International Journal of Contemporary Pediatrics
Palraj A et al. Int J Contemp Pediatr. 2026 Aug;13(8):1556-1559
https://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20262438

Case Report

Navigating secondary loss of response: breakthrough midbrain ischemia in deficiency of adenosine deaminase 2: a case report

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Received: 16 June 2026
Accepted: 14 July 2026

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ABSTRACT

Deficiency of adenosine deaminase 2 (DADA2) is a monogenic autoinflammatory vasculopathy that may present in childhood with lacunar infarcts in deep perforator territories. Tumor necrosis factor-alpha (TNF-alpha) inhibitors have changed the outlook for stroke-predominant disease, but ischemic events can still occur during treatment. An 8-year-old girl with recurrent brainstem and deep gray matter lacunar infarcts had normal magnetic resonance angiography and negative autoimmune and antiphospholipid testing. Genetic analysis confirmed a homozygous pathogenic ADA2 variant. She received infliximab 100 mg intravenously every two months with aspirin, but after five doses developed a new right paramedian superior midbrain infarct. Infliximab was stopped and subcutaneous adalimumab 40 mg every two weeks was started. After 18 doses of adalimumab, she has had no further cerebrovascular events. TNF-alpha blockade markedly reduces stroke risk in DADA2, but it does not abolish it. In this child, switching from infliximab to adalimumab was followed by neurological stability. For a vasculitis-predominant patient without hematologic failure, an intra-class switch is a practical option to consider before hematopoietic cell transplantation, with continued neurologic surveillance.

Keywords: DADA2, ADA2 deficiency, Pediatric stroke, Lacunar infarction, Tumor necrosis factor inhibitors, Case report

INTRODUCTION

Deficiency of adenosine deaminase 2 (DADA2) is an autosomal recessive inborn error of immunity caused by biallelic pathogenic variants in ADA2, formerly CECR1. The first reports described patients with fever, polyarteritis nodosa-like vasculopathy, and early lacunar strokes.[1,2,11] Although the phenotype is now recognized to include immune dysregulation and hematologic disease, the neurological pattern remains distinctive: small-vessel infarcts in the brainstem or deep gray matter, often without an angiographic large-vessel lesion.[3,6-8]

TNF-alpha blockade has the strongest clinical support for vasculitis-and stroke-predominant DADA2.[4,5,9] Rare ischemic events have still been described after TNF-alpha inhibitor initiation and while changing between agents.[6] The bedside question is what to do when a child has a new lacunar infarct despite regular treatment. We describe a girl with genetically confirmed DADA2 who developed a new midbrain infarct on infliximab and then remained clinically stable after changing to adalimumab.

CASE REPORT

An 8-year-old girl was evaluated for recurrent ischemic strokes involving the brainstem and deep gray matter. She was born to non-consanguineous parents after an unremarkable perinatal course. There was no family history of early-onset stroke, systemic vasculitis, or immunodeficiency.

Her first neurological event occurred at 4 years of age, when she developed acute diplopia and left oculomotor nerve palsy. Brain magnetic resonance imaging (MRI) showed an acute lacunar infarct in the left paramedian midbrain (Figure 1). She was managed conservatively and remained clinically stable for several years.

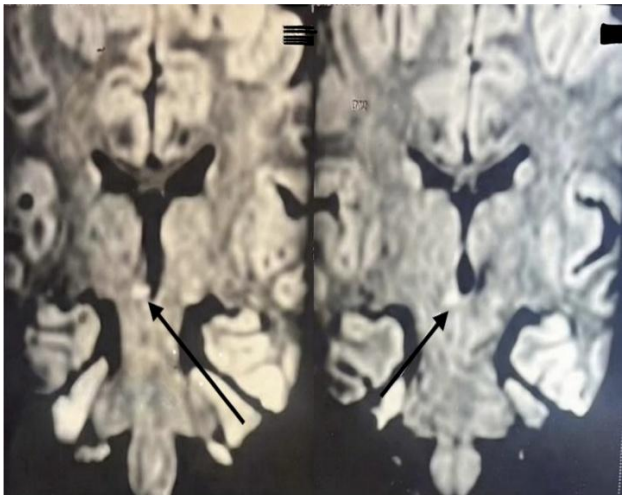

Figure 1: Initial presentation at 4 years of age.

*Brain MRI demonstrates an acute lacunar infarct involving the left paramedian midbrain at the level of the oculomotor nucleus (arrows), corresponding to the patient's left oculomotor palsy.

At 8 years of age, she developed a second acute cerebrovascular event. Brain MRI showed a new acute lacunar infarct in the medial left thalamus and subthalamic region, without mass effect or hemorrhagic transformation. Chronic midbrain infarcts were also present. Magnetic resonance angiography (MRA) showed no large-vessel narrowing, occlusion, or aneurysmal change.

On examination during this admission, the only focal findings were residual ocular motor abnormalities from the earlier stroke. There were no clinical features of systemic infection, connective tissue disease, or large-vessel vasculitis.

Baseline laboratory testing showed mild anemia with hemoglobin 9.2 g/dL. Erythrocyte sedimentation rate and C-reactive protein were not elevated. Antinuclear antibody, antineutrophil cytoplasmic antibodies, anticardiolipin antibodies, anti-beta2 glycoprotein I antibodies, and lupus anticoagulant were negative (Table 1). Cardiac and coagulation evaluations did not identify an embolic or thrombotic source.

The pattern of recurrent deep perforator infarcts with normal angiography and unrevealing autoimmune and thrombophilia testing raised suspicion for a monogenic vasculopathy. Genetic analysis confirmed a homozygous pathogenic ADA2 variant, establishing the diagnosis of DADA2.

Pre-biologic screening by the thoracic medicine team ruled out active or latent tuberculosis. Because she had a vasculitis-predominant phenotype without documented hematologic failure, infliximab 100 mg intravenously every two months was started with aspirin 75 mg daily. She received five infliximab doses.

At 9 years of age, while receiving regular infliximab infusions, she again developed neurological symptoms. Repeat brain MRI showed a new acute lacunar infarct in the right paramedian superior midbrain, with chronic infarcts in the left thalamus, midbrain, and hemipons (Figure 2). Repeat MRA showed no large-vessel involvement or hemorrhagic transformation.

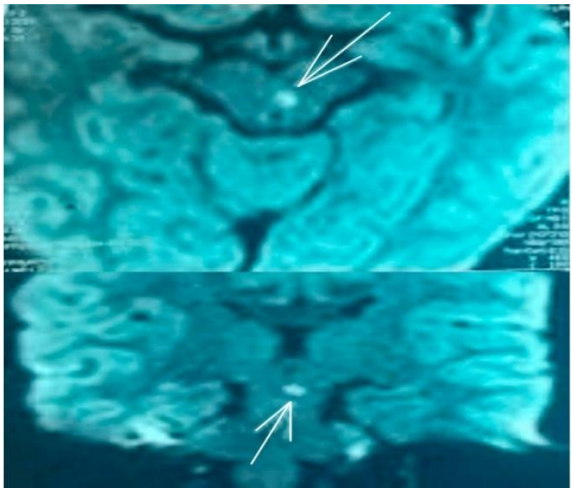

Figure 2: Breakthrough ischemic event during infliximab therapy.

*Brain MRI demonstrates focal restricted diffusion in the right paramedian superior midbrain (arrows), consistent with a new acute lacunar infarct. The same study also showed chronic infarcts in the left thalamus, midbrain, and hemipons.

Infliximab was stopped after this breakthrough ischemic event. She was changed to subcutaneous adalimumab 40 mg every two weeks, while aspirin 75 mg daily was continued. After 18 doses of adalimumab, she remains neurologically stable with no further cerebrovascular events. The clinical course is summarized in Table 2.

Table 1: Baseline laboratory investigations during evaluation of recurrent ischemic stroke.

Investigations	Result	Reference range	Unit
Hemoglobin	9.2	11.5-15.5	g/dl
Total leukocyte count	8,800	4,000-11,000	cells/microL
Neutrophils	58.9	40-75	%
Lymphocytes	32.6	20-45	%

Continued.

Investigations	Result	Reference range	Unit
Erythrocyte sedimentation rate	8	0-20	mm/h
C-reactive protein	1.4	<5	mg/l
Random blood sugar	73	70-140	mg/dl
Blood urea	20	15-40	mg/dl
Serum creatinine	0.5	0.3-0.7	mg/dl
Total bilirubin	0.8	0.2-1.2	mg/dl
Direct bilirubin	0.4	0-0.3	mg/dl
Aspartate aminotransferase	25	10-40	U/l
Alanine aminotransferase	10	7-56	U/l
Alkaline phosphatase	156	50-150	U/l
Total protein	6.8	6.0-8.3	g/dl
Serum albumin	4.0	3.5-5.0	g/dl
Thyroid stimulating hormone	0.27	0.4-4.0	mIU/l
Antinuclear antibody by indirect immunofluorescence	Negative	Negative	-
ANCA (MPO, PR3)	Negative	Negative	-
Anticardiolipin antibodies (IgG, IgM)	Negative	Negative	-
Anti-beta2 glycoprotein I antibodies (IgG, IgM)	Negative	Negative	-
Lupus anticoagulant	Negative	Negative	-
Mantoux test	Negative	Negative	-

*ANCA: antineutrophil cytoplasmic antibody; MPO: myeloperoxidase; PR3: proteinase 3.

Table 2: Clinical course and treatment timeline.

Age (in years)	Clinical event	Key findings/neuroimaging	Treatment / outcome
4	Acute diplopia and left oculomotor palsy	Acute left paramedian midbrain lacunar infarct	Conservative management; clinically stable
8	Recurrent ischemic event	Acute medial left thalamic and subthalamic infarcts; MRA without large-vessel abnormality	Diagnostic evaluation initiated
8	Etiologic evaluation	Normal inflammatory markers; negative autoimmune and antiphospholipid testing; no embolic or thrombotic source identified	Genetic testing requested
8	Diagnosis	Homozygous pathogenic ADA2 mutation	DADA2 confirmed
9	Breakthrough ischemic event on infliximab	New acute midbrain infarct on infliximab; no large-vessel involvement on MRA	Infliximab discontinued
≥9	Follow-up after switch	No further cerebrovascular events after 18 adalimumab doses	Adalimumab 40 mg every two weeks plus aspirin 75 mg daily; neurologically stable

DISCUSSION

The key observation in this case is a new small midbrain infarct while the child was receiving regular infliximab. The distribution of her infarcts in the midbrain, thalamus, subthalamic region, and hemipons fits the recognized DADA2 neurological phenotype. These events occurred with normal MRA and negative autoimmune and antiphospholipid testing, which is typical of the small-vessel pattern described in DADA2 cohorts.[6-8,11]

Treatment data still favor TNF-alpha blockade in stroke-predominant DADA2. In the largest anti-TNF cohort, ischemic event rates fell markedly after treatment, and vasculitis activity also improved.[4] International consensus statement supports TNF-alpha inhibitors for inflammatory vasculopathy, while separating this indication from marrow failure/severe immunodeficiency, where other approaches may be needed.[3,5,9]

Why this child had a breakthrough infarct is uncertain. We did not have infliximab trough levels or anti-drug antibody testing. The possibilities include inadequate drug exposure, anti-drug antibodies, persistent small-vessel inflammation despite quiet systemic markers, or another stroke mechanism not found on evaluation. Because vascular inflammation in DADA2 may not be reflected by routine inflammatory markers, the normal ESR and CRP did not exclude active neurovascular disease.[10]

In that setting, staying within TNF-alpha blockade was a deliberate choice. She had a vasculitis-predominant phenotype, no documented marrow failure or severe immunodeficiency, and no large-vessel lesion for intervention. After changing to adalimumab, she

remained clinically stable through 18 doses. This single case cannot show that adalimumab is superior to infliximab, but it supports considering another TNF-alpha inhibitor before abandoning the class.

Hematopoietic cell transplantation can correct hematologic and immunologic manifestations of DADA2 and has been associated with prevention of new vascular events after successful engraftment.[12] Even so, it is a major intervention and is usually considered for marrow failure, severe immunodeficiency, malignancy, or refractory disease. In a child with an otherwise vasculitis-predominant phenotype, a monitored switch to another TNF-alpha inhibitor is a reasonable step before transplant is considered.

The practical lesson is surveillance. A child on biologic therapy who develops diplopia, ocular motor signs, ataxia, or other brainstem-localizing symptoms still needs urgent neuroimaging, even if inflammatory markers are normal and MRA is unchanged.

CONCLUSION

Breakthrough lacunar infarction can occur in DADA2 despite TNF-alpha inhibitor therapy. When this happens, clinicians should reassess adherence, drug exposure, anti-drug antibodies when available, and alternative stroke mechanisms. In vasculitis-predominant disease without hematologic failure, switching from infliximab to another TNF-alpha inhibitor such as adalimumab is worth considering before hematopoietic cell transplantation.

In a child with recurrent brainstem or deep gray matter lacunar infarcts and normal MRA, DADA2 should remain high in the differential diagnosis. Normal ESR, CRP, and large-vessel imaging do not exclude active DADA2-related small-vessel disease. After a stroke on one TNF-alpha inhibitor, evaluate drug exposure and other stroke mechanisms; if the phenotype is vasculitis-predominant and there is no hematologic failure, another TNF-alpha inhibitor may be a reasonable next step.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Palraj A, Rajamurugan APS, Subramanian ARP, Mahadevan S. Navigating secondary loss of response: breakthrough midbrain ischemia in deficiency of adenosine deaminase 2: a case report. Int J Contemp Pediatr 2026;13:1556-9.