Deficiency of Adenosine Deaminase 2 (DADA2) – A New Autoinflammatory Disease with Multisystem Features

A male child born to a non-consanguineous couple had been extensively investigated for recurrent, prolonged febrile episodes from 2005 to 2011. The fever episodes were accompanied by multisystem manifestations consisting of myalgia, arthralgia, rashes, recurrent and episodic severe abdominal pain (one episode leading to an appendicectomy), episcleritis, generalized adenopathy and hepatomegaly [1]. Mutation testing for then known auto-inflammatory diseases including Tumor necrosis factor receptor associated periodic syndrome (TRAPS) was negative. TRAPS was considered as the best fit clinical diagnosis considering that literature had identified subsets of patients with a clinical profile matching TRAPS without mutations in the *TNFRSF1A* gene. The family was advised to start Tumor necrosis factor (TNF) blocker, etanercept at the dose of 0.4 mg/kg subcutaneously twice weekly, after tuberculosis screening. The patient's symptoms including fever, arthralgia, myalgia, and abdominal pain abated rapidly with normalization of his anthropometry over the next 2 years. His complete blood counts, Erythrocyte Sedimentation Rate (ESR) and C Reactive Protein (CRP), also normalized and stayed stable over the next seven years.The cost of etanercept lead to a gradual, progressive self-titration of dose to 0.4 mg/kg every 20-22 days, at which point symptoms would recur.

In January 2019, at age 20 years, he was diagnosed with asymptomatic hypertension (180/120 mmHg) during a pre-employment check. Urinalysis was normal and serum creatinine was 0.91 mg/dL with e-GFR of 114 mL/hr. His 2D-echocardiogram showed mild concentric left ventricular hypertrophy with grade 2 diastolic dysfunction suggesting long-standing hypertension. The ejection fraction was 60%. His kidneys were of normal size. A magnetic resonance angiogram (MRA) showed diffuse narrowing of the right renal artery and scarring of the right kidney (***Fig.* 1**). Positron emission tomography computerized tomography (PET-CT) did not show any vascular inflammation. Whole exome sequencing (WES) in the patient and his asymptomatic parents identified compound heterozygous mutations (p. Gly47Arg (c.139G>C; p.G47R) and a splice mutation c.753+2T>A). His father and mother were carriers of the respective mutations. The patient was started on antihypertensive therapy and etanercept was increased to 0.8 mg/kg once weekly starting April 2019. He is doing well since and is presently additionally receiving metoprolol 50 mg once daily.

DADA2 was described independently by two groups in 2014, and considerable time after our patients first presentation and report [2,3]. Now over 200 patients have been reported globally. Its prevalence is higher in endogamous populations (Middle Eastern countries) or in founder populations (Finnish, Dutch). Our patient hails from the endogamous Agarwal community and we have since diagnosed two other children of the same community with DADA2 homozygous for the p.Gly47Arg (c.139G>C; p.G47R) mutation.

Typically features begin in early childhood or adolescence. Vasculopathy/vasculitis (polyarteritis nodosa, lacunar infarcts) and hematological manifestations remain the cardinal features [4]. Hypertension has been described in 21%, renal artery stenosis in 4% of patients, and cases with large vessel involvement have been reported. Notable in our patient is an episode of acute abdomen for which he underwent appendicectomy. Uncommonly DADA2 can present as a polyarteritis nodosa (PAN)-like disease in adults. Screening such patients for ADA2 activity can radically modify management.

Laboratory findings are non-specific and include elevated acute phase reactants during flares and raised transaminases. Positive lupus anticoagulant autoantibodies have been noted in some. Sharma, *et al*. [5] have reported DADA2 in a 35 year old woman also from the Aggarwal community, who presented as a APLA-like syndrome with recurrent abortions [5]. The G47R pathogenic variant has been described in DADA2 patients from Middle East and South Asia and with an allele frequency higher than in other populations (Caucasian, Latino, African). Functional protein assay on fresh serum or plasma samples, which detects low or absent ADA2 enzymatic activity or measuring ADA2 catalytic activity on dried plasma filter paper spots can provide a rapid confirmatory protein diagnosis.

Despite the increasing availability and reducing costs of genetic testing, challenges of cost, interpretation, and long turn-around times exist. Our patient's samples awaited analysis at National Institutes of Health (NIH) (a global referral center for autoinflammatory diseases) for WES and were fast-tracked after recent developments. It was serendipitous that the child was started on etanercept in 2011. Retrospectively, spacing the

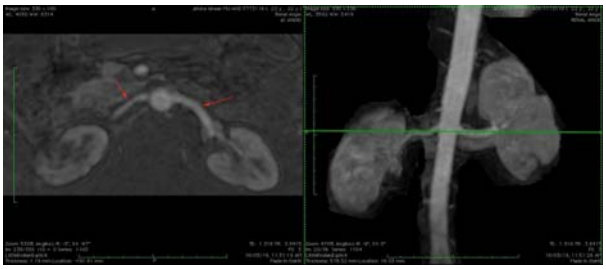

Fig. 1 *MR angiogram showing diffuse narrowing of the right renal artery and scarring of the right kidney.*

doses for cost considerations was not prudent since the child has developed a vasculopathy with renal scarring. Anti-TNF agents prevent and eliminate vasculitis symptoms in DADA2 patients with a remarkable reduction in ischemic stroke risk [6]. They decrease inflammatory burden of the disease, increase growth and development, and improve some hematological manifestations such as anemia and thrombocytopenia. Thalidomide has been reported useful in a large study. Aspirin and anticoagulants are contraindicated since hemorrhage may complicate the stroke. Hematopoietic stem cell transplantation can be curative in patients who present with bone marrow failure or are non-responsive to anti-TNF therapy [4].

In conclusion, pediatricians in India must be aware of this recently discovered entity and its myriad presentations, including PAN, early-onset strokes, arterial obliterations, immunodeficiency, and aplastic anemia. With high rates of consanguinity and endogamy in several parts of India, we believe more patients of hereditary auto-inflammatory diseases would be diagnosed with increasing physician awareness and availability of genetic testing.

Published online: August 14, 2020; *PII:* S097475591600231

RAJU KHUBCHANDANI[1]* AND IVONA AKSENTIJEVICH[2]
[1]*Department of Pediatric Rheumatology, SRCC Children's Hospital, Mumbai, India; and*
[2]*Inflammatory Disease Section, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, USA.*
**rajukhubchandani@yahoo.co.in*

REFERENCES

1. Dhanrajani A, Khubchandani RP. Modified regimen of etanercept for tumor necrosis factor receptor associated periodic syndrome (TRAPS) like illness. Indian Pediatr. 2014;51:55-7.
2. Zhou Q, Yang D, Ombrello A, Zavialov A, Toro C, Zavialov A, *et al*. Early-onset stroke and vasculopathy associated with mutations in ADA2. N Engl J Med. 2014; 370:911-20.
3. Navon Elkan P, Pierce S, 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.
4. 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.
5. Sharma A, Naidu G, Chattopadhyay A, Acharya N, Jha S, Jain S. Novel CECR1 gene mutations causing deficiency of adenosine deaminase 2, mimicking antiphospholipid syndrome. Rheumatology. 2019;58:181-2.
6. Ombrello A, Qin J, Hoffmann P, Kumar P, Stone D, Jones A, *et al*. Treatment strategies for deficiency of adenosine deaminase 2. N Engl J Med. 2019; 380:1582-4.

Crisponi/Cold Induced Sweating Syndrome Type 1 With a Private Cytokine Receptor Like Factor 1 (CRLF1) Mutation in an Indian Family

Crisponi/cold induced sweating syndrome type 1 (CS/CISS1; Mendelian Inheritance in Man [MIM] #272430), a rare autosomal recessive disorder, is possibly under-recognised due to its complex phenotype with likely misinterpretation of symptoms. Worldwide, there are fewer than 100 reported cases and we present the second Indian patient with a *CRLF1* genetic mutation [1-4]. A 1½-month-boy presented with intermittent high-grade fever, episodic contractions of facial and neck muscles and feeding difficulties since birth. He was sixth born to a non-consanguineous healthy couple hailing from North India. There was history of two sibling deaths, a male and a female in third week of life. Both the babies were born at term gestation, had normal birth weight but associated with birth asphyxia followed by progressive feeding abnormalities and abnormal posturing. His three elder female siblings were all alive and healthy. There was history of one spontaneous abortion in mother. Antenatal course of the present pregnancy was uneventful; mother received 2 doses of tetanus toxoid. The baby was delivered vaginally at term gestation with a birth weight of 3.25 kg. He was non-vigorous with meconium stained liquor but cried after stimulation. He required NICU stay with oxygen therapy and intravenous antibiotics though all laboratory investigations including sepsis work up were within normal limits. At presentation at 1½ months of life, he had fever (103°F), tachycardia, tachypnea, SpO2 of 98% at room air but clear chest. He was underweight (3.7 Kg) with normal length (60 cm) and head circumference (36.5cm). He had a round expressionless face (***Fig.*****1a**) with bilateral camptodactyly and clinodactyly with adduction of thumbs (***Fig.*****1b**) and overriding of the toes of both feet (***Fig.*****1c**). Neurological examination revealed a weak cry and decreased spontaneous motor activity. There were paroxysms of facial and neck muscle contraction leading to puckering of lips, tight eye closure, neck extension (***Fig.*** **1d**) along with inward rotation of the upper limbs and clenching of the hands lasting a few minutes. These episodes were associated with crying and often precipitated by tactile or painful stimulation with a frequency of 25-30 episodes during daytime. Episodes were absent during rest and sleep. Partial remission was obtained with clonazepam administration. Initially, possibilities of hypoxic ischemic encephalopathy, neonatal sepsis with meningitis, neonatal tetanus, Sandifer syndrome and inborn error of metabolism were considered.