational change and impair the catalytic function of the enzyme[6]. ADA2 plays a role in inflammation by promoting macrophage differentiation, inducing proliferation of monocytes, and inducing the expression of genes in neutrophils coding for some proinflammatory cytokines[4]. However, its role in the pathogenesis of a DBA-like phenotype remains largely unknown. Based on the site of the mutation, the functions of ADA2 may be affected at different levels. It is important to note that there are reports of DADA2 patients with catalytic domain mutations who presented with PAN-like phenotype in the absence of immunologic and hematologic findings[2,31]. Thus, further analyses are necessary for the clarification of the genotype–phenotype correlation.

We had 2 patients with DADA2 who had one *ADA2* mutation; heterozygotes with the phenotype have previously been reported[32]. Possible explanations are the presence of a mutation in the promotor region or other interacting genetic factors. However, the fact that the enzyme activity was at an in-between level in the healthy heterozygotes while it was way below normal in the DADA2 patients with one *ADA2* mutation indicates the advantage of enzyme testing. We now suggest that a test be done first for the enzyme activity in siblings of patients with DADA2.

Enzyme levels are crucial in the initial stage of diagnosis; however, there is no practical use of enzyme levels for followup of patients with DADA2. Persistently low ADA2 activities in patients with DADA2 who are in clinical and laboratory remission with anti-TNF treatment suggests that the clinical features of these patients are seen through inflammatory pathways, possibly related to TNF. Caorsi, *et al* have already shown higher TNF secretion from stimulated monocytes of patients with DADA2 compared to healthy controls[32]. Anti-TNF treatment probably suppresses the inflammation induced by the inflammatory macrophages in DADA2 but is not expected to normalize the ADA2 activity, which was shown in our study as well. Our results also suggest that discontinuing anti-TNF treatment may not be reasonable unless ADA2 activity is restored with a curative therapy such as HSCT.

We suggest that remission in patients with DADA2 could be described as no clinical features and normal APR. It is not certain whether we can taper the dose of anti-TNF therapy in remitting patients. Lifelong anti-TNF treatment is indeed challenging. Further, it is not suitable for the patients with DBA-like phenotype. HSCT seems a curative therapeutic option for DADA2, especially in patients with predominant hematologic and immunologic features[33]. In a cohort of 14 patients with DADA2, HSCT was performed for bone marrow dysfunction and/or immunodeficiency and was shown to restore ADA2 enzyme activity[11]. Larger cohort studies are required to reach a firm conclusion about the curative potential of HSCT in DADA2.

There are several unmet needs in DADA2, such as the need for prenatal diagnosis or testing asymptomatic siblings. We confirm that enzyme activity can guide us in deciding on therapy in patients in whom only one *ADA2* mutation has been shown.

There are a few limitations of our study. DADA2 patients with one *ADA2* mutation might have another mutation in *ADA2* that we were not able to detect. In addition, it is not possible to totally exclude DADA2 diagnosis without genetic testing in the diseased controls with normal ADA2 activity.

This study highlights the diagnostic potential of ADA2 activity measurement in suspected patients. We also suggest a phenotype–genotype correlation in our cohort. Further, we suggest for the first time that a simple laboratory test such as platelet count may help for differentiating DADA2 from PAN.

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