REVIEW

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Deficiency of Adenosine Deaminase 2

Adenozin Deaminaz 2 Eksikliği

Çağrı Coşkun[1], Şule Ünal[1,2,3]

[1]*Hacettepe University Faculty of Medicine, Department of Pediatric Hematology, Ankara, Türkiye*
[2]*Hacettepe University Research Center for Fanconi Anemia and Other Inherited Bone Marrow Failure Syndromes, Ankara, Türkiye*
[3]*Hacettepe University Research Center for Genomics and Rare Diseases, Ankara, Türkiye*

Abstract

Adenosine deaminase 2 (ADA2) deficiency is an autosomal recessively inherited autoinflammatory disorder caused by loss-of-function mutations in the *ADA2* gene. Although the pathogenesis involves the triggering of a proinflammatory cascade due to increased production of inflammatory cytokines such as tumor necrosis factor (TNF)-α and dysregulation of neutrophil extracellular trap formation resulting from an excess accumulation of extracellular adenosine, the pathogenetic mechanism still needs further clarification due to the broad clinical spectrum. In addition to the initially described vasculitis-related symptoms, hematological, immunological, and autoinflammatory symptoms are now well recognized. The diagnosis is made by demonstration of pathogenic variants of *ADA2* with biallelic loss of function and identification of low plasma *ADA2* catalytic activity. Currently, TNF-α inhibitors are the treatment of choice for controlling vasculitis manifestations and preventing strokes. However, in patients presenting with severe hematologic findings, TNF-α inhibitors are not the treatment of choice and hematopoietic stem cell transplantation has been shown to be successful in selected cases. Recombinant ADA2 protein and gene therapy are promising treatment modalities for the future. In conclusion, ADA2 deficiency has a broad phenotype and should be considered in the differential diagnosis of different clinical situations. In this review, we summarize the disease manifestations of ADA2 deficiency and available treatment options.

Keywords: Deficiency of adenosine deaminase 2, *ADA2* gene, Pure red cell aplasia, Autoinflammatory disease, Immunodeficiency

Öz

Adenozin deaminaz 2 (ADA2) eksikliği, *ADA2* genindeki işlev kaybı mutasyonlarının neden olduğu otozomal resesif geçişli otoenflamatuvar bir hastalıktır. Patogenez, tümör nekroz faktörü (TNF)-alfa gibi enflamatuvar sitokinlerin üretiminin artması nedeniyle proinflamatuvar bir kaskadın tetiklenmesini ve ekstraselüler adenozinin aşırı birikiminden kaynaklanan nötrofil ekstraselüler tuzak oluşumu disregülasyon sürecini içermesine rağmen, geniş klinik spektrum nedeniyle patogenetik mekanizmanın hala daha fazla açıklığa kavuşturulması gerekmektedir. Başlangıçta tanımlanan vaskülitle ilişkili semptomlara ek olarak, hematolojik, immünolojik ve otoinflamatuar semptomlar da artık iyi tanınmaktadır. Tanı, *ADA2*'nin biallel fonksiyon kaybı ile patojenik varyantlarının gösterilmesi ve düşük plazma *ADA2* katalitik aktivitesinin tanımlanması ile konur. Günümüzde TNF alfa inhibitörleri, vaskülit belirtilerini kontrol altına almak ve felçleri önlemek için tercih edilen tedavidir. Şiddetli hematolojik bulgularla başvuran hastalarda, TNF alfa inhibitörleri tercih edilen tedavi değildir ve hematopoetik kök hücre naklinin seçilmiş vakalarda başarılı olduğu gösterilmiştir. Rekombinant ADA2 proteini ve gen tedavisi gelecek için umut verici tedavi yöntemleridir. Sonuç olarak, ADA2 geniş bir fenotipe sahiptir ve farklı klinik durumlarda ayırıcı tanıda göz önünde bulundurulmalıdır. Bu derlemede, ADA2 eksikliğinin hastalık belirtilerini ve mevcut tedavi seçeneklerini özetlemeyi amaçladık.

Anahtar Sözcükler: Adenozin deaminaz 2 eksikliği, *ADA2* geni, Saf kırmızı hücre aplazisi, Otoenflamatuvar hastalık, İmmün yetmezlik

Introduction

Adenosine deaminase 2 (ADA2) deficiency is a monogenic autoinflammatory disease with a wide clinical spectrum [1,2]. It was first described in 2014 as a vasculitis syndrome very similar to polyarteritis nodosa (PAN) and more than 400 cases have been published to date [2,3,4]. In the last decade, numerous other manifestations have been reported, including vasculitis, immunodeficiency, hematological abnormalities, and autoinflammation [2,5]. The patients initially described were of Georgian, Jewish, German, and Turkish origin, but deficiency

Address for Correspondence/Yazışma Adresi: Şule Ünal, M.D., Hacettepe University Faculty of Medicine, Department of Pediatric Hematology; Hacettepe University Research Center for Fanconi Anemia and Other Inherited Bone Marrow Failure Syndromes; Hacettepe University Research Center for Genomics and Rare Diseases, Ankara, Türkiye
Phone : +90 312 305 11 70
E-mail : suleunal2003@hotmail.com ORCID: orcid.org/0000-0002-3842-8788

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of ADA2 (DADA2) is being increasingly reported among other ethnic groups [5,6]. While the first identified cases were mostly seen in childhood, cases of DADA2 presenting in adulthood are increasingly being recognized [2,6]. Although homozygous and combined heterozygous mutations in the *ADA2* gene leading to reduced ADA2 activity are known to cause this disease, the pathogenesis of the disease is not fully understood [5]. ADA2 enzyme deficiency causes an increase in extracellular adenosine levels and triggers a proinflammatory cascade [6]. Detection of decreased activity of the ADA2 enzyme and/or identification of biallelic mutations in the *ADA2* gene are used in the diagnosis [7].

Pathophysiology of DADA2

Adenosine deaminases are an important part of the purinergic pathway. They catalyze the deamination of adenosine to inosine and deoxyadenosine to deoxyinosine. The two main isoforms with adenosine deaminase activity in humans are ADA1 and ADA2 [5,7,8]. ADA1 is a 40-kDa monomer found in almost all cells, whereas ADA2 is a 57-kDa homodimer produced mainly by monocytes and myeloid cells, increased in stress conditions and secreted into the extracellular space. ADA1 and ADA2 have structurally non-identical catalytic sites. However, the catalytic activity of ADA2 is much lower than that of ADA1. Therefore, it can only function at higher adenosine concentrations, in conditions such as hypoxia, inflammation, and tumor growth. ADA1 and ADA2 have specific roles in the immune system and one enzyme cannot be compensated by the other [5,7,8].

The pathogenesis of DADA2 is not fully understood. Cases of DADA2 show skewed monocyte differentiation with increased numbers of pro-inflammatory M1 macrophages and decreased numbers of anti-inflammatory M2 macrophages. This monocyte/macrophage polarization leads to endothelial disruption with increased release of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 [7,9,10]. In addition, DADA2 causes chronic activation of neutrophils, resulting in myeloperoxidase-mediated endothelial damage (Figure 1) [9].

Neutrophil extracellular trap formation (NETosis) is a form of cell death characterized by the release of globular proteins bound to a condensed chromatin network. Although NETosis appears to be beneficial for the host, dysregulation of this pathway can lead to tissue damage and inflammation. DADA2 increases extracellular adenosine levels. Adenosine induces NETosis via NADPH oxidase and peptidyl arginine deaminase, and NETosis occurs in tissues and circulation affected by DADA2 [6,11]. The formation of NETs and M1 macrophages triggers enough TNF-α to cause inflammation. As a result, a vicious cycle of inflammation and vasculopathy occurs [7,11]. Furthermore, TNF-α plays a role in bone marrow failure in patients with aplastic anemia and it is thought that increased TNF-α levels in this group of patients may be one of the mechanisms behind the hematological manifestations of the disease. Low-density granulocyte levels have also been found to be increased in patients with DADA2, and this is partially involved in the pathogenesis of vasculitis through NETosis [11]. In patients with DADA2, there is upregulation of the genes stimulated by type 1 interferon (IFN), which has been shown to decrease with treatment [7,9,10]. It has also been shown that high plasma IL-18 levels may be associated with the activated IFN-γ pathway, the pathogenesis of hematological manifestations, and lack of response to anti-TNF therapy. Tie-1 (tyrosine-protein kinase

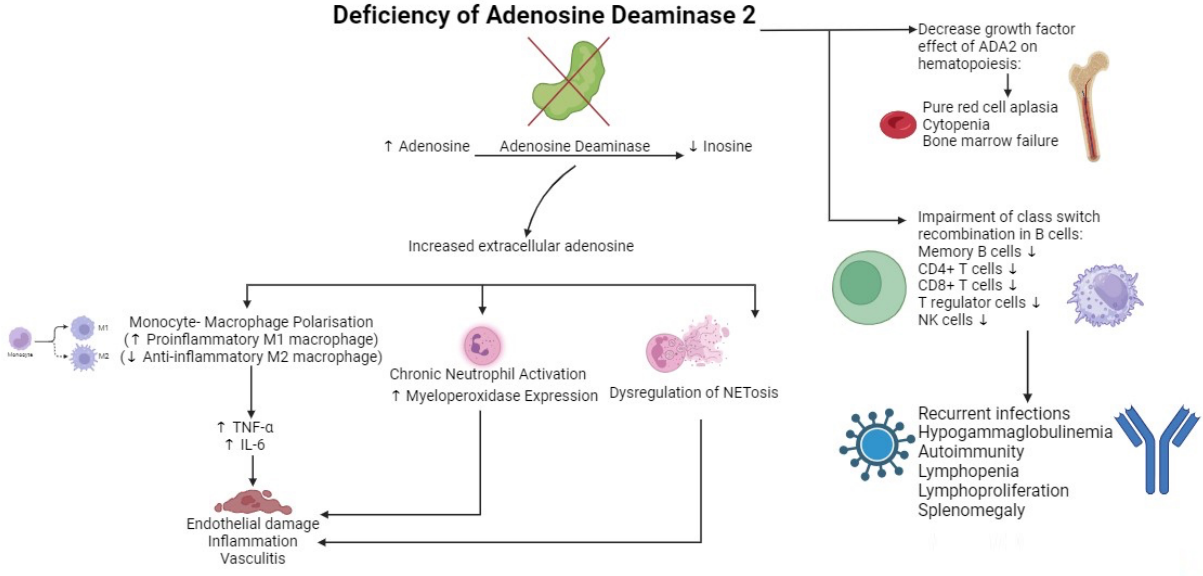

Figure 1. The potential pathophysiologic mechanisms of adenosine deaminase 2 (ADA2) deficiency with the clinical consequences (drafted in BioRender).

receptor), Tie-2 (tyrosine-protein kinase receptor), sFlt-1 (soluble vascular endothelial growth factor receptor-1), sRAGe (soluble isoform of a receptor for advanced glycation end products), and TNF-α levels are increased in patients with PAN-like DADA2 and can be used as biomarkers [12].

The pathogenesis of the vasculitic phenotype is better understood while the mechanisms underlying the hematological and immunological manifestations of DADA2 have not been fully elucidated. ADA2 functions as a growth factor by inducing the differentiation of monocytes into macrophages, macrophage differentiation, and proliferation. This may explain its effect on hematopoiesis. Low ADA2 activity is still considered sufficient for normal hematopoiesis. However, mutations causing very low or undetectable enzyme activity could manifest with hematological symptoms. Extracellular adenosine regulates the B, T, and natural killer (NK) subgroups of lymphocytes. ADA2 may play a role in the survival and activation of immune cells through both internal and extracellular effects. Studies have also shown that ADA2 secreted from monocytes acts as an autocrine factor that stimulates the differentiation of monocytes into macrophages and dendritic cells, and these effects explain the relationship among DADA2 deficiency, immunodeficiency, and autoimmunity [5,6,7,13]. Additionally, transcriptomic analyses of the proerythroblasts of patients with classical Diamond-Blackfan anemia (DBA) and patients with DADA2 deficiency who presented with a DBA-like phenotype were found to have similar transcriptomic features, indicating an inflammatory bone marrow niche [14].

Molecular Background of DADA2

Biallelic mutations on chromosome 22q11.1 encoding the ADA2 protein have been associated with DADA2 phenotypes. Most patients are compound heterozygous for missense mutations, but homozygous genotypes have also been described. To date, hundreds of disease-causing mutations have been identified. Missense mutations, genomic deletions, nonsense mutations, and splicing mutations are among the pathogenic variants [6]. The most commonly reported mutation is the missense mutation p.Gly47Arg (p.G47R). Other widely reported mutations include p.Gly47Ala, p.Arg169Gln, p.Tyr453Cys, and p.Thr360Al. Although these mutations have been reported in various ethnic groups, they are more common in founder populations. The homozygous p.G47R mutation was identified in all Georgian Jews and most Turkish patients with early-onset PAN. Another founder mutation reported in Dutch, Belgian, and Finnish populations is the p.R169Q variant, while p.Thr360Ala is more common in Italian patients. The carrier frequency in North European populations is 1:500 while it is significantly lower in African, Latin, and Asian societies. Although many communities have identified DADA2 patients, it is assumed that many mutations associated with milder phenotypes are still not recognized [10].

The relationship between genotype and phenotype is intriguing. Increasing evidence suggests various presentations of DADA2, even among patients with the same mutations, in terms of the age of onset and symptoms. In a family of Iraqi origin, four adult family members with homozygous mutations were described as asymptomatic at the time of reporting [10]. Various epigenetic and environmental factors could play a role in phenotype and disease severity.

Özen et al. [15] found that dimerization domain mutations were associated with a vasculitis-like phenotype, while catalytic domain mutations were strongly associated with hematological presentations. In another study, the pathogenic p.(Tyr453Cys) mutation was associated with livedoid skin rash, while p.(Arg169Gln) mutation led to hypogammaglobulinemia with hematologic abnormalities [16,17]. G47R, the most common mutation in individuals of Turkish and Georgian ancestry, is associated with a PAN-like phenotype, while the R169Q mutation, common in European populations, is associated with a predisposition to stroke. In the study conducted by Wang et al. [18] in a Chinese pediatric population, none of the patients had the G47R mutation and there was only one patient with the R169Q mutation without hematological or neurological symptoms.

Lee et al. [19] reported that mutations leading to minimal residual activity of ADA2 are frequently associated with hematological phenotypes such as pure red cell aplasia (PRCA) and DBA-like phenotype compared to mutations with at least 3% enzymatic activity in patients with a vasculitic phenotype.

Clinical Findings

Since the first description of PAN-like vasculitis associated with DADA2, clinical findings related to DADA2 have been increasingly reported [5,20]. Besides the predominant vasculopathy phenotype, other reported clinical manifestations include autoinflammation, immunodeficiency, hematological abnormalities, and lymphoproliferation [5]. However, there are overlapping phenotypes in addition to totally asymptomatic patients (Figure 2). The age of onset is usually in childhood, with 25% of patients presenting before the age of 1 year and the majority before the age of 10 [8]. However, the disease has also been reported in adults [5]. Recurrent stroke and infection are the most important causes of mortality in DADA2 with a mortality rate of 8% [8,10].

• Vasculitis

The most common clinical feature of DADA2 is vasculopathy affecting small and medium-sized arteries [8,10,20]. The clinical phenotype ranges from limited skin involvement to systemic vasculitis with multi-organ involvement and high mortality [20]. Cutaneous manifestations are the most common feature of DADA2, reported in 75% of cases [8]. The most common skin

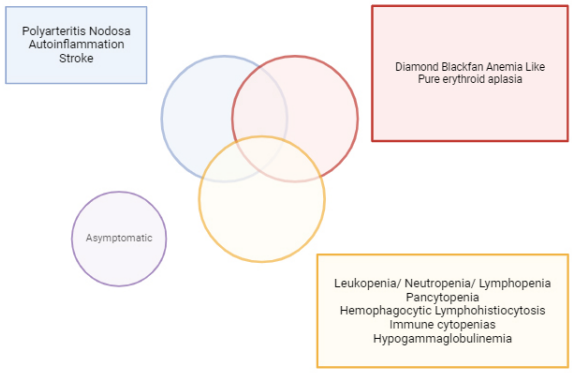

Figure 2. Clinical phenotypes are highly variable in patients with adenosine deaminase 2 (ADA2) deficiency (drafted in BioRender).

manifestation of DADA2 is livedo racemosa. Erythema nodosum, skin ulcerations, Raynaud's phenomenon, nodular rash, and macular erythema have also been described among other skin eruptions [10,20]. Skin biopsy often shows diffuse neutrophil and macrophage infiltration in the interstitium and perivascular T lymphocytes without obvious features of vasculitis [20].

Half of the reported patients have central nervous system (CNS) symptoms. The hallmark sign of CNS vasculopathy is the recurrence of ischemic lacunar strokes [10,20]. Other CNS manifestations include cranial nerve palsy, diplegia, paraplegia, peripheral polyneuropathy, sensorineural hearing loss, mononeuritis multiplex, labyrinthitis, neuromyelitis, encephalopathy, and cerebral atrophy [8,10]. Vasculitis can also affect the gastrointestinal tract, kidney, liver, and other organs. Gastrointestinal symptoms are reported in 10% of these patients and include abdominal pain and inflammatory bowel disease. Less frequently, intestinal perforation, celiac disease, and aneurysms in mesenteric arteries are also reported [8,20]. Renal involvement in DADA2 is seen as arterial hypertension, renal artery aneurysm, renal artery stenosis, and glomerulonephritis with glomerular scar formation [8,10]. Symptoms that indicate liver involvement include high transaminase levels, hepatosplenomegaly, and portal hypertension [8,10].

• Immune Deficiency

Unlike the severe combined immunodeficiency found in ADA1 deficiency, DADA2 is associated with a milder form of immunodeficiency. Humoral immunodeficiency is more common, and the most common abnormality reported is low immunoglobulin (Ig) M levels [5]. In addition, panhypogammaglobulinemia, lymphopenia, neutropenia, decreased number of B lymphocytes, low class-switched B cells, impaired response to vaccines, low NK cells, and low number of T lymphocytes can also be revealed in DADA2 [5]. In 15%-20% of patients with DADA2, a pronounced phenotype of immunodeficiency can be observed in the form of recurrent infections, and this phenotype can mimic common variable immunodeficiency (CVID). Especially in patients with immunodeficiencies like CVID where vasculopathy symptoms are seen, DADA2 should be considered in the differential diagnosis [20]. In addition to CVID-like presentations in DADA2, infections caused by fungal infections, molluscum contagiosum, warts, and herpes viruses have been reported, suggesting combined immunodeficiency [20].

• Lymphoproliferation

The lymphoproliferative phenotype can cover a broad spectrum, from benign follicular hyperplasia to malignant proliferation [8]. Benign lymphoproliferation caused by follicular hyperplasia is a well-known feature of DADA2. Patients typically present with hepatosplenomegaly and generalized lymphadenopathy. Recently, biallelic mutations associated with DADA2 were reported in patients with a phenotype resembling autoimmune lymphoproliferative syndrome (ALPS) [10]. Distinguishing it from classical ALPS, hypogammaglobulinemia and lymphopenia support a diagnosis of DADA2, whereas double-negative T-cell levels are usually within normal limits in cases of DADA2 [8,20].

Malignant lymphoproliferation or neoplasms are rare. Two patients were diagnosed with T-cell large granulocytic lymphocytic leukemia and four patients were diagnosed with Hodgkin lymphoma. Cutaneous acute myeloid leukemia and diffuse large B-cell lymphoma have also been rarely reported in patients with DADA2 [8,20].

• Hematological Findings

The spectrum of hematological involvement adds another interesting dimension to DADA2 [21]. Since the first descriptions of DADA2, bone marrow hypofunction resulting in erythroblastopenia, leukopenia, neutropenia, and thrombocytopenia has been demonstrated [20]. Anemia occurs in many patients and can be multifactorial, ranging from anemia of inflammation to autoimmune hemolytic anemia. Refractory anemia resembling PRCA or DBA has been described in 10% of patients [5,6]. PRCA, first described by Hashem et al. [13] and Ben-Ami et al. [22], is characterized by the absence of red cell precursors in the bone marrow and manifests as normocytic anemia with a marked decrease in reticulocytes [8,10]. DBA is a congenital form of PRCA and usually presents early in life with macrocytic anemia [20,23]. However, the pure erythroid aplasia seen in DADA2, which can present at any age of life, can be distinguished from DBA by the absence of congenital abnormalities and dysmorphic findings [23]. In addition, in DADA2 deficiency with pure erythroid aplasia, erythrocyte adenosine deaminase activities and fetal hemoglobin levels are normal while mean corpuscular volume is elevated [23,24,25]. Patients with DADA2 phenotypes may have additional

features such as low B cells and hypogammaglobulinemia [25]. The finding of hepatosplenomegaly may be a clue in differentiating DADA2 from DBA [6,20]. In addition to erythroid hypoactivity, other bone marrow cell lines may also be affected by DADA2. Neutropenia is a prominent finding and has been widely described. Low IgM or panhypogammaglobulinemia and lymphopenia have also been reported. In a recent study, thrombocytopenia and pancytopenia were detected in 10% of patients with DADA2 [20].

Autoimmune cytopenia has also been reported in DADA2 [6,20]. Clues to the etiology in this patient group include a history of stroke, vasculopathic ulcers, hypogammaglobulinemia, and recurrent infections in addition to accompanying lymphopenia, neutropenia, thrombocytopenia (Evans syndrome), and lymphoproliferation with or without increased double-negative T-cells [6,8,20]. A small number of patients may have a positive direct antiglobulin test without significant hemolysis or PRCA. In summary, the co-occurrence of autoimmune hemolytic anemia and erythroblastopenia can be considered as another hematological presentation of DADA2 [20].

The origin of the hematological symptoms is still unclear. When bone marrow biopsies were examined, reticular fibrosis was observed in addition to characteristic lymphocyte aggregates, and normal myeloid development was found in bone marrow analysis in a patient with severe neutropenia. Based on these findings, it was suggested that anemia and lymphopenia may result from altered interactions between the bone marrow microenvironment and activated myeloid and other immune cells of the bone marrow [8]. Autoimmunity may be an underlying cause, but an increase in autoantibodies has not been demonstrated in most patients [5]. It has been suggested that the absence of ADA2, which functions as a growth factor, may lead to bone marrow failure. This was confirmed by the fact that hematological symptoms are often seen together with more deleterious mutations that lead to severe DADA2 [5,6].

Compared to the vasculitic phenotype, PRCA and other bone marrow failure phenotypes occur earlier in life. Only up to 20% of patients with a predominant hematological phenotype experience vasculitis-related symptoms. However, DADA2 should be considered in the differential diagnosis of bone marrow failure and aplastic anemia, even in the absence of the inflammatory phenotype [6,10].

Hematological findings such as macrophage activation syndrome, non-immune hemolytic anemia, and myelofibrosis have been seen in a small number of cases of DADA2 [6].

Diagnosis

The diagnosis of DADA2 is based on the measurement of plasma or serum ADA2 enzymatic activity and/or the use of genetic tests that help identify the *ADA2* gene [2,7]. The ADA2 activity test can rule out DADA2 by providing results in a short period. There are two protein tests used to show DADA2. The first of these tests measures plasma/serum ADA2 activity by high-performance liquid chromatography on plasma/dried blood spots, while the second test evaluates serum ADA2 levels by enzyme-linked immunosorbent assay [8,26]. Unmeasurable ADA2 levels are considered diagnostic for DADA2, while normal ADA2 levels are sufficient to exclude DADA2. However, the use of these tests to determine ADA2 activity is currently limited to a few laboratories worldwide that are certified to measure ADA2 activity [2,26].

Sanger sequencing and, as part of a broader approach, whole-exome or whole-genome sequencing are standard molecular genetic tests for DADA2. Additional genetic evaluation of ADA2 enzyme activity and non-coding sequences and copy number variations should be considered in cases in which genetic findings are not sufficient to make a diagnosis but clinical suspicion remains high [2,7]. Most patients have biallelic loss-of-function mutations in the *ADA2* gene. Individuals with monoallelic pathogenic or possibly pathogenic *ADA2* variants are considered carriers [2,5]. Measurement of ADA2 enzyme activity is strongly recommended for individuals with monoallelic or biallelic *ADA2* variants of unknown significance, since some patients may also have intronic pathogenic variants on the other allele, as well [2].

Once an index case is diagnosed, the patient's siblings and parents should be encouraged to undergo family screening, even in the absence of symptoms. Genetic counseling for reproductive decision-making, prenatal testing, and psychosocial support is important [2,6]. If hematopoietic stem cell transplantation (HSCT) is considered as a treatment option, screening potential donors for DADA2 is recommended [2].

Treatment

The treatment of patients with DADA2 primarily depends on the clinical features [20].

Vasculitic/Autoinflammation Phenotype

In the past, steroids were widely used to control systemic inflammation for patients with the vasculitic/autoinflammatory phenotype. However, problems such as exacerbation of inflammation during dose reduction, inadequate success in preventing stroke recurrence, and lack of response to steroids have been reported [6,10,20]. Azathioprine, methotrexate, calcineurin inhibitors, cyclophosphamide, mycophenolate mofetil, and sirolimus have not been sufficiently successful in suppressing inflammation [8,10]. One patient with PAN who was a carrier of a mutation associated with familial Mediterranean fever was reported to benefit from colchicine [8,10]. Anti-IL-1 therapies such as anakinra and canakinumab were not successful in reducing inflammation. The anti-IL-6 agent tocilizumab

was successful in one patient with Castleman syndrome, but recurrent paralysis was seen in other groups of treated patients [6,8,10]. Since ADA2 is present in plasma, it was thought that monthly infusions of fresh frozen plasma could be used to replace ADA2 activity. However, the short half-life of ADA2 and the need for frequent infusions of large volumes of fresh frozen plasma rendered this therapeutic approach unfavorable [6,7,10]. Thalidomide treatment resulted in complete remission in seven patients, but thalidomide was discontinued due to side effects associated with neurotoxicity such as peripheral neuropathy. The use of antiplatelet and antioxidant drugs can reduce the risk of hemorrhage. Given the high incidence of ischemic and hemorrhagic events in patients with DADA2, the use of these agents is not recommended until the disease is well controlled [10,27].

TNF blockade is the mainstay of therapy in the vasculopathy and inflammatory phenotypes of DADA2 [6,20]. TNF inhibitors are effective in controlling fever attacks and vasculopathy and preventing strokes [6,10]. They have also been found to significantly reduce acute-phase reactants, improve complete blood count findings, and reduce perivascular TNF infiltration [6]. Although soluble TNF receptor (etanercept) and various monoclonal antibodies against TNF (adalimumab, infliximab, golimumab) have all been shown to be effective, etanercept and adalimumab are currently more widely used [2,6]. Lack of response to these agents has become a problem and the detection of neutralizing antibodies in patients under treatment has led to a decrease in treatment efficacy. Switching from monoclonal antibodies to fusion proteins, giving higher doses of treatment, and decreasing the dosing interval resulted in satisfactory clinical outcomes [5,6]. In addition, use of disease-modifying antirheumatic drugs such as methotrexate could be utilized to minimize the development of these neutralizing antibodies [2]. The initiation of anti-TNF therapy in asymptomatic patients is controversial. Although some centers prefer to use anti-TNF therapy to reduce the risk of new ischemic events, others argue that the efficacy of anti-TNF agents is reduced due to neutralizing antibodies in such prophylactic use [6,8]. Patients should be monitored because of the possible immunosuppressive effect secondary to these drugs [6,8].

Immune Deficiency Phenotype

Ig therapy and antibiotic prophylaxis may be used in patients with recurrent infections and hypogammaglobulinemia [2]. The success rate of steroids and other immunosuppressive therapies in preventing hematological symptoms is variable. Although TNF blockers are effective in mild cases such as lymphopenia and inflammation-induced anemia, they are ineffective in the treatment of severe hematological conditions such as bone marrow failure and PRCA. Rituximab is effective in the treatment of autoimmune cytopenia [20]. Considering the prevalence of underlying immunodeficiency and the use of immunosuppressive drugs, routine inactivated vaccines are recommended for patients not receiving intravenous Ig therapy [2].

Hematological Phenotype

The hematological features of DADA2 are less responsive to corticosteroids, except for mild anemia secondary to chronic inflammation [19]. According to the literature, corticosteroid sensitivity in patients with DBA-like DADA2 is 44%, whereas this rate is about 80% in patients with classic DBA [15]. Other immunosuppressive drugs (azathioprine, mycophenolate mofetil, cyclosporine, and anti-thymocyte globin) have shown variable responses in conditions such as PRCA and other hematological phenotypes [20]. Mild manifestations (e.g., lymphopenia) respond to TNF blockers, while they are ineffective in treating severe hematological manifestations (e.g., bone marrow failure, PRCA).

HSCT is considered the definitive treatment for the hematological and immunological manifestations of DADA2 [20]. HSCT improved disease symptoms, normalized ADA2 levels, and reduced key cytokines such as TNF-α, IL-1, and IL-6. Indications for HSCT include immunodeficiency, refractory cytopenia, bone marrow failure, and benign and malignant lymphoproliferation [2,6,20]. Hashem et al. [13] presented multicenter HSCT experiences involving 30 DADA2 patients who underwent a total of 38 HSCTs and showed that HSCT improved the hematological phenotype in all cases. HSCT is not the initial treatment of choice in cases of the vasculitic phenotype. HSCT performed in the absence of immune cytopenia, bone marrow failure, or immunodeficiency but rather only in the presence of vasculitic manifestations is a treatment option for patients without access to anti-TNF agents [13]. HSCT in the presence of the vasculitic phenotype should not involve high-dose or targeted busulfan and/or cyclophosphamide or high-dose radiation. Preventive measures should be taken for the increased risk of sinusoidal obstruction syndrome [13]. In addition, HSCT may be a treatment option for patients receiving long-term treatment with anti-TNF inhibitors who develop neutralizing anti-drug antibodies [13]. Finally, care should be taken in donor selection, and asymptomatic family members who are homozygous should be discarded from potential donor selection [10]; additionally, carriers for DADA2 should be avoided if possible since that has been reported to have an impact on outcome [13]. In the report by Hashem et al. [13], overall survival and graft-versus-host disease-free survival rates were 97% and 73%, respectively, after 2 years of follow-up and all patients showed improvement in hematological findings [13].

Carmona-Rivera et al. [11] found that the use of recombinant ADA2 can improve NETosis, one of the main pathophysiological changes of ADA2 deficiency. Thus, advanced gene therapy

aimed at reconstituting exogenous ADA2 may be promising for the future [11]. Additionally, Janus kinase inhibitors are another possible treatment option that should be considered in the future [1,8,27].

However, some patients have an overlap of clinical symptoms, while some patients who initially present with features of bone marrow failure may subsequently develop vasculitic features. The treatment of these patients should be individualized accordingly.

Conclusion

DADA2 is a disease with potentially high morbidity and mortality, and it can present with highly variable phenotypes. The availability of diagnostic methods needs to be expanded. A multidisciplinary approach is very important in the early diagnosis and treatment of this disease.

Authorship Contributions

Concept: Ç.C., Ş.Ü.; Design: Ç.C., Ş.Ü.; Data Collection or Processing: Ç.C., Ş.Ü.; Analysis or Interpretation: Ç.C., Ş.Ü.; Literature Search: Ç.C., Ş.Ü.; Writing: Ç.C., Ş.Ü.

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