RESEARCH PAPER

Expanding the Clinical Spectrum of Adenosine Deaminase 2 Deficiency Presenting with Posterior Polar Cataract and Distal Sensory Neuropathy: A Case Report

Dr. U Viveka[1], Dr. Pooja P[2], Dr. Abinaya Pv[3*], Janardanan Subramonia Kumar[4]

[1,2,3,4] General Medicine, SRM Medical College and Research Centre, Chennai, Tamilnadu, India.

[1] Postgraduate, Email: vu1455@srmist.edu.in, ORCID: 0009-0000-8140-4792

[2] Postgraduate, Email: pp9991@srmist.edu.in, ORCID: 0009-0006-0421-1827

[3*] Assistant Professor, (Corresponding Author) Email: abinayap3@srmist.edu.in, ORCID: 0009-0002-5114-3709

[4] Professor, Head of Department, Email: kumarj1@srmist.edu.in, ORCID: 0000-0003-1355-5833

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ABSTRACT

Deficiency of adenosine deaminase 2 (DADA2) is a rare autosomal recessive autoinflammatory disorder caused by pathogenic variants in the ADA2 gene and may clinically mimic autoimmune or vasculitic diseases, leading to delayed diagnosis. We report a 24-year-old male born of a consanguineous marriage who presented with recurrent transient neurological deficits, sensory loss, and progressive visual disturbance. His clinical course was notable for repeated ischemic strokes, livedo reticularis with ulcerative skin lesions, epididymo-orchitis, and prior intestinal ischemia requiring surgical resection for distal ileal perforation. Laboratory evaluation, including autoimmune and thrombophilia workup, was unremarkable. Neuroimaging demonstrated chronic lacunar infarcts, nerve conduction studies revealed distal sensory axonal neuropathy, and ophthalmologic examination showed bilateral posterior polar cataracts. Genetic analysis confirmed a homozygous pathogenic missense variant in the ADA2 gene, establishing the diagnosis of DADA2. Treatment with anti-tumour necrosis factor therapy, corticosteroids, immunosuppressants, antiplatelet agents, and anticoagulation resulted in clinical stabilisation without further vascular events on follow-up. This case broadens the recognised phenotypic spectrum of DADA2 by highlighting the coexistence of distal sensory neuropathy and posterior polar cataract, and underscores the importance of early genetic diagnosis and targeted therapy in preventing irreversible organ damage.

Keywords: Autoinflammatory Diseases; Lacunar Stroke; Livedo Reticularis; Mesenteric Ischemia; Tumor Necrosis Factor Inhibitors; Polyarteritis Nodosa.

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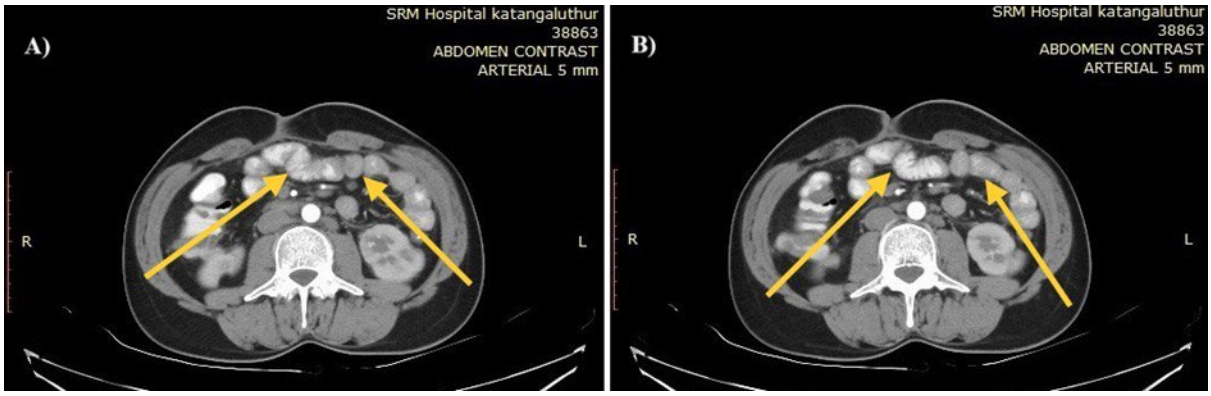
Case Report:

A 24-year-old male born of a second-degree consanguineous marriage presented with sudden-onset transient weakness of all four limbs associated with distal numbness and visual disturbance. The neurological deficit developed acutely, lasted approximately two hours, and resolved completely. There was no history suggestive of cerebellar involvement, bowel or bladder dysfunction, myopathy, or neuromuscular junction disorder. Systemic symptoms such as fever or recent infection were absent. He also reported prior testicular pain and swelling, and ultrasonography had demonstrated epididymo-orchitis. His medical history included two similar transient ischemic episodes over the preceding three years.

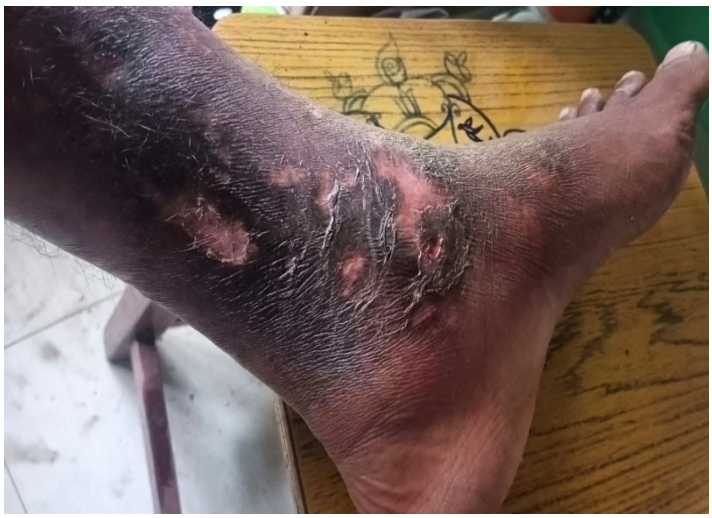
One year earlier, he had developed small-bowel obstruction secondary to superior mesenteric artery thrombosis with distal ileal perforation, confirmed on contrast-enhanced computed tomography of the abdomen (Table/Fig 1). He underwent emergency laparotomy with ileal resection, ileo-ascending colon anastomosis, and diversion loop ileostomy.

Table/Fig 1: Contrast-enhanced axial CT scan of the abdomen (arterial phase) showing multiple distal ileal perforations (yellow arrows).



On examination, the patient was conscious, afebrile, and haemodynamically stable. Previous episodes of recurrent ulcers over the medial and lateral malleoli with livedo reticularis were documented (Table/Fig 2). Neurological examination at presentation was largely normal due to resolution of weakness, with a Mini-Mental State Examination score of 30/30. Sensory evaluation showed loss of fine touch, vibration, and proprioception up to the shin in both lower limbs and impaired fine touch in the hands. Cranial nerve and cerebellar examinations were normal. Ophthalmologic evaluation revealed bilateral posterior polar cataracts.

Table/Fig 2: Healed livedo reticularis with ulcerative lesions over the medial aspect of the ankle.



Laboratory investigations, including complete hemogram, thrombophilia profile, and autoimmune markers, were within normal limits (Table/Fig 3). Nerve conduction studies demonstrated distal symmetrical sensory axonal neuropathy involving the lower limbs with median and ulnar sensory involvement in the right upper limb. Magnetic resonance imaging of the brain showed chronic lacunar infarcts in the thalamic region (Table/Fig 4).

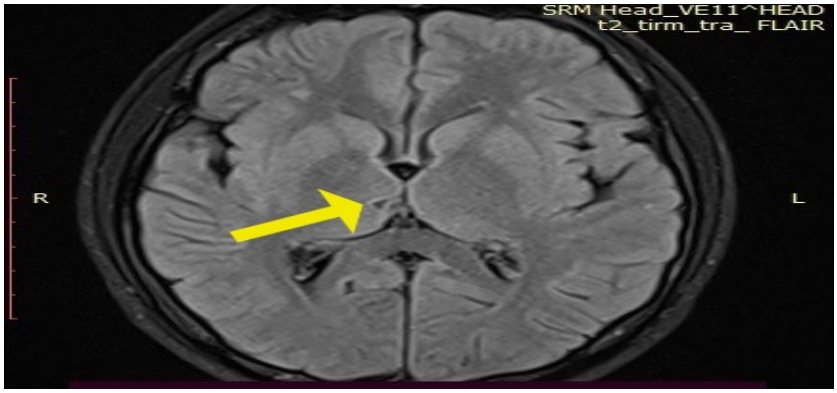
Table/Fig 3. Laboratory investigations

Test	Parameter	Result	Normal Values
Complete Hemogram	Hemoglobin (Hb)	12.1g/dl	Male: 13.8-17.2 g/dL, Female: 12.1-15.1 g/dL
	White Blood Cell (WBC)	8450cells/mcl	4,500-11,000 cells/mcL
	Platelet Count	216000cells/mcl	150,000-450,000 cells/mcL

Renal Function Analysis	Urea	22 mg/dL	7-20 mg/dL
	Serum Creatinine	0.7 mg/dL	Male: 0.74-1.35 mg/dL, Female: 0.59-1.04 mg/dL
Random Blood Glucose	Glucose	106 mg/dL	70-140 mg/dL
Electrolytes	Sodium	138 mEq/L	135 to 145 mEq/L
	Potassium	4.8 mmol/L	3.5 to 5 mmol/L
	Chloride	104 mEq/L	98 to 106 mEq/L
	Bicarbonate	26 mEq/L	24 to 30 mEq/L
	ESR	15mm/hr	0-15mm/hr
	CRP	Negative	
Thrombophilia	Protein C	69.5	65-135 IU/dL
	Protein S	115.6	60-150%
	Homocysteine	7 mcmol/L	5 to 15mcmol/L
	Antithrombin III	92	80-120%
	Factor V Leiden mutation	Negative	
	Antiphospholipid antibody	Negative	
Auto immune Profile	Anti nuclear antigen (ANA)	Negative	

Table/Fig 4: Magnetic resonance imaging of the brain (axial T2-FLAIR sequence) showing chronic lacunar infarcts in the thalamic region.

Considering the young age, recurrent strokes without atherosclerotic risk factors, negative autoimmune and thrombophilia workup, consanguinity, dermatologic manifestations, and systemic vascular involvement, a monogenic vasculitic disorder was suspected. Genetic testing identified a homozygous missense pathogenic



variant in the ADA2 gene (NM_001282225.2: c.139G>A; p.Gly47Arg), confirming the diagnosis of DADA2 (Table/Fig 5).

Table/Fig 5. Genetic analysis confirming ADA2 deficiency

Parameter	Result
Gene	ADA2 (NM_001282225.2)
Nucleotide Change	c.139G>A
Protein Change	p.Gly47Arg
Variant Type	Missense
Zygosity	Homozygous
Pathogenicity	Pathogenic
In Silico Prediction	Damaging (DANN, SIFT, PROVEAN, MutationTaster)
Population Frequency	Rare (gnomAD database)
ClinVar Database	Pathogenic (rs202134424)
Variant Classification	Pathogenic (ACMG guidelines)
Clinical Correlation	Phenotype overlaps with ADA2 deficiency features
Variant Coverage (Ref)	15 reads
Variant Coverage (Alt)	223 reads
Sequencing Depth ≥20X	Achieved
Coverage	92.71%
Quality Threshold	97.10%

The patient was initiated on subcutaneous adalimumab 40 mg every two weeks along with oral prednisolone, which was gradually tapered over six weeks. Azathioprine was added as a steroid-sparing immunosuppressant, and dual antiplatelet therapy, statins, and anticoagulation were prescribed for secondary stroke prevention. He was discharged in stable condition and remained clinically stable on follow-up without further vascular events.

This case emphasises the need to consider rare monogenic vasculitides such as DADA2 in young individuals presenting with recurrent vascular events and multisystem involvement. Early genetic confirmation and timely initiation of targeted therapy may prevent irreversible complications and improve long-term outcomes.

DISCUSSION

Deficiency of adenosine deaminase 2 (DADA2) is a rare autosomal recessive autoinflammatory disorder caused by biallelic loss-of-function mutations in the *CECR1/ADA2* gene located on chromosome 22. The disease is characterised by immune dysregulation, systemic vasculopathy, and haematological abnormalities, resulting in a wide spectrum of clinical manifestations [1]. Since its initial description in 2014, DADA2 has increasingly been recognised as a multisystem disorder that may mimic autoimmune and vasculitic conditions such as systemic lupus erythematosus, polyarteritis nodosa, and antiphospholipid syndrome, often leading to diagnostic delay [2].

Although the disease commonly presents in childhood or early adulthood, marked clinical heterogeneity contributes to under-recognition. Cutaneous features such as livedo reticularis or racemosa, nodules, and ulcerations are frequent, while recurrent lacunar ischemic strokes involving the thalamus, basal ganglia, or brainstem represent a characteristic neurological manifestation. Gastrointestinal complications including intestinal ischemia, necrosis, or perforation and haematological abnormalities such as cytopenias may also occur. Reduced immunoglobulin levels with recurrent infections further reflect underlying immune dysfunction. A history of consanguinity and the presence of systemic inflammation in the absence of autoimmune serological markers provide important diagnostic clues. Routine laboratory investigations are often non-specific, making genetic confirmation the diagnostic gold standard [3,4].

Therapeutic strategies primarily focus on suppression of inflammation and prevention of vascular events. Tumour necrosis factor-α inhibitors, including etanercept and adalimumab, constitute the cornerstone of treatment and have demonstrated effectiveness in reducing stroke

recurrence and systemic disease activity. Corticosteroids and conventional immunosuppressive agents may provide symptomatic benefit but are less effective in halting disease progression. Therefore, early diagnosis and timely initiation of targeted therapy are critical to prevent irreversible neurological injury and life-threatening gastrointestinal complications [5,6].

The present case illustrates several classical manifestations of DADA2, including recurrent ischemic strokes, livedo reticularis, and intestinal ischemia, along with negative autoimmune and thrombophilia profiles, all of which are consistent with previously reported clinical patterns [7,8]. However, the coexistence of bilateral posterior polar cataract and distal sensory axonal neuropathy represents an unusual phenotypic association. Ocular involvement is rarely described in DADA2 and may reflect chronic inflammatory or microvascular mechanisms. Similarly, peripheral neuropathy is an uncommon manifestation and is thought to result from vasculopathy affecting the vasa nervorum [9,10].

Cutaneous involvement, reported in the majority of patients, often serves as an early clinical clue, as observed in this case with malleolar ulcers and livedo reticularis. Gastrointestinal manifestations, though less frequent, can be severe and include mesenteric ischemia, thrombosis, and perforation, all of which significantly increase morbidity. The absence of conventional autoantibodies and a negative thrombophilia workup further support the likelihood of an underlying monogenic autoinflammatory disorder in young individuals presenting with unexplained vascular events [11,12]. Definitive diagnosis relies on identification of pathogenic *ADA2* variants or demonstration of reduced enzymatic activity, though access to such testing may be limited in routine clinical settings [13].

Management typically involves long-term immunosuppression with TNF-α inhibitors, frequently combined with corticosteroids or steroid-sparing agents such as azathioprine, mycophenolate mofetil, or methotrexate. Antiplatelet and anticoagulant therapies are often employed for secondary stroke prevention, although treatment should be individualised based on clinical profile and bleeding risk [14].

The identification of posterior polar cataract and sensory axonal neuropathy in a genetically confirmed case expands the recognised phenotypic spectrum of DADA2 and underscores the need for heightened clinical suspicion in young patients with multisystem vascular involvement that remains unexplained after standard evaluation. Early recognition, multidisciplinary management, and sustained follow-up are essential to improve long-term outcomes and reduce disease-related morbidity [15].

CONCLUSION

This patient's uncommon clinical features including posterior polar cataract and sensory axonal neuropathy emphasised the potential for DADA2 to present with atypical systemic manifestations beyond its typical presentation. Diagnosis of deficiency of adenosine deaminase 2 (DADA2) is crucial because of its potential to emulate an autoimmune or prothrombotic vasculitis, often leading to diagnostic delays. Young individuals presenting with recurrent strokes, systemic inflammation, and livedoid skin lesions and also uncommon features such as cataract and sensory neuropathy in the absence of specific conventional risk factors or serologic autoimmune markers along with consanguineous parentage should prompt genetic testing for early diagnosis and prompt intervention. Timely initiation of disease-modifying therapies particularly anti-TNF alpha inhibitors and steroids can prevent grave complications, improve outcomes thereby reducing patient morbidity. This case reinforces that DADA2 can exhibit phenotypic variability ranging from traditional vasculitic features to atypical systemic involvement

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