Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors have declared no conflicts of interest.

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Accepted 17 May 2019
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Rheumatology 2020;59:254–256
doi:10.1093/rheumatology/kez260
Advance Access publication 10 July 2019

Deficiency of adenosine deaminase 2: a case series revealing clinical manifestations, genotypes and treatment outcomes from Turkey

Rheumatology key message

- Deficiency of adenosine deaminase 2 may present with amyloidosis, immunodeficiency and cytopenia in addition to vasculitic manifestations.

Dear Editor, Deficiency of adenosine deaminase 2 (DADA2) was first described in patients with biallelic mutations in the adenosine deaminase 2 (ADA2) gene on chromosome 22q11.1 and is characterized by recurrent fever, livedo racemosa and early onset strokes. Clinical manifestations of DADA2 may resemble the spectrum of polyarteritis nodosa (PAN) [1, 2]. Furthermore, several reports also suggested that DADA2 may cause broad spectrum manifestations, including only haematological involvement or lymphoproliferation [3, 4].

In this report, we share our experience of DADA2 in view of clinical manifestations, genotypes, treatment procedures and outcomes. Herein, we present five patients from three families, of which one, with renal amyloidosis successfully treated by canakinumab, was reported previously elsewhere [5].

The median age at symptom onset and DADA2 diagnosis were 10 (range, 10–13) and 15 (range, 11–25) years respectively. All patients were followed up for a median 12 months after DADA2 diagnosis. Persistent livedo racemosa was present in three patients, whereas abdominal pain ($n = 3$), hepatomegaly ($n = 3$), splenomegaly ($n = 3$), recurrent fever ($n = 2$), oral aphthous ($n = 1$), arthralgia ($n = 4$), arthritis ($n = 1$) and proteinuria/renal amyloidosis ($n = 1$) were the other prominent findings. Laboratory studies revealed mild lymphopenia and thrombocytopenia in two patients and one patient, respectively. Three patients had low serum IgM levels without recurrent infections and acute phase reactants were mildly elevated in four patients. Only two siblings with PAN-like phenotype underwent skin biopsy, which revealed necrotizing medium vessel vasculitis in the older brother, whereas the younger sister had non-specific vasculitis. Contrary to the majority of literature revealing the neurological aspects of DADA2, only one patient with a prior diagnosis of PAN had sensory neuropathy on routine EMG. The clinical characteristic, genotypes and treatment modalities are summarized in Table 1.

Beside the classical vasculitic phenotype of DADA2, unusual phenotypes such as cytopenia, lymphoproliferative disease and immunodeficiency have also been determined [3, 4]. Our patients are similar to the previous studies with the presence of previous PAN diagnosis in one patient, but fever and persistent livedo reticularis in three of five patients. We also introduce two patients without any signs of vasculitis, mainly presenting with systemic inflammation, hepatosplenomegaly, cytopenia and hypogammaglobulinaemia.

Table 1 Clinical manifestations and ADA2 genotypes of patients with deficiency of adenosine deaminase 2

	P1	P2	P3, sibling of P2	P4	P5, sibling of P4
Gender	F	F	M	F	F
Consanguinity	Yes	Yes	Yes	Yes	Yes
Age at disease onset, years	10	12	10	13	10
Age at diagnosis, years	20	15	25	13.5	11
Recurrent fever	No	Yes	Yes	No	No
Oral aphthous	No	Yes	No	No	No
Skin symptoms	Persistent livedo racemosa	Persistent livedo racemosa	Persistent livedo racemosa	None	None
Gastrointestinal symptoms	Abdominal pain	No	Abdominal pain	No	Abdominal pain
Myalgia	No	No	Yes	No	No
Arthritis/arthralgia	No/Yes	No/Yes	No/Yes	Yes/Yes	No/Yes
Haematological involvement	Mild lymphopenia	No	No	No	Mild lymphopenia, Thrombocytopenia
Immunological involvement	Low serum IgM	Normal Immunoglobulins	Normal Immunoglobulins	Low serum IgM	Low serum IgM
Elevation of APRs	No	Yes	Yes	Yes	Yes
Autoantibodies	No	No	No	No	No
Hepatomegaly/splenomegaly	No/No	No/No	No/No	Yes/Yes	Yes/Yes
Renal involvement	No	No	No	ProteinuriaRenal amyloidosis	No
Previous treatment	ND	ND	Systemic steroid, NSAID	Systemic steroid, CSA, colchicine	Colchicine
Current treatment and duration	Etanercept for 8 months	Etanercept for 8 months	Etanercept for 8 months	Canakinumab for 21 months	Etanercept for 8 months and IVIG for three months
Neurological symptoms	No	No	No	No	No
EMG	Normal	Normal	Sensory neuropathy	Normal	Normal
Cranial MRI	Normal	Normal	NA	Normal	Normal
Renal and portal Doppler US	Normal	Normal	Normal	Normal	Normal
Skin biopsy result	NA	Hydropic degeneration in basal layer, perivascular lymphocytes in dermis	Necrotizing medium-vessel vasculitis	NA	NA
ADA2 gene sequencing result	Y453C/Y453C	G47R/G47R	G47R/G47R	T317Rfs*25/ T317Rfs*25	T317Rfs*25/ T317Rfs*25
Plasma ADA2 activity	0 mU/g protein	0 mU/g protein	0 mU/g protein	0 mU/g protein	0 mU/g protein
Outcome	Marked improvement in skin lesions	Decrease in febrile episodes and marked improvement in skin lesions	Decrease in febrile myalgia episodes and complete resolution of livedo racemosa	Proteinuria disappeared	APR decreased with etanercept treatment, cytopenia improved after first IVIG replacement.

ADA2: adenosine deaminase 2; APR: acute phase reactant; CSA: ciclosporin A; EMG: electromyogram; NA: not applicable; ND; not determined. Autoantibodies included anti-nuclear antibody, anti-DNA, anti-cardiolipin IgM/IgG and anti-phospholipid IgM/IgG.

Genotype–phenotype correlation was studied in case series from different parts of the world. Firstly, the most frequent mutations were G47R in Turkish and Georgian ancestry, and R169Q in the European population. Previous studies linked G47R mutation with poor prognosis and PAN-like phenotype rather than livedo reticularis with CNS disease [6]. Additionally, Van Montfrans *et al.* suggested that median ADA2 activity was significantly lower in patients with stroke [7]. In contrast, all of our patients with absent ADA2 activity have not had neurological involvement including stroke so far.

We have been treating four of our patients with etanercept, of which one was cotreated with monthly IVIG replacement for resistant bicytopenia. All of them had favourable clinical and laboratory response without significant side effects. The remaining one patient was successfully treated with monthly canakinumab for renal amyloidosis, as we reported before [5]. However, there are still many questions and doubts on the treatment of DADA2. We do not know exactly with what drug and when to start therapy, or in addition how long patients should be on therapy. Anti-TNF agents, including etanercept and adalimumab, were the most commonly reported with benefits in improving the vasculitic signs and preventing strokes. Even though corticosteroids were reported to control the symptoms, patients usually became steroid dependent. Cyclophosphamide, methotrexate, azathioprine and calcineurin inhibitors yielded a little success. Although several patients with documented hypogammaglobulinaemia underwent IVIG replacement, its effects on disease symptoms and outcomes are not known [8]. One recent paper was novel in demonstrating the benefits of allogenic haematopoietic cell transplantation on both clinical symptoms and ADA2 activity [7]. Further studies are needed to investigate the role of ADA2 and enzymatic replacement or haematopoietic cell transplantation on the treatment of DADA2. Beside the aforementioned treatment options, we believe that recombinant ADA2 enzyme may be a more curative treatment option in the future. Until then, physicians may consider anti-TNF agents for vasculitis phenotype, anti-IL1 agents for amyloidosis and adding IVIG replacement for symptomatic immunodeficiencies or resistant cytopenia.

In conclusion, DADA2 is now known to present not only with vasculitis or PAN-like phenotype but also with amyloidosis, immunodeficiency and cytopenia. Nonetheless, livedo reticularis, fever, early-onset stroke, splenomegaly, lymphopenia and hypogammaglobulinaemia should be the clues for a DADA2 diagnosis. Further prospective multicentre, even international studies are needed to confirm the genotype–phenotype correlations and efficacy of different treatment modalities in DADA2.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

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Accepted 3 June 2019

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Rheumatology 2020;59:256–259
doi:10.1093/rheumatology/kez262
Advance Access publication 10 July 2019

Efficacy of abatacept for Felty's syndrome

Rheumatology key message

- Abatacept might be a novel therapy in place of rituximab for FS, particularly in cases with severe neutropenia.

Sir, FS is defined as the presence of RA, neutropenia and splenomegaly. FS occurs in a subset of fewer than 1% of