LETTERS TO THE EDITOR
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Extreme Phenotypic Variation in Siblings with Identical Homozygous Mutations Causing ADA2 Deficiency: A Case Series

ADA2 Eksikliğine Neden Olan Aynı Homozigot Mutasyonlara Sahip Kardeşlerde Aşırı Fenotipik Varyasyon: Olgu Serisi

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To the Editor,

Deficiency of adenosine deaminase-2 (DADA2; MIM # 615688) is a rare autoinflammatory disorder caused by homozygous mutations in the *ADA2* gene (MIM # 607575). Since the initial description of DADA2 (1, 2), a wide range of clinical manifestations have been reported (3), which led the disease to be broadly classified into three phenotypes: polyarteritis nodosa (PAN)-like, Diamond-Blackfan anemia (DBA)–like, and immune deficiency phenotype (4, 5). To date, the *ADA2* gene has been found to harbor over 100 mutations distributed over all exons that cause the disease (3, 6). Previous research has attempted to explain the basis for the broad spectrum of DADA2 phenotypes by focusing on the location of pathogenic variants within *ADA2* (5). However, affected individuals with the identical *ADA2* mutations have been reported to develop different disease courses with differing ages of onset (6); therefore, the genotype-phenotype association in DADA2 has still not been fully understood. Herein we describe four children with DADA2 from two distinct families (family A and B), illustrating how the same mutation can result in significant variations in disease manifestations even in siblings.

Case A1 was a 9-year-old girl with recurrent fever, myalgia, and arthralgia, which had developed over the last six months. Her parents were consanguineous, and she had a healthy older brother and a younger sister (case A2). Her clinicodemographic characteristics are summarized in **Table 1**. During follow-up, she developed severe proteinuria and hypoalbuminemia along with elevated creatinine levels. Subsequently, a kidney biopsy demonstrated amyloidosis, which also involved the intestinal system. The bone marrow investigation was nondiagnostic. Although familial Mediterranean fever (FMF) was initially suspected, analysis of the *MEFV* gene did not reveal any mutations. Moreover, autoimmune lymphoproliferative syndrome was excluded. Additionally, common congenital neutropenia genes had no pathogenic mutations. The patient did not improve despite all the treatment and unfortunately died before her diagnosis was established. Case A2 presented with fatigue, fever, abdominal pain, and frequent upper respiratory tract infections (**Table 1**). The bone marrow study revealed hypoactivity of erythroid precursors. Considering the patient's severe neutropenia, reduced IgA and IgM levels, a family history involving an older sister with intestinal and renal amyloidosis, as well as the consanguinity of the parents, an inherited immune

dysregulation was suspected. Whole exome sequencing (WES) during a routine make-up revealed the homozygous *ADA2* deletion. The patient ultimately underwent hematopoietic stem cell transplantation (HSCT). Currently, the patient is free of any additional health issues.

A 2-year-old girl (case B1) was referred due to monthly erythrocyte transfusion dependency since she was 4 months old. Her clinicodemographic characteristics were given in **Table 1**. Hemoglobin electrophoresis, osmotic fragility tests, and serum LDH levels were all normal, and the direct antiglobulin test was negative. Additionally, glucose-6-phosphate dehydrogenase (G6PD) and pyrimidine 5-nucleotidase (P5′N) deficiencies were excluded. Bone marrow aspiration revealed a notable decrease in erythroid precursors. The findings pointed towards DBA; however, corticosteroid treatment was unsuccessful, and Sanger sequencing of the *RPS19* gene was normal. Finally, WES detected the homozygous c.1072G>A (p.Gly358Arg) mutation in the *ADA2* gene. The patient is now being considered for HSCT. Case B1 has a younger sister who was found to be homozygous for the same *ADA2* mutation (case B2). She has been routinely scheduled for follow-up, and to date, she remains asymptomatic.

Case A1 was considered to predominantly demonstrate the vasculitis-like phenotype. However, the severe neutropenia and the history of frequent infections suggest immune dysfunction as well. On the other hand, case A2 is a classic example of the hematological DADA2 phenotype. Case A2 also had recurrent upper respiratory tract infections and low IgA and IgM, suggesting minor disruption of immune functions. Case B1 exhibited the hematological phenotype of the disease; intriguingly, despite sharing the identical mutated alleles with her older sister, case B2 still remains asymptomatic at the age of four.

A recent study suggested that catalytic domain mutations (exon 7) were responsible for pure red cell aplasia (5). Based on this, our expectation would be to see DBA-like phenotypes in all cases presented here. However, case A1 exhibited a PAN-like phenotype, and case B2 has been completely symptom-free. The discrepancy in disease severity and presentation of the disease at different ages, although siblings were affected by the same homozygous mutation, may reinforce the role of epigenetic and environmental influences on the *ADA2* gene. In fact, a Finnish follow-up study of DADA2 patients revealed bacterial dental or respiratory infections as a trigger of the vascular flares of the disease (7).

With the limited insights about the pathology of DADA2, TNF inhibitors are a prominent choice of treatment, especially for the vasculitis phenotype (8). However, trying to suppress the inflammation in case A1 with steroids, colchicine, and tocilizumab was unsuccessful in our management. For the hematologic phenotype, HSCT has been reported to be an effective treatment strategy (3), which was proven in case A2. An HLA-matched donor is still being searched for case B1.

In conclusion, this report shows the siblings from two separate families of Turkish origin who were affected by the same mutations in the *ADA2* gene yet displayed different phenotypes of the DADA2 spectrum. More research in this field is warranted to better understand the pathology of the disease with different manifestations and to ensure optimal personalized management strategies.

Keywords: Deficiency of Adenosine Deaminase 2, DADA2, Vasculitis, Diamond-Blackfan Anemia, Child, Polyarteritis Nodosa

Declarations

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***Authors contributions*:** T.A., S.O., and S.U. provided the clinical follow-up of the affected individuals. M.D.A. and S.U. contributed to conceptualization and data collection. M.D.A. wrote the initial manuscript, and S.U., S.O., and A.C. supervised the text and critically revised the manuscript. A.C. and A.G. performed genetic studies for the *ADA2* gene. All the authors have seen and approved the final article.

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Table 1. Demographic and clinical features of DADA2 patients.

	Case A1	Case A2	Case B1	Case B2
Age (years)				
At symptom onset	9	6	<1	N/A
At admission	9	7	2	<1
At genetic diagnosis	N/A	9	6	<1
Current	N/A	11	11	4
ADA2 Mutation	hom. ΔExon7	hom. ΔExon7	hom. c.1072G>A: p.Gly358Arg	hom. c.1072G>A: p.Gly358Arg
Gender	Female	Female	Female	Female
Ethnicity	Turkish	Turkish	Turkish	Turkish
Consanguinity	+	+	-	-
Recurrent Fever	+	-	-	-
Recurrent Infections	+	+	-	-
Myalgia/arthralgia	Myalgia	Myalgia	-	-
Neurologic involvement	-	-	-	-
Hematological involvement	Anemia, leukopenia	Anemia, leukopenia	Anemia	-
Immunological Involvement	Hypogammaglobulinemia	Low IgA and IgM	-	-
Gastrointestinal involvement	Abdominal pain, hepatosplenomegaly, intestinal amyloidosis, melena	Abdominal pain, hepatosplenomegaly	Secondary hemochromatosis	-
Renal involvement	Nephrotic syndrome	-	-	-
Dermatological findings	Aphthous tongue lesions, bullous lesion on the left elbow, gingival erythema, oral mucositis	Multiple warts on the fifth finger of the right hand	-	-
Other findings	Cervical lymphadenopathy, pretibial edema, eyelash trichomegaly	Pallor (skin and conjunctival)	Tired and sleepy appearance	-
Laboratory Results*				
Hb (g/dL)	9.7	6.2	8.1	Normal range
WBC (cells/mm^3)	1000	3900	10700	Normal range
ANC (cells/mm^3)	170	1700	3500	Normal range
ALC (cells/mm^3)	800	1500	6300	Normal range
Autoantibody Panel**	-	-	-	N/A
Direct/Indirect Coombs Tests	+/-	-/-	-/-	N/A
Bone marrow findings	Hypocellular bone marrow, increased presence of T-lymphoid precursors, dysmorphic erythroid and myeloid precursors, reduction in granulocyte precursors	Slightly hypocellular bone marrow, hypoactive erythroid precursors, reduction in megakaryocytes, dysplastic changes in myeloid precursors	Normocellular bone marrow, reduction in erythroid precursors	N/A
Previous treatment	CAS, CIP, COL, ES, G-CSF, IV Albumin, IVIG, Mpm, MP, TEC, TOZ, TPN	ES, PT	Deferasirox, ES, MP, UDCA, Vitamin E	-
Current treatment	N/A	BM transplantation	Deferasirox, ES, UDCA, Vitamin E	-

Outcome	Deceased	Cure	Awaiting BM donor match	Asymptomatic
Case A1 and Case A2; Case B1 and Case B2 are siblings. *Laboratory results at admission. **Autoantibody panel includes ANA (antinuclear antibody), anti-dsDNA, ANCA (antineutrophil cytoplasmic antibody), aPL (antiphospholipid antibody), aCL (anticardiolipin antibody), lupus anticoagulants, ASMA (anti-smooth muscle antibodies) and LKM-1 (liver kidney microsomal autoantibodies). ALC: absolute lymphocyte count; ANC: absolute neutrophil count; BM: bone marrow; CAS: caspofungin; CIP: ciprofloxacin; COL: colchicine; ES: erythrocyte suspension; G-CSF: granulocyte-colony stimulating factor; Hb: hemoglobin; hom.: homozygous; IVIG: Intravenous immune globulin; Mpm: meropenem; MP: methylprednisolone; N/A: not applicable; PT: platelet transfusion, TEC: teicoplanin; TOZ: tocilizumab; TPN: total parenteral nutrition; UDCA: ursodeoxycholic acid; WBC: white blood cell; ΔExon7: deletion of exon 7.				