Young Stroke and Systemic Manifestations: Deficiency of Adenosine Deaminase-2 (DADA-2)

Sir,

DADA 2 (Deficiency of Adenosine deaminase-2) is an autosomal recessive monogenic vasculitic syndrome caused by loss of function homozygous or compound heterozygous mutations in the ADA2 (also known as cat eye syndrome chromosome region, candidate 1 gene; CECR1) gene. It was first described in the year 2014 by Zhou *et al*. as an early onset stroke and vasculopathy syndrome.[1] The onset of the disease is usually in childhood; however, case reports in adults with onset as late as 59 years of age have also been reported. The clinical features include fever; mucocutaneous manifestations (livedo racemosa); neurological manifestations in the form of ischemic or hemorrhagic strokes, polyneuropathy; gastro-intestinal manifestations; hypertension; arthritis; hepato-splenomegaly and immunodeficiency (hypogammaglobulinemia and lymphoproliferation). We report a case of a 28-year-old male with young-onset hypertension and recurrent strokes who had a homozygous missense variant in exon 2 of the CECR1 (ADA-2) gene confirming the diagnosis of DADA-2. He responded to the treatment with TNF-alpha inhibitor, etanercept.

A 28-year-old male, born out of non-consanguineous marriage from North-West India belonging to Aggarwal community, presented with history of recurrent neurologic deficits since the last 14 years, in the form of right-hand grip weakness, two episodes of left hemiparesis, two episodes of right hemiparesis and one episode of binocular horizontal transient diplopia. Patient was diagnosed with hypertension nine years ago which is well controlled with antihypertensive treatment. He complained of low backache and arthralgias involving bilateral ankle and knee joints for the past 1.5 years. He also had hair loss and varicose veins. There was no history of photosensitive rash, dryness of eyes or mouth, Raynaud's phenomenon. On examination, he was conscious and oriented with stable vital parameters. His neurological examination revealed normal higher mental functions and cranial nerves with asymmetric spasticity of bilateral upper and lower limbs (right > left), exaggerated deep tendon reflexes and bilateral extensor plantar response. His gait was spastic. Patient was admitted at our hospital for detailed evaluation. Previous MRI brain image showed left medullary infarct. Current MRI brain was suggestive of small right basal ganglia bleed while MR angiogram was normal [Figure 1a, b]. Serum CRP was raised. Scalp skin biopsy was suggestive of cicatricial alopecia. ANA, dsDNA, ANCA, and APLA antibodies were negative. Ultrasound abdomen and renal artery Doppler were normal. Clinical exome sequencing revealed a homozygous missense variant in exon 2 of the CECR1 gene (ADA2) that results in the amino acid substitution of Arginine for Glycine at codon 47 (p.Gly47Arg) confirming the diagnosis of Deficiency of Adenosine Deaminase-2 (DADA-2). He was managed with an anti-TNF agent, etanercept. At 1 year follow up, the patient was stable with no fresh symptoms.

The deficiency of adenosine deaminase-2 (DADA-2) is recently described as an autoimmune disease caused by mutations in the CECR1 (ADA-2) gene. It is one of the rare causes of stroke in young, associated with varied systemic manifestations in the form of polyarteritis nodosa (PAN), livedo reticularis, ulcerations of the extremities, arthritis, recurrent infections, and peripheral neuropathy.[1,2] Vasculopathy involving small- to medium-size vessels is a major clinical manifestation of DADA-2. Skin and central nervous system are most commonly involved. Neurological manifestations have been reported in

around 50–60% of cases, majority of whom had ischemic strokes.[2,3] A single-center study has reported occurrence of hemorrhagic strokes in 25% of DADA-2 patients.[4] Sharma et al recently published a case series of 33 DADA-2 patients, majority of whom (>50%) presented with neurological manifestations, which is a distinguishing feature from adult PAN in which CNS manifestations are observed in <5% of patients. None of these patients had hypogammaglobulinemia. Majority of these patients were treated with TNF inhibitors. [5] Adult onset DADA2 differed from Paediatric onset cases in having lesser constitutional symptoms and haematological manifestations.[5]

DADA2-associated mutations are located over the entire coding region of ADA2. The majority of patients are compound heterozygous for missense mutations.[1,6] Patients homozygous for the same founder mutation may have a variable age of presentation, frequency, and intensity of symptoms. Parents of DADA2 patients are typically unaffected, which means that 50% of normal enzymatic activity is sufficient for the protein functions.[7]

Patients may have anemia, neutropenia, or thrombocytopenia, raised erythrocyte sedimentation rate, CRP, or liver transaminases.[6] Skin biopsy in patients with cutaneous PAN may reveal non-granulomatous, necrotizing vasculitis of small to medium size arteries.[1] The MRI Brain shows lacunar infarcts in the deep-brain nuclei and the brain stem with sparing of subcortical white matter.[6]

Diagnosis of DADA2 in adults requires a high index of suspicion and presence of one the following: 1) Childhood PAN 2) History of familial PAN 3) Early onset strokes with systemic inflammation 4) Immunodeficiency with vasculopathy 5) PAN without Hepatitis B infection 6) PAN which is non-responsive to treatment.

The recommended treatment for DADA-2 includes steroids and anti-TNF agents (infliximab, adalimumab, etanercept). Azathioprine, methotrexate, cyclophosphamide, cyclosporine, and tacrolimus have also been used previously but with little success. At present, anti-TNF alpha therapy is considered to be the treatment of choice by experts, which remains to be confirmed by a randomized trial.[1,2] A recent cohort study by Laird *et al*. which included 49 DADA-2 patients, out of which 24 had histories of stroke, has shown a key role of anti-TNF treatment in reducing stroke episodes in these patients.[8] Thalidomide has also been found to be effective; however, potential toxic effects on the peripheral nervous system is a matter of concern with this therapy. Hematopoietic stem cell transplantation might be an effective treatment option especially in those with immunodeficiency or bone marrow dysfunction.[9,10] It can be considered in patients with hematologic, immunologic manifestations or those with vasculopathy. In future, gene therapy may evolve as a promising treatment option.

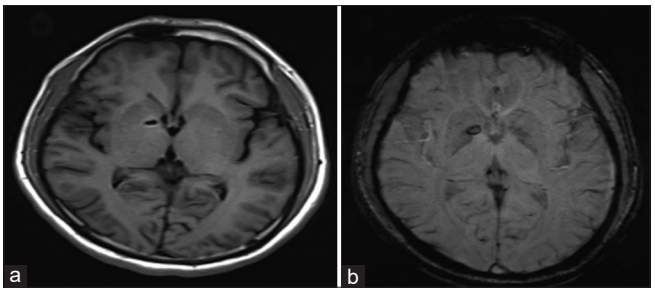

Figure 1: a,b: T1W MRI Brain and Susceptibility weighted image (SWI) image showing small right basal ganglia hemorrhage

To summarize, we report a case of a young male with recurrent neuro-deficits and systemic features with a genetically confirmed diagnosis of DADA-2, who responded well to treatment with etanercept. This case highlights the importance of considering DADA-2 as a differential diagnosis in patients with recurrent neurologic deficits at a young age associated with other systemic manifestations. The accurate diagnosis followed by treatment with immunosuppression can prevent further attacks and morbidity.

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Conflicts of interest

There are no conflicts of interest.

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