North Clin Istanb 2023;10(4):411–417
doi: 10.14744/nci.2022.45380

Original Article PEDIATRICS

Deficiency of adenosine deaminase 2 as an unrecognized cause of early-onset stroke and cranial nerve palsy

Elif Celikel,[1] Fatma Aydin,[1] Zahide Ekici Tekin,[1] Tuba Kurt,[1] Muge Sezer,[1] Nilufer Tekgoz,[1] Cuneyt Karagol,[1] Serkan Coskun,[1] Melike Mehves Kaplan,[1] Aysegul Nese Citak Kurt,[2] Banu Celikel Acar[1]

[1]Department of Pediatric Rheumatology, Ankara City Hospital, Ankara, Turkiye

[2]Department of Pediatric Neurology, Yildirim Beyazit University Faculty of Medicine, Ankara, Turkiye

ABSTRACT

OBJECTIVE: The aim of this study is to evaluate the clinical, laboratory, and radiological findings and prognosis of patients with adenosine deaminase 2 deficiency (DADA2) and to highlight the conditions that DADA2 should be considered in the differential diagnosis in patients with neurological findings.

METHODS: A case series of six DADA2 patients was presented in this retrospective, descriptive study. Clinical and laboratory data, treatment protocols, and prognosis of the patients were recorded. A diagnosis of DADA2 was established by ADA2 enzyme activity assay and/or *ADA2* gene sequencing.

RESULTS: Six patients with DADA2 were included in the study. The median age at symptom onset was 6.5 years (range 3.5–13.5 years). The median time to diagnosis from the initial presentation was 9 (3–72) months. Consanguinity was present in the families of 4 cases. The skin, nervous system, and musculoskeletal system were the most commonly involved systems. Vasculitis mimicking polyarteritis nodosa (PAN) was the predominant phenotype (n=4) in our case series. Four patients with PAN-like features had neurological involvement. Ischemic strokes were found in 3 patients, cranial nerve palsy in 2 patients, and seizures in 2 patients. The *CECR1* gene was analyzed in all patients. We analyzed plasma ADA2 enzyme activity only in one patient. Anti-tumor necrosis factor (TNF)-α therapy was initiated. Inflammation was suppressed and remission was achieved in all patients.

CONCLUSION: DADA2 should be considered in patients with PAN-like disease, a history of familial PAN/vasculitis, early-onset strokes/neurological involvement with systemic inflammation. Furthermore, anti-TNF-α therapy appears to be beneficial for the treatment of DADA2.

Keywords: ADA2 deficiency; children; livedo racemosa; stroke; vasculitis.

Cite this article as: *Celikel E, Aydin F, Ekici Tekin Z, Kurt T, Sezer M, Tekgoz N, et al. Deficiency of adenosine deaminase 2 as an unrecognized cause of early-onset stroke and cranial nerve palsy. North Clin Istanb 2023;10(4):411–417.*

Deficiency of adenosine deaminase 2 (DADA2) is a monogenic autoinflammatory disease defined by features of autoinflammation, vasculitis, hematological involvement, lymphoproliferation, immunodeficiency, and autoimmunity in young children [1, 2]. DADA2 is an autosomal recessive disease associated with loss of function pathogenic variants in ADA2, previously named *CECR1* gene [1, 2].

Received: September 15, 2021 *Revised:* February 02, 2022 *Accepted:* June 30, 2022 *Online:* August 02, 2023

Correspondence: Elif CELIKEL, MD. Ankara Sehir Hastanesi, Cocuk Romatoloji Klinigi, Ankara, Turkiye.
Tel: +90 312 552 60 00 e-mail: elifcelikel06@gmail.com

ADA2 has main roles in maintaining the endothelial integrity, regulating neutrophil activation, and the balance between pro-inflammatory (M1) and anti-inflammatory (M2) macrophages and monocytes. Although the pathophysiological mechanism is uncertain, it is assumed that dysregulation in macrophage differentiation and changes in M2 and M1 macrophage distribution are involved. Tissue damage occurs as a result of uncontrolled activation of neutrophils, endothelial cell dysfunction, and the release of pro-inflammatory cytokines [3–5].

Although the presentation of DADA2 resembles early-onset polyarteritis nodosa (PAN), it is widely variable with an expanding phenotype. Common clinical and laboratory findings of the disease are fever, livedo racemosa/reticularis, skin ulcers, early-onset ischemic and/or hemorrhagic strokes, dysregulated immune function, lymphoproliferation, cytopenias, and systemic inflammation [6, 7]. Patients characterized by vasculitis may have skin findings, neurological involvement, gastrointestinal manifestations, and hepatic disease. Ischemic strokes in the brain stem, thalamus, basal ganglia, and internal capsule may be observed in patients with PAN-like features. Neurological findings also include small, deep intracerebral hemorrhage, cerebral vessel aneurysm, and central and peripheral neuropathy [5, 6]. Recurrent strokes can lead to serious neurological disorders in patients, such as persistent ataxia, dysarthria, and cranial nerve (CN) palsy.

This study aims to evaluate the clinical, laboratory, and radiological findings and prognosis of six pediatric cases with DADA2. In addition, it is planned to emphasize the conditions that DADA2 should be considered in the differential diagnosis in patients with neurological findings in our case series.

Highlight key points

- ADA2 deficiency should be considered when evaluating with PAN-like findings, familial history of PAN/vasculitis, early-onset stroke/neurological involvement with systemic inflammation, autoimmunity and atypical immunodeficiency syndromes.
- In patients with DADA2 carrying the p.Gly47Arg mutation; vasculitis/vasculopathy and related neurological findings are detected more frequently.
- Anti-TNF-α agents were effective in controlling the inflammation, vasculopathy, and prevention of strokes.

MATERIALS AND METHODS

Patients with a diagnosis of DADA2 followed up in a tertiary hospital rheumatology department were included in this retrospective, descriptive study. DADA2 was diagnosed by *ADA2* gene sequencing and/or ADA2 enzyme activity assay.

The data collected from the patient's files included demographics, family and patient's medical history, presenting symptoms, clinical features and course, laboratory parameters, diagnostic investigations (diagnostic imaging or biopsies), genetic investigation, and medications. Extensive investigations included complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum creatinine, urea nitrogen level, proteinuria, hematuria, and immunological parameters including serum C3, C4, anti-neutrophil cytoplasmic antibodies (ANCAs), antinuclear antibodies (ANA), antidouble-stranded DNA (anti-dsDNA), lupus anticoagulant and anticardiolipin antibody, anti-beta 2 glycoprotein 1, and thrombophilia panel.

Clinical remission was defined as the absence of active vasculitis, recovery/stabilization of disease-related organ damage, and absence of systemic inflammation.

Genetic analysis was screened with the next generation sequencing (Miseq-Illumina). ADA2 enzyme activity was evaluated in serum by spectrophotometric method.

Written consent from the patients was obtained according to the Declaration of Helsinki. The study was approved by the Ethical Committee of Ankara City Hospital (May 04, 2021- no: 9).

Statistical Analysis

IBM SPSS Statistics for Windows, version 26.0 (SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis. Results are given as median (minimum-maximum) as appropriate. Categorical variables were summarized as counts (percentages).

RESULTS

Six patients with DADA2 were included in the study. The median age at symptom onset was 6.5 years (3.5–13.5 years). The median time from initial admission to diagnosis was 9 (3–72) months. There was consanguinity in the families of 4 patients. The demographic, clinical, and laboratory characteristics of patients are given in Table 1.

Table 1. Characteristics of patients with DADA2

Gender	Patient 1 M	Patient 2 M	Patient 3 F	Patient 4 M	Patient 5 M	Patient 6 F
Age at onset (years)	1.5	7	13	8	1.5	3
Age of diagnosis (years)	7.5	8	13.5	11	2	5
Follow-up Time (months)	10	28	18	18	30	60
Consanguinity	+	+	+	_	+	_
Any relative with DADA2	None	+	+	None	None	None
ADA2 mutation	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)	_	_	_	_	_	Low (0.47 IU/L)
Cutaneous findings	Livedo racemosa	Raynaud phenomenon, Digital ulcer	Livedo racemosa	Livedo racemosa, Raynaud phenomenon, Digital ulcer	None	Livedo racemosa
Neurological findings	6th nerve palsy, right thalamic infarct	Seizures, bilateral occipital infarct	None	7th nerve palsy, thalamic lacunar infarct	None	Seizures, optic atrophy
Immunological findings	None	None	None	None	None	None
Hematological findings	None (Platelet count: 366×10^9/L)	None (Platelet count: 289×10^9/L)	None (Platelet count: 262×10^9/L)	None (Platelet count: 198×10^9/L)	Anemia (Platelet count: 324×10^9/L)	None (Platelet count: 302x10^9/L)
Renovascular findings	None	Hypertension, proteinuria	None	Hypertension	None	None
PAN-like findings	Abdominal pain, fever, arthralgia	Abdominal pain, fever, arthralgia	None	Abdominal pain, fever, arthralgia	Fever	Fever, abdominal pain
ESR (mm/h), median (min–max)	5 (3–48)	18 (8–73)	8 (5–49)	18 (4–44)	18 (7–47)	21 (5–47)
CRP (mg/L), median (min–max)	27 (5–72)	32 (5–151)	12 (4–52)	42 (5–96)	11 (3–68)	9 (1–68)
Autoantibody Positivity	–	–	–	–	–	–
Previous diagnosis	–	Polyartheritis nodosa?/ Behcet's Disease?	–	Familial Mediterranean fever	Familial Mediterranean fever	–
Treatment (Before diagnosis of DADA2)	–	*Corticosteroid*, Cyclophosphamide, Infliximab	–	Colchicine	Colchicine	Colchicine
Treatment (After the diagnosis of DADA2)	Etanercept	Etanercept	Etanercept	Etanercept	Etanercept	Etanercept
Outcome	Remission	Remission	Remission	Remission	Remission	Remission

The skin, nervous system, and musculoskeletal system were the most commonly involved systems, affecting 83.3%, 66.6%, and 50% of all patients, respectively. Vasculitis mimicking PAN was the predominant phenotype (66.6%) in our case series. PAN-like features in 4 patients are as follows: fatigue in 4, fever in 4, arthritis/arthralgia in 4, myalgia in 2, gastrointestinal involvement in 4, skin involvement in 4, neurologic involvement in 4, hypertension in 2, and renal involvement in 2.

Five patients were diagnosed by *ADA2* gene sequencing and one patient by ADA2 enzyme activity. Except for patient 6 (ADA2 level: 0.47 U/L), the level of ADA2 enzyme could not be studied in our patients. Five patients were homozygous for the p.Gly47Arg mutation, whereas patient 5 was heterozygous for p.Gly47Arg.

Patient 1 (18 months) presented with deviation of the left eye and the inability to move the eye outward and was diagnosed as having CN VI palsy.' Magnetic resonance imaging (MRI) showed a right thalamic lacunar infarct. After 5 years of follow-up in the department of pediatric neurology, vasculitic rashes started on his lower limbs. A homozygous p.Gly47Arg mutation in *ADA2* gene, which causes DADA2, was found in the patient.

Patient 2 (7 years old) was admitted with necrosis of the 3rd–4th distal phalanges of his left hand. He also had a fever (lasting 5 days), hypertension, and seizures. A bilateral occipital lacunar infarction was detected on MRI. Based on his clinical manifestations and history, a diagnosis of vasculitis such as PAN, Behcet's disease (BD) was suspected. Autoimmune markers, and chest and abdominal CT angiography did not confirm possible diagnoses. Malignancies, infectious, and autoimmune diseases were excluded. His immunoglobulin levels and complete lymphocyte subset panel were normal. He, who did not meet the PAN and BD diagnostic criteria, was treated with a provisional diagnosis of vasculitis [pulse methylprednisolone (30 mg/kg, 3 days) and cyclophosphamide (500 mg/m^2)]. Considering his clinical manifestations such as digital necrosis and elevated levels of inflammatory markers, DADA2 was suspected. *ADA2* gene sequencing was performed. *ADA2* gene sequencing results revealed that he had homozygous mutations in *ADA2* gene p.Gly47Arg mutation. Infliximab treatment was started initially due to Behçet's-like disease the patient. After the diagnosis of DADA2, the treatment was changed to etanercept due to the difficulty of administering infliximab. Patient 3 (cousin of patient 2) had livedo racemose and systemic inflammation. The *ADA2* gene mutation was identified as homozygous p.Gly47Arg, as was her cousin.

Patient 4 (8 years old) had been followed up with a diagnosis of Familial Mediterranean Fever previously. His *MEFV* gene analysis was E148Q heterozygous. He was admitted to the hospital with a 15-day history of unilateral facial nerve palsy and arthritis. The patient had a history of fatigue, muscle pain, and intermittent fever for the past 3 weeks. Physical examination revealed fever (38.3°C), arthritis in the right ankle, and left peripheral facial nerve palsy. It was also found out that he had right facial paralysis 3 years ago. MRI showed a thalamic lacunar infarct. Vasculitis diagnosis was suspected due to constitutional findings, arthritis, and neurological involvement. The diagnosis was confirmed by detecting a homozygous p.Gly47Arg mutation in the *ADA2* gene.

Patient 5 (1.5 years old) was admitted to our hospital with recurrent fever. Blood, urine, stool, and cerebrospinal fluid cultures performed to investigate the cause of fever were negative. His *MEFV* gene analysis was normal. ANA, anti-dsDNA, ANCA, and immunoglobulin levels were normal as well as his echocardiogram, chest radiography, and abdominal ultrasonography were normal. Laboratory tests showed a high CRP (68 mg/dL) and ESR (47 mm/h), blood count changes (hemoglobin 9.6 g/dL, leukocytes 16.4×10^9/L, platelets 324×10^9/L). A heterozygous p.Gly47Arg mutation in *ADA2* gene was found in the patient.

The patient 6 (3 years old) was admitted with a livedoid rash on the trunk and legs, recurrent fever, and abdominal pain. Acute phase reactants were moderately high. A skin biopsy performed due to the fact that the rashes were resistant resulted in negative for vasculitis. The enzyme activity of ADA2 analyzed with suspected DADA2, was found to be low (0.47 IU/L) and *ADA2* gene mutation was identified as homozygous p.Gly47Arg. Etanercept treatment was started and remission was achieved. Colored visual symptoms were observed in the 2nd year of etanercept treatment. Neurological examination revealed centro-parieto-temporal spines on electroencephalography and MRI was normal. Antiepileptic drugs were added to the treatment. There was no complaint in the follow-up.

Once DADA2 diagnosis was established, anti-tumor necrosis factor (TNF)-α therapy was initiated in 6 patients after tuberculosis infection was excluded. After the initiation of anti-TNF-α therapy, clinical findings improved and inflammation was suppressed in 6 patients. Seizures were observed in only one patient during follow-up.

DISCUSSION

In this study, clinical and laboratory findings, genetic investigations, and treatment responses of 6 patients with DADA2 were described. The vasculitic phenotype was prominent in our patients. Hence, we suggest that DADA2 should be considered in the case of; PAN-like features, having neurological findings and having a family member with similar findings. Early diagnosis and subsequent administration of anti-TNF-α therapy may reduce the morbidity and mortality of this disease.

The diagnosis of DADA2 is established in a patient with biallelic loss-of-function *ADA2* pathogenic variants identified by *ADA2* gene sequencing and/or low (<5% of normal) or undetectable ADA2 enzyme activity in plasma or serum. The measurement of ADA2 activity is diagnostic when DNA sequencing reveals only one pathogenic variant [5]. Genotype-phenotype correlation is not clear due to different phenotypic presentations, environmental factors affecting gene expression, and compound heterozygosity. So far, the exact relationship between the type and location of the mutation and the phenotype of DADA2 has not been determined. Moreover, clinical manifestations can be highly variable in relatives with the same mutations. The most common pathogenic variants in patients with DADA2 are p.Gly47Arg or p.Arg169Gln [2, 8]. However, while vasculitis phenotypes are more commonly associated with missense mutations, those with hematological involvement are more likely to have mutations including insertions/deletions, nonsense, or missense mutations. In addition, *ADA2* mutations have been shown to affect the dimerization domain in patients with PAN-like findings and the catalytic domain in patients with immunodeficiency and hematologic involvement [9]. p.Gly47Arg mutation was detected in all 6 patients. This mutation has been reported to be pathogenic and cause vasculopathy and early-onset stroke [1]. Detection of infarct in half of our patients and the dominance of the vasculitic phenotype were consistent with their mutations. Although patient 5 in our case series had clinical findings consistent with DADA2, a heterozygous ADA2 mutation was detected. Ozen et al. [10] showed that the serum ADA2 activity of patients with a single *ADA2* mutation was as low as that of DADA2 patients with homozygous mutations.

A distinction between PAN and cutaneous PAN (cPAN) to DADA2 is not clear. PAN is necrotizing arteritis of medium or small arteries that affects the skin, musculoskeletal system, gastrointestinal system, kidneys, and peripheral nervous system [10]. However, cPAN is a necrotizing vasculitis of the small and medium arteries that primarily affects the skin. Systemic organ involvement is not typically expected, although there are extracutaneous symptoms such as fatigue, arthralgia, and neuropathy [11]. Similar to DADA2, cPAN may present as necrotizing, medium-sized vascular arteritis characterized by subcutaneous nodules, ulcers, and livedoid rash. Skin biopsies in DADA2 may show medium vessel vasculitis, as seen in cPAN/PAN, or leukocytoclastic vasculitis [12]. Findings such as stenosis and/or aneurysm on angiography may be more common in patients with PAN than with DADA2. The predominant phenotype was vasculitis with PAN-like findings in our case series. In these patients, fatigue, fever, arthritis/arthralgia, myalgia, gastrointestinal involvement, skin involvement, and neurological involvement were prominent. PAN diagnosis was excluded due to the presence of neurological findings, having a relative with similar symptoms, and the absence of imaging and biopsy findings compatible with PAN. On the other hand, DADA2 has many faces other than vasculitis [11]. Since its discovery, the phenotype of DADA2 has significantly broadened to include not only vasculitis but also hematologic manifestations and immunodeficiency. Ozen et al. [13] suggested that the normal thrombocyte count and thrombocytopenia in DADA2 may help in differentiating from PAN, where thrombocytosis is expected. As expected, thrombocytosis was not detected in any of our DADA2 patients.

Various findings associated with peripheral and central neuropathy have been reported in approximately 50% of DADA2 patients. A case of ischemic stroke at the age of 5 months has been reported [14]. In another study, familial DADA2 cases were presented, and ischemic stroke paraplegia and severe mental retardation were reported in one of the cases [15]. Typical MR images are acute and chronic lacunar ischemic infarction detected in subcortical white matter in the deep brain nuclei and/or brainstem. Caorsi et al. [16] analyzed the prevalence of *ADA2* mutations in 48 patients from 43 families in patients diagnosed with livedo reticularis and/or hemorrhagic/ischemic stroke in the context of inflammation or PAN. Biallelic homozygous or compound heterozygous *ADA2* mutations were found in 15 of 48 patients. Ten patients had one or more cerebral strokes during follow-up. Similarly, lacunar ischemic infarction was detected in three of our patients. CN palsies usually include CN III, IV, VI, and VII [17, 18]. CN VI and VII palsies were seen in our two patients. In patient 1, vasculitis findings occurred 5 years after pa-

ralysis of the VI CN. In conclusion, DADA2 should be considered in children diagnosed with PAN-like features, livedoid rash, and early-onset stroke.

In the past, immunosuppressive drugs such as steroids, azathioprine, cyclosporin, tacrolimus, cyclophosphamide, and methotrexate have been used to suppress systemic inflammation in early-onset PAN and recurrent stroke [8, 18–20]. Currently, the main treatment is anti-TNF agents (etanercept, infliximab, and adalimumab), based on data from both the first two reports and subsequent studies [2 ,21–24]. Navon Elkan et al. [2] showed that anti-TNF-α drugs have a positive effect in 10/13 patients with PAN, and Ombrello et al. [25] reported similar results in 12 DADA2 patients. Anti-TNF-α agents were effective in controlling fever episodes, inflammation, vasculopathy, and prevention of strokes. Ombrello showed no recurrence of stroke in 15 patients with DADA2 after anti-TNF alpha therapy. Before the initiation of anti-TNF therapy, 15 patients had a cumulative DADA2 duration of 2077 patient months (i.e., from birth) and a cumulative total of 55 strokes. After the initiation of anti-TNF, patients experienced no stroke during 733 patient months [25].

The low number of patients and the inability to measure ADA2 e7zyme levels in all patients are the limitations of the study.

Conclusion

Recognition of the expanding spectrum of DADA2 is important for the timely diagnosis and management of this disease with high morbidity. DADA2 should be considered when evaluating patients with PAN-like features, history of familial PAN/vasculitis, early-onset strokes/neurological involvement with systemic inflammation, and atypical immunodeficiency syndromes with autoimmunity.

Ethics Committee Approval: The Ankara City Hospital Clinical Research Ethics Committee granted approval for this study (date: 04.05.2021, number: 9).

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Authorship Contributions: Concept – EC, FA, ANCK, BCA; Design – ZET, TK, MS, EC; Supervision – EC, BCA; Materials – EC, FA, MS, TK, NT; Data collection and/or processing – EC, FA, ZET, TK, MS, NT, CK, SC, MMK, ANCK, BCA; Analysis and/or interpretation – EC, BCA, FA; Literature review – EC, BCA, FA, ZET; Writing – EC, BCA; Critical review – EC, FA, ZET, TK, MS, NT, CK, SC, MMK, ANCK, BCA.

REFERENCES

1. Zhou Q, Yang D, Ombrello AK, Zavialov AV, Toro C, Zavialov AV, et al. Early-onset stroke and vasculopathy associated with mutations in ADA2. N Engl J Med 2014;370:911–20. [CrossRef]
2. Navon Elkan P, Pierce SB, Segel R, Walsh T, Barash J, Padeh S, et al. Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy. N Engl J Med 2014;370:921–31. [CrossRef]
3. Zavialov AV, Gracia E, Glaichenhaus N, Franco R, Zavialov AV, Lauvau G. Human adenosine deaminase 2 induces differentiation of monocytes into macrophages and stimulates proliferation of T helper cells and macrophages. J Leukoc Biol 2010;88:279–90. [CrossRef]
4. Zavialov AV, Engstrom A. Human ADA2 belongs to a new family of growth factors with adenosine deaminase activity. Biochem J 2005;391:51–7. [CrossRef]
5. Meyts I, Aksentijevich I. Deficiency of Adenosine Deaminase 2 (DADA2): updates on the phenotype, genetics, pathogenesis, and treatment. J Clin Immunol 2018;38:569–78. [CrossRef]
6. Kendall JL, Springer JM. The many faces of a monogenic autoinflammatory disease: adenosine deaminase 2 deficiency. Curr Rheumatol Rep 2020;22:64. [CrossRef]
7. Caorsi R, Penco F, Schen F, Gattorno M. Monogenic polyarteritis: the lesson of ADA2 deficiency. Pediatric Rheumatology 2016;14:51.
8. Van Montfrans JM, Hartman EA, Braun KP, Hennekam EA, Hak EA, Nederkoorn PJ, et al. Phenotypic variability in patients with ADA2 deficiency due to identical homozygous R169Q mutations. Rheumatology (Oxford) 2016;55:902–10. [CrossRef]
9. Batu ED, Karadag O, Taskiran EZ, Kalyoncu U, Aksentijevich I, Alikasifoglu M, et al. A case series of adenosine deaminase 2-deficient patients emphasizing treatment and genotype-phenotype correlations. J Rheumatol 2015;42:1532–4. [CrossRef]
10. Ozen S. The changing face of polyarteritis nodosa and necrotizing vasculitis. Nat Rev Rheumatol 2017;13:381–6. [CrossRef]
11. Criado PR, Marques GF, Morita TC, de Carvalho JF. Epidemiological, clinical and laboratory profiles of cutaneous polyarteritis nodosa patients: report of 22 cases and literature review. Autoimmun Rev 2016;15:558–63. [CrossRef]
12. Gonzalez Santiago TM, Zavialov A, Saarela J, Seppanen M, Reed AM, Abraham RS, et al. Dermatologic features of ADA2 deficiency in cutaneous polyarteritis nodosa. JAMA Dermatol 2015;151:1230–4.
13. Özen S, Batu ED, Taşkıran EZ, Özkara HA, Ünal Ş, Güleray N, et al. A Monogenic disease with a variety of phenotypes: deficiency of adenosine deaminase 2. J Rheumatol 2020;47:117–25. [CrossRef]
14. Sahin S, Adrovic A, Barut K, Ugurlu S, Turanli ET, Ozdogan H, et al. Clinical, imaging and genotypical features of three deceased and five surviving cases with ADA2 deficiency. Rheumatol Int 2018;38:129–36.
15. Sozeri B, Ercan G, Dogan OA, Yıldız J, Demir F, Doğanay L. The same mutation in a family with adenosine deaminase 2 deficiency. Rheumatol Int 2021;41:227–33. [CrossRef]
16. Caorsi R, Penco F, Grossi A, Insalaco A, Omenetti A, Alessio M, et al. ADA2 deficiency (DADA2) as an unrecognised cause of early onset polyarteritis nodosa and stroke: a multicentre national study. Ann Rheum Dis 2017;76:1648–56. [CrossRef]
17. Lee PY. Vasculopathy, immunodeficiency, and bone marrow failure: the intriguing syndrome caused by deficiency of adenosine deaminase 2. Front Pediatr 2018;6:282. [CrossRef]
18. Aksentijevich I, Sampaio Moura N, Barron K. Adenosine deaminase 2 deficiency. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, et al. GeneReviews® [Internet]. Seattle (WA): Univer-

sity of Washington; 2019.
19. Barut K, Sahin S, Kasapcopur O. Pediatric vasculitis. Curr Opin Rheumatol 2016;28:29–38. [CrossRef]
20. Kisla Ekinci RM, Balci S, Hershfield M, Bisgin A, Dogruel D, Altintas DU, et al. Deficiency of adenosine deaminase 2: a case series revealing clinical manifestations, genotypes and treatment outcomes from Turkey. Rheumatology (Oxford) 2020;59:254–6. [CrossRef]
21. Ombrello A, Stone D, Hoffmann P, Jones A, Barham B, Barron K, et al. The deficiency of adenosine deaminase type 2-results of therapeutic intervention. Pediatr Rheumatol Online J 2015;13 Suppl 1:O40.
22. Sahin S, Adrovic A, Barut K, Baran S, Tahir Turanli E, Canpolat N, et al. A 9.5-year-old boy with recurrent neurological manifestations and severe hypertension, treated initially for polyarteritis nodosa, was subsequently diagnosed with adenosine deaminase type 2 deficiency (DADA2) which responded to anti-TNF-α. Paediatr Int Child Health 2020;40:65–8. [CrossRef]
23. Tanatar A, Karadağ ŞG, Sözeri B, Sönmez HE, Çakan M, Kendir Demirkol Y, et al. ADA2 deficiency: case series of five patients with varying phenotypes. J Clin Immunol 2020;40:253–8. [CrossRef]
24. Çakan M, Aktay-Ayaz N, Karadağ ŞG, Tahir-Turanlı E, Stafstrom K, Bainter W, et al. Atypical phenotype of an old disease or typical phenotype of a new disease: deficiency of adenosine deaminase 2. Turk J Pediatr. 2019;61:413–7. [CrossRef]
25. Ombrello AK, Qin J, Hoffmann PM, Kumar P, Stone D, Jones A, et al. Treatment strategies for deficiency of adenosine deaminase 2. N Engl J Med 2019;380:1582–4. [CrossRef]