A case of adenosine deaminase-2 deficiency ... or not?

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INTRODUCTION

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Adenosine deaminase 2 (ADA 2):

• Primarily an extracellular protein with substantially less affinity for adenosine than ADA1
• May contribute to the degradation of extracellular adenosine, a signaling molecule that controls a variety of cellular responses
• the role of ADA2 in extracellular adenosine homeostasis is still under debate.
• the phenotypes associated with its absence suggested a significant role in regulating vascular development and inflammation.

The deficiency of adenosine deaminase-2 (DADA2)

• is a recently described autoinflammatory and metabolic disease evolving with childhood-onset polyarteritis nodosa, strokes, livedo racemosa and immune deficiency
• has been associated with various forms of immunodeficiency, pure red cell aplasia (PRCA), and bone marrow failure (BMF).
• determined by hypofunctional mutations of the CECR1 (ADA2) gene
• autosomal recessive

Clinical features:

• Livedo racemosa
• Neurologic involvement, including small lacunar infarction
• Peripheral vasculitis, digital ischemia, skin ulcerations
• Peripheral neuropathy
• Systemic inflammation
• Mild immune deficiency
• Splenomegaly
• Adenomegaly
• Portal hypertension

• It is quite possible that ADA2 has one or more other functions independent of its enzymatic activity (Schnappauf, et 2020).
Case description

A 26-year male patient, with a vasculitis with stroke at the age of 8, presented for headache.

Examination revealed livedo racemosa, a sluggish speech and splenomegaly.

Laboratory tests:
- inflammation (CRP 22 mg/L, normal <6 mg/L)
- selective IgG deficiency (545 mg/dL, normal 700-1600 mg/dL)
- antinuclear, antiphospholipid and anti-neutrophil cytoplasm antibodies, complement fractions and hepatitis B, C and HIV serology were normal

Other causes of splenomegaly?

Low-grade, persistent splenomegaly (16 cm in the long axis)

Tests for Gaucher and Niemann-Pick- negative
- Beta-glucosidase, beta-galactosidase normal
- Acid sphingomyelinase low in the blood spot analysis - but genetic tests ruled out a Niemann-Pick disease


Extended profile for autoimmune hepatitis - negative
- AMA-M2, M2-3E, Sp100, PML, gp120, LKM-1, LC1, SLA/LP, SS-A, Ro-52, Scl-70, CENP-A, CENP-B, PGDH

Deficiency of adenosine deaminase 2

- Vasculitis
- Pure red cell aplasia
- Bone marrow failure
- Residual ADA2 activity
- Insertion / deletion / frameshift

Lee et al. 2020. Genotype and functional correlates of disease phenotype in deficiency of ADA2
Genetics

A 109 genes assessment (autoinflammatory syndromes panel, Invitae, US) revealed two heterozygous variants of unknown significance (VUS) in ADA2:

- a c.620T>G (p.Phe270Cys), exon 4, suggested by predictive algorithms to be disruptive
- c.967G>A (p.Val323Ile), exon 7, for which the predictive algorithms did not agree (SIFT: deleterious, PolyPhen-2 probably damaging, Align GVGD Class 0).

Other heterozygous variants found in the patient:

- NOD2 c.2104C>T (p.Arg702Trp) - increased risk allele for Crohn’s disease
- RAG1 c.967G>A (p.Val323Ile) - VUS
- TNFRSF13B c.178C>T (p.Arg60Cys) - VUS

Is it a DADA2?

- Although the clinical picture suggested DADA2, the enzymatic test for ADA2 (Synlab) did not confirm the enzyme deficiency;
- Calprotectine values and recto-colonoscopy were normal; he had no symptoms for Crohn’s disease up to now;
- Cerebral MRI, ophthalmologic examinations did not found any new signs of vasculitis;
- Abdominal angioMRI – normal;
- Splenomegaly- without current signs of portal hypertension;

Treatment

- glucocorticoids (0.5 mg/kg, dose tapered to withdrawal);
- azathioprine (2 mg/kg);
- no immunoglobulin substitution required;

Follow-up

- clinical improvement and biological improvement (disappearance of inflammation);
- He is being monitored for the potential vasculitic organ involvement.
Discussions

• ADA2- enzyme in the purine catabolism, expressed in myeloid cells;
• Hematologic: chronic variable immune deficiency (CVID), isolated Ig deficiencies, mild anemia, pancytopenia, autoimmune lymphoproliferative syndrome (ALPS)-like, Castleman disease-like syndrome;
• Clinical spectrum is expanding;
• Response to anti-TNF alpha therapy
• ADA2 pathogenic variants may not be detected by conventional sequencing and genetic testing and may require the incorporation of additional diagnostic methods.

Therapies introduced in DADA2
• glucocorticoids,
• azathioprine
• cyclosporine
• cyclophosphamide
• hydroxichloroquine
• i.v. immunoglobulin
• thalidomide
• biologics: anti-TNFs (etanercept, adalimumab etc) Anti-IL6 (tocilizumab)

• The establishment of genotype-phenotype correlations in DADA2 has important therapeutic implications. Treatment with TNF inhibitors has proven effective in controlling vascular inflammation and reducing the risk of strokes, but seems to be less effective in patients with BMF and PRCA, and might even be detrimental given the increase in infection frequency seen in patients with BMF (Schnappauf, et 2020).

Pleiotropy in the deficiency of ADA 2. Lee et al. demonstrate a relationship between residual ADA2 enzymatic activity and clinical phenotype. It is still unclear, though, whether ADA2 may have additional as yet unknown functions, the preferential inhibition of which could also contribute to pleiotropy (modified after Schnappauf et 11 2020).
Conclusions

- The patient is being tested further in order to clarify a DADA2 or other type of vasculitis and treat it optimally;
- Currently available assays for ADA2 enzymatic activity based on HPLC or spectrophotometric methodologies are not sensitive enough to identify subtle differences in ADA2 activity in patient serum; the transfection system was introduced to generates ADA2 enzyme activity levels that are approximately 20-fold higher than physiologic ADA2 activity, allowing sufficient resolution among genetic variants (Schnappauf, Kastner et al 2020);
- Knowing that ADA2 pathogenic variants may not be detected by conventional sequencing/ genetic testing, these patients may require the incorporation of additional diagnostic methods;
- The management is multidisciplinary, with common follow-up during transition from pediatrics to adult medicine (rheumatology, neurology, immunology or internal medicine), with the involvement of the genetician;
- DADA2 is a prototypic disease at the limit between rheumatology and inborn metabolic diseases;
- Knowledge is being gained for future solving of the atypical cases and for the completion of new clinical presentations and therapies; genetic testing and enzymatic testing are necessary in DADA2 cases and in atypical cases as well, along with long-term follow-up;

References