Ethnic Genotype: Phenotype Correlation and Treatment of DADA2. A Single-center Cohort

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ABSTRACT **Background:** Deficiency of adenosine deaminase 2 (DADA2) is a rare autosomal recessive disorder caused by loss-of-function mutations in the *ADA2* gene, with a broad phenotype spanning systemic vasculitis, hematologic, immune deficiency, and autoinflammatory manifestations.

Objectives: To describe a decade of DADA2 management within a uniquely diverse population.

Methods: We conducted a single-center retrospective cohort study of genetically confirmed DADA2 patients. Demographics, clinical manifestations, laboratory findings, treatments, and long-term outcomes were reviewed.

Results: Seventeen pediatric patients were included from two ethnic groups: Arab Muslim (12/17, 70%) and Georgian Jewish (5/17, 29%). The median age at symptom onset was 3.5 months and at diagnosis 4 years. Phenotypes were purely vasculitic/inflammatory (5/17), purely hematologic (3/17), mixed hematologic-inflammatory (6/17), or mixed hematologic-immunodeficiency (3/17). None had isolated immune deficiency. The purely vasculitic/inflammatory phenotype was confined to Georgian Jewish patients, all homozygous for p.Gly47Arg, presenting with cutaneous and ischemic manifestations. Twelve patients received TNF-α inhibitors: 9 achieved complete response, 1 partial, and 2 none, with no subsequent strokes. Arab patients presented more often with fever, red cell aplasia, cytopenias, and immunodeficiency at younger ages. Three patients underwent hematopoietic stem cell transplantation (HSCT). Two responded favorably, one died of infection-related complications after engraftment.

Conclusions: We observed a distinct, ethnicity-driven genotype–phenotype correlation: Georgian Jewish patients with homozygous p.Gly47Arg had a pure vasculitic/inflammatory phenotype responsive to TNF-α inhibitors, whereas Arab patients harbored heterogeneous variants with hematologic/immune deficiency phenotype potentially benefiting from HSCT. Early, genetically informed diagnosis and phenotype-driven, multidisciplinary management are essential to improve outcomes.

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KEY WORDS: autoinflammatory disease, deficiency of adenosine deaminase 2 (DADA2), red cell aplasia, tumor necrosis factor (TNF) inhibitors, hematopoietic stem cell therapy (HSCT)

Deficiency of adenosine deaminase 2 (DADA2) was first described in 2014 as an autosomal recessive autoinflammatory disease caused by biallelic pathogenic variants in the adenosine deaminase 2 gene (CECR1) on chromosome 22q11. It was initially characterized as a vasculopathy presenting with early-onset stroke, ischemic events, or cutaneous polyarteritis nodosa (PAN)-like vasculitis [1,2]. The recognized spectrum has since broadened. At least half of the patients with pathogenic *ADA2* variants present with predominant hematologic or immunologic manifestations, frequently without vasculopathy [3]. Many pathogenic *ADA2* variants have been identified, usually inherited in an autosomal recessive pattern [4], although some dominant-negative variants confer disease in heterozygous carriers [5].

The pathogenesis is not completely understood. *ADA2* is an extracellular enzyme expressed in myeloid cells and critical for macrophage differentiation and activation. Deficient enzymatic activity skews macrophage polarization toward the proinflammatory M1 subtype, increasing tumor necrosis factor (TNF)-α and promoting endothelial dysfunction, vasculitis, and ischemia [6-9]. TNF inhibitors are generally first-line and highly effective for the inflammatory vasculitis, but they have limited effect on the hematologic and immunologic manifestations [10]. Hematopoietic stem cell transplantation (HSCT) may benefit selected patients, although long-term evidence remains limited.

In this study, we describe our decade-long experience managing pediatric DADA2 at a single tertiary referral center. The ethnically distinct composition of our cohort of Georgian Jewish patients and Arab Muslim patients offers a unique opportunity to examine ethnicity-specific genotype–phenotype patterns and their treatment implications.

PATIENTS AND METHODS

STUDY DESIGN AND SETTING

A single-center retrospective cohort study was conducted at Safra Children's Hospital, Sheba Medical Center, a tertiary referral center.

INCLUSION AND EXCLUSION CRITERIA

We included all pediatric patients (< 18 years of age at diagnosis) with DADA2 confirmed genetic (biallelic pathogenic *ADA2*/*CECR1*) variants who received care at our institution between 1999 and 2024. For one patient, who died in 1999, the genetic confirmation was confirmed in her sister.

DIAGNOSIS

Cases were diagnosed in accordance with the international consensus diagnostic criteria for DADA2 [11]. Genetic testing was performed in our laboratories or externally. Plasma *ADA2* enzyme activity, an important diagnostic adjunct, was unavailable.

DATA COLLECTION

Demographics, clinical manifestations, laboratory findings (hematologic indices, immunoglobulin levels, inflammatory markers, autoantibodies), treatments, and outcomes were extracted from the computerized medical record using a standardized form.

PHENOTYPE CLASSIFICATION

Patients were classified by predominant clinical phenotype (vasculitic/inflammatory, hematologic, immune deficiency, or mixed) over the entire follow-up period.

STATISTICAL ANALYSIS

Given the small cohort and disease rarity, descriptive statistics were used. Continuous variables are reported as median (range/interquartile range), and categorical variables as counts and percentages.

ETHICS

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the institutional review board of Sheba Medical Center (IRB 9385-12 SMC).

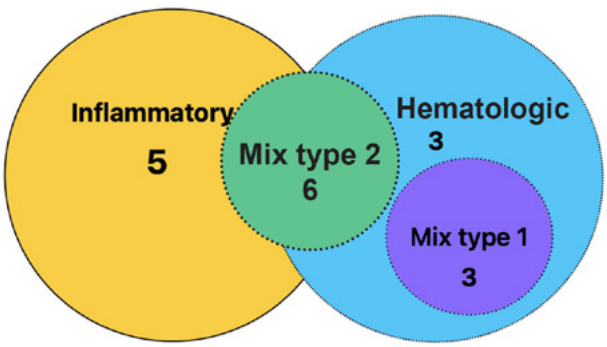
RESULTS

CLINICAL MANIFESTATIONS

Seventeen pediatric patients with clinically and genetically confirmed DADA2 were included from two ethnic groups: Arab Muslim (12/17, 70%) and Georgian Jewish (5/17, 30%). The patients were classified by predominant phenotype: vasculitic/inflammatory, hematologic, or mixed (hematologic-immunologic [mix type 1] or hematologic-inflammatory [mix type 2]); [Figure 1]. Clinical and demographic characteristics by subgroup are summarized in Table 1.

Figure 1. Subdivision of the cohort population into types

Numbers represent the number of patients in the group
Mix type 1 = hematologic: immunologic
Mix type 2 = hematologic: inflammatory



A purely vasculitic/inflammatory phenotype occurred exclusively in Georgian Jewish patients (5/17), who all carried the homozygous p.Gly47Arg (G47R) variant and presented with skin manifestations and ischemic events. None had hematologic or immunodeficiency features.

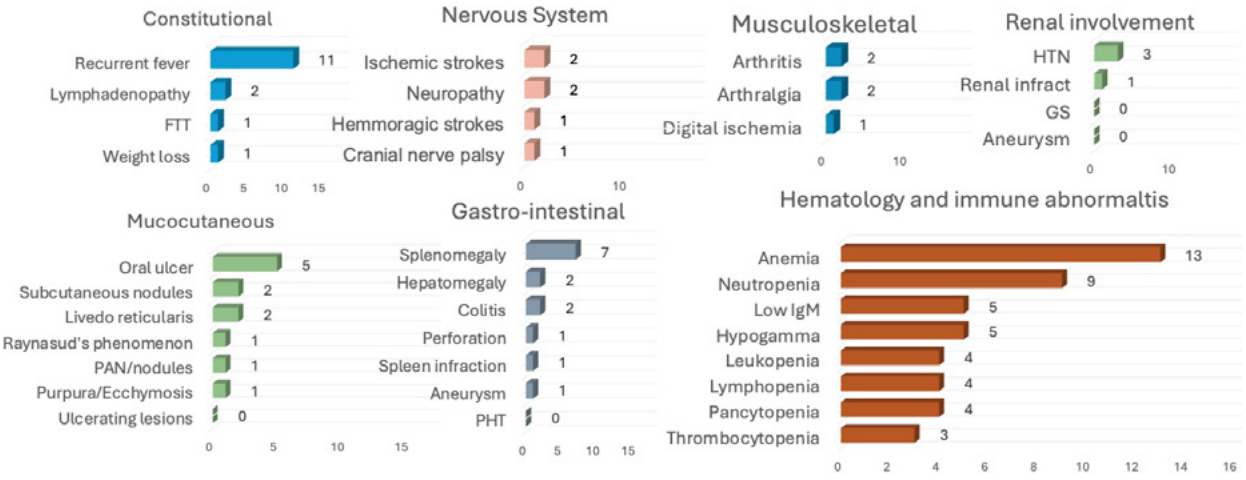
In the Arab subgroup (12/17), the hematologic and immunodeficiency phenotypes were more pronounced. Common features were red cell aplasia and cytopenias, which presented at a young age. Unlike the Georgian Jewish subgroup, parental consanguinity was present in most of the Arab cases (10/12). However, the genotype was diverse, including p.(Leu451Pro) (n=1), p.(Phe178Ser) (n=1), p.(Ala491Asnfs*32) (n=2), p.(Arg49Glyfs*4) (n=1), p.(Gly316Arg) (n=2), p.(Arg49Alafs*13) (n=1), and p.(Asp261Profs) (n=1). Phenotypes were mixed. Half had combined inflammatory-hematologic manifestations, a quarter pure red cell aplasia (PRCA), and a quarter hematologic plus immunodeficiency. None had an isolated vasculitic/inflammatory phenotype [Figure 2].

Table 1. Cohort population characteristic divided into subgroups

	All DADA2	Inflammatory	Hematologic: PRCA	Hematologic: Inflammatory	Hematologic + immune def
Patient, n	17	5	3	6	3
Age of onset in months, median (range)	3.5 (1.75–15)	13 (2–30)	1 (1–4.5)	12 (1–48)	5 (3.5–6)
Age of diagnosis in years, median (range)	4 (2–9)	6.5 (3–9.5)*	4 (3–5)	7 (2–9)	1.2 (0.8–1.6)
Sex (male, female)	11/17 (65% female)	4/5 (80% female)	2/3 (67% female)	3/6 (50% female)	2/3 (67% female)
Ethnic origin					
Georgian Jews	5/17 (29%)	100%	0	0	0
Arab	12/17 (70%)	0	100%	100%	100%
Consanguinity	10/17 (59%)	0	2/3 (67%)	6/6 (100%)	2/3 (67%)
Siblings with DADA2 or deceased	7/17 (41%)	2/5 (40%)	0	4/6 (67%)	1/3 (33%)
Death	3/17 (18%)	1/5 (20%)	0	2/6 (33%)	0

*1 patient died before diagnosis
DADA2 = deficiency of adenosine deaminase 2, PRCA = pure red cell aplasia

Figure 2. Bar diagram representing the clinical manifestations of the patients



In our cohort, the most common constitutional symptom was recurrent fever (11 patients). The principal hematologic presentation was anemia, usually PRCA, and typically within the first year of life. Neutropenia occurred in 9 and thrombocytopenia in 3 patients. Low IgM and hypogammaglobulinemia were the most common immune-deficiency findings (5 patients each). Mucocutaneous manifestations occurred in 12/17, most often oral ulcers (5 patients). Livedo reticularis was seen in 2, subcutaneous nodules in 2, and Raynaud's phenomenon, purpura, and digital ischemia in 1 each. Three patients had cerebrovascular accidents (2 ischemic, 1 hemorrhagic), with single cases of renal and splenic infarction.

Inflammatory markers (C-reactive protein [CRP]) were elevated during flares, mainly in inflammatory phenotypes. Median CRP at presentation was 29 mg/L (8.4–114.5), higher in the vasculitic/Inflammatory (30 mg/L, 18.6–50.8) and inflammatory-hematologic (214 mg/L, 111.6–270) subgroups than in the hematologic (6.7 mg/L, 5.8–8.7) and hematologic-immune deficiency (7.6 mg/L, 5.6–8.1) subgroups.

Antinuclear antibody (ANA) serology was performed in 12 patients. Only two showed low-titer positivity (1:160 and 1:320).

TREATMENT

Twelve patients with vasculitic/inflammatory or mixed hematologic-inflammatory phenotypes received TNF-α inhibitors: etanercept (7) and adalimumab (4). One patient with adverse effects also received infliximab, golimumab, and certolizumab.

Complete response was defined as resolution of clinical inflammatory manifestations with normalization of inflammatory markers and no new ischemic events. Of the 12 treated, 9 achieved complete response, 1 (an inflammatory-hematologic patient with PRCA) partial response, and 2 (hematologic patients with predominant PRCA) no response. None had a stroke after treatment [Table 2].

Three patients with hematologic or mixed hematologic phenotypes underwent HSCT. Two were successful without DADA2-related complications. HSCT normalized the hematologic and immune-deficiency features, and both remained free of vasculitic events during follow-up. The third, with a neutropenia phenotype, was transplanted during an uncontrolled Fusarium infection and died shortly after engraftment. The death was attributed to infection-related complications rather than primary DADA2 progression. He had been diagnosed at 2.5 years of age and died one year after presentation. Eight patients received corticosteroids (maintenance or pulse), two received intravenous immunoglobulin (IVIG) as replacement for the immune-deficiency phenotype, and six required recurrent blood transfusions.

Three deaths occurred. The first was a young Georgian Jewish girl who died of an ischemic complication before TNF inhibitors were widely used. Her younger sister was treated with TNF inhibitors. She was still alive at 20 years of age. The other two were siblings with neutropenia who died of infection, one awaiting a suitable HSCT donor, the other after transplantation.

DISCUSSION

This single-center study adds to the growing understanding of DADA2. Several phenotypic classifications have been proposed. For example, Lee et al. [4] described vasculitis, PRCA, bone marrow failure, and overlapping groups. We classified patients into two principal subgroups: a vasculitic/inflammatory subgroup, characterized by vasculitis with ischemic manifestations affecting various target organs, including the skin; and a hematologic subgroup, defined by PRCA or other cytopenias with or without immune deficiency (hypogammaglobulinemia, lymphopenia), plus a mixed subgroup with overlapping features, similar to the classification of Barron and colleagues [12]. Our manifestations align with the literature, except that Meyts and co-authors [13] reported cutaneous involvement in approximately 75% of patients (oral ulcers in only 7%), whereas oral ulcers were our most frequent mucocutaneous finding. The ethnic composition of our cohort highlights the association between ancestry, genotype, and phenotype. The p.Gly47Arg missense variant, origi-

Table 2. Treatment comparison divided by subgroups

	All DADA2	Inflammatory	Hematologic: PRCA	Hematologic: Inflammatory	Hematologic + immune def
TNF-α inhibitors (8 etanercept, 5 adalimumab, 1 infliximab, 1 golimumab and 1 certolizumab)#	12/17 (70%)	4/5 (80%), complete response*	1/3 (33%), no response	5/6 (83%), Complete response, 1/6 (16%), no response	1/3 (33%), partial response
HSCT candidate**	8/17 (47%)		2/3 (67%)	4/6 (67%)**	2/3 (67%)
HSCT transplanted***	3/17 (18%)		1/3 (33%)	1/6 (16%)***	1/3 (33%)
Steroids (maintenance)	6/17 (35%)	1/5 (20%)		4/6 (66%)	1/3 (33%)
Hypertension treatment	3/17 (18%)		1/3 (33%) after HSCT	2/6 (33%)	
Methotrexate	3/17 (43%)	1/5 (20%)		2/6 (33%)	
Neupogen	4/17 (23%)			3/6 (50%)	1/3 (33%)
Blood transfusions	6/17 (35%)		3/3 (100%)	2/6 (33%)	1/3 (33%)

*1 patient died before anti-TNF treatment
**1 patient died before transplant
***1 patient died post transplantation, due to complicated fungal infection pre- and post-transplant
#1 patient was treated with all the treatments due to unfavorable adverse effects
DADA2 = deficiency of adenosine deaminase 2, HSCT = hematopoietic stem cell transplantation, PRCA = pure red cell aplasia, TNF = tumor necrosis factor

nally linked to vasculitis [1,2], was present in all Georgian Jewish patients and manifested exclusively as a vasculitic/inflammatory phenotype without hematologic involvement. Presentation was sometimes limited to recurrent fever and elevated inflammatory markers years before ischemic events, warranting suspicion for DADA2 in this population. TNF inhibitor therapy was highly successful in these patients, and we recommend it as first-line care. Although certain heterozygous dominant-negative *ADA2* variants can cause DADA2 [6], including p.Gly47Arg, all our patients were homozygous.

The Arab Muslim subgroup exhibited more diverse genotypes and phenotypes, reinforcing the findings of Ben-Ami and colleagues [14]. These patients generally presented younger, often within the first year of life, frequently with PRCA or a Diamond-Blackfan anemia diagnosis. Despite frequent consanguinity, the *ADA2* variants were highly heterogeneous. Presentation can be misleading, consisting primarily of cytopenias or immunodeficiency without inflammatory features, which may appear later or not at all. A high index of suspicion is therefore warranted, and once diagnosed, a personalized, multidisciplinary, phenotype-driven strategy is advised.

Since 2014, accumulating evidence supports TNF inhibitors in preventing vascular crises and ischemic events [15,16]. Mechanistically, TNF blockade reverses the proinflammatory state and shifts macrophage polarization from M1 toward M2, with improved endothelial integrity on post-treatment biopsies [17].

Our findings corroborate these reports [10,12,15-17]. Tumor necrosis factor inhibitors (TNFi) therapy was highly effective for the vasculitic/inflammatory phenotype, reducing systemic inflammation and ischemic risk; however, the therapy had virtually no effect on the immunologic or hematologic components. Patients with mixed phenotypes including inflammatory features may still benefit from TFNi, so the treatment should be considered and tailored to presentation. Consistent with earlier research, ANA serology lacked diagnostic utility. Since DADA2 is a genetic autoinflammatory disease mostly affecting the innate immune system, autoantibodies are not a characteristic feature. We do not recommend routine serological testing in DADA2.

For the hematologic subgroup, HSCT remains the only definitive treatment. Hashem and co-authors [18] reported 30 transplanted DADA2 patients with a 2-year overall survival of 97% and GvHD-free relapse-free survival of 73%, no new vascular events, and resolution of hematologic and immunologic phenotypes. In our cohort, two of the three transplants succeeded while one patient died, underscoring the importance of transplanting while patients are in good clinical condition. HSCT was offered to other patients but most declined due to family preference or unfavorable circumstances.

For patients without effective options, future gene therapy may offer promise. Hong et al. [19] showed that lentiviral ADA2 gene therapy restored enzyme activity in a humanized mouse model, providing a foundation for clinical translation.

Our study has several limitations. First, it was conducted at a single-center and included a retrospective analysis of only 17 patients, which constrained statistical power for subgroup comparisons. As a tertiary referral center, the cohort was subject to referral and selection bias, and phenotype and ethnic frequencies may not reflect the wider DADA2 population. Second, retrospective data collection may introduce information bias and incomplete capture of variables. Our observations, particularly the ethnicity-specific patterns, should be interpreted with caution and confirmed in larger, multicenter cohorts.

In summary, our findings emphasize the broad spectrum of DADA2 and the importance of early, genetically informed diagnosis and multidisciplinary, phenotype-driven management.

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Capsule

Blood pressure levels and outcomes in type 2 diabetes

Wang et al. conducted a comprehensive dose-response meta-analysis to characterize the relationship between blood pressure levels and clinical outcomes in individuals with type 2 diabetes mellitus. The investigators analyzed data from 5.87 million participants enrolled in multiple prospective cohort studies. The analysis demonstrated a nonlinear (J-shaped) relationship between blood pressure and adverse outcomes. Cardiovascular and mortality risks increased progressively with higher systolic blood pressure (SBP) levels, while excessively low blood pressure was also associated with increased adverse outcomes, particularly among high-risk patients. The lowest overall risk was observed within an intermediate blood pressure range rather than at the lowest achievable values. For most cardiovascular outcomes, maintaining moderately controlled SBP was associated with the greatest reduction in risk. Very aggressive blood pressure lowering did not consistently provide additional benefit and, in some populations, was associated with an increased risk of adverse events, supporting concerns regarding overtreatment.

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Eitan Israeli

Capsule

Pyrin's partner revealed

Mutations in *MEFV*, which encodes the cytosolic pattern recognition receptor pyrin, are linked to the autoinflammatory disorder familial Mediterranean fever (FMF); however, mechanisms linked to mutations in the B30.2 domain of pyrin have been unresolved. A trio of studies have shown that the B30.2 domain interacts with CDC42, which promotes pyrin oligomerization and inflammasome formation. **Iwata** et al. used a genotype-first approach to characterize missense mutations in *MEFV*, which identified interactions between B30.2 and CDC42. **Aoki** et al. and **Feng** et al. identified mutations in CDC42 linked to a different autoinflammatory syndrome. Together, these studies showed that B30.2 or CDC42 mutations enhanced their binding affinity, which caused uncurbed inflammasome activation. These studies redefine our understanding of pyrin activation and offer insight into immune defects in individuals with previously uncharacterized mutations.

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