

# 'More Than Just Skin in the Game'. DADA2 Autoinflammatory Syndrome and Stroke in the Young

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## Abstract

A 21-year-old man had a long-standing history of leg ulcers and hyperpigmentation over the feet. Over a span of 8 months, he had an acute ischemic stroke followed by a basal ganglia hemorrhage. He was finally diagnosed with DADA2 syndrome after genetic sequencing. The implications of this new syndrome and its links to stroke in the young are presented in this article.

**Keywords:** DADA2, DADA2, vasculopathy, stroke in the young, stroke, DADA2, stroke, livedo, stroke, skin ulcers, stroke, vasculitis

## INTRODUCTION

Deficiency of adenosine deaminase 2 (DADA2) is a recently described monogenic autoinflammatory childhood with small and medium vessel vasculopathy.<sup>[1]</sup> It was initially described as a syndrome of recurrent fever, livedo racemosa, early-onset strokes and peripheral vasculopathy. We describe a young man with recurrent strokes due to DADA2 mutation.

## CASE PRESENTATION

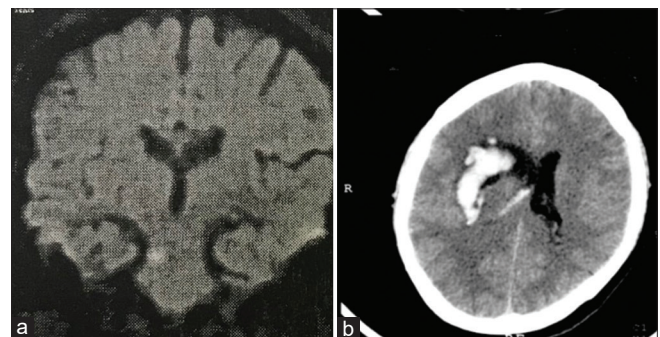
At 21 years of age, our patient developed an ischemic midbrain stroke with left ataxic hemiparesis and was started on 75 mg of Aspirin. He had painful ulcerative lesions on both legs of 12 years duration. Examination revealed erythematous macular lesions [livedo racemose] with shallow ulcers and hyperpigmentation on both legs. Work up including anti-phospholipid antibodies [APLA] was negative. Warfarin was added to prevent further thrombotic episodes. Eight months later, he developed a right basal ganglionic intra-cerebral haemorrhage [ICH] and left hemiplegia [grade 0/5 power MRC] [Figures 1 and 2]. Aspirin and Warfarin were discontinued. A muscle and skin biopsy were suggestive of vasculitis [Table 1]. Workup for lupus anticoagulant, APLA, ANA, anti ds-DNA antibodies, VDRL, cryoglobulins and hypercoagulable work-up were negative. Cardiac evaluation was normal. CT angiogram showed narrowing of the cavernous portion of right ICA, right MCA and its branches. The combination of livedo racemosa and multiple strokes suggested a diagnosis of Sneddon's syndrome, Childhood polyarteritis nodosa [c-PAN] or DADA 2 syndrome [Table 1].

He was started on baclofen and physiotherapy. Six years later, whole exome sequencing [WES] revealed a homozygous pathogenic missense variant, p.Gly47Arg exon 2 of the adenosine deaminase 2 [ADA2] gene.

He has remained asymptomatic but remains unemployed and dependent on parental support. Our patient was not started on any anti-TNF agents due to financial issues.

## DISCUSSION

Monogenic autoinflammatory syndromes [MAIS] are characterized by periodic episodes of systemic inflammation of endogenous origin and can mimic systemic vasculitis. MAIS with cerebrovascular manifestations include DADA2 and Familial Mediterranean fever (FMF).<sup>[1,2]</sup> Adenosine deaminases (ADA)



**Figure 1:** (a) Rt midbrain infarct [MRI DWI coronal image]. (b) Right basal ganglia hemorrhage

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**Table 1: Differential diagnosis of vasculitic stroke syndromes**

Primary antiphospholipid syndrome (PAPS)
Polyarteritis nodosa
Livedoid vasculitis
Cryoglobulinemia
Cold agglutinin disease
Systemic lupus erythematosus
Divry-Van Bogaert syndrome
DADA 2 syndrome
Cerebral thromboangiitis obliterans (Buerger 's disease)
Reversible cerebral vasoconstriction syndrome
MELAS syndrome
Primary CNS angiitis
Sneddon syndrome

are key enzymes in purine metabolism. Deficiency of ADA1, leads to severe combined immunodeficiency (SCID) in young children due to accumulation of cytotoxic intermediaries and death of developing lymphocytes. SCID patients present with profound lymphopenia, unlike DADA2. Deficiency of ADA2 causes DADA2 which resembles PAN, with multisystem involvement and features of medium and small vessel vasculitis or vasculopathy in >75% of cases. However, CNS involvement is commoner in DADA2 than PAN [50% v/s 5%]. Skin biopsy shows features of vasculitis or panniculitis. DADA2 is confirmed by gene sequencing or plasma ADA2 activity assay.<sup>[3]</sup> Our patients' homozygous variant is described in patients of Middle Eastern and South Asian ancestries. Biallelic pathogenic loss of function mutations in this gene causes a deficiency of ADA2. DADA2-associated mutations are inherited as homozygous or compound heterozygous variants. They can be identified by a single gene Sanger sequencing testing, or by next generation sequencing technologies such as WES. If genetic testing is inconclusive, protein test is recommended.<sup>[4,5]</sup> DADA2 has a wide spectrum of clinical manifestations [Table 2]. The clinical features of DADA2 in childhood-onset and adult-onset cases are quite similar; however, children have an increased prevalence of constitutional symptoms and adults have an increased prevalence of anaemia or other hematologic manifestations.<sup>[6]</sup>

Clear guidelines are not available regarding therapy in asymptomatic patients or stopping therapy in inactive disease although anti-TNF therapy is highly recommended in all cases with confirmed two pathogenic variants in ADA2 or very low ADA2 activity.<sup>[7,8]</sup> Anti-TNF [TNFi] agents such as Etanercept or hematopoietic stem cell transplantation (HSCT) are useful in patients with severe hematological disease.<sup>[9]</sup> Other TNFi such as adalimumab, infliximab as well as biosimilar TNFi are equally useful. Antiplatelet and anticoagulant medications should be avoided.

There are multiple etiologies of ICH in DADA2 – including haemorrhagic conversion of ischemic strokes, use of antiplatelets or due to the primary vasculopathy itself.<sup>[10]</sup>

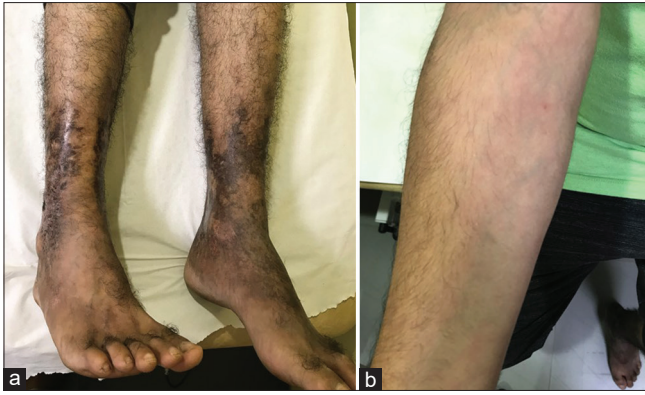
**Table 2: Clinical features of DADA2**

General manifestations	Fever Hypertension Hepatosplenomegaly Testicular pain Pregnancy loss
Skin involvement	Livedo reticularis/racemosa, Nodules Skin ulcers Purpura, Raynaud's phenomenon Erythema nodosum
Musculo –skeletal	Myalgias, arthralgias, arthritis Digital ischemia
Renal involvement	Proteinuria Hematuria
Hematological manifestations	Pancytopenia Anemia Pure red cell aplasia Immune thrombocytopenia Neutropenia Hypogammaglobulinemia Low IgG and IgM levels Lymphoproliferative disease Lymphadenopathy Hypocellular bone marrow
Neurological manifestations	Ischemic Stroke Hemorrhagic stroke Transient ischemic attacks Central retinal artery occlusion Peripheral neuropathy Myositis Myalgia Cranial neuropathy Sensorineural hearing loss Optic nerve atrophy, Spastic paraparesis PRES-like encephalopathy
Vascular manifestations	Reduced peripheral pulses Focal myocarditis Pancreatic infarction
Laboratory findings	Elevated CRP, ESR Elevated transaminases Absence of antineutrophilic cytoplasmic antibodies (ANCA) Positive lupus anticoagulant (50% of patients)

As our patient developed both an ischemic stroke and a haemorrhagic stroke within a span of 8 months, we discontinued both the antiplatelets and anticoagulants. We have initiated a discussion regarding further treatment options in our patient. Neurologists should be aware of these auto-inflammatory entities in the differential diagnosis of vasculitis and strokes. Stroke with DADA2 is underreported in the Indian literature.<sup>[6,11]</sup>

## SUMMARY

- DADA2 is a rare cause of stroke in young.



**Figure 2:** (a) Hyperpigmentation and healed ulcers with scarring on both legs. (b) Livedo racemose

- DADA2 should be considered in the presence of Livedo racemosa, Stroke or multisystem involvement even without a family history.
- Genetic testing can confirm the diagnosis
- Therapeutic options include anti-TNF agents or HSCT.

#### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

#### Conflicts of interest

There are no conflicts of interest.

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